

# **The Peri-operative Management of Patients on Anticoagulant Therapy**

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**No conflict of interest to declare**

# Learning Objectives

1. Update : new evidence on “bridging”; BSH Guidance 2016
2. Vitamin K antagonists (e.g. Warfarin) & Direct Oral Anticoagulants (DOACs): elective and emergency peri-operative management
3. How DOACs affect global assays of coagulation and pitfalls in assay interpretation
4. A brief summary of the available reversal strategies for DOACs

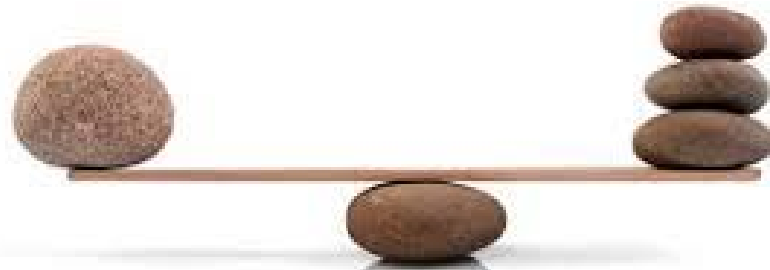


# Can you advise.....?

- Frequently encountered clinical query
- Not straightforward –
  - Many issues to consider
    - Stratification of patients according to thrombotic and bleeding risk
    - Is interruption of antithrombotic therapy necessary
    - When to discontinue and when to resume therapies
    - If an anticoagulant “bridge” is necessary
  - Lack of high quality evidence until 2015
  - Empiric use of many different strategies and protocols
  - No consensus regarding optimal peri-operative strategy
  - 4 new non vit K oral anticoagulants



# Balancing Risks



Pre-operative assessment must consider each patient's risk for thromboembolic events **BALANCED** against the risk for peri-operative bleeding



# Definition of “Bridging”

“the administration of a short-acting anticoagulant such as LMWH or UFH (*at treatment dose*) during the time when a long-acting anticoagulant such as warfarin is withheld before surgery, and subsequently after the surgery or procedure until the long-acting anticoagulant is again within the target therapeutic range”



# Procedures associated with very low bleeding risk

## **PERI-OPERATIVE INTERRUPTION OF WARFARIN IS NOT NECESSARY**

- MINOR DENTAL PROCEDURES
  - SDCEP advisory document
- DERMATOLOGICAL
- CATARACT SURGERY
- JOINT INJECTIONS
- ENDOSCOPY: BSG and ESGE guidelines , 2016
- PPM and defibrillator surgery :

Perry DJ, Nokes TJ, Helliwell PS. Br Dent J. 2007; 203 389-393; [www.sdcep.org.uk/published-guidance/anticoagulants-and-antiplatelets](http://www.sdcep.org.uk/published-guidance/anticoagulants-and-antiplatelets), 2016

Alcalay J. Dermatol Surg 2001; 27(8): 756-8

Billingsley EM, Maloney ME. Dermatol Surg 1997; 23 (5): 381-3

Jamula E, Anderson J, Douketis JD. Thromb Res 2009; 124 (3): 292-9

Ahmed I, Gertner e, Nelson WB et al..Heart Rhythm 2010; 7: 745-9

Ahmed I, Gertner E. J Hosp Med. 2011, 2: S1

Veitch AM, Vanbiervliet G, Gershlick AH et al. Gut 2016;65 374-389

# Assessment of Bleeding Risk

## Patient specific

- History of bleeding
- Mechanical mitral valve
- Active cancer
- Thrombocytopenia  
(BLEEDMAP risk score)

### HAS-BLED score

- Hypertension, abnormal renal and liver function, stroke, bleeding predisposition, labile INR, elderly (>65yrs), drugs/alcohol

## Procedure specific

- Highly vascular organs
- Bleeding into confined critical locations
- Bowel resection with risk of bleeding at anastomotic sites
- Also urological procedures, colonic polyp resection broad base, major surgery associated with extensive tissue injury (joint arthroplasty, cancer surgery)



