Managing Bleeding in Patients on Direct Oral Anticoagulants

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Disclosure

- Speaker has the following disclosures:
  - Consultant/Clinical Investigator for Janssen
  - Grant/research support from NHLBI, Roche
- All conflicts resolved through peer review.

Objectives - Pharmacists

1. Compare bleeding risk among various patient populations receiving a direct oral anticoagulant
2. Review management strategies for reversal of the anticoagulant effect of direct oral anticoagulants
3. Describe drugs in the pipeline for management of bleeding associated with direct oral anticoagulant use

Objectives - Technicians

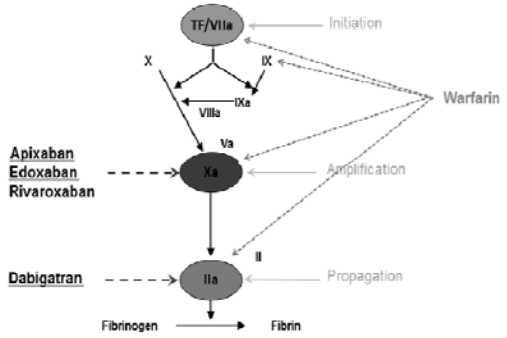
1. List the risks for bleeding among patients receiving a direct oral anticoagulant
2. Review methods to reverse the effects of direct oral anticoagulants
3. Describe drugs in the pipeline for management of bleeding associated with direct oral anticoagulant use

Nomenclature

- NOAC
  - New/Novel oral anticoagulants
  - NO anticoagulants
- NVKOA
  - Non vitamin K oral anticoagulants
- TSOAC
  - Target specific anticoagulants
- DOAC
  - Direct oral anticoagulants

Barnes G, et.al. J Thromb Haemost 2015; 13: 1154–60.

Mechanism of Action



Adapted from Weitz JI, et. al. J Thromb Haemost 2005; 3: 1843-53.

DOACs vs Warfarin

Advantages

- Rapid onset/offset
- Short T1/2
- Predictable PK / fixed dosing
- Fewer drug interactions
- No need for routine monitoring
- Convenience

Disadvantages

- Short T ½ = strict adherence
  - Monitoring adherence
- Drug accumulation in renal impairment
- No reliable, clinically available assay to determine levels
- Lack of dosing flexibility
- High acquisition cost
- Fewer approved indications
- No specific antidote

DOACs: US Indications and Dosage

FDA Indication / Dosage	Apixaban (Eliquis)	Dabigatran (Pradaxa)	Edoxaban (Savaysa)	Rivaroxaban (Xarelto)
Stroke Prevention in Atrial Fibrillation	✔	✔	✔	✔
VTE Treatment Acute Extended	✔ ✔	✔* ✔	✔* ✔	✔ -
Major Orthopedic Surgery (THA/TKA)	✔	-	-	✔
Available dose strengths	2.5mg; 5mg (tablets)	75mg; 150mg (capsules)	15mg; 30mg; 60mg (tablets)	10mg; 15mg; 20mg (tablets)

*Dabigatran and Edoxaban approved for acute VTE treatment only after an initial course of at least 5 days of a parenteral anticoagulant

Pharmacology of DOACs

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Bioavailability	50%	3%-7%	62%	80%-100% [10-mg] 66% [20-mg]
Tmax	1-3 hours	1-3 hours	1-2 hours	2-4 hours
Onset of anticoagulant effect	Within 3 hours	Within 2 hours	Within 1- 2 hours	Within 4 hours
CYP metabolism	25% CYP3A4	No	CYP3A4 (minimal)	30% CYP3A4, CYP2J2
Renal excretion	25%	80%	50%	33%
Half-life	8-14 hours	12-17 hours	10-14 hours	6-9 hours; 12-13hrs elderly
Dialyzable	No	Yes	No	No
Dosing frequency	BID	BID	Once daily	Once daily

CYP=cytochrome P450; Tmax=time to maximum concentration

Segal D, et.al. Drug Discov Today. 2014;19(9):1465-1470; Greinacher A, et.al. Thromb Haemostasis. 2015;113(5):931-942.

Objectives

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Definition of Bleeding

Severity	Definition
Major	• Involves major organ including central nervous system (intracranial or epidural), pericardial, intraocular, retroperitoneal, intra-articular, intramuscular with compartment syndrome • Clinically overt bleeding with a drop in hemoglobin at least 2g/dl • Requires transfusion of at least 2 units • Requires surgical correction • Requires intravascular vasoactive agents
NMCRB	Clinically overt bleeding that does not satisfy criteria for major bleeding but requires • Hospitalization or increased level of care, or • Prompt physician guided medical or surgical treatment, or • A change in antithrombotic therapy
Minor	• Self terminating • Does not require an office visit • No hospitalization of treatment by a health care professional

NMCRB: non-major clinically relevant bleeding

Kovacs et al. JACC 2015;65(13):1340-60.

