Management of antithrombotic associated bleeding

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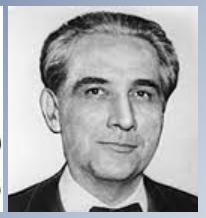
History of anticoagulant therapy



Anticoagulant in spoiled sweet clover (K.P. Link)

First clinical use of 4-hydroxycoumarin

Warfarin mechanism elucidated (J. Suttie)

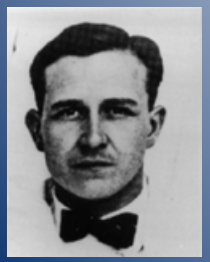
Warfarin dosing/INR

Warfarin clinical trials

Oral thrombin and Xa inhibitors

1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010

Heparin discovered by medical student (McLean)



Clinical use of heparin

Requirement for plasma cofactor discovered (K. Brinkhous)

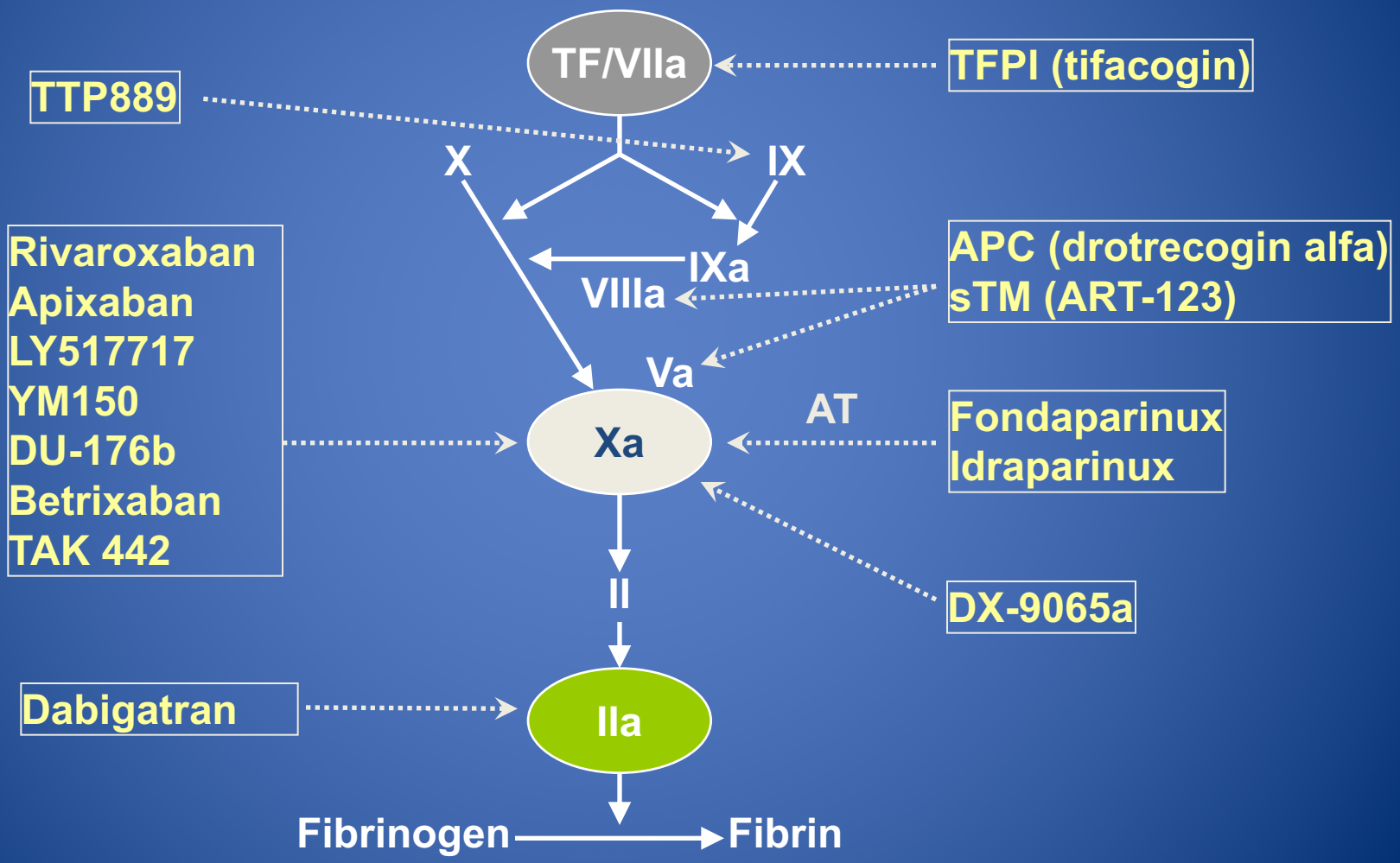
Cont infusion of heparin; aPTT monitoring

LMWH (J. Hirsch)

