Nuovi e vecchi anticoagulanti - come reagire quando sanguina?

Bellinzona 06.04.17

Inga Hegemann, Klinik für Hämatologie USZ

Agenda

- bleeding rates and differences DOAC* and VKA*
  - minor, major bleeding, intracranial haemorrhage ICH
  - studies vs. real life

- therapy or reversal
  - general and specific
  - efficacy, adverse effects

- reintroduction of anticoagulation

- case

*direct oral anticoagulants, vitamin k antagonists

Definitions ISTH

Major bleeding: = fatal and/or
- ↓hemoglobin 20g/l
  = / > 2 units packed red cells
- critical area:
  intracranial, intraspinal,
  intraocular, retroperitoneal,
  pericardial, intramuscular
  + compartment syndrome

Minor bleeding: not above
- clinical relevant: medical
  surgical treatment,
  hospitalization
- change in anticoagulation

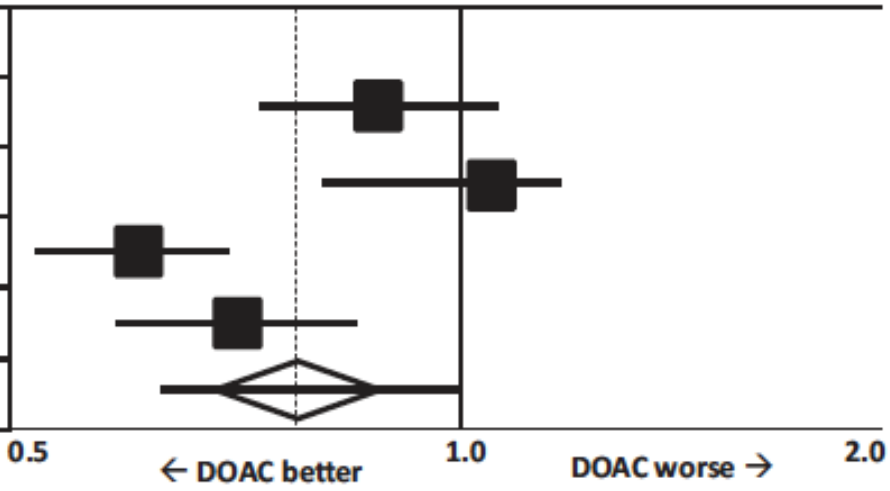
Bleeding profiles DOAC and VKA phase III studies

	Dabigatran		Rivaroxaban	Apixaban	Edoxaban	
	RE-LY		ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48	
NOAC regimen	110 mg bid	150 mg bid	20 mg od[a]	5 mg bid[b]	30 mg od[c]	60 mg od[c]
Comparator arm	Warfarin		Warfarin	Warfarin	Warfarin	
Total number of patients randomized	18,113		14,264	18,201	21,105	
Major bleeding[d]						
DOAC vs. warfarin (%/y)	2.92 vs. 3.61	3.40 vs. 3.61	3.6 vs. 3.4	2.13 vs. 3.09	1.61 vs. 3.43	2.75 vs. 3.43
HR (95% CI)	0.80 (0.70–0.93)[e]	0.94 (0.82–1.08)[e]	1.04 (0.90–1.20)	0.69 (0.60–0.80)	0.47 (0.41–0.55)	0.80 (0.71–0.91)
p-Value	0.003	0.41	0.58	< 0.001	< 0.001	< 0.001
Intracranial bleeding						
DOAC vs. warfarin (%/y)	0.23 vs. 0.76	0.32 vs. 0.76	0.5 vs. 0.7	0.33 vs. 0.80	0.26 vs. 0.85	0.39 vs. 0.85
HR (95% CI)	0.30 (0.19–0.45)[e]	0.41 (0.28–0.45)[e]	0.67 (0.47–0.93)	0.42 (0.30–0.58)	0.30 (0.21–0.43)	0.47 (0.34–0.63)
p-Value	< 0.001	< 0.001	0.02	< 0.001	< 0.001	< 0.001

Weitz JI 2017

Bleeding profiles DOAC and VKA phase III studies

Drug (Trial)	RR (95% CI)	p value
Dabigatran (RE-LY)	0.94 (0.82-1.07)	0.34
Rivaroxaban (ROCKET AF)	1.03 (0.90-1.18)	0.72
Apixaban (ARISTOTLE)	0.71 (0.61-0.81)	<0.0001
Edoxaban (ENGAGE AF-TIMI 48)	0.80 (0.71-0.90)	0.0002
Combined	0.86 (0.73-1.00)	0.06



Major bleeding rate is higher in VTE studies

Parks AL 2017

Risk factors for hemorrhage

- age
- history of bleeding
- diabetes, anemia, hypertension
- congestive heart failure
- renal or liver disease
- cancer
- alcohol
- co-medication (antiplatelet, antiinflammatory)
- falls
- coagulation control
- genetic polymorphisms
- biomarkers

