

“Sick days”, renal failure and the need for dabigatran toxicity reversal

Cashman H.¹, Banaczek P.², Roberts D.^{3,4}, Welch S.², Joseph J.¹.

1. Haematology Department St. Vincent's Hospital Sydney, 2. Pharmacy Department St. Vincent's Hospital Sydney, 3. Clinical Pharmacology & Toxicology St. Vincent's Hospital Sydney, 4. NSW Poisons Information Centre, Sydney Children's Hospital Network

Contact: patricia.banaczek@svha.org.au

Background

- Idarucizumab is a humanized monoclonal antibody fragment that is indicated for the reversal of dabigatran¹.
- Idarucizumab binds to both bound and unbound dabigatran with a higher affinity of ~350-fold compared to that of dabigatran for thrombin¹.
- Idarucizumab to dabigatran interaction is characterized by a rapid on-rate (milliseconds) with a very slow off-rate, which is consistent with high-affinity binding¹.
- Many studies have shown that even with the use of Idarucizumab, early intervention with renal replacement therapy can facilitate dabigatran clearance in the setting of AKI^{1,2}.
- “Sick days” or acute illness can increase the risk of adverse drug events caused by the changes to physiology and pharmacokinetics, even requiring dose adjustments during prolonged illness³.

Objective

To report a case of rebound dabigatran levels after idarucizumab reversal in a patient with acute kidney injury.

Clinical Features

64-year-old male with acute onset right-sided weakness and facial droop associated with abdominal pain, vomiting, hypotension and profuse diarrhoea.

His medical history included atrial fibrillation on amiodarone and dabigatran (110mg twice daily), congestive heart disease on furosemide, metoprolol, ramipril and rosuvastatin.

Admission blood tests noted coagulopathy: thrombin time >200 seconds [range 10-12], prothrombin time 131 seconds [range 11-15], activated partial thromboplastin time 145 seconds [range 25-35] and INR 11.2.

Dabigatran anti-IIa level was 2230ng/mL [range 30-130]. Creatinine was, 209umol/L [range 60-100] consistent with acute kidney injury (AKI).

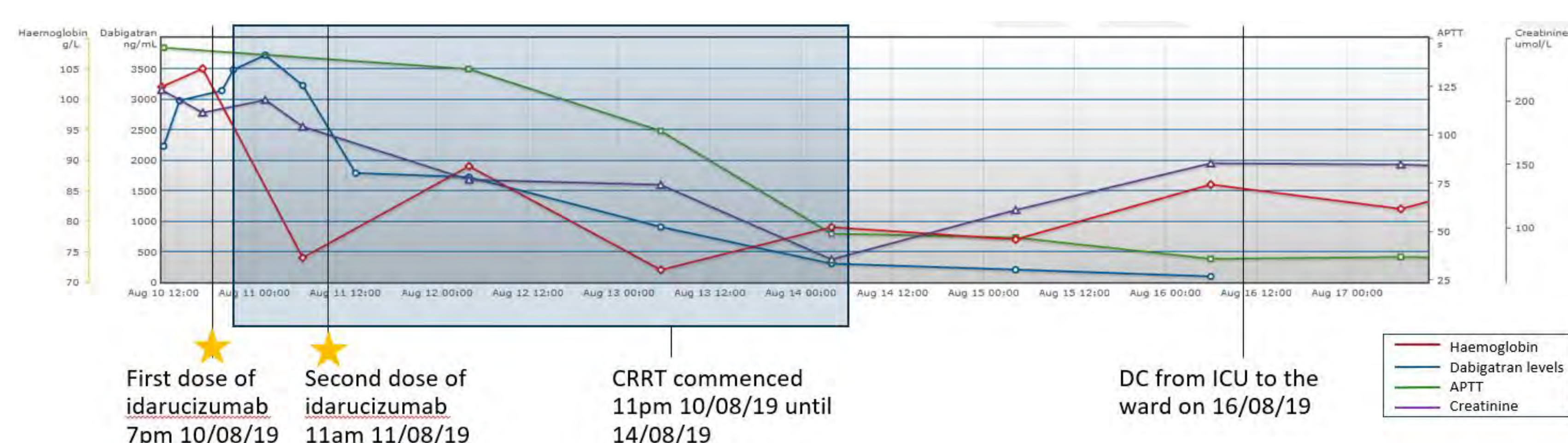


Figure 1: Graph comparing the patient's dabigatran levels, haemoglobin and APTT prior to and after clinical intervention of idarucizumab and CRRT, along with changes to creatinine levels