LMWH trials

Fondaparinux trials

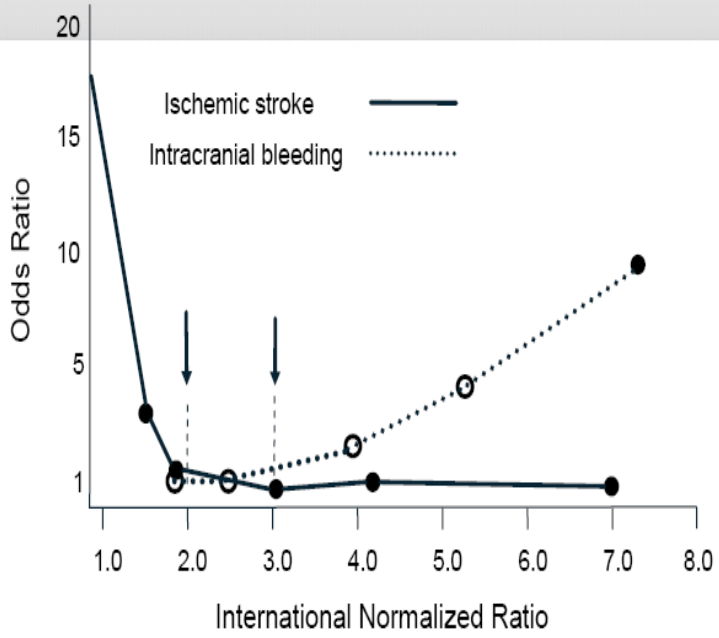
Anticoagulants



Adapted from Weitz & Bates, *J Thromb Haemost* 2007

Prevention of Atrial Fibrillation-Related Stroke

Need for Intense Monitoring With OAC



Narrow therapeutic index: INR < 2.0 = higher risk for stroke

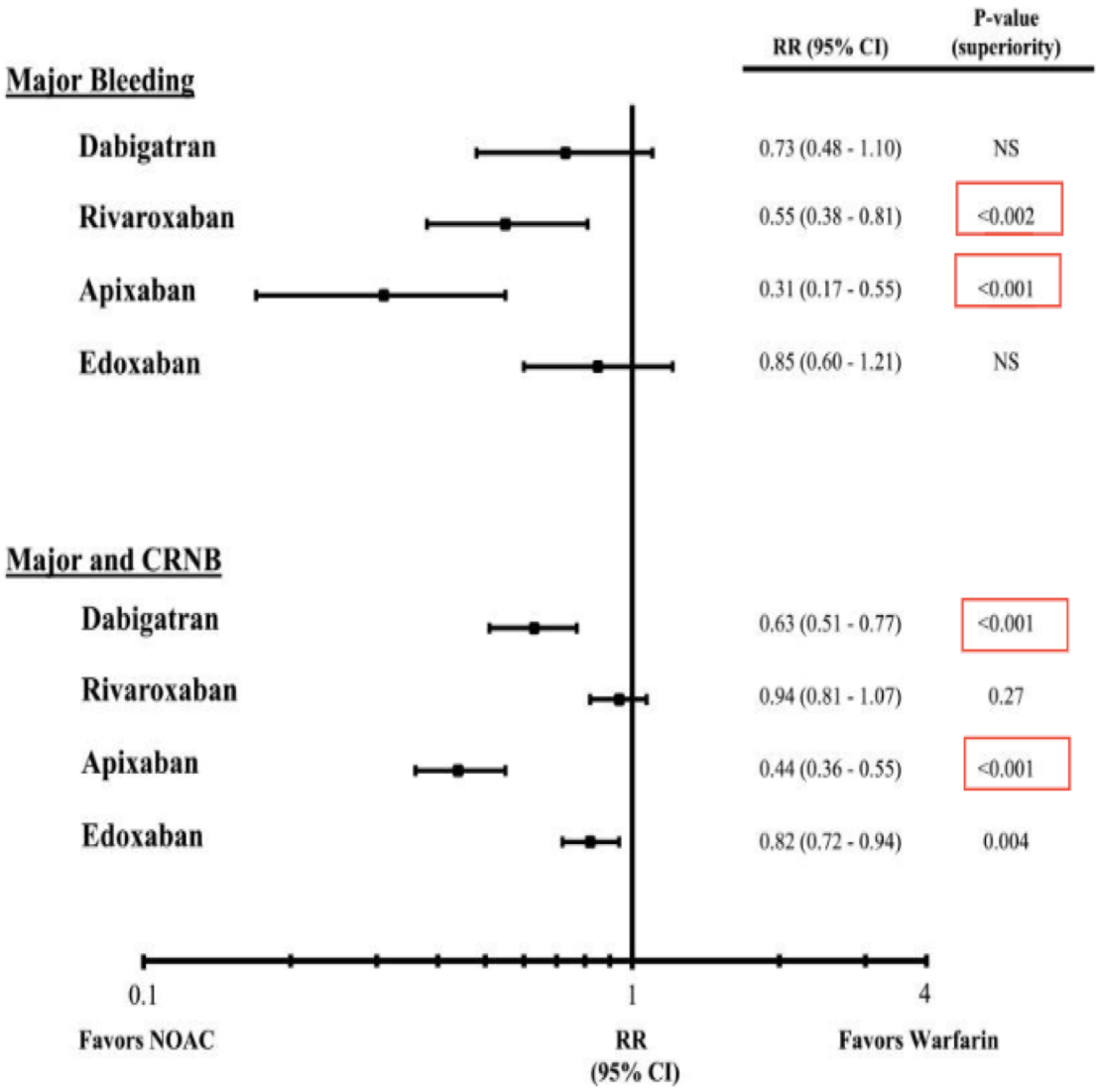
INR > 3.0 = higher risk for bleeding

Unpredictable INR (food/drug interactions, low specificity)

theheart.org | MedscapeCME Cardiology

Reprinted with permission from: Fuster V, et al. *Eur Heart J.* 2006;27:1979-2030.

