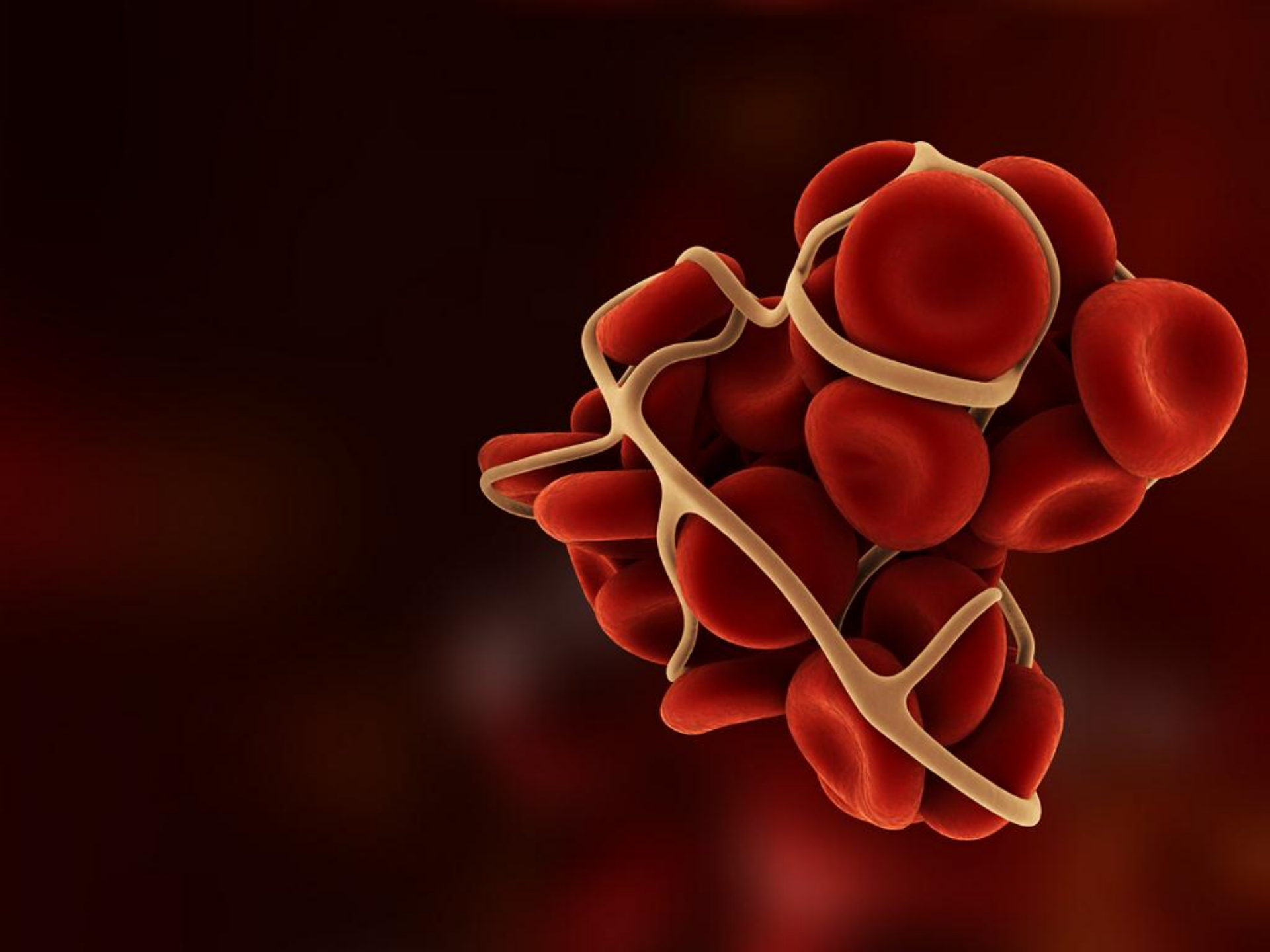


The New Oral Anticoagulants (NOACs)

Dr Gordon Royle

Haematologist,
Middlemore Hospital

Disclaimers

- Boehringer-Ingelheim
- Bayer
- Sanofi
- Douglas Pharmaceuticals

Preventing disasters: lessons learned

A cautionary tale (suitably anonymised)

- A patient in a NOAC trial was involved in in low speed vehicle accident
- Told ambulance officers he was in NOAC trial – carried wallet card and alert bracelet – ambulance officer had not heard of study drug
- Emergency Department medical officer asked if he was on warfarin: “not sure”
- INR was 1.3 – ***assessed as having no significant coagulopathy from warfarin***
- Haematologist called – agreed INR made it improbable patient was on therapeutic warfarin – *was unaware of possibility of other anticoagulant*

- No attempt at reversal of anticoagulation
- patient continued to bleed, and passed away
- Post-mortem anti-Xa level came back as 0.6 – i.e. equivalent to therapeutic enoxaparin (Clexane) - while INR was only 1.3.

Issues, lessons, and comments:

- Bleeding may have been ‘surgical’ – i.e. nothing to do with the anticoagulant.