Bleeding in „real life“*

%/year

	DOAC	VKA
Major bleeding	2.5	2.5-3.7
ICH**	0.34	0.44

* observational, registry, cohorts,** intracranial hemorrhage

Bleeding in „real life“*

	DOAC		VKA
Major bleeding	2.5	=	2.5-3.7
ICH**	0.34	=	0.44

* observational, registry, cohorts,** intracranial hemorrhage

Bleeding in „real life“

970 patients (806 major bleeding), italian cohort

	DOAC	VKA
GI bleeding	46%	25%
ICH	21%	51%

Becattini C et al 2017

Bleeding in „real life“ and mortality

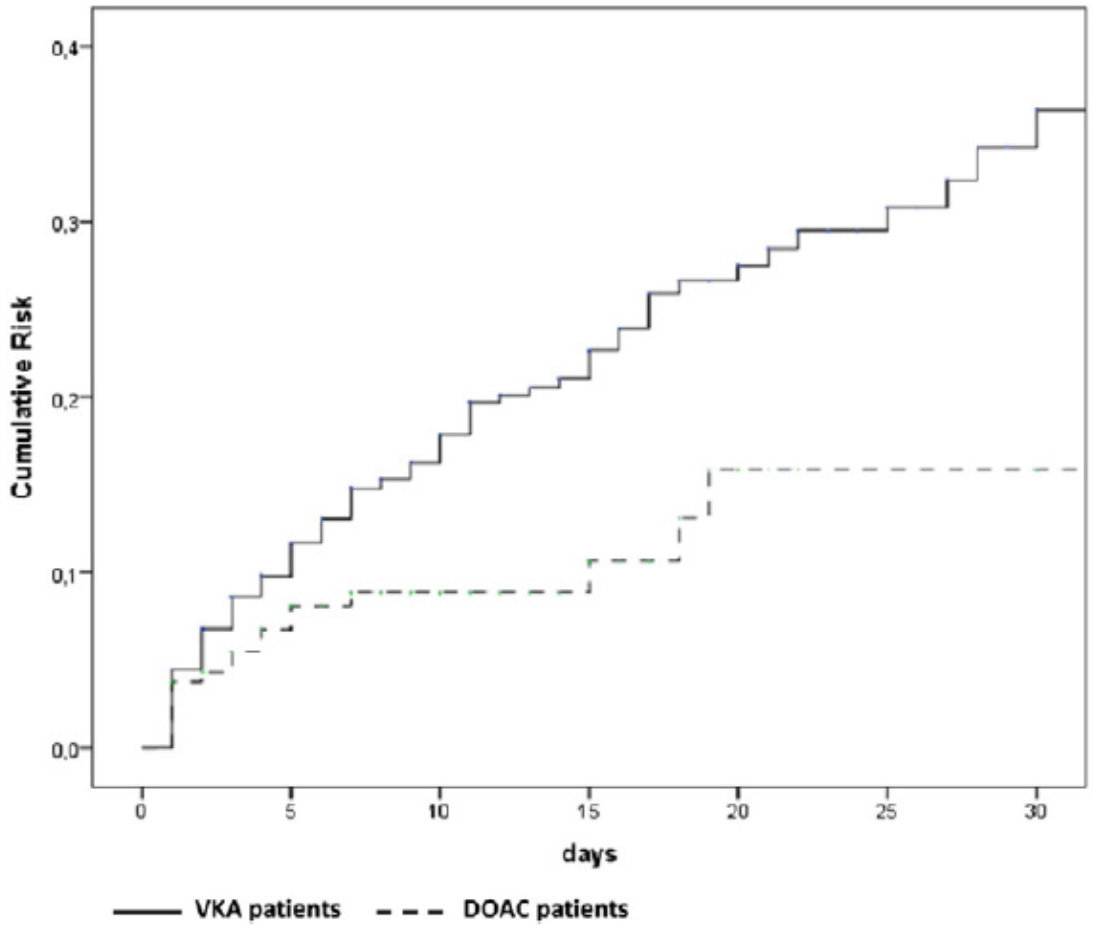
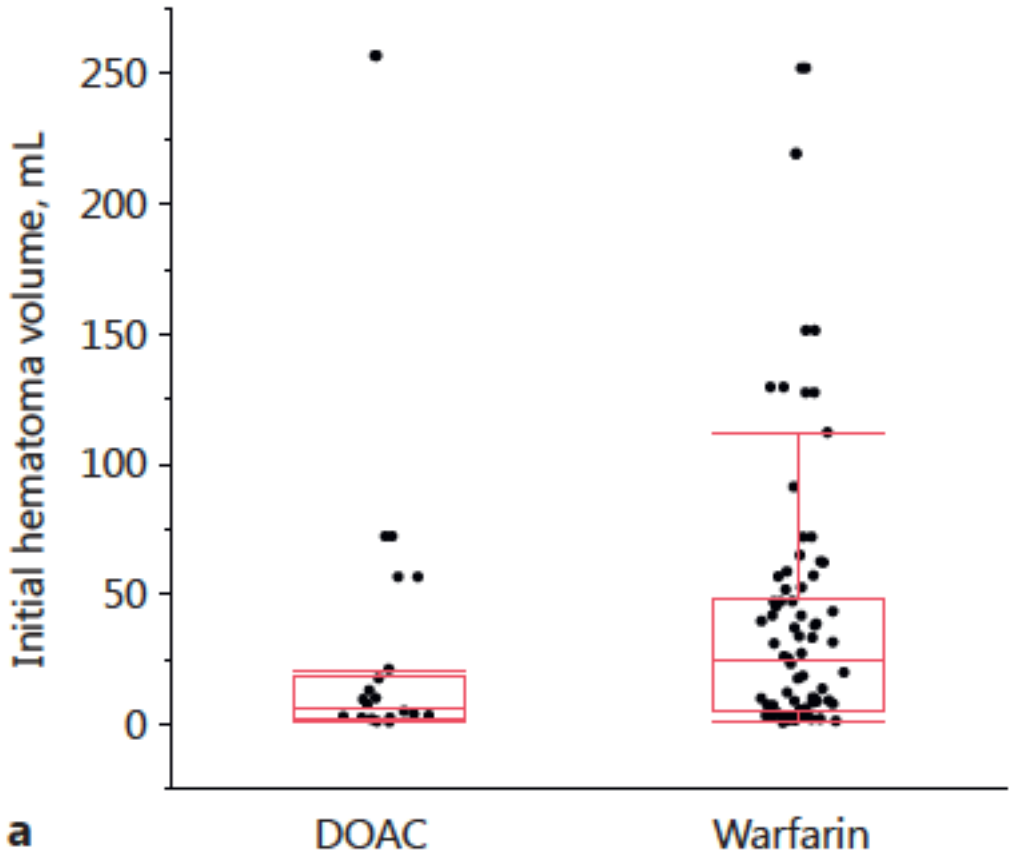


Fig. 2. Kaplan Meier curves for cumulative risk of death at 30 days in DOAC and VKA patients.