Self-Assessment 1:

The following is true about the incidence of DOAC associated MB reported in Phase III clinical trials

A. MB is >4% in patients treated for SPAF
B. MB is <4% in patients treated for SPAF
C. MB is > 2% in patients treated for acute VTE
D. MB is < 2% in patients treated for acute VTE
E. Unsure

DOAC: Bleeding Profile in Treatment of Acute VTE

	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-COVER	RE-COVER II	EINSTEIN DVT	EINSTEIN PE	AMPLIFY	Hokusai-VTE
Dose	150mg bid	150mg bid	15mg bid x 21 d then, 20mg od	15mg bid x 21 d then, 20mg od	10mg bid x 7d then, 5mg bid	60mg od[a]
Comparator	UFH/Warf	UFH/Warf	Enox/VKA	Enox/VKA	Enox/Warf	UFH/Warf
MB/NMCRB *DOAC vs Comparator (%)*	5.6 vs 8.8*	5.0 vs 7.9	8.1 vs 8.1	10.3 vs 11.4	4.3 vs 9.7*	8.5 vs 10.3*
MB *DOAC vs Comparator (%)*	1.6 vs 1.9	1.2 vs 1.7	0.8 vs 1.2	1.1 vs 2.2 *	0.6 vs 1.8*	1.4 vs 1.6
ICH (%)	0 vs 0.24	0.16 vs 0.16	0.12 vs 0.12	0.12 vs 0.46	0.11 vs 0.22	0.12 vs 0.44
GI (%)	0.7 vs 0.4	0.5 vs 0.8	0.06 vs 0.18	0 vs 0	0.26 vs 0.67	0.02 vs 0.05

[a] 30mg od in patients with creatinine clearance 30-50ml/min, body weight ≤ 60kg or receiving concomitant treatment with a potent p-glycoprotein inhibitor
bid, twice daily; GI; Gastrointestinal; ICH, intracranial; MB, Major bleeding; NMCRB, Non Major Clinically Relevant Bleeding, od, once daily; UFH, unfractionated heparin;
* p< 0.05

Schulman S, et al. N ENG J Med 2009;361:2342-52.; Schulman S, et al. Circulation 2014.; 129: 764–772; Prins MH, et al. Thromb J 2013; 11: 21.;The EINSTEIN Investigators. N Engl J Med 2010; 363: 2499–2510.; EINSTEIN–PE Inv .N Engl J Med 2012; 366: 1287–1297.; Agnelli G, et al. N Engl J Med 2013; 369: 799–808.; The Hokusai-VTE Investigators. N Engl J Med 2013; 369: 1406–1415.

DOAC: Bleeding Profile in Extended VTE Treatment

	Dabigatran		Rivaroxaban	Apixaban	
	RE-SONATE	RE-MEDY	EINSTEIN EXT	AMPLIFY-EXT	
Dose	150mg BID	150mg BID	20mg od	2.5mg BID	5mg BID
Comparator	Placebo	Warfarin	Placebo	Placebo	
MB/NMCRB *DOAC v Comparator* (%)	5.3 vs 1.8*	5.6 vs 10.2*	6.0 vs 1.2*	3.2 vs 2.7	4.3 vs 2.7
MB *DOAC v Comparator* (%)	0.3 vs 0	0.9 vs 1.8	0.7 vs 0	0.2 vs 0.5	0.1 vs 0.5

bid, twice daily; MB, Major bleeding; od, once daily; NMCRB, Non Major Clinically Relevant Bleeding, od, once daily
* p< 0.05

Schulman S, et al. N Engl J Med 2013; 368: 709–718.; The EINSTEIN Investigators. N Engl J Med 2010; 363: 2499–2510.; Agnelli G, et al. N Engl J Med 2013; 368: 699–708.