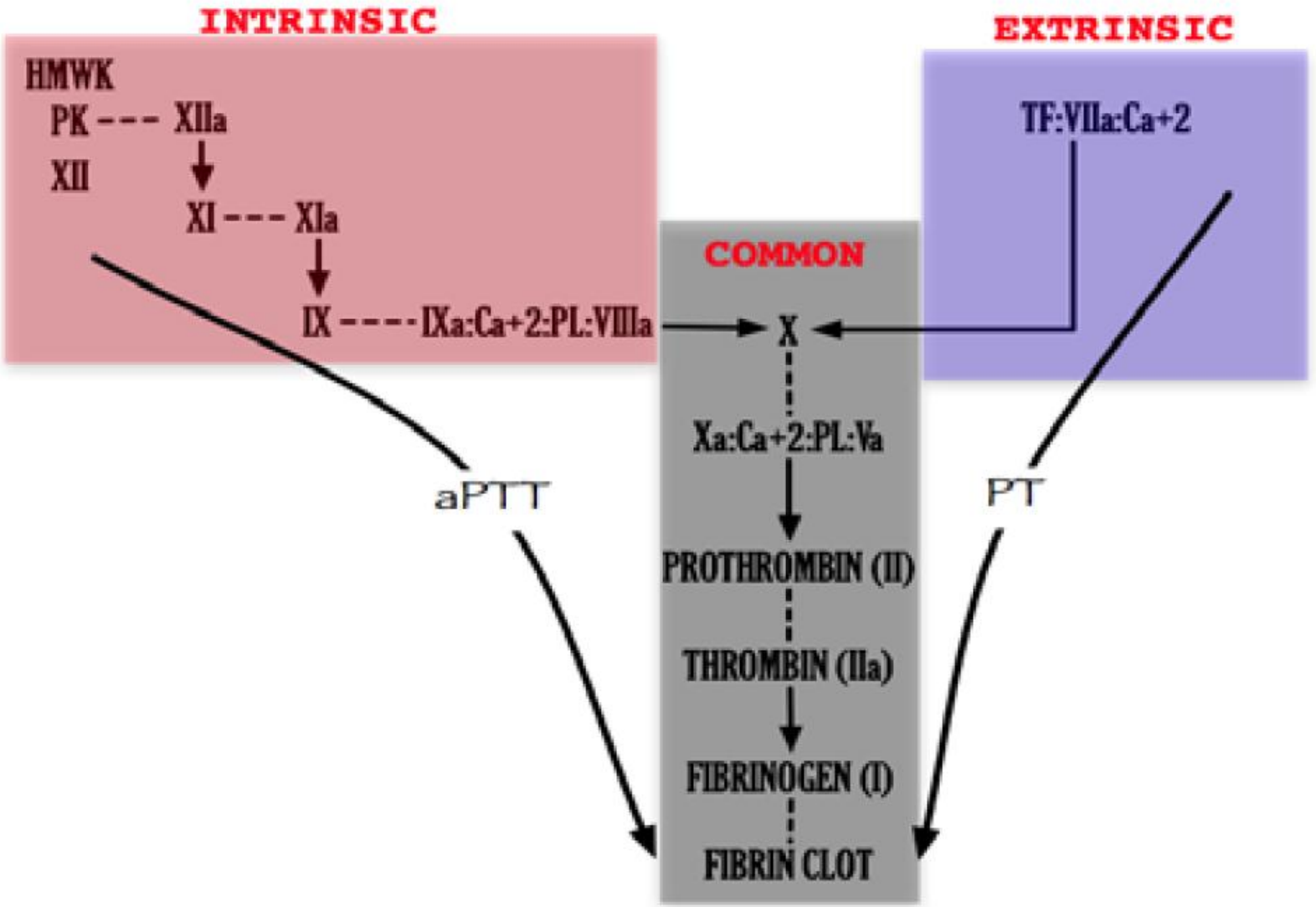
  - Lack of evidence for effectiveness of reversal measures

    ≠

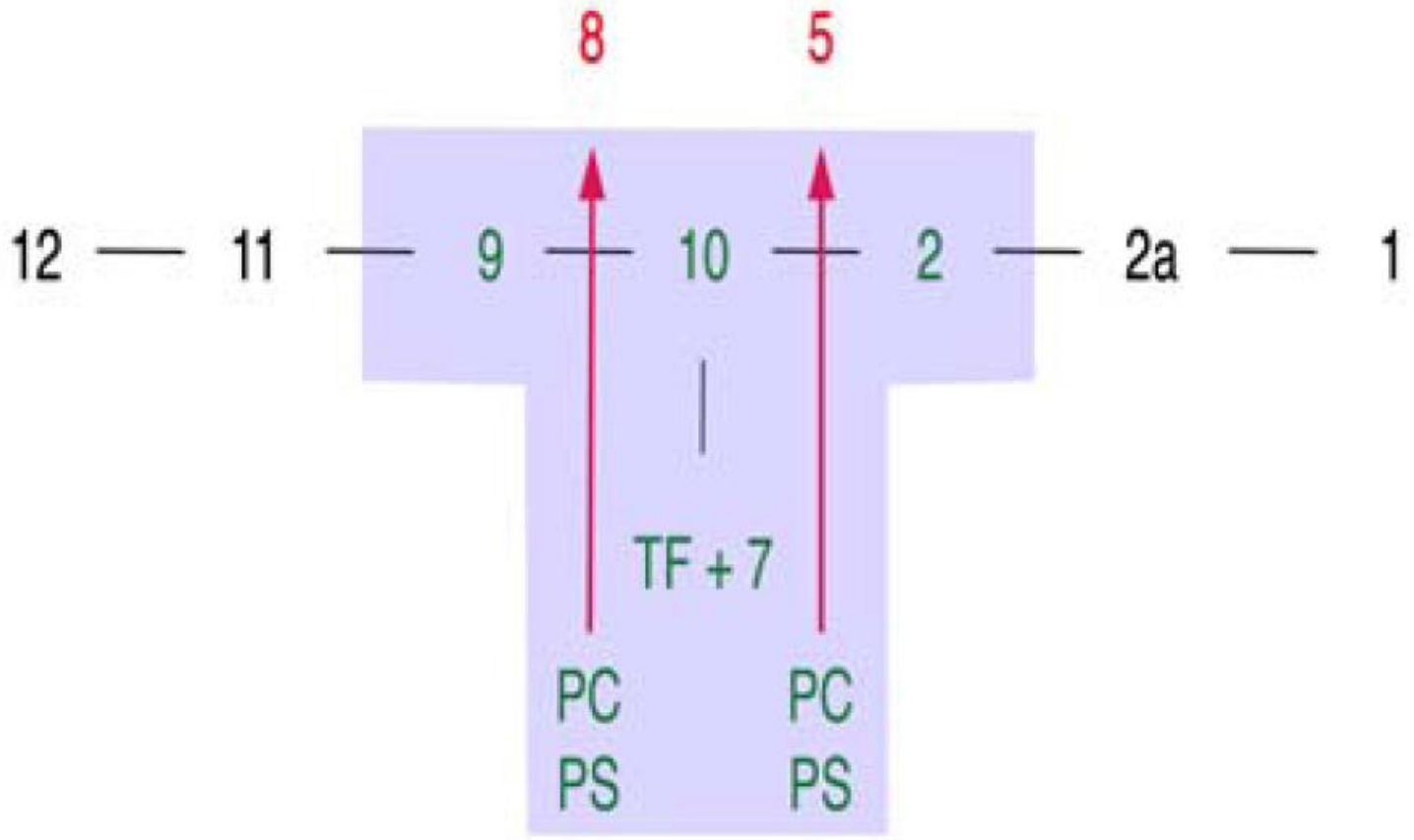
    Evidence that they don’t work!