Becattini C et al 2017

ICH in „real life“

prospective study Japan 89 patients



Adachi T et al 2017

ICH in „real life“

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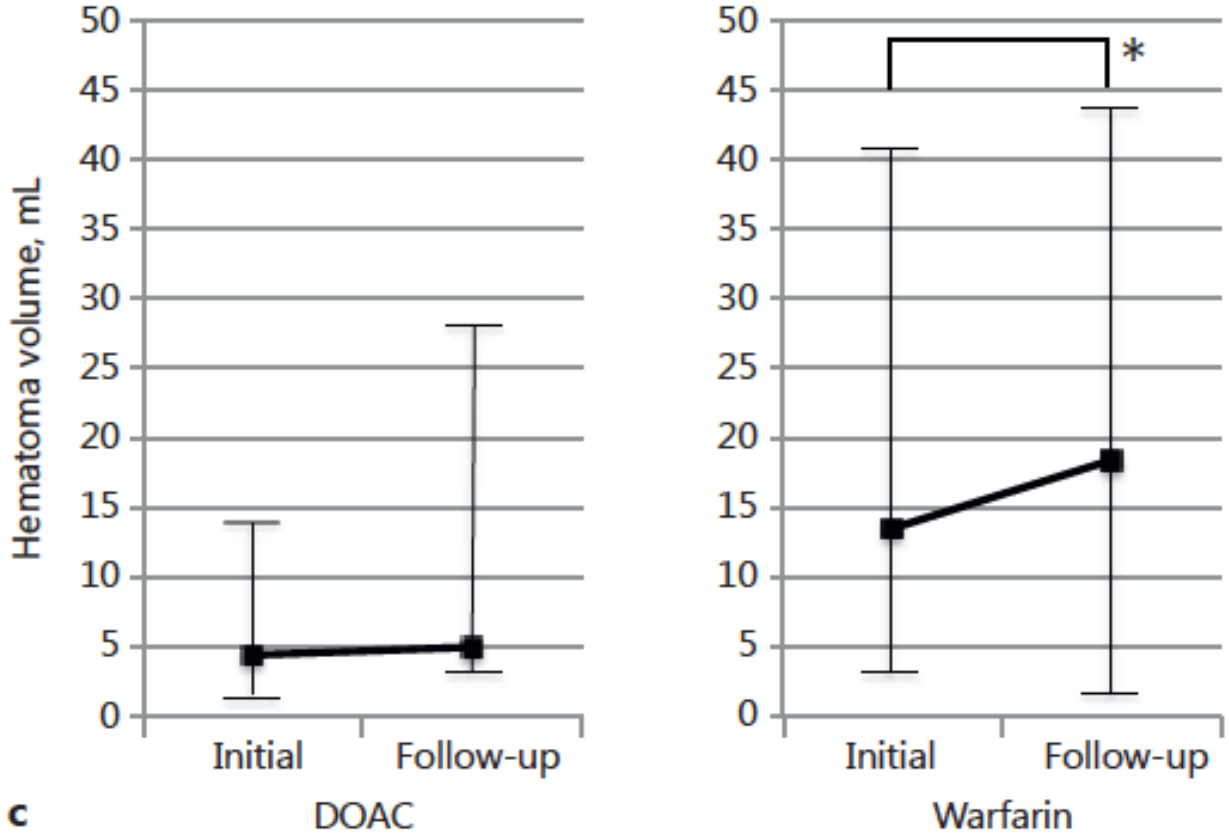
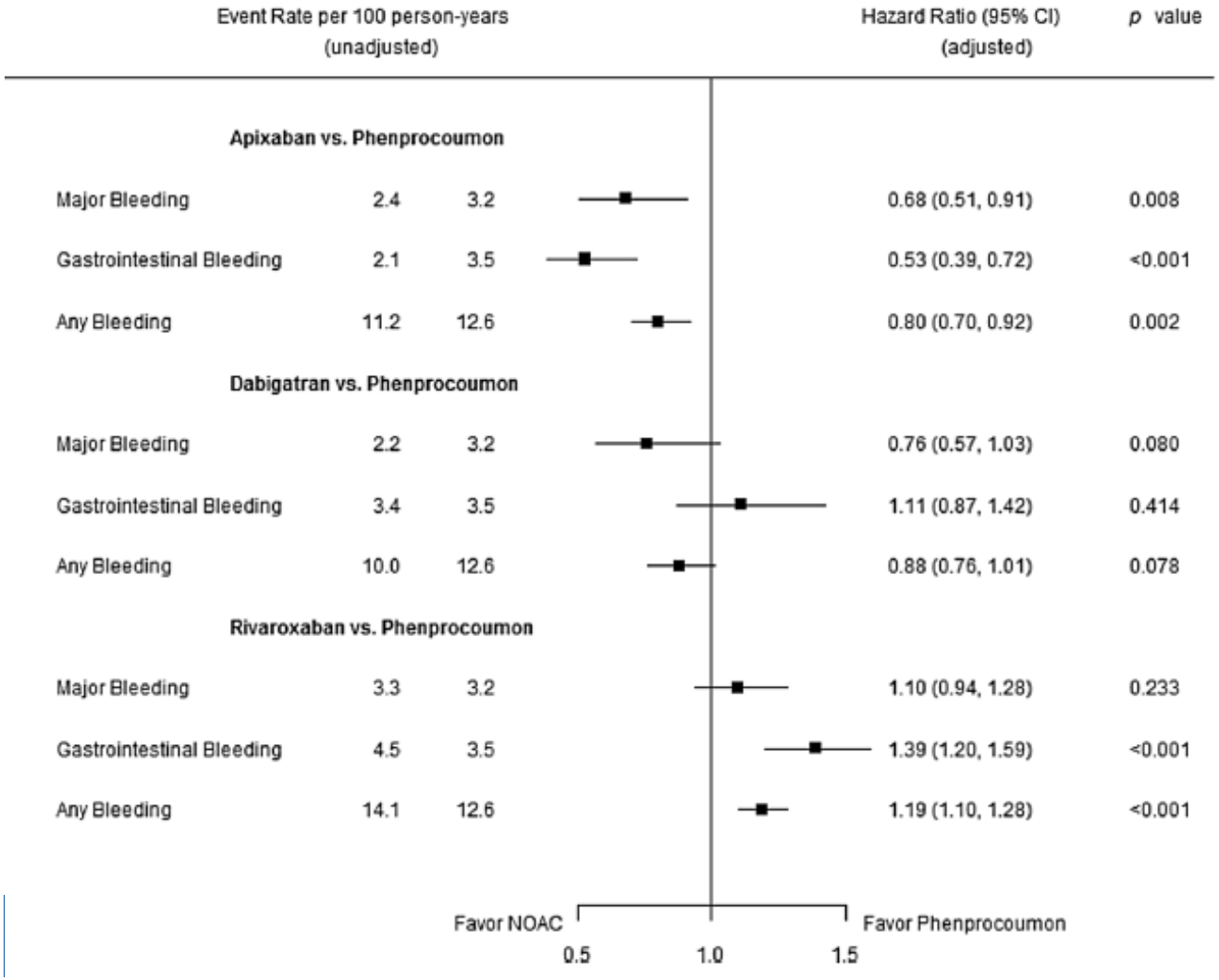


