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What's new in atrial fibrillation?

A report from the Big Picture Meeting, Stellenbosch, March 2020

Introduction

The evidence from clinical trials of DOACs, starting with the results of the RE-LY trial announced some 10 years ago, is increasingly being supplemented by clinical practice data from international and local registries. The inclusion of patients' data in registries has improved overall ease-of-recruitment in clinical trials and reduced the costs of obtaining relevant data. This is because patients entered into registries give informed consent that their clinical data can be used anonymously. This has also increased the importance of registries, such as the Global Registry on Long-Term Oral Anti-thrombotic treatment in patients with Atrial Fibrillation (GLORIA-AF), in interpreting clinical practice.

These registries spotlight clinically important issues that should be the focus of ongoing education and experience-sharing among clinicians. These include underdosing in general and particularly in elderly and frail patients, adherence to therapy, and anticoagulation strategies during interventions such as cardioversion and ablation.

LEARNING OBJECTIVES

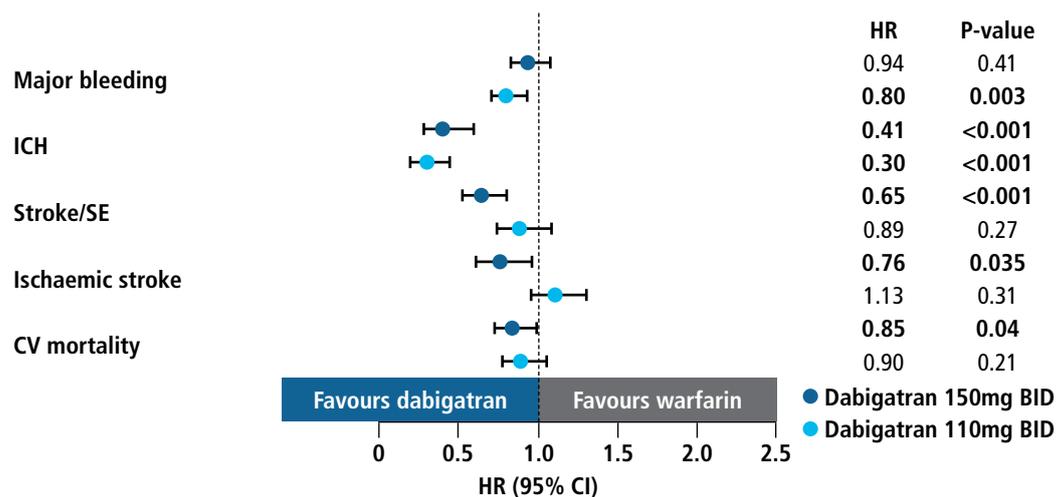
You will learn:

- To translate the latest trial and real-world data on direct oral anticoagulant (DOAC) therapy into daily clinical practice
- To evaluate and treat vulnerable groups, such as the elderly, frail and those with renal insufficiency, with adequate DOAC dosing
- How interventions such as cardioversion and ablation should/should not modify coagulation therapy
- To manage bleeding risks and bleeding events in patients on DOACs.

Reviewing the RE-LY trial and today's clinical practice

It is useful to return to the initial RE-LY trial results to assess these data in the light of current medical practice. The efficacy and safety of dabigatran was established in the RE-LY trial of dabigatran vs INR-adjusted warfarin and, importantly,

showed that the difference in bleeding, particularly intracranial haemorrhage, was not that different between the two, regardless of whether the 110mg bid or the 150mg bid dose was used (Figure 1).¹



Bold values indicate statistical significance; SE, systemic embolism embolism; ICH, intracranial haemorrhage

Figure 1. The efficacy and safety of dabigatran vs INR-adjusted warfarin was established in the RE-LY trial

In the context of preventing ischaemic stroke, the 150mg dose of dabigatran was shown to be very effective, with a hazard ratio of 0.65. “Taking the similar bleeding risk but efficacy difference of the two doses into account, underdosing at 110mg bid in patients who qualify for the higher dose (<80 years and HAS-BLED score <3) reduces stroke prevention capability and is usually not clinically warranted,” Professor Huisman warned.

