RHYTHM 2015

Arrhythmias & Heart Failure: New Insights & Technological Advances

Palais du Pharo, Marseille, France May 28-30, 2015

What to do in case of hemorragia with NOAC ?

L Camoin –Jau
Service d'Hématologie
APHM
Marseille

EBAC®

www.rhythmcongress.com

Disclosure

- Boehringer
- Bayer
- Daishi
- Sanofi
- BMS

Pharmacodynamic and kinetic properties of new oral anticoagulants.

	Time to peak concentration (hours)	Half-life (hours)	Extent of renal excretion
Dabigatran	1-3	12-14	80-85 %
Rivaroxaban	2-4	7-17	36 %
Apixaban	1-3	8-14	25 %

Acta Anaesthesiol Scand 2014; ***58:*** *651–659*

Management of the bleeding patient on NOAC

How much drug is on board ?

- Timing of last dose
- Drug half-life
- Renal function
- Concomitant medications (anti-platelet drugs, P-glycoprotein and CYP 3A4 enzyme inhibitors)
- Blood levels

Measurement of anticoagulant activity of NOACs

Test		Dabigatran	Rivaroxaban	Apixaban
Specific		Anti-IIa	Anti-Xa	Anti-Xa
Non specific	aPTT	↑↑ ↑	↑	↑
	PT	↑	↑↑	↑
	TT	↑↑ ↑	No effect	No effect

- Heidbuchel H et al. Europace 2013;15:625–51

When should I consider reversing anticoagulation in a bleeding patient?

- Dabigatran
  - aPTT ratio >1.2
  - Drug level >30-50 ng/ml

- Rivaroxaban
  - PT < 70 %
  - Drug level >30-50 ng/ml

- Apixaban,
  - Drug level >30-50 ng/ml

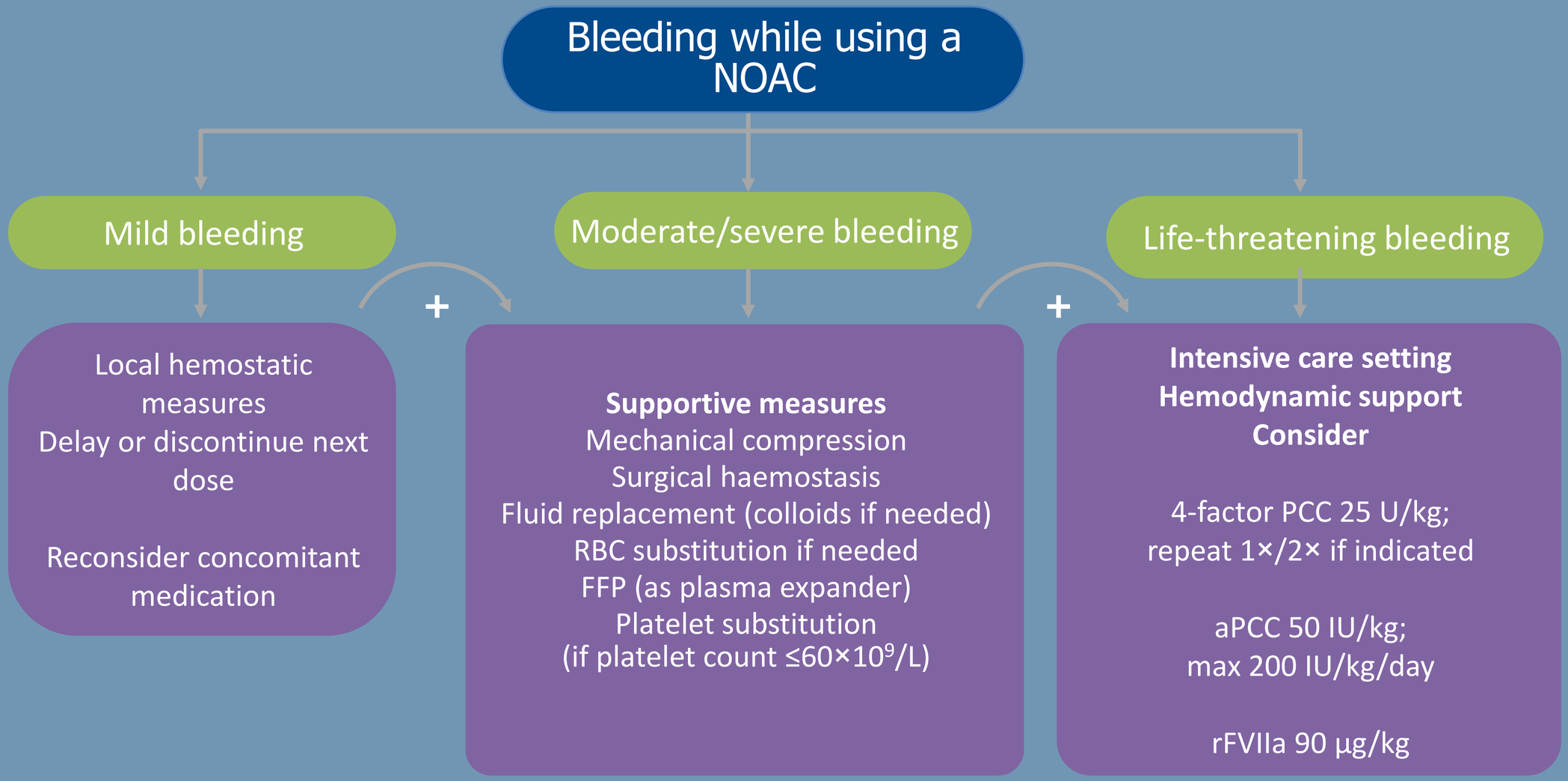
Drug level > 400 ng/ml
Major hemorraghic risk