- Normal baseline coag screen does not imply normal haemostatic function!

Coagulation Cascade



A Little Simpler



- The only reason we screen with PR, APTT (and platelet count) is that until now these tests pick up most ‘naturally occurring’ coagulopathies – plus warfarin and heparin

Test	Naturally occurring conditions it picks up	Medications it picks up	
APTT (intrinsic pathway)	Haemophilia (F VIII, IX) The lupus anticoagulant	Heparins Dabigatran	
Prothrombin ratio (extrinsic pathway)	Liver failure	Warfarin / Vit K deficiency	
Echis ratio	Liver failure		

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- A take-home point: **A normal PR and APTT do not exclude all coagulopathies**
- The new oral anticoagulants require new tests…

  - or recycling of older, disused tests – eg the dilute thrombin clotting time (dTCT)

- **The ideal anticoagulant would be:**

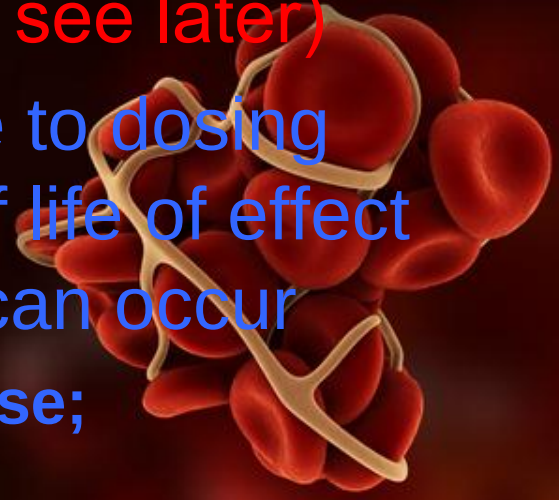
- One dose fits all
- No INR testing
- Oral dosing
- Free from side effects
- Free from significant drug interactions
- ***Prevents clots without causing bleeding***
- cheap

Are we closer to the ideal with the NOACS?

- One dose fits all (almost)
- No *regular* (INR) testing
- Oral dosing
- Relatively free from side effects
- Few significant drug interactions
- Better risk-benefit ratio than warfarin in AF (ie closer to the ideal)
- Cheap if improved efficacy and reduced ICH rate taken into account

- **BUT…**

- "the good news is you don't have to test the INR;
  the bad news is you don't have to test the INR"
- INR levels assess not only therapeutic effect, but compliance
- Some labs can however test drug levels
  – but interpreting their significance can be problematic
- easier to suspend effect transiently for surgical procedures – skip two days' dose (but see later)
- but requires more stringent adherence to dosing than warfarin, as half life of drug = half life of effect (unlike warfarin) - breakthrough clots can occur
  - **NB do not necessarily restart at full dose; may need to bridge postoperatively**



Meet the NOACS

	dabigatran (Pradaxa)	rivaroxaban (Xarelto)	apixaban (Eliquis)	edoxaban
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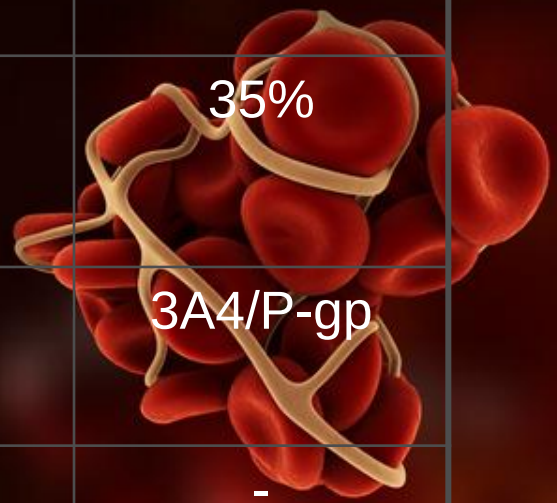
Terminal half life	12-14 hours	5-9 hours (11-13 in elderly)	12 hours	9-11 hours
dosing	b.d.	once daily	b.d.	once daily
renal excretion	80%	33% direct (+33% after metabolised)	25%	35%
interactions	P-gp	3A4/P-gp	3A4	3A4/P-gp
Prodrug?	yes	-	-	-



