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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRADAXA safely and effectively. See full prescribing information for PRADAXA.

PRADAXA® (dabigatran etexilate) capsules, for oral use
Initial U.S. Approval: 2010

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, and (B) SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy (2.4, 2.5, 2.6, 5.1).

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis (5.3). Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated (5.3).

INDICATIONS AND USAGE

PRADAXA is a direct thrombin inhibitor indicated:

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (1.1)
- For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days (1.2)
- To reduce the risk of recurrence of DVT and PE in patients who have been previously treated (1.3)
- For the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery (1.4)

DOSAGE AND ADMINISTRATION

- Non-valvular Atrial Fibrillation:
  - For patients with CrCl >30 mL/min: 150 mg orally, twice daily (2.1)
  - For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily (2.1)
- Treatment of DVT and PE:
  - For patients with CrCl >30 mL/min: 150 mg orally, twice daily after 5-10 days of parenteral anticoagulation (2.1)
- Reduction in the Risk of Recurrence of DVT and PE:
  - For patients with CrCl >30 mL/min: 150 mg orally, twice daily after previous treatment (2.1)
- Prophylaxis of DVT and PE Following Hip Replacement Surgery:
  - For patients with CrCl >30 mL/min: 110 mg orally first day, then 220 mg once daily (2.1)
- Review recommendations for converting to or from other oral or parenteral anticoagulants (2.4, 2.5)
- Temporarily discontinue PRADAXA before invasive or surgical procedures when possible, then restart promptly (2.6)

DOSAGE FORMS AND STRENGTHS

Capsules: 75 mg, 110 mg and 150 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)
- History of serious hypersensitivity reaction to PRADAXA (4)
- Mechanical prosthetic heart valve (4)

WARNINGS AND PRECAUTIONS

- Bleeding: PRADAXA can cause serious and fatal bleeding (5.2)
- Bioprosthetic heart valves: PRADAXA use not recommended (5.4)
- Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome: PRADAXA use not recommended (5.6)

ADVERSE REACTIONS

Most common adverse reactions (>15%) are gastritis-like symptoms and bleeding (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- P-gp inducers rifampin: Avoid coadministration with PRADAXA (5.5)
- P-gp inhibitors in patients with CrCl 30-50 mL/min: Reduce dose or avoid (7)
- P-gp inhibitors in patients with CrCl <30 mL/min: Not recommended (7)

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding not recommended. (8.2)
Geriatric use: Risk of bleeding increases with age (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, and (B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. If anticoagulation with PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4, 2.5, 2.6) and Warnings and Precautions (5.1)]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of PRADAXA and neuraxial procedures is not known**

***[see Warnings and Precautions (5.3)]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation

PRADAXA is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

1.2 Treatment of Deep Venous Thrombosis and Pulmonary Embolism

PRADAXA is indicated for the treatment of deep venous thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5-10 days.

1.3 Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism

PRADAXA is indicated to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in patients who have been previously treated.

1.4 Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery

PRADAXA is indicated for the prophylaxis of deep vein thrombosis and pulmonary embolism, in patients who have undergone hip replacement surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Indication	Dosage	
Reduction in Risk of Stroke and Systemic Embolism in Non-valvular AF	CrCl >30 mL/min:	150 mg twice daily
	CrCl 15 to 30 mL/min:	75 mg twice daily
	CrCl <15 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl 30 to 50 mL/min with concomitant use of P-gp inhibitors:	Reduce dose to 75 mg twice daily if given with P-gp inhibitors dronedarone or systemic ketoconazole.
	CrCl <30 mL/min with concomitant use of P-gp inhibitors:	Avoid co-administration
Treatment of DVT and PE **Reduction in the Risk of Recurrence of DVT and PE**	CrCl >30 mL/min:	150 mg twice daily
	CrCl ≤30 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl <50 mL/min with concomitant use of P-gp inhibitors:	Avoid co-administration
Prophylaxis of DVT and PE Following Hip Replacement Surgery	CrCl >30 mL/min:	110 mg for first day, then 220 mg once daily
	CrCl ≤30 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl <50 mL/min with concomitant use of P-gp inhibitors:	Avoid co-administration

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Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of PRADAXA is 150 mg taken orally, twice daily. For patients with severe renal impairment (CrCl 15-30 mL/min), the recommended dose of PRADAXA is 75 mg twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Dosing recommendations for patients with a CrCl <15 mL/min or on dialysis cannot be provided.

Treatment of Deep Venous Thrombosis and Pulmonary Embolism
For patients with CrCl >30 mL/min, the recommended dose of PRADAXA is 150 mg taken orally, twice daily, after 5-10 days of parenteral anticoagulation. Dosing recommendations for patients with a CrCl ≤30 mL/min or on dialysis cannot be provided *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
For patients with CrCl >30 mL/min, the recommended dose of PRADAXA is 150 mg taken orally, twice daily after previous treatment. Dosing recommendations for patients with a CrCl ≤30 mL/min or on dialysis cannot be provided *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
For patients with CrCl >30 mL/min, the recommended dose of PRADAXA is 110 mg taken orally 1-4 hours after surgery and after hemostasis has been achieved, then 220 mg taken once daily for 28-35 days. If PRADAXA is not started on the day of surgery, after hemostasis has been achieved initiate treatment with 220 mg once daily. Dosing recommendations for patients with a CrCl ≤30 mL/min or on dialysis cannot be provided *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.2, 12.3)]*.

2.2 Dosing Adjustments
Assess renal function prior to initiation of treatment with PRADAXA. Periodically assess renal function as clinically indicated (i.e., more frequently in clinical situations that may be associated with a decline in renal function) and adjust therapy accordingly. Discontinue PRADAXA in patients who develop acute renal failure while on PRADAXA and consider alternative anticoagulant therapy.

Generally, the extent of anticoagulation does not need to be assessed. When necessary, use aPTT or ECT, and not INR, to assess for anticoagulant activity in patients on PRADAXA *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
In patients with moderate renal impairment (CrCl 30-50 mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole can be expected to produce dabigatran exposure similar to that observed in severe renal impairment. Reduce the dose of PRADAXA to 75 mg twice daily *[see Warnings and Precautions (5.5), Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Dosing recommendations for patients with CrCl ≤30 mL/min cannot be provided. Avoid use of concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
Dosing recommendations for patients with CrCl ≤30 mL/min or on dialysis cannot be provided. Avoid use of concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.3) and Clinical Pharmacology (12.2, 12.3)]*.

2.3 Instructions to Patients
Instruct patients to swallow the capsules whole. PRADAXA should be taken with a full glass of water. Breaking, chewing, or emptying the contents of the capsule can result in increased exposure *[see Clinical Pharmacology (12.3)]*.

If a dose of PRADAXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of PRADAXA should not be doubled to make up for a missed dose.

2.4 Converting from or to Warfarin
When converting patients from warfarin therapy to PRADAXA, discontinue warfarin and start PRADAXA when the INR is below 2.0.

When converting from PRADAXA to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:
- For CrCl ≥50 mL/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing PRADAXA.
- For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing PRADAXA.
- For CrCl <15 mL/min, no recommendations can be made.

Because PRADAXA can increase INR, the INR will better reflect warfarin's effect only after PRADAXA has been stopped for at least 2 days *[see Clinical Pharmacology (12.2)]*.

2.5 Converting from or to Parenteral Anticoagulants
For patients currently receiving a parenteral anticoagulant, start PRADAXA 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

For patients currently taking PRADAXA, wait 12 hours (CrCl ≥30 mL/min) or 24 hours (CrCl <30 mL/min) after the last dose of PRADAXA before initiating treatment with a parenteral anticoagulant *[see Clinical Pharmacology (12.3)]*.

2.6 Discontinuation for Surgery and Other Interventions
If possible, discontinue PRADAXA 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding. Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

If surgery cannot be delayed, there is an increased risk of bleeding *[see Warnings and Precautions (5.2)]*. This risk of bleeding should be weighed against the urgency of intervention *[see Warnings and Precautions (5.1, 5.3)]*. Use a specific reversal agent (idarucizumab) in case of emergency surgery or urgent procedures when reversal of the anticoagulant effect of dabigatran is needed. Refer to the idarucizumab prescribing information for additional information. Restart PRADAXA as soon as medically appropriate.

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3 DOSAGE FORMS AND STRENGTHS

150 mg capsules with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a white opaque body imprinted in black with "R150".

110 mg capsules with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a light blue opaque body imprinted in black with "R110".

75 mg capsules with a white opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a white opaque body imprinted in black with "R75".

4 CONTRAINDICATIONS

PRADAXA is contraindicated in patients with:

- Active pathological bleeding *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.
- History of a serious hypersensitivity reaction to PRADAXA (e.g., anaphylactic reaction or anaphylactic shock) *[see Adverse Reactions (6.1)]*.
- Mechanical prosthetic heart valve *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including PRADAXA, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant and restart PRADAXA as soon as medically appropriate *[see Dosage and Administration (2.4, 2.5, 2.6)]*.

5.2 Risk of Bleeding

PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue PRADAXA in patients with active pathological bleeding *[see Dosage and Administration (2.2)]*.

Risk factors for bleeding include the concomitant use of other drugs that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs). PRADAXA's anticoagulant activity and half-life are increased in patients with renal impairment *[see Clinical Pharmacology (12.2)]*.

Reversal of Anticoagulant Effect:
A specific reversal agent (idarucizumab) for dabigatran is available when reversal of the anticoagulant effect of dabigatran is needed:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding

Hemodialysis can remove dabigatran; however the clinical experience supporting the use of hemodialysis as a treatment for bleeding is limited *[see Overdosage (10)]*. Prothrombin complex concentrates, or recombinant Factor VIIa may be considered but their use has not been evaluated in clinical trials. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of dabigatran. Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

To reduce the potential risk of bleeding associated with the concurrent use of dabigatran and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of dabigatran *[see Clinical Pharmacology (12.3)]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of dabigatran is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

5.4 Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves

The safety and efficacy of PRADAXA in patients with bileaflet mechanical prosthetic heart valves was evaluated in the RE-ALIGN trial, in which patients with bileaflet mechanical prosthetic heart valves (recently implanted or implanted more than three months prior to enrollment) were randomized to dose adjusted warfarin or 150 mg, 220 mg, or 300 mg of PRADAXA twice a day. RE-ALIGN was terminated early due to the occurrence of significantly more thromboembolic events (valve thrombosis, stroke, transient ischemic attack, and myocardial infarction) and an excess of major bleeding (predominantly post-operative pericardial effusions requiring intervention for hemodynamic compromise) in the PRADAXA treatment arm as compared to the warfarin treatment arm. These bleeding and thromboembolic events were seen both in patients who were initiated on PRADAXA post-operatively within three days of mechanical bileaflet valve implantation, as well as in patients whose valves had been implanted more than three months prior to enrollment. Therefore, the use of PRADAXA is contraindicated in patients with mechanical prosthetic valves *[see Contraindications (4)]*.

The use of PRADAXA for the prophylaxis of thromboembolic events in patients with atrial fibrillation in the setting of other forms of valvular heart disease, including the presence of a bioprosthetic heart valve, has not been studied and is not recommended.