DOAC: Bleeding Profile in NVAF (vs Warfarin)

	Dabigatran		Rivaroxaban	Apixaban	Edoxaban	
	RE-LY		ROCKET AF	ARISTOLE	ENGAGE AF-TIMI 48	
Dose	110mg bid	150mg bid	20mg od[a]	5mg bid[b]	30mg od[c]	60mg od[c]
MB[d] *DOAC v W (%/yr)*	2.92 vs 3.61*	3.40 vs 3.61[e]	3.6 vs 3.4	2.13 vs 3.09*	1.61 vs 3.43*	2.75 vs 3.43*
ICH *DOAC v W (%/yr)*	0.23 vs 0.76*	0.32 vs 0.76*	0.50 vs 0.70*	0.33 vs 0.80*	0.26 vs 0.85*	0.39 vs0.85*
GI *DOAC v W (%/yr)*	1.15 vs 1.07	1.56 vs 1.07*	2.00 vs 1.24*	0.76 vs 0.86	0.82 vs 1.23*	1.51 vs 1.23*
Fatal *DOAC v W (%/yr)*	0.2 vs 0.3	0.2 vs 0.3*	0.2 vs 0.5*	34 vs 55 *patients*	0.13 vs 0.38*	0.21 vs 0.38*

[a] 15mg if CrCl 30-49ml/min, [b] 2.5mg bid in patients with two or more of the following; age ≥ 80 years, body weight ≤ 60kg or serum creatinine ≥ 1.5mg/dl; [c] dose was halved if any of the following characteristics were presented at randomization or during the study: estimated CrCL 30-50 ml/min, a body weight ≤ 60kg, or the concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors); [d] definitions of major bleeding varied between studies; bid, twice daily; DOAC, Direct Oral Anticoagulant; GI; Gastrointestinal; ICH, intracranial hemorrhage; MD, Major bleeding; od, once daily; * Statistically Significant, p< 0.05

Connolly SJ, et al. N Engl J Med 2009; 361: 1139–1151.; Connolly SJ, et al. N Engl J Med 2010; 363: 1875–1876.; Connolly SJ, et al. N Engl J Med 2014; 371:1464–1465.; Patel MR, et al. N Engl J Med 2011; 365: 883–891.; Nessel C, et al. Chest 2012; 142: 84A–84A.; Granger CB, et al. N Engl J Med 2011; 365: 981–992.; Giugliano RP, et al. N Engl J Med 2013; 369: 2093–2104.

Self Assessment - 2

Compared to results from Phase III randomized clinical trials, DOAC associated major bleeding in "real-world" observational studies is:

A. Higher
B. Lower
C. Similar
D. Unsure

DOAC: Bleeding Profiles in Published Real-World Studies

	DOACs	Setting	N	MB	Fatal	Other
Beyer-W (2014)	Rivaroxaban	VTE or AF	1,776	3.4%/yr	6.3%*	**NMCR:** 19.7%
Larsen (2014)	Dabigatran Warfarin	AF	33,945	**D150**: 2.1-2.2%/yr **W:** 2.6-3.7%/yr	**D150:** 0.2-0.3%/yr **W:** 0.4-0.5%/yr	***ICH:*** **D150:** 0.2-0.3%/yr **W:** 0.7-1.0%/yr
Hernand. (2015)	Dabigatran Warfarin	AF	9,404	**D:** 9.0% **W:** 5.9%	NR	***ICH:*** **D:** 0.6%; **W:** 1.8% ***GI:*** **D:** 17.4%; **W:** 10.0%
FDA (2014)(2015)	Dabigatran Warfarin	AF	>134,000	NR	NR	***ICH:*** **D:** 0.3%/yr **W:** 1.0%/yr ***GI:*** **D:** 3.4%/yr **W:** 2.7%/yr

D, Dabigatran; GI, gastrointestinal; ICH: Intracranial hemorrthage; NMCR: Non-major clinically relevant; NR, not reported; W, Warfarin
*at 90days in patients hospitalized for bleeding

Beyer-Westendorf J, et al. Blood 2014;124 955–962.; Larsen TB, et al. Am J Med 2014;127: 650–656; Hernandez I, et al. JAMA Intern Med 2015;175:18–24. Food and Drug Administration. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm. Graham DJ, et al. Circulation 2015; 131: 157–164.

Major Bleeding: Case Fatality Rates

	Warfarin		DOACs	
	N	%	N	%
ROCKET AF	55/386	14%	27/395	7%
Dabigatran systematic review	53/407*	13%	57/627*	9%
ARISTOTLE	55/462	12%	34/327	10%
ENGAGE AF-TIMI 48	59/524	11%	32/418 21/254	8% 8%

* Estimated from paper

Patel MR, et al. N Engl J Med 2011;365:883-891.; Majeed A, et al. Circulation 2013;128: 2325-2332.; Granger CB, et al. N Engl J Med 2011; 365:981-992.; Giugliano RP, et al. N Engl J Med 2013; 369:2093-2104.

