Management von Blutungen unter Antikoagulantien und antithrombozytären Substanzen

Tamam Bakchoul

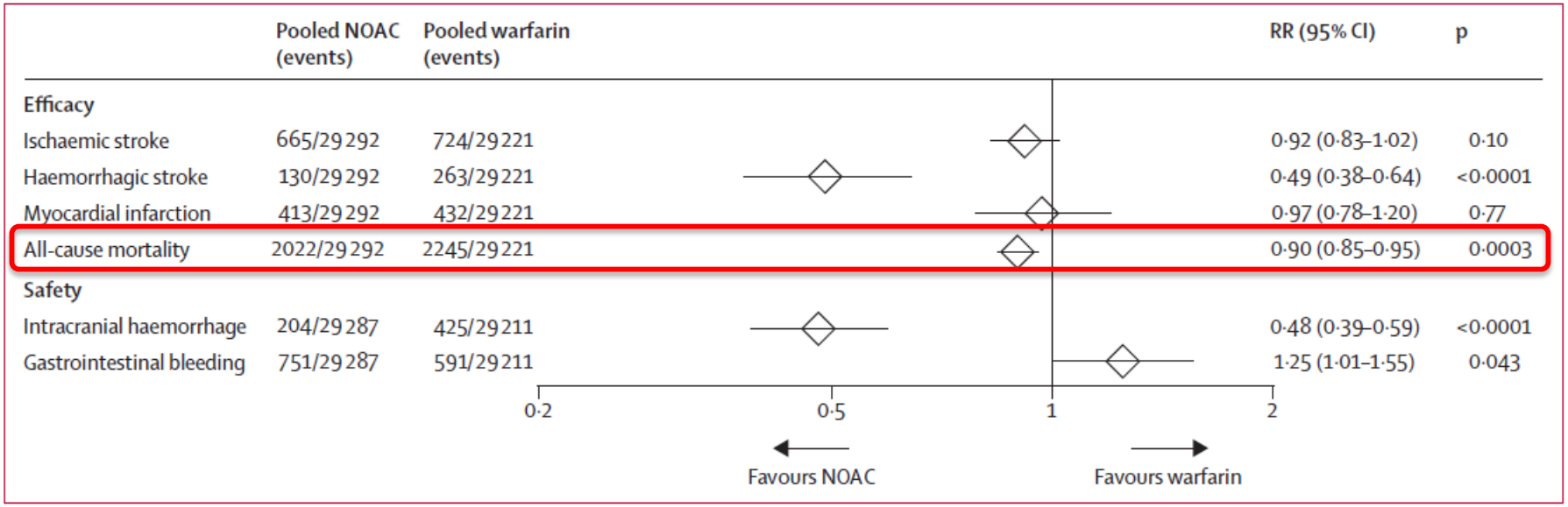
Faculty of Medicine Tubingen

Bleeding under anticoagulation

Vit-K antagonists vs. DOACs

- Meta-analysis of the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48
- 29,292 DAOCs (Dabigatran, Rivaroxaban; Apixaban; Endoxaban) and 29,221 warfarin

Efficany and safety



Ruf C et al, Lancet 2014

Bleeding under anticoagulation

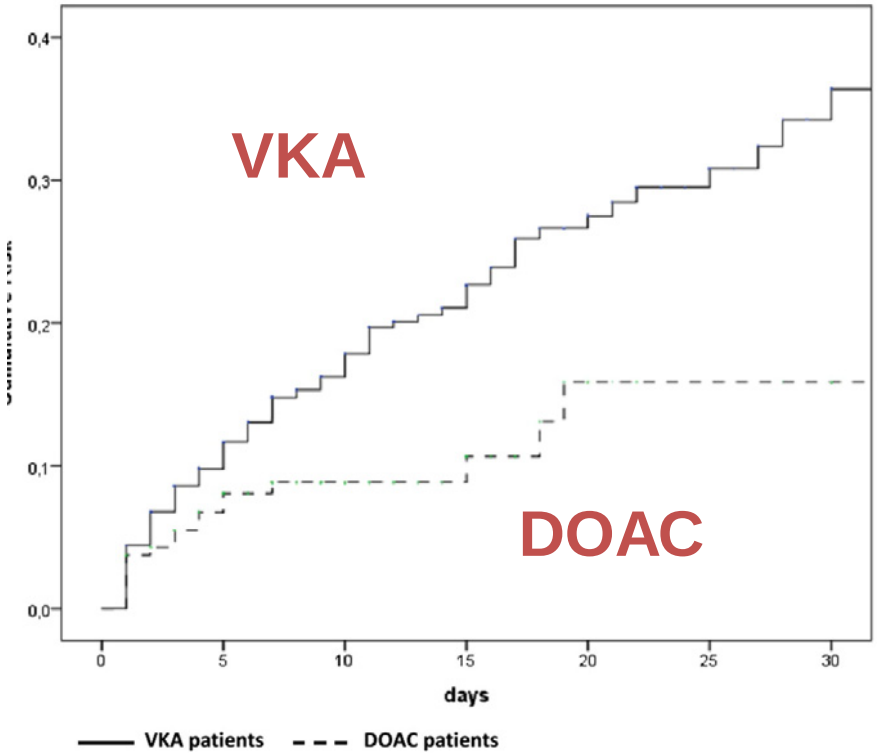
Vit-K antagonists vs. DOACs

- 806 patients with major bleeding on VKA (75%) vs. DOAC (24%)

Site of major bleeding

MBs	TOT (N = 806)	DOAC (N = 191)	VKA (N = 615)	OR 95% CI	p
Intracranial, n (%)	354 (44)	41 (21)	313 (51)	0.26 0.18–0.39	<0.001
Gastrointestinal, n (%)	239 (30)	88 (46)	151 (25)	2.62 1.87–3.68	<0.001
Soft/muscle, n (%)	80 (10)	11 (6)	69 (11)	0.48 0.25–0.93	0.027
Retroperitoneal, n (%)	33 (4)	2 (1)	31 (5)	0.20 0.05–0.84	0.015
Genito-urinary, n (%)	27 (3)	15 (8)	12 (2)	4.28 1.97–9.32	<0.001
Pleural/pericardial/ peritoneal, n (%)	21 (3)	5 (3)	16 (3)	1.01 0.36–2.78	ns
Articular, n (%)	18 (2)	9 (5)	9 (1)	3.33 1.30–8.51	0.008
Upper airways, n (%)	15 (2)	9 (5)	6 (1)	5.02 1.76–14.29	0.001
Ocular, n (%)	9 (1)	9 (5)	0	–	<0.001
Spinal, n (%)	5 (1)	0	5 (1)	–	ns
Other, n (%)	5 (1)				

Risk of death



Becanttini C et al, Int J Cardiol 2017

Management of bleeding under DOAC

Nonspecific hemostatic agents

- Prothrombic complex concentrates (50 U/kg)
- Recombinant activated factor VII (90 U/kg)

Levy, Jh et al, J Thromb Haemost. 2017
Weitz JI et al, Thromb Haemost. 2015

Management of bleeding under DOAC

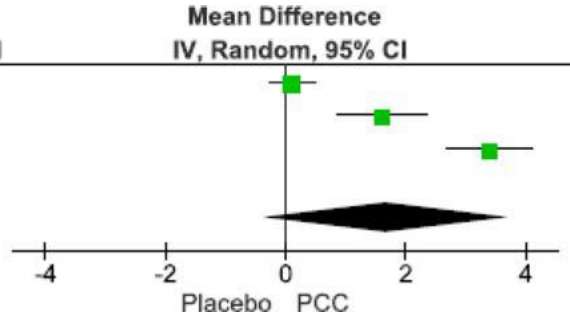
Nonspecific hemostatic agents (PCC)

- Prothrombic complex concentrates (50 U/kg) correct lab measurements

Prothrombin time reversal

Study or Subgroup	Control Mean	Control SD	Control Total	Experimental Mean	Experimental SD	Experimental Total	Weight	Mean Difference IV, Random, 95% CI
Brown 2015	12.8	0.47	12	12.7	0.48	12	34.1%	0.10 [-0.28, 0.48]
Cheung 2015	13.4	0.8	6	11.8	0.5	6	32.9%	1.60 [0.85, 2.35]
Eerenberg 2011	16.2	0.8	12	12.8	1	12	33.0%	3.40 [2.68, 4.12]
Total (95% CI)			30			30	100.0%	**1.68 [-0.33, 3.70]**

Heterogeneity: Tau² = 3.07; Chi² = 65.98, df = 2 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.64 (P = 0.10)

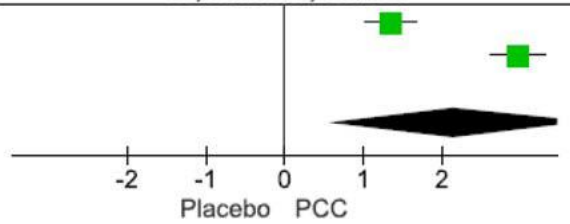


Dabi

Thrombin potential reversal

Study or Subgroup	Control Mean	Control SD	Control Total	Experimental Mean	Experimental SD	Experimental Total	Weight	Mean Difference IV, Random, 95% CI
Brown 2015	6.19	0.35	12	4.84	0.48	12	50.1%	1.35 [1.01, 1.69]
Zahir 2014	5.9	0.72	33	2.93	0.72	31	49.9%	2.97 [2.62, 3.32]
Total (95% CI)			45			43	100.0%	**2.16 [0.57, 3.75]**