Hazard ratios (HR) for major bleeding or major plus clinically relevant nonmajor bleeding (CRNB) in phase 3 trials comparing NOACs with conventional therapy for acute VTE treatment



These DOACs have never been compared directly with each other

BLOOD, 14 AUGUST 2014 x VOLUME 124, NUMBER 7

PHARMA & HEALTHCARE | 9/24/2012 @ 4:36PM | 1,592 views

"Dramatic" Increase In Bleeding Accompanies Addition Of Oral Anticoagulant Therapy In ACS

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CORRESPONDENCE

Bleeding Risk with Dabigatran in the Frail Elderly

N Engl J Med 2012; 366:864-866 | March 1, 2012 | DOI: 10.1056/NEJMc1112874

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To the Editor:

Since July 1, 2011, the thrombin inhibitor dabigatran has been available in New Zealand for stroke prevention in patients with atrial fibrillation. There are no restrictions on prescribing, and access is free to patients through government funding. Approximately 7000 patients started treatment in the first 2 months.

Actual bleeding rates

- FDA Drug Safety Communication

  Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate)

- European Medicines Agency

http://www.fda.gov/Drugs/ DrugSafety/ucm326580.htm
http://eudravigilance.ema.europa.eu/ human/index.asp

Real World Studies / Data

Phase 4 trials

Registries

Post Authorisation safety/efficacy studies

Prospective/Retrospective Observational studies

Pharmco-economic studies

How well does the drug perform in the real world ?

Outcomes as expected from clinical trials ?

Is the drug being used as recommended ?
Eg indications, dose, duration

Compliance issues ?

Improved QOL ?

Healthcare costs ?

Real-life studies have their inherent weaknesses :

- non-controlled and heterogeneous patient groups
- Physicians' prescribing bias in dosing and choice of patients
- uncontrolled influence of non-compliance, other concomitant medications and co-morbidities

BUT provide a wealth of data and insight into how DOACs are used in the real world

Management of bleeding

- Best Strategy – PREVENT bleeds

- Know your Drug and Bleeding risks;
  - Patient selection
  - Dose adjustment

- Know what to do when bleeding occurs

Bleeding risk scores

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension i.e. uncontrolled BP	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Aged ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INR	1
Vascular disease [prior MI, PAD, or aortic plaque]	1	Age (e.g. >65)	1
Aged 65-74 years	1	Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1
Sex category [i.e. female gender]	1		

Pisters et al, Chest 2010

Assessing bleeding risk

- Older patients have a 2-fold increased risk of bleeding

  - relative risk of intracranial hemorrhage was 2.5 in patients aged >85 years compared with patients 70–74 years old[1]

- Comorbidity (such as mild renal insufficiency, hepatic dysfunction, or diabetes) increased risk of bleeding by about 2.5

- Combined use of anticoagulant and antiplatelets – increased GI haemorrhage[2]

1. Hutton et al, Drugs aging, 1999
2. Hallas et al. BMJ. 2006;

Which one?

Choosing an anticoagulant		
Consideration	**Preferred drug**	**Rather than**
CrCL < 15 ml/min	Warfarin	
CrCL 15 - 29 ml/min	Warfarin	Apixaban, rivaroxaban, edoxaban
CrCL 30 - 50 ml/min	Warfarin, rivaroxaban, apixaban, edoxaban	Dabigatran
Liver dysfunction	Warfarin	Apixaban, rivaroxaban, dabigatran
Previous intracranial bleed	Apixaban, rivaroxaban, edoxaban, dabigatran	Warfarin
Previous GI bleed	Apixaban, edoxaban, warfarin	Dabigatran, rivaroxaban
ACS	Rivaroxaban, apixaban, edoxaban, warfarin	Dabigatran
Dyspepsia	Rivaroxaban, apixaban,edoxaban, warfarin	Dabigatran
Poor compliance	Warfarin	Apixaban, rivaroxaban, edoxaban, dabigatran

161(6):755-6.