Adachi T et al 2017

Bleeding in „real life“ differences between DOAC

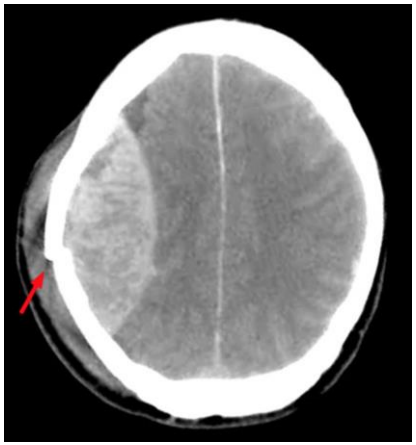
CARBOS study post-marketing surveillance AF 35013 pat:

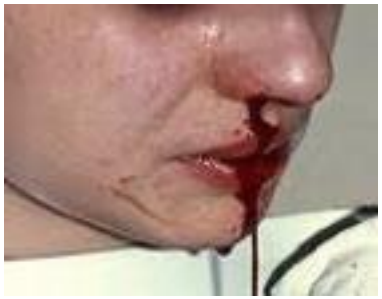
3633 Apixaban
3138 Dabigatra
12063 Rivarox
16179 Phenpro

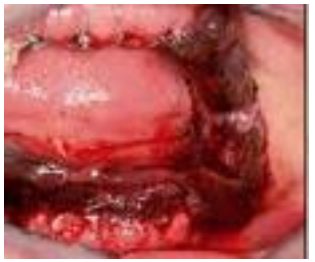


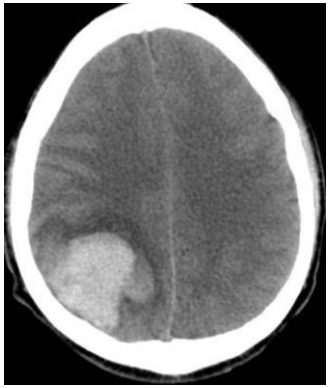
Hohnloser SH et al 2017

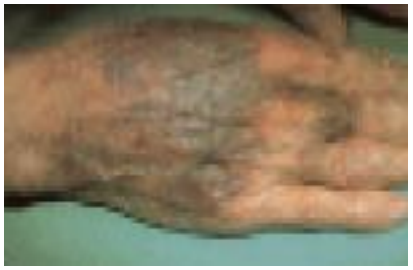
Bleeding under anticoagulation











Bleeding under anticoagulation

Verication of relationship ??

which anticoagulant
dose
time of intake

other factors : trauma, ulcer, cancer?

laboratory: INR, TT, anti-Xa activity

Bleeding under anticoagulation **VKA**

-STOP intake
-measure
-reduce dose
-antagonization

	VKA	**vitamin K**	
- half-life	5d		10h
- start of action	2-3d	oral	4-6h
		i.v.	1-3h

Bleeding under anticoagulation **VKA**

INR 5-9 minor bleeding:	STOP VKA vitamin K(?)
INR >5 major bleeding:	hospitalization vitamin K reversal (?)

