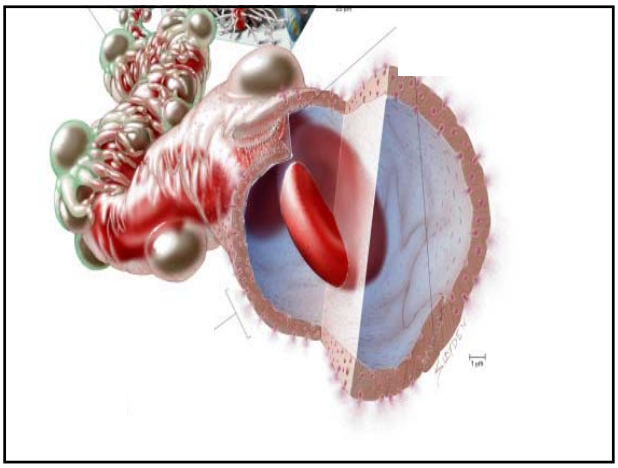


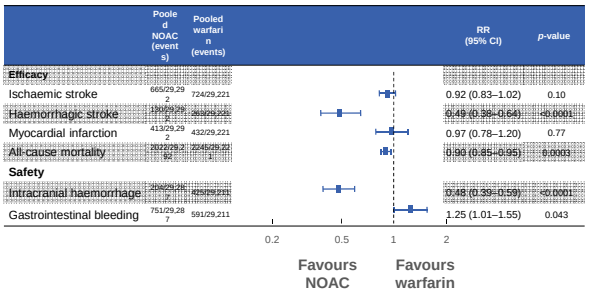
ANTICOAGULATION AND BLEEDING MANAGMENT

Peter Verhamme
Bloedings- en Vaatziekten
Vascular Medicine and Haemostasis
UZ Leuven

BLEEDING WHILE ON AN ANTICOAGULANT: WHAT HAVE WE LEARNT?

Less critical bleeding with NOACs
Different bleeding pattern with NOACs
Patient characteristics drive bleeding
Proactive measures to reduce bleeding risk
Guidance to manage bleeding

NOACs vs VKA: Improved Clinical outcomes



Ruff CT *et al, Lancet* 2014;383:955–962

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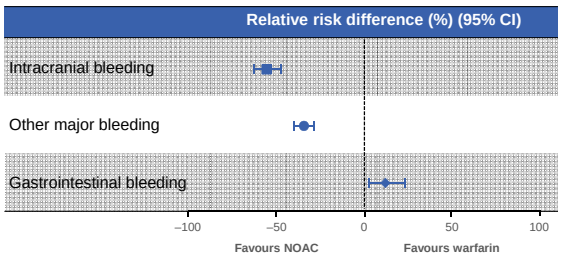
VKAS VERSUS NOACS: ORGAN-SPECIFIC PATTERNS OF BLEEDING

Meta-analysis: ARISTOTLE, ENGAGE AF, RE-LY and ROCKET AF



84,540 patients and 4781 bleeding events
Vanassche T *et al, Thromb Haemost* 2014;112:918–923

Bleeding While on an Anticoagulant: What Have We Learnt?

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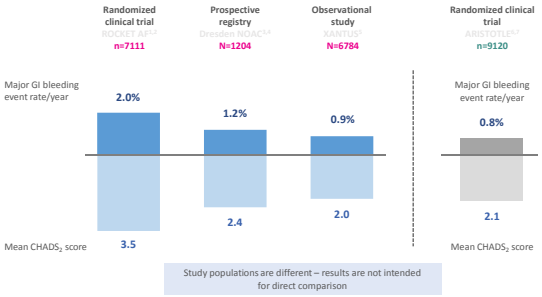
Risk of GI Bleeding Varies Between Populations



1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Sherwood MW *et al, J Am Coll Cardiol* 2015;66:2271–2281; 3. Hecker J *et al, Thromb Haemost* 2016;115:939–949; 4. Förster K *et al*, Presented at ASH 2013: abstract 214; 5. Camm AJ *et al, Eur Heart J* 2016;37:1145–1153; 6. Granger CB *et al, N Eng J Med* 2011;365:981–992; 7. Hylek EM *et al, J Am Coll Cardiol* 2014;63:2141–2147

Risk Factors for Bleeding

Age
Male sex
High blood pressure — **Treat**
Use of platelet inhibitors — **Avoid**
History of GI bleeding — **PPI**
Anaemia — **Assess**

Goodman SG *et al, J Am Coll Cardiol* 2014;63:891–900

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Initial Management of Serious Bleeding Events

Identify and control source of bleeding
Supportive care to stabilize patient
Assess (anti)coagulation
- How much drug is on board? Which and when?
- PT/aPTT and renal function

Heidbuchel H *et al, Europace* 2015;17:1467–1507; Weitz JI *et al, Circulation* 2012;126:2428–2432

WHAT CAN WE LEARN FROM ROUTINE COAGULATION TESTS?

