Idarucizumab for dabigatran (PRADAXA) reversal

A clinical in-service

Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

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Learning outcomes

- Explain the safe and effective use of idarucizumab* in the reversal of the anticoagulant effect of dabigatran.
- Demonstrate the administration of idarucizumab.
- Identify patients who should be treated with idarucizumab.
- Identify departments within your facility that require information and education regarding idarucizumab.
- Develop a process for ensuring timely access to idarucizumab in your facility.
- Recognise your obligations under the special access scheme.

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Disclaimer

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This in-service is for medical education purposes only.

This clinical in-service may be relevant to:

- Emergency staff
- Haematologists
- Anaesthetists
- Nurses (in relevant departments)
- Hospital pharmacists
- Gastroenterologists
- Geriatricians
- Orthopaedic surgeons
- Cardiologists
- Other staff involved in acute patient management

Overview

Section 1: An overview of dabigatran (Pradaxa)

Section 2: What is idarucizumab?†

Section 3: The evidence for idarucizumab

Section 4: How to use idarucizumab

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Section 1

An overview of dabigatran (Pradaxa)

Section 1: An overview of dabigatran (Pradaxa)*

- Dabigatran is an oral anticoagulant.[1]
- Available as 75 mg, 110 mg, and 150 mg capsules.[1]
- Australian approved indications:*
  - Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke;
  - Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement); and
  - Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.*[1]

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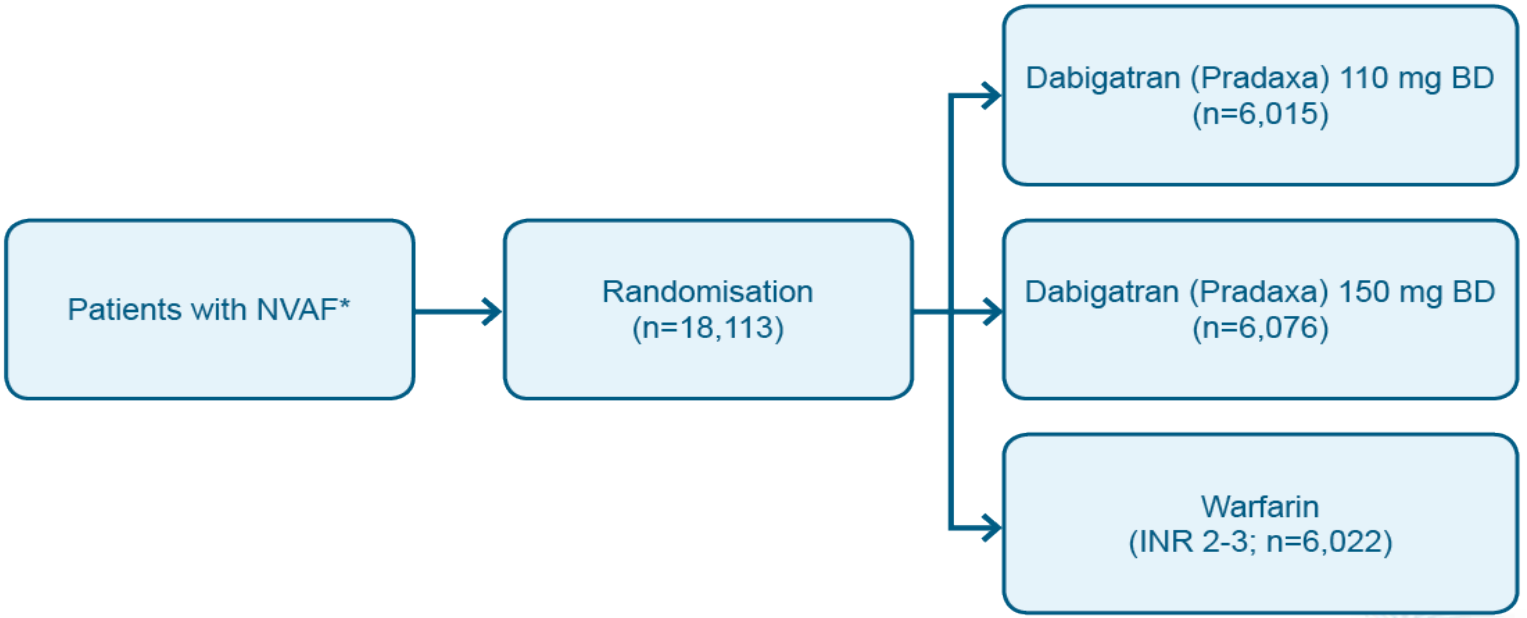
*Please review the full Approved Product Information before prescribing Pradaxa.

Reference: 1. Boehringer Ingelheim Pty Ltd. Pradaxa Approved Product Information, 24th August 2015.

The RE-LY study design

- A non-inferiority study designed to evaluate the efficacy and safety of dabigatran compared to warfarin.[1]

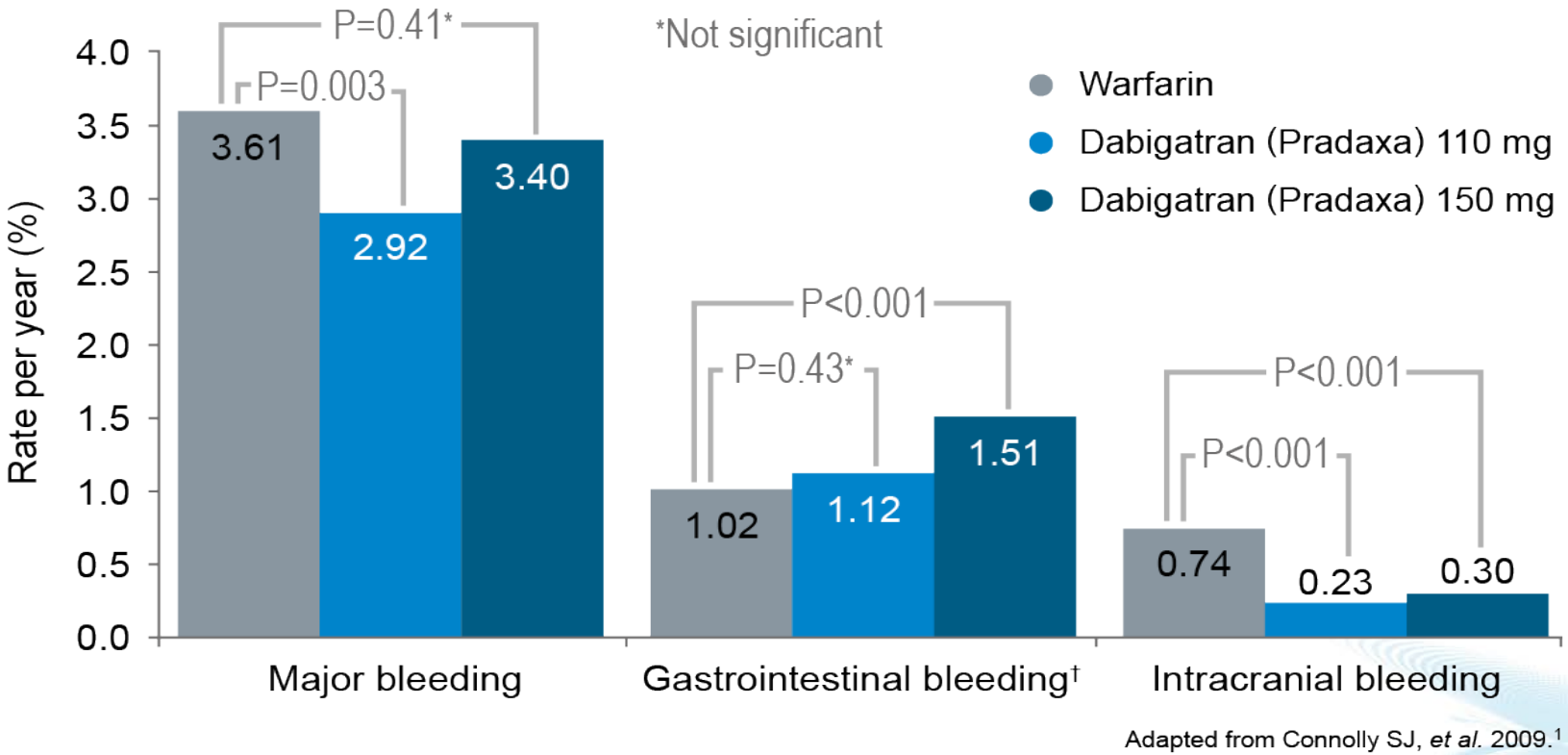


*NVAF=non-valvular atrial fibrillation.

Reference: 1. Connolly SJ, *et al. New Engl J Med.* 2009; 361(12): 1139–1151.

RE-LY study: safety outcomes

RATES OF BLEEDING EVENTS BY TREATMENT GROUP[1]



Adapted from Connolly SJ, *et al.* 2009.[1]

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†Gastrointestinal bleeding could be life threatening or non-life threatening.

Reference: 1. Connolly SJ, *et al. New Engl J Med.* 2009; 361(12): 1139–1151; Connolly SJ, *et al. N Engl J Med.* 2014; 371(15): 1464–1465.

RE-LY study: key clinical outcomes

Dabigatran 110 mg BD	Dabigatran 150 mg BD
• Similar rates of stroke and systemic embolism (non-inferior); • Lower rates of major haemorrhage compared to warfarin; • Lower rates of life threatening bleeds compared to warfarin; • Lower risk of intracranial bleeding compared to warfarin; and • Similar rates of gastrointestinal bleeding compared to warfarin.[1]	• Lower rates of stroke and systemic embolism; • Comparable rates of major haemorrhage compared to warfarin; • Lower rates of life threatening bleeds compared to warfarin; • Lower risk of intracranial bleeding compared to warfarin; and • Higher rates of gastrointestinal bleeding compared to warfarin.[1]

Reference: 1. Connolly SJ, *et al. New Engl J Med.* 2009; 361(12):1139–1151.

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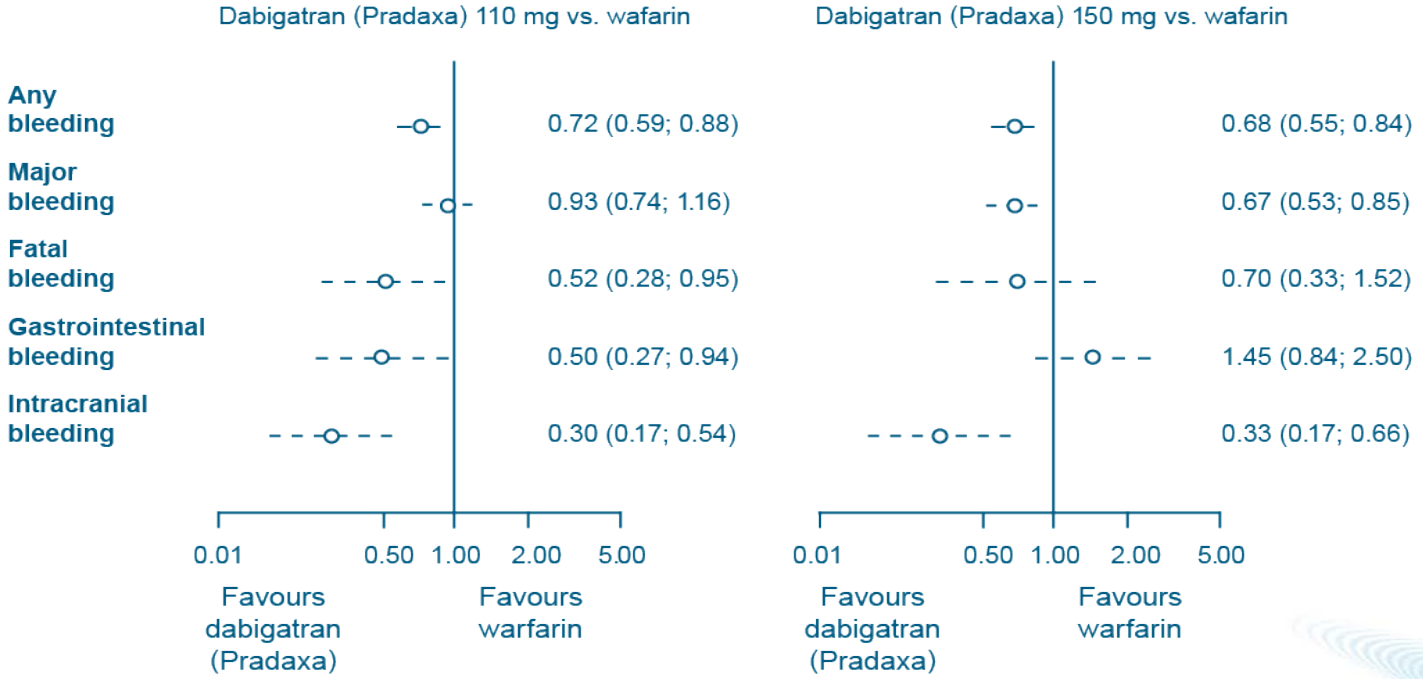
Dabigatran (Pradaxa) real-world data