Self Assessment - 3

In clinical practice, patients who develop DOAC associated major bleeding are treated with factor concentrates:

A. 100% of the time
B. 50% of the time
C. 25% of the time
D. < 10% of the time
E. Unsure

How are Bleeds Managed? Dresden DOAC^ Registry

Bleeding Events [1082 bleeds/762 patients*]	Conservative	Surgery	RBC	Vit K	FFP	PCC	rFVIIa
Minor (637; 58.9%)	637/637 (100%)	0	0	0	0	0	0
NMCRB (379; 35%)	328/379 (86.5%)	51/379 (13.5%)	0	0	0	0	0
Major (66; 6.1%)	41/66 (62.1%)	25/66 (37.9%)	40/66 (60.6%)	1/66 (1.5%)	6/66 (9.1%)	6/66 (9.1%)	0
Total	1006/1082 (93%)	76/1082 (7%)	40/1082 (3.7%)	1/1082 (0.1%)	6/1082 (0.6%)	6/1082 (0.6%)	0

NMCRB, Non-major clinically relevant bleeding
^Rivaroxaban
*Data in the "as treated population"

Beyer-Westendorf J et al. Blood 2014;124(6):955-62.

Who is at Risk and What is the Need for a Bleeding Reversal Solution?

- Real-world bleeding rates are mostly reflective of clinical trials
  - although variations in outcomes observed among studies /settings
- Patients experiencing major bleeding:
  - tend to be older
  - have more comorbidities
    - Hypertension
    - CAD
    - Heart failure
    - Renal disease
  - tend to receive transfusions but NOT clotting factors
- Major bleeding leads to fatal bleeding
- Rapid control of bleeding is expected to improve clinical outcomes
  - Benefits of prompt anticoagulant reversal have not yet been proven

Tamayo S et al. Clin Cardiol. 2014; 38(2):63-8.; Beyer-Westendorf et al. Blood 2014;125(6):955-62.

What are Clinical Parameters for Successful Bleeding Management?

- Mortality
  - 30 days post-bleed all-cause mortality
- Thrombosis
- Length of ICU admittance
- ICH hematoma expansion
- Hemoglobin status
- Resource utilization
  - Transfusions
  - Platelets
  - Coagulation factors

Majeed A et al. Circulation 2013;128(21):2325-32.

Objectives

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3. Describe drugs in the pipeline for management of bleeding associated with direct oral anticoagulant use

Self-Assessment 4

A 62-year-old female on apixaban 2.5 mg PO BID for VTE prophylaxis after a total hip arthroplasty presents to the ED with mild hematuria. She is hemodynamically stable. When asked, she states she last took her apixaban yesterday morning, and missed her evening dose due to not feeling well.

What are options for managing her bleeding episode?

A. Hemodialysis to remove the apixaban
B. Oral activated charcoal to remove the apixaban
C. Concentrated factors (PCC, aPCC, rFVIIa) to reverse apixaban
D. Supportive care and investigate for source of the bleed
E. Unsure

What Parameters Guide the use of a Reversal Agent in the Acutely Bleeding Patient?

- Predictable reversibility
- Need to acutely reverse anticoagulant effect
  - emergency surgery
- Renal function
- Magnitude/risk of rebound anticoagulation
- Cost
- FDA indication considerations

Miyares M et al. Am J Health-Syst Pharm 2012l69(17):1473-84.

Reversal Strategies

	Strategy	Mechanism
Non-Specific	Activated charcoal	Decontamination
	Hemodialysis	Accelerated elimination (dabigatran only)
	FFP	Coagulation factors / proteins
	PCC PCC3 (Bebulin®/Profilnine®) PCC4 (KCentra®)	Replacement of coagulation factors FII, FIX, FX, Heparin* FII, FVII, FIX, FX, Proteins C&S, AT, Heparin
	rVIIa (Novo Seven®)	aFVII
	aPCC (Feiba® NF)	Activated coagulation factors FII, aFVII, FIX, FX, Protein C
Specific	Andexanet	Recombinant inactive factor-Xa
	Idarucizumab	Monoclonal antibody
	Ciraparantag (Aripazine;PER977)	Small synthetic molecule

*Bebulin only

Quality of Evidence

In vitro studies	Animal studies	Healthy volunteers
May not simulate in vivo biology	Animals may differ from humans	Healthy volunteers may differ from patients
Laboratory endpoints may not predict clinical outcomes	Artificial injury models may differ from clinical bleeding	Laboratory endpoints may not predict clinical outcomes

Clotting Factors for DOAC Reversal

- **Clinical outcomes data** on the efficacy of PCC, aPCC and rFVIIa for the reversal of DOACs are lacking
- Available evidence is limited (healthy human volunteers, animal models, in vitro studies) with conflicting results
- These agents may be considered in addition to maximum supportive measures in patients with severe/life-threatening bleeding
- The net clinical benefit should be considered in light of their prothrombotic potential (~ 1.4% for PCC; up to 10% with rFVIIa)

Siegal DM et al. Drug Discov Today. 2014;19(9):1465-70.