5.5 Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure

The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided *[see Clinical Pharmacology (12.3)]*.

P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran *[see Clinical Pharmacology (12.3)]*. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

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Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
Reduce the dose of PRADAXA to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with PRADAXA in patients with moderate renal impairment (CrCl 30-50 mL/min). Avoid use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) *[see Drug Interactions (7.1) and Use in Specific Populations (8.6)]*.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Avoid use of PRADAXA and concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Drug Interactions (7.2) and Use in Specific Populations (8.6)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
Avoid use of PRADAXA and concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Drug Interactions (7.3) and Use in Specific Populations (8.6)]*.

5.6 Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome
Direct-acting oral anticoagulants (DOACs), including PRADAXA, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple-positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:

- Increased Risk of Thrombotic Events after Premature Discontinuation *[see Warnings and Precautions (5.1)]*
- Risk of Bleeding *[see Warnings and Precautions (5.2)]*
- Spinal/Epidural Anesthesia or Puncture *[see Warnings and Precautions (5.3)]*
- Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves *[see Warnings and Precautions (5.4)]*
- Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome *[see Warnings and Precautions (5.6)]*

The most serious adverse reactions reported with PRADAXA were related to bleeding *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
The RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study provided safety information on the use of two doses of PRADAXA and warfarin *[see Clinical Studies (14.1)]*. The numbers of patients and their exposures are described in Table 1. Limited information is presented on the 110 mg dosing arm because this dose is not approved.

Table 1 Summary of Treatment Exposure in RE-LY

	PRADAXA 110 mg twice daily	PRADAXA 150 mg twice daily	Warfarin
Total number treated	5983	6059	5998
Exposure			
> 12 months	4936	4939	5193
> 24 months	2387	2405	2470
Mean exposure (months)	20.5	20.3	21.3
Total patient-years	10,242	10,261	10,659

Drug Discontinuation in RE-LY
The rates of adverse reactions leading to treatment discontinuation were 21% for PRADAXA 150 mg and 16% for warfarin. The most frequent adverse reactions leading to discontinuation of PRADAXA were bleeding and gastrointestinal events (i.e., dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea).

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Bleeding [see Warnings and Precautions (5.2)]
Table 2 shows the number of adjudicated major bleeding events during the treatment period in the RE-LY study, with the bleeding rate per 100 subject-years (%). Major bleeding is defined as bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells, bleeding at a critical site or with a fatal outcome. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 2 Adjudicated Major Bleeding Events in Treated Patients[a]

Event	PRADAXA 150 mg N = 6059 n (%/year[b])	Warfarin N = 5998 n (%/year[b])	PRADAXA 150 mg vs. Warfarin HR (95% CI)
Major Bleeding[c]	350 (3.47)	374 (3.58)	0.97 (0.84, 1.12)
Intracranial Hemorrhage (ICH)[d]	23 (0.22)	82 (0.77)	0.29 (0.18, 0.46)
Hemorrhagic Stroke[e]	6 (0.06)	40 (0.37)	0.16 (0.07, 0.37)
Other ICH	17 (0.17)	46 (0.43)	0.38 (0.22, 0.67)
Gastrointestinal	162 (1.59)	111 (1.05)	1.51 (1.19, 1.92)
Fatal Bleeding[f]	7 (0.07)	16 (0.15)	0.45 (0.19, 1.10)
ICH	3 (0.03)	9 (0.08)	0.35 (0.09, 1.28)
Non-intracranial[g]	4 (0.04)	7 (0.07)	0.59 (0.17, 2.02)

[a]Patients during treatment or within 2 days of stopping study treatment. Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories.
[b]Annual event rate per 100 pt-years = 100 * number of subjects with event/subject-years. Subject-years is defined as cumulative number of days from first drug intake to event date, date of last drug intake + 2, death date (whatever occurred first) across all treated subjects divided by 365.25. In case of recurrent events of the same category, the first event was considered.
[c]Defined as bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site or with fatal outcome.
[d]Intracranial bleed included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.
[e]On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14 Clinical Studies.
[f]Fatal bleed: Adjudicated major bleed as defined above with investigator reported fatal outcome and adjudicated death with primary cause from bleeding.
[g]Non-intracranial fatal bleed: Adjudicated major bleed as defined above and adjudicated death with primary cause from bleeding but without symptomatic intracranial bleed based on investigator's clinical assessment.

There was a higher rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg than in patients receiving warfarin (6.6% vs. 4.2%, respectively).

The risk of major bleeds was similar with PRADAXA 150 mg and warfarin across major subgroups defined by baseline characteristics (see Figure 1), with the exception of age, where there was a trend towards a higher incidence of major bleeding on PRADAXA (hazard ratio 1.2, 95% CI: 1.0 to 1.5) for patients ≥75 years of age.

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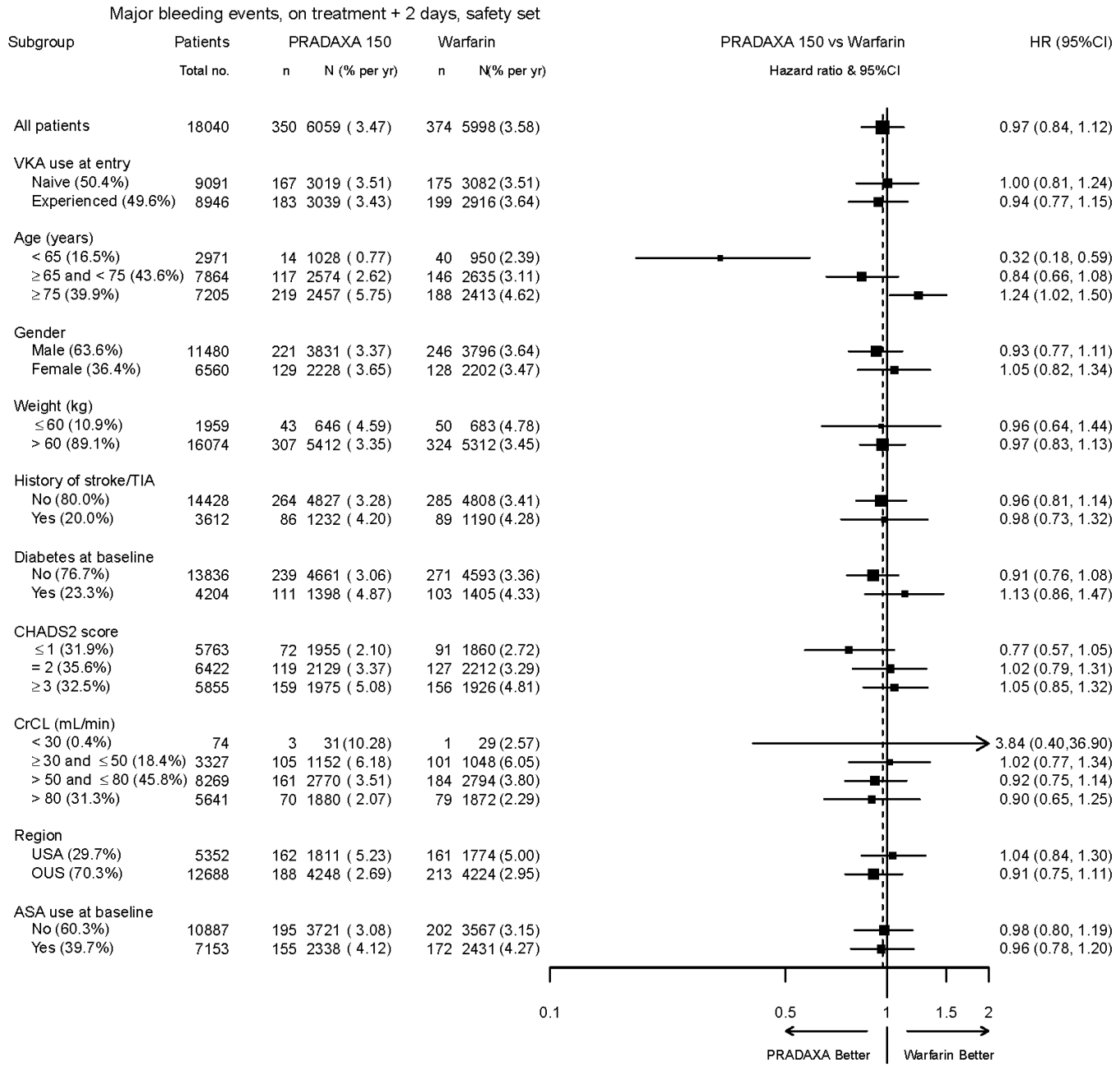
Figure 1 Adjudicated Major Bleeding by Baseline Characteristics Including Hemorrhagic Stroke Treated Patients



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Gastrointestinal Adverse Reactions

Patients on PRADAXA 150 mg had an increased incidence of gastrointestinal adverse reactions (35% vs. 24% on warfarin). These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and gastrointestinal ulcer).

Hypersensitivity Reactions

In the RE-LY study, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in <0.1% of patients receiving PRADAXA.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism

PRADAXA was studied in 4387 patients in 4 pivotal, parallel, randomized, double-blind trials. Three of these trials were active-controlled (warfarin) (RE-COVER, RE-COVER II, and RE-MEDY), and one study (RE-SONATE) was placebo-controlled. The demographic characteristics were similar among the 4 pivotal studies and between the treatment groups within these studies. Approximately 60% of the treated patients were male, with a mean age of 55.1 years. The majority of the patients were white (87.7%), 10.3% were Asian, and 1.9% were black with a mean CrCl of 105.6 mL/min.

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Bleeding events for the 4 pivotal studies were classified as major bleeding events if at least one of the following criteria applied: fatal bleeding, symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding), bleeding causing a fall in hemoglobin level of 2.0 g/dL (1.24 mmol/L or more, or leading to transfusion of 2 or more units of whole blood or red cells).

RE-COVER and RE-COVER II studies compared PRADAXA 150 mg twice daily and warfarin for the treatment of deep vein thrombosis and pulmonary embolism. Patients received 5-10 days of an approved parenteral anticoagulant therapy followed by 6 months, with mean exposure of 164 days, of oral only treatment; warfarin was overlapped with parenteral therapy. Table 3 shows the number of patients experiencing bleeding events in the pooled analysis of RE-COVER and RE-COVER II studies during the full treatment including parenteral and oral only treatment periods after randomization.