FXa-inhibitors (riva, apixa, edo): Prothrombin Time (PT)

Prolonged
suggests on-therapy levels (or above)
(riva > edo > apixaban)

Normal
does not exclude on-therapy
high levels unlikely (riva > edo > apixaban)

Cuker, JTT 2016

WHAT CAN WE LEARN FROM ROUTINE COAGULATION TESTS?

Dabigatran: aPTT

Prolonged
suggests on-therapy levels (or above)

Normal
does not exclude on-therapy
high levels unlikely

Cuker, JTT 2016

HOW TO SUPPORT HAEMOSTASIS?

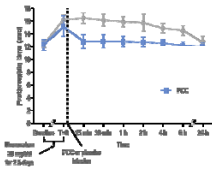
Non-specific support of haemostasis
- Procoagulants (PCCs)
- Antifibrinolytics

Reversal agents
- Idarucizumab
- Andexanet

PHASE I STUDY SHOWED REVERSAL OF RIVAROXABAN-INDUCED ANTICOAGULATION WITH PCC

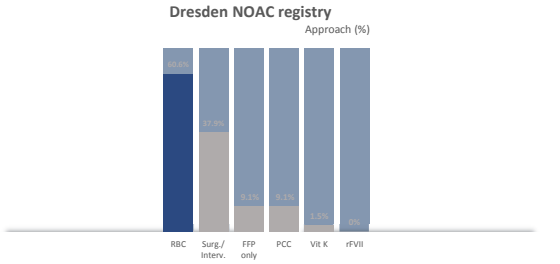
20 mg rivaroxaban was administered bid followed by PCC (Cofact®, 50 U/kg bodyweight)

Prolongation of PT was reversed completely by PCC



ETP, endogenous thrombin potential
Eerenberg ES et al, Circulation 2011;124:1573–1579

STANDARD CLINICAL MEASURES SUFFICIENT TO MANAGE MAJOR BLEEDING IN THE MAJORITY OF CASES



Major bleeding events mostly treated in the real world

Beyer-Westendorf J et al, Blood 2014;124:955–962

NOAC reversal agents in development

NOAC reversal agents are investigational compounds under development and have not been approved for use in the EU.

1. Adapted from Greinacher A et al. Thromb Haemost 2015;113:931–42;
2. Clinicaltrials.gov: NCT02104947; 3. Pollack CV et al. Thromb Haemost. 2015;114:198–205;
4. ClinicalTrials.gov Identifier: NCT02329327; 5. ClinicalTrials.gov Identifier: NCT02207257

The NEW ENGLAND JOURNAL of MEDICINE

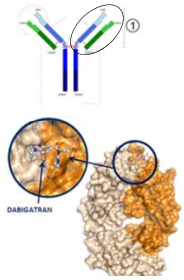
ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

NEJM, Aug 6th 2015

Idarucizumab: specific reversal agent for dabigatran

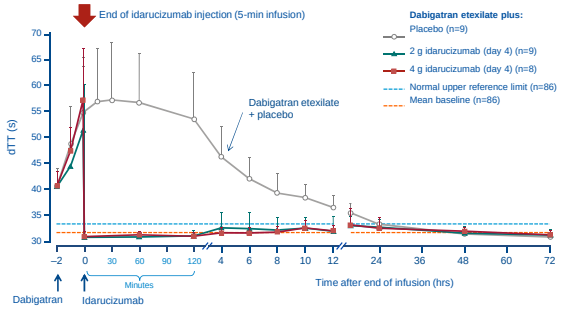


Idarucizumab
IDARUCIZUMAB

- Humanized Fab fragment
- Binding affinity **~350 × higher** than dabigatran to thrombin
- No procoagulant or anticoagulant effects expected
- IV administration, onset of action within 1 min Short half-life

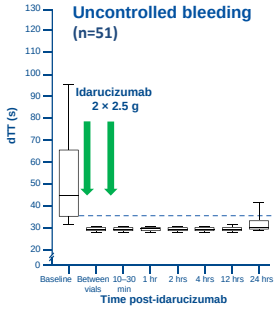
Schiele F et al. Blood 2013;121:3554–62; Stangier J et al. ISTH 2015; OR320