Published Ex Vivo Studies of Non-Specific Agents

Reversal strategy	Dabigatran-treated plasma [volunteer or patient]	Factor Xa inhibitor-treated plasma [volunteer or patient]
PCC	Corrected some TG indices[1] Corrected PT, aPTT, TT and some TG indices[2] No correction of Hemoclot assay[2]	R: Corrected PT[2] Variably corrected TG indices[1,2] No correction of anti-Xa activity[2] A: Partial effect [4-PCC][6]
aPCC	Corrected some TG indices[1] Corrected PT, aPTT, and some TG indices[2,3] No correction of Hemoclot assay[2]	R: Corrected PT[2] Corrected TG indices[1,2] No correction of anti-Xa activity[2] A: Normalized fibrin network, corrected latency and quantitative parameters (aPCC>4-PCC/rVIIa)[6] E: Partial reversal of PT, aPTT, anti-FXa[7]
rVIIa	Corrected some TG indices[1] No correction of PT, aPTT, TG indices[4,5] No correction of Hemoclot assay[4,5]	R: Corrected PT[2] Variably corrected TG indices[1] No correction of anti-Xa activity[2] A: Partial effect[6] E: Partial reversal of PT, aPTT, anti-FXa[7]

A, Apixaban; aPTT, activated partial thromboplastin time; aPCC, activated prothrombin complex concentrate; E, Edoxaban; R, Rivaroxaban; PCC, prothrombin complex concentrate; PT, prothrombin time; rVIIa, recombinant activated factor VII; TG, thrombin generation; TT, thrombin time;

1.Marlu R, et al. Thromb Haemost 2012;108(22):217-24; 2.Herrmann R, et al. Thromb Haemost 2014;111(5):989-95; 3.Khoo TL, et al. Int J Lab Hematol 2013;35(2):222–224; 4.Providencia R, et al. Thromb Res 2014;134(6):1253–64; 5.Larsen TB, et al. J Am Coll Cardiol 2013;61(22):2264–2273; 6. Martin AC, et al. J Thromb Haemost 2015;13(9):426-36; 7. Halim AB, et al. Thromb Res 2014;134:909-913.

Published Human Studies of Non-Specific Agents

Reversal Strategy	Dabigatran-treated Healthy volunteers	Factor Xa inhibitor-treated Healthy volunteers
PCC	No correction of aPTT, ECT, TT[1]	R: Corrected PT[1] Corrected PT (4-PCC > 3-PCC)[2] Corrected some TG indices (3-PCC>4-PCC)[2] No effect on aPTT, anti-Xa activity[2] E: Reversal of prolonged bleeding duration and bleeding volume after punch biopsy (4-PCC 50IU/kg) dose[3] A: Corrected PT, partially restored ETP (4-PCC 37.5/25IU/kg)[4]
aPCC	N/A	N/A
rVIIa	N/A	N/A

aPTT: activated partial thromboplastin time; aPCC, activated prothrombin complex concentrate; E, edoxaban; ECT, ecarin clotting time; ETP, endogenous thrombin potential; R, Rivaroxaban; PCC, prothrombin complex concentrate; PT, prothrombin time; rVIIa, recombinant activated factor VII; TG, thrombin generation ; TT, thrombin time;

1. Eerenberg ES, et al. Circulation 2011;124(14):1573–1579; 2. Levi M, et al. J Thromb Haemost 2014;12(9):1428–1436; 3. Zahir H, et al. Circulation 2015;131(1):82–90; 4. Cheung YW, et al. J Thromb Haemost 2015;Aug 13; epub ahead of print