Bleeding under anticoagulation **VKA**

Principle	Agent	Time frame	Target population
Competitive neosynthesis of vitamin K–dependent factors[a]	Vitamin K intravenously Vitamin K orally	6–12 h 12–24 h	Adjunct in life-threatening bleeding Non-major bleeding
Substitution with vitamin K–dependent factors[a]	Plasma PCC	4–24 h 10–30 min	Life-threatening bleeding—if PCC not available Life-threatening bleeding
By-passing agents	rFVIIa aPCC	Minutes 20–40 min	Not recommended Not recommended

reversal: PCC >> plasma ACCP guidelines
25 – (50) IU/kg body weight

Schulman S 2017

Bleeding under anticoagulation

Indications for reversal (all anticoagulants)

- life-threatening bleed (ICH)
- ongoing bleeding
- critical organ or closed space
- expected long delay spontaneous restoration
- need for urgent intervention

Weitz JI 2017

Bleeding under anticoagulation

Indications for reversal (all anticoagulants)

- life-threatening bleed (ICH)
- ongoing bleeding
- critical organ or closed space
- expected long delay spontaneous restoration
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thrombophilic risk ?

Bleeding under anticoagulation DOAC

- Mild bleeding: local interventions
- Major bleeding:
  - STOP DOAC (half-life)
  - charcoal (dabigatran 1-3 h)
  - consider specific antagonization
  - (dabigatran dialysis, CVVF)
  - embolization / surgery

Bleeding under anticoagulation DOAC

Specific antidotes:

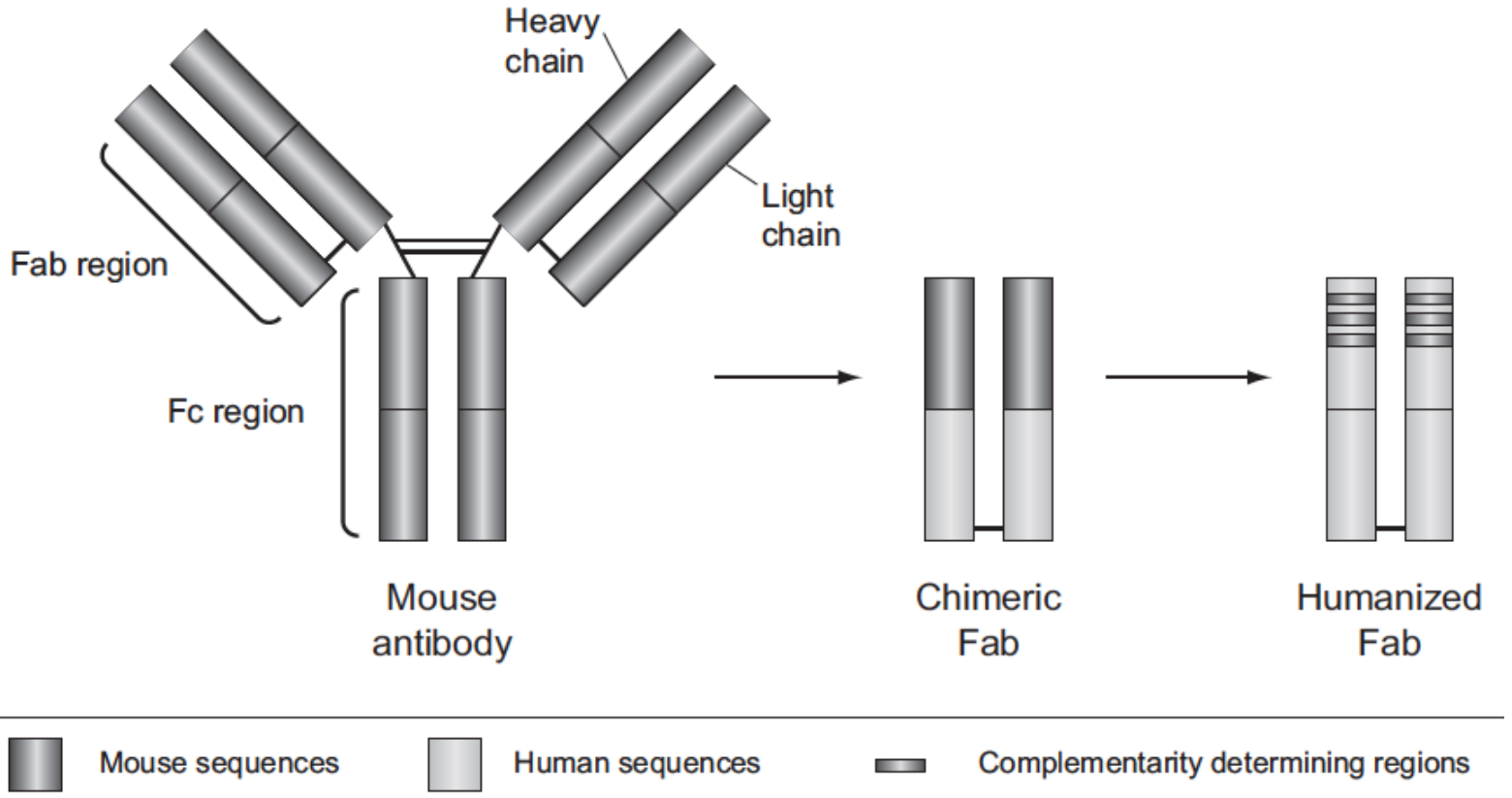
Dabigatran: Idarucizumab (Praxbind®)

Anti-Xa Inhibitors: Andexanet α (study program, not licenced)

All DOAC: Ciraparatag (studies ongoing, healthy volonteers)