Heterogeneity: Tau² = 1.28; Chi² = 42.44, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.67 (P = 0.008)



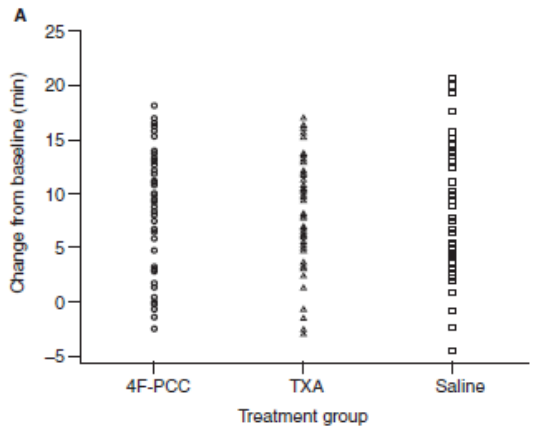
Da Luz L et al, Transfusion 2017

Management of bleeding under DOAC

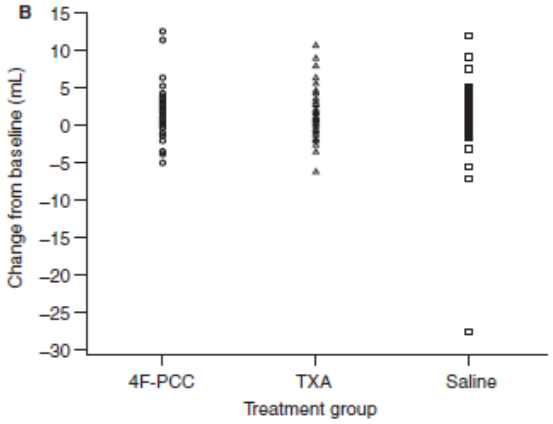
Nonspecific hemostatic agents (PCC)

- PCCs have no significant effect to prevent bleeding induced by factor Xa inhibitors (healthy donors)

Bleeding time



Blood loss

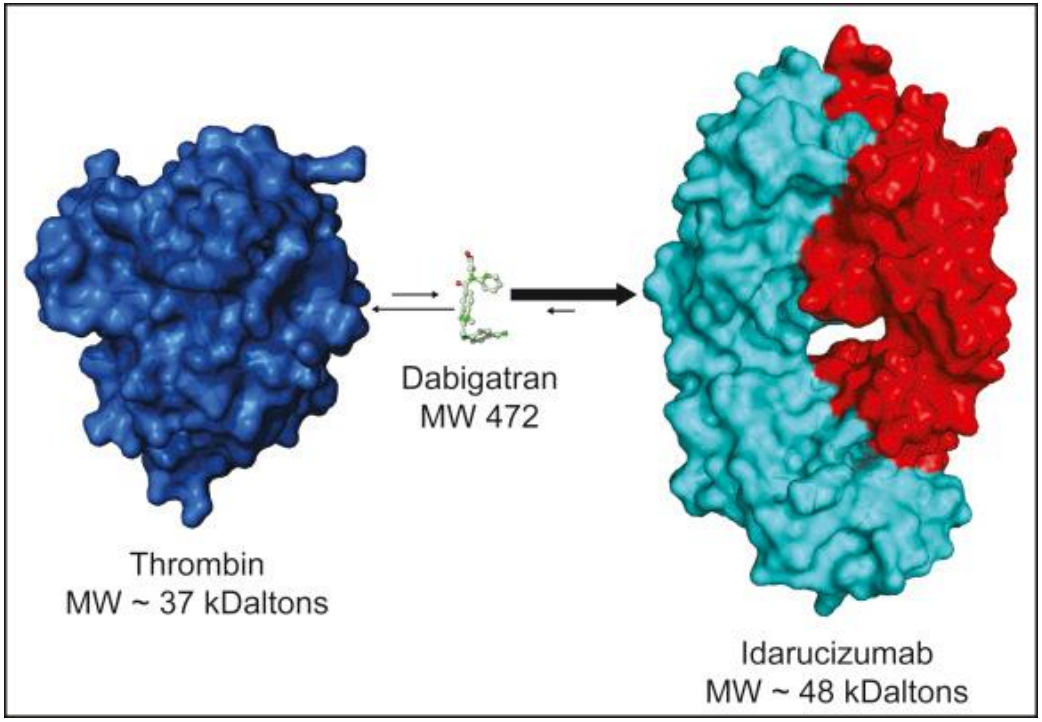


Healthy donors receiving Rivaroxaban

Management of bleeding under DOAC

Antidotes (Anti-FIIa-Inhibitors)

Idarucizumab:	anti-Dabi-Fab
Molecular mass:	48 kDa
Half-life:	47 min, 10h
Dose:	2x 2.5 g i.v.



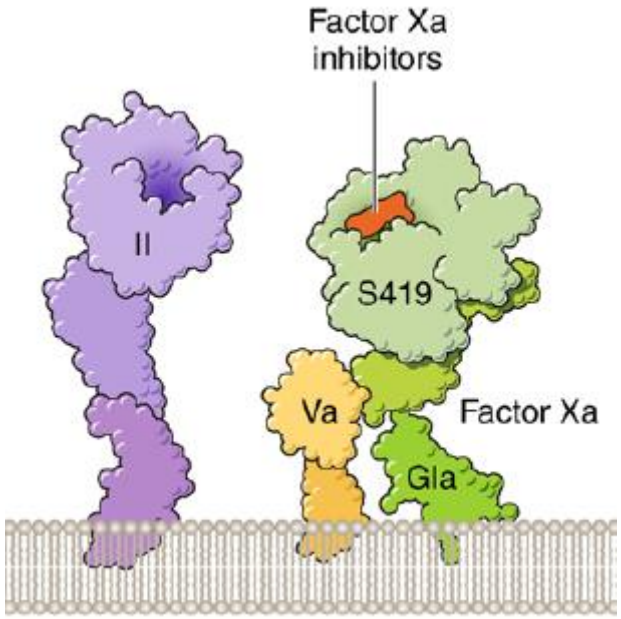
Lu G et al 2013, Nature Medicine 2013

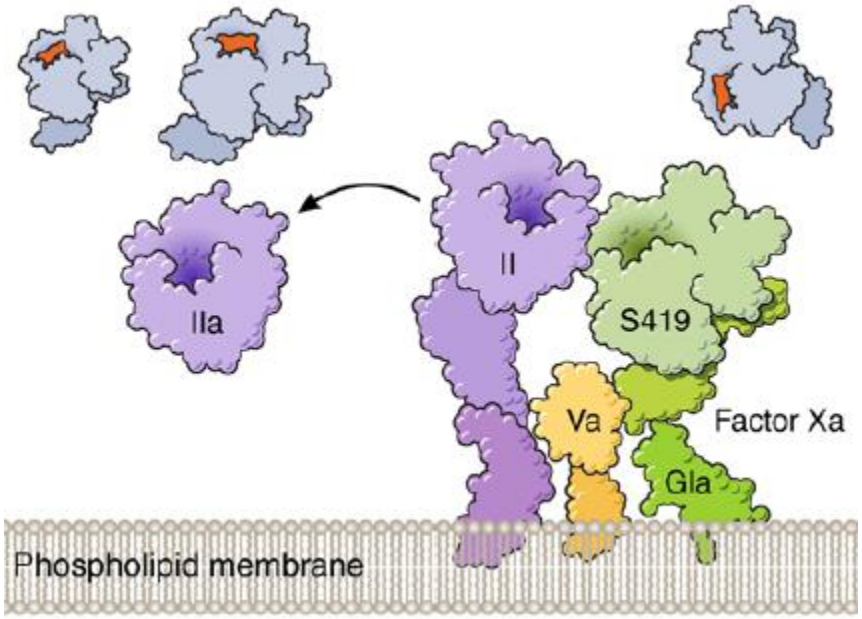
Management of bleeding under DOAC

Antidotes (Anti-FXa-Inhibitors)

Andexanet alfa:	recomb. modified Fxa
Molecular mass:	39 kDa
Half-life:	6h
Dose:	400-800 mg i.v.

Andexanet alpha



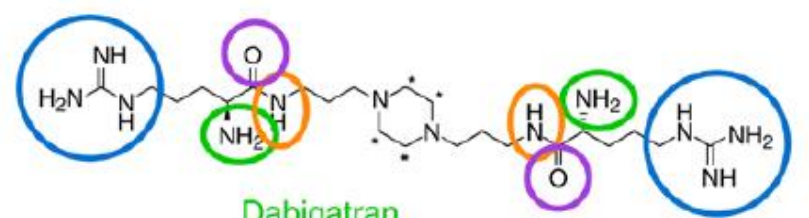


Ruf C et al, Circulation 2016

Management of bleeding under DOAC

Antidotes (Anti-FXa-Inhibitors)

Ciraparantag:	synthetic molecule
Molecular mass:	0.5 kDa
Half-life:	12-24h
Dose:	100-300 mg i.v.