Reversal Considerations for DOACs

- Supportive care
- Discontinuation of drug

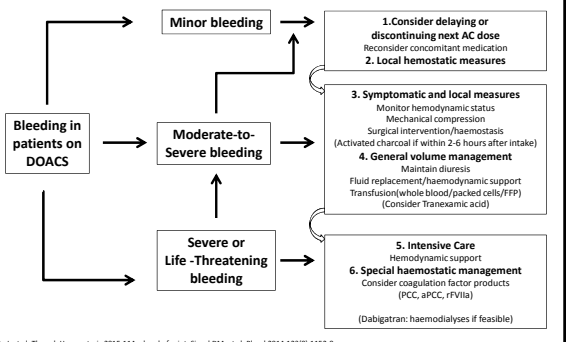
Likely sufficient for many patients

	Apixaban	Edoxaban	Dabigatran	Rivaroxaban
Oral activated charcoal	Yes	Unclear	Yes	Yes
Hemodialysis	No	No	Yes	No
FFP	No	No	No	No
Activated factor VII	Unclear	Unclear	Unclear	Unclear
3-factor PCC	Unclear	Unclear	Unclear	Unclear
4-factor PCC	Possible	Possible	Possible	Possible

Clotting Factors: Real-World Considerations

- No agents are currently approved to reverse the anticoagulant effects of DOACs in cases of active bleeding
- Efficacy data for reversal of F-Xa inhibitors with PCCs in this setting are limited
- The need to be able to quickly reverse the anticoagulant effect of DOACs is an ongoing concern
- Until a specific reversal agent becomes available for clinical use, hemostatic resuscitation remains the mainstay of treatment in the event of hemorrhagic complications

Management of DOAC Associated Bleeding



Weitz J, et al. Thromb Haemostasis 2015;114; ahead of print; Siegal DM, et al. Blood 2014;123(8):1152-8.

Reversal Agent	Dose(s) for Reversal of Specific Anticoagulant		
	Warfarin	**Dabigatran**	**F-Xa Inhibitors**
PCC3	25-50 units/kg	…	50 units/kg
PCC4	25-50 units/kg	25-50 units/kg	25-50 units/kg
rFVIIa	17.7-53.4 µg/kg	20-120 µg/kg	20-120 µg/kg
aPCC		Up to 25 units/kg initially with subsequent doses based on response;	Up to 25 units/kg initially; no data available in patients with active bleeding;
Building of PCC4	PCC3 50 units/kg + rFVIIa 1mg; if rFVIIa not available, addition of small dose FFP (1-2 units) could be considered	No data available; possibly extrapolate doses from warfarin reversal	No data available; possibly extrapolate doses from warfarin reversal

Nutescu EA, et al. Am J Health Syst Pharm. 2013;70(21):1914-29

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Self-Assessment 5

A 56-year-old female on dabigatran 150mg mg PO BID for SPAF presents to the ED with major head trauma and needs emergent surgery. She took her last dabigatran dose 2 hours ago.

Which specific antidote is a good option to rapidly reverse the anticoagulant effect of dabigatran

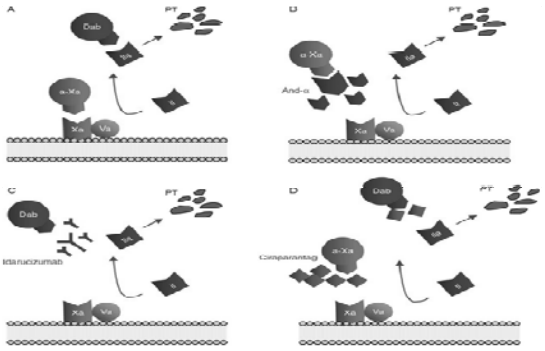
A. Andexanet alfa
B. Ciraparantag
C. Idarucizumab
D. A and B
E. B and C

Specific Reversal Agents in Development for DOACs

Agent	Target	Structure	Mechanism
Idarucizumab Boehringer Ingelheim	Dabigatran	Humanized antibody fragment	Non-competitive binding to Dabigatran with 350 times greater than thrombin
Andexanet alfa Portola	FXa Inhibitors	Recombinant human FXa analogue, catalytically inactive	Binds competitively to direct FXa inhibitors
Ciraparantag Perosphere	Universal Dabigatran, FXa inhibitors, heparins, fondaparinux	Small synthetic molecule	Binds through non covalent hydrogen bonding and charge–charge interactions

Crowther M, et al. Blood 2013;122:A3636; Crowther M, et al. J Thromb Haemost 2013;11:AS20.1; Crowther M, et al. J Thromb Haemost 2013;12:ACOA01; Crowther M, et al. Circulation 2014;130:A2116; Gold MA, et al. J Am Coll Cardiol 2015;65:A23; Glund S, et al. Circulation 2013;128:A17765; Glund S, et al. Blood 2014;124:344

