10-11-12 Ottobre 2016

Palazzo Bonin Longare

Vicenza

Terapia anticoagulante orale: trattamento delle complicanze emorragiche

Vittorio Pengo

Clinica Cardiologica

Università di Padova

POTENTIAL PROBLEMS WITH DOACs

Adherence and persistence to treatment: very important in light of the short half-life of new oral anticoagulants

Renal Function

Treatment of major or life threatening bleeding

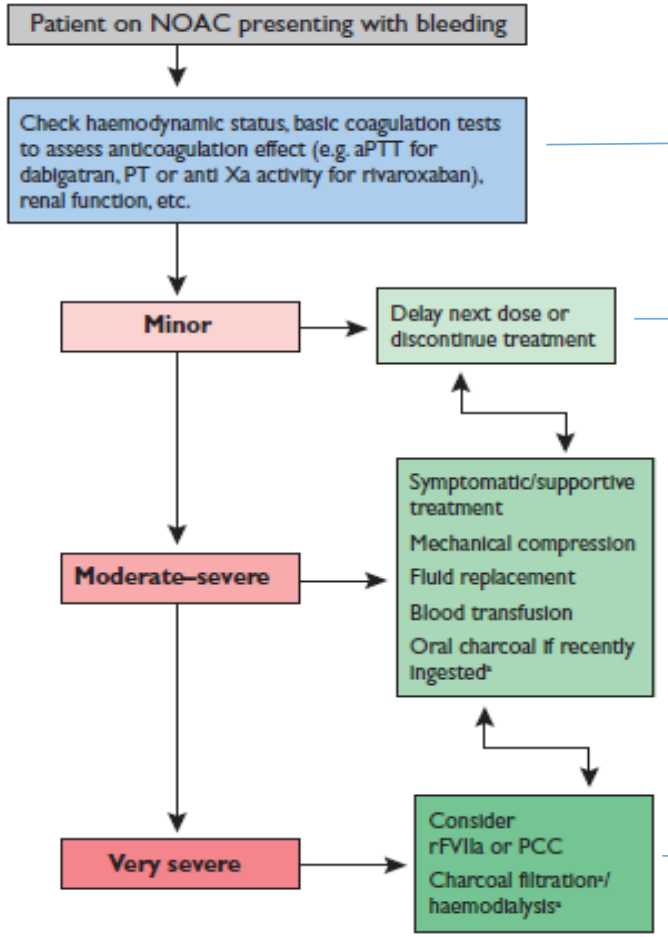
Coagulation assays and interpretation

Potential drug interactions

Side-effects and potential drop-out

Costs

How to treat bleeding during DOACs



- Do not use aPTT and PT
- Use dTT for dabigatran and anti factor Xa for other NOACs

- Be careful to stop tratment for negligible bleeding

- No FVIIa as first choice

ESC Guidelines 2012

Reversal with Factor VIIa

- *Activated recombinant Factor VII : rFVIIa* is not approved for general hemostatic agent

  No clinical data confirm specific dosing and timing in patients

  Very short half life, very expensive

  Potentially dangerous (thromboembolic events)

Vale anche per warfarin

EMORRAGIE GRAVI/PERICOLOSE PER LA VITA:

- Sospendere NAO
- Rimpiazzo dei fluidi,
- Trasfusioni (Globuli rossi, plasma, fibrinogeno)

- **FEIBA** (Complesso Protrombinico Attivato) : **40 UI/kg** (prima scelta per Dabigatran)
- **Complessi Protrombinici a 3 o 4 fattori: 50 UI/kg** (prima scelta per i Xabani)
- rFVIIa (90-100µg/kg) (se falliscono i primi)

- Emodialisi (solo per Dabigatran)