# Assessment of thromboembolic risk

## *Previously used system*

### Patient related risk factors

Risk stratum	Mechanical heart valve	Atrial fibrillation	VTE
High	<ul style="list-style-type: none"><li>· any mitral valve prosthesis</li><li>· caged-ball / tilting disc aortic valve prosthesis</li><li>· recent (within 6 mo) stroke or TIA</li></ul>	<ul style="list-style-type: none"><li>· CHADS<sub>2</sub> score of 5 or 6</li><li>· recent (within 3 mo) stroke or TIA</li><li>· rheumatic valvular heart disease</li></ul>	<ul style="list-style-type: none"><li>· recent (within 3 months) VTE</li><li>· severe thrombophilia (e.g. deficiency of protein C, S, AT, APLAbs, multiple abnormalities)</li></ul>
Moderate	<ul style="list-style-type: none"><li>· bileaflet aortic valve prosthesis and one or more of : Afib, prior stroke or TIA, hypertension, diabetes, congestive cardiac failure, age &gt;75y</li></ul>	<ul style="list-style-type: none"><li>· CHADS<sub>2</sub> score 3 or 4</li></ul>	<ul style="list-style-type: none"><li>· VTE within the past 3-12 mo</li><li>· Non-severe thrombophilia (e.g. heterozygous factor V Leiden or prothrombin gene mutation)</li><li>· recurrent VTE</li><li>· active cancer (treated within 6 mo or palliative)</li></ul>
Low	<ul style="list-style-type: none"><li>· bileaflet aortic valve prosthesis without Afib and no other risk factors for stroke</li></ul>	<ul style="list-style-type: none"><li>· CHADS<sub>2</sub> score of 0 to 2 (assuming no prior stroke or TIA)</li></ul>	<ul style="list-style-type: none"><li>· VTE &gt;12 mo previous and no other risk factors</li></ul>

Adapted from Douketis JD, Spyropoulos A, Spencer FA, Mayr M et al. Chest 2012; 141 (2) (Suppl): e326S-350S

CHADS<sub>2</sub>: estimates the postoperative risk for stroke

Gage BF, Waterman AD, Shannon W et al. JAMA 2001; 285 (22):2864-70

Cumulative score: CCF, hypertension, age >75yrs, diabetes mellitus (each 1 point) and stroke or TIAs (each 2 points)

# Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

- BRIDGE AF Trial; funded by NIH, ClinicalTrials.gov: NCT00786474
- Background: Uncertainty regarding the need for bridging anticoagulation in the elective surgery setting in patients on warfarin for atrial fibrillation

- Hypothesis: withholding bridging would be non-inferior to bridging with LMWH for the prevention of perioperative arterial thromboembolism and would be superior with respect to major bleeding
- Randomised double blind placebo-controlled trial
- Random assignment to
  - either bridging anticoagulation therapy with LMWH (100 units dalteparin /Kg sc BD),
  - or matching placebo sc BD,
  - from day-3 prior to procedure until 24 hrs before procedure ,
  - then for 5-10 days post-procedure

# BRIDGE-AF

- Warfarin stopped 5 days pre-procedure and resumed 24 hrs after procedure
- F/U for 30 days post-operatively
- Primary outcomes: arterial thromboembolism (stroke, systemic embolism, TIA) and major bleeding

- RESULTS: 1884 patients enrolled: 950 assigned to receive no bridging; 934 assigned to receive bridging
- The incidence of arterial embolism was 0.4% in no bridging group vs 0.3% in the bridging group: CI 0.6-0.8, P=0.01 for non-inferiority
- The incidence of major bleeding was 1.3% in the non-bridging group vs 3.2% in the bridging group (RR, 0.41; CI 0.20-0.78, P=0.005 for superiority)
- CONCLUSION: in patients with AF foregoing bridging anticoagulation was non-inferior to bridging anticoagulation for the prevention of arterial thromboembolism and decreased the risk of major bleeding.