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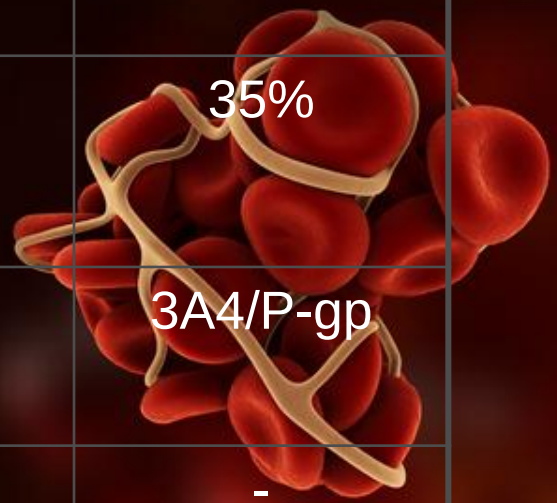

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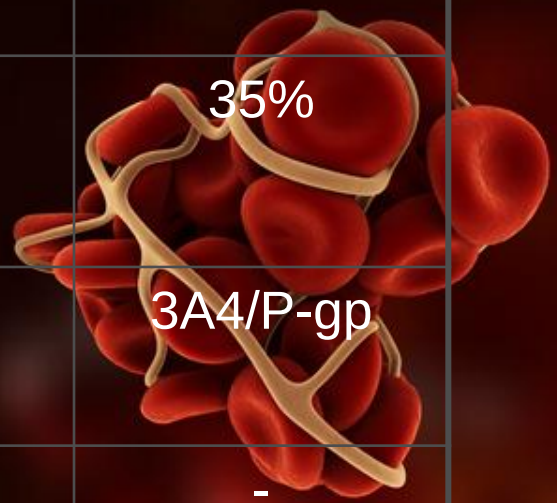

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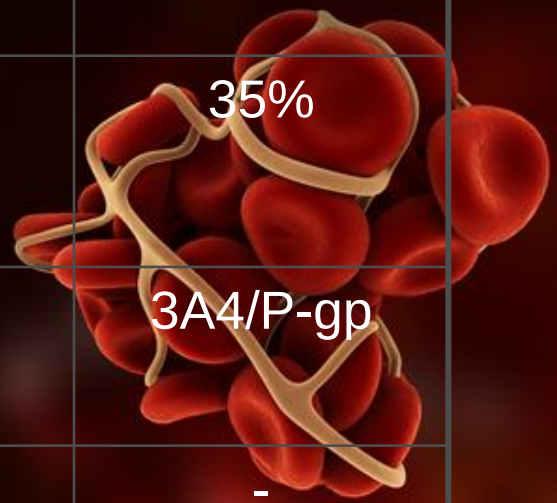

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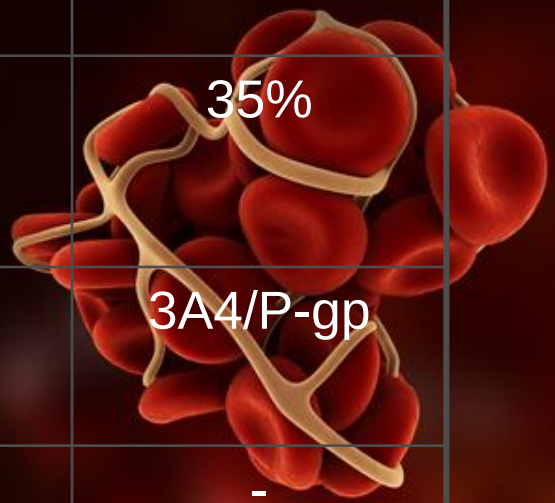

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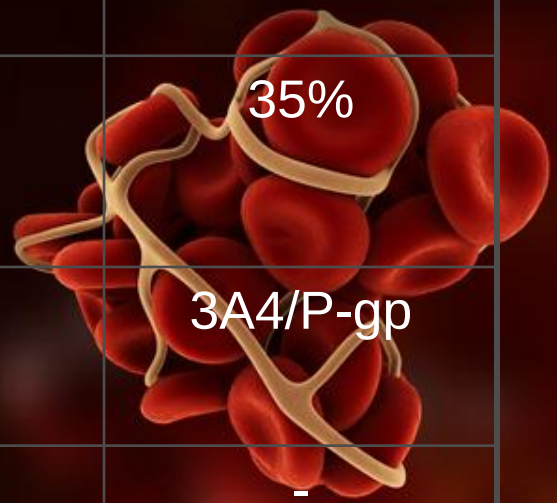