Bleeding under anticoagulation DOAC

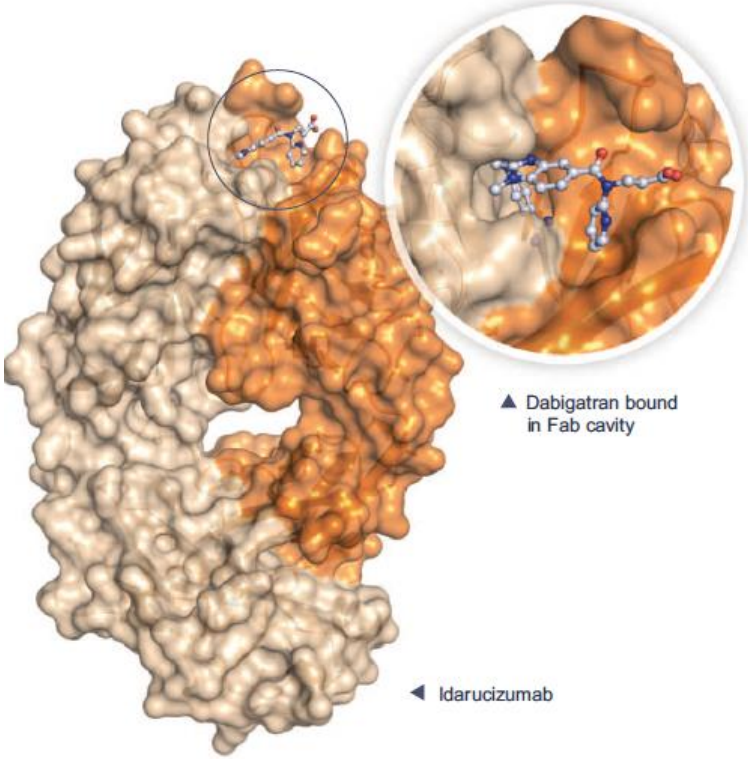
Specific antidotes: Dabigatran: Idarucizumab (Praxbind®)



Eikelboom JW 2015

Bleeding under anticoagulation DOAC

Specific antidotes: Dabigatran: Idarucizumab (Praxbind®)

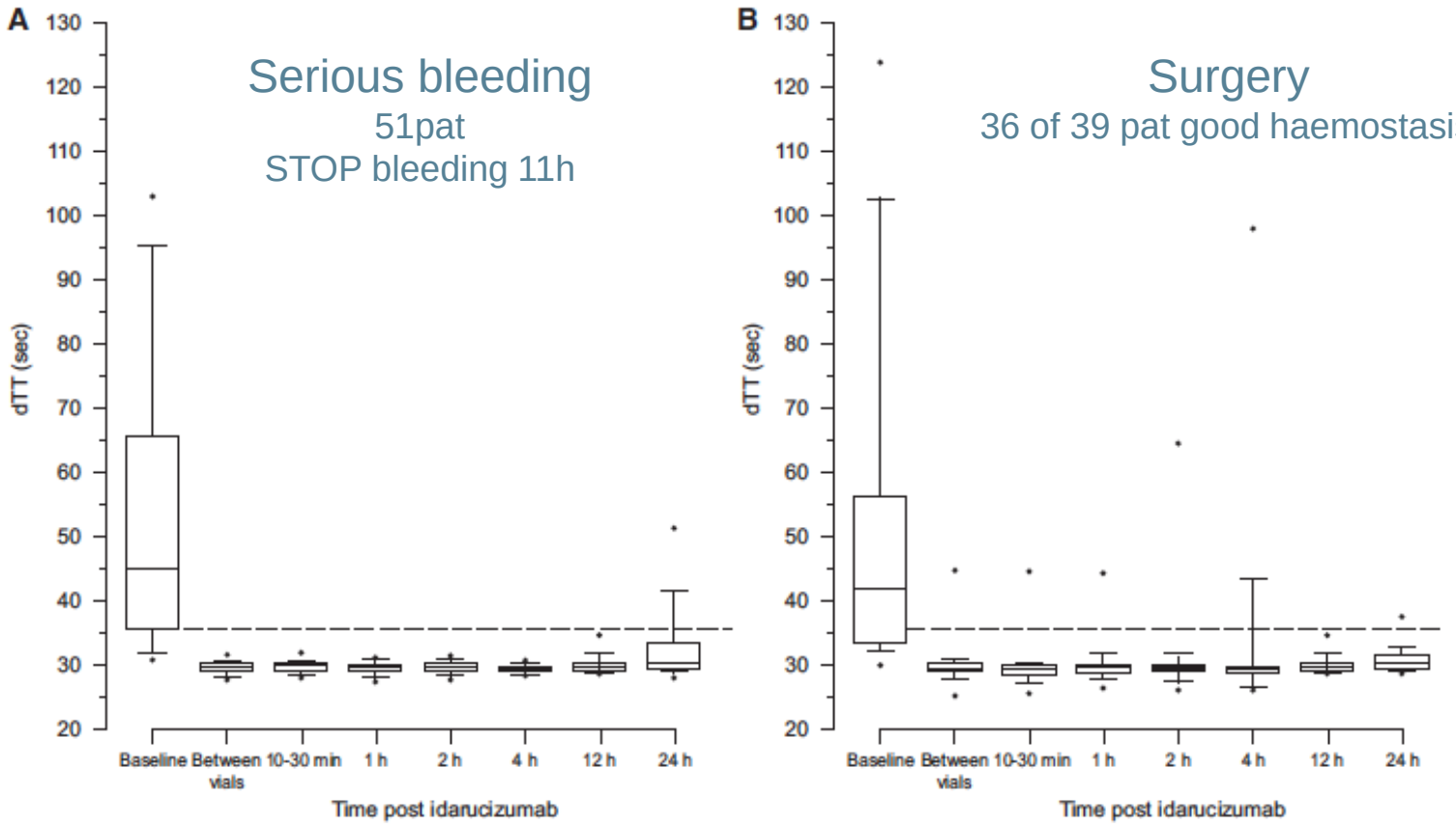


350 ↑ affinity thrombin
iv bolus 5 g
half-life 1st 45min, 2nd 8h
distribution volume 7 l
costs 3000 CHF