# When to consider bridging

	<u>Consider</u> bridging with treatment dose heparin/LMWH in:
<b>VTE</b>	Patients with a VTE within previous 3 months  Previous VTE when on therapeutic anticoagulation with target INR 3.5
<b>AF</b>	Patients with a previous stroke/TIA in last 3 months  Patients with a previous stroke/TIA and 3 or more of: CCF, hypertension (>140/90mmHg or on medication); age ≥75 yrs; diabetes mellitus
<b>MHV</b>	MHV patients other than those with a bileaflet aortic valve and no other risk factors

Individual assessments for triple positive antiphospholipid antibody syndrome and cancer associated VTE

# Practical Issues when Bridging

- Detailed written plan in case notes for multidisciplinary team
- Take account of patient's weight, age and renal function, past history, baseline INR and FBC
- Clear communication with patient and provision of a written plan with contact numbers
- Memory and cognitive function very important
- Provision of LMWH in pre-filled syringes
- Patient education and written plan for patient
- Takes time and effort

# Warfarin instructions

- Outpatient strategy: simple instructions and easy to follow
- Stop warfarin 5 days in advance of elective surgery
  - Limited data in relation to other VKAs
  - Elimination half-life of warfarin is 36-48 hours
  - So cessation 5 days prior to operation corresponds to 5 elimination half-lives
  - Allows sufficient time for the regeneration of functional vit K-dependent coagulation factors to achieve normal haemostasis

*Elderly patients may have slower warfarin elimination*

*Patients with a higher baseline INR may require a longer period of warfarin interruption*

- **The INR should be determined the day prior to surgery, if possible**
  - So that vit K can be given if INR  $\geq 1.5$  to reduce the risk of cancellation
- **The INR should be checked on the day of surgery**

RCT compared a 5-day vs 1-day warfarin +vit K interruption before surgery; the 5-day group had a significantly lower mean INR on the day of surgery compared with the 1-day interruption group despite vit K (1.24 vs 1.61,  $p < 0.01$ )

Steib A, Barre J, Mertes M et al. J Thromb Haemost 2010;8(3):499-503



# Post-operative instructions: WARFARIN

- Early resumption of warfarin after surgery possible due to expected delay of 5-7 days before therapeutic anticoagulant effect
  - Can start on evening of day of operation, or day 1 post-op, or when oral intake resumes
  - Only re-start if post-operative haemostasis is controlled
- What warfarin dosage?
  - 2 cohort studies
    - 650-patient prospective cohort study, warfarin resumed at **maintenance dose** within 24 hrs of operation, mean time to achieve therapeutic INR  $\geq 2.0$  was 5.1 days (*Kovacs MJ, Kearon C et al. Circulation 2004;110(12):1658-63*)
    - Resume warfarin with a **doubling of maintenance dose for initial 2 postoperative days** mean time to achieve therapeutic INR  $\geq 2.0$  is 4.6 days (*Douketis JD, Johnson JA, Turpie AG. Arch Intern Med 2004; 164 (12):1319-26*)