Drug interactions

- **Dabigatran** - verapamil and amiodarone: increased plasma concentration of dabigatran

  - carbemazepine and rifampicin: decreased plasma concentration of dabigatran

- **Rivaroxaban** - CYP3A4 inhibitors e.g. azoles, rifampicin and P-glycoprotein inhibitors e.g.Digoxin, Ritonavir: may increase plasma concentration

- **Apixaban** - as Rivaroxaban

- **Edoxaban** - as Rivaroxaban

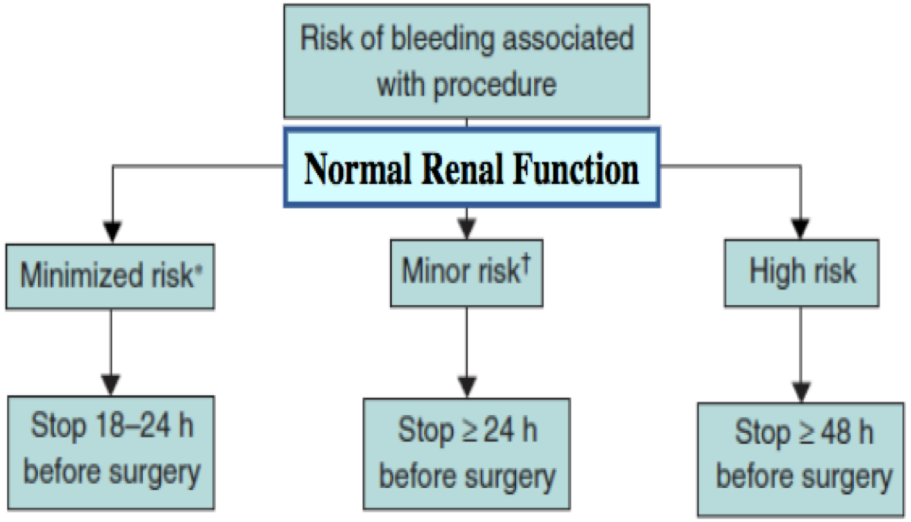
Switching to a DOAC

Conversion	Start times recommenced
From VKAs to NOAC	Discontinue VKA and start DOAC when INR<2
From NOAC to parenteral	Start parenteral anticoagulant 12 h after last dose of DOAC
From parenteral to NOAC	Start DOAC at the same time or up to 2 hours before the next s/c dose. For continuous infusions, start DOAC at the time of discontinuation of the continuous infusion.
From NOAC to VKAs	Start times for VKAs are based on renal function

Blood 2012 119: 3016-3023

Peri-surgery Management of DOACs

Check Renal Function before surgery



Creatinine clearance (ml/min)	Risk of bleeding	Suggested interruption (h) Rivaroxaban	Apixaban	Dabigatran
≥ 80	Low	≥ 24	≥ 24	≥ 24
	High	≥ 48	≥ 48	≥ 48
50–79	Low	≥ 24	≥ 24	≥ 36
	High	≥ 48	≥ 48	≥ 72
30–49	Low	≥ 24	≥ 24	≥ 48
	High	≥ 48	≥ 48	≥ 96
15–29	Low	≥ 36	≥ 36	Not indicated
	High	≥ 48	≥ 48	Not indicated
< 15	No indication for any agent			