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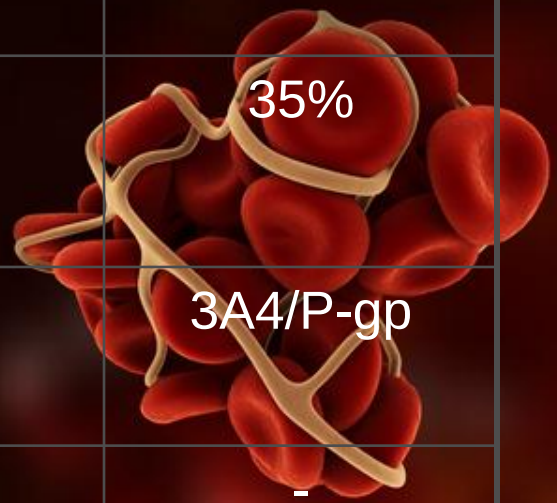
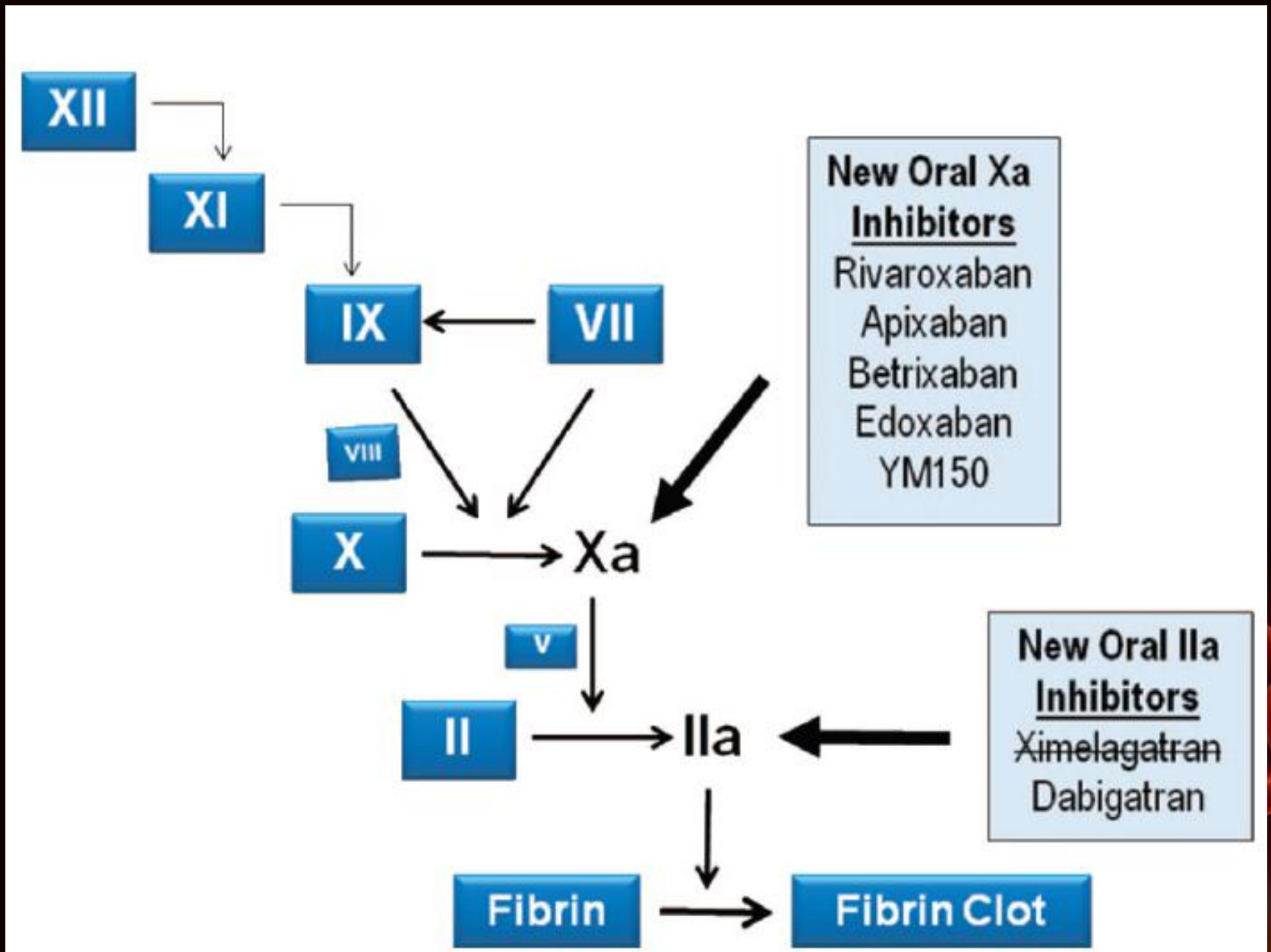



XII
XI
IX
VII
VIII
X
Xa
V
II
IIa
Fibrin
Fibrin Clot
New Oral Xa Inhibitors
Rivaroxaban
Apixaban
Betrixaban
Edoxaban
YM150
New Oral IIa Inhibitors
~~Ximelagatran~~
Dabigatran

- Current registration for stroke prevention in non-valvular AF:
  - **dabigatran (funded)**
  - **rivaroxaban (unfunded as yet)**
- Which patients are likely to benefit from being on dabigatran?

  Bleeding issues are largely confined to
  - **the elderly (> ~80 years),**
  - **those with borderline renal function (creatinine / eGFR may not tell the whole story) – or who may develop it**
  - **Weight <60Kg**
- **Take home point: *avoid dabigatran in patients with one or more of these!***

dabigatran

- Specific contraindications:
  - **creat clearance < 30;**
  - **severe liver impairment**
  - **haemorrhagic stroke within last 6/12**
  - **Or known haemorrhagic tendency (risk of, or from, bleeding, eg neuraxial procedures)**
  - **IV ketoconazole**
  - **Pregnancy and lactation**