Dunn A. J Thromb Thrombolysis 2006; 21 (1):85-89

Dunn AS, Spyropoulos AC, Turpie AG. J Thromb Haemost 2007; 5(11): 2211-2218

Darvish-Kazem S, Douketis JD Semin Thromb Haemost 2012; 38 (7) 652-660

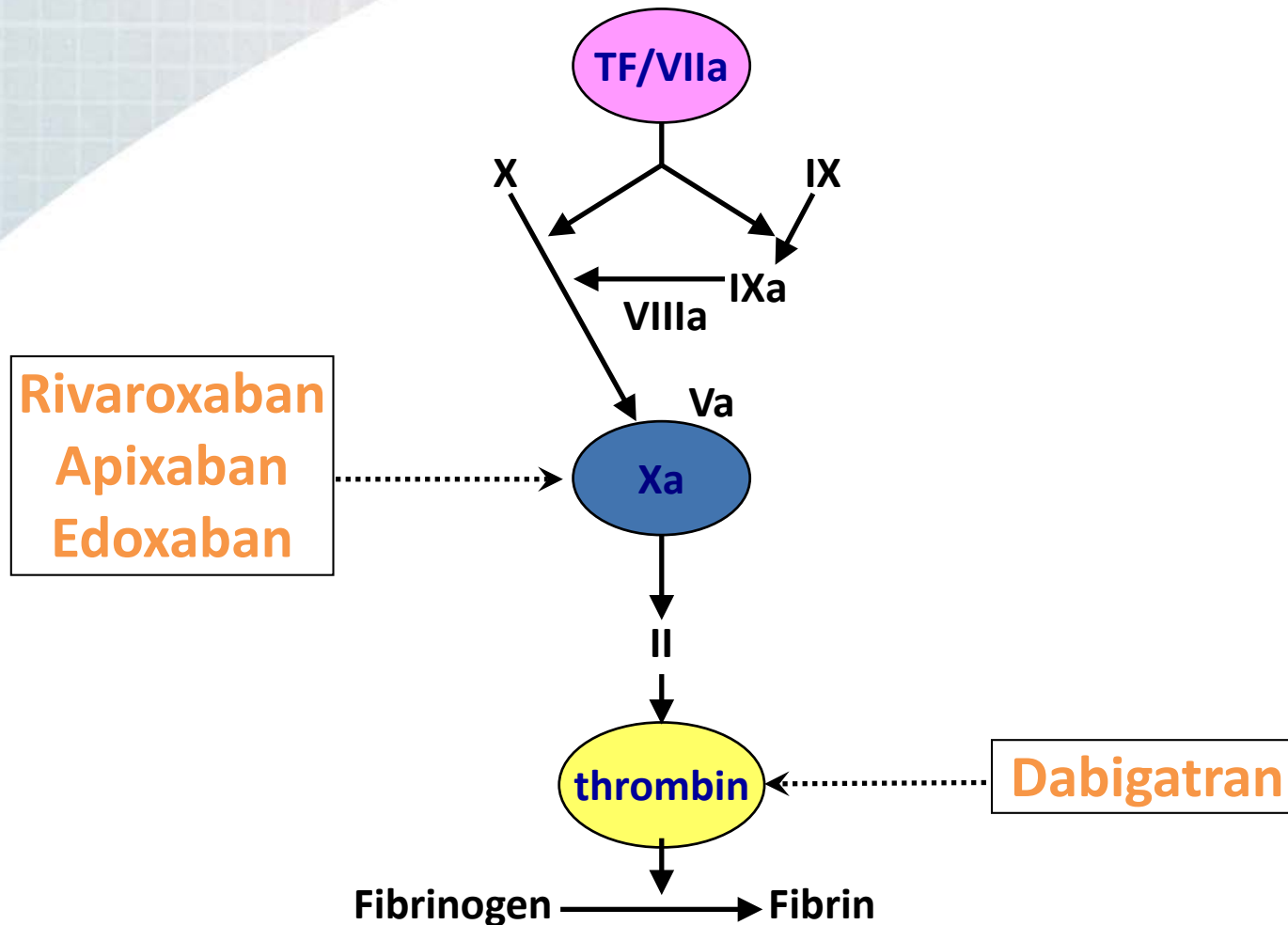
Keeling et al. BJ Haematol 2016, 175: 602-613

# Emergency surgery in patients on warfarin/VKAs

- If surgery can be delayed for 6-8 hours, give iv vit K 5mg to restore coagulation factors
- if delay not possible then give 25-50 iu/Kg four-factor prothrombin complex concentrate (PCC), and check INR post-administration
- Post-operatively, either no LMWH or prophylactic dose for 48 hours
- Then can use therapeutic LMWH if haemostasis is adequate; can split LMWH into BD dosing regimen

# Peri-operative management of patients on direct oral anticoagulants “DOACs”

# Direct Oral Anticoagulants



## CHARACTERISTICS OF THE DIRECT ORAL ANTICOAGULANTS

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
Time to maximum effect	1.5-2h	2h	3-4h	1-2h	5 days
Half-life	12-17h	5-9h	8-15h	10-14h	36-48h
Plasma protein binding	35%	92-95%	87%	40-59%	99%
Renal elimination	80%	33%	25%	50%	0%
Interactions	P-gp	P-gp, CYP3A4	P-gp, CYP3A4	P-gp, CYP3A4	CYP2C9 (S) CYP1A2 (R)
Food effect	Absorption delayed	Required for absorption	Not reported	no	Dark green vegetables etc
Route of administration	Oral Twice daily	Oral Once daily	Oral Twice daily	Oral Once daily	Oral Once daily

The new oral anticoagulants exert effect almost immediately, so caution required in re-starting post-operatively.