Eikelboom et al JW 2015

Bleeding under anticoagulation DOAC

RE-VERSE AD Dabigatran:Idarucizumab (Praxbind®)



Eikelboom JW 2015

Bleeding under anticoagulation DOAC

RE-VERSE AD Dabigatran:Idarucizumab (Praxbind®)

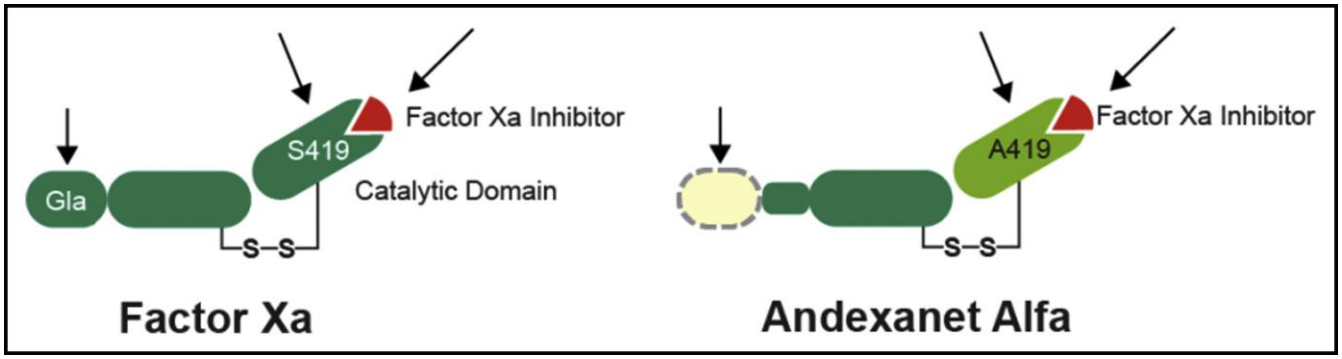
5 thromboembolic events

1	2 days after reversal
4	day 7-26

propably higher with PCC

Eikelboom JW 2015

Bleeding under anticoagulation DOAC: anti-XA Andexanet α



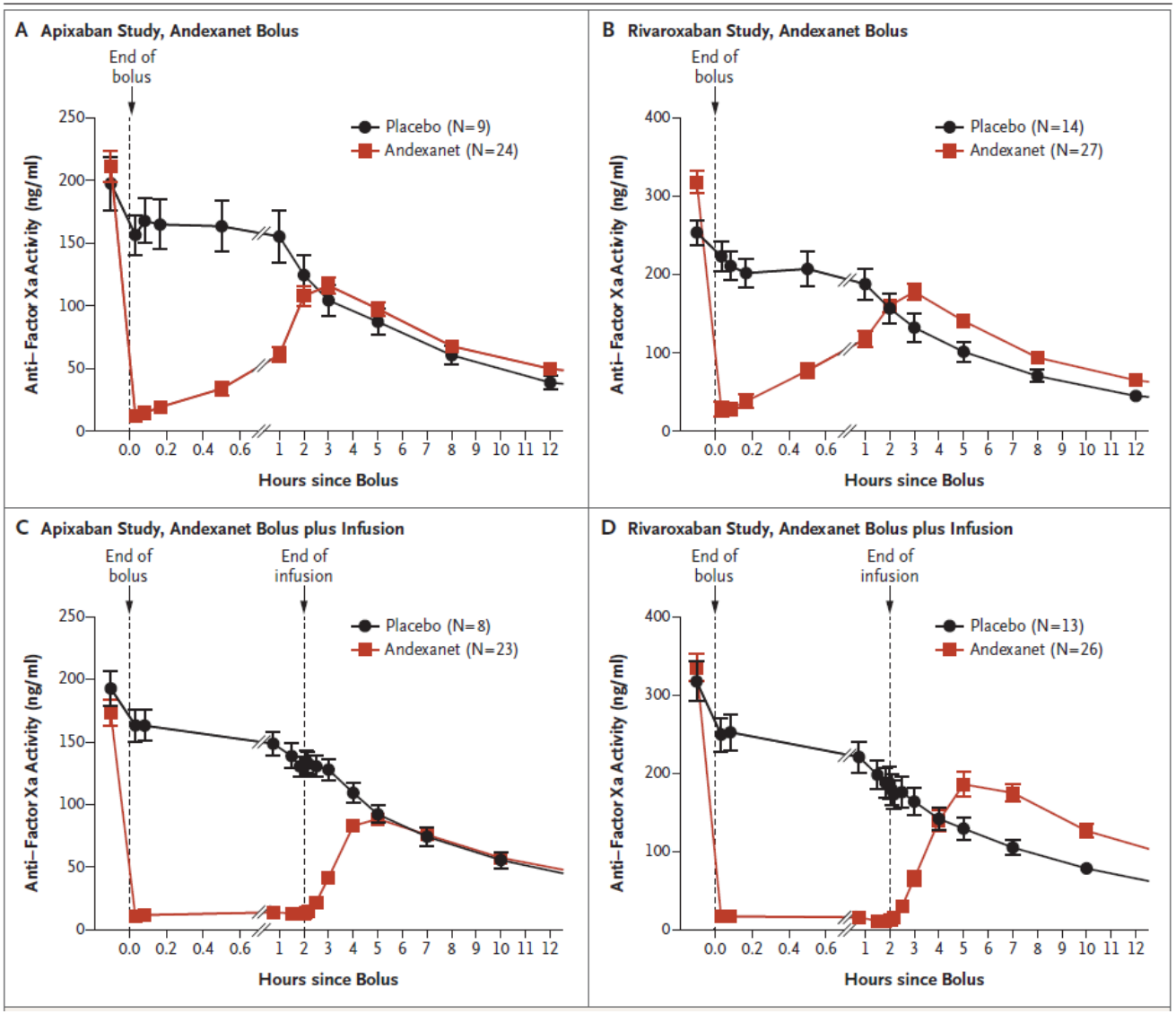
Decoy "factor Xa"