Specific Reversal Agents: MOA



Andres Enriquez et al. Europace 2015;europace.euv030 (with permission)

Specific Reversal Agents: Animal and *In vitro* Studies

Agent	Animal Models	*In vitro* Studies
Idarucizumab	Reduction in blood loss and mortality in a porcine liver trauma model	Reversal of prolonged clotting time induced by Dabigatran
Andexanet alfa	Reduced blood loss induced by Rivaroxaban in mouse (tail transection) and rabbit (liver laceration) models	Complete and dose-dependent reversal of Apixaban and Rivaroxaban in human plasma
Ciraparantag	Reversed anticoagulation/decreased bleeding in a rat-tail transection model with all DOACs	Complete reversal of anti-Xa activity of Apixaban, Edoxban and Rivaroxaban

Andres Enriquez et al. Europace 2015;europace.euv030

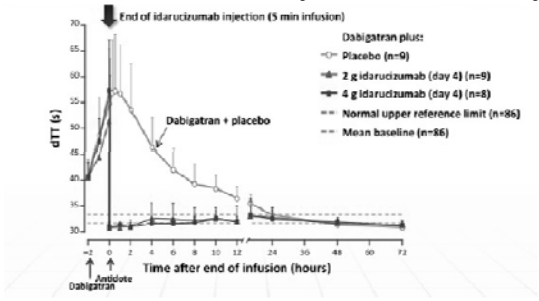
Specific Reversal Agents: Clinical Trials

Treatment	Study	Status	Population	N
Idarucizumab	**RE-VERSE-AD** [Dabigatran]	Phase III Ongoing *[prelim data NEJM2015]*	Life-threatening bleeding[a] Emergency surgery/ invasive procedure[b]	300* 90**
Andexanet alfa	**ANNEXA-A** [Apixaban]	Phase III-Part 1&2 completed	Healthy volunteers	33
	ANNEXA-R [Rivaroxaban]	Phase III-Part1 completed/Part2 ongoing	Healthy volunteers	41
	ANNEXA-E [Edoxaban]	Phase II ongoing/ Phase III planned		
Ciraparantag	**[Edoxaban]**	Phase I complete Phase II ongoing	Healthy volunteers	80

* Total estimated number of enrollment.; ** number of cases included in interim analysis.; a, GroupA.; b, Group B;

Crowther M. American Heart Association Scientific Sessions; Nov. 15-19, 2014; Crowther M, et al. ISTH 2015;13(Suppl 2): LB004.
Gold AM, et al. *J Am Coll Cardiol*. 2015;doi:10.1016/S0735-1097(15)60023-7, Pollack et al. N Engl J Med 2015;373:511-20; Ansell JE, et al. N Engl J Med 2014; 371:2141-2142.

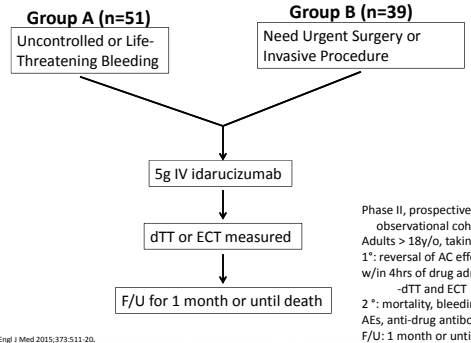
Idarucizumab: Healthy Volunteer Study



Glund et al. AHA 2013

Immediate, complete and sustained reversal of dabigatran

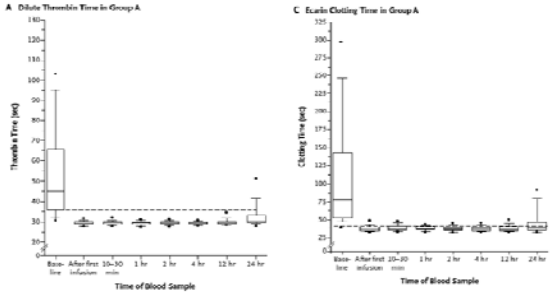
Idarucizumab: RE-VERSE-AD Study Design



Phase II, prospective, observational cohort
Adults > 18y/o, taking Dabi
1°: reversal of AC effect w/in 4hrs of drug admin -dTT and ECT
2 °: mortality, bleeding status, AEs, anti-drug antibodies
F/U: 1 month or until death

Pollack et al. N Engl J Med 2015;373:511-20.