A *post hoc* analysis from RE-LY supported the EU approach to dose selection (also followed in South Africa), when the EU-label dabigatran dosing choice was used in simulation; these results compared favourably to the overall RE-LY results, showing support for this approach, which

is also advocated by the European Society of Cardiology (2012).²

Underdosing of all DOACs in clinical practice is common, including with the FXa inhibitors, rivaroxaban and apixaban. According to the Institute for Healthcare Informatics, USA, underdosing occurs more commonly than might be expected from phase III trials. This is especially true for the FXa inhibitors (Figure 2). “We need to be very careful when we give a reduced dose of any DOAC that we are not inappropriately reducing the dose, particularly in younger patients with lower bleeding risk scores, as was seen in practice data from the ORBIT-AF II registry in the USA.”³

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Professor Huisman

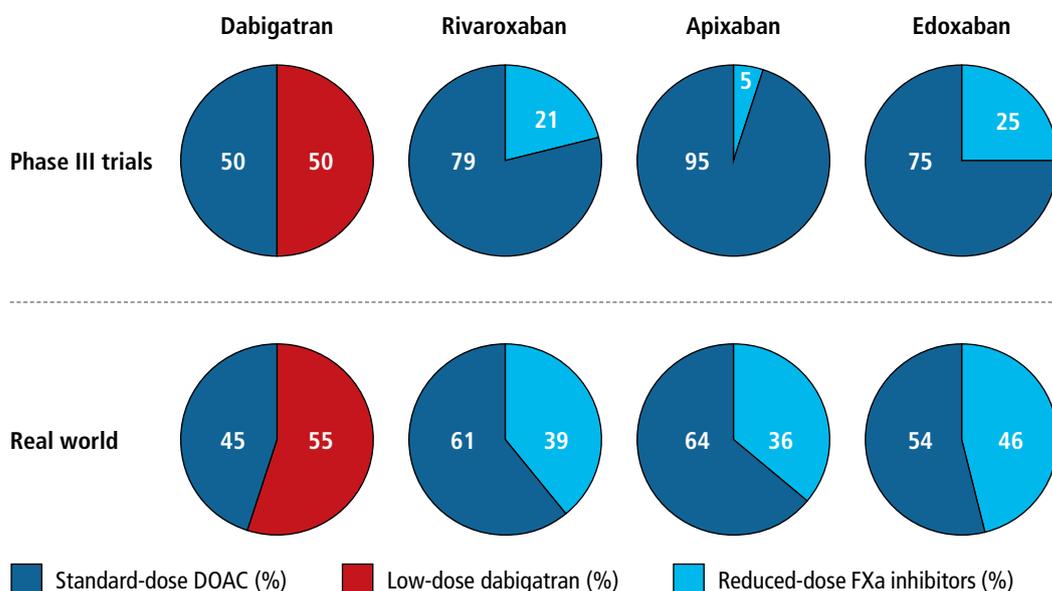


Figure 2. Use of reduced FXa inhibitor doses may be more common in practice than would be expected based on phase III trials

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Evaluating real-world data

The best real-world data come from prospective registries with pre-defined clinical pathways, rather than retrospective data that come from large insurance claim databases. In this regard, GLORIA-AF provides prospectively collected, real-world information on dabigatran,

including from South Africa. Its objectives are summarised in Table 1. Patients were eligible for GLORIA-AF recruitment if they were older than 18 years, newly diagnosed with non-valvular AF and had a CHA₂DS₂-VASc score ≥1.