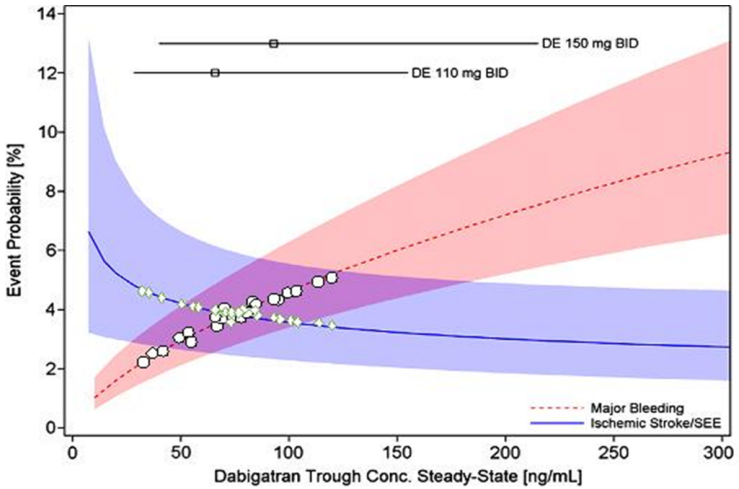
Linee guida Regione del Veneto 2014

La determinazione della concentrazione ematica dei NOACs serve in PS?

- Si perchè l'emorragia potrebbe avere una causa diversa dal farmaco
- Si perchè si può valutare il ripristino della coagulazione dopo il trattamento

- Servono test specifici per la determinazione della concentrazione: SI
- La determinazione è costosa? NO
- Test comuni solo in assenza di quelli specifici

Dabigatran



In media la concentrazione di Dabigatran è 175 ng/mL (117-275 ng/mL) al picco; 91 ng/mL (61-143 ng/mL) a valle

dTT (Hemoclot)>65 sec a 12 ore dall'assunzione → RISCHIO EMORRAGICO

aPTT>80 sec a 12 ore dall'assunzione (in mancanza di dTT)

van Ryn J et al. Thromb Haemost 2010; Huisman M et al. Thromb Haemost 2012

Rivaroxaban

In media rivaroxaban= 215 ng/mL al picco (22-535 ng/mL); 32 ng/mL (6-239 ng/mL) a valle

Richiedere dosaggio rivaroxaban

Anti Xa activity (ng/ml)

PT ratio (in assenza di anti Xa) = 1.5 (approssimativamente rivaroxaban 215ng/ml)

Non richiedere INR

van Ryn J et al. Thromb Haemost 2010; Huisman M et al. Thromb Haemost 2012

Apixaban

Anti Xa activity (ng/ml)

Non richiedere PT ratio

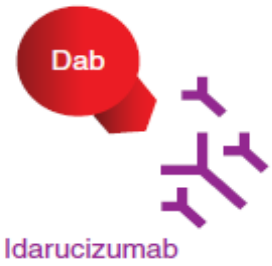
Non richiedere INR

Strategies for anticoagulation reversal

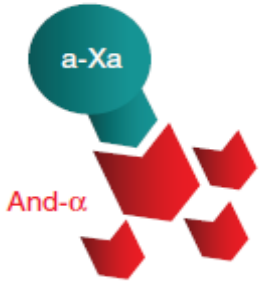
	Warfarin	Dabigatran	Rivaroxaban, apixaban, and edoxaban
General measures	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support
Activated charcoal	Consider if last dose <2 h	Consider if last dose <2 h	Consider if last dose <2 h
Haemodialysis	No benefits (highly protein bound)	Removes 62–68% of circulating drug	No benefits (highly protein bound)
Coagulation factors	PCC (25 U/kg, repeat if necessary) FFP (10–15 ml/kg) rFVIIa (90 ug/kg)	PCC (25 U/kg, repeat if necessary) rFVIIa (90 ug/kg)	PCC (25 U/kg, repeat if necessary) or FEIBA (50 IE/kg, max 200 IE/day) rFVIIa (90 ug/kg)
Specific inhibitors	Vitamin K (5–10 mg IV)	Idarucizumab (Phase 1) Ciraparantag (preclinical)	Andexanet alfa (Phases 1–3) Ciraparantag (Phase 1)

PCC, prothrombin complex concentrates; rFVIIa, recombinant-activated factor VII.