Table 3 Bleeding Events in RE-COVER and RE-COVER II Treated Patients

	Bleeding Events-Full Treatment Period Including Parenteral Treatment		
	PRADAXA 150 mg twice daily N (%)	**Warfarin N (%)**	**Hazard Ratio (95% CI)[c]**
Patients	**N=2553**	**N=2554**	
Major bleeding event[a]	37 (1.4)	51 (2.0)	0.73 (0.48, 1.11)
Fatal bleeding	1 (0.04)	2 (0.1)	
Bleeding in a critical area or organ	7 (0.3)	15 (0.6)	
Fall in hemoglobin ≥2 g/dL or transfusion ≥2 units of whole blood or packed red blood cells	32 (1.3)	38 (1.5)	
Bleeding sites for MBE[b]			
Intracranial	2 (0.1)	5 (0.2)	
Retroperitoneal	2 (0.1)	1 (0.04)	
Intraarticular	2 (0.1)	4 (0.2)	
Intramuscular	2 (0.1)	6 (0.2)	
Gastrointestinal	15 (0.6)	14 (0.5)	
Urogenital	7 (0.3)	14 (0.5)	
Other	8 (0.3)	8 (0.3)	
Clinically relevant non-major bleeding	101 (4.0)	170 (6.7)	0.58 (0.46, 0.75)
Any bleeding	411 (16.1)	567 (22.7)	0.70 (0.61, 0.79)

Note: MBE can belong to more than one criterion.
[a]Patients with at least one MBE.
[b]Bleeding site based on investigator assessment. Patients can have more than one site of bleeding.
[c]Confidence interval

The rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg in the full treatment period was 3.1% (2.4% on warfarin).

The RE-MEDY and RE-SONATE studies provided safety information on the use of PRADAXA for the reduction in the risk of recurrence of deep vein thrombosis and pulmonary embolism.

RE-MEDY was an active-controlled study (warfarin) in which 1430 patients received PRADAXA 150 mg twice daily following 3 to 12 months of oral anticoagulant regimen. Patients in the treatment studies who rolled over into the RE-MEDY study had a combined treatment duration of up to more than 3 years, with mean exposure of 473 days. Table 4 shows the number of patients experiencing bleeding events in the study.

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Table 4 Bleeding Events in RE-MEDY Treated Patients

	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI)[c]
Patients	**N=1430**	**N=1426**	
Major bleeding event[a]	13 (0.9)	25 (1.8)	0.54 (0.25, 1.16)
Fatal bleeding	0	1 (0.1)	
Bleeding in a critical area or organ	7 (0.5)	11 (0.8)	
Fall in hemoglobin ≥2 g/dL or transfusion ≥2 units of whole blood or packed red blood cells	7 (0.5)	16 (1.1)	
Bleeding sites for MBE[b]			
Intracranial	2 (0.1)	4 (0.3)	
Intraocular	4 (0.3)	2 (0.1)	
Retroperitoneal	0	1 (0.1)	
Intraarticular	0	2 (0.1)	
Intramuscular	0	4 (0.3)	
Gastrointestinal	4 (0.3)	8 (0.6)	
Urogenital	1 (0.1)	1 (0.1)	
Other	2 (0.1)	4 (0.3)	
Clinically relevant non-major bleeding	71 (5.0)	125 (8.8)	0.56 (0.42, 0.75)
Any bleeding	278 (19.4)	373 (26.2)	0.71 (0.61, 0.83)

Note: MBE can belong to more than one criterion.
[a]Patients with at least one MBE.
[b]Bleeding site based on investigator assessment. Patients can have more than one site of bleeding.
[c]Confidence interval

In the RE-MEDY study, the rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg was 3.1% (2.2% on warfarin).

RE-SONATE was a placebo-controlled study in which 684 patients received PRADAXA 150 mg twice daily following 6 to 18 months of oral anticoagulant regimen. Patients in the treatment studies who rolled over into the RE-SONATE study had combined treatment duration up to 9 months, with mean exposure of 165 days. Table 5 shows the number of patients experiencing bleeding events in the study.

Table 5 Bleeding Events in RE-SONATE Treated Patients

	PRADAXA 150 mg twice daily N (%)	Placebo N (%)	Hazard Ratio (95% CI)[c]
Patients	**N=684**	**N=659**	
Major bleeding event[a]	2 (0.3)	0	
Bleeding in a critical area or organ	0	0	
Gastrointestinal[b]	2 (0.3)	0	
Clinically relevant non-major bleeding	34 (5.0)	13 (2.0)	2.54 (1.34, 4.82)
Any bleeding	72 (10.5)	40 (6.1)	1.77 (1.20, 2.61)

Note: MBE can belong to more than one criterion.
[a]Patients with at least one MBE.
[b]Bleeding site based on investigator assessment. Patients can have more than one site of bleeding.
[c]Confidence interval

In the RE-SONATE study, the rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg was 0.7% (0.3% on placebo).

Clinical Myocardial Infarction Events
In the active-controlled VTE studies, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA [20 (0.66 per 100 patient-years)] than in those who received warfarin [5 (0.17 per 100 patient-years)]. In the placebo-controlled study, a similar rate of non-fatal and fatal clinical myocardial infarction was reported in patients who received PRADAXA [1 (0.32 per 100 patient-years)] and in those who received placebo [1 (0.34 per 100 patient-years)].

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Gastrointestinal Adverse Reactions
In the four pivotal studies, patients on PRADAXA 150 mg had a similar incidence of gastrointestinal adverse reactions (24.7% vs. 22.7% on warfarin). Dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) occurred in patients on PRADAXA in 7.5% vs. 5.5% on warfarin, and gastritis-like symptoms (including gastritis, GERD, esophagitis, erosive gastritis and gastric hemorrhage) occurred at 3.0% vs. 1.7%, respectively.

Hypersensitivity Reactions
In the 4 pivotal studies, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in 0.1% of patients receiving PRADAXA.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
PRADAXA was studied in 5476 patients, randomized and treated in two double-blind, active-controlled non-inferiority trials (RE-NOVATE and RE-NOVATE II). The demographic characteristics were similar across the two studies and between the treatment groups within these studies. Approximately 45.3% of the treated patients were male, with a mean age of 63.2 years. The majority of the patients were white (96.1%), 3.6% were Asian, and 0.3% were black with a mean CrCl of 92 mL/min.

Bleeding events for the RE-NOVATE and RE-NOVATE II studies were classified as major bleeding events if at least one of the following criteria applied: fatal bleeding, symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or retroperitoneal bleeding), bleeding causing a fall in hemoglobin level of 2.0 g/dL (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells, requiring treatment cessation or leading to re-operation.

The RE-NOVATE study compared PRADAXA 75 mg taken orally 1-4 hours after surgery followed by 150 mg once daily, PRADAXA 110 mg taken orally 1-4 hours after surgery followed by 220 mg once daily and subcutaneous enoxaparin 40 mg once daily initiated the evening before surgery for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients who had undergone hip replacement surgery. The RE-NOVATE II study compared PRADAXA 110 mg taken orally 1-4 hours after surgery followed by 220 mg once daily and subcutaneous enoxaparin 40 mg once daily initiated the evening before surgery for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients who had undergone hip replacement surgery. In the RE-NOVATE and RE-NOVATE II studies, patients received 28-35 days of PRADAXA or enoxaparin with median exposure of 33 days. Tables 6 and 7 show the number of patients experiencing bleeding events in the analysis of RE-NOVATE and RE-NOVATE II.

Table 6 Bleeding Events in RE-NOVATE Treated Patients

	PRADAXA 220 mg N (%)	**Enoxaparin N (%)**
Patients	**N=1146**	**N=1154**
Major bleeding event	23 (2.0)	18 (1.6)
Clinically relevant non-major bleeding	48 (4.2)	40 (3.5)
Any bleeding	141 (12.3)	132 (11.4)

Table 7 Bleeding Events in RE-NOVATE II Treated Patients

	PRADAXA 220 mg N (%)	**Enoxaparin N (%)**
Patients	**N=1010**	**N=1003**
Major bleeding event	14 (1.4)	9 (0.9)
Clinically relevant non-major bleeding	26 (2.6)	20 (2.0)
Any bleeding	98 (9.7)	83 (8.3)

In the two studies, the rate of major gastrointestinal bleeds in patients receiving PRADAXA and enoxaparin was the same (0.1%) and for any gastrointestinal bleeds was 1.4% for PRADAXA 220 mg and 0.9% for enoxaparin.

Gastrointestinal Adverse Reactions
In the two studies, the incidence of gastrointestinal adverse reactions for patients on PRADAXA 220 mg and enoxaparin was 39.5% and 39.5%, respectively. Dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) occurred in patients on PRADAXA 220 mg in 4.1% vs. 3.8% on enoxaparin, and gastritis-like symptoms (including gastritis, GERD, esophagitis, erosive gastritis and gastric hemorrhage) occurred at 0.6% vs. 1.0%, respectively.

Hypersensitivity Reactions
In the two studies, drug hypersensitivity (such as urticaria, rash, and pruritus) was reported in 0.3% of patients receiving PRADAXA 220 mg.

Clinical Myocardial Infarction Events
In the two studies, clinical myocardial infarction was reported in 2 (0.1%) of patients who received PRADAXA 220 mg and 6 (0.3%) of patients who received enoxaparin.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of PRADAXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post approval use of PRADAXA: angioedema, thrombocytopenia, esophageal ulcer, alopecia, neutropenia, agranulocytosis.

7 DRUG INTERACTIONS
7.1 Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided *[see Clinical Pharmacology (12.3)]*.

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P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran *[see Clinical Pharmacology (12.3)]*. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

In patients with moderate renal impairment (CrCl 30-50 mL/min), reduce the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitors dronedarone or systemic ketoconazole. The use of the P-gp inhibitors verapamil, amiodarone, quinidine, clarithromycin, and ticagrelor does not require a dose adjustment of PRADAXA. These results should not be extrapolated to other P-gp inhibitors *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

The concomitant use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

7.2 Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism

Avoid use of PRADAXA and P-gp inhibitors in patients with CrCl <50 mL/min *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

7.3 Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery

In patients with CrCl ≥50 mL/min who have concomitant administration of P-gp inhibitors such as dronedarone or systemic ketoconazole, it may be helpful to separate the timing of administration of dabigatran and the P-gp inhibitor by several hours. The concomitant use of PRADAXA and P-gp inhibitors in patients with CrCl <50 mL/min should be avoided *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6) and Clinical Pharmacology (12.2, 12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on PRADAXA use in pregnant women are insufficient to determine drug-associated risks for adverse developmental outcomes. There are risks to the mother associated with untreated venous thromboembolism in pregnancy and a risk of hemorrhage in the mother and fetus associated with the use of anticoagulants *(see Clinical Considerations)*. In pregnant rats treated from implantation until weaning, dabigatran increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition at an exposure 2.6 times the human exposure. At a similar exposure, dabigatran decreased the number of implantations when rats were treated prior to mating and up to implantation (gestation Day 6). Dabigatran administered to pregnant rats and rabbits during organogenesis up to exposures 8 and 13 times the human exposure, respectively, did not induce major malformations. However, the incidence of delayed or irregular ossification of fetal skull bones and vertebrae was increased in the rat *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnancy confers an increased risk for thromboembolism that is higher for women with underlying thromboembolic disease and certain high-risk pregnancy conditions. Published data describe that women with a previous history of venous thrombosis are at high risk for recurrence during pregnancy.

Fetal/Neonatal adverse reaction

Use of anticoagulants, including PRADAXA, may increase the risk of bleeding in the fetus and neonate. Monitor neonates for bleeding *[see Warnings and Precautions (5.2)]*.

Labor or delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. PRADAXA use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider discontinuation or use of shorter acting anticoagulant as delivery approaches *[see Warnings and Precautions (5.2, 5.3)]*.