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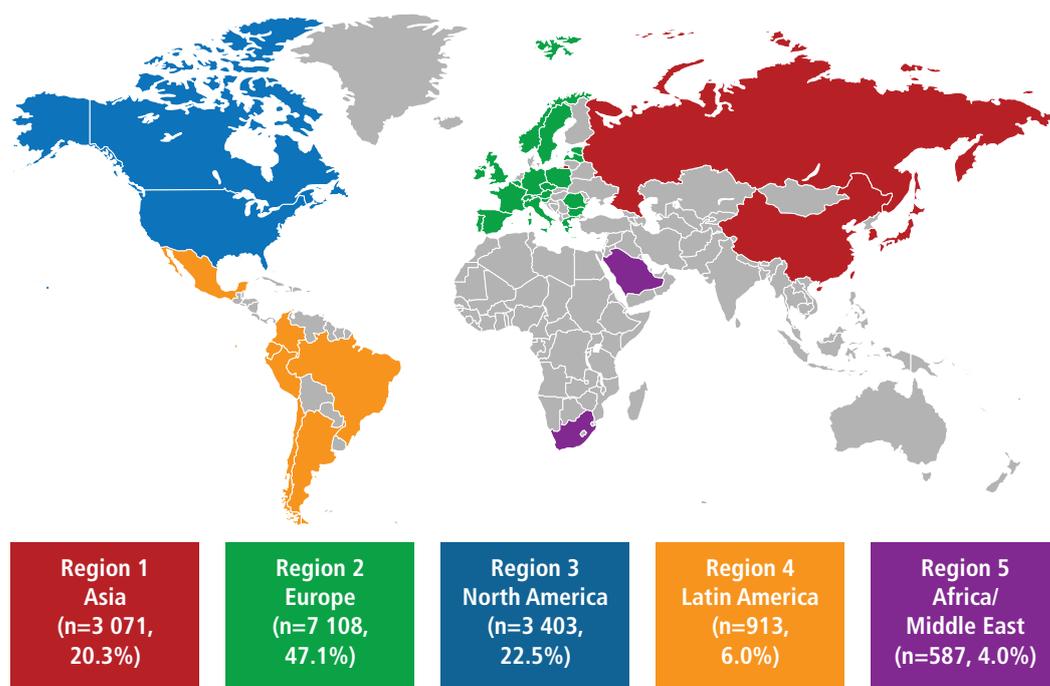
1	To characterise patients newly diagnosed with non-valvular AF at risk of stroke in various regions of the world
2	To describe patterns of antithrombotic treatment for stroke prevention in patients with newly diagnosed non-valvular AF
3	To collect data on the effectiveness and safety of DOACs compared with vitamin K antagonists (warfarin) during routine patient care

A phase II study that evaluated a two-year follow-up of dabigatran therapy included patients at high-risk of stroke with a range of AF types, typical of clinical practice (Figure 3). The patients in GLORIA-AF are similar to those recruited in the RE-LY study, but with a tendency to include healthier patients,

a feature typical of most registries. Examining these data, it is concerning that in some areas of the world, particularly Asia, some 20% of patients did not receive any anticoagulation; in all other regions, more patients received a DOAC than a vitamin K antagonist.

Final phase II baseline analysis included

15 092 patients
(enrolled Nov 2011–Dec 2014)



Care setting: University hospital, 33.7%; specialist office, 30.3%; community hospital, 26.3%; primary care, 6.4%; outpatient or anticoagulation clinic, 2.5%; other, 0.8%

Figure 3. GLORIA-AF phase II enrolled >15 000 patients

Adherence is a problem

The probability of AF patients discontinuing DOAC treatment at two years has been shown to be in the region of 70%. Some countries have achieved better results, such as the Netherlands, where real-world data have shown that 60% of patients continue to take their therapy up to two years, while 40% ceased therapy despite their stroke risk remaining high.

Within the GLORIA-AF phase II trial, stroke and bleeding rates were lower than

in the comparable EU label analysis of RE-LY, reflecting perhaps the natural tendency of registries to recruit healthier patients. The results of the phase III GLORIA-AF study, reflecting the three-year follow-up of all enrolled patients will be presented in late 2020. "It is vital that clinicians remind and encourage their patients to continue taking their medication," Professor Huisman stressed.