Enriquez A, Europace March 26,2015



Fab fragments anti dab
of humanized monoclonal
antibodies

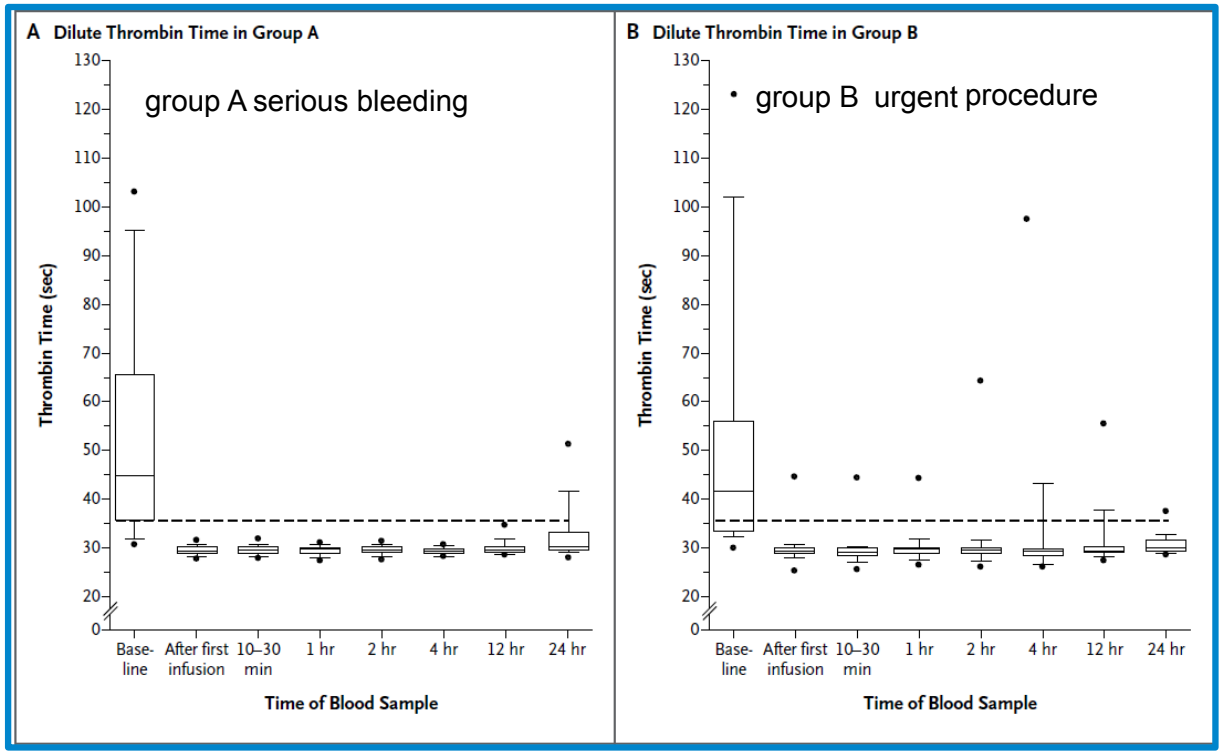


Andexanet alfa:
Modified recombinant Factor Xa
Is catallitically inactive and lacks the
Membrane binding γ-carboxyglutammic
acid (Gla domain) of native Fxa. However
it retains the ability to bind direct Factor
Xa inhibitors

