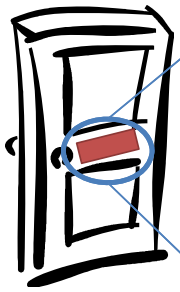
NOVEL ORAL ANTICOAGULANTS IN CKD

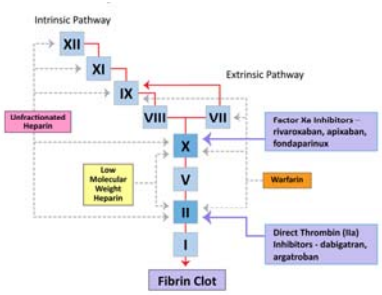
Mark Crowther with thanks to Dr David Garcia



Department of Anticoagulant Archeology and Nephrology

Is it time to abandon vitamin K antagonists ?

- **Why we love them**
  - Monitoring
  - Cheap
  - Highly effective for many indications
  - 100% brand recognition and universal experience
- **Why we don't like them**
  - Monitoring and the "pest factor"
  - Variability between and within individuals
  - Bleeding including ICH
  - Probably cause enhanced vascular disease and perhaps death in CKD patients



Adapted from Leo Pharma slide set

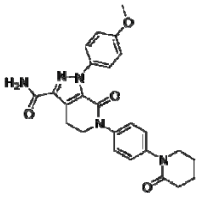
- What does the future hold ?
  - Gradual erosion in use of VKAs however they will continue to be used in selected patient populations

Table of contents

- Quick introduction to DOACs
- Managing bleeding
- Use of DOACs with renal insufficiency

Apixaban (Eliquis)

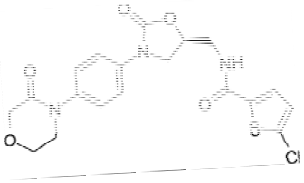
- Oral, direct FXa inhibitor
- Inhibits free FXa and prothrombinase activity
- Highly effective, rapidly acting inhibitor of coagulation
- Bioavailability ~ 50%
- Half-life: 9–14 h
- Excretion: 75% biliary, 25% renal
- Highly protein bound so not responsive to dialysis
- Dosages greater than 25 mg poorly absorbed due to dissolution rate limits



Source: Wikipedia

Rivaroxaban (Xarelto)

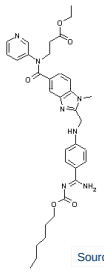
- High bioavailability and rapid onset of action
- Half-life of up to 9 hours at steady state in healthy young subjects, and up to 12 hours in subjects aged >75 years
- Plasma concentrations and pharmacodynamic effects correlate closely
- Pharmacodynamic effects last for 24 hours after a single dose
- Low propensity for drug–drug interactions
- Fixed doses for all patients in phase III
- Highly protein bound so not responsive to dialysis



Source: Wikipedia

Dabigatran (Pradaxa):

- Oral prodrug: dabigatran etexilate
  - converted completely to active dabigatran
- Terminal elimination $t_{½}$ of 14–17 hours
  - Twice-daily (bid) dosing to eliminate "trough periods"
- Bioavailability of 6.5%
- No food interactions
- Eliminated mainly by renal excretion (80%)
  - Contraindicated with creatinine clearance < 30 ml/min
  - Dose reduction 220mg to 150 mg OD with calculated CrCl 30 to 50
  - May be responsive to dialysis



Source: Wikipedia

Why are we worried about renal insufficiency?