No need for bridging anticoagulation with heparin pre-operatively in view of half-life:

- Stop 1-2 days before elective surgery if renal function is normal

# Peri-operative Management: a pragmatic approach

## Timing for last dose of anticoagulant

	96hrs	72hrs	48hrs	24hrs
Xa inhibitors		High risk and renal	High risk /or renal	Low risk
Dabigatran	High risk <b>and</b> renal Creat cl 30-49ml/min	High risk <b>and</b> renal Creat cl 50-80ml/min	High risk <b>or</b> low risk +renal Creat cl 50-80ml/min	Low risk and no renal

Current strategies for elective surgery do not routinely include measurement of either non-specific or specific coagulation parameters to assist in quantification of DOAC levels.



## Re-introduction of DOACs post-surgery

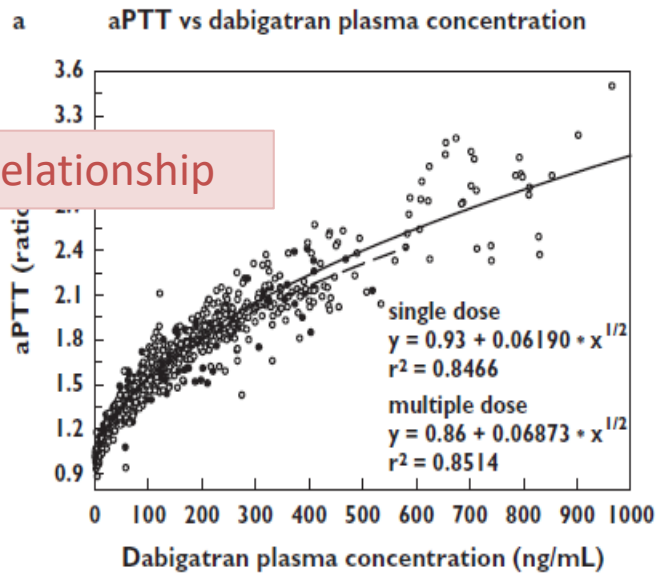
- Rapidly absorbed with maximum concentrations within hours post-ingestion – leaving the patient fully anticoagulated
  - Given the experience from LMWH bridging avoid new oral anticoagulants for 48-72 hours post high bleeding risk procedures, and for 6-12 or 24 hours post low bleeding risk procedures – depends on the procedure.
- Use LMWH prophylaxis while waiting to re-introduce the DOAC
- A suggested alternative strategy is to use lower doses of new oral anticoagulants – off licence approach, except in elective total hip and knee arthroplasty



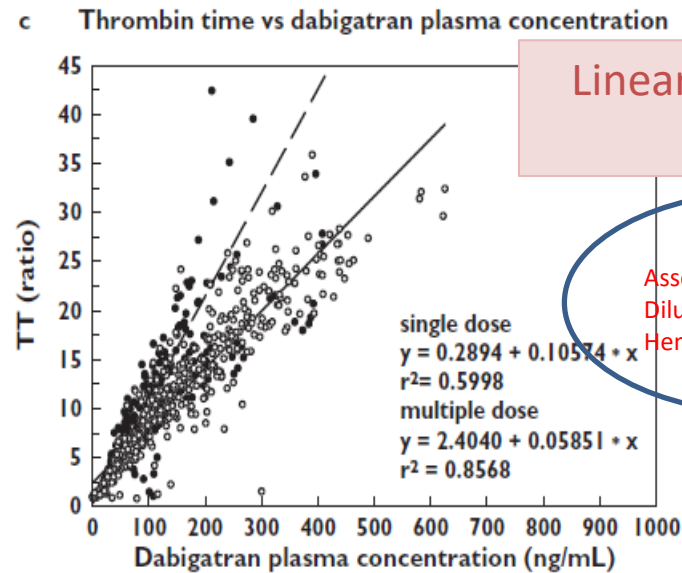
# Emergency Surgery: decision making

- When was the last dose taken?
- Stop drug; try to postpone surgery with a high bleeding risk for at least 1-2 half lives of drug and provide supportive care
- Is the drug still present?
  - Check anti-Xa level for apixaban, rivaroxaban and edoxaban, and diluted thrombin time (Hemoclot assay) for dabigatran
    - but uncertainty over the concentration of each drug that equates to haemostatic safety
    - variation in specific assay results from lab to lab dependent on reagents and instrumentation
- Does the drug need reversed?
  - What is the strategy?
- Neuraxial anaesthesia contra-indicated if an anticoagulant effect cannot be excluded