Literature Review

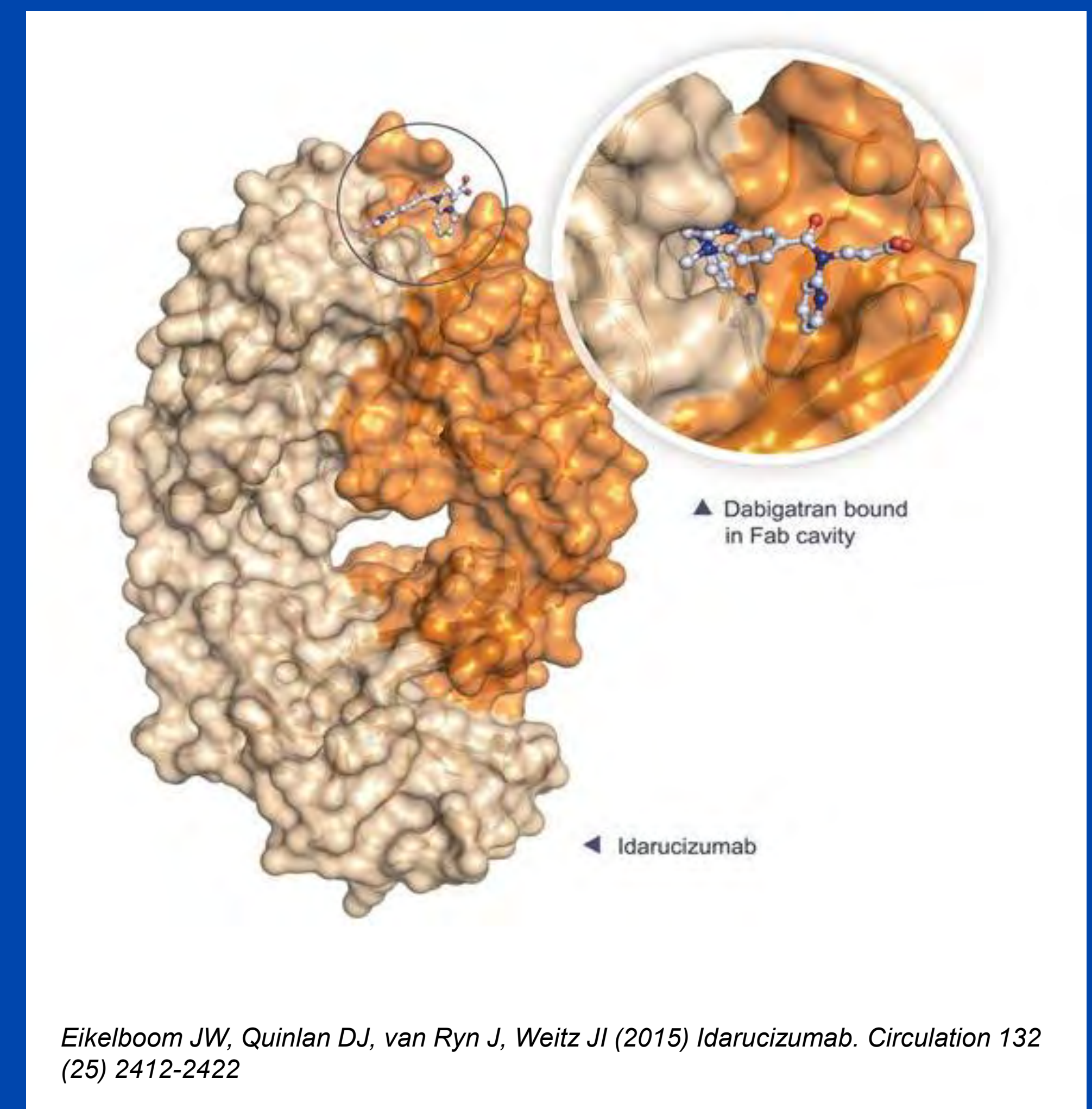
In the RE-LY trial, full reversal of dabigatran was achieved. Recent studies have suggested that idarucizumab efficacy may be reduced with extremes of kidney function⁴. Risks for dehydration and AKI include vomiting, diarrhoea and other medications. AKI reduces dabigatran clearance, leading to accumulation and toxicity.

Action plans and guidance cards for “sick days” have been used in similar settings for withholding medications including GLP-1 receptor agonists, metformin and diuretics to prevent adverse events⁵. A recent review did not provide guidance on dabigatran adjustments⁶.

Pharmacist Interventions, Case Progress and Outcomes

Coagulopathy persisted after 5g idarucizumab. Pharmacists, haematologists and intensivists assessed the requirements for a second dose of idarucizumab and the use of continuous renal replacement therapy (CRRT) for persistent dabigatran toxicity.

