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M.B.B.S. (Hons)
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The New Oral Anticoagulants: what emergency physicians need to know

HK College of Emergency Medicine
Joint Clinical and Didactic Lectures
7 Aug 2013

Outline of talk

1. What are new oral anticoagulants
2. Bleed x Vitamin K Antagonist (VKA) vs. NOAC
3. Any lab test useful?
4. How to reverse of NOAC

Bleeding with VKA

- Reduce factor II VII IX X and PC PS
- Most feared: intra-cerebral hemorrhage (ICH)
- 0.5-1.2% per year, 40% die
- Among 125195 Canadian Af age>66
- 3.8% per year (5yr)
- 18% major bleed die in 7 days.
- No prove that reversal saves lives.

Limitations of VKA therapy

VKA therapy has several limitations leading to underuse and leaving patients at risk of bleeding

- Narrow therapeutic window (INR range 2-3)
- Unpredictable response
- Numerous drug-drug interactions
- Numerous food-drug interactions
- Warfarin resistance
- Slow onset/offset of action
- Routine coagulation monitoring
- Frequent dose adjustments

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137;
2. Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

Novel Oral Anti-Coagulants (NOAC)

- **Direct Thrombin Inhibitors**
  - Dabigatran
- **Direct Xa Inhibitors**
  - Rivaroxaban
  - Apixaban
  - Edoxaban

Reversible mild hemophilias

Advantages of New Oral Anticoagulants Over Warfarin