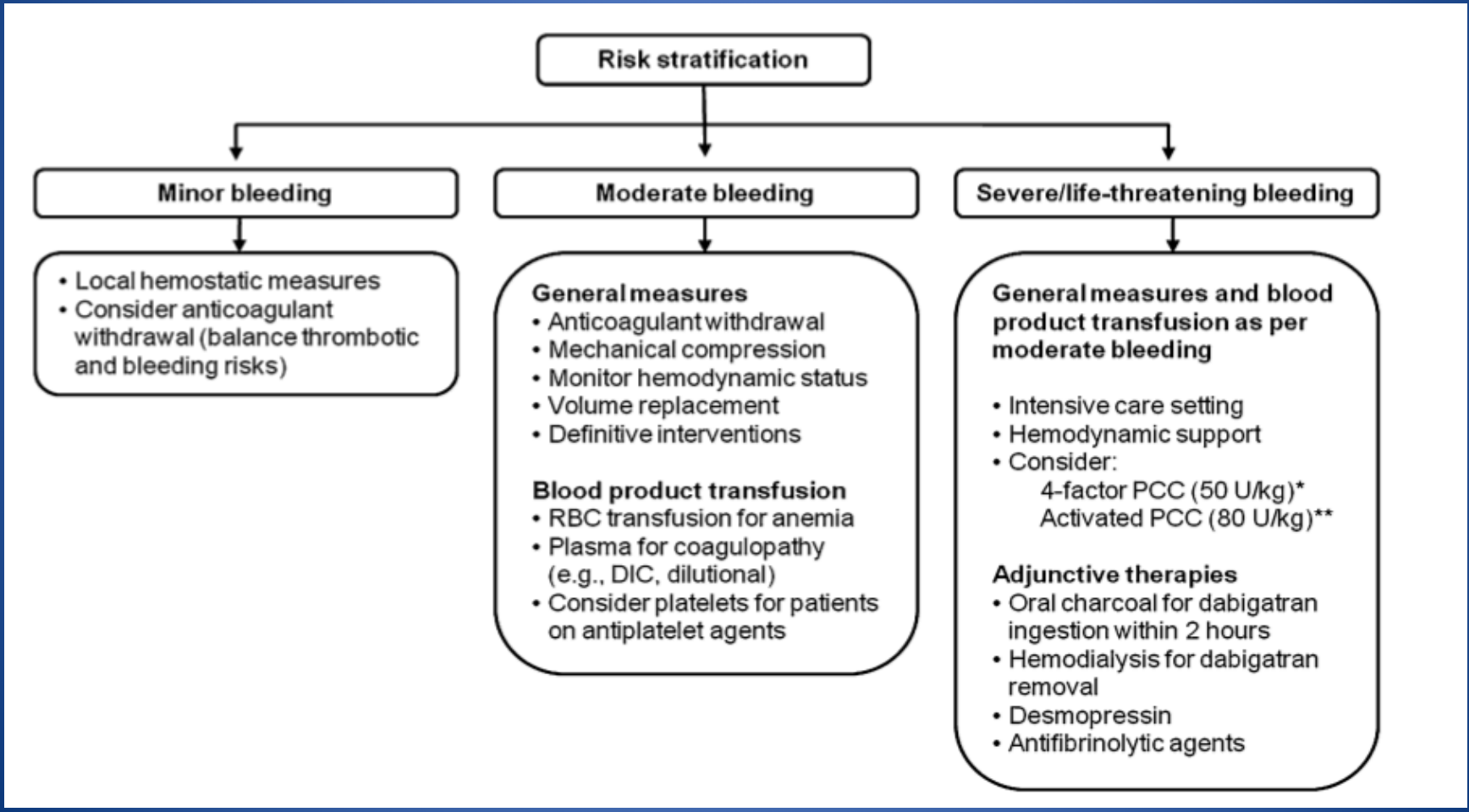
Effects of DOACs on coagulation assays

Measuring the anticoagulant effect of NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Plasma peak	2h after ingestion	1-4h post ingestion	1-2h after ingestion	2-4h after ingestion
Plasma trough	12-24h after ingestion	12-24h after ingestion	12-24h after ingestion	16-24h after ingestion
PT	cannot be used	cannot be used	prolonged but no known relation with bleeding risk	prolonged: may indicate excess bleeding risk but local calibration required
INR	cannot be used	cannot be used	cannot be used	cannot be used
aPTT	at trough >2x ULN suggests excess bleeding risk	cannot be used	prolonged but no known relation with bleeding risk	cannot be used
dTT	At trough >200ng/ml ≥ 65s: excess bleeding risk	cannot be used	cannot be used	cannot be used
Anti-FXa assays	n/a	no data yet	quantitative; no data on threshold values for bleeding or thrombosis	quantitative; no data on threshold values for bleeding or thrombosis
Ecarin clotting time	at trough >2x ULN: excess bleeding risk	not affected; cannot be used	not affected; cannot be used	not affected; cannot be used