Data

Animal Data

Dabigatran has been shown to decrease the number of implantations when male and female rats were treated at a dosage of 70 mg/kg (about 2.6 to 3.0 times the human exposure at MRHD of 300 mg/day based on area under the curve [AUC] comparisons) prior to mating and up to implantation (gestation Day 6). Treatment of pregnant rats after implantation with dabigatran at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Dabigatran administered to pregnant rats and rabbits during organogenesis up to maternally toxic doses of 200 mg/kg (8 and 13 times the human exposure, respectively, at a MRHD of 300 mg/day based on AUC comparisons) did not induce major malformations, but increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat.

Death of offspring and mother rats during labor in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with dabigatran at a dose of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300 mg/day based on AUC comparisons).

8.2 Lactation

Risk Summary

There are no data on the presence of dabigatran in human milk, the effects on the breastfed child, or on milk production. Dabigatran and/or its metabolites were present in rat milk. Breastfeeding is not recommended during treatment with PRADAXA.

8.3 Females and Males of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including Pradaxa should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

8.4 Pediatric Use

Safety and effectiveness of PRADAXA in pediatric patients have not been established.

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8.5 Geriatric Use

Of the total number of patients in the RE-LY study, 82% were 65 and over, while 40% were 75 and over. The risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable in all age groups *[see Warnings and Precautions (5), Adverse Reactions (6.1), and Clinical Studies (14.1)]*.

8.6 Renal Impairment

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation

No dose adjustment of PRADAXA is recommended in patients with mild or moderate renal impairment *[see Clinical Pharmacology (12.3)]*. Reduce the dose of PRADAXA in patients with severe renal impairment (CrCl 15-30 mL/min) *[see Dosage and Administration (2.1, 2.2) and Clinical Pharmacology (12.3)]*. Dosing recommendations for patients with CrCl <15 mL/min or on dialysis cannot be provided.

Adjust dose appropriately in patients with renal impairment receiving concomitant P-gp inhibitors *[see Warnings and Precautions (5.5), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism

Patients with severe renal impairment (CrCl ≤30 mL/min) were excluded from RE-COVER.

Dosing recommendations for patients with CrCl ≤30 mL/min or on dialysis cannot be provided. Avoid use of PRADAXA with concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.2), and Clinical Pharmacology (12.3)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery

Patients with severe renal impairment (CrCl <30 mL/min) were excluded from RE-NOVATE and RE-NOVATE II.

Dosing recommendations for patients with CrCl <30 mL/min or on dialysis cannot be provided.

Avoid use of PRADAXA with concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.3) and Clinical Pharmacology (12.2, 12.3)]*.

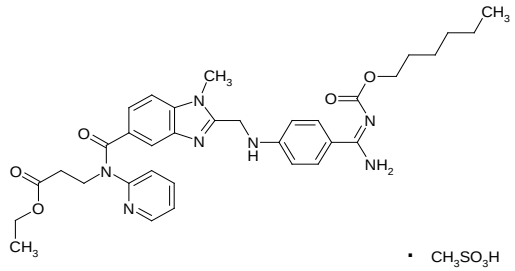
10 OVERDOSAGE

Accidental overdose may lead to hemorrhagic complications. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding. A specific reversal agent (idarucizumab) is available.

Dabigatran is primarily eliminated by the kidneys with a low plasma protein binding of approximately 35%. Hemodialysis can remove dabigatran; however, data supporting this approach are limited. Using a high-flux dialyzer, blood flow rate of 200 mL/min, and dialysate flow rate of 700 mL/min, approximately 49% of total dabigatran can be cleared from plasma over 4 hours. At the same dialysate flow rate, approximately 57% can be cleared using a dialyzer blood flow rate of 300 mL/min, with no appreciable increase in clearance observed at higher blood flow rates. Upon cessation of hemodialysis, a redistribution effect of approximately 7% to 15% is seen. The effect of dialysis on dabigatran's plasma concentration would be expected to vary based on patient specific characteristics. Measurement of aPTT or ECT may help guide therapy *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

11 DESCRIPTION

The chemical name for dabigatran etexilate mesylate, a direct thrombin inhibitor, is β-Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate. The empirical formula is $C_{34}H_{41}N_7O_5 \cdot CH_4O_3S$ and the molecular weight is 723.86 (mesylate salt), 627.75 (free base). The structural formula is:



Dabigatran etexilate mesylate is a yellow-white to yellow powder. A saturated solution in pure water has a solubility of 1.8 mg/mL. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol.

PRADAXA capsules are supplied in 75 mg, 110 mg, and 150 mg strengths for oral administration. Each capsule contains dabigatran etexilate mesylate as the active ingredient: 150 mg dabigatran etexilate (equivalent to 172.95 mg dabigatran etexilate mesylate), 110 mg dabigatran etexilate (equivalent to 126.83 mg dabigatran etexilate mesylate), or 75 mg dabigatran etexilate (equivalent to 86.48 mg dabigatran etexilate mesylate) along with the following inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shell is composed of carrageenan, hypromellose, potassium chloride, titanium dioxide, black edible ink, and FD&C Blue No. 2 (150 mg and 110 mg capsules only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.

12.2 Pharmacodynamics

At recommended therapeutic doses, dabigatran etexilate prolongs the coagulation markers such as aPTT, ECT, and TT. INR is relatively insensitive to the exposure to dabigatran and cannot be interpreted the same way as used for warfarin monitoring.

The aPTT test provides an approximation of PRADAXA's anticoagulant effect. The average time course for effects on aPTT, following approved dosing regimens in patients with various degrees of renal impairment is shown in Figure 2. The curves represent mean levels without confidence intervals; variations should be expected

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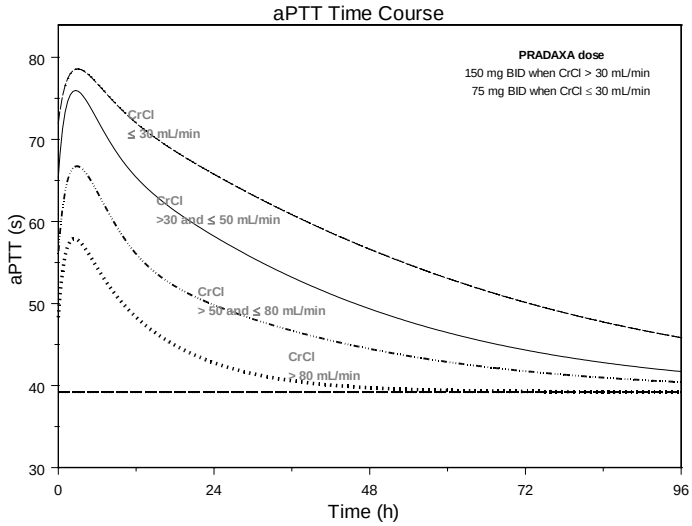
when measuring aPTT. While advice cannot be provided on the level of recovery of aPTT needed in any particular clinical setting, the curves can be used to estimate the time to get to a particular level of recovery, even when the time since the last dose of PRADAXA is not precisely known. In the RE-LY trial, the median (10^{th} to 90^{th} percentile) trough aPTT in patients receiving the 150 mg dose was 52 (40 to 76) seconds.

Figure 2 Average Time Course for Effects of Dabigatran on aPTT, Following Approved PRADAXA Dosing Regimens in Patients with Various Degrees of Renal Impairment*



*Simulations based on PK data from a study in subjects with renal impairment and PK/aPTT relationships derived from the RE-LY study; aPTT prolongation in RE-LY was measured centrally in citrate plasma using PTT Reagent Roche Diagnostics GmbH, Mannheim, Germany. There may be quantitative differences between various established methods for aPTT assessment.

The degree of anticoagulant activity can also be assessed by the ecarin clotting time (ECT). This test is a more specific measure of the effect of dabigatran than activated partial thromboplastin time (aPTT). In the RE-LY trial, the median (10^{th} to 90^{th} percentile) trough ECT in patients receiving the 150 mg dose was 63 (44 to 103) seconds.

In orthopedic hip surgery patients, maximum aPTT response (Emax) to dabigatran and baseline aPTT were higher shortly after surgery than at later time points (e.g. ≥3 days after surgery).

Cardiac Electrophysiology
No prolongation of the QTc interval was observed with dabigatran etexilate at doses up to 600 mg.

12.3 Pharmacokinetics
Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Pharmacokinetics described here refer to the sum of dabigatran and its glucuronides. Dabigatran displays dose-proportional pharmacokinetics in healthy subjects and patients in the range of doses from 10 to 400 mg.

Absorption
The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3 to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. After oral administration of dabigatran etexilate in healthy volunteers, C_{max} occurs at 1 hour post-administration in the fasted state. Coadministration of PRADAXA with a high-fat meal delays the time to C_{max} by approximately 2 hours but has no effect on the bioavailability of dabigatran; PRADAXA may be administered with or without food.

The oral bioavailability of dabigatran etexilate increases by 75% when the pellets are taken without the capsule shell compared to the intact capsule formulation. PRADAXA capsules should therefore not be broken, chewed, or opened before administration.

Distribution
Dabigatran is approximately 35% bound to human plasma proteins. The red blood cell to plasma partitioning of dabigatran measured as total radioactivity is less than 0.3. The volume of distribution of dabigatran is 50 to 70 L. Dabigatran pharmacokinetics are dose proportional after single doses of 10 to 400 mg. Given twice daily, dabigatran's accumulation factor is approximately two.

Elimination
Dabigatran is eliminated primarily in the urine. Renal clearance of dabigatran is 80% of total clearance after intravenous administration. After oral administration of radiolabeled dabigatran, 7% of radioactivity is recovered in urine and 86% in feces. The half-life of dabigatran in healthy subjects is 12 to 17 hours.

Metabolism
After oral administration, dabigatran etexilate is converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran is subject to conjugation forming pharmacologically active acyl glucuronides. Four positional isomers, 1-O, 2-O, 3-O, and 4-O-acylglucuronide exist, and each accounts for less than 10% of total dabigatran in plasma.

Renal Impairment
An open, parallel-group single-center study compared dabigatran pharmacokinetics in healthy subjects and patients with mild to moderate renal impairment receiving a single dose of PRADAXA 150 mg. Exposure to dabigatran increases with severity of renal function impairment (Table 8). Similar findings were observed in the RE-LY, RE-COVER and RE-NOVATE II trials.

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Table 8 Impact of Renal Impairment on Dabigatran Pharmacokinetics

Renal Function	CrCl (mL/min)	Increase in AUC	Increase in C_{max}	$t_{1/2}$ (h)
Normal	≥ 80	1x	1x	13
Mild	50-80	1.5x	1.1x	15
Moderate	30-50	3.2x	1.7x	18
Severe[+]	15-30	6.3x	2.1x	27

[+]Patients with severe renal impairment were not studied in RE-LY, RE-COVER and RE-NOVATE II. Dosing recommendations in subjects with severe renal impairment are based on pharmacokinetic modeling *[see Dosage and Administration (2.1, 2.2) and Use in Specific Populations (8.6)]*.