	Dabigatran		
Edoxaban	Rivaroxaban		
Dabigatran	Apixaban	Dabigatran	
Rivaroxaban	Argatroban	Rivaroxaban	
UFH/LMWH	UFH/LMWH	UFH/LMWH	Edoxaban
Fondaparinux	Fondaparinux	Fondaparinux	Apixaban

Computer-aided energy minimization modeling predicts 8 non-covalent binding sites on ciraparantag for NOACs or heparins

Ansell J et al, N Engl J Med 2014

Management of bleeding under DOAC

RE-VERSE AD (Study Design)

- Reversal Effect of Iduracizumab on Active Dabigatran
- Multicenter, prospective, open-label study
- 5 g of intravenous idarucizumab to reverse dabigatran
- Group A: uncontrolled bleeding (301)
- Group B: urgent procedure (202)

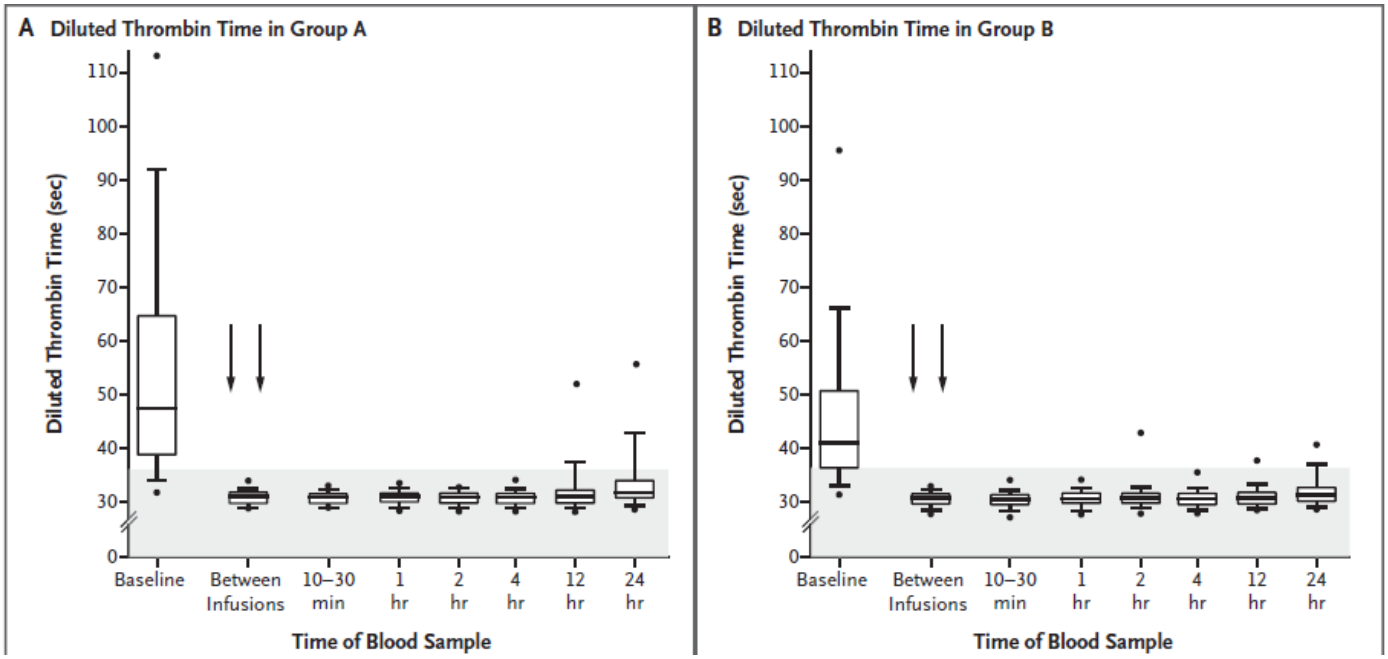
Pollack C, N Engl J Med. 2017

Management of bleeding under DOAC

RE-VERSE AD (Results)

- 100% reversal of dabigatran (95% CI,100 to 100) in the diluted thrombin time or the ecarin clotting time.

Uncontrolled bleeding (n=301) **Urgent procedure (n=202)**



Pollack C, N Engl J Med. 2017

Management of bleeding under DOAC

RE-VERSE AD (Results)

Bleeding (A, n=301):

- 137 (45.5%) GI bleeding and 98 (32.6%) ICH
- Median time to the cessation of bleeding was 2.5 hours

Thombosis (n=301/202):

6.3% and 7.4% (A vs. B)

Mortality

18.8% and 8.9% (A and B)

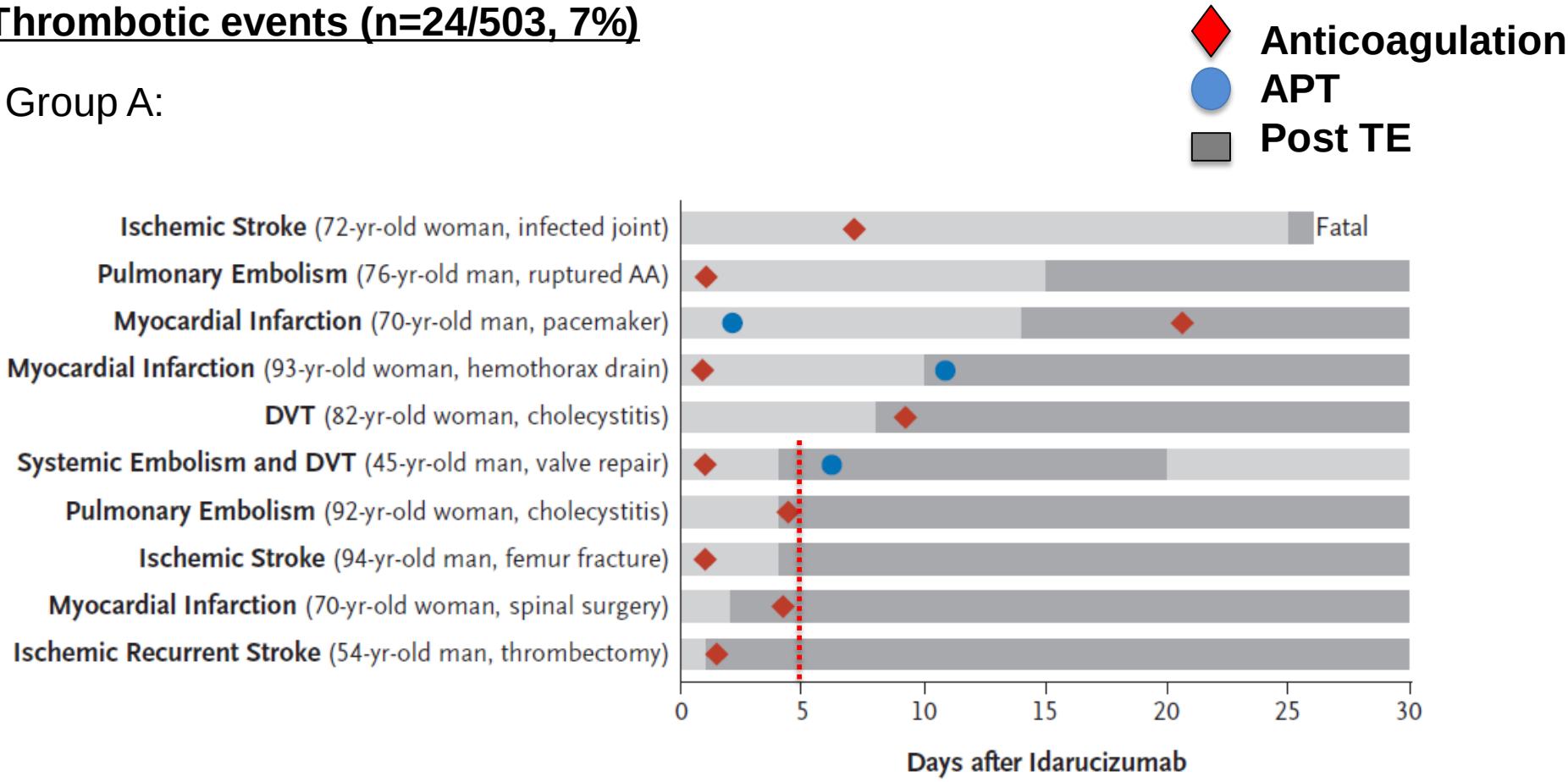
Pollack C, N Engl J Med. 2017

Management of bleeding under DOAC

RE-VERSE AD (Results)

Thrombotic events (n=24/503, 7%)

Group A:



Pollack C, N Engl J Med. 2017

Management of bleeding under DOAC

ANNEXA-4 (Study Design)

- The Andexanet Alpfa, a Novel Antidote to the Anticoagulation Effect of FXA inhibitors
- Multicenter, prospective, open-label study
- 67 patients with major bleeding under Rivaroxaban, Apixaban, Enoxaban, enoxaparin
- 400 mg (bolus) and 480 mg (infusion, 2h); or 800 mg (bolus) and 960 mg (infusion)