VITAMIN K ANTAGONIST-NAÏVE STRATUM PER TREATMENT GROUP HAZARD RATIOS (95% CONFIDENCE INTERVAL)



Adapted from Larsen TB, *et al.* 2014.[1]

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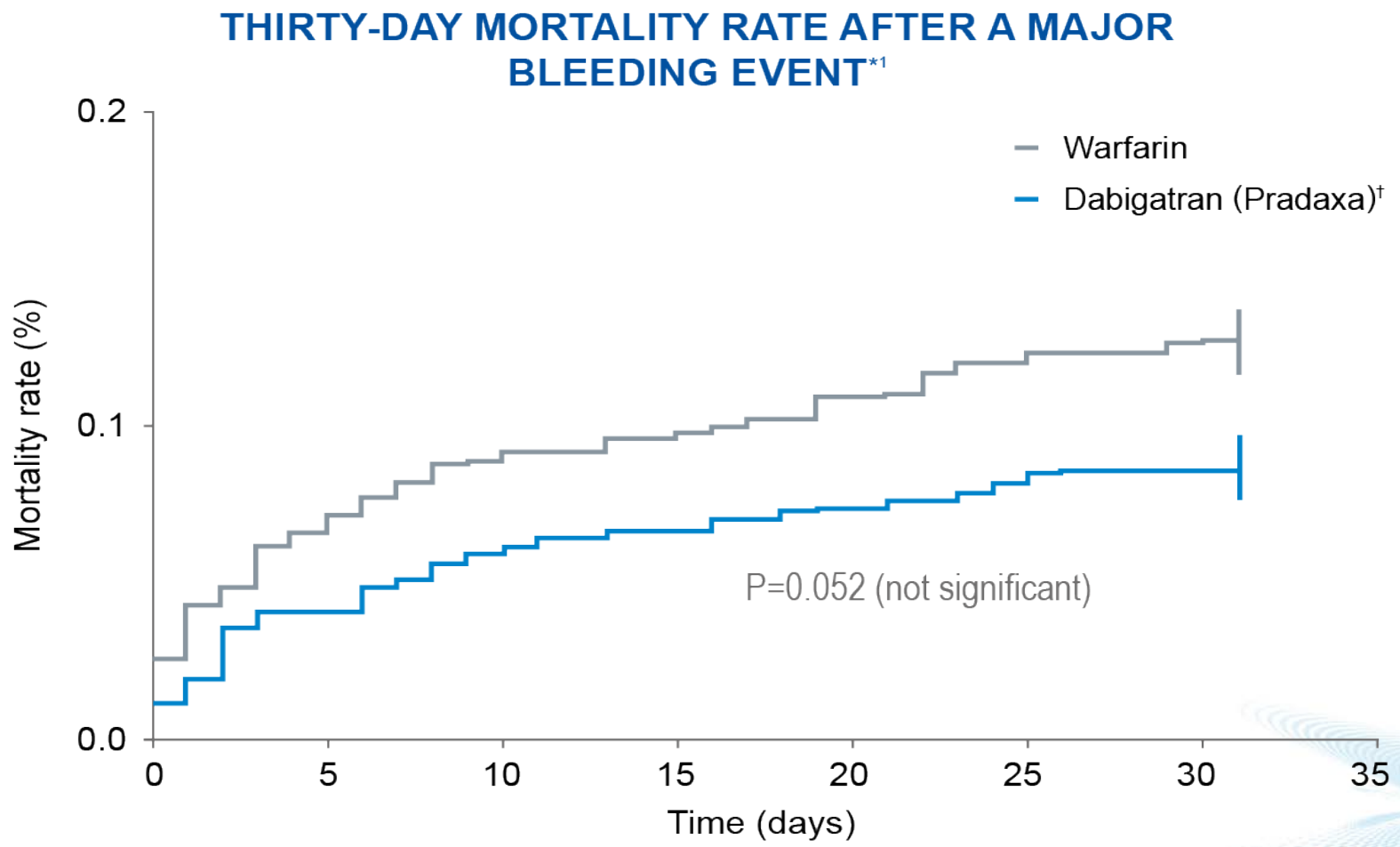
Reference: 1. Larsen TB, *et al. Am J Med.* 2014; 127: 650–656.

Outcome of major bleeds with dabigatran (Pradaxa)

- A pooled analysis from AF and VTE trials.[1]
- Revealed that, despite no reversal agent:
  - Outcomes for patients who experienced a major bleed on dabigatran were comparable to warfarin;
  - The same level of overall resources were required for management;
  - Patients experienced a comparable prognosis; and
  - Time in intensive care was significantly shorter (P=0.01) vs. warfarin.[1]

Reference: 1. Majeed A, *et al. Circulation.* 2013; 128: 2325–2332.

Outcome of major bleeds with dabigatran (Pradaxa)



Adapted from Majeed A, *et al.* 2013.[1]

*From a pooled, *post-hoc* analysis. †Includes combined data for Pradaxa 110 mg BD and 150 mg BD.

Reference: 1. Majeed A, *et al. Circulation*. 2013; 128: 2325–2332.

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Preoperative interruption of NOACs: guidelines

PREOPERATIVE INTERRUPTION OF NEW ORAL ANTICOAGULANTS: A SUGGESTED MANAGEMENT APPROACH[1]

Drug (doses)†	Renal function	Low bleeding risk surgery‡ (2 or 3 drug half-lives between last dose and surgery)	High bleeding risk surgery§ (4 or 5 drug half-lives between last dose surgery)
Dabigatran (Pradaxa) (150 mg twice daily)			
Half-life, 12-17 h	Normal or mild impairment (CrCl ≥ 50 mL/min)	Last dose: 24 h before surgery	Last dose: 48-72 h before surgery
Half-life, 13-23 h	Moderate impairment (CrCl 30-49 mL/min)	Last dose: 48-72 h before surgery	Last dose: 96 h before surgery
Rivaroxaban (20 mg once daily)			
Half-life, 5-9 h (healthy)	Normal or mild impairment (CrCl ≥ 50 mL/min)	Last dose: 24 h before surgery	Last dose: 48-72 h before surgery
Half-life, 9-13 h	Moderate impairment (CrCl 30-49 mL/min)	Last dose: 48 h before surgery	Last dose: 72 h before surgery
Apixaban (5 mg twice daily)			
Half-life, 7-8 h	Normal or mild impairment (CrCl ≥ 50 mL/min)	Last dose: 24 h before surgery	Last dose: 48-72 h before surgery
Half-life, 17-18 h	Moderate impairment (CrCl 30-49 mL/min)	Last dose: 48 h before surgery	Last dose: 72 h before surgery

Adapted from Tran H, *et al.* 2014.[1]

†Estimated half-life based on calculated renal clearance using the Cockcroft-Gault equation. ‡Aiming for mild to moderate residual anticoagulant effect at surgery (<12–25%). §Aiming for no or minimal residual anticoagulant effect (<3–6%) at surgery·. CrCl=creatinine clearance.

Reference: 1. Tran H, *et al. Int Med J*. 2014; 44: 525.

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Why is a reversal agent necessary?

- Anticoagulation therapy is one of the most common forms of medical intervention.[1]
- Bleeding is the primary complication of anticoagulants.[1]
- Bleeding is a risk of all anticoagulants, even when maintained within normal therapeutic ranges.[1]
- Although the incidence of major bleeding was less with dabigatran when used as indicated when compared to warfarin, life threatening bleeding can still occur.[2]
- A reversal agent provides a valuable tool for emergency situations.[1]

References: 1. Crowther MA, *et al. Blood*. 2008; 111: 4871–4879. 2. Pollack CV, *et al. New Engl J Med.* 2015; 373: 511–520.

Section 2

What is idarucizumab?*

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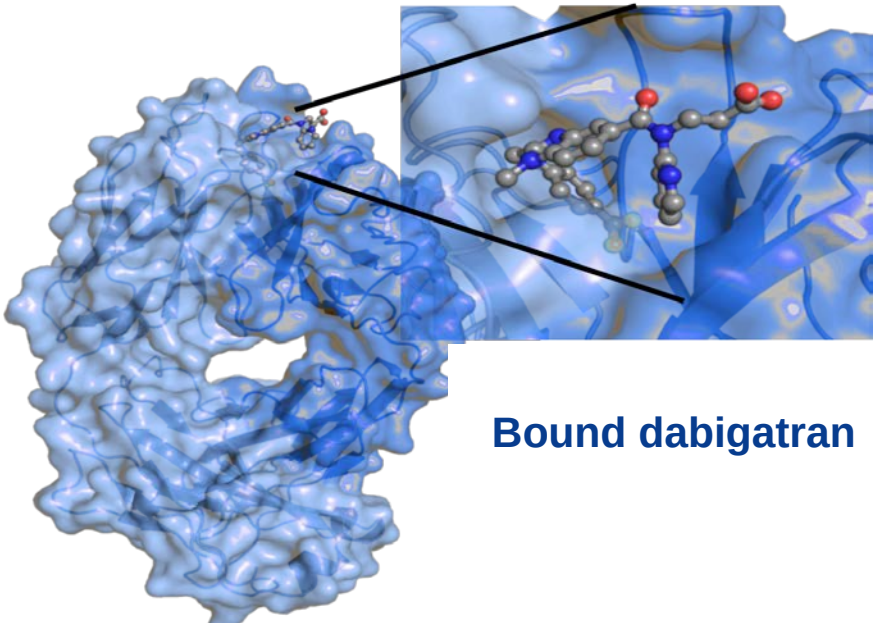
*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Idarucizumab*

- A specific reversal agent for dabigatran only.[1,2]
- Humanised Fab fragment that binds dabigatran.[2]
- Affinity for dabigatran ~350 times higher than thrombin.[2]
- Low immunogenicity.[2]
- No prothrombotic or anticoagulant effects.[2,3]
- Because it is a specific antibody, it will not reverse the effects of other anticoagulants.[2]



Bound dabigatran

idarucizumab

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. Fab=Fragment antigen binding

References: 1. Pollack CV, *et al. New Engl J Med.* 2015; 373: 511–520. 2. Schiele F, *et al. Blood.* 2013; 121: 3554–3562. 3. Glund S, *et al. Thromb Haemost*. 2015; 113(5): 943–951.

Idarucizumab* pharmacokinetics

- IV administration, resulting in fast onset.[1]
- Rapid decline over 4 hours (dominated by renal elimination).[1]
- Short half-life (initial half-life 47 min).[1]
- Idarucizumab binds both free and thrombin-bound dabigatran.[2]
- The idarucizumab-dabigatran complex (together with unbound idarucizumab) are eliminated by the kidneys.[1]

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References: 1. Glund S, *et al. Thromb Haemost*. 2015; 113(5): 943–951. 2. Pollack CV, *et al. New Engl J Med.* 2015; 373: 511–520.

Special Access Scheme intended usage

- As of November 2015, idarucizumab is not registered by the TGA.
- Idarucizumab should only be used in patients treated with dabigatran when rapid reversal of the anticoagulant effects of dabigatran is required:
  - For emergency surgery/urgent procedures; or
  - In life threatening or uncontrolled bleeding.[1,2]
- Anticoagulation for elective surgery can be adequately managed by withholding dabigatran for 24 to 72 hours prior to surgery.[3]
- Idarucizumab is not necessary for all surgeries or procedures.[2]

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TGA=Therapeutic Goods Administration.

References: 1. Pollack CV, *et al. New Engl J Med.* 2015; 373: 511–520. 2. Boehringer Ingelheim Pty Ltd. Data on File, 2015.3. Boehringer Ingelheim Pty Ltd. Pradaxa Approved Product Information, 24th August 2015.

Coagulation tests for dabigatran

- Accurate assessment of dabigatran levels is not necessary prior to administration of idarucizumab[†]. It is important to determine whether the patient is currently being treated with dabigatran, and this can be achieved by clinical history from the patients or their relatives.[1]
- Coagulation tests can help in detecting the presence of dabigatran:
  - dTT (quantitative, specific)
  - aPTT (semi-qualitative, not specific)
  - TT (semi-quantitative, specific).[‡2]
- Ask the patient or their family whether the patient is taking dabigatran; or
- Check to see if they have a patient card or review medical record.