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Professor Huisman

Continuing DOAC therapy or not during ablation?

"There are now good data available supporting the continued use of DOACs during ablation procedures." Two clinical trials have shown that either dabigatran or apixaban offer a good alternative to uninterrupted warfarin/non-vitamin K antagonism (Figure 4).

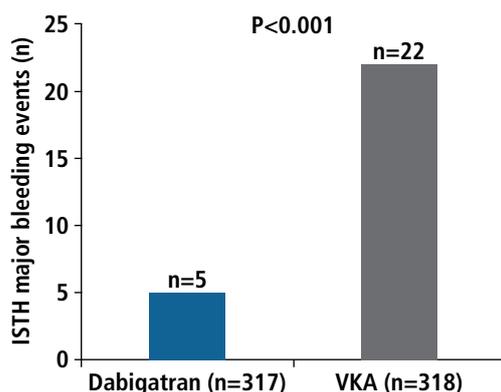
In the RE-CIRCUIT trial,⁴ a randomised, open-label, multicentre controlled trial with blinded end-point assessment, 600 patients underwent ablation while continuing treatment with either dabigatran (150mg bid) or

warfarin, targeting an INR of 2-3. The incidence of major bleeding events during and up to eight weeks post-ablation was lower with dabigatran than warfarin, while minor bleeding events were similar on both treatments. One thromboembolic event occurred in the warfarin-treated group and none in the dabigatran-treated group. Apixaban has also been shown to be safe and effective in respect of bleeding, stroke and cognitive functioning in a study of a similar number of patients undergoing ablation.⁵

RE-CIRCUIT

N=635

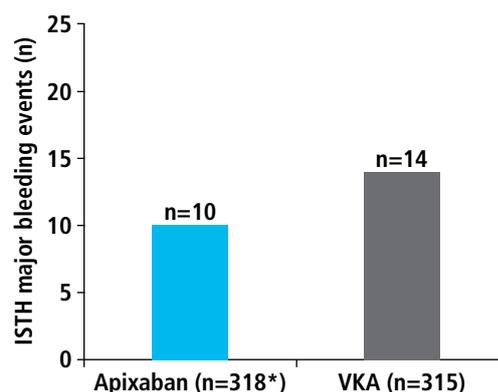
Bleeding events during and up to 60 days after ablation



AXAFA-AFNET 5

N=633

Bleeding events from randomisation to 90 days after randomisation



No inter-study comparisons can be made

*Apixaban dosing 5mg BID (n=317); 2.5mg BID (n=1), Dabigatran 110mg BID

Figure 4. Ablation: 150mg dabigatran demonstrated significant risk reduction in major bleeding events vs warfarin; apixaban 5mg did not demonstrate such a risk reduction vs warfarin^{4,5}

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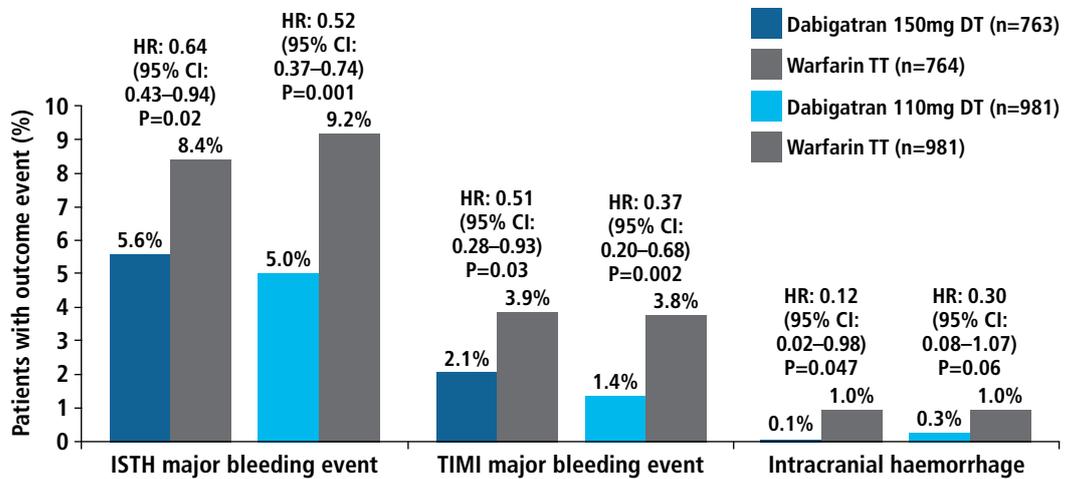
Anticoagulation post-PCI in AF patients