Can Journal of Cardiol 2014; 30 : 381

Reversal of NOACs

- Activate coagulation to overcome the effect of the drug
- Neutralize drug

Activate coagulation to overcome the effect of the drug
EHRA algorithm



Heidbuchel H et al. Europace 2013;15:625–51 ; Siegal D et al, Blood 2014; 123: 1152

Adjuntive therapies for severe/life-threatening bleeding

Remove drug by hemofiltration or hemodialysis

- Restricted to non-protein bound drug (dabigatran are partly unbound)
- Limited availability, expensive, burdensome
- Slow drug clearance (hours)
- Only partially effective

Oral charcoal for dabigatran ingestion within 2 hours

Desmopressin

Antifibrinolytic agents

Siegal D et al, Blood 2014; 123: 1152
Can Journal of Cardiol 2014; 30 : 381

Neutralize the effects of the drug
Specific antidotes

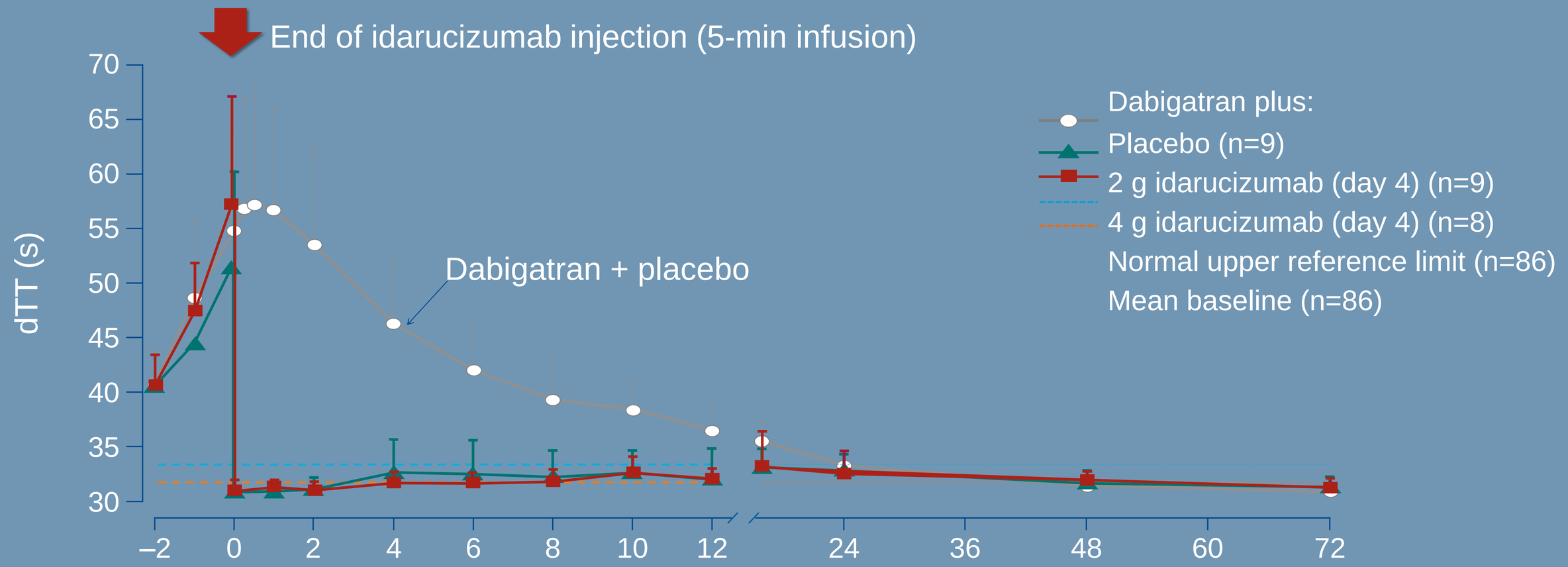
	Idarucizumab : PraxBind®	**Andexanet alpha**	**Aripazine**
Structure	Humanized Fab fragment	Human rXa	Synthetic small molecule
Target	Dabigatran	FXa inhibitors	Universal
Binding	Non competitive High affinity (35O times greater affinity than thrombin)	Competitive	Synthetic small molecule: charge–charge interactions (heparin); hydrogen bonds (NOACs)
Investigation status	**Phase III** Patients requiring urgent surgery/major bleeding; May 2014 **Submitted for approval** Mar 2015	**Phase III** Patients with bleeding; Jan 2015	**Phase II** Ongoing