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[†] Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. [‡]Consult internal guidance on reference ranges for each test. dTT=diluted thrombin time; aPTT=activated partial thromboplastin time; TT=thrombin time.

Reference: 1. Boehringer Ingelheim Pty Ltd. Pradaxa Approved Product Information, 24th August 2015. 2. van Ryn J, *et al. Thromb Haemost.* 2010; 103(6): 1116-1127.

Coagulation tests for dabigatran

- Diluted thrombin time (dTT; e.g. the Hemoclot® Thrombin Inhibitor assay):[1,2]
  - dTT is a sensitive assay to measure dabigatran using standard laboratory equipment.[1,2]
  - There is a direct linear relationship between dTT and dabigatran plasma concentration.[2]
  - High trough levels of dabigatran (dTT >200 ng/mL) are associated with higher risk of bleeding.[3]
- aPTT provides an approximate indication of the anticoagulation intensity achieved with dabigatran and should be conducted in association with a standard TT test:
  - A normal aPTT does not exclude dabigatran
  - A normal TT excludes dabigatran
  - A prolonged TT suggests dabigatran.[4]

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References: 1. van Ryn J, *et al. Thromb Haemost.* 2010; 103(6): 1116-1127. 2. Stangier J, *et al. Blood Coagul and Fibrinolysis* 2012;23:138–143.
3. Boehringer Ingelheim Pty Ltd. Pradaxa Approved Product Information, 24th August 2015. 4. Favaloro EJ, Lippi G. *Semin Thromb Hemost.* 2015; 41(2): 208–227.

Section 3

The evidence for idarucizumab*

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Healthy volunteer studies[1-3]

- **Part 1:** The objective was to investigate safety, tolerability, and pharmacokinetics of single rising doses of idarucizumab.*[1]
- **Part 2:** Dose finding, and to explore effectiveness idarucizumab in reversing dabigatran anticoagulant activity.[2]
- **In Part 1:**
  - A total of 110 healthy male volunteers received single rising doses of idarucizumab or placebo.
  - Doses were given as a 1-hour infusion of 20 mg to 8 g over 10 dose steps and as a 5-minute infusion of 1, 2, or 4 g.[1]
- **Conclusion:** In this first-in-human study of the specific dabigatran antidote idarucizumab, peak plasma exposure was reached quickly, followed by rapid elimination. In the absence of dabigatran, idarucizumab had no effect on coagulation parameters or ETP. Idarucizumab was safe and well tolerated at all administered doses, as either a 1-hour or 5-min infusion.[1]

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Glund S, *et al. Thromb Haemost.* 2015;113: 943–951. 2. Glund S, *et al. Lancet.* 2015; 386: 680–690 3. Glund S, *et al.* ASH Annual Meeting and Exposition. San Francisco, CA, USA, 6–9 December 2014; abstract 344

Idarucizumab* phase I

- Trial in healthy volunteers.[1]
- Randomised, placebo-controlled, double-blind phase I trial.[1]
- Assessed the safety, tolerability, and efficacy of idarucizumab on the reversal of dabigatran-induced anticoagulation.[1]
- Doses below, equal to, and above equimolar dosing to total dabigatran in the body.[1]

Glund *et al.* 2015

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Glund S, *et al. Lancet.* 2015; 386(9994): 680–690.

Idarucizumab* phase I

Primary safety endpoint:

- Incidence of adverse events judged to be related to treatment by investigators.[1]

Secondary endpoints:

- Measurements of dTT, ECT, aPTT, TT, and ACT; and
- Pharmacokinetic measures of total dabigatran and unbound dabigatran (on days 3 and 4).[1]

Glund *et al.* 2015

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. dTT=diluted thrombin time; ECT=ecarin clotting time; aPTT=activated partial thromboplastin time; TT=thrombin time; ACT=activated clotting time.

Reference: 1. Glund S, *et al. Lancet.* 2015; 386(9994): 680–690.

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Phase I: healthy volunteers* (part 2)

- Healthy male volunteers (n=47) aged 18 to 45 years with a body mass index (BMI) of 18.5–29.9 kg/m^2.[1]
- No exclusion criteria other than relevant deviation from a healthy condition.[1]
- 12 participants (9 randomly assigned to idarucizumab† and 3 to placebo) were enrolled into each of the 1 g, 2 g, or 5 g plus 2.5 g idarucizumab groups.[1]
- 11 participants (8 assigned to idarucizumab and 3 assigned to placebo) were enrolled into the 4 g idarucizumab group (due to recruitment difficulties).[1]

Glund *et al.* 2015

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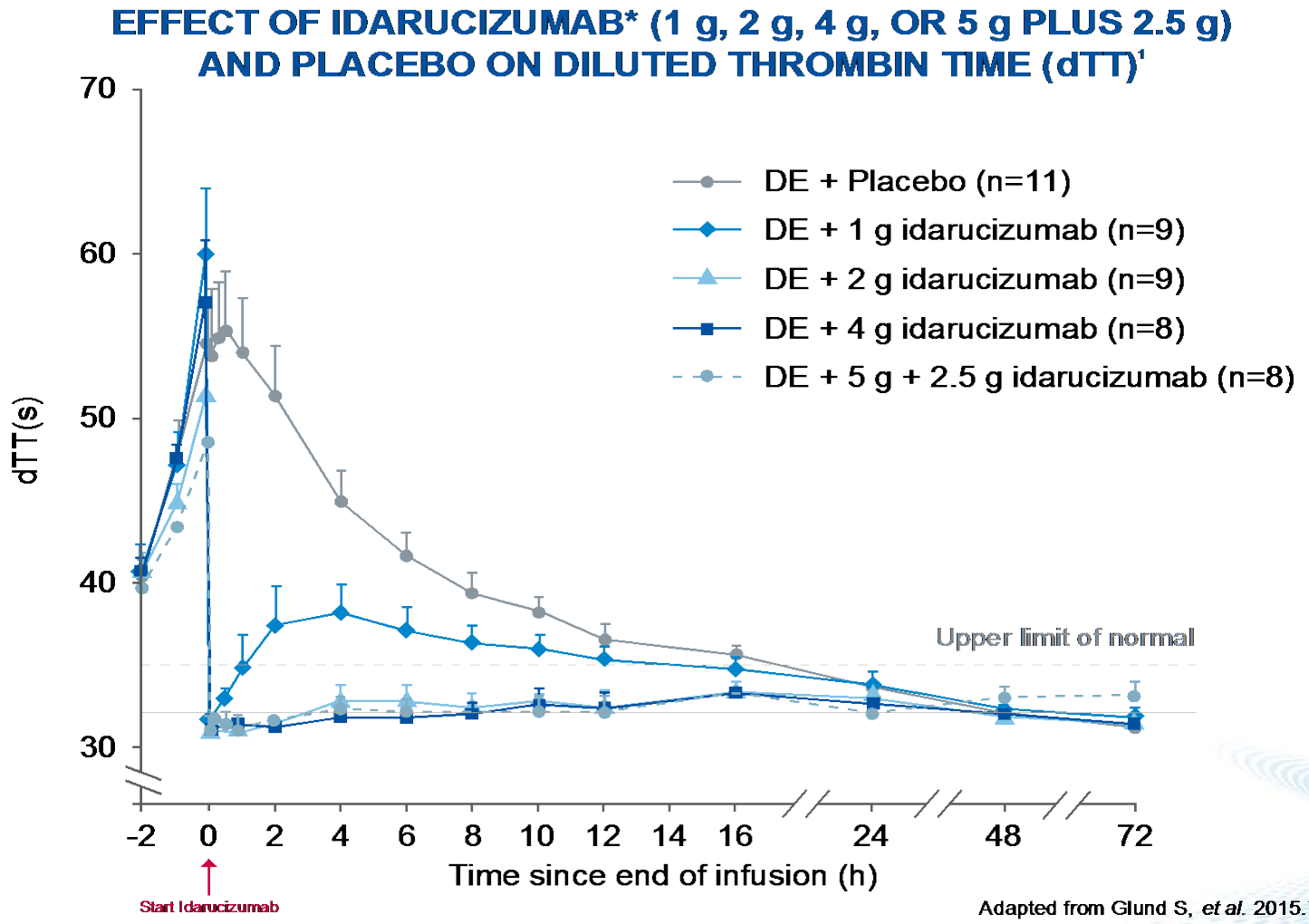
*Dose-finding study. †Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Glund S, *et al. Lancet.* 2015; 386(9994): 680–690.

Phase I (part 2): results[1]



Glund *et al.* 2015

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. DE=dabigatran etexilate.

Reference: 1. Glund S, *et al. Lancet.* 2015; 386(9994): 680–690.

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Phase I (part 2): conclusions

- Idarucizumab* was associated with immediate, complete, and sustained reversal of dabigatran-induced anticoagulation in healthy males.[1]
- Idarucizumab was safe and well tolerated.[1]
- No unexpected or clinically-relevant safety concerns were identified.[1]

Glund *et al.* 2015

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Glund S, *et al. Lancet.* 2015; 386(9994): 680–690.

Phase I: healthy, elderly and renally-impaired subjects

- A phase Ib, randomised, double-blind, placebo-controlled, two-way crossover study.[1]
- Aimed to evaluate the safety, tolerability, and pharmacodynamics of idarucizumab* after dabigatran pre-treatment in males and females who were:
  - Healthy middle-aged (45-64 years, BMI 18.5-29.9 kg/m^2);
  - Elderly (65-80 years, BMI 18.5-32.0 kg/m^2); and
  - Renally-impaired volunteers (45-80 years, BMI 18.5-32.0 kg/m^2, CrCl 30-90 ml/min at screening).[1]
- Participants underwent re-exposure.[1]

Glund *et al.* 2014

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. BMI=body mass index.

Reference: 1. Glund S, *et al.* ASH 2014; abstr 334.

Phase I: healthy, elderly and renally-impaired subjects

- **Primary endpoints:**
  - Safety, tolerability, and immunogenicity of idarucizumab.*[1]
  - Reversal of prolongation of blood coagulation time by dabigatran.[1]
  - Restoration of anticoagulation after re-exposure to dabigatran following idarucizumab infusion.[1]

Glund *et al.* 2014

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Glund S, *et al.* ASH 2014; abstr 334.

Elderly and renally-impaired patients

- A total of 46 volunteers completed the study protocol.[1]

Healthy group	Renally-impaired group
• Aged 45–64 years (middle-aged) and body mass index (BMI) 18.5 to 29.9 kg/m^2.[1] • Aged 65–80 years (elderly) and BMI 18.5 to 32.0 kg/m^2.[1]	• Aged 45–80 years and BMI 18.5 to 32.0 kg/m^2.[1] • CrCl at screening: - Mild: 60 to <90 mL/min; and - Moderate: 30 to <60 mL/min.[1]