Binds all anti-Xa inhibitors

Alanine substitution –> no prothrombin activation

No Gla domain -> no assembly prothrombinase complex

Bleeding under anticoagulation DOAC: anti-XA Andexanet alpha

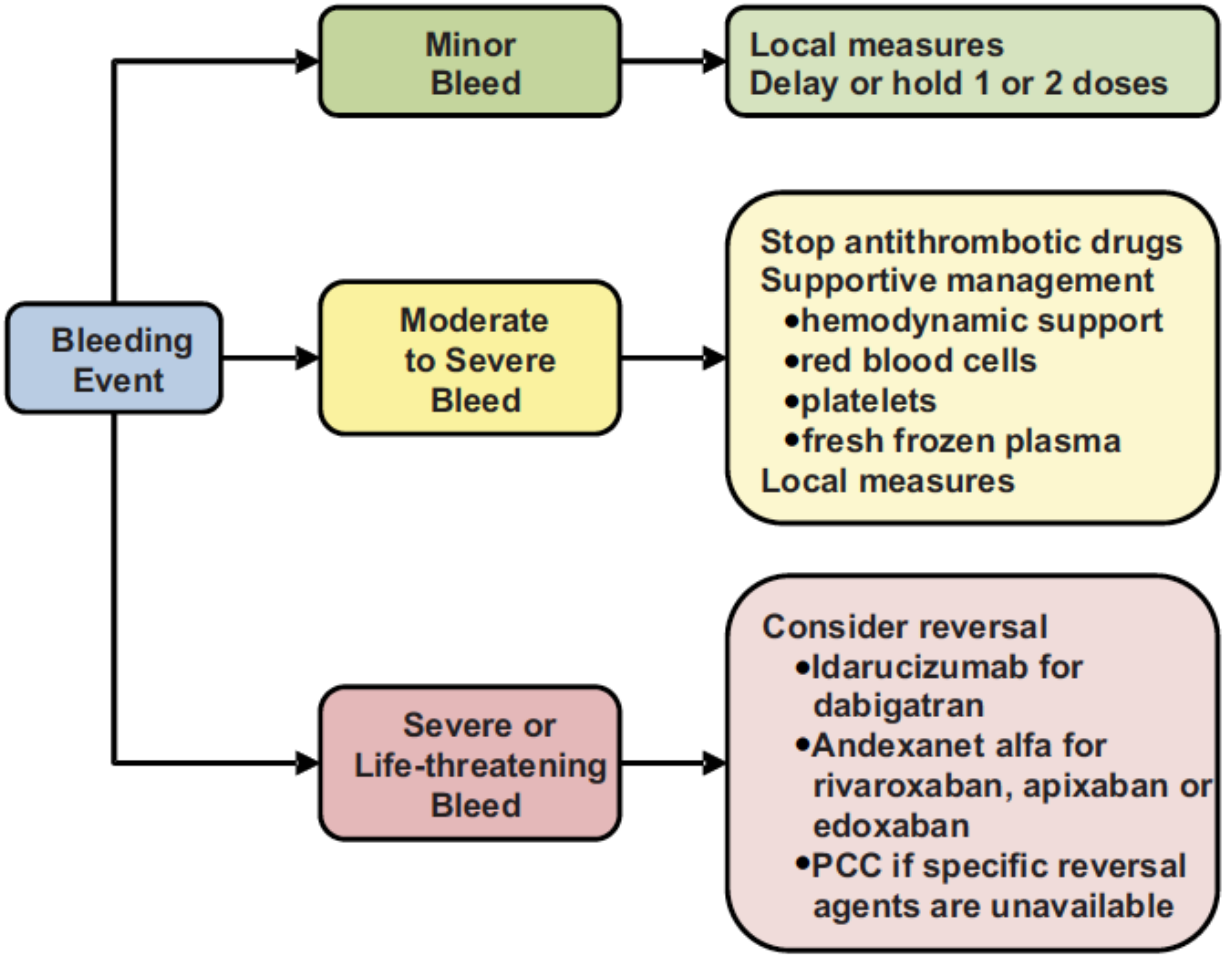


Effective hemostasis **79%**
Conolly SJ et al NEJM 2016

Siegal D NEJM 2015

Bleeding under anticoagulation DOAC

Suggested management



Weitz JI 2017

Bleeding under anticoagulation DOAC

Resumption of anticoagulation:

- majority will benefit from restarting
- 7 d after GI bleeding*
- risk assessment:
  - $CHADS_2$ VASC
  - HASBLED
  - 3 months after VTE
- consider UFH or LMWH
- consider lower dosage (apixaban 2.5 mg bd)

*retrospective data

Grazie

Thank you

Merci

Vielen Dank

!