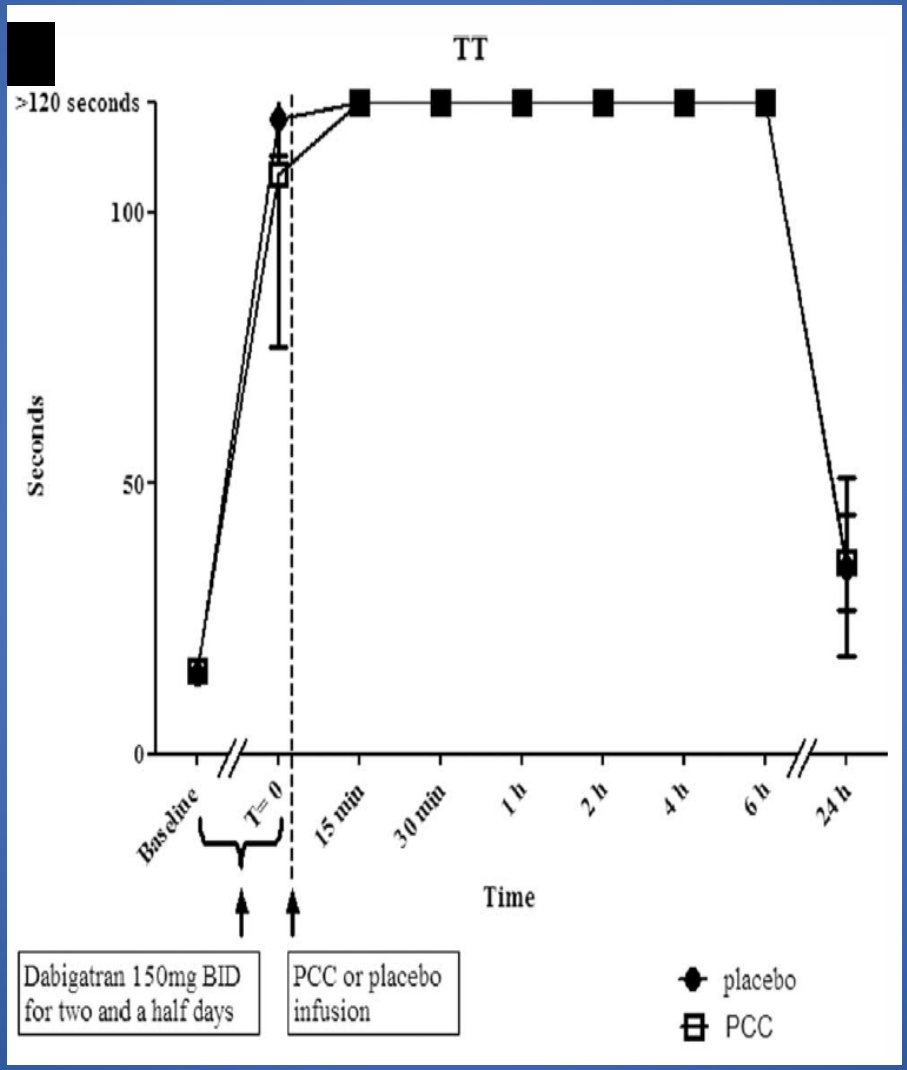
www.escardio.org/EHRA

Management of bleeding



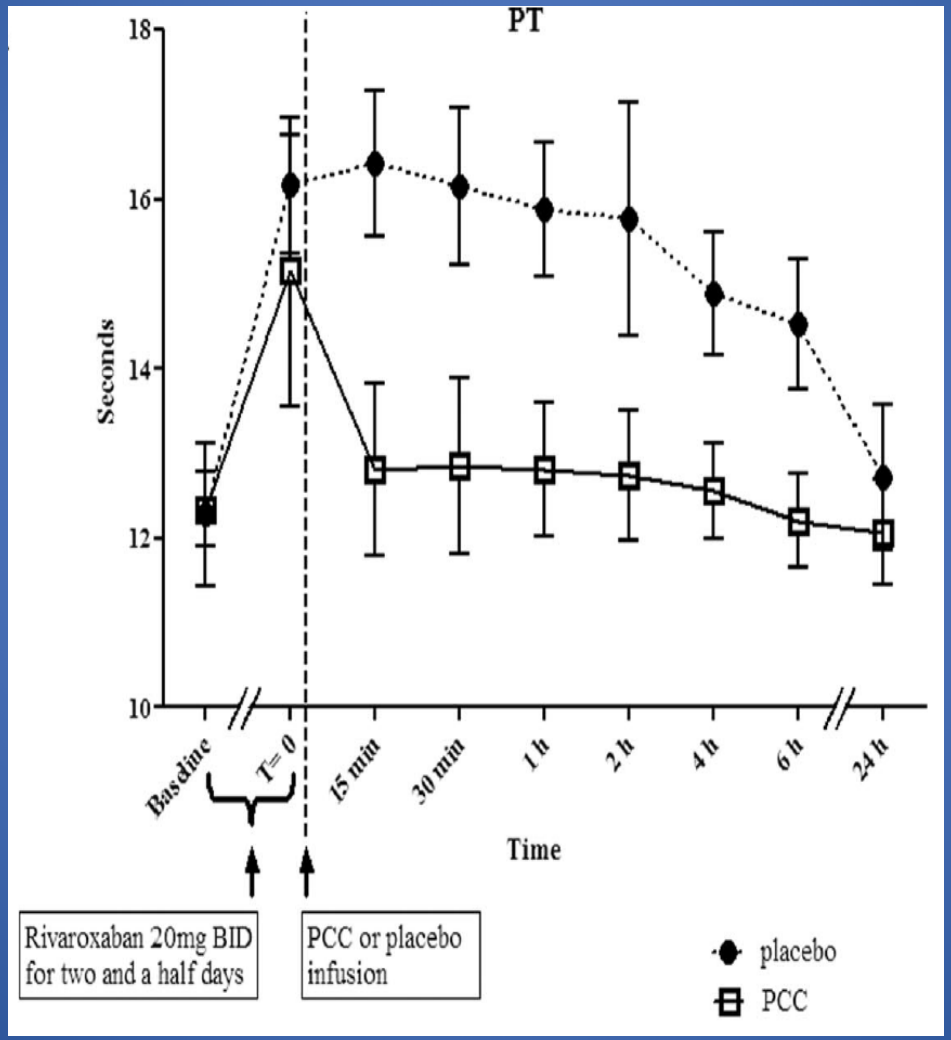
Siegal et al, Blood 2014; 123: 1152-1158

No reversal of the anticoagulant effect of dabigatran by prothrombin complex concentrate



Eerenberg et al, Circulation. 2011 Oct 4;124(14):1573-9

Reversal of the anticoagulant effect of rivaroxaban by prothrombin complex concentrate



Eerenberg et al, Circulation. 2011 Oct 4;124(14):1573-9

Reversal of unfractionated heparin

- Stop the drug
- General measures

- Protamine sulphate (1 mg per 80–100 units UFH)
- Maximum recommended dose of 50 mg protamine
- Timing

Reversal of low molecular weight heparin

- Protamine sulphate (1 mg per 80–100 units UFH)
  - consider second dose
- Maximum recommended dose of 50 mg protamine
- Timing
- rFVIIa