Glund *et al.* 2014

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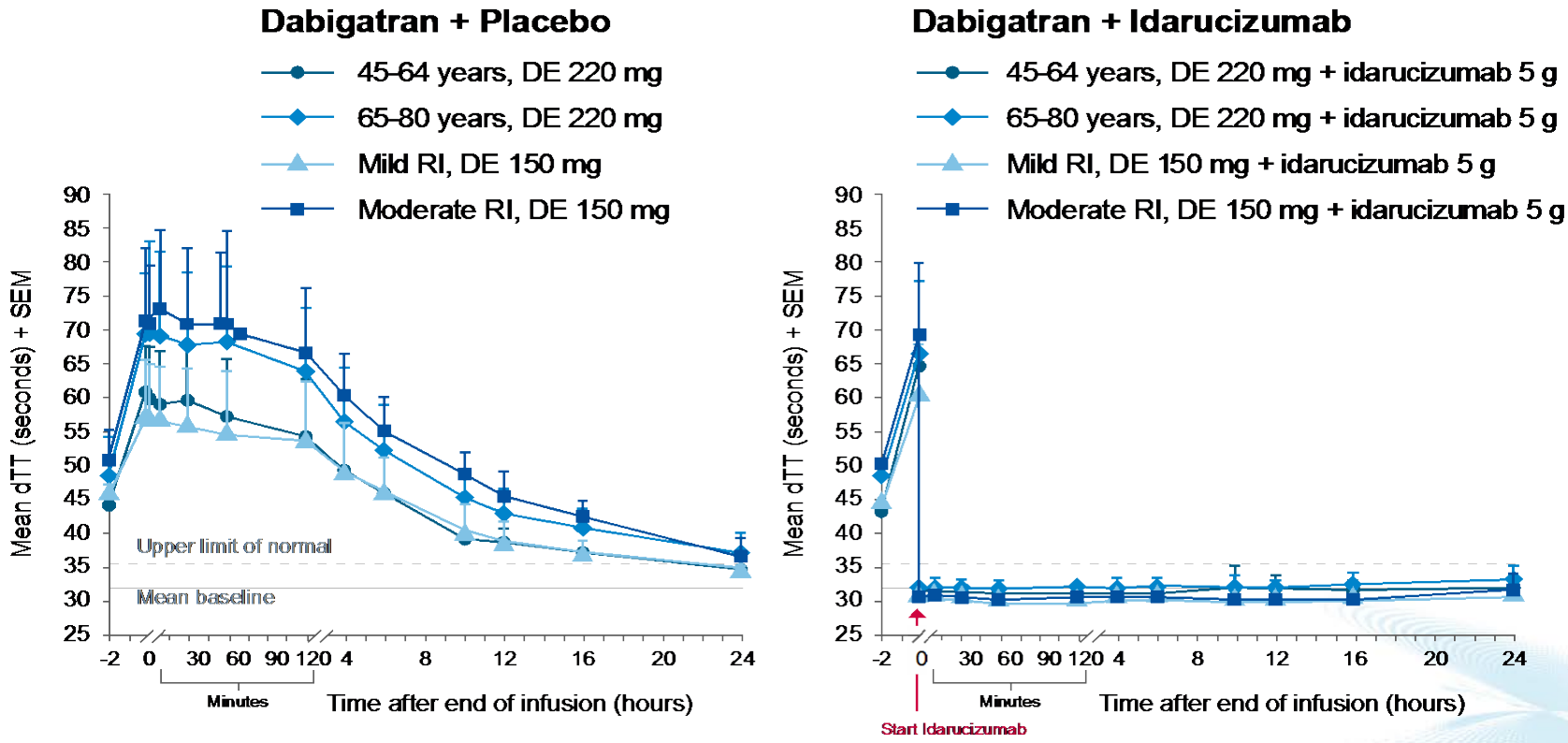
Reference: 1. Glund S, *et al.* ASH 2014; abstr 334.

Immediate and sustained reversal in healthy, elderly and renally-impaired participants[1]

- Immediate reversal of anticoagulant effect.[1]

REVERSAL OF DABIGATRAN CLOTTING TIME WITH IDARUCIZUMAB*[1]



Adapted from Glund S, *et al.* 2014.[1]

Glund *et al.* 2014

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. DE=dabigatran etexilate ; dTT=diluted thrombin time; RI=renal impairment; SEM=standard error of the mean.

Reference: 1. Glund S, *et al.* ASH 2014; abstr 334.

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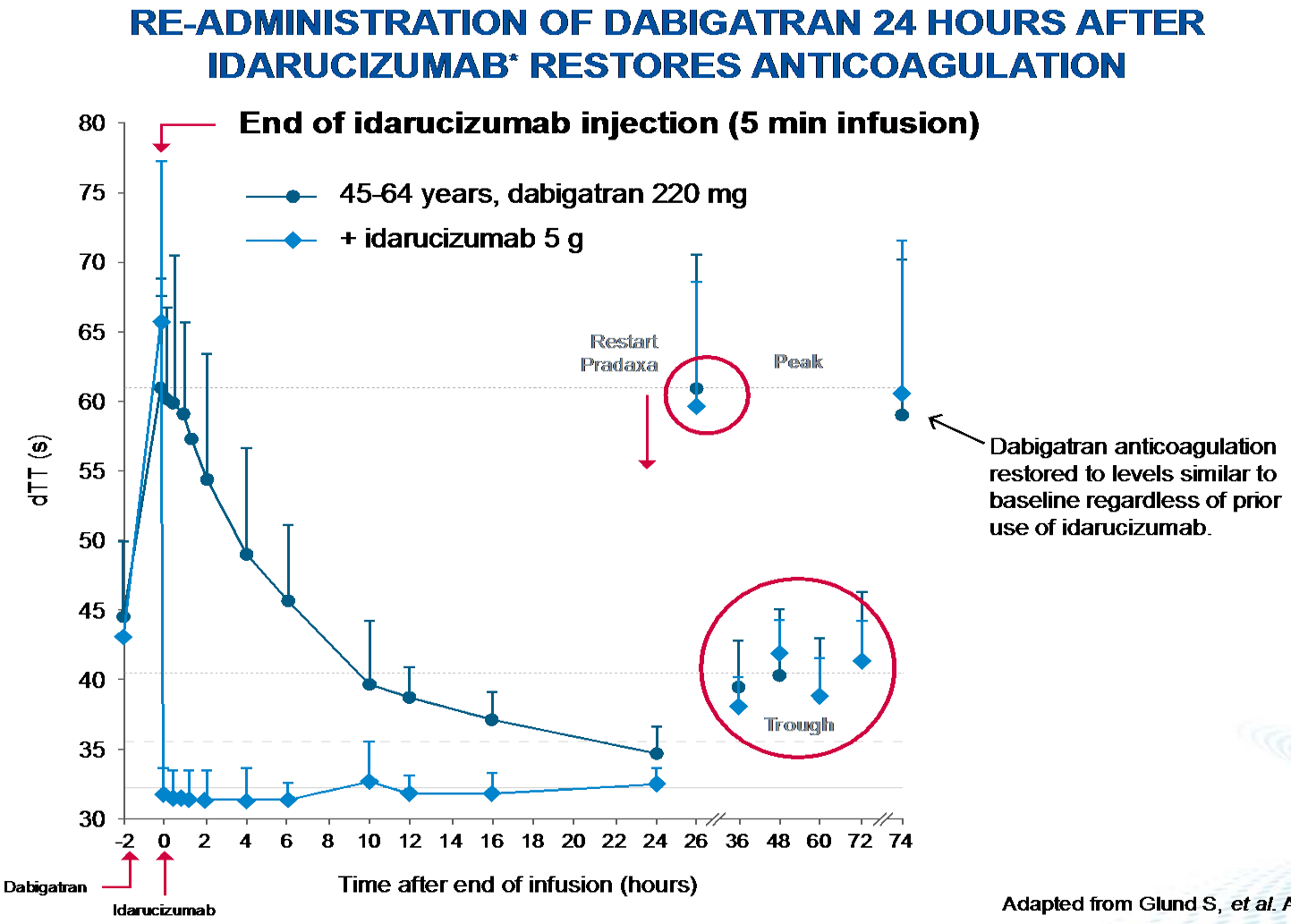
Restoration of anticoagulation[1]



Adapted from Glund S, *et al.* ASH 2014.[1]

Glund *et al.* 2014

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. dTT=diluted thrombin time.

Reference: 1. Glund S, *et al.* ASH 2014; abstr 334.

Phase I: safety analyses

- No clinically relevant drug-related adverse events or relevant changes in safety parameters observed.[1]
- No adverse events indicative of immunogenic reactions observed.[1]
- Adverse events and local tolerability reactions were similar for placebo and active treatment.[1]

Glund *et al.* 2014

Boehringer Ingelheim

Reference: 1. Glund S, *et al.* ASH 2014; abstr 334.

Phase I: safety analyses

- Doses of up to 8 g did not appear to result in procoagulant effects in healthy subjects.[1]
- No relationship was observed between drug dose, sex, gender, or renal function and frequency of adverse events.[1]
- A dose-dependent, transient increase in urine protein and low-weight proteins was observed, but values returned to normal range within 4–24 hours.[1]

Glund *et al.* 2014

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Reference: 1. Glund S, *et al.* ASH 2014; abstr 334.

Phase 1: conclusions

- Idarucizumab* led to complete and sustained reversal of dabigatran-induced anticoagulation in male and female subjects:
  - Of different age; and
  - With mild and moderate renal function.[1]
- Dabigatran therapy could be restarted 24 hours after idarucizumab[1]
- Idarucizumab was well tolerated.[1]
- Anticoagulation was again reversed when a second dose of idarucizumab was administered 2 months later.[1]

Glund *et al.* 2014

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Glund S, *et al.* ASH 2014; abstr 334.

RE-VERSE AD (interim analysis)†

- Interim results (n=90) published June 2015.[1]
- Ongoing, multicentre, prospective cohort study.[1]
- Plan to recruit up to 300 patients.[1]
- Interim results published June 2015.[1]
- Aimed to determine the safety and efficacy of 5 g of idarucizumab* in dabigatran patients who:
  - Had uncontrolled or life threatening bleeding (Group A; n=51); or
  - Required emergency surgery/urgent procedure (Group B; n=39).[1]

Pollack *et al.* 2015

†Interim analysis is based on data from 90 patients. *Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Pollack CV, *et al*. *N Engl J Med.* 2015; 373(6): 511–520.

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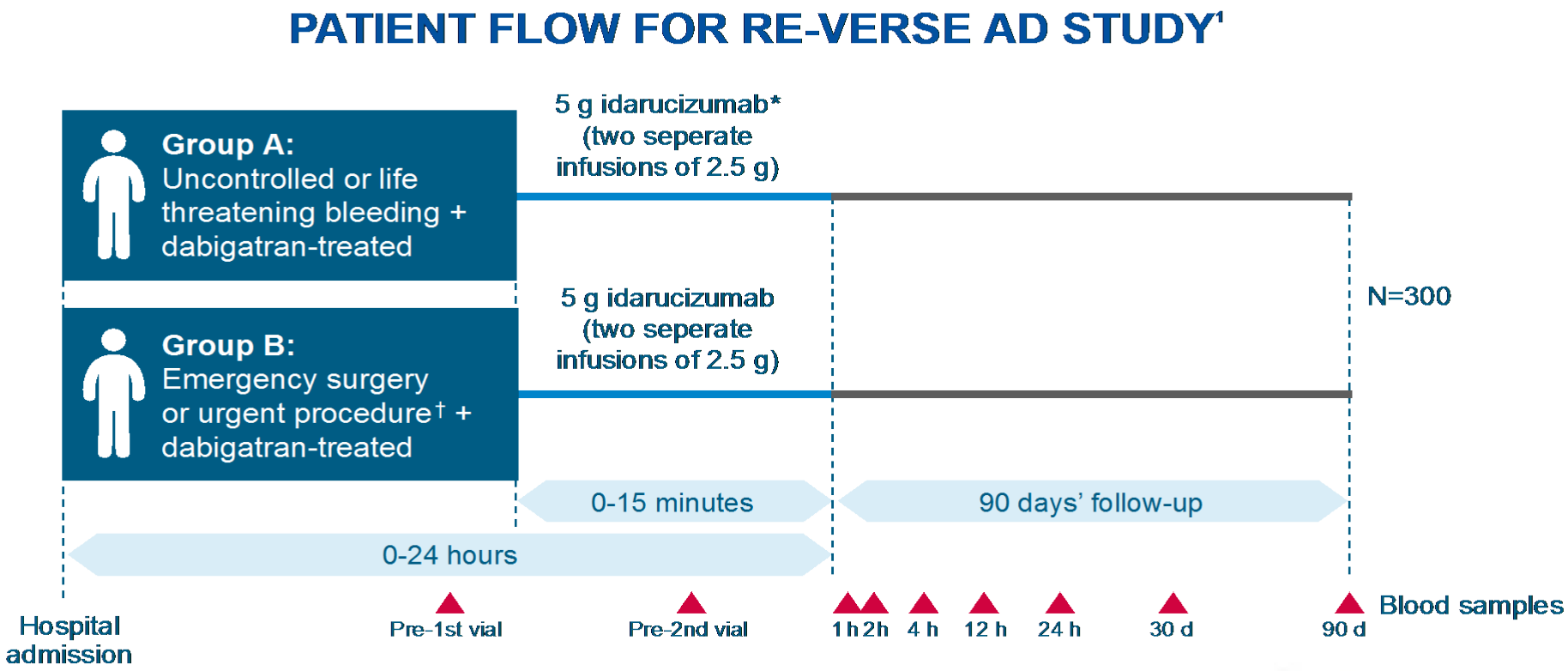
RE-VERSE AD study design



Adapted from Pollack CV, *et al.* 2015.[1]

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. †Other than bleeding.

Reference: 1. Pollack CV, *et al. N Engl J Med.* 2015; 373(6): 511–520.

RE-VERSE AD study design

- **Primary endpoint:**
  - Maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab;*
  - Determined on the basis of the dilute thrombin time or ECT.[1]
- **Secondary endpoint:**
  - Restoration of haemostasis;
  - Group A: time to cessation of bleeding;
  - Group B: occurrence of major intraoperative bleeding;
  - Duration of reversal; and
  - Pharmacokinetics of dabigatran-idarucizumab.[1]

Pollack *et al.* 2015

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ECT=ecarin clotting time.

