Clinical Practice Guideline:
What is the role of reversal agents in the management of ED patients with dabigatran-associated hemorrhage?

References and Literature Grading

1. Schiele F, et al. A specific antidote for dabigatran: functional and structural characterization. *Blood* 2013;121(18):3354-62.
2. Eerenberg ES, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;124(14):1573-9.
3. Marlu R, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers. *Thromb Haemost* 2012;108(2):217-24.
4. Arellano-Rodrigo E, et al. Coagulation Factor Concentrates Fail to Restore Alterations in Fibrin Formation Caused by Rivaroxaban or Dabigatran in Studies With Flowing Blood From Treated Healthy Volunteers. *Transfus Med Rev* 2015;29(4):242-9.
5. Glund S, et al. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. *Thromb Haemost* 2015;113(5):943-51.
6. Glund S, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. *Lancet* 2015;386(9994):680-90.
7. Pollack CV Jr, et al. Design and rationale for RE-VERSE AD: A phase 3 study of idarucizumab, a specific reversal agent for dabigatran. *Thromb Haemost* 2015;114(1):198-205.
8. Pollack CV Jr, et al. Idarucizumab for Dabigatran Reversal. *N Engl J Med* 2015;373(6):511-20.
9. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Br Med J* 2008;336:924-6.

Article Grading
Search terms: dabigatran reversal
Tier 1: 17 (3 relevant)
Tier 2: 2
Tier 3: 4
Tier 4: 7
Tier 5: 161

Systematic Reviews (Tier 1)

Yogaratnam D, et al. Idarucizumab for reversal of dabigatran. Ann Pharmacother 2016. Epub ahead of print]

Thibault N, et al. Idarucizumab for reversing dabigatran-induced anticoagulation: a systematic review. Am J Ther 2016. Epub ahead of print.

Frontera JA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care. 2016 Feb;24(1):6-46.

RCTs (Tier 2)

Glund S, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. Lancet. 2015 Aug 15;386(9994):680-90.

Eerenberg ES, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011 Oct 4;124(14):1573-9.

Tier 3

Glund S, et al. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. Thromb Haemost. 2015 May;113(5):943-51.

Marlu R, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers. Thromb Haemost. 2012 Aug;108(2):217-24.

Tier 4

Pollack CV Jr, et al. Idarucizumab for Dabigatran Reversal. N Engl J Med. 2015 Aug 6;373(6):511-20.

Arellano-Rodrigo E, et al. Coagulation Factor Concentrates Fail to Restore Alterations in Fibrin Formation Caused by Rivaroxaban or Dabigatran in Studies With Flowing Blood From Treated Healthy Volunteers. Transfus Med Rev. 2015 Oct;29(4):242-9.

Pollack CV Jr, et al. Design and rationale for RE-VERSE AD: A phase 3 study of idarucizumab, a specific reversal agent for dabigatran. Thromb Haemost. 2015 Jul;114(1):198-205.

Search terms: dabigatran bleeding

Tier 1: 216
Tier 2: 20 (1 relevant, already included in other search)
Tier 3: 45 (no additional relevant articles)
Tier 4: 56 (2 additional relevant articles, already included in other search)

Publications	**Grade**	**Quality**	**Comments**
Yogaratnam D, et al. Ann Pharmacother 2016.	F	Good	This is a review of the key trials that let to idarucizumab's FDA approval. The authors nicely describe their methods but they did not perform a meta-analysis.

Thibault N, et al. Am J Ther 2016.	F	Adequate	This is a systematic review of the current studies evaluating the use of idarucizumab for reversing dabigatran-associated anticoagulation. The authors description of methodology is adequate. They simply report on the studies by Na et al, Honickel et al, Glund et al, and Pollak et al.
Frontera JA, et al. Neurocrit Care 2016.	F	Good	This is a clinical guideline put forth by a 13-member committee of the Neurocritical Care Society and the Society of Critical Care Medicine. The guideline nicely describes its methodology. Nonetheless, this is a review of the available evidence for reversing antithrombotics (including dabigatran) in the setting of an ICH. Regarding dabigatran, this guideline recommends discontinuing the drug, guiding therapy by bleeding and not by lab values, administering charcoal if ingestion within 2 hrs of presentation, and idarucizumab. Idarucizumab is given a strong recommendation. If idarucizumab is not available, this guideline recommends consideration of PCC, aPCC, and hemodialysis.
Glund S, et al. Lancet 2015.	B	Outstanding	A randomized, placebo-controlled, double-blind phase I trial of idarucizumab in healthy male volunteers given dabigatran. Two-part study: rising dose assessment of idarucizumab, dose-finding, proof-of-concept investigation. 47 patients placed into 4 categories of increasing dose of idarucizumab. Primary safety endpoint was incidence of adverse events judged by treatment investigators. At doses of 2 gms or higher, idarucizumab reversed abnormal coagulation tests. Study did not assess reversal in bleeding patients. Boehringer Ingelheim involved in study design, data collection, data analysis, data interpretation, review and writing of manuscript, and decision to submit for publication.
Eerenberg ES, et al. Circulation 2011.	B	Outstanding	A randomized, double-blind, placebo-controlled crossover trial of just 12 healthy patients given dabigatran and rivaroxaban. Subjects got NOAC for 2.5 days. On 3rd day, given infusion of 4-factor PCC with measurement of lab values. PCC normalized PT, ETP in rivaroxaban arm. PCC did not reverse aPTT, TT, or ECT in dabigatran arm. Dose of PCC 50 IU/kg. Small study of young, healthy volunteers. Did not include patients with active hemorrhage. Funded by Sanquin (Netherlands) supplier of PCC.
Glund S, et al. Thromb Haemost 2015.	B	Outstanding	An RCT assessing idarucizumab PK in healthy volunteers

			Funded by Boehringer Ingelheim
Marlu R, et al. Thromb Haemost 2012.	C	Adequate	Measured laboratory parameters of dabigatran reversal in healthy volunteers after a one-time oral dose. Reversal of anticoagulation was tested in vitro using prothrombin complex concentrate (PCC), rFVIIa or FEIBA® at various concentrations. Although PCC increased ETP-AUC, only rFVIIa and FEIBA corrected the altered lag-time.
Pollack CV, et al. NEJM 2015.	C	Poor	Conducted in patients needing reversal but lacked a control group. Idarucizumab seems to reverse laboratory markers of anticoagulation from dabigatran rapidly and completely, including dilute thrombin time and ecarin clotting time. Median investigator-reported time to cessation of bleeding was 11.4 hours. 21 of the 90 patients in the NEJM study had 'serious adverse effects' including thrombotic events.
Pollack CV, et al. Thromb Haemost 2015.	C	Adequate	Description of the REVERSE-AD methodology (Idarucizumab) Sponsored by Boehringer Ingelheim
Arellano-Rodrigo E, et al. Transfus Med Rev 2015.	C	Adequate	Healthy volunteers received dabigatran 150 mg q 12 hours X 5 days. Concentrations of rFVIIa (Novoseven; NovoNordisk, Bagsvaerd, Denmark) equivalent to 270 µg/kg, aPCC (Feiba; BaxterAG, Vienna, Austria) at 75 U/kg, and the 4-factor PCC (Beriplex; CSL Behring GmbH, Marburg, Germany) at 50 IU/kg were spiked into blood samples. Dabigatran treatment significantly prolonged both PT and aPTT in blood samples drawn 2 to 3 hours after the last intake. Although rFVIIa or aPCC partially improved all the parameters, PCC did not modify the prolonged aPTT observed after dabigatran treatment.