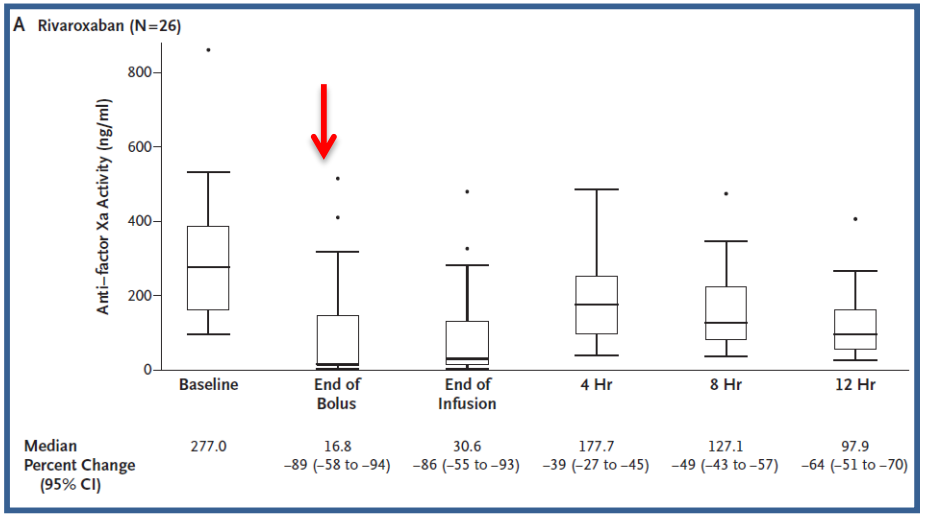
Connolly S, N Engl J Med. 2017

Management of bleeding under DOAC

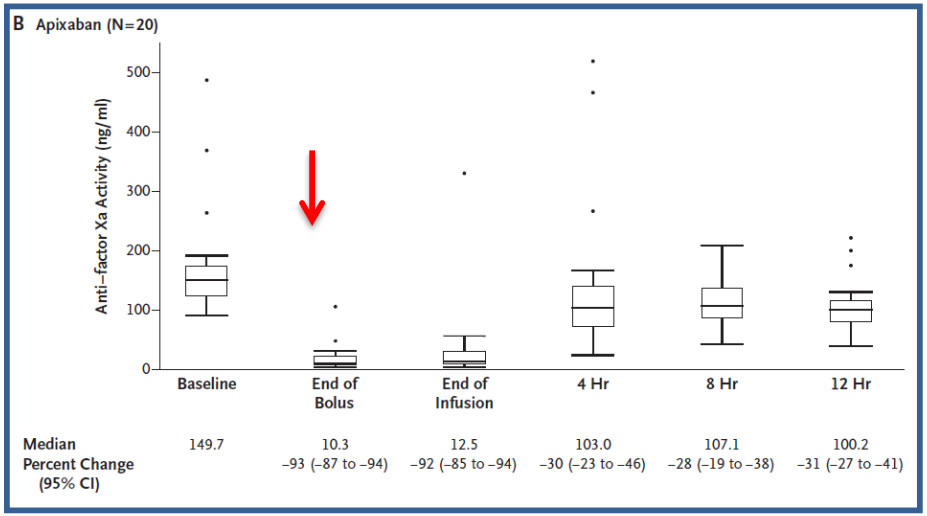
ANNEXA-4 (Results)

- 89% reversal of anti-FXa (95% CI, 58-94%)

Rivaroxaban/Andexanet



Apixaban/Andexanet

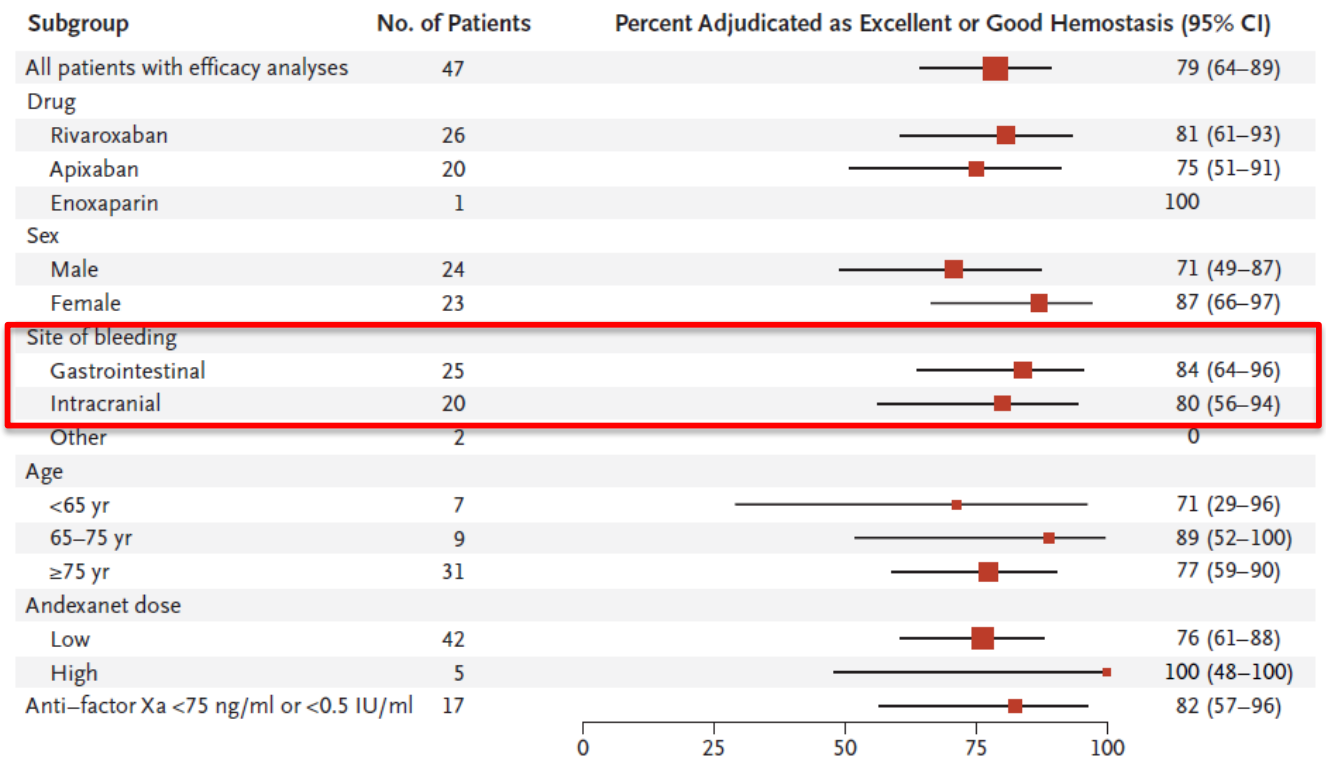


Connolly S, N Engl J Med. 2017

Management of bleeding under DOAC

ANNEXA-4 (Results)

- **Hemostatic efficacy** (no increase in ICH volume, no decrease in Hb for GI or cessation of visible bleeding)
- 79% showed excellent or good hemostsis after Andexanet alpha



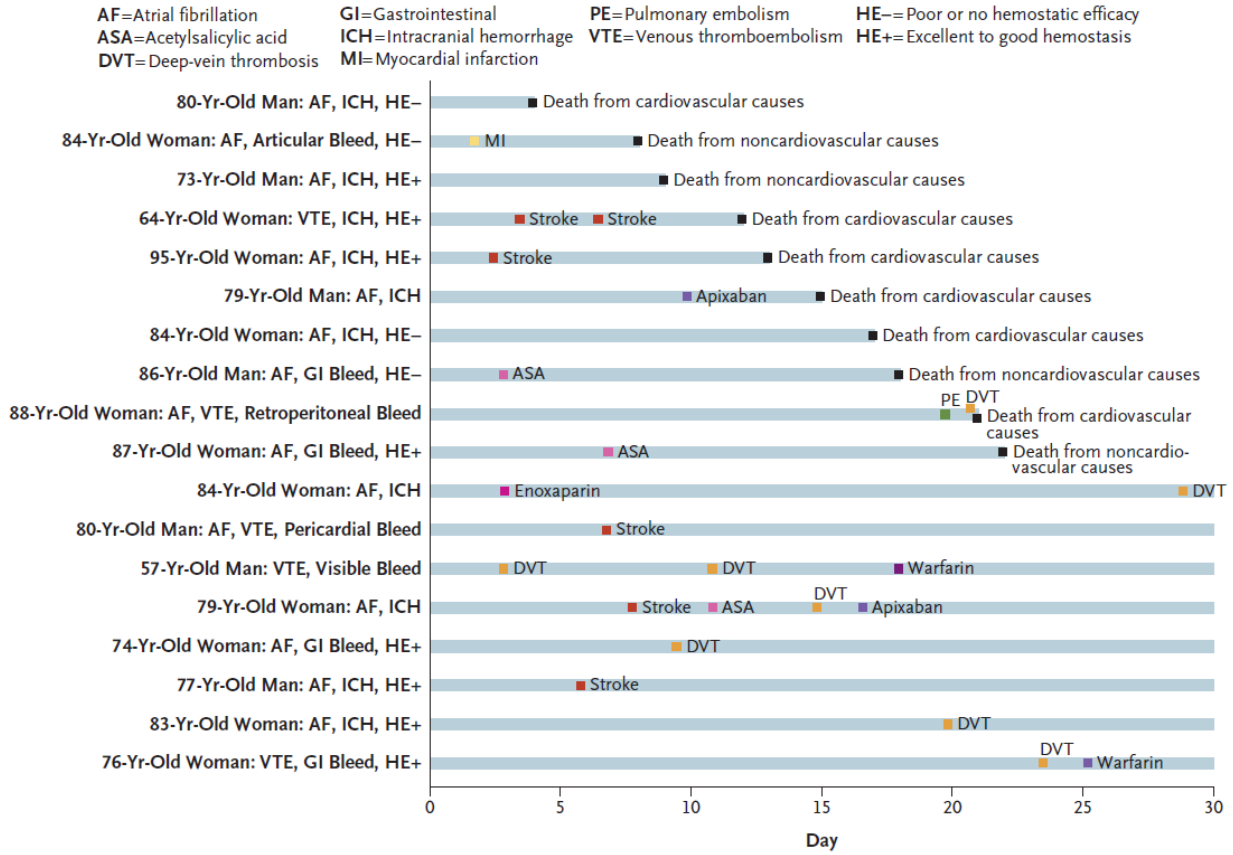
Subgroup	No. of Patients	Percent Adjudicated as Excellent or Good Hemostasis (95% CI)
All patients with efficacy analyses	47	79 (64–89)
Drug		
Rivaroxaban	26	81 (61–93)
Apixaban	20	75 (51–91)
Enoxaparin	1	100
Sex		
Male	24	71 (49–87)
Female	23	87 (66–97)
Site of bleeding		
Gastrointestinal	25	84 (64–96)
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)