Reversal of argatroban/danaparoid/fondaprinux

- Stop the drug
- General measures

- No specific antidote

Reversal of VKA

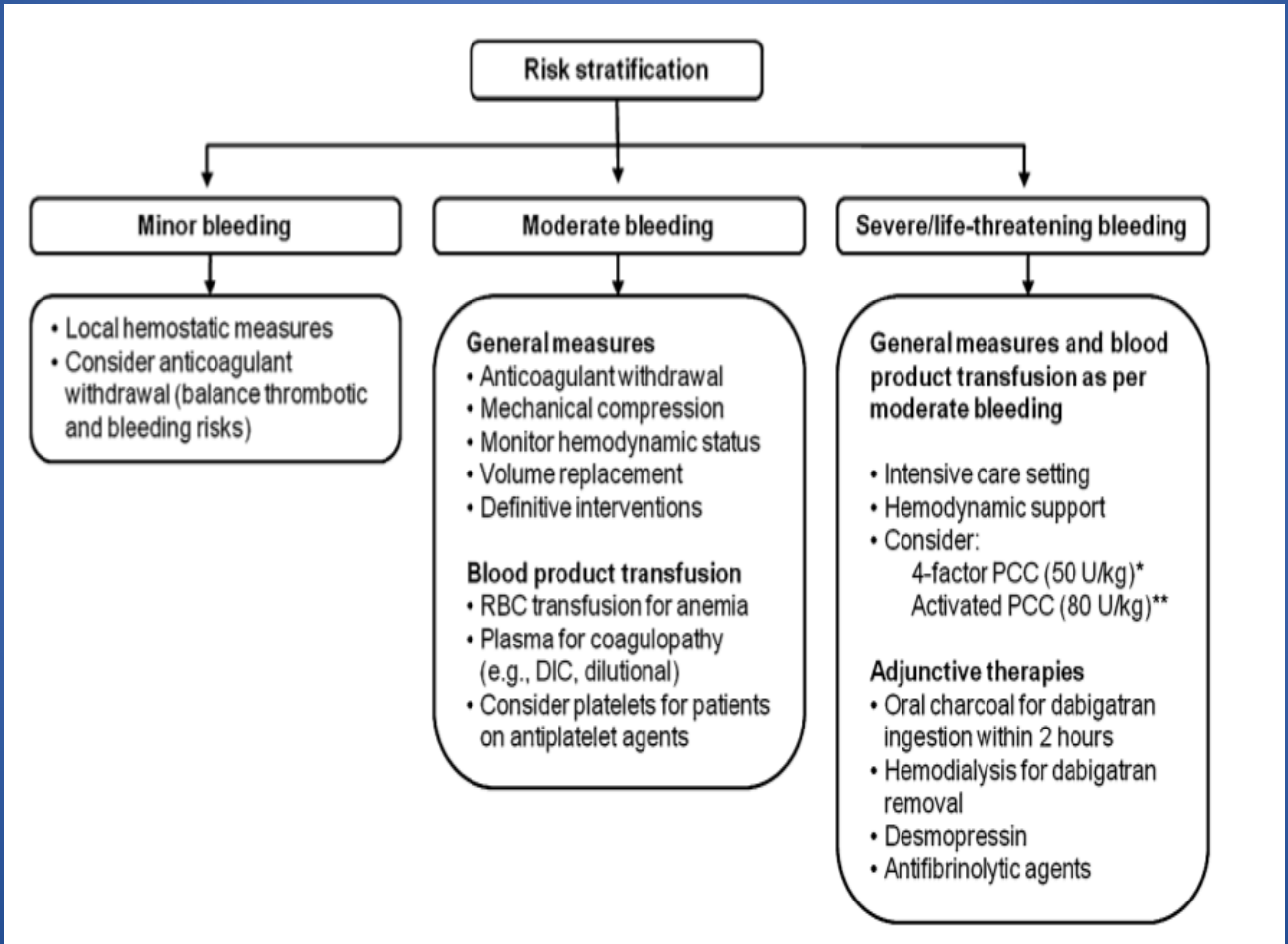
Major bleeding

- 25-50 units of 4 factor PCC
- 5mg Vitamin K IV

Non-major bleeding

- Consider 4 factor PCC
- Vitamin K 1-3mg IV

Reversal of DOACs



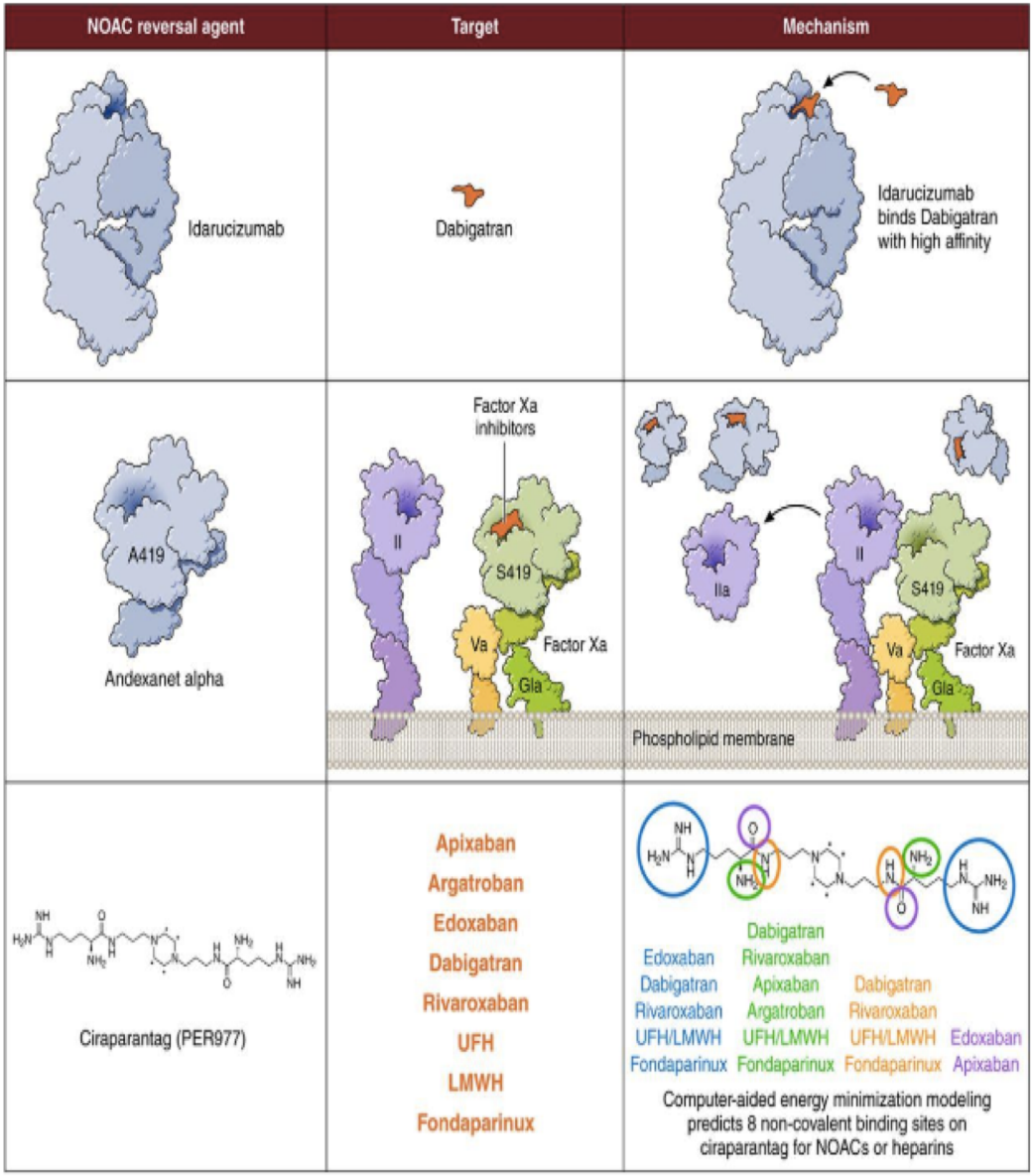
Development of antidotes to non vitamin K antagonist oral anticoagulants

	Target	Mechanism of action	Investigation status
Idarucizumab	Dabigatran	Humanized Fab: specifically binds dabigatran (binding affinity ~350 × higher than binding of dabigatran to thrombin)	Bleeding patients and surgical patients[2]
Andexanet alfa (PRT064445)	FXa inhibitors	Recombinant human FXa variant: competitive affinity for direct FXa inhibitors	Healthy volunteers[3,4]
Aripazine (PER977)	Universal	Synthetic small molecule: charge–charge interactions (heparin); hydrogen bonds (NOACs)	Phase I[5]

3. Clinicaltrials.gov: NCT02220725;

4. Clinicaltrials.gov: NCT02207725;

5. http://www.perosphere.com/content/news/httpwww.perosphere.comcontentnewsreleases042513.htm accessed January 2015



Christian T. Ruff et al. Circulation. 2016;134:248-261

Idarucizumab (Dabi-Fab) is a humanized Ab fragment that binds to dabigatran, preventing it from binding to thrombin and neutralizing its anticoagulant effect.

Andexanet alfa (And-a) is a modified inactive recombinant FXa that binds circulating FXa inhibitors, allowing native FXa to convert prothrombin to thrombin and restore the coagulation cascade.

Ciraparantag - small synthetic molecule that competitively binds the NOACs, restoring activity of blocked coagulation factors.

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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.

News Release

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U.S. FDA Approves Portola Pharmaceuticals' Andexxa®, First and Only Antidote for the Reversal of Factor Xa Inhibitors

– Breakthrough Product is a Major Advance in the Treatment of Patients Hospitalized with Life-Threatening Bleeding –

– Company to Host Conference Call on Friday, May 4, 2018 at 8:30 a.m. ET –

Reversal of anti-platelet associated bleeding

- Stop the drug
- General measures

- Consider platelet transfusion

Management of bleeding with anti-fibrinolytics

- Stop infusion of fibrinolytic drugs and other antithrombotic drugs

- Administer intravenous tranexamic acid 1 g tds
- Administer cryoprecipitate or fibrinogen concentrate

Conclusion

- Prevention is better than cure
- Management guided by severity of bleed and encompasses drug cessation, general measures and drug specific measures
- Bleeding rates likely to become less of a concern in future with DOACs

Any questions?