Idarucizumab: an antidote specific to dabigatran

- Restoration of coagulation
  - Potent binding affinity ~350 times higher than the binding of dabigatran to thrombin
  - No procoagulant or anticoagulant effects
  - Short half-life
- Easy and rapid administration
  - IV administration, immediate onset of action
- Low risk of adverse reactions
  - No Fc receptor binding
  - No endogenous targets

Glund et al. Thromb Haemost. 2015;
Schiele et al. Blood 2013

Idarucizumab demonstrated immediate, complete, and sustained reversal of dabigatran in healthy subjects



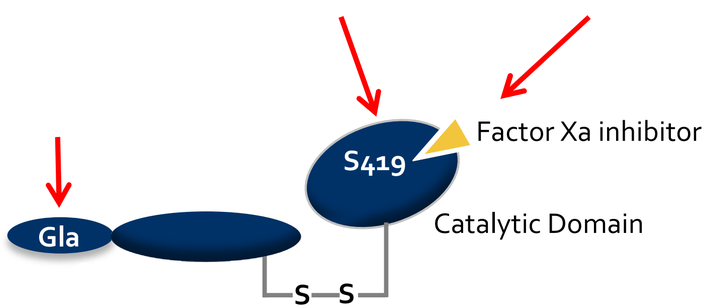
'Normal upper reference limit' refers to (mean+2SD) of 86 pre-dose measurements from a total of 51 subjects

Glund S et al. AHA 2013; abstr 17765

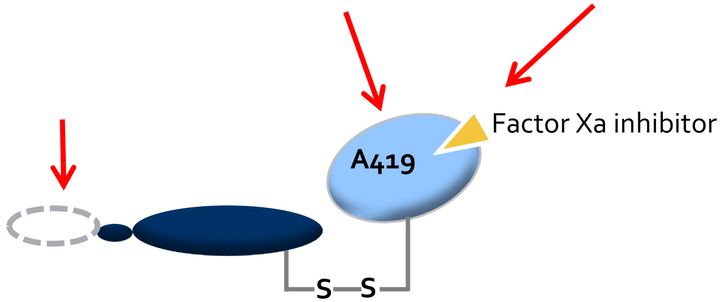
Andexanet : reverse activity of FXa inhibitors

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



Factor Xa



Andexanet Alfa

- 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

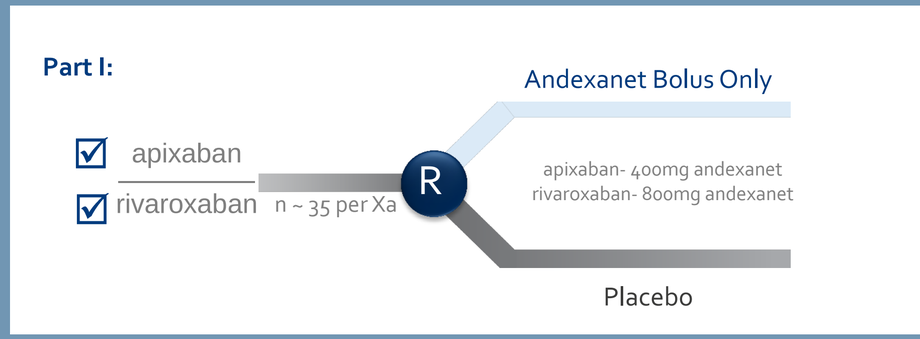
Nature Medicine (2013),19(4): 446-51

ANNEXA™
Phase 3 Registration-enabling Studies

Andexanet alfa administration was well tolerated in subjects aged 50-65

Andexanet significantly, rapidly and reversibly reduced anti-fXa activity and free rivaroxaban, and restored thrombin generation to baseline (pre-rivaroxaban) levels

Andexanet produced normalization of coagulation parameters within 2 minutes of completion of infusion



In summary

- Bleeding in patients receiving NOACs occurs with a frequency less to VKAS
- Most bleedings are minors or moderates
- Major or life-threatening bleeding require proceduralist-led interventions, life sustaining therapies and non specific procoagulant medications
- Specific antidotes will be soon available