Hepatic Impairment
Administration of PRADAXA in patients with moderate hepatic impairment (Child-Pugh B) showed a large inter-subject variability, but no evidence of a consistent change in exposure or pharmacodynamics.

Drug Interactions
A summary of the effect of coadministered drugs on dabigatran exposure is shown in Figures 3.1 and 3.2.

In the orthopedic hip surgery patients, limited clinical data with P-gp inhibitors is available.

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Figure 3.1 Effect of P-gp Inhibitor or Inducer (rifampicin) Drugs on Peak and Total Exposure to Dabigatran (Cmax and AUC). Shown are the Geometric Mean Ratios (Ratio) and 90% Confidence Interval (90% CI). The Perpetrator and Dabigatran Etexilate Dose and Dosing Frequency are given as well as the Time of Perpetrator Dosing in Relation to Dabigatran Etexilate Dose (Time Difference)

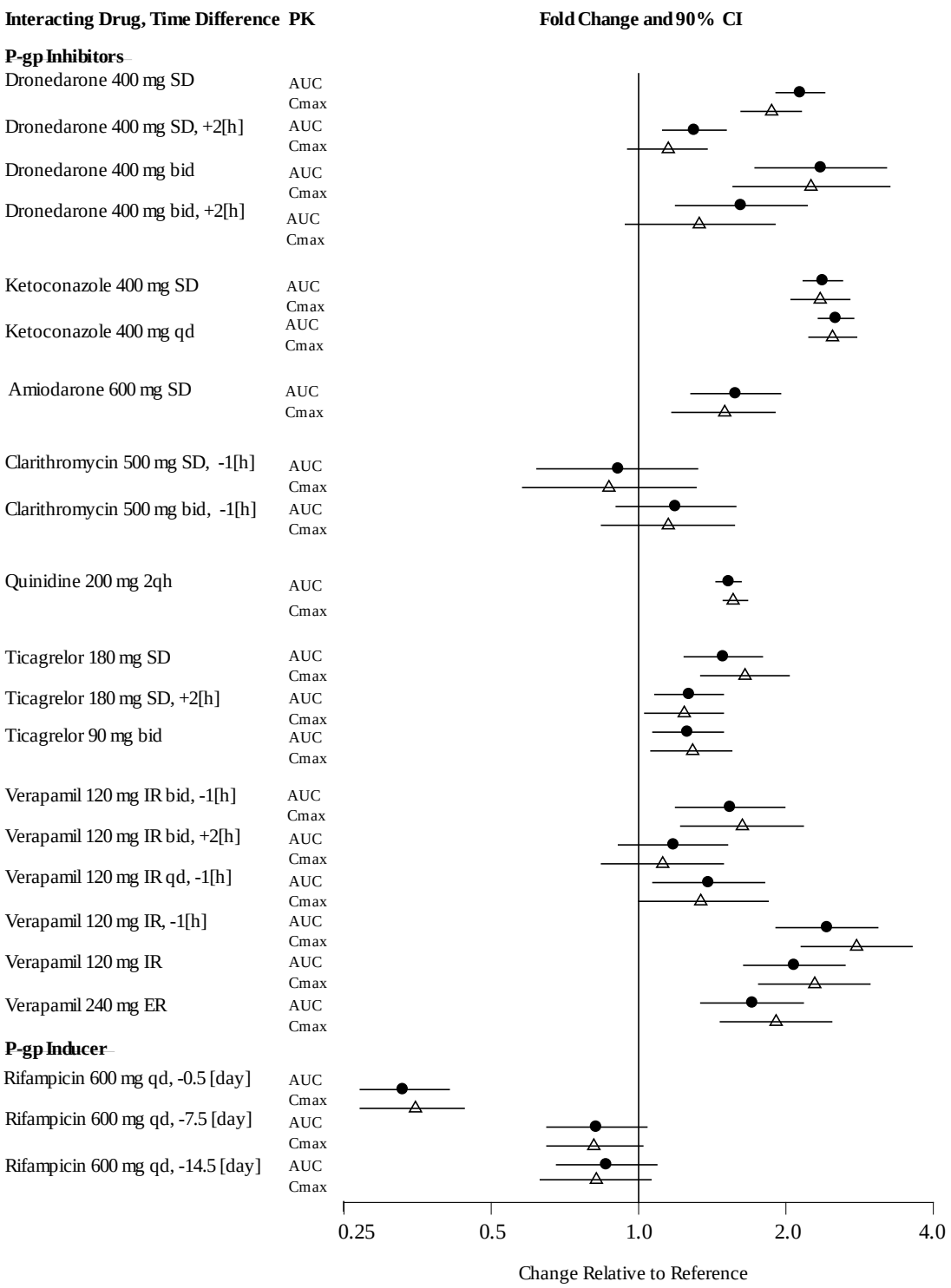

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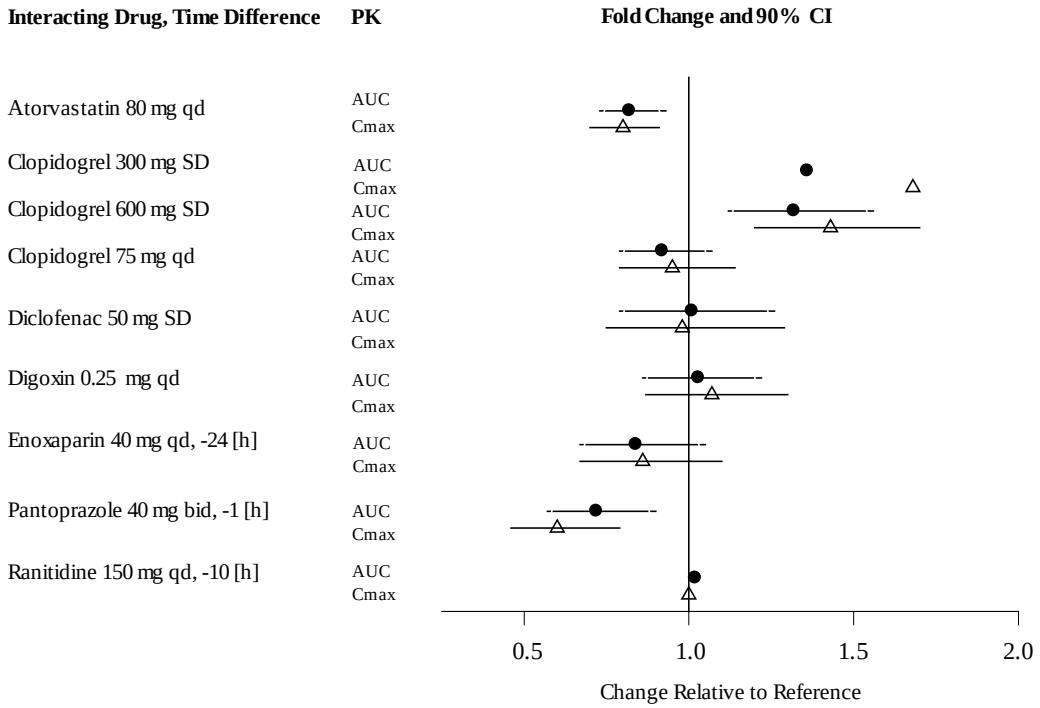
Figure 3.2 Effect of Non-P-gp Inhibitor or Inducer, Other Drugs, on Peak and Total Exposure to Dabigatran (Cmax and AUC). Shown are the Geometric Mean Ratios (Ratio) and 90% Confidence Interval (90% CI). The Perpetrator and Dabigatran Etexilate Dose and Dosing Frequency are given as well as the Time of Perpetrator Dosing in Relation to Dabigatran Etexilate Dose (Time Difference)



In RE-LY, dabigatran plasma samples were also collected. The concomitant use of proton pump inhibitors, H2 antagonists, and digoxin did not appreciably change the trough concentration of dabigatran.

Impact of Dabigatran on Other Drugs
In clinical studies exploring CYP3A4, CYP2C9, P-gp and other pathways, dabigatran did not meaningfully alter the pharmacokinetics of amiodarone, atorvastatin, clarithromycin, diclofenac, clopidogrel, digoxin, pantoprazole, or ranitidine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dabigatran was not carcinogenic when administered by oral gavage to mice and rats for up to 2 years. The highest doses tested (200 mg/kg/day) in mice and rats were approximately 3.6 and 6 times, respectively, the human exposure at MRHD of 300 mg/day based on AUC comparisons.

Dabigatran was not mutagenic in *in vitro* tests, including bacterial reversion tests, mouse lymphoma assay and chromosomal aberration assay in human lymphocytes, and the *in vivo* micronucleus assay in rats.

In the rat fertility study with oral gavage doses of 15, 70, and 200 mg/kg, males were treated for 29 days prior to mating, during mating up to scheduled termination, and females were treated 15 days prior to mating through gestation Day 6. No adverse effects on male or female fertility were observed at 200 mg/kg or 9 to 12 times the human exposure at MRHD of 300 mg/day based on AUC comparisons. However, the number of implantations decreased in females receiving 70 mg/kg, or 3 times the human exposure at MRHD based on AUC comparisons.

14 CLINICAL STUDIES

14.1 Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation

The clinical evidence for the efficacy of PRADAXA was derived from RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy), a multi-center, multi-national, randomized parallel group trial comparing two blinded doses of PRADAXA (110 mg twice daily and 150 mg twice daily) with open-label warfarin (dosed to target INR of 2 to 3) in patients with non-valvular, persistent, paroxysmal, or permanent atrial fibrillation and one or more of the following additional risk factors:

- Previous stroke, transient ischemic attack (TIA), or systemic embolism
- Left ventricular ejection fraction <40%
- Symptomatic heart failure, ≥ New York Heart Association Class 2
- Age ≥75 years
- Age ≥65 years and one of the following: diabetes mellitus, coronary artery disease (CAD), or hypertension

The primary objective of this study was to determine if PRADAXA was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke (ischemic and hemorrhagic) and systemic embolism. The study was designed to ensure that PRADAXA preserved more than 50% of warfarin's effect as established by previous randomized, placebo-controlled trials of warfarin in atrial fibrillation. Statistical superiority was also analyzed.

A total of 18,113 patients were randomized and followed for a median of 2 years. The patients' mean age was 71.5 years and the mean $CHADS_2$ score was 2.1. The patient population was 64% male, 70% Caucasian, 16% Asian, and 1% black. Twenty percent of patients had a history of a stroke or TIA and 50% were Vitamin K antagonist (VKA) naïve, defined as less than 2 months total lifetime exposure to a VKA. Thirty-two percent of the population had never been exposed to a VKA. Concomitant diseases of patients in this trial included hypertension 79%, diabetes 23%, and CAD 28%. At baseline, 40% of patients were on aspirin and 6% were on clopidogrel. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%.