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Pollack CV, *et al*. *N Engl J Med.* 2015; 373(6): 511–520.

RE-VERSE AD patient characteristics

	Group A (n=51)	Group B (n=39)	Total (N=90)
Male, n (%)	32 (63)	18 (46)	50 (56)
Age (yrs), median (min, max)	77.0 (48, 93)	76.0 (56, 93)	76.5 (48, 93)
Creatinine clearance (Cockroft-Gault)			
Median (min, max) (mL/min)	54 (16, 187)	60 (11, 171)	58 (11, 187)
<30 ml/min, n (%)	5 (10)	7 (18)	12 (13)
30 to <50 ml/min, n (%)	14 (27)	6 (15)	20 (22)
50 to <80 ml/min, n (%	16 (31)	11 (28)	27 (30)
≥80 ml/min, n (%)	6 (12)	9 (23)	15 (17)
Missing, n (%)	10 (20)	6 (15)	16 (18)
Elevated dTT at baseline, n (%)	40 (78)	28 (72)	68 (76)
Elevated ECT at baseline, n (%)	47 (92)	34 (87)	81 (90)

Adapted from Pollack CV, *et al.* 2015.[1]

Pollack *et al.* 2015

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dTT=diluted thrombin time; ECT=ecarin clotting time.

Reference: 1. Pollack CV, *et al. N Engl J Med.* 2015; 373(6): 511–520.

RE-VERSE AD nature of enrolled events

	Group A (n=51)
Type of bleeding	
Intracranial	18
Trauma	9
Gastrointestinal	20
Other*	11

*Other bleeding types: urogenital, epistaxis, liver, aortic aneurism and aortic dissection.

	Group B (n=39)
Reason for surgery†	
Aortic dissection	1
Pericardial tamponade	1
Peritonitis	1
Acute mesenteric ischaemia with sepsis	2
Bone fractures	8
Acute cholecystitis	5
Acute renal insufficiency, catheter placement	4
Acute appendicitis	3
Joint/wound infection	3
Abscess (suprapubic, scrotal)	2

†Other reasons for surgery (one patient each) were: acute deterioration of aortic valve; small bowel obstruction; pneumothorax; probable perforation of the viscera; incarcerated umbilical hernia; lumbar puncture; left leg gangrene; unstable angina, ureteral obstruction, and hydronephrosis.

Adapted from Pollack CV, *et al*. 2015.[1]

Pollack *et al.* 2015

Boehringer Ingelheim

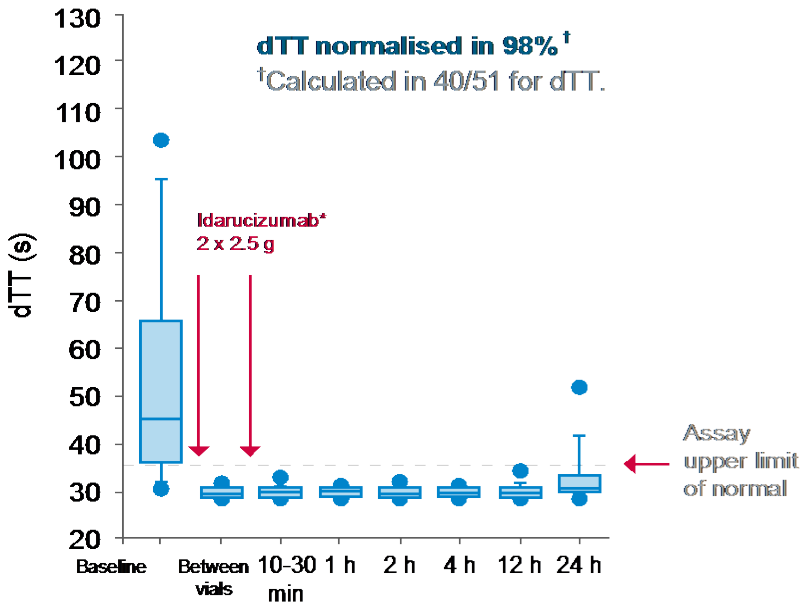
Reference: 1. Pollack CV, *et al*. *N Engl J Med.* 2015; 373(6): 511–520.

RE-VERSE AD: results

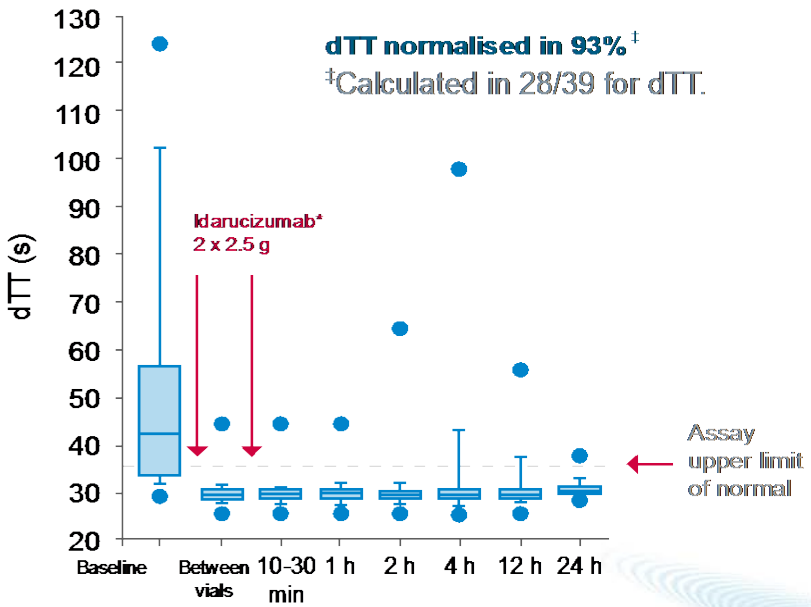
- Immediate reversal of anticoagulation.[1]

DILUTED THROMBIN TIME (dTT)[1]

Group A:
Patients with uncontrolled bleeding (N=51)



Group B:
Patients undergoing emergency procedures (N=39)



Median maximum reversal within 4 hours 100% (95% CI: 100-100)

Adapted from Pollack CV, *et al.* 2015.[1]

Pollack *et al.* 2015

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Pollack CV, *et al. N Engl J Med.* 2015; 373(6): 511–520.

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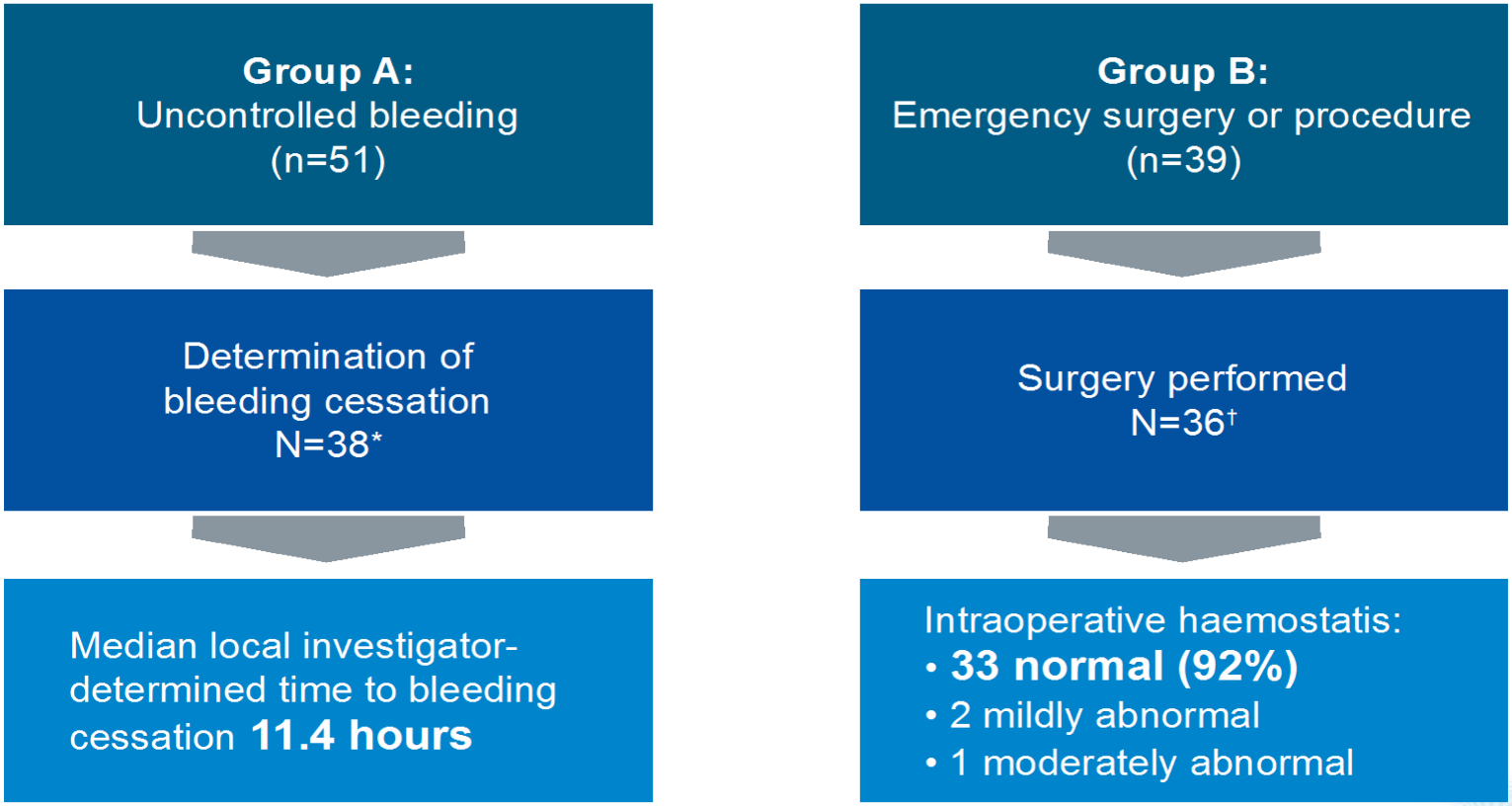
Achieving haemostasis‡1

‡Secondary endpoints.



Adapted from Pollack CV, *et al.* 2015.[1]

Pollack *et al.* 2015

*Not ascertained in 13 patients, 3 with no baseline assessment (5 intracranial haemorrhage, 4 gastrointestinal bleed, 2 intramuscular bleed, 2 pericardial/retroperitoneal bleed); †Planned surgery not performed in 3 patients (1 intentional overdose case, haemodialysis averted, 2 too unstable for surgery despite reversal).

Reference: 1. Pollack CV, *et al. N Engl J Med.* 2015; 373(6): 511–520.

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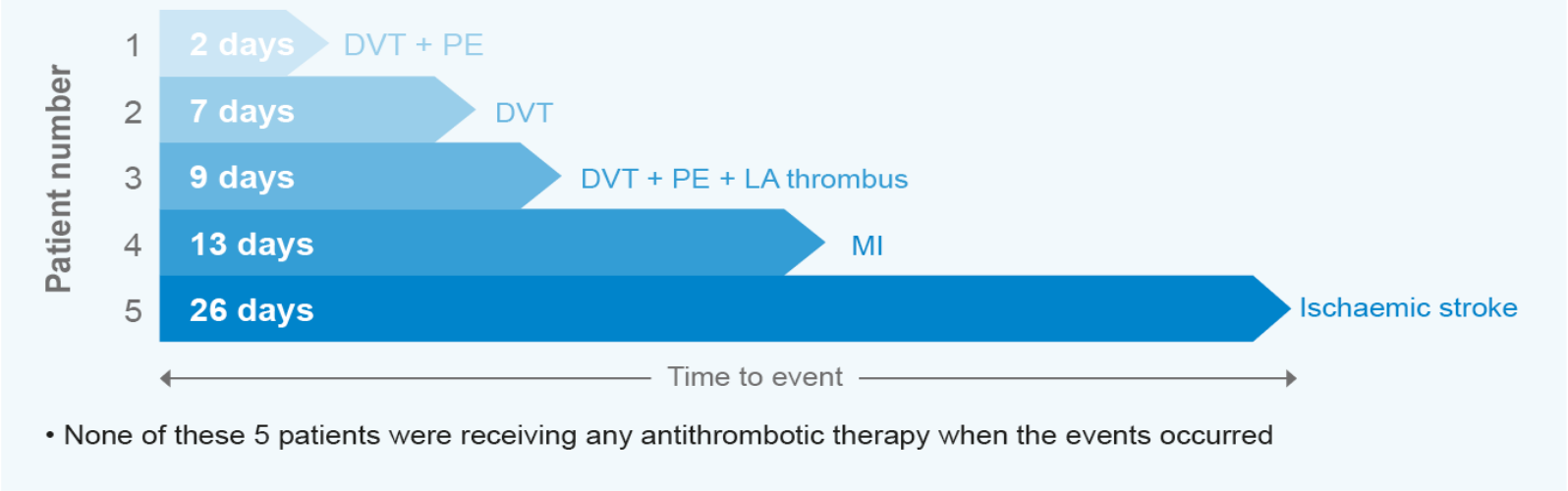
RE-VERSE AD: safety analysis

- No safety concerns and no evidence of prothrombotic or immunogenic effect were seen after idarucizumab* administration.[1]
- No cases of hypersensitivity observed.[1]
- 5 thrombotic events were reported in REVERSE AD:



Adapted from Pollack CV, *et al.* 2015.[1]

- 18 deaths (9 in each group):
  - RE-VERSE AD did not exclude patients who were seriously ill; and
  - All deaths related to presenting index event and comorbidities.[1]

Pollack *et al.* 2015

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

DVT=deep vein thrombosis; PE=pulmonary embolism; LA=left arterial; MI=myocardial infarction.