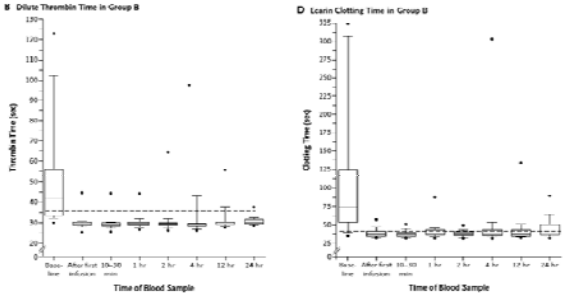
Idarucizumab: REVERSE-AD Results Group A



- median maximum percentage reversal was 100%
- 98% had normalized dTT; 89% had normalized ECT; effect w/in minutes
- no apparent toxic effects or rebound hypercoagulable state

Pollack et al. N Engl J Med 2015;373:511-20.

Idarucizumab: REVERSE-AD Results Group B



- median maximum percentage reversal was 100%; NL hemostasis in 92% who had procedure
- 93% had normalized dTT; 88% had normalized ECT; effect w/in minutes
- no apparent toxic effects or rebound hypercoagulable state

Pollack et al. N Engl J Med 2015;373:511-20.

Andexanet alfa: ANNEXA-A Part 1

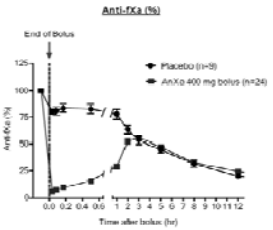
Healthy Volunteers (n=33)

Apixaban 5mg BID x 4d

Randomized

Andexanet alfa 400mg IV bolus (n=24)

Placebo (n=9)



- Rapid normalization of anti-Xa activity and thrombin levels with peak effect few minutes after bolus
- All treated subjects achieved ≥90% reversal; effect lasted 1-2 hrs

Crowther M. Circulation 2014;130:2105-26.

Andexanet alfa: ANNEXA-A Part2

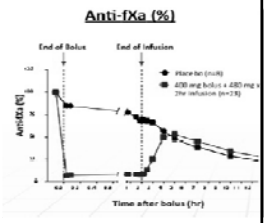
Healthy Volunteers (n=31)

Apixaban 5mg BID x 4d

Randomized

Andexanet alfa 400mg IV bolus + infusion 4mg/min x 120min (n=23)

Placebo (n=8)



- Rapid reversal of AC effect, sustained for duration of infusion
- Following bolus, anti-Xa activity reversed by 93.5% (p<0.001)
- After 2h infusion, anti-Xa activity remained reversed by 92.7% (p<0.001)

Crowther M et al. ISTH 2015;13(Suppl 2): LB004

Andexanet alfa: ANNEXA-R

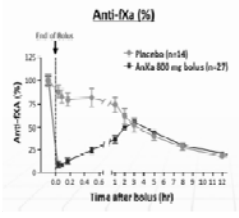
Healthy Volunteers (n=41)

Rivaroxaban 20mg od x 4d

Randomized

Andexanet alfa 800mg IV bolus (n=27)

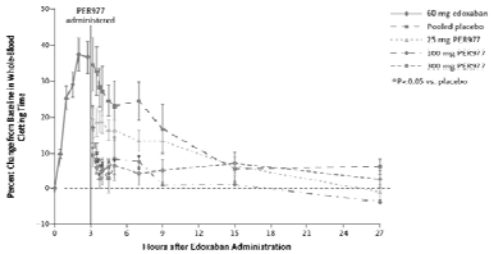
Placebo (n=14)



- 26 of 27 patients had a 90 percent or greater reduction in anti-Xa activity (p<0.001)
- Phase 2 ongoing: infusion 8mg/min x 120min

Gold AM, et al. *J Am Coll Cardiol*. 2015;doi:10.1016/S0735-1097(15)60023-7.

Ciraparantag: Edoxaban (Part1)



- Double blind, placebo-controlled; N=80 healthy subjects;
- Single oral 60-mg dose of edoxaban, followed 3 hours later by single IV dose of 25 mg, 100 mg, or 300 mg of Ciraparantag (PER977)or placebo
- Hemostasis restored w/in 10-30 min after 100-300mg Ciraparantag admin/maintained 24hrs
- No evidence of procoagulant activity; AE: mild/transient (flushing, dysgeusia)

Ansell JE, et al. N Engl J Med 2014; 371:2141-2142

Summary

- DOACs are associated with reduced rates of major, fatal and intracranial bleeding compared to warfarin
- Maximum supportive measures are the mainstay of managing bleeding
- Additional studies are needed to assess the safety and efficacy of non-specific agents
- Specific antidotes are on the horizon