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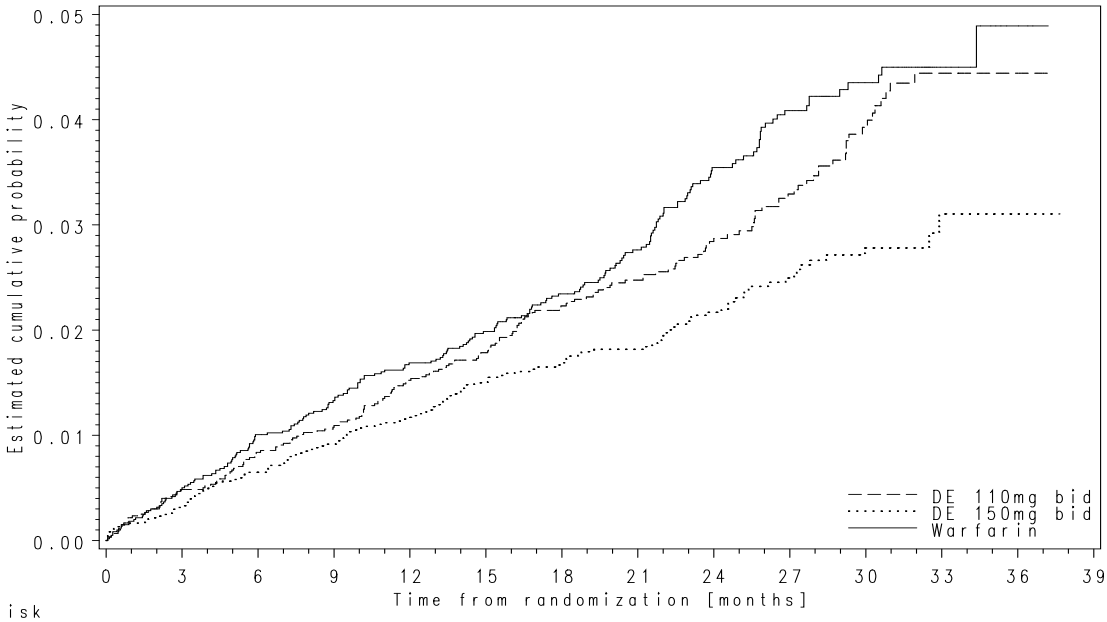
Relative to warfarin and to PRADAXA 110 mg twice daily, PRADAXA 150 mg twice daily significantly reduced the primary composite endpoint of stroke and systemic embolism (see Table 9 and Figure 4).

Table 9 First Occurrence of Stroke or Systemic Embolism in the RE-LY Study*

	PRADAXA 150 mg twice daily	PRADAXA 110 mg twice daily	Warfarin
Patients randomized	6076	6015	6022
Patients (% per yr) with events	135 (1.12%)	183 (1.54%)	203 (1.72%)
Hazard ratio vs. warfarin (95% CI)	0.65 (0.52, 0.81)	0.89 (0.73, 1.09)	
P-value for superiority	0.0001	0.27	
Hazard ratio vs. PRADAXA 110 mg (95% CI)	0.72 (0.58, 0.91)		
P-value for superiority	0.005		

* Randomized ITT

Figure 4 Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism



Subjects at risk

DE 110mg bid	6015	5927	5862	5797	5713	5481	4615	3778	3132	2386	1446	495	87
DE 150mg bid	6076	6010	5940	5861	5782	5555	4700	3847	3238	2428	1481	494	90
Warfarin	6022	5937	5862	5782	5719	5438	4615	3702	3091	2338	1364	383	76

The contributions of the components of the composite endpoint, including stroke by subtype, are shown in Table 10. The treatment effect was primarily a reduction in stroke. PRADAXA 150 mg twice daily was superior in reducing ischemic and hemorrhagic strokes relative to warfarin.

Table 10 Strokes and Systemic Embolism in the RE-LY Study

	PRADAXA 150 mg twice daily	Warfarin	Hazard ratio vs. warfarin (95% CI)
Patients randomized	6076	6022	
Stroke	123	187	0.64 (0.51, 0.81)
Ischemic stroke	104	134	0.76 (0.59, 0.98)
Hemorrhagic stroke	12	45	0.26 (0.14, 0.49)
Systemic embolism	13	21	0.61 (0.30, 1.21)

In the RE-LY trial, the rate of all-cause mortality was lower on dabigatran 150 mg than on warfarin (3.6% per year versus 4.1% per year). The rate of vascular death was lower on dabigatran 150 mg compared to warfarin (2.3% per year versus 2.7% per year). Non-vascular death rates were similar in the treatment arms.

The efficacy of PRADAXA 150 mg twice daily was generally consistent across major subgroups (see Figure 5).

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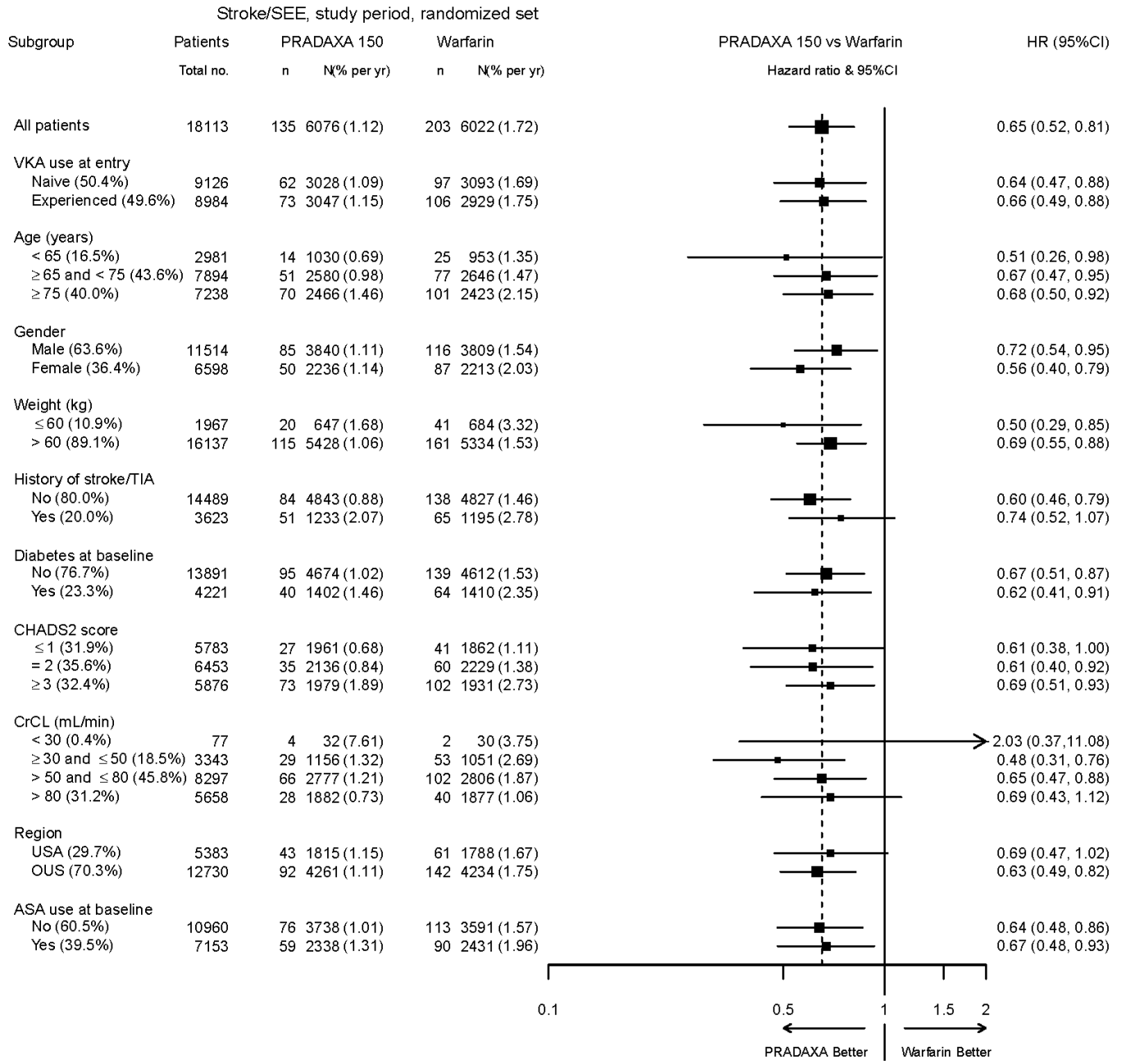
Figure 5 Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics*



* Randomized ITT
Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

In RE-LY, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA (0.7 per 100 patient-years for 150 mg dose) than in those who received warfarin (0.6).

14.2 Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism

In the randomized, parallel group, double-blind trials, RE-COVER and RE-COVER II, patients with deep vein thrombosis and pulmonary embolism received PRADAXA 150 mg twice daily or warfarin (dosed to target INR of 2 to 3) following initial treatment with an approved parenteral anticoagulant for 5-10 days.

In RE-COVER, the median treatment duration during the oral only treatment period was 174 days. A total of 2539 patients (30.9% patients with symptomatic PE with or without DVT and 68.9% with symptomatic DVT only) were treated with a mean age of 54.7 years. The patient population was 58.4% male, 94.8% white, 2.6% Asian, and 2.6% black. The concomitant diseases of patients in this trial included hypertension (35.9%), diabetes mellitus (8.3%), coronary artery disease (6.5%), active cancer (4.8%), and gastric or duodenal ulcer (4.4%). Concomitant medications included agents acting on renin-angiotensin system (25.2%), vasodilators (28.4%), serum lipid-reducing agents (18.2%), NSAIDs (21%), beta-blockers (14.8%), calcium channel blockers (8.5%), ASA (8.6%), and platelet inhibitors excluding ASA (0.6%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 60% in RE-COVER study.

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In RE-COVER II, the median treatment duration during the oral only treatment period was 174 days. A total of 2568 patients (31.8% patients with symptomatic PE with or without DVT and 68.1% with symptomatic DVT only) were treated with a mean age of 54.9 years. The patient population was 60.6% male, 77.6% white, 20.9% Asian, and 1.5% black. The concomitant diseases of patients in this trial included hypertension (35.1%), diabetes mellitus (9.8%), coronary artery disease (7.1%), active cancer (3.9%), and gastric or duodenal ulcer (3.8%). Concomitant medications included agents acting on renin-angiotensin system (24.2%), vasodilators (28.6%), serum lipid-reducing agents (20.0%), NSAIDs (22.3%), beta-blockers (14.8%), calcium channel blockers (10.8%), ASA (9.8%), and platelet inhibitors excluding ASA (0.8%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 57% in RE-COVER II study.

In studies RE-COVER and RE-COVER II, the protocol specified non-inferiority margin (2.75) for the hazard ratio was derived based on the upper limit of the 95% confidence interval of the historical warfarin effect. PRADAXA was demonstrated to be non-inferior to warfarin (dosed to target INR of 2 to 3) (Table 11) based on the primary composite endpoint (fatal PE or symptomatic non-fatal PE and/or DVT) and retains at least 66.9% (RE-COVER) and 63.9% (RE-COVER II) of the historical warfarin effect, respectively.