There are now good data available supporting the continued use of DOACs during ablation procedures

Triple antithrombotic therapy has been the standard of care after percutaneous coronary intervention (PCI), but it is associated with a high risk of bleeding. The RE-DUAL PCI study compared dabigatran 110mg or 150mg bid plus a P2Y₁₂ inhibitor to triple therapy with warfarin, a P2Y₁₂ inhibitor and aspirin. Outside the USA, dabigatran 110mg was used in elderly patients (≥80 years of age; ≥70 years in Japan) as the comparator dose. The primary endpoint was a major or a clinically relevant, non-major bleeding event during follow-up of 14 months. The RE-DUAL PCI trial results favoured dabigatran use in AF patients with acute

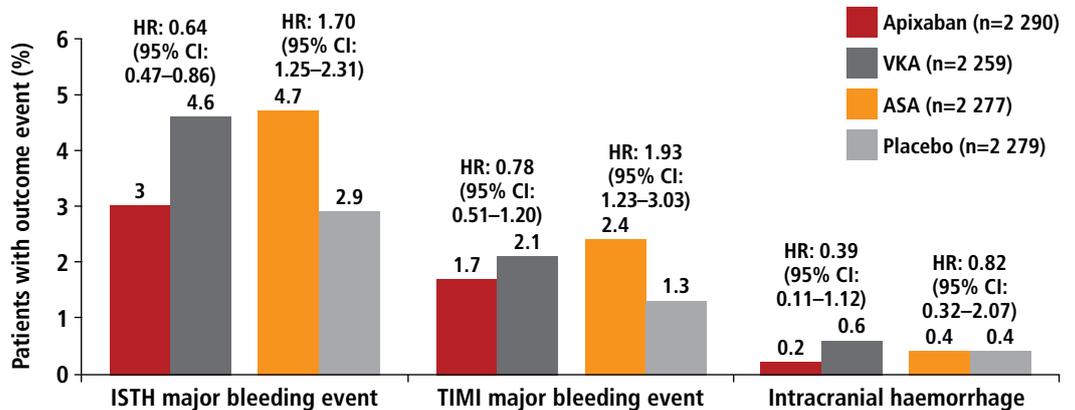
coronary syndrome and/or undergoing PCI, as equally the AUGUSTUS trial favoured the use of apixaban (Figures 5 and 6) in a dual-therapy approach.^{7,8}

Subsequent analysis of the RE-DUAL PCI trial with regard to the super elderly (<75 versus >75 years) showed a higher risk of thromboembolic events with dabigatran 110mg in the older patients compared to those younger than 75 years. The 150mg dose in the >75-year-old patients did not lower overall bleeding risk.⁹ This age differentiation may be helpful in dose selection of dabigatran dual therapy in the patients older than 75 years.



ISTH major bleeding definition: fatal, critical organ (including ICH), clinically overt bleeding with fall in haemoglobin >2g/dL; TIMI major bleeding definition: fatal, ICH, clinical overt bleeding with fall in haemoglobin >5g/dL. DT, dual therapy; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis in Myocardial Infarction; TT, triple therapy

Figure 5. RE-DUAL PCI: significantly lower rates of ISTH and TIMI major bleeding for dabigatran DT vs warfarin TT



Overall, 1 097 patients (23.9%) did not undergo PCI. ASA, acetylsalicylic acid; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis in Myocardial Infarction