Idarucizumab showed **immediate, complete, and sustained** reversal of dabigatran anticoagulation in a healthy volunteer study



•Normal upper reference limit' refers to (mean+2 SD) of 86 predose measurements from a total of 51 subjects; AE, adverse event; dTT, diluted thrombin time
•Glund et al. Lancet 2015; data on file

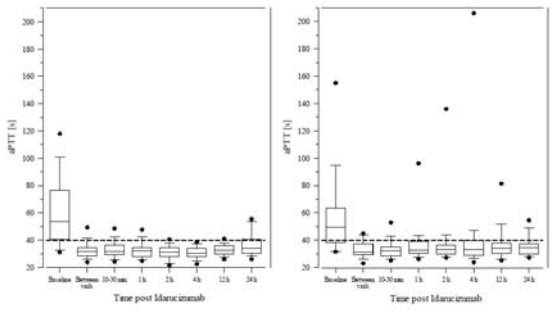
Idarucizumab to reverse dabigatran in patients with bleeding: interim results



Reversal sustained over 12 hours in 90% of patients

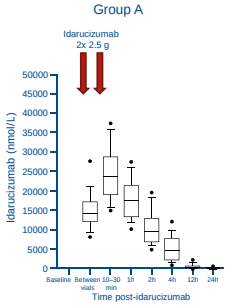
Pollack CV et al. N Engl J Med 2015;373:511–20

Reversal was also evident on aPTT results



Pollack CV et al. N Engl J Med 2015

Idarucizumab levels



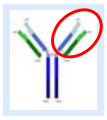
Idarucizumab levels are very low 12 hours after application

Pollack et al. NEJM 2015

NOAC reversal agents in development

Idarucizumab[1]
Target: dabigatran

Andexanet alfa
(PRT064445)[1]
Target: FXa inhibitors



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4. ClinicalTrials.gov Identifier: NCT02329327; 5. ClinicalTrials.gov Identifier: NCT02207257

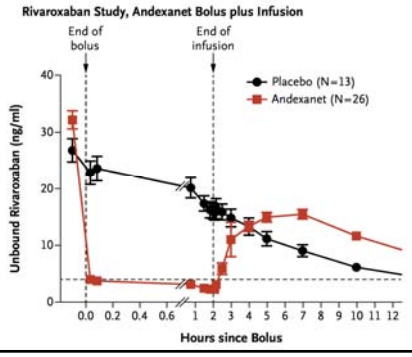
Andexanet:

Designed to Reverse Activity of direct and indirect Factor Xa Inhibitors

- fXa decoy to bind molecules that target and inhibit fXa
- Np **catalytic activity**
- No GLA domain

Nature Medicine
(2013),19(4): 446-51

Andexanet: Reversal of Rivaroxaban



Siegal, NEJM 2015

The NEW ENGLAND JOURNAL of MEDICINE

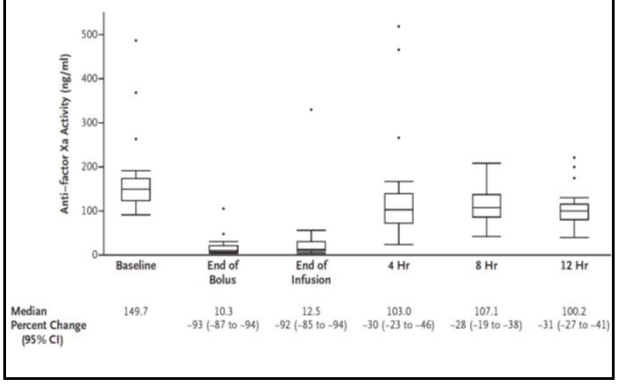
ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

Sept 22, 2016

Anti-factor Xa Activity: Apixaban



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Dabigatran (Pradaxa)
Rivaroxaban (Xarelto)
Apixaban (Eliquis)
Edoxaban (Lixiana)

PK/PD	DABIGATRAN 150/110 BD	RIVAROXABAN 20/15 OD	APIXABAN 5/2.5 BD	EDOXABAN 60/30 OD
target	thrombine	fXa	fXa	fXa
t tot C_{max}	**2h**	**2h**	**2h**	**2h**
Renal clearance	**80%**	1/3	1/3	1/2
Half-life	**12h**	**12h**	**12h**	**12h**