Reference: 1. Pollack CV, *et al. N Engl J Med.* 2015; 373(6): 511–520.

RE-VERSE AD interim analysis: conclusions†

In a cohort of multi-morbid, elderly patients taking dabigatran who presented with life threatening emergencies, idarucizumab*
5 g provided:

- Immediate and complete reversal of dabigatran-induced anticoagulation in 88–98% of patients;
- Cessation of bleeding in under 12 hours (mean);
- Normal intraoperative haemostasis in 92% of patients undergoing procedures;
- No immunogenic reactions; and
- No evidence of prothrombotic events.[1]

Pollack *et al.* 2015

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†Interim analysis is based on data from 90 patients. *Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Pollack CV, *et al*. *N Engl J Med.* 2015; 373(6): 511–520.

Section 4

How to use idarucizumab*

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Special Access Scheme intended usage

- As of November 2015, idarucizumab is not registered by the TGA.
- Idarucizumab should only be used in patients treated with dabigatran when rapid reversal of the anticoagulant effects of dabigatran is required:
  - For emergency surgery/urgent procedures; or
  - In life threatening or uncontrolled bleeding.[1,2]
- Anticoagulation for elective surgery can be adequately managed by withholding dabigatran for 24 to 72 hours prior to surgery.[3]
- Idarucizumab is not necessary for all surgeries or procedures.[2]

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TGA=Therapeutic Goods Administration.

References: 1. Pollack CV, *et al. New Engl J Med.* 2015; 373: 511–520. 2. Boehringer Ingelheim Pty Ltd. Data on File, 2015.3. Boehringer Ingelheim Pty Ltd. Pradaxa Approved Product Information, 24th August 2015.

Contraindications and precautions

- Known hypersensitivity to idarucizumab* and its excipients:[1]
  - In patients with hereditary fructose intolerance who may react to sorbitol, the risk of treatment with idarucizumab must be weighed against the potential benefit of emergency treatment.[2]
- Idarucizumab contains 2.2 mmol (or 50 mg) sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.[2]
- There is no data on the use of idarucizumab in pregnancy or breastfeeding.[2]

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

References: 1. Pollack CV, *et al. New Engl J Med.* 2015; 373: 511–520. 2. Boehringer Ingelheim Pty Ltd. Data on File.

Preparation and administration of idarucizumab*

DOSAGE

5 g provided as two separate vials each containing 2.5 g/50 ml idarucizumab solution for intravenous infusion/injection.[1]

PREPARATION

Ensure aseptic technique when handling the solution for infusion/injection.[1]

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. The solution is ready for infusion/injection.[1]

ADMINISTRATION

Option 1: Bolus injection
Administer as a bolus injection by injecting both vials consecutively one after another via syringe.[1]

Option 2: Intravenous infusion
Administer as two consecutive infusions by hanging the vials.[1]

- If using a pre-existing line for administration of idarucizumab, flush the line with 0.9 % Sodium Chloride injection, USP solution prior to infusion. No other infusion should be administered in parallel via the same intravenous access.[1]
- Do not mix idarucizumab with other medicinal products.[1]
- Idarucizumab reverses the anticoagulant effects of dabigatran immediately after the administration of the complete 5 g dose.[†2]

[†]As shown in clinical trials.

DURATION OF TREATMENT

The recommended dose is 5 g, given as two doses of 2.5 g within 15 minutes of each other. The injection of each vial should take no longer than 5-10 minutes.[1]

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

References: 1. Boehringer Ingelheim Pty Ltd. Data on File, 2015. 2. Glund S, *et al. ASH.* 2014; abstr 334.

Further handling instructions for idarucizumab*

- Idarucizumab should be stored at between 2°C and 8°C (do not freeze).[1]
- It may be stored at 25°C for up to 48 hours if kept in original packaging.[1]
- Once exposed to light, idarucizumab may be stored for up to 6 hours.[1]
- Idarucizumab is for single-use only, as the product does not contain preservatives.[1]

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Boehringer Ingelheim Pty Ltd. Data on File, 2015.

Resuming dabigatran after idarucizumab*

- A benefit-risk assessment ultimately needs to be made by the treating physician.
- Restarting dabigatran after idarucizumab restored anticoagulation to initiation-like levels in healthy, middle-aged volunteers.[1]
- This was irrespective of whether dabigatran was administered 24 hours following idarucizumab or placebo treatment.[1]
- Absence of antithrombotic therapy exposes patients to the thrombotic risk of their underlying disease or condition. Anticoagulation can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved.[2]

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reference: 1. Glund S, *et al.* ASH 2014; abstr 334. 2. Boehringer Ingelheim Pty Ltd. Data on File, 2015.

Adverse events

- Reduced potential for immunogenic reactions.[1]
- Adverse events and local tolerability reactions similar for placebo and active treatment (phase I).[2]
- No procoagulant effects.[2]
- No cases of hypersensitivity were observed.[1]
- All serious adverse events leading to later deaths appeared to be associated with coexisting conditions.[1]

References: 1. Pollack CV, *et al. New Engl J Med.* 2015; 373: 511–520. 2. Glund S, *et al. Thromb Haemost.* 2015; 113(5): 943–951.

TGA guidelines for Special Access Scheme

- The Australian guidelines for the reporting of adverse outcomes associated with the use of unapproved therapeutic goods under the Special Access Scheme (“Access to unapproved therapeutic goods via the Special Access Scheme”) are available at the following web page: https://www.tga.gov.au/access-unapproved-therapeutic-goods-special-access-scheme

- Refer specifically to the section “The requirements for Reporting of adverse outcomes associated with the use of unapproved therapeutic goods under the Special Access Scheme” on pages 22-25 for detailed information on the reporting requirements for unapproved products.

- A copy of these Guidelines has been provided in the Treatment Plan.

TGA=Therapeutic Goods Administration.

TGA reporting responsibilities

- The **onus for reporting adverse drug reactions from Special Access Scheme usage** in accordance with these **guidelines lies primarily with the treating doctor.**

- **The treating doctor is required to report to the TGA, the details of any actual or suspected adverse drug reactions (ADR) associated with the unapproved product (idarucizumab*), of which he/she becomes aware.**

- The “TGA Blue Card”, or an alternative appropriate form, is used to report adverse drug reactions to the TGA.

- A copy of the TGA “Blue Card” is available in the Service Treatment Pack.

- **Definition ADR:** For unapproved medicines, adverse drug reactions are all noxious and unintended responses to a medicinal product suspected to be related to any dose of the medicine.

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

TGA “Blue form”

Australian Government
Department of Health
Therapeutic Goods Administration

TGA use only

Report of suspected adverse reaction to medicines or vaccines

See statement about the collection and use of personal information overleaf, and please attach any additional data to this form

Patient initials or medical record number:	Sex: M ☐ F ☐	Date of birth or age:
	Weight (kg):	

Suspected medicine(s)/vaccine(s)

Medicine/vaccine (please use trade names; include batch number and AUST R or AUST L number if known)	**Dosage** (Dose number for vaccines eg 1st DTP)	Date begun	Date stopped	Reason for use

Other medicine(s)/vaccine(s) taken at the time of the reaction

Medicine/vaccine	**Dosage**	Date begun	Date stopped	Reason for use

Reaction(s): Date of onset of reaction (for vaccines time after administration): / /

Describe: (please provide as much detail as possible and include any results of relevant laboratory data and other investigations)

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Reporting process – TGA

- The treating doctor must report adverse drug reactions to idarucizumab*, of which he/she becomes aware, as soon as possible to the TGA (i.e. receipt by TGA within 15 days of awareness).

- Mail:

  Medicines Safety Monitoring
  Pharmacovigilance and Special Access Branch
  Therapeutic Goods Administration
  PO Box 100
  WODEN ACT 2606

Fax: 02 6232 8392, or
Email: adr.reports@tga.gov.au

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

Reporting process – BI

- Treating doctors should also send a copy of this report on the same day to BI Pharmacovigilance to ensure this information is also captured within the company's global safety database.

- This information is used to monitor the risk/benefit profile of the product, update documents such as the approved Product Information, and to meet sponsor reporting requirements to global health authorities.

A copy of the report should be sent to BI Pharmacovigilance by:

Fax: 02 8875 8699, or

Secure email: PV_Local_Australia@boehringer-ingelheim.com

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Additional safety reporting

- If the treating doctor wishes to report additional safety information related to either idarucizumab* or Pradaxa† usage to the TGA and BI, the same form and process can be used.

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. †Please review the full Approved Product Information before prescribing Pradaxa.

Available resources

- In-Service Slide Deck
- Reference Guide
- Reference Chart
- Reference Lanyard
- Ordering supplies of idarucizumab* Map
- Frequently Asked Questions and Answers
- Mode of Action Video
- Treatment Plan
- Initial Supply Form
- Re-Supply Form (inc.TGA Category A SAS Form†)
- *TGA Blue Card Report Form*
- Key Considerations for Clinicians

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*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

†This is included as an electronic copy with the re-supply form.

For further information please contact Boehringer Ingelheim at

MEDsra.AU@boehringer-ingelheim.com

STREAMLINED AUTHORITY CODE 4269 for stroke prevention in non-valvular atrial fibrillation

PBS Information: Authority required (STREAMLINED) for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation and one or more risk factors for developing stroke or systemic embolism. Authority required (STREAMLINED) for prevention of venous thromboembolism in a patient undergoing total hip replacement or total knee replacement. This product is not listed on the PBS for treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE), or for the prevention of recurrent DVT and PE in adults. Refer to PBS Schedule for full authority information.

Please review Product Information before prescribing.