Small synthetic molecule
competitively binding
NOACs

Enriquez A, Europace March 26,2015

Idarucizumab for Dabigatran Reversal

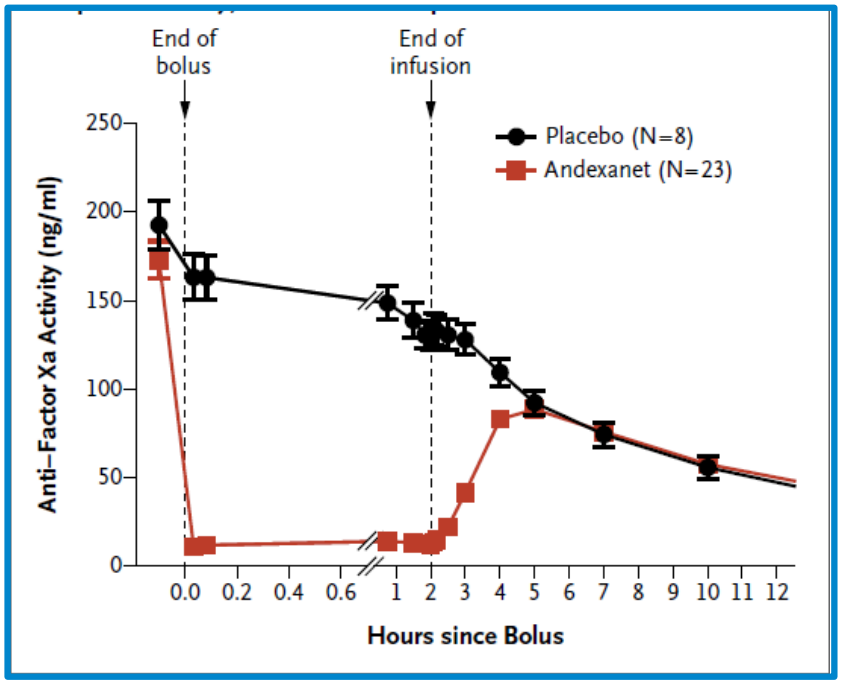


The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of 5 mg idarucizumab

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

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Healthy older volunteers were given 5 mg of apixaban twice daily (A) or 20 mg of rivaroxaban daily (B).



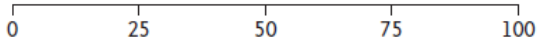
A Bolus: 400mg plus 4mg/min infusion

B Bolus: 800mg plus 8mg/min infusion

N Engl J Med 2015;373:2413-24.

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Subgroup	No. of Patients	Percent Adjudicated as Excellent or Good Hemostasis (95% CI)
All patients with efficacy analyses	47	79 (64–89)
Drug		
Rivaroxaban	26	81 (61–93)
Apixaban	20	75 (51–91)
Enoxaparin	1	100
Sex		
Male	24	71 (49–87)
Female	23	87 (66–97)
Site of bleeding		
Gastrointestinal	25	84 (64–96)
Intracranial	20	80 (56–94)
Other	2	0
Age		
<65 yr	7	71 (29–96)
65–75 yr	9	89 (52–100)
≥75 yr	31	77 (59–90)
Andexanet dose		
Low	42	76 (61–88)
High	5	100 (48–100)
Anti–factor Xa <75 ng/ml or <0.5 IU/ml	17	82 (57–96)



N Engl J Med 2016;375:1131-41.

Issues to be considered to minimize the risk of hemorrhagic stroke in partients with atrial fibrillation.

Issue	Remarks
Use of NOAC instead of AVK	**Expected an approximate 50% risk reduction**
Blood pressure control	**For both NOAC and AVK**
Systematic evaluation of renal and hepatic function	**Especially for NOAC**
Drugs and food interactions	**Especially for AVK**
Reduce the risk of fall	**For both NOAC and AVK**
Discontinuation of antiplatelet therapy	**If not strictly indicated**
Prescriber education	**Especially for NOAC**
Time adherence to treatment	**Especially for NOAC**
Lower the intensity of anticoagulation	**For both NOAC and AVK**
LAA closure	**In special situations**

LAA: left atrial appendage; NOAC: New oral anticoagulants; VKA: Vitamin K antagonist

Zoppellaro G. Expert Opinion Drug Safety 2015