Impaired renal clearance will lead to bioaccumulation and avoidable bleeding

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The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis

Chatree Chai-Adisaksopha,[1,2] Mark Crowther,[1] Tetsuya Isayama,[3] and Wendy Lim[1]

	Relative risk	Lower 95% CI	Upper 95% CI
Major bleeding	0.72	0.62	0.85
Fatal bleeding	0.53	0.43	0.64
Intracranial bleeding	0.43	0.37	0.50
CRNMB *	0.78	0.68	0.90
Total bleeding	0.76	0.71	0.82
GI Bleeding	0.94	0.75	1.19

- **Studies enrolled a total of 102 607 patients although not all studies were evaluable for each outcome**
- **"Real world studies" come to varying conclusions about total +/- major bleeding probably explained by methods and patient groups**

*** Clinically relevant non-major bleeding**

(*Blood.* 2014;124(15):2450-2458)

Managing bleeding

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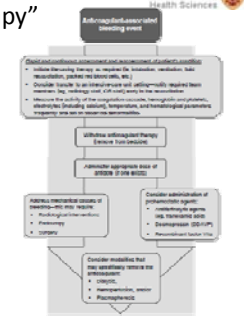
"Non-specific blood thickening therapy"

1. Stop drug
2. Investigate and treat cause
3. Administer antidote
4. Test integrity of coagulation system
5. Use non-specific blood thickeners
   1. DDAVP
   2. Amicar/Tranaxemic acid
6. Transfuse to replace deficient factors or if transfusion will reverse drug
   1. Avoid "reflex transfusion"
   2. Use the appropriate product
7. Consider dialysis or other maneuvers to remove drug
8. By the time all this is complete most drugs will have been cleared



Crowther Warkentin Blood 2008
Siegal Crowther EHJ 2013

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Reversal agents

Prothrombin Complex concentrates

- Human derived blood products designed to specifically antagonize the anticoagulant effect of warfarin
- 4 factor and 3 factor are discussed but in Canada 3 factor PCC is difficult to find

Edoxaban Effects on Bleeding Following Punch Biopsy and Reversal by a 4-Factor Prothrombin Complex Concentrate

Hanim Zahir, PhD*; Karen S. Brown, PhD*; Alexander G. Vandell, PharmD, PhD; Madhuri Desai, MS; Jen-Fue Maa, PhD; Victor Dishy, MD; Barbara Lomeli, MD; Annette Feussner; Wengin Feng, PhD; Ling He, PhD; Michael A. Grosso, MD; Hans J. Lanz, MD; Elliott M. Antman, MD

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02047565. (*Circulation*. 2015;131:82-90. DOI: 10.1161/CIRCULATIONAHA.114.013445.)

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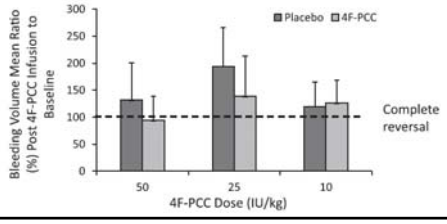
- Phase 1 single centre double-blind, randomized, placebo controlled trial
- 2-way crossover
- 110 subjects, PCC 50, 25, or 10 IU/kg following administration of 60 mg edoxaban



aPCC

Therapy with activated prothrombin complex concentrate is effective in reducing dabigatran-associated blood loss in a porcine polytrauma model

Markus Honickel[1]; Benjamin Maron[1]; Joanne van Ryn[2]; Till Braunschweig[3]; Hugo ten Cate[4]; Henri M. H. Spronk[4]; Rolf Rossaint[1]; Oliver Grottke[1]

Blood loss, survival and haemodynamic variables

Overall mean blood loss 12 min post-injury was 794 ± 50 ml, with no significant differences between groups. Total blood loss was 3807 ± 570 ml in control animals, which was not significantly different from the aPCC25 group (3690 ± 454 ml). All animals in both groups died before the end of the observation period; mean survival time 91 min (range: 65–146 min) and 133 min (range: 82–187 min), respectively; p=NS. In contrast, in the aPCC50 group, a significant reduction in total blood loss (1639 ± 276 ml) compared with both the control and aPCC25 groups ($p<0.0001$ for both comparisons) was observed. All animals in the aPCC50 group survived until the end of the 300-min observation period ($p<0.05$ vs control and aPCC25 groups).