The Product Information can be accessed at www.boehringer-ingelheim.com.au/PI

PRADAXA® (dabigatran etexilate) 110 mg and 150 mg capsules. MINIMUM PRODUCT INFORMATION. INDICATION: Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke (SPAF). CONTRAINDICATIONS: Known hypersensitivity to dabigatran, dabigatran etexilate or excipient (e.g. sunset yellow FCF CI15985); severe renal impairment (CrCL < 30mL/ min); haemorrhagic manifestations, bleeding diathesis, spontaneous or pharmacological impairment of haemostasis; lesion or condition if considered significant risk factor for major bleeding (including current or recent gastrointestinal ulceration, malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities)*; concomitant treatment with any other anticoagulants except when switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter*; indwelling spinal or epidural catheter and during the first two hours after removal; hepatic impairment or liver disease expected to have any impact on survival; history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding; gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated; conditions associated with increased risk of bleeding; concomitant treatment with systemic ketoconazole, cyclosporin*, itraconazole* or dronedarone; simultaneous initiation of treatment with dabigatran etexilate and oral verapamil; prosthetic heart valve replacement. PRECAUTIONS: Haemorrhagic risk: moderate renal impairment (CrCL 30-50 mL/min), congenital or acquired coagulation disorders, thrombocytopenia or functional platelet defects, active ulcerative gastrointestinal disease, recent gastrointestinal bleeding, recent biopsy or major trauma, brain, spinal or ophthalmic surgery, bacterial endocarditis, age ≥ 75 years, fibrinolytic agents. Myocardial infarction. Concomitant administration with: acetylsalicylic acid, NSAIDs, clopidogrel, unfractionated heparins and heparin derivatives, low molecular weight heparins, fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, ticagrelor, vitamin K antagonists, selective serotonin re-uptake inhibitors, selective serotonin norepinephrine re-uptake inhibitors, P-gp inhibitors: amiodarone, verapamil, tacrolimus, ritonavir, tipranavir, nelfinavir, saquinavir, quinidine, clarithromycin, P-gp inducers. Surgical interventions may require temporary discontinuation and anticoagulant monitoring is warranted; clearance in patients with renal impairment may take longer. Not recommended in patients undergoing hip fracture surgery. Pregnancy (Category C). Lactation. Children. Patients < 50 kg. See full PI. INTERACTIONS: See CONTRAINDICATIONS and PRECAUTIONS. ADVERSE EFFECTS: Bleeding and signs of bleeding, dyspepsia, gastritis-like symptoms, diarrhoea, nausea, vomiting, constipation, flatulence, dysphagia, nasopharyngitis, dyspnoea, cough, dyspnoea exertional, upper respiratory tract infection, bronchitis, pneumonia, influenza, sinusitis, urinary tract infection, dizziness, headache, syncope, insomnia, atrial fibrillation, cardiac failure congestive, cardiac failure, palpitations, angina pectoris, hypertension, hypotension, rash, gout, arthralgia, back pain, pain in extremity, osteoarthritis, musculoskeletal pain, muscle spasms, oedema peripheral, fatigue, asthenia, chest pain, chest discomfort, fall, abnormal liver function tests. Less common adverse reactions see full PI. DOSAGE AND ADMINISTRATION for SPAF: Assess renal function (Cockcroft-Gault method) prior to treatment initiation, in clinical situations that could lead to renal function decline and at least once a year in patients ≥ 75 years or with moderate renal impairment. Swallow capsule whole with water, with or without food. Recommended dose: 300 mg (one 150 mg capsule twice daily). Age ≥ 75 years: reduced dose of 220 mg (one 110 mg capsule twice daily). Moderate renal impairment, higher risk of bleeding: reduced dose of 220 mg (one 110 mg capsule twice daily) may be considered. Special populations see full PI. August 2015. Pradaxa® is a registered trademark of Boehringer Ingelheim Pty Limited, ABN 52 000 452 308, 78 Waterloo Road, North Ryde NSW 2113. AUS/PRA-151512. S&H BOIPX0015 November 2015.

*Please note changes in Product Information.

Boehringer Ingelheim

Please review Product Information before prescribing.

The Product Information can be accessed at www.boehringer-ingelheim.com.au/PI

PRADAXA® (dabigatran etexilate) 110 mg and 150 mg capsules. MINIMUM PRODUCT INFORMATION. INDICATION: Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.* CONTRAINDICATIONS: Known hypersensitivity to dabigatran, dabigatran etexilate or excipient (e.g. sunset yellow FCF CI15985); severe renal impairment (CrCL < 30mL/min); haemorrhagic manifestations, bleeding diathesis, spontaneous or pharmacological impairment of haemostasis; lesion or condition if considered significant risk factor for major bleeding (including current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities)*; concomitant treatment with any other anticoagulants e.g. heparins, heparin derivatives, oral anticoagulants except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter*; indwelling spinal or epidural catheter and during the first two hours after removal; hepatic impairment or liver disease expected to have any impact on survival; history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding; gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated; conditions associated with increased risk of bleeding; concomitant treatment with systemic ketoconazole, cyclosporin, itraconazole* or dronedarone; simultaneous initiation of treatment with dabigatran etexilate and oral verapamil; prosthetic heart valve replacement. PRECAUTIONS: Haemorrhagic risk: moderate renal impairment (CrCL 30-50 mL/min), congenital or acquired coagulation disorders, thrombocytopenia or functional platelet defects, active ulcerative gastrointestinal disease, recent gastrointestinal bleeding, recent biopsy or major trauma, brain, spinal or ophthalmic surgery, bacterial endocarditis, age ≥ 75 years, fibrinolytic agents. Acute pulmonary embolus in haemodynamically unstable patients, or in those requiring thrombolysis or pulmonary embolectomy*. Myocardial infarction. Concomitant administration with: acetylsalicylic acid, NSAIDs, clopidogrel, unfractionated heparins and heparin derivatives, low molecular weight heparins, fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, ticagrelor, vitamin K antagonists, selective serotonin re-uptake inhibitors, selective serotonin norepinephrine re-uptake inhibitors, P-gp inhibitors: amiodarone, verapamil, tacrolimus, ritonavir, tipranavir, nelfinavir, saquinavir, quinidine, clarithromycin, P-gp inducers. Surgical interventions may require temporary discontinuation and anticoagulant monitoring is warranted; clearance in patients with renal impairment may take longer. Not recommended in patients undergoing hip fracture surgery. DVT/PE patients with active cancer*. Pregnancy (Category C). Lactation. Children. Patients < 50 kg. See full PI. INTERACTIONS: See CONTRAINDICATIONS and PRECAUTIONS. ADVERSE EFFECTS: Bleeding and signs of bleeding, dyspepsia, gastritis-like symptoms, diarrhoea, nausea, vomiting, constipation, flatulence, dysphagia, nasopharyngitis, dyspnoea, cough, dyspnoea exertional, upper respiratory tract infection, bronchitis, pneumonia, influenza, sinusitis, urinary tract infection, dizziness, headache, syncope, insomnia, atrial fibrillation, cardiac failure congestive, cardiac failure, palpitations, angina pectoris, hypertension, hypotension, rash, gout, arthralgia, back pain, pain in extremity, osteoarthritis, musculoskeletal pain, muscle spasms, oedema peripheral, fatigue, asthenia, chest pain, chest discomfort, fall, abnormal liver function tests. Less common adverse reactions see full PI. DOSAGE AND ADMINISTRATION: Assess renal function (Cockcroft-Gault method) prior to treatment initiation, in clinical situations that could lead to renal function decline and at least once a year in patients ≥ 75 years or with moderate renal impairment. Swallow capsule whole with water, with or without food. Recommended dose: 300 mg (one 150 mg capsule twice daily). following treatment with a parenteral anticoagulant for at least 5 days. For duration of therapy, see full PI.* Age ≥ 75 years: reduced dose of 220 mg (one 110 mg capsule twice daily). Moderate renal impairment, higher risk of bleeding: reduced dose of 220 mg (one 110 mg capsule twice daily) may be considered. Special populations see full PI. August 2015. Pradaxa® is a registered trademark of Boehringer Ingelheim Pty Limited, ABN 52 000 452 308, 78 Waterloo Road, North Ryde NSW 2113. AUS/PRA-151512. S&H BOIPX0015 November 2015.

*Please note changes in Product Information.

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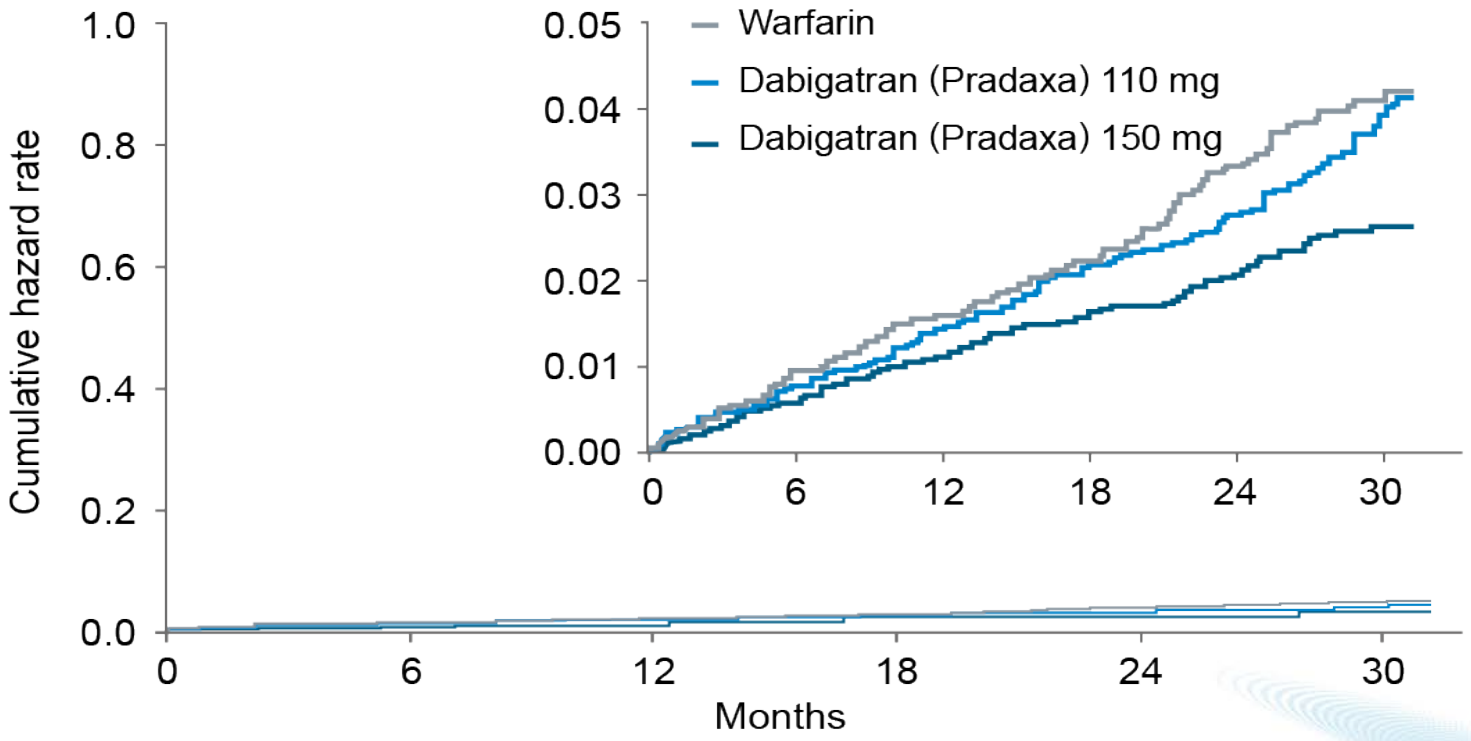
APPENDIX

RE-LY study: stroke prevention

CUMULATIVE HAZARD RATES FOR STROKE OR SYSTEMIC EMBOLISM ACCORDING TO TREATMENT GROUP[1]



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Pradaxa 110 mg	6015	5862	5710	4593	2945	1385
Pradaxa 150 mg	6076	5939	5779	4682	3044	1429

Adapted from Connolly SJ, *et al.* 2009.[1]

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Reference: 1. Connolly SJ, *et al. New Engl J Med.* 2009; 361(12): 1139–1151.

Bleeding management

MANAGEMENT OF BLEEDING IN PRADAXA-TREATED* PATIENTS: ASTH GUIDELINES†[1]

- Initiate standard resuscitation; and
- Take blood.

STOP Treatment

Mild bleeding

- Local haemostatic measures; and
- Delay next dose of NOAC.

Clinically significant bleeding

- Oral charcoal if <2 hours since ingestion
- Local haemostatic measures.
- Maintain adequate hydration.
- Transfusion support:

Red cell transfusion if indicated;
Platelet transfusion if platelets < 50 x 10^9/L; and
Use FFP if concerned about dilutional coagulopathy.

- Consider pro-haemostatic agent if bleeding persists.

Life threatening bleeding

- As per clinically significant bleeding;
- Consider use of PCC, FEIBA, tranexamic acid; and
- Consider haemodialysis.

Adapted from Tran H, *et al.* 2014.[1]

*Please review the full Approved Product Information before prescribing Pradaxa. †Recommendation based on limited non-clinical data; ASTH= Australian Society of Thrombosis and Haemostasis; NOAC=new oral anticoagulants; FFP=fresh, frozen plasma; PCC=prothrombin complex; FEIBA=Factor VIII inhibitor bypassing fraction.

Reference: 1. Tran H, *et al. Int Med J.* 2014; 44: 525-536.