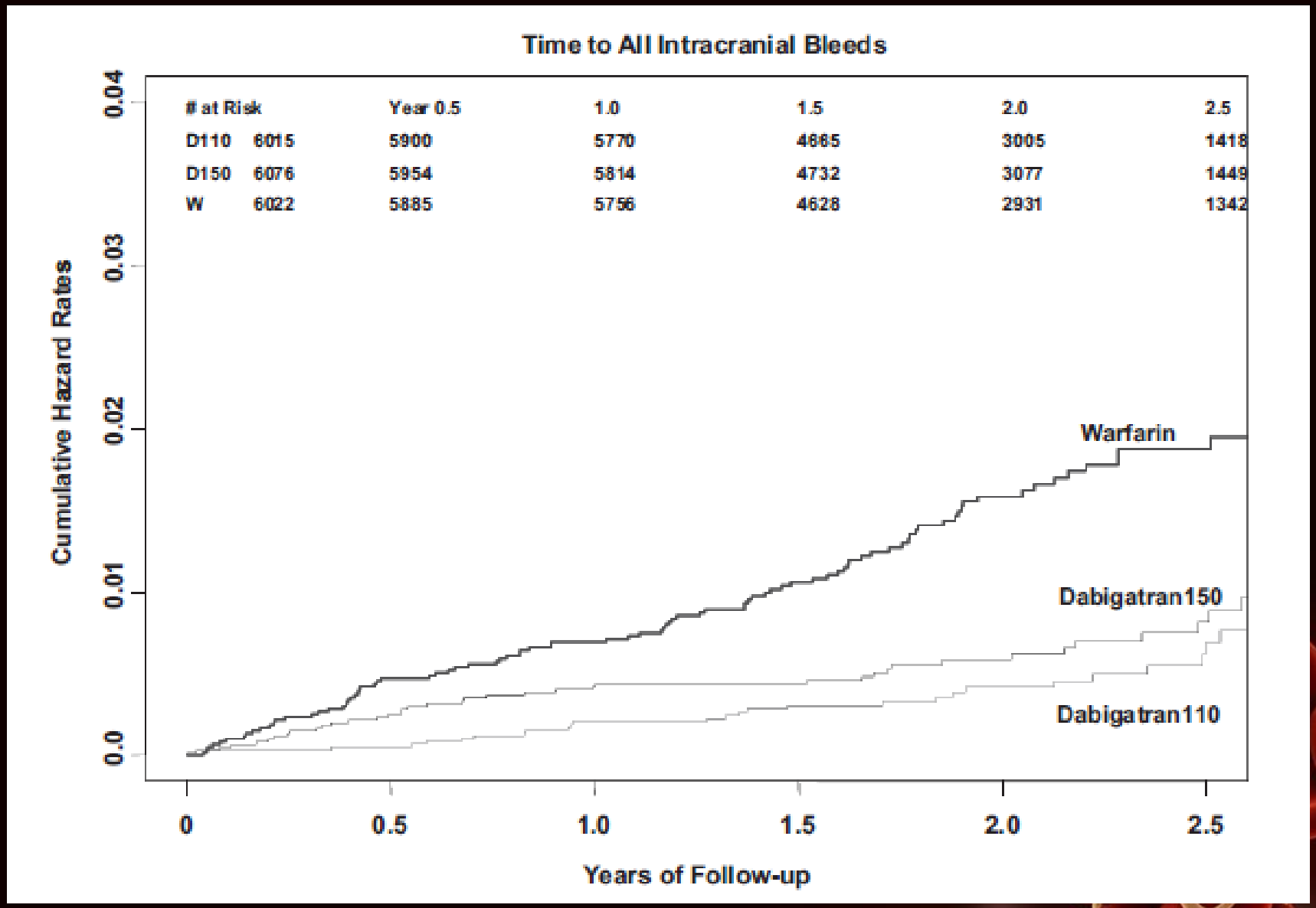
Who are the *most* suitable patients?

- Those for whom warfarin is a problem due to:
  - **Access**
    - Venous
    - Geographical – eg live on an island
  - **INR variation (diet, medication, etc)**
  - ***Side effects***

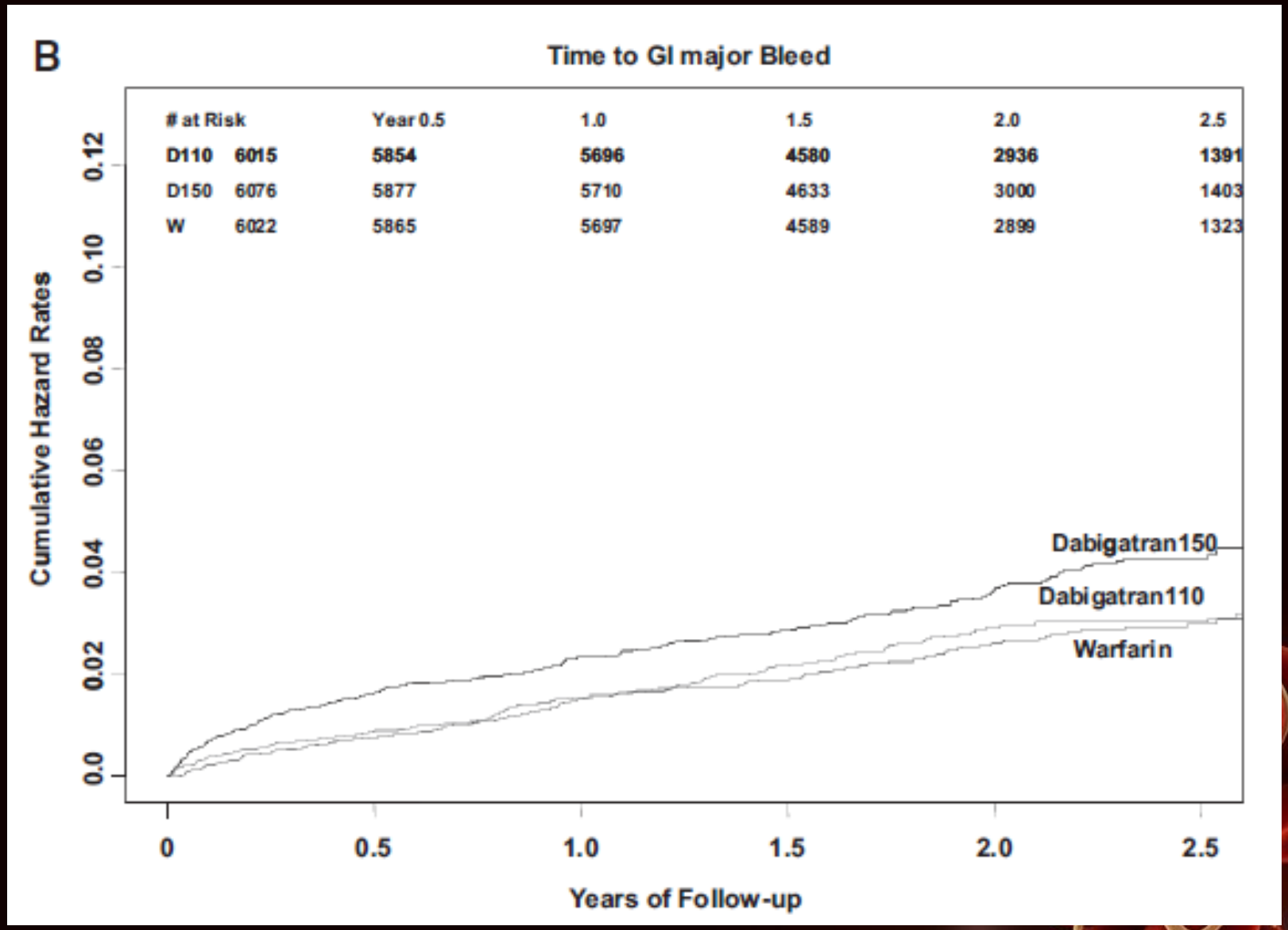
Dabigatran: stroke prevention in non-valvular AF