Connolly S, N Engl J Med. 2017

Management of bleeding under DOAC

ANNEXA-4 (Results)

- **Thrombotic events:** 12 patients (18%)
- **Death:** 10 patients (15%)



Connolly S, N Engl J Med. 2017

Management of bleeding under DOAC

The use of antidotes (ISTH recommendations)

Indications for use	**Life-threatening bleeding :** Intracranial hemorrhage, symptomatic, uncontrollable hemorrhage
	Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary or intramuscular with compartment syndrome
	Persistent major bleeding: despite local hemostatic measures
	Need for **urgent intervention** that is associated with a **high risk of bleeding**
	Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery, lumbar puncture, cardiac or vascular surgery, hepatic or other major organ surgery
Potential indication for use	Need for **urgent surgery** or intervention in patients with **acute renal failure**
Antidote should not be used	**Elective** surgery
	Gastrointestinal bleeds **that respond** to supportive measures
	High drug levels **without associated bleeding**
	Surgery or intervention that **can be delayed**

Ley J et al 2017, JTH 2017

Management of bleeding under DOAC

To be considered…..

- With antidotes available, the safety profile of the DOACs will be enhanced
- Postmarketing registries are needed to better determine the clinical utility
- The antidotes impact on clinical outcomes in patients with serious underlying disorders

Management of bleeding under DOAC

To recommend in clinically relevant bleeding….

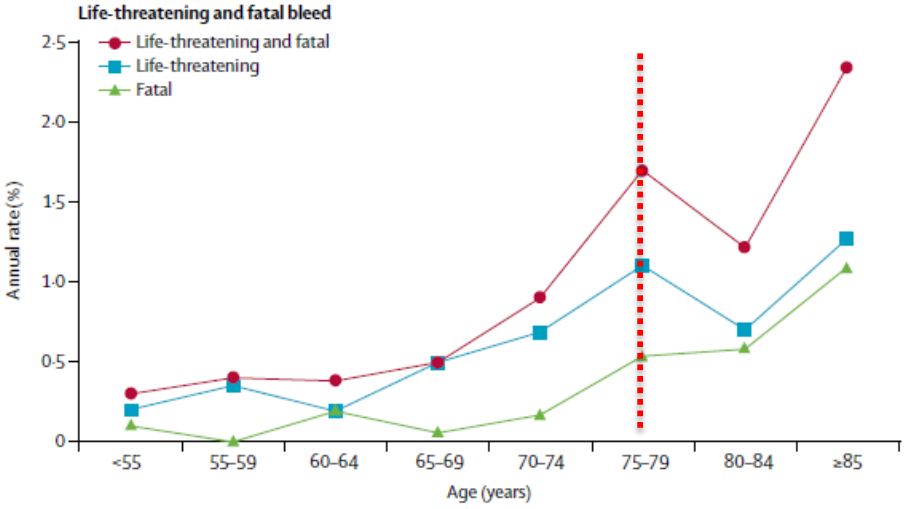
- Stop anticoagulation
  - Maintain diuresis or consider dialysis
    - Support hemostasis (transfusion)
      - Use antidote if applicable
        - If not available, consider aPCC or rFVIIa

Management of bleeding under APT

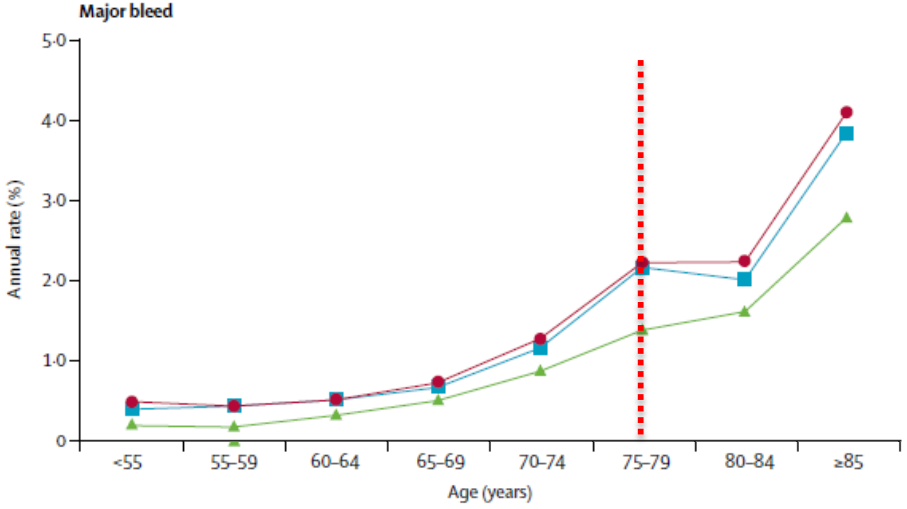
Bleeding on long-term APT

- Prospective population-based cohort study
- 3,166 patients with a first transient ischaemic attack, ischaemic stroke, or myocardial infarction treated with antiplatelet drugs (mainly aspirin based, without PPI).