Following injury, all animals developed haemorrhagic shock with

http://dx.doi.org/10.1160/TH15-03-0266
Thromb Haemost 2016; 115: 271–284

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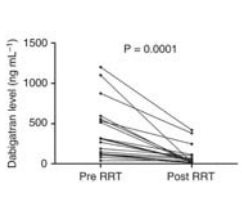
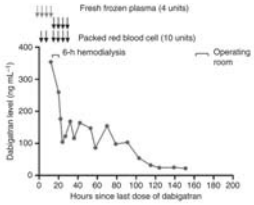
Dialysis for dabigatran





To cite this article: Chai-Adisaksopha C, Hillis C, Lim W, Boonyawat K, Moffat K, Crowther M. Hemodialysis for the treatment of dabigatran-associated bleeding: a case report and systematic review. *J Thromb Haemost* 2015; **13**: 1790–8.

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Tailored reversal agents

Idarucizumab: a specific reversal agent for dabigatran

Praxbind idarucizumab INJECTION 5g

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Idarucizumab

FDA News Release

FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa

Praxbind approved for specific emergency situations

AUTHORIZATION WITH CONDITIONS OF

PRAXBIND™ (idarucizumab) for the treatment in adults as an antidote for dabigatran etexilate (Pradaxa®) when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery or urgent procedures and in life-threatening or uncontrolled bleeding.

April 29, 2016

Dear Health Care Professional(s),

Approved in the US October 15th 2015
Approved in Canada April 29th, 2016

Praxbind idarucizumab INJECTION 5g

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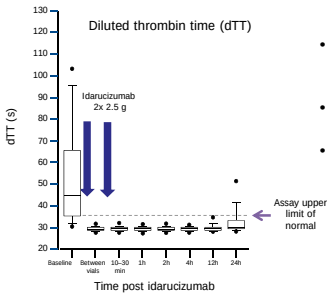
RE-VERSE AD: Reversal of Dabigatran Anticoagulant Effect with Idarucizumab:

	Group A (n=51)
Type of bleeding,‡ n (%)	
Intracranial	18 (35)
Trauma	9 (18)
Gastrointestinal	20 (39)
Other*	11 (22)

	Group B (n=39)
Reason for surgery,† n (%)	
Aortic dissection	1 (3)
Pericardial tamponade	1 (3)
Peritonitis	1 (3)
Acute mesenteric ischaemia with sepsis	2 (5)
Bone fractures	8 (21)
Acute cholecystitis	5 (13)
Acute renal insufficiency, catheter placement	4 (10)
Acute appendicitis	3 (8)
Joint/wound infection	3 (8)
Abscess (suprapubic, scrotal)	2 (5)

*'Other' bleeding types: urogenital, epistaxis, liver, aortic aneurism and aortic dissection. ‡Patients may have had more than one type of bleeding †Other reasons for surgery (one patient each) were: acute deterioration of aortic valve; small bowel obstruction; pneumothorax; probable perforation of the viscera; incarcerated umbilical hernia; lumbar puncture; left leg gangrene; unstable angina, ureteral obstruction, and hydronephrosis.
Pollack CV Jr, et al. N Engl J Med. 2015;373(6):511-20.

RE-VERSE AD: Reversal of Dabigatran Anticoagulant Effect with Idarucizumab: Bleeding patients

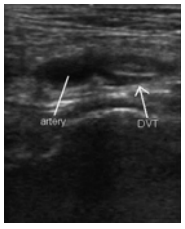


- Almost immediate and complete reversal of anticoagulant effect
- Effect preserved for up to 24 hours
- If there are concerns about very high drug levels consider TCT after conclusion of injection

dTT: diluted thrombin time; ECT: ecarin clotting time
Pollack CV Jr, et al. N Engl J Med. 2015;373(6):511-20.

RE-VERSE AD: Reversal of Dabigatran Anticoagulant Effect with Idarucizumab: Thrombotic Events

- 5 patients over 90 days of follow up
  - 1 early event* (DVT + PE) 2 days after idarucizumab administration
  - 4 events 7–26 days after idarucizumab administration
- Are thromboses due to the reversal or unmasking of underlying procoagulant state (or both)?