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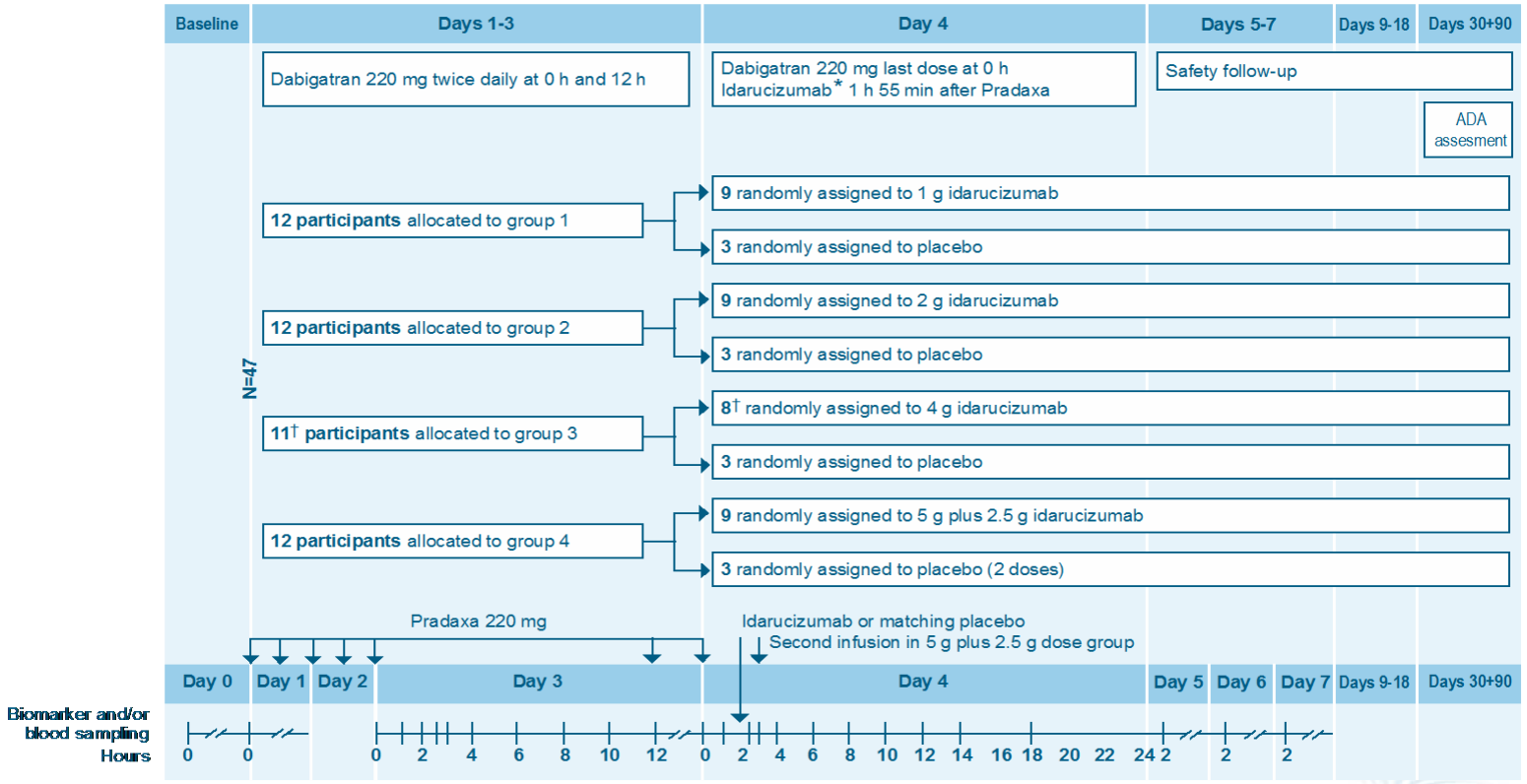
Phase I: healthy volunteers

STUDY DESIGN SCHEMA[1]



Adapted from Glund S, *et al.* 2015.[1]

- Part 1 of the study was a dose escalation assessment, followed by Part 2, a dose-finding/proof of concept study.[1]

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. ADA=antidrug antibodies; idarucizumab was administered as one 5-min infusion (1 g, 2 g, 4 g dose groups), or as two 5-min infusions 1 h apart (5 g plus 2.5 g dose group); †The authors had planned to recruit nine participants to this group, but due to recruitment difficulties only eight were enrolled.

Reference: 1. Glund S, *et al. Lancet.* 2015; 386(9994): 680–690.

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Mortality data

SERIOUS ADVERSE EVENTS LEADING TO DEATH[1]

Age/gender	Group	Serious adverse event that led to death	Days from treatment to death
82/F	B	Cardiac arrest	<1
93/M	B	Circulatory collapse	<1
88/F	B	Haemodynamic collapse	<1
87/F	B	Septic shock	1
60/M	B	Sepsis and shock, GI bleed	1
60/M	A	Respiratory failure progression	1
77/M	A	Intracranial haemorrhage new	1
69/M	A	Intracranial haemorrhage progression	2
87/M	B	Multi-organ failure	2
69/M	A	Intracranial haemorrhage progression	4
83/F	A	Pulmonary oedema	11
78/F	B	Cardiac arrest	21
72/F	B	Ischaemic stroke	26
73/M	A	Congestive heart failure	30
80/M	A	Parkinson's disease	43
83/M	A	General health deterioration	42
86/F	A	Pneumonia	94
80/M	B	Progression of malignancy	101

Adapted from Pollack CV, *et al.* 2015.[1]

Pollack *et al.* 2015

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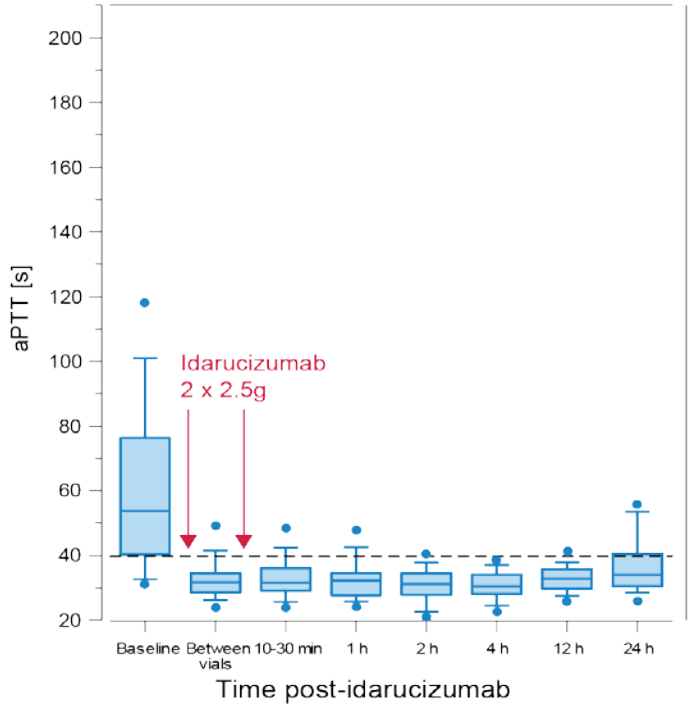
Reference: 1. Pollack CV, *et al. N Engl J Med.* 2015; 373(6): 511–520.

RE-VERSE AD: results

Activated Partial Thromboplastin Time (aPTT)[1]

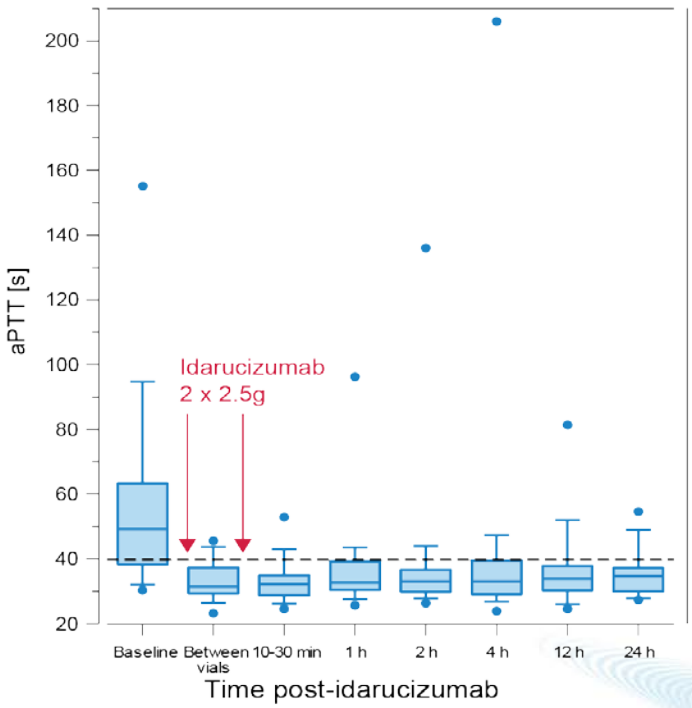
Group A:
Patients with uncontrolled bleeding (N=51)

A



Group B:
Patients undergoing emergency procedures (N=39)

B



A normal aPTT does not always exclude dabigatran presence and should be conducted with a standard TT test[2,3].

Pollack *et al.* 2015

Boehringer Ingelheim

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia. TT=thrombin time

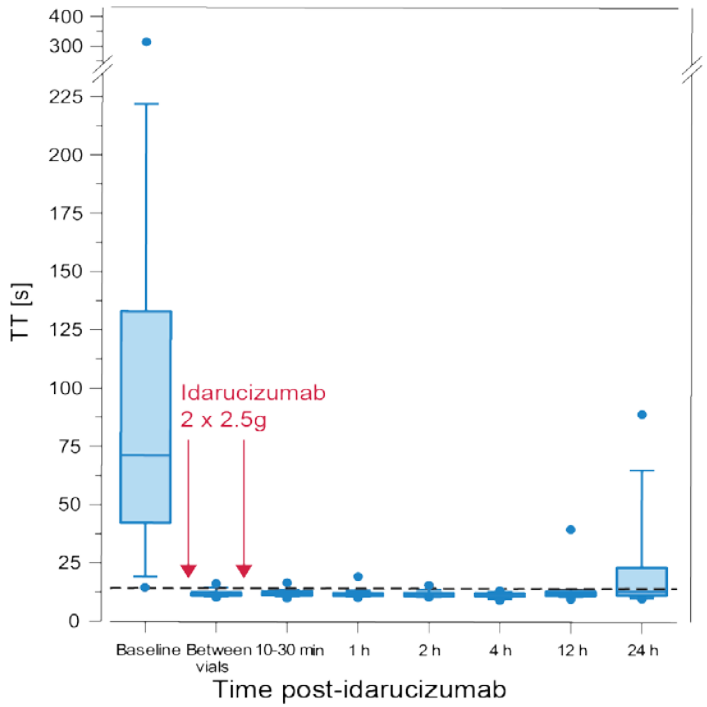
References: 1. Pollack CV, *et al. New Engl J Med.* 2015; 373: 511–520. 2. van Ryn J, *et al. Thromb Haemost.* 2010; 103(6): 1116-1127. 3. Favaloro EJ, Lippi G. *Semin Thromb Hemost.* 2015; 41(2): 208–227.

RE-VERSE AD: results

Thrombin Time (TT)[1]

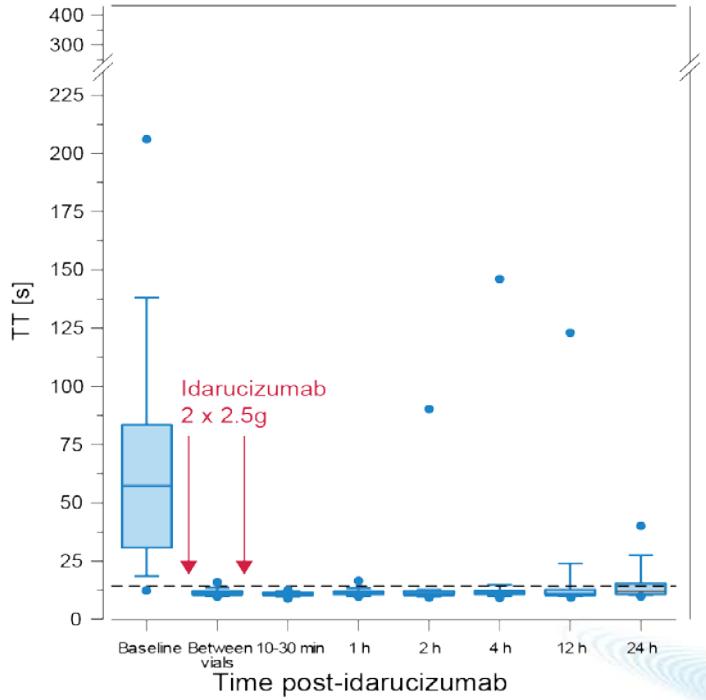
C

Group A:
Patients with uncontrolled bleeding (N=51)



D

Group B:
Patients undergoing emergency procedures (N=39)



A normal TT test excludes the presence of dabigatran.
A prolonged TT confirms the presence of dabigatran[2,3].

Pollack *et al.* 2015

Boehringer Ingelheim

*Please note as of the publication of this resource, the Therapeutic Goods Administration (TGA) has not registered idarucizumab for use in Australia.

References: 1. Pollack CV, *et al. New Engl J Med.* 2015; 373: 511–520. 2. van Ryn J, *et al. Thromb Haemost.* 2010; 103(6): 1116-1127. 3. Favaloro EJ, Lippi G. *Semin Thromb Hemost.* 2015; 41(2): 208–227.