Life-threatening and fatal bleeding



Major bleeding



Li L et al, Lancet 2017

Management of bleeding under APT

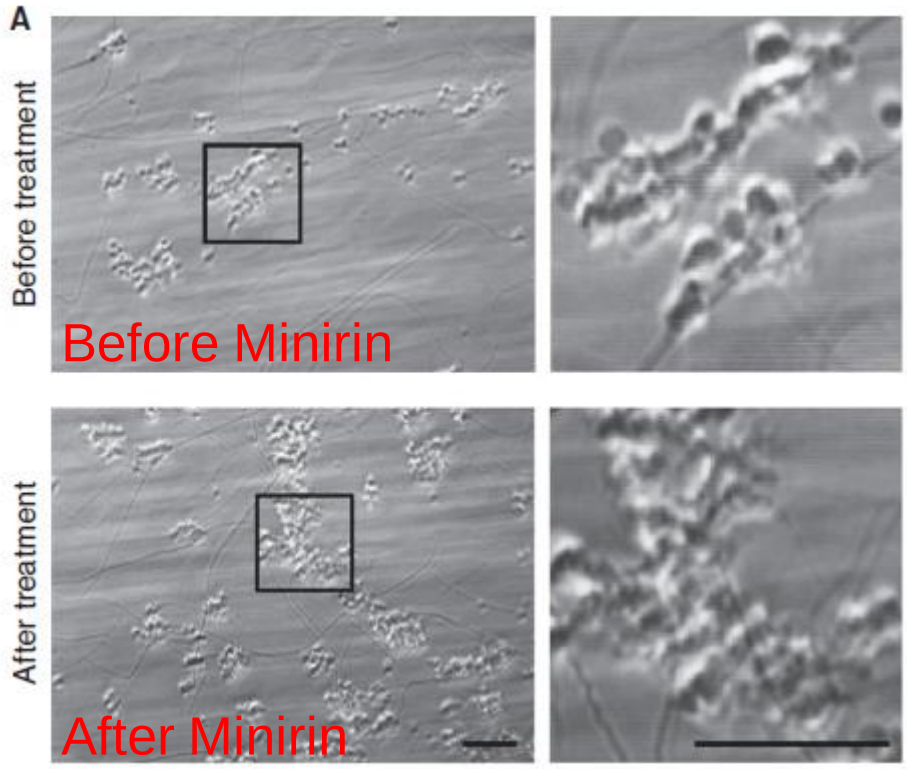
Nonspecific hemostatic agents

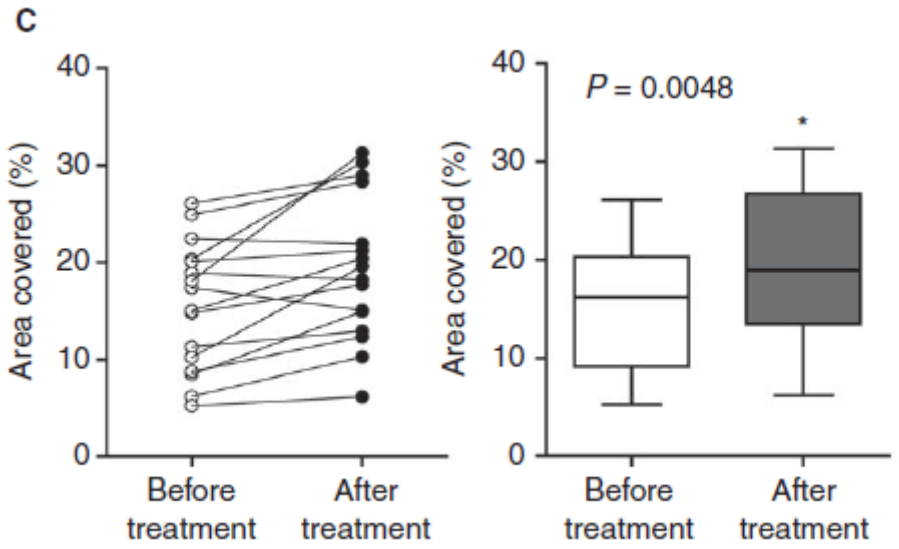
- Desmopressin
- Tranexamic acid
- Recombinant activated factor VII

Management of bleeding under APT

Nonspecific hemostatic agents (DDVAP)

- Desmopressin treatment of patients with bleeding complications after cardiothoracic surgery enhances platelet activation and thrombus formation under flow





Swieringe F et al, J Thromb Haemost. 2015

Management of bleeding under APT

Nonspecific hemostatic agents (DDVAP)

- Desmopressin (0.3 µg/KG i.v.) may be usefull to reverse PLT function
- Meta-analysis of RT: 596 patients, cadiac surgery under APT or CPB

Blood loss

A

Study or Subgroup	Desmopressin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dilthey 1993	1.84	1.61	19	3.45	1.88	20	14.8%	−1.61 [−2.71,−0.51]
Despotis 1999	1.1	1.5	50	2.2	2.3	51	23.1%	−1.10 [−1.86,−0.34]
Bignami 2016	1.37	2.42	25	1.93	3.31	29	9.0%	−0.56 [−2.09, 0.97]
Gratz 1992	2.38	1.26	29	2.9	2.1	30	19.6%	−0.52 [−1.40, 0.36]
Steinlechner 2011	1.45	1.64	20	1.65	1.61	23	17.3%	−0.20 [−1.17, 0.77]
de Prost 1992	3.4	2.6	47	3.2	2.4	45	16.3%	0.20 [−0.82, 1.22]
Total (95% CI)			**190**			**198**	**100.0%**	**−0.65 [−1.16, −0.13]**

Heterogeneity: Tau² = 0.15; Chi² = 7.87, df = 5 (*P* = 0.16); I² = 36%
Test for overall effect: Z = 2.48 (*P* = 0.01)

Mean Difference IV, Random, 95% CI

−4 −2 0 2 4

Favours [Desmopressin] Favours [Placebo]

Risk of Bias: A B C D E F G

Re-operation

B

Study or Subgroup	Desmopressin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Sheridan 1994	9	20	18	24	15.9%	0.60 [0.35, 1.03]
Dilthey 1993	13	19	19	20	36.9%	0.72 [0.52, 0.99]
Mongan 1992	9	13	12	16	20.8%	0.92 [0.58, 1.46]
Bignami 2016	14	25	15	29	18.4%	1.08 [0.66, 1.77]
Pleym 2004	11	46	9	46	8.0%	1.22 [0.56, 2.67]
Total (95% CI)		**123**		**135**	**100.0%**	**0.83 [0.66, 1.04]**
Total events	56		73			

Heterogeneity: Tau² = 0.01; Chi² = 4.63, df = 4 (*P* = 0.33); I² = 14%
Test for overall effect: Z = 1.63 (*P* = 0.10)

Risk Ratio M-H, Random, 95% CI

0.1 0.2 0.5 1 2 5 10

Favours [Desmopressin] Favours [Placebo]

Risk of Bias: A B C D E F G

Desborough M et al, J Thromb Haemost. 2017

Management of bleeding under APT

ATACAS (Study Design)

- Aspirin and Tranexamic Acid for Coronary Artery Surgery
- Multicenter, double-blind trial in patients undergoing CABG with recent APT
- 4,662 patients on aspirin were randomly assigned to receive tranexamic acid 50-100 mg/KG or saline.

Myles P et al, N Engl J Med 2017

Management of bleeding under APT

ATACAS (Study Design)

- Tranexamic acid reduces postoperative bleeding without a higher risk of death or thrombotic complications.

Table 3. Outcomes and Adverse Events.

Outcome or Event	Tranexamic Acid Group (N=2311)	Placebo Group (N=2320)	Risk Ratio (95% CI)	P Value
Primary outcome: death, myocardial infarction, stroke, renal failure, pulmonary embolism, or bowel infarction — no./total no. (%)	386/2310 (16.7)	420/2320 (18.1)	0.92 (0.81–1.05)	0.22
Death	26/2310 (1.1)	33/2320 (1.4)	0.79 (0.47–1.32)	0.43
Myocardial infarction	269/2310 (11.6)	300/2320 (12.9)	0.90 (0.77–1.05)	0.19
Stroke	32/2309 (1.4)	35/2320 (1.5)	0.92 (0.57–1.48)	0.81
Renal failure	98/2309 (4.2)	96/2320 (4.1)	1.03 (0.78–1.35)	0.88
Pulmonary embolism	15/2309 (0.6)	15/2320 (0.6)	1.00 (0.49–2.05)	>0.99
Bowel infarction	8/2309 (0.3)	3/2320 (0.1)	2.68 (0.71–10.09)	0.15
Primary outcome not including renal failure — no./total no. (%)*	324/2310 (14.0)	362/2320 (15.6)	0.90 (0.78–1.03)	0.14
Reoperation — no./total no. (%)				
Due to any cause	32/2310 (1.4)	65/2320 (2.8)	0.49 (0.32–0.75)	0.001
Due to major hemorrhage	18/2310 (0.8)	50/2320 (2.2)	0.36 (0.21–0.62)	<0.001
Due to cardiac tamponade	14/2310 (0.6)	23/2320 (1.0)	0.61 (0.32–1.19)	0.19
Transfusion of red cells during hospitalization — no./total no. (%)	759/2311 (32.8)	1086/2320 (46.8)		
No. of units of red cells that were transfused during hospitalization				<0.001
Median	2	2		
Interquartile range	1–3	2–4		
Transfusion of any blood products during hospitalization — no./total no. (%)	876/2311 (37.9)	1269/2320 (54.7)		
No. of units of any blood products that were transfused during hospitalization				<0.001

Myles P et al, N Engl J Med 2017

Management of bleeding under APT

Nonspecific hemostatic agents (aFVII)

- Single-center, randomized, placebo-controlled, double-blind, dose-escalation, exploratory phase I trial
- FVIIa (10-20 µg/kg) reversed the effect of clopidogrel on blood loss (punch biopsy)

Table 3. Effect of rFVIIa and Placebo Treatment on Bleeding Duration and Blood Loss After Platelet Inhibition with Clopidogrel

	n	Post-clopidogrel (Bx1) mean[a] (CV)	Post-rFVIIa or placebo treatment (Bx2) mean[b] (CV)	Ratio of means at Bx2 (rFVIIa vs placebo) (95% CI)	*P* value
Bleeding duration (min)					
Placebo	13	30.7 (0.4)	30.4 (0.3)		
5 µg/kg rFVIIa	6	40.3 (0.4)	36.9 (0.4)	1.22 (0.88, 1.70)	0.255
10 µg/kg rFVIIa	6	26.1 (0.4)	24.0 (0.3)	0.81 (0.58, 1.12)	0.145
20 µg/kg rFVIIa	12	29.2 (0.4)	25.1 (0.3)	0.83 (0.66, 1.06)	0.106
Blood loss (mL)					
Placebo	13	15.9 (0.7)	23.2 (0.5)		
5 µg/kg rFVIIa	6	28.1 (0.8)	18.9 (0.6)	0.81 (0.45, 1.48)	0.501
10 µg/kg rFVIIa	6	11.3 (0.8)	10.3 (0.6)	0.44 (0.25, 0.80)	0.007
20 µg/kg rFVIIa	12	15.6 (0.8)	11.6 (0.6)	0.50 (0.33, 0.76)	0.001