Captured from MEDSCAPE

Andexanet for reversal of both direct and indirect Xa inhibitors

Andexanet: Designed to Reverse Activity of Factor Xa Inhibitors

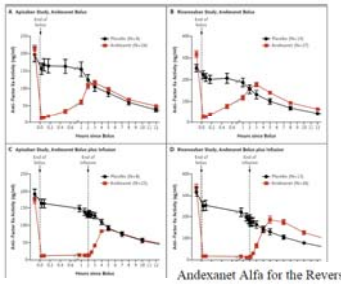
Nature Medicine (2013),19(4): 446-51

Recombinant engineered version of human factor Xa produced in CHO cells

- Acts as a fXa decoy and retains high affinity for all direct fXa inhibitors
- Change of serine to alanine to eliminate catalytic activity and prevent prothrombin cleavage
- GLA domain removed to prevent anticoagulant effect

- No known interaction with other coagulation factors except Tissue Factor Pathway Inhibitor (TFPI)
- Retains high affinity for Antithrombin III-inhibitor complex and can reverse ATIII-dependent anticoagulant effects of enoxaparin and fondaparinux in vitro and in vivo

Summary results from healthy older volunteers



- Apixaban: 400 mg +/- 4 mg/min infusion for 2 hours
- Rivaroxaban: 800 mg +/- 8 mg/min for 2 hours

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

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.,

- multicentre, open-label, single-group study
- 67 patients who had acute major bleeding
  - within 18 hours after a factor Xa inhibitor
- evaluated for changes in anti–factor Xa and clinical hemostasis
- efficacy population: 47 patients had a baseline value for anti–factor Xa activity of at least 75 ng per milliliter

This article was published on August 30, 2016, at NEJM.org.

- median anti– factor Xa activity decreased by 89% (rivaroxaban) and by 93% (apixaban)
- 12 hours after the andexanet infusion, clinical hemostasis was adjudicated as excellent or good in 37 of 47 patients in the efficacy analysis (79%; 95% CI, 64 to 89)
- Thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up
  - Only one of these patients had restarted anticoagulation prior to their thrombotic event

Summary for andexanet

- Specific, short half-life agent that binds to an inactivates a variety of Xa inhibiting anticoagulants
- Administered as either bolus or bolus + infusion
- Does not change underlying PK of the anticoagulant

Now back to the topic of the talk…

As with all new drugs…

- Limited data in patients with renal failure
- Lots of rumours (but relatively little data) for our ancient anticoagulants

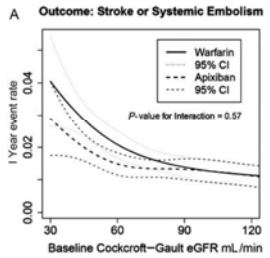
Special Populations in the Phase III Randomized Trials of DOACs

Trial Name	Study	Year	Dosing	Total N	eCrCl 30-50
Dabigatran					
RECOVER I/II	VTE	2009/14	150 bid	5107	245
RE-LY	AF	2009	150/110 bid	18113	3505
Rivaroxaban					
EINSTEIN-DVT	DVT	2010	20 qd	3449	235
EINSTEIN-PE	PE	2012	20 qd	4832	398
ROCKET-AF	AF	2011	20 qd	14262	2949
Apixaban					
AMPLIFY	VTE	2013	5 bid	5395	338
ARISTOTLE	AF	2011	5 bid	18201	3017
Edoxaban					
HOKUSAI	VTE	2013	60 qd	8240	541
ENGAGE-AF	AF	2013	60/30 qd	21105	4074

NB: Many of these trials included pre-specified dose adjustments for reduced renal function.