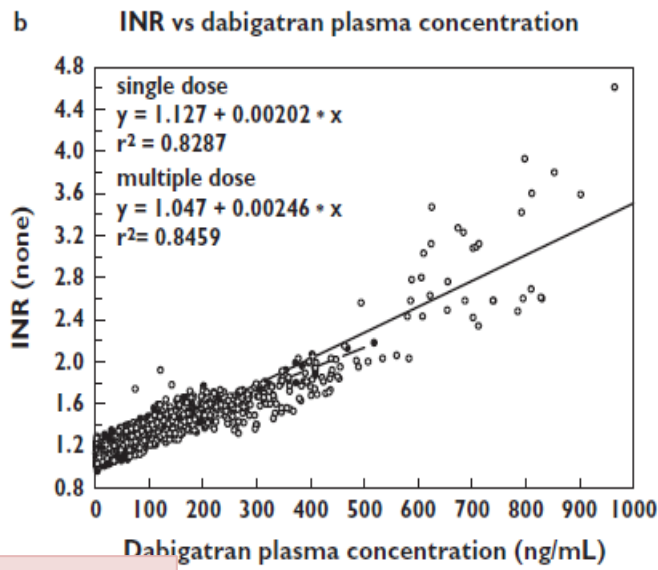


Curvilinear relationship

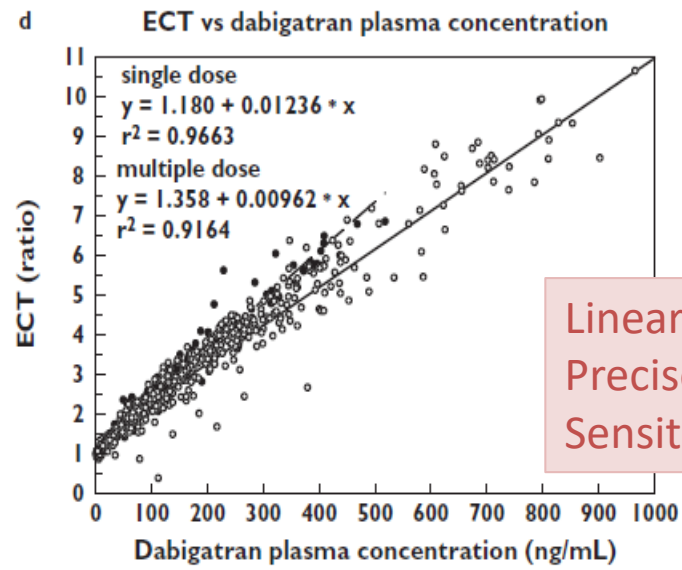


Linear relationship  
Too sensitive

Assess dabigatran effect  
Dilute thrombin time  
Hemoclot assay



Linear relationship  
Low sensitivity  
Not suitable



Linear relationship  
Precise  
Sensitive

**Plots of global assays vs Dabigatran concentration (ng/ mL)**

# Pro-haemostatic agents

- Use of PCC and aPCC to reduce risk of peri-surgical bleeding?
  - Data relates to animal expts and in vitro studies
  - Potential for adverse thrombotic outcomes
- Few data to support use in emergency surgery
  - BSH suggest use PCC in the event of diffuse coagulopathic bleeding
  - BSH recommend use of tranexamic acid to reduce bleeding

# Specific reversal agents for DOACs

IDARUCIZUMAB:  
Target:  
dabigatran

Phase I

Phase II

Phase III  
Patients requiring  
urgent surgery/with  
major bleeding;  
May 2014

EMA  
and  
FDA  
Approval  
2015/16

SMC  
Approval  
2016

Andexanet alfa  
(PRT064445)  
Target: FXa  
inhibitors

Phase I

Phase II

Phase III  
Patients with  
major bleeding  
Jan 2015

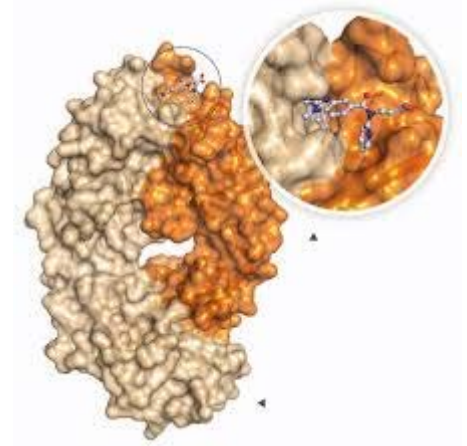
Ciraparantag  
(PER977)  
Target: universal