Skolnick B et al, Anesth Analg. 2011

Management of bleeding under APT

PACTH (Study Design)

- Randomized multicenter trial
- 190 patients with spontaneous intracerebral haemorrhage
- APT for at least 7 days
- Standard care vs. standard care plus platelet transfusion

Baharoglu M et al, Lancet 2016

Management of bleeding under APT

PACTH (Results)

- Death occurred significantly more often in PLT transfusion group (OR 2.05, p=001)

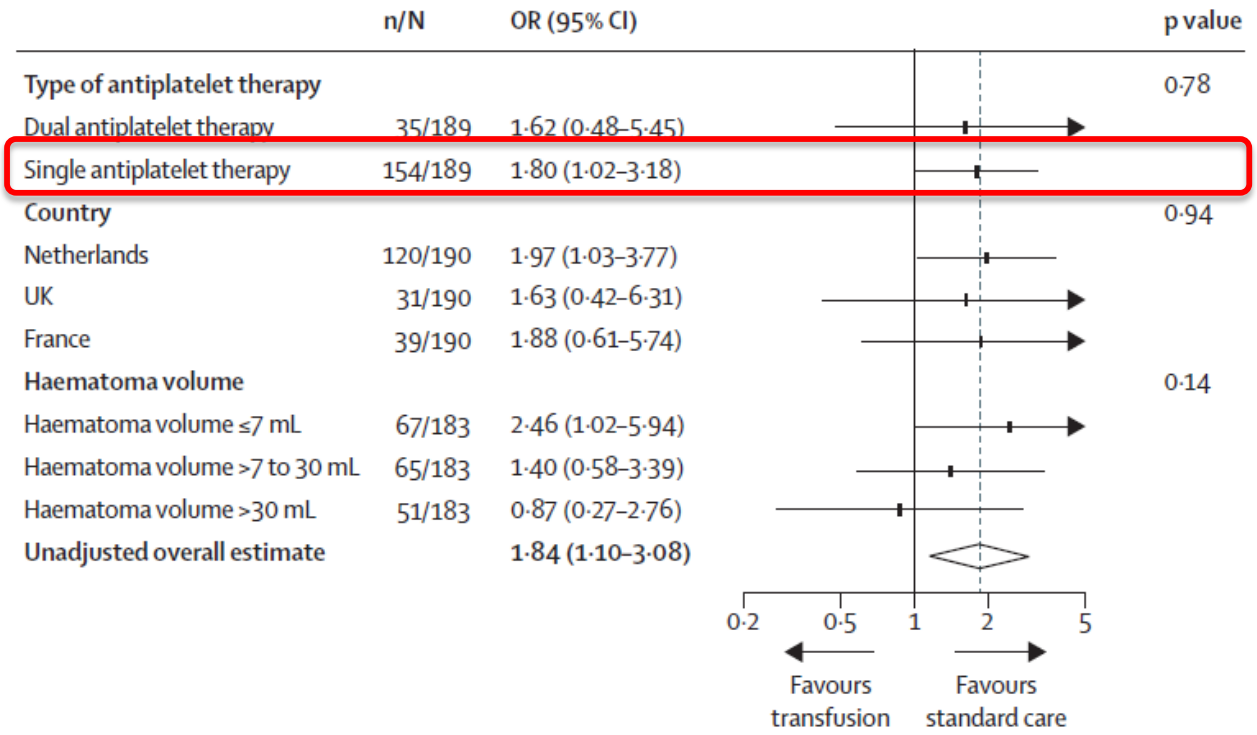
	As-treated population		
	Platelet transfusion group (n=95)	Standard care group (n=95)	Odds ratio (95% CI)
Any SAE	40 (42%)	28 (29%)	1·74 (0·96–3·17)
Any fatal SAE	23 (24%)	16 (17%)	1·58 (0·77–3·22)
SAE due to ICH	24 (25%)	13 (14%)	2·13 (1·01–4·50)
ICH enlargement	15 (16%)	13 (14%)	1·18 (0·53–2·64)
Brain oedema	5 (5%)	0	11·61 (0·63–212·94)
Brain herniation	2 (2%)	0	5·11 (0·24–107·83)
Intraventricular extension	6 (6%)	0	13·87 (0·77–249·82)
Hydrocephalus	4 (4%)	1 (1%)	4·13 (0·45–37·67)
SAE due to thromboembolism	4 (4%)	1 (1%)	4·13 (0·45–37·67)
Ischaemic stroke	1 (1%)	0	3·03 (0·12–75·37)
Myocardial infarction	1 (1%)	1 (1%)	1·00 (0·06–16·23)
Extremity embolism	2 (2%)	0	5·11 (0·24–107·81)
Pulmonary embolism	1 (1%)	0	3·03 (0·12–75·37)

Baharoglu M et al, Lancet 2016

Management of bleeding under APT

PACTH (Results)

- Platelet transfusion seems inferior to standard care to treat ICH during APT



Baharoglu M et al, Lancet 2016

Management of bleeding under APT

To be considered…..

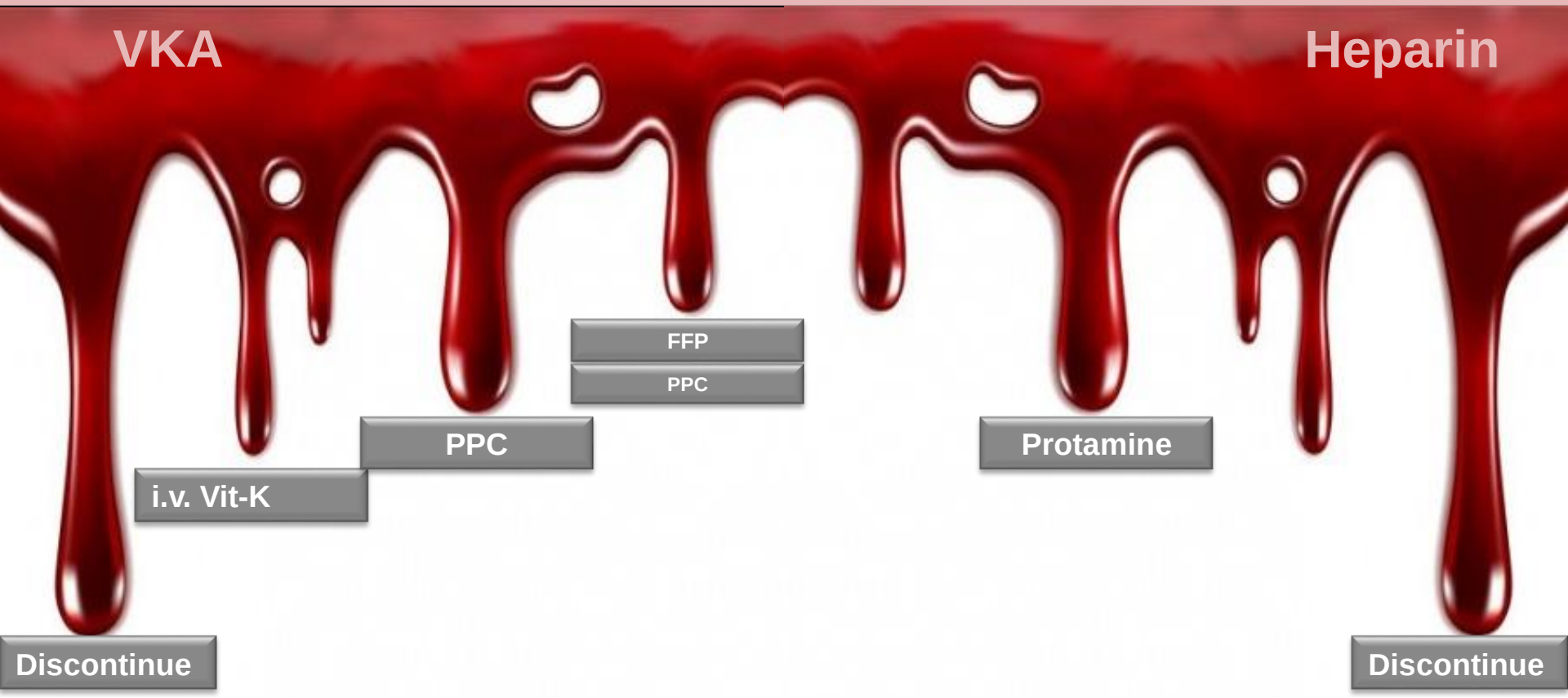
- Patient-individualized risk assessment
- Avoidance of triple antithrombotic strategies (if possible)
- No antidotes are available
- Platelet transfusion needs more assessment
- Risk-minimization (PPI, H. pylori eradication, no NSAID)

Management of bleeding under APT

To be recommended in clinically relevant bleeding…..