Risk of Anticoagulant-associated Major Bleeding Increases with Lower GFR

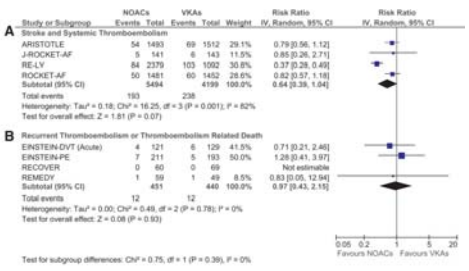
- We have an assumption that heparin and warfarin are safe in patients with renal insufficiency
- We have learned the LMWH and DOACs are unsafe with renal failure
- **BOTH OF THESE ASSUMPTIONS MAY BE INCORRECT**
  - **ARISTOTLE**



European Heart Journal (2012) **33**, 2821–2830
doi:10.1093/eurheartj/ehs274

Comparisons between Novel Oral Anticoagulants and Vitamin K Antagonists in Patients with CKD

Ziv Harel,* Michelle Sholzberg,† Prakesh S. Shah,‡ Katerina Pavenski,† Shai Harel,* Ron Wald,* Chaim M. Bell,§ and Jeffrey Perl*



No evidence of difference in efficacy for Atrial Fibrillation or Venous Thrombosis
Most studies excluded patients with ESRD

J Am Soc Nephrol 25: 431–442, 2014.

That is all well and good but what should we do…

Venous Thromboembolism in Renally Impaired Patients and Direct Oral Anticoagulants (VERDICT)

This study is not yet open for participant recruitment. (see Contacts and Locations)
Verified August 2016 by Centre Hospitalier Universitaire de Saint Etienne

Sponsor:
Centre Hospitalier Universitaire de Saint Etienne

Collaborator:
Ministry of Health, France

ClinicalTrials.gov Identifier:
NCT02664155

First received: January 22, 2016
Last updated: August 11, 2016
Last verified: August 2016
History of Changes

We should do studies !

Apixaban with renal failure

Patients with End-Stage Renal Disease on Dialysis

In patients with eCrCL 15 - 24 mL/min, no dosing recommendation can be made as clinical data are very limited.

Because there are no data in patients with creatinine clearance < 15 ml/min, or in those undergoing dialysis, apixaban is not recommended in these patients (see ACTION AND CLINICAL PHARMACOLOGY, Renal Impairment).

and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

http://www.pfizer.ca/sites/g/files/g10028126/f/201607/ELIQUIS_PM_184464_16June2016_E_marketed.pdf
Access 21 Sept 2016

https://packageinserts.bms.com/pi/pi_eliquis.pdf
Accessed 21 Sept 2016

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Rivaroxaban with renal failure

XARELTO should be used with caution in patients with moderate renal impairment (CrCl 30-49 mL/min), especially in those concomitantly receiving other drugs which increase rivaroxaban plasma concentrations (see **DOSAGE AND ADMINISTRATION – Renal Impairment**, and **DRUG INTERACTIONS – Drug-Drug Interactions**).

Physicians should consider the benefit/risk of anticoagulant therapy before administering XARELTO to patients with moderate renal impairment having a creatinine clearance close to the severe renal impairment category (CrCl < 30 mL/min), or in those with a potential to have deterioration of renal function to severe impairment during therapy.

There are insufficient safety data in patients with severe renal impairment (CrCl < 30 mL/min) as these patients were excluded from pivotal Phase III trials. **Therefore, the use of XARELTO is not recommended in patients with severe renal impairment.** Patients who develop acute renal failure while on XARELTO should discontinue such treatment.

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Renal Impairment, *my opinion*

- Moderate renal impairment (Cr Cl 30-50 mL/min):
  - All DOACs at least as safe as warfarin
    - Apixaban safer?
    - Check package insert for dose adjustments!
- Severe renal impairment (Cr Cl < 30 mL/min):
  - Avoid all DOACs pending more data
  - Consider risks and benefits of *any* anticoagulation carefully
  - If a DOAC is chosen, get informed consent and consider monitoring for bioaccumulation

Summary

- Use with caution with reduced CrCl, use package insert to guide treatment and don't give to patients with CrCl < 25 mL/min
  - **BUT**
- Assumes the alternate is safer and more effective
  - **THEREFORE**
- Watch for updates as Standard of Care may change quickly !
  - Undertake research
  - ? Utility of monitoring

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