- Re-Ly study: dabigatran in AF vs warfarin
- Dabigatran 150mg bd: fewer strokes than warfarin, dabigatran 110mg bd have fewer bleeds.
- Maintenance dose = 150mg BD or 110mg if Creat clearance 30-50ml/min/>75-80 years
- ***Both have less intracranial haemorrhage than on warfarin*** (? sensitivity of warfarin to tissue factor?)
- Extracranial bleeding may be higher in those aged >75
- Benefit greatest when compared to those with poor INR control
- Increased risk of bleeding in renal impairment

Connolly et al (2010). NEJM 363:1875-6.



Eikelboom et al (2011) Circulation 123:2363-72.



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Switching

- From warfarin to dabigatran:
  - ***Stop warfarin, drift INR to ≤2.0, start dabigatran at fixed time of day***
- Clexane to dabigatran
  - **Give dabigatran 0-2 hours *before* next clexane dose is due**
- Dabigatran to clexane or heparin
  - **Start 12 hours after the last dose of dabigatran**
- Heparin infusion to dabigatran
  - **Give dabigatran at the time the heparin infusion is stopped**

Perioperative Management

- For minor procedures e.g. dental surgery, may not need to be discontinued
- Other procedures = plan ahead (not reversible!)
- Timing of discontinuation dependent on patient's renal function

Renal function (CrCl, mL/min)	Half-life of dabigatran (hours)[d]	Timing of discontinuation after last dose of dabigatran before surgery	
		Standard risk of bleeding	High risk of bleeding[e]
> 80	13 (11-22)	24 hours	2-4 days
> 50 to ≤ 80	15 (12-34)	24 hours	2-4 days
> 30 to ≤ 50	18 (13-23)	At least 2 days (48 hours)	4 days
≤ 30[f]	27 (22-35)	2-5 days	> 5 days

Pharmac guidelines: Testing and Perioperative Management of Dabigatran.

Dabigatran risk assessment and actions

	HIGH PATIENT FACTOR RISK	LOW PATIENT FACTOR RISK	MONITORING	SURGERY
LOW BLEEDING RISK	Withhold Dabigatran the evening before and morning of surgery	Withhold Dabigatran the evening before and morning of surgery	No blood collection required	Surgery can proceed
MODERATE BLEEDING RISK	FOUR FULL DAYS without dabigatran prior to surgery	TWO FULL DAYS without dabigatran prior to surgery	Collect blood on induction and send for baseline APTT, TCT and dabigatran level.	Surgery can proceed before blood results are available
HIGH BLEEDING RISK	SEVEN FULL DAYS without dabigatran prior to surgery	FOUR FULL DAYS without dabigatran prior to surgery	Check TCT and dabigatran assay level the night before and morning of surgery. Ideally these patients should NOT be first on the list	Surgery cannot proceed until results are checked. Proceed if TCT normal OR serum dabigatran assay is less than 0.01mmol/L

Recommencement after Surgery

- Elective surgery where haemostasis secure – restart with single capsule at 50% total daily dose 1-4 hours after surgery
- Commence usual daily dose next day
- Delay restarting if wound not stable/significant wound losses
- If significant risk thrombosis but bleeding concerns - may need short term use of heparin