- Stop antiplatelet therapy
  - Consider platelet transfusion
    - i.v. PPI to prevent GI-bleeding
      - Desmopression is safe and efficient
        - Tranexamic acid reduces post-surgical bleeding
          - Recomb. activated FVII (with platelet transfusion)

Management of bleeding



Management of bleeding

DOAC

APT

Dailysis

Idarucizumab /Andexanet

PPC

aFVII

Tranexamic Acid

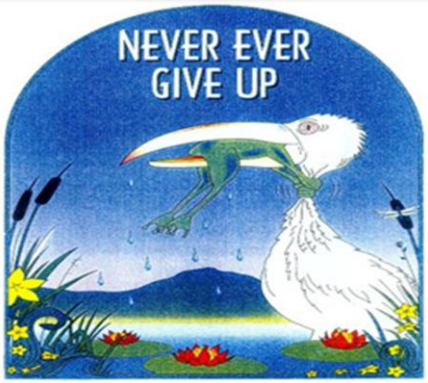
Platelets

DDVAP

Wait and watch is the best antidote

Discontinue

Discontinue



Rückfragen Tel.: 07071 29-81601
Email: tamam.bakchoul@med.uni-tuebingen.de

ZKT Tübingen

UNIVERSITÄTS KLINIKUM TÜBINGEN

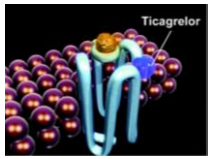
Deutsches Rotes Kreuz
DRK-Blutspendedienst
Baden-Württemberg | Hessen
gemeinnützige GmbH

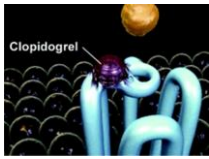
ISTH™
International Society on Thrombosis and Haemostasis

Deutsche Forschungsgemeinschaft
DFG

Management of bleeding under APT

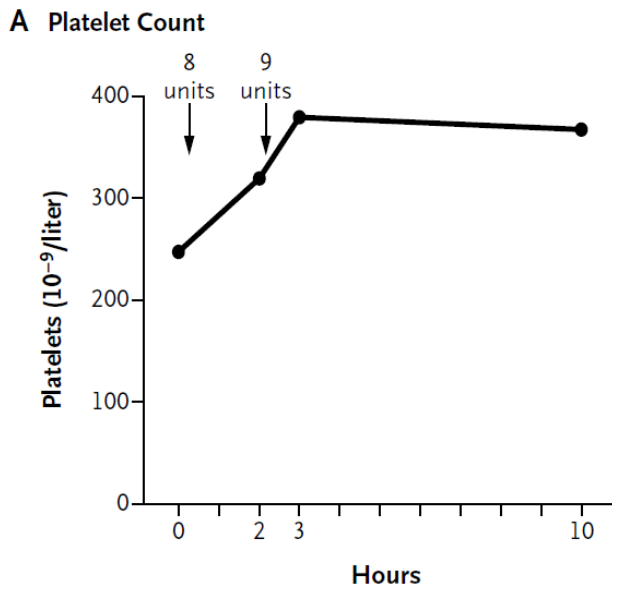
Ticagrelor

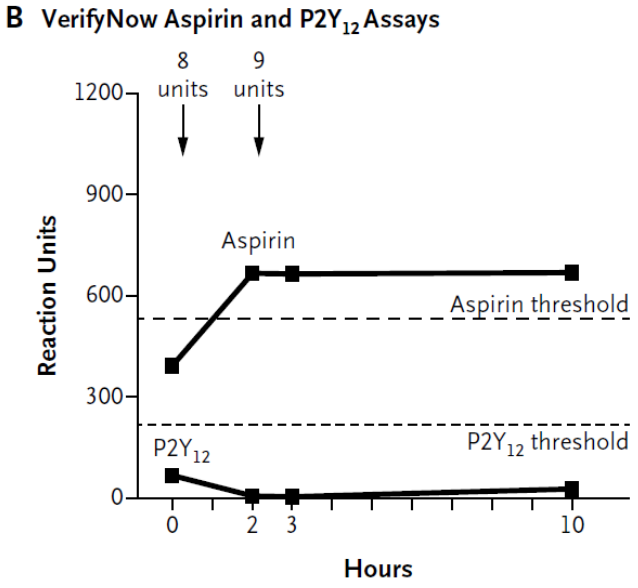


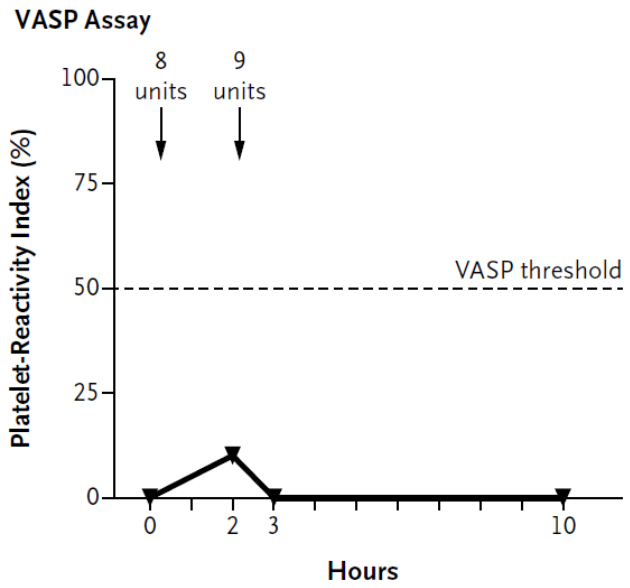


- Platelet transfusion seems to be inefficient to reverse reversible APTs

- 65-year-old man admitted with Stroke (on ticagrelor 90 mg bid, ASS 75 mg for DES)
- No hemorrhagic transformation, thrombolysis was immediately performed
- 12 h later, the patient had a decreased level of consciousness, CT: intracranial hematoma.





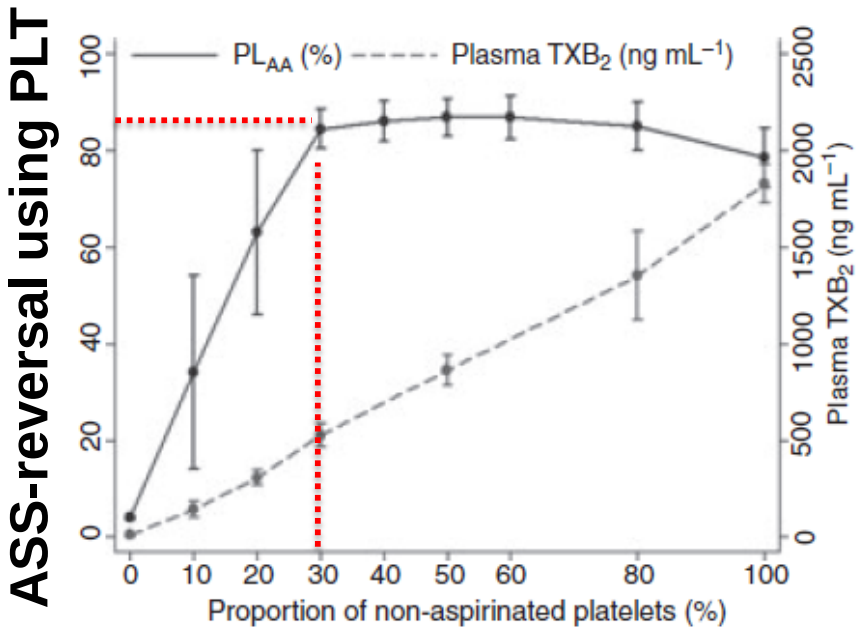


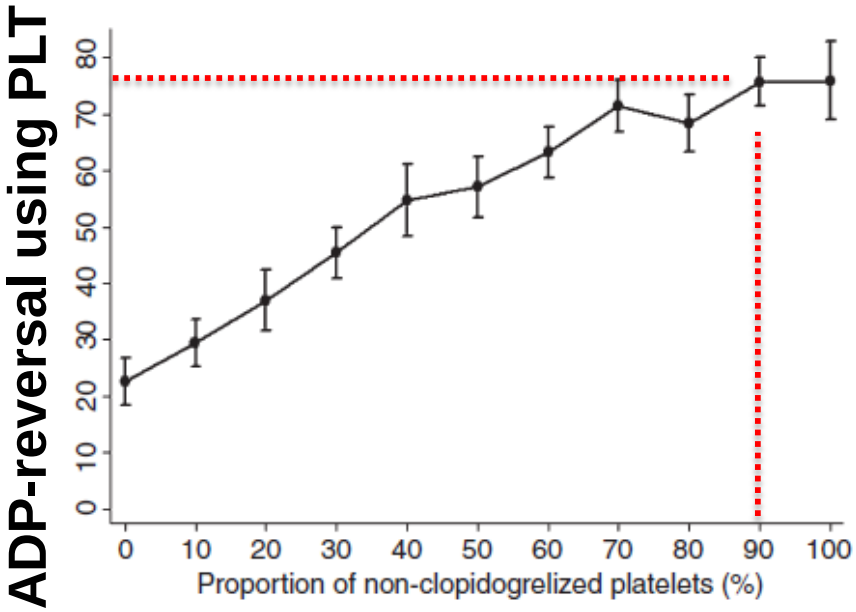
Godier A, N Engl J Med 2015

Management of bleeding under APT

Ticagrelor

- Platelet transfusion seems to be inefficient to reverse reversible APTs





Li et al.; JTH 2012

Management of bleeding under APT

Ticagrelor

- Serum-Albumin is as effective as PC to reverse PLT function ex vivo.