Figure 6. AUGUSTUS: lower rates of ISTH major bleeding or CRNM (not major) bleeding events with apixaban vs vitamin K antagonist, and placebo vs ASA

Bleeding management on DOAC therapy

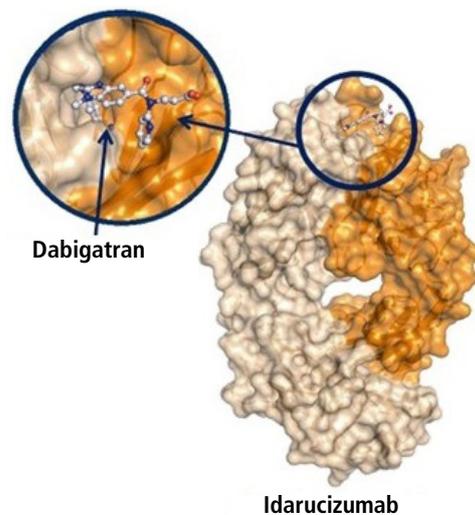
The incidence of major bleeding on DOAC therapy is estimated to be around 4% per year; 0.6-1% of patients will need a reversal agent, as evaluated by the

responsible clinician. “This is, of course, not an insignificant figure as approximately 8-10% of major bleeding events lead to death.”

Specific reversal agent for dabigatran

Idarucizumab*, the specific reversal agent for dabigatran, is widely available and easy to use; although not yet available in every hospital in South Africa. It ensures immediate and sustained reversal of the anticoagulant effect of dabigatran when needed and is easily given as a fixed intravenous 5g dose (two vials of 2.5g) (Figure 7).⁹ It is used mainly in the context of emergency surgery or an urgent intervention, and occasionally to reverse life-threatening or uncontrolled bleeding. Dabigatran

can be restarted after 24 hours, but in the event of a major intracranial bleed, it should only be reintroduced much later. “We must understand that patients experiencing a major bleeding event are often very fragile and elderly (>75 years). The complications sometimes seen after use of a reversal agent are due to the fragility of patients, rather than any effect of the reversal agent itself, as idarucizumab is remarkably safe to use.”



- Humanised antibody (Fab) fragment
- Specific to dabigatran
- Binding affinity for dabigatran ~350× higher than dabigatran thrombin, resulting in essentially irreversible binding
- Ready to use solutions for IV administration, immediate onset of action
- No intrinsic procoagulant or anticoagulant activity
- No endogenous targets
- Idarucizumab–dabigatran complex is eliminated quickly (within a few hours)

Figure 7: Clinical features of idarucizumab, the reversal agent for dabigatran

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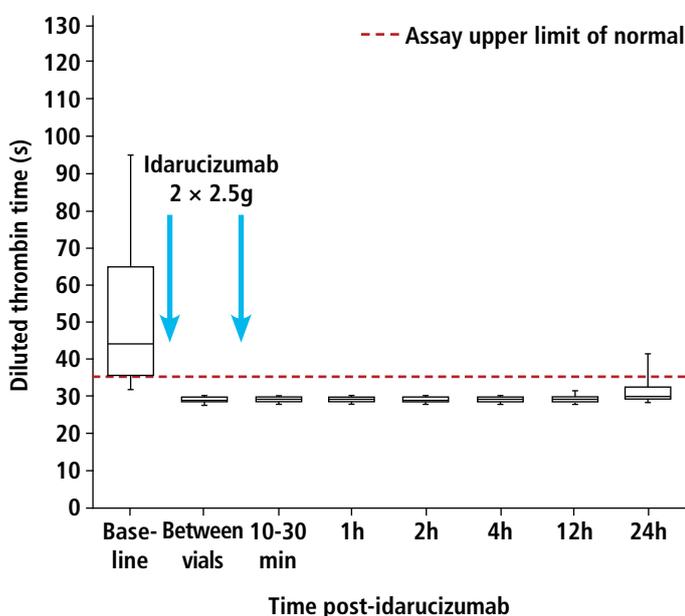
*Idarucizumab was approved for use in South Africa in December 2019