Table 11 Primary Efficacy Endpoint for RE-COVER and RE-COVER II – Modified ITT[a] Population

	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard ratio vs. warfarin (95% CI)
RE-COVER	**N=1274**	**N=1265**	
Primary Composite Endpoint[b]	34 (2.7)	32 (2.5)	1.05 (0.65, 1.70)
Fatal PE[c]	1 (0.1)	3 (0.2)	
Symptomatic non-fatal PE[c]	16 (1.3)	8 (0.6)	
Symptomatic recurrent DVT[c]	17 (1.3)	23 (1.8)	
RE-COVER II	**N=1279**	**N=1289**	
Primary Composite Endpoint[b]	34 (2.7)	30 (2.3)	1.13 (0.69, 1.85)
Fatal PE[c]	3 (0.2)	0	
Symptomatic non-fatal PE[c]	9 (0.7)	15 (1.2)	
Symptomatic recurrent DVT[c]	30 (2.3)	17 (1.3)	

[a]Modified ITT analyses population consists of all randomized patients who received at least one dose of study medication.
[b]Number of patients with one or more event.
[c]Number of events. For patients with multiple events each event is counted independently.

In the randomized, parallel group, double-blind, pivotal trial, RE-MEDY, patients received PRADAXA 150 mg twice daily or warfarin (dosed to target INR of 2 to 3) following 3 to 12 months of treatment with anticoagulation therapy for an acute VTE. The median treatment duration during the treatment period was 534 days. A total of 2856 patients were treated with a mean age of 54.6 years. The patient population was 61% male, and 90.1% white, 7.9% Asian and 2.0% black. The concomitant diseases of patients in this trial included hypertension (38.6%), diabetes mellitus (9.0%), coronary artery disease (7.2%), active cancer (4.2%), and gastric or duodenal ulcer (3.8%). Concomitant medications included agents acting on renin-angiotensin system (27.9%), vasodilators (26.7%), serum lipid reducing agents (20.6%), NSAIDs (18.3%), beta-blockers (16.3%), calcium channel blockers (11.1%), aspirin (7.7%), and platelet inhibitors excluding ASA (0.9%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 62% in the study.

In study RE-MEDY, the protocol specified non-inferiority margin (2.85) for the hazard ratio was derived based on the point estimate of the historical warfarin effect. PRADAXA was demonstrated to be non-inferior to warfarin (dosed to target INR of 2 to 3) (Table 12) based on the primary composite endpoint (fatal PE or symptomatic non-fatal PE and/or DVT) and retains at least 63.0% of the historical warfarin effect. If the non-inferiority margin was derived based on the 50% retention of the upper limit of the 95% confidence interval, PRADAXA was demonstrated to retain at least 33.4% of the historical warfarin effect based on the composite primary endpoint.

Table 12 Primary Efficacy Endpoint for RE-MEDY – Modified ITT[a] Population

	PRADAXA 150 mg twice daily N=1430 N (%)	Warfarin N=1426 N (%)	Hazard ratio vs. warfarin (95% CI)
Primary Composite Endpoint[b]	26 (1.8)	18 (1.3)	1.44 (0.78, 2.64)
Fatal PE[c]	1 (0.07)	1 (0.07)	
Symptomatic non-fatal PE[c]	10 (0.7)	5 (0.4)	
Symptomatic recurrent DVT[c]	17 (1.2)	13 (0.9)	

[a]Modified ITT analyses population consists of all randomized patients who received at least one dose of study medication.
[b]Number of patients with one or more event.
[c]Number of events. For patients with multiple events each event is counted independently.

In a randomized, parallel group, double-blind, pivotal trial, RE-SONATE, patients received PRADAXA 150 mg twice daily or placebo following 6 to 18 months of treatment with anticoagulation therapy for an acute VTE. The median treatment duration was 182 days. A total of 1343 patients were treated with a mean age of 55.8 years. The patient population was 55.5% male, 89.0% white, 9.3% Asian, and 1.7% black. The concomitant diseases of patients in this trial included hypertension (38.8%), diabetes mellitus (8.0%), coronary artery disease (6.0%), history of cancer (6.0%), gastric or duodenal ulcer (4.5%), and heart failure (4.6%). Concomitant medications included agents acting on renin-angiotensin system (28.7%), vasodilators (19.4%), beta-blockers (18.5%), serum lipid reducing agents (17.9%), NSAIDs (12.1%), calcium channel blockers (8.9%), aspirin (8.3%), and platelet inhibitors excluding ASA (0.7%). Based on the outcome of the primary composite endpoint (fatal PE, unexplained death, or symptomatic non-fatal PE and/or DVT), PRADAXA was superior to placebo (Table 13).

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Table 13 Primary Efficacy Endpoint for RE-SONATE – Modified ITT[a] Population

	PRADAXA 150 mg twice daily N=681 N (%)	Placebo N=662 N (%)	Hazard ratio vs. placebo (95% CI)
Primary Composite Endpoint[b]	3 (0.4)	37 (5.6)	0.08 (0.02, 0.25) p-value <0.0001
Fatal PE and unexplained death[c]	0	2 (0.3)	
Symptomatic non-fatal PE[c]	1 (0.1)	14 (2.1)	
Symptomatic recurrent DVT[c]	2 (0.3)	23 (3.5)	

[a]Modified ITT analyses population consists of all randomized patients who received at least one dose of study medication.
[b]Number of patients with one or more events.
[c]Number of events. For patients with multiple events each event is counted independently.

14.3 Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery

In the randomized, parallel group, double-blind, non-inferiority trials, RE-NOVATE and RE-NOVATE II patients received PRADAXA 75 mg orally 1-4 hours after surgery followed by 150 mg daily (RE-NOVATE), PRADAXA 110 mg orally 1-4 hours after surgery followed by 220 mg daily (RE-NOVATE and RE-NOVATE II) or subcutaneous enoxaparin 40 mg once daily initiated the evening before surgery (RE-NOVATE and RE-NOVATE II) for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients who have undergone hip replacement surgery.

Overall, in RE-NOVATE and RE-NOVATE II, the median treatment duration was 33 days for PRADAXA and 33 days for enoxaparin. A total of 5428 patients were treated with a mean age of 63.2 years. The patient population was 45.3% male, 96.1% white, 3.6% Asian, and 0.4 % black. The concomitant diseases of patients in these trials included hypertension (46.1%), venous insufficiency (15.4%), coronary artery disease (8.2%), diabetes mellitus (7.9%), reduced renal function (5.3%), heart failure (3.4%), gastric or duodenal ulcer (3.0%), VTE (2.7%), and malignancy (0.1%). Concomitant medications included cardiac therapy (69.7%), NSAIDs (68%), vasoprotectives (29.7%), agents acting on renin-angiotensin system (29.1%), beta-blockers (21.5%), diuretics (20.8%), lipid modifying agents (18.2%), any antithrombin/anticoagulant (16.0%), calcium channel blockers (13.6%), low molecular weight heparin (7.8%), aspirin (7.0%), platelet inhibitors excluding ASA (6.9%), other antihypertensives (6.7%), and peripheral vasodilators (2.6%).

For efficacy evaluation all patients were to have bilateral venography of the lower extremities at 3 days after last dose of study drug unless an endpoint event had occurred earlier in the study. In the primary efficacy analysis, PRADAXA 110 mg orally 1-4 hours after surgery followed by 220 mg daily was non-inferior to enoxaparin 40 mg once daily in a composite endpoint of confirmed VTE (proximal or distal DVT on venogram, confirmed symptomatic DVT, or confirmed PE) and all cause death during the treatment period (Tables 14 and 15). In the studies 2628 (76.5%) patients in RE-NOVATE and 1572 (78.9%) patients in RE-NOVATE II had evaluable venograms at study completion.

Table 14 Primary Efficacy Endpoint for RE-NOVATE

	PRADAXA 220 mg N (%)	Enoxaparin N (%)
Number of Patients[a]	**N=880**	**N= 897**
Primary Composite Endpoint	53 (6.0)	60 (6.7)
Risk difference (%) vs. enoxaparin (95% CI)	-0.7 (-2.9, 1.6)	
Number of Patients	**N=909**	**N=917**
Composite endpoint of major VTE[b] and VTE related mortality	28 (3.1)	36 (3.9)
Number of Patients	**N=905**	**N=914**
Proximal DVT	23 (2.5)	33 (3.6)
Number of Patients	**N=874**	**N=894**
Total DVT	46 (5.3)	57 (6.4)
Number of Patients	**N=1137**	**N=1142**
Symptomatic DVT	6 (0.5)	1 (0.1)
PE	5 (0.4)	3 (0.3)
Death	3 (0.3)	0

[a]Full Analysis Set (FAS): The FAS included all randomized patients who received at least one subcutaneous injection or one oral dose of study medication, underwent surgery and subjects for whom the presence or absence of an efficacy outcome at the end of the study was known, i.e., an evaluable negative venogram for both distal

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and proximal DVT in both legs or any of the following: positive venography in one or both legs, or confirmed symptomatic DVT, PE, or death during the treatment period.
[b]VTE is defined as proximal DVT and PE

Table 15 Primary Efficacy Endpoint for RE-NOVATE II

	PRADAXA 220 mg N (%)	**Enoxaparin N (%)**
Number of Patients[a]	**N=792**	**N= 786**
Primary Composite Endpoint	61 (7.7)	69 (8.8)
Risk difference (%) vs. enoxaparin (95% CI)	-1.1 (-3.8, 1.6)	
Number of Patients	**N=805**	**N=795**
Composite endpoint of major VTE[b] and VTE related mortality	18 (2.2)	33 (4.2)
Number of Patients	**N=804**	**N=793**
Proximal DVT	17 (2.1)	31 (3.9)
Number of Patients	**N=791**	**N=784**
Total DVT	60 (7.6)	67 (8.5)
Number of Patients	**N=1001**	**N=992**
Symptomatic DVT	0	4 (0.4)
PE	1 (0.1)	2 (0.2)
Death	0	1 (0.1)

[a]Full Analysis Set (FAS): The FAS included all randomized patients who received at least one subcutaneous injection or one oral dose of study medication, underwent surgery and subjects for whom the presence or absence of an efficacy outcome at the end of the study was known, i.e., an evaluable negative venogram for both distal and proximal DVT in both legs or any of the following: positive venography in one or both legs, or confirmed symptomatic DVT, PE, or death during the treatment period.
[b]VTE is defined as proximal DVT and PE

16 HOW SUPPLIED/STORAGE AND HANDLING

PRADAXA 75 mg capsules have a white opaque cap imprinted with the Boehringer Ingelheim company symbol and a white opaque body imprinted with “R75”. The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0355-09 Unit of use bottle of 60 capsules
- NDC 0597-0355-56 Blister package containing 60 capsules (10 x 6 capsule blister cards)

PRADAXA 110 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a light blue opaque body imprinted with “R110”. The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0108-54 Unit of use bottle of 60 capsules
- NDC 0597-0108-60 Blister package containing 60 capsules (10 x 6 capsule blister cards)

PRADAXA 150 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a white opaque body imprinted with “R150”. The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0360-55 Unit of use bottle of 60 capsules
- NDC 0597-0360-82 Blister package containing 60 capsules (10 x 6 capsule blister cards)

Bottles
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Once opened, the product must be used within 4 months. Keep the bottle tightly closed. Store in the original package to protect from moisture.