Phase I

Phase II  
Ongoing



# Idarucizumab



- Humanised Fab fragment
- Binding affinity ~350 times higher than dabigatran to thrombin
- No intrinsic procoagulant or anticoagulant activity
  - intravenous dosing by bolus or rapid infusion
  - immediate onset of action

ORIGINAL ARTICLE

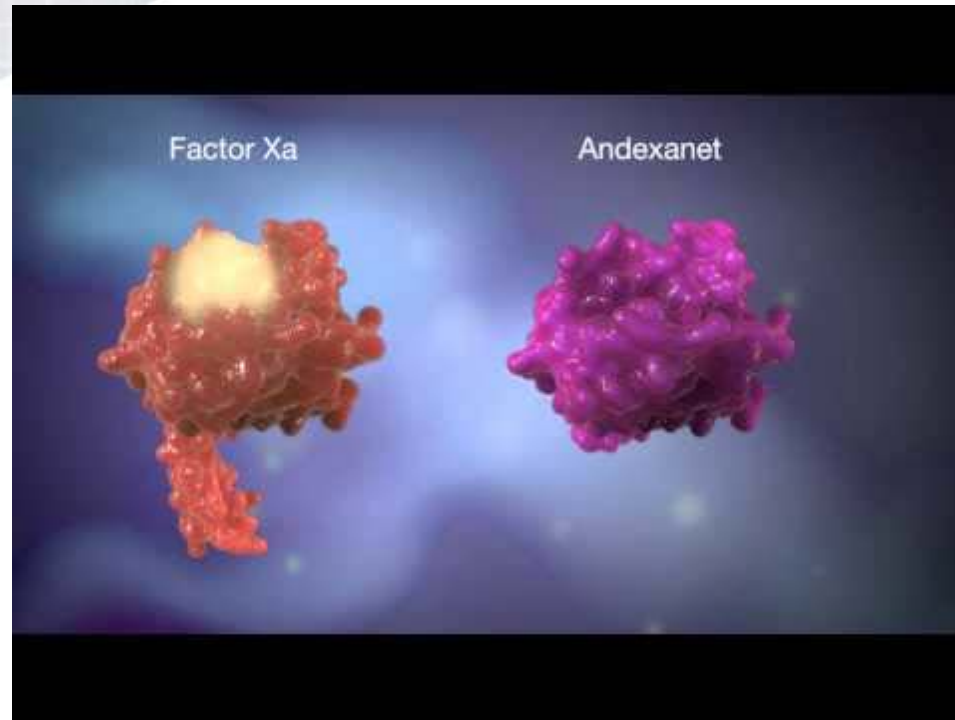
# Idarucizumab for Dabigatran Reversal

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.

Prospective trial of 5g Idarucizumab to 36 patients undergoing an invasive procedure

- Normal intra-operative haemostasis reported in 33
- Mildly abnormal haemostasis in 2
- Moderately abnormal haemostasis in 1
- 1 thrombotic event within 72 hrs after Idarucizumab
- Major reversal of coagulation tests in 88-98% of patients

# Andexanet alfa



Recombinant human factor Xa decoy protein  
Reverses the inhibition of fXa in healthy volunteers (ANNEXA – A and R trials)  
Siegal et al. NEJM 2015, 373:2413-2424

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\*

Interim report (67 patients) for the ANNEXA-4 trial. Cohort study.

Initial bolus + subsequent 2 hour infusion in patients with acute major bleeding associated with fXa inhibitors; effective haemostasis (“excellent” or “good”) described in 79% of patients; thrombotic events in 12 patients (18%) during follow-up



# SUMMARY

- New guidance on peri-operative management for patients on anticoagulants published by BSH in October 2016
  - standardises peri-operative advice for the multidisciplinary team
  - outlines the few indications for “bridging” patients on warfarin
  - offers a pragmatic approach to elective and emergency surgery in patients on DOACs
  - Idarucizumab is SMC-approved and licensed for reversal of dabigatran



# Warfarin

3 mg  
28 tablets

28 tablets



## Any questions?