CRRT was commenced and repeat idarucizumab dose was given resulting in patient recovery. Prior to discharge the suitability of ongoing dabigatran therapy was discussed (Figure 1).



Discussion

Dabigatran-induced coagulopathy can persist after idarucizumab due to a high initial concentration and/or redistribution from the extravascular compartment (Figure 2)¹.

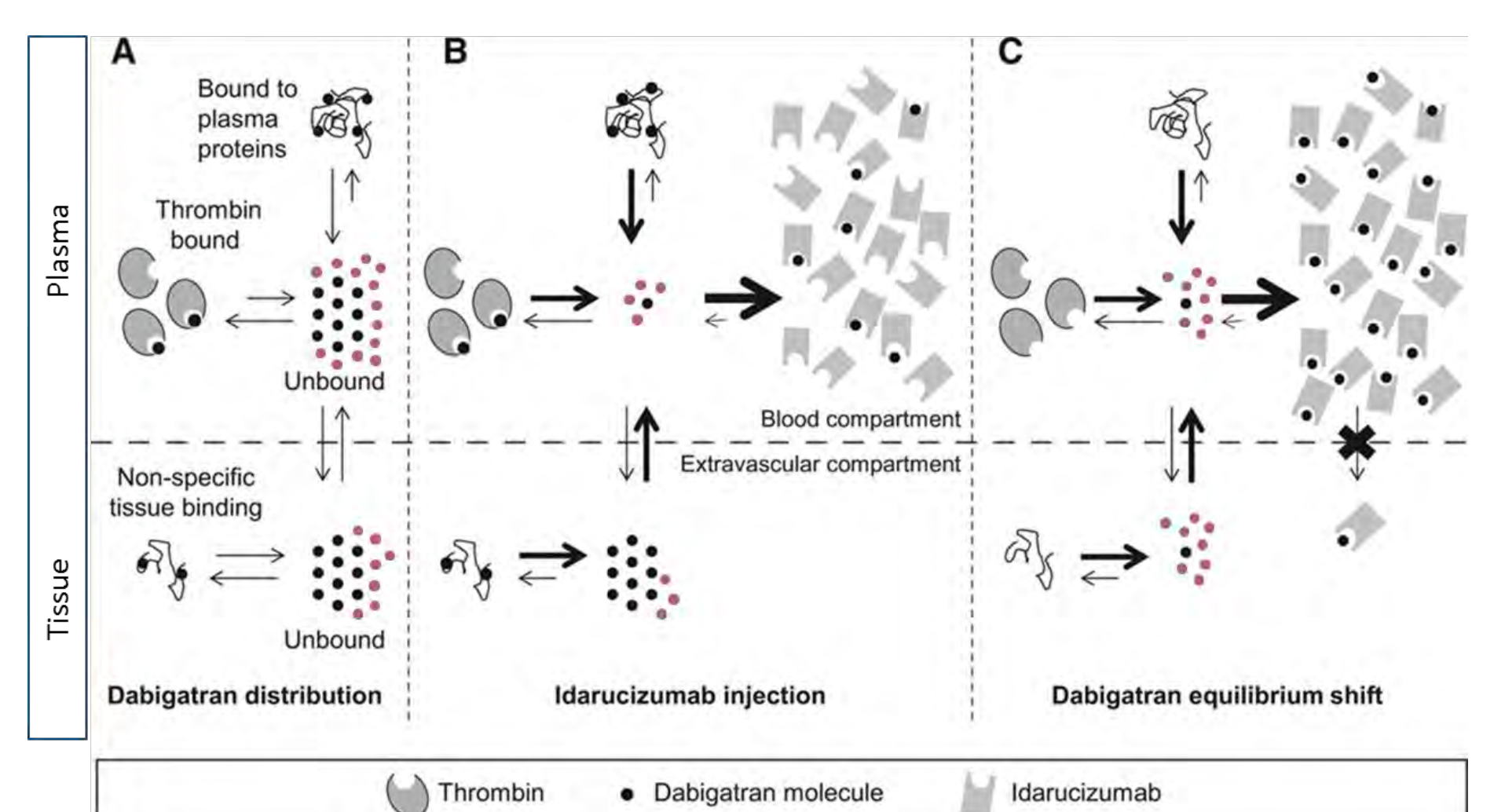


Figure 2: Changes in the distribution of dabigatran after idarucizumab administration¹

As this case suggests, idarucizumab reversal of dabigatran is complex and requires frequent monitoring of laboratory results. CRRT may be required for significantly elevated dabigatran levels. Further work is required to develop patient guidance on modifying dabigatran on “sick days” to prevent toxicity.

Acknowledgements

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