Blisters
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original package to protect from moisture.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Instructions for Patients

- Tell patients to take PRADAXA exactly as prescribed.
- Remind patients not to discontinue PRADAXA without talking to the health care provider who prescribed it.
- Keep PRADAXA in the original bottle to protect from moisture. Do not put PRADAXA in pill boxes or pill organizers.
- When more than one bottle is dispensed to the patient, instruct them to open only one bottle at a time.
- Instruct patient to remove only one capsule from the opened bottle at the time of use. The bottle should be immediately and tightly closed.
- Advise patients not to chew or break the capsules before swallowing them and not to open the capsules and take the pellets alone.
- Advise patients that the capsule should be taken with a full glass of water.

[see Boxed Warning, Dosage and Administration (2.3)]

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Bleeding
Inform patients that they may bleed more easily, may bleed longer, and should call their health care provider for any signs or symptoms of bleeding *[see Warnings and Precautions (5.2)]*.

Instruct patients to seek emergency care right away if they have any of the following, which may be a sign or symptom of serious bleeding:

- Unusual bruising (bruises that appear without known cause or that get bigger)
- Pink or brown urine
- Red or black, tarry stools
- Coughing up blood
- Vomiting blood, or vomit that looks like coffee grounds

Instruct patients to call their health care provider or to get prompt medical attention if they experience any signs or symptoms of bleeding:

- Pain, swelling or discomfort in a joint
- Headaches, dizziness, or weakness
- Reoccurring nose bleeds
- Unusual bleeding from gums
- Bleeding from a cut that takes a long time to stop
- Menstrual bleeding or vaginal bleeding that is heavier than normal

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient to contact his or her physician immediately *[see Boxed Warning]*.

Gastrointestinal Adverse Reactions
Instruct patients to call their health care provider if they experience any signs or symptoms of dyspepsia or gastritis:

- Dyspepsia (upset stomach), burning, or nausea
- Abdominal pain or discomfort
- Epigastric discomfort, GERD (gastric indigestion)

[see Adverse Reactions (6.1)]

Invasive or Surgical Procedures
Instruct patients to inform their health care provider that they are taking PRADAXA before any invasive procedure (including dental procedures) is scheduled *[see Dosage and Administration (2.6)]*.

Concomitant Medications
Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so their health care provider knows about other treatments that may affect bleeding risk (e.g., aspirin or NSAIDs) or dabigatran exposure (e.g., dronedarone or systemic ketoconazole) *[see Warnings and Precautions (5.2, 5.5)]*.

Prosthetic Heart Valves
Instruct patients to inform their health care provider if they will have or have had surgery to place a prosthetic heart valve *[see Warnings and Precautions (5.4)]*.

Pregnancy
Advise patients to inform their healthcare provider immediately if they become pregnant or intend to become pregnant during treatment with PRADAXA *[see Use in Specific Populations (8.1)]*.

Lactation
Advise patients not to breastfeed if they are taking PRADAXA *[see Use in Specific Populations (8.2)]*.

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MEDICATION GUIDE
PRADAXA (pra dax a)
(dabigatran etexilate)
capsules

Read this Medication Guide before you start taking PRADAXA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about PRADAXA?

- People with atrial fibrillation (a type of irregular heartbeat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. PRADAXA lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking PRADAXA, you may have increased risk of forming a clot in your blood.

  Do not stop taking PRADAXA without talking to the doctor who prescribes it for you. Stopping PRADAXA increases your risk of having a stroke.

  PRADAXA may need to be stopped, if possible, prior to surgery or a medical or dental procedure. Ask the doctor who prescribed PRADAXA for you when you should stop taking it. Your doctor will tell you when you may start taking PRADAXA again after your surgery or procedure. If you have to stop taking PRADAXA, your doctor may prescribe another medicine to help prevent a blood clot from forming.

- PRADAXA can cause bleeding which can be serious, and sometimes lead to death. This is because PRADAXA is a blood thinner medicine that lowers the chance of blood clots forming in your body.
- **You may have a higher risk of bleeding if you take PRADAXA and**:
  - are over 75 years old
  - have kidney problems
  - have stomach or intestine bleeding that is recent or keeps coming back, or you have a stomach ulcer
  - take other medicines that increase your risk of bleeding, including:
    - aspirin or aspirin-containing products
    - long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
    - a medicine that contains warfarin sodium
    - a medicine that contains heparin
    - a medicine that contains clopidogrel bisulfate
    - a medicine that contains prasugrel
  - have certain kidney problems and also take a medicine that contains dronedarone or ketoconazole tablets.

    Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.
- PRADAXA can increase your risk of bleeding because it lessens the ability of your blood to clot. While you take PRADAXA:
  - you may bruise more easily
  - it may take longer for any bleeding to stop

  Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding:
  - unexpected bleeding or bleeding that lasts a long time, such as:
    - unusual bleeding from the gums
    - nose bleeds that happen often
    - menstrual bleeding or vaginal bleeding that is heavier than normal
  - bleeding that is severe or you cannot control
  - pink or brown urine
  - red or black stools (looks like tar)
  - bruises that happen without a known cause or get larger
  - cough up blood or blood clots
  - vomit blood or your vomit looks like “coffee grounds”
  - unexpected pain, swelling, or joint pain
  - headaches, feeling dizzy or weak

  Take PRADAXA exactly as prescribed. Do not stop taking PRADAXA without first talking to the doctor who prescribes it for you. Stopping PRADAXA may increase your risk of a stroke.

  PRADAXA may need to be stopped, if possible, for one or more days before any surgery, or medical or dental procedure. If you need to stop taking PRADAXA for **any reason**, talk to the doctor who prescribed PRADAXA for you to find out when you should stop taking it. Your doctor will tell you when to start taking PRADAXA again after your surgery or procedure.

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- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like PRADAXA, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine.
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine.

  If you take PRADAXA and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots. Tell your doctor right away if you have back pain, tingling, numbness, muscle weakness (especially in your legs and feet), loss of control of the bowels or bladder (incontinence).

See "What are the possible side effects of PRADAXA?" for more information about side effects.

What is PRADAXA?

PRADAXA is a prescription blood thinner medicine that lowers the chance of blood clots forming in your body. PRADAXA is used to:

- reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to blood clots forming and increase your risk of a stroke.
- treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism) and reduce the risk of them occurring again.
- to help prevent blood clots in the legs and lungs of people who have just had hip replacement surgery.

PRADAXA is not for use in people with artificial (prosthetic) heart valves.

It is not known if PRADAXA is safe and works in children.

Who should not take PRADAXA?

Do not take PRADAXA if you:

- currently have certain types of abnormal bleeding. Talk to your doctor before taking PRADAXA if you currently have unusual bleeding.
- have had a serious allergic reaction to PRADAXA. Ask your doctor if you are not sure.
- have ever had or plan to have a valve in your heart replaced

What should I tell my doctor before taking PRADAXA?

Before you take PRADAXA, tell your doctor if you:

- have kidney problems
- have ever had bleeding problems
- have ever had stomach ulcers
- have antiphospholipid syndrome (APS)
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if PRADAXA will harm your unborn baby. Tell your doctor right away if you become pregnant during treatment with PRADAXA.

  Females who are able to become pregnant: Talk with your healthcare provider about pregnancy planning during treatment with PRADAXA. Talk with your healthcare provider about your risk for severe uterine bleeding if you are treated with blood thinner medicines, including PRADAXA.
- are breastfeeding or plan to breastfeed. It is not known if PRADAXA passes into your breast milk. You and your doctor should decide if you will take PRADAXA or breastfeed.

Tell all of your doctors and dentists that you are taking PRADAXA. They should talk to the doctor who prescribed PRADAXA for you, before you have **any** surgery, or a medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some of your other medicines may affect the way PRADAXA works. Certain medicines may increase your risk of bleeding. See "**What is the most important information I should know about PRADAXA?**"

Especially tell your doctor if you take:

- a medicine that contains rifampin

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take PRADAXA?

- Your doctor will decide how long you should take PRADAXA. **Do not stop taking PRADAXA without first talking with your doctor. Stopping PRADAXA may increase your risk of having a stroke or forming blood clots.**
- **Take PRADAXA exactly as prescribed by your doctor.**

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- Take PRADAXA capsules twice a day (approximately every 12 hours).
- If you miss a dose of PRADAXA, take it as soon as you remember. If your next dose is less than 6 hours away, skip the missed dose. Do not take two doses of PRADAXA at the same time.
- Swallow PRADAXA capsules whole. Do not break, chew, or empty the pellets from the capsule.
- You can take PRADAXA with or without food.
- You should take PRADAXA with a full glass of water.
- Do not run out of PRADAXA. Refill your prescription before you run out. If you plan to have surgery, or a medical or a dental procedure, tell your doctor and dentist that you are taking PRADAXA. You may have to stop taking PRADAXA for a short time. See "**What is the most important information I should know about PRADAXA?**".
- If you take too much PRADAXA, go to the nearest hospital emergency room or call your doctor.
- Call your doctor or healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your doctor or healthcare provider may need to check you.
- PRADAXA comes in a bottle or in a blister package.
- Only open 1 bottle of PRADAXA at a time. Finish your opened bottle of PRADAXA before opening a new bottle.
- After opening a bottle of PRADAXA, use within 4 months. See "**How should I store PRADAXA?**"
- When it is time for you to take a dose of PRADAXA, only remove your prescribed dose of PRADAXA from your open bottle or blister package.
- Tightly close your bottle of PRADAXA right away after you take your dose.

What are the possible side effects of PRADAXA?

PRADAXA can cause serious side effects, including:

- See "**What is the most important information I should know about PRADAXA?**"
- Allergic Reactions. In some people, PRADAXA can cause symptoms of an allergic reaction, including hives, rash, and itching. Tell your doctor or get medical help right away if you get any of the following symptoms of a serious allergic reaction with PRADAXA:
  - chest pain or chest tightness
  - swelling of your face or tongue
  - trouble breathing or wheezing
  - feeling dizzy or faint

Common side effects of PRADAXA include:

- indigestion, upset stomach, or burning
- stomach pain

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of PRADAXA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PRADAXA?

- Store PRADAXA at room temperature 68°F to 77°F (20°C to 25°C). After opening the bottle, use PRADAXA within 4 months. Safely throw away any unused PRADAXA after 4 months.
- **Keep PRADAXA in the original bottle or blister package to keep it dry (protect the capsules from moisture). Do not put PRADAXA in pill boxes or pill organizers.**
- **Tightly close your bottle of PRADAXA right away after you take your dose.**

Keep PRADAXA and all medicines out of the reach of children.

General information about the safe and effective use of PRADAXA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PRADAXA for a condition for which it was not prescribed. Do not give PRADAXA to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about PRADAXA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about PRADAXA that is written for health professionals.

For more information about PRADAXA, including current prescribing information and Medication Guide, go to www.pradaxa.com or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906, or scan the code below to go to www.pradaxa.com.

What are the ingredients in PRADAXA?

Active ingredient: dabigatran etexilate mesylate

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Inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shell is composed of carrageenan, hypromellose, potassium chloride, titanium dioxide, black edible ink, and FD&C Blue No. 2 (150 mg and 110 mg capsules only).

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