Bleeding

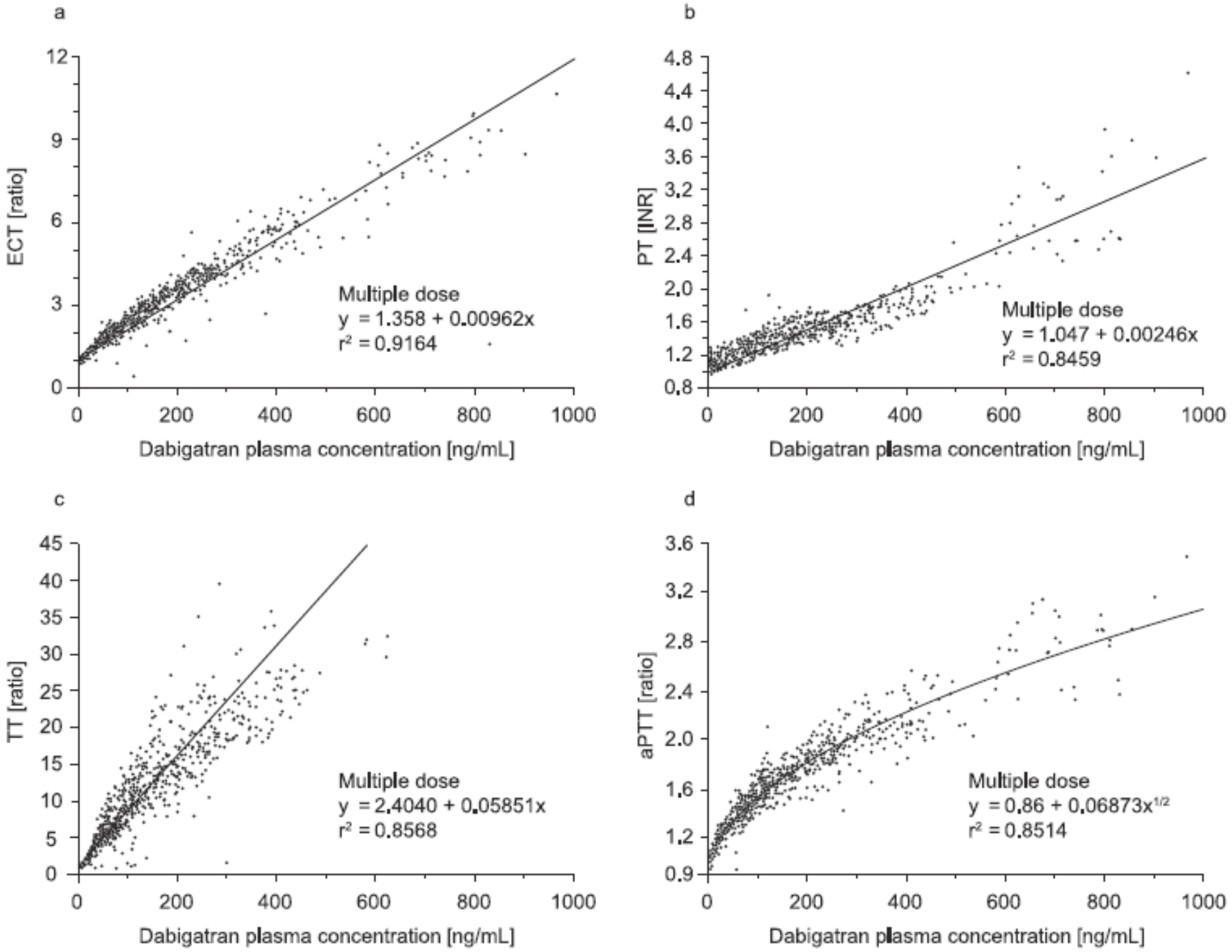
- Specific antidote not yet available here
- Discontinuation of drug may be enough in patients with normal renal function and mild bleeding

Bleeding

- Local measures – eg compression
- Maintain adequate diuresis (- renal excretion)
- Only FFP/cryoprecipitate if severe deficiency of one or more factors e.g. in context of DIC or major transfusion; could add 1-2U FFP to PTX
- Platelet transfusion if eg taking aspirin or clopidogrel, or if thrombocytopenic
- Use of prothrombinex and rFVIIa need to be discussed with haematologist on call
- Maintain optimal body temperature, pH and calcium
- Consider tranexamic acid
- ***Consult Haematology***
- May require dialysis

When to Test for Dabigatran Anticoagulant Effect

- bleeding/suspected overdose
- perioperative period (especially acute surgery)


a
ECT [ratio]
Multiple dose
y = 1.358 + 0.00962x
r² = 0.9164
Dabigatran plasma concentration [ng/mL]
b
PT [INR]
Multiple dose
y = 1.047 + 0.00246x
r² = 0.8459
Dabigatran plasma concentration [ng/mL]
c
TT [ratio]
Multiple dose
y = 2.4040 + 0.05851x
r² = 0.8568
Dabigatran plasma concentration [ng/mL]
d
aPTT [ratio]
Multiple dose
y = 0.86 + 0.06873x^1/2
r² = 0.8514
Dabigatran plasma concentration [ng/mL]

How to test for Dabigatran Anticoagulant Effect

- INR relatively insensitive (only supratherapeutic doses give INR ~2.0)
- Echis ratio more sensitive than INR
- APTT moderately sensitive but curve flattens off higher doses, and may remain elevated after all drug gone
- Thrombin time (TT) very (too!) sensitive with linear response curve – may take 10 days to normalise
- Take home point: if dTCT normal, patient safe for surgery.
- *Prolonged clotting tests may be multifactorial*

Rivaroxaban

Effect on Lab tests:

- Very little!
  - **Only measureable when drug conc high**
  - **Modest elevation of PR eg 1.2 (depends on thromboplastin; some more sensitive to factor X inhibition)**
  - **Possibility of "INR-riva" cf "INR-VKA"**
- Best to specifically test for anti-Xa activity – consult Haematology

Rivaroxaban

Perioperative management:

- stop drug (and correct any other contributing factors)
- measure anti-Xa activity (qualitative only)
- Prothrombinex and/or Novo-7 may be useful (*in vitro* data)
- call Haematology
- not dialysable
- tranexamic acid?
- note patients likely to have VTE risk