Reversal agent for Factor Xa inhibitors

Andexanet alfa is a decoy factor X, and acts by competitively binding with FXa inhibitors, low-molecular-weight heparins, unfractionated heparin and fondaparinux. "Different doses of the reversal agent are needed for apixaban and rivaroxaban, complicating clinical use." Andexanet alfa is approved in the USA and Europe for patients treated with apixaban or rivaroxaban (but not yet for edoxaban). As andexanet alfa has similar binding affinities to FXa, it leads to only temporary inactivation of the FXa inhibitors, limiting its potential for a sustained effect.

Idarucizumab, on the other hand, has been shown to provide immediate, complete and sustained reversal of dabigatran in healthy volunteers while andexanet alfa's effect was not sustained beyond the two-hour infusion. In the RE-VERSE AD trial of idarucizumab,¹⁰ a wide group of patients representative of clinical practice was included: patients needing urgent surgery, patients with a recent history of thrombotic events, severe sepsis or who had received a prior vitamin K antagonist, recombinant Factor VIIa or blood plasma in the previous seven days (Figure 8).

Group A: Uncontrolled bleeding



Group B: Emergency surgery or procedure

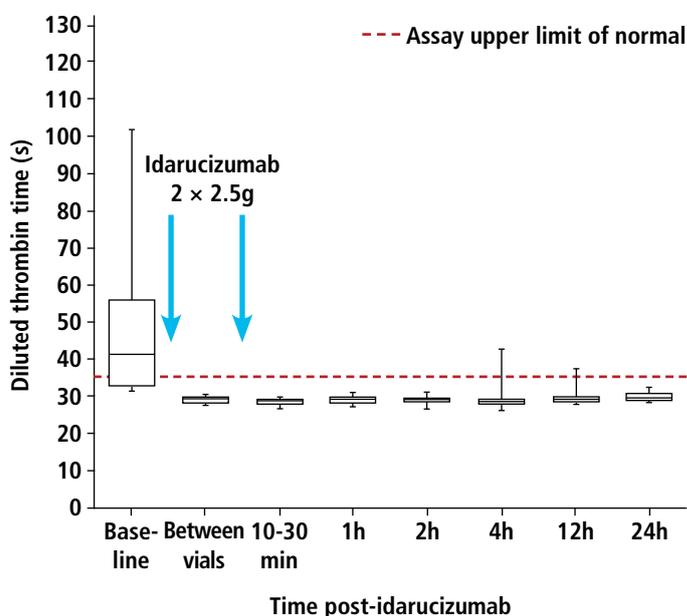


Figure 8. RE-VERSE AD™ interim results: idarucizumab provided immediate reversal of dabigatran in patients with bleeding or requiring surgery

In summary, idarucizumab is easy to administer and has no contraindications. It can be infused intravenously (5g given in two doses as a consecutive intravenous infusion over 5-10 minutes each) or injected intravenously as a 5g dose given in two separate consecutive bolus injections. Importantly, idarucizumab can be used alongside other supportive therapy

and allows for anticoagulation to be resumed soon after administration.

Additional Reading: A useful guide to the stopping and re-initiation of non-vitamin K antagonist oral anticoagulant therapy in elective surgery in patients with AF was recently issued by the European Rhythm Association.¹¹

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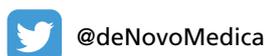
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KEY LEARNINGS

- Underdosing of all DOACs in clinical practice is common; it is important not to inappropriately reduce doses, particularly in younger patients with lower bleeding risk scores
- Adherence to DOACs is problematic; at two years, approximately 70% of AF patients have discontinued treatment
- Data supports the continued use of DOACs during ablation procedures. In older AF patients (>75 years) having undergone PCI, a higher risk of thromboembolic events was seen with dabigatran 110mg bid, as compared to 150mg bid
- Idarucizumab, a specific reversal agent against dabigatran, has been registered for use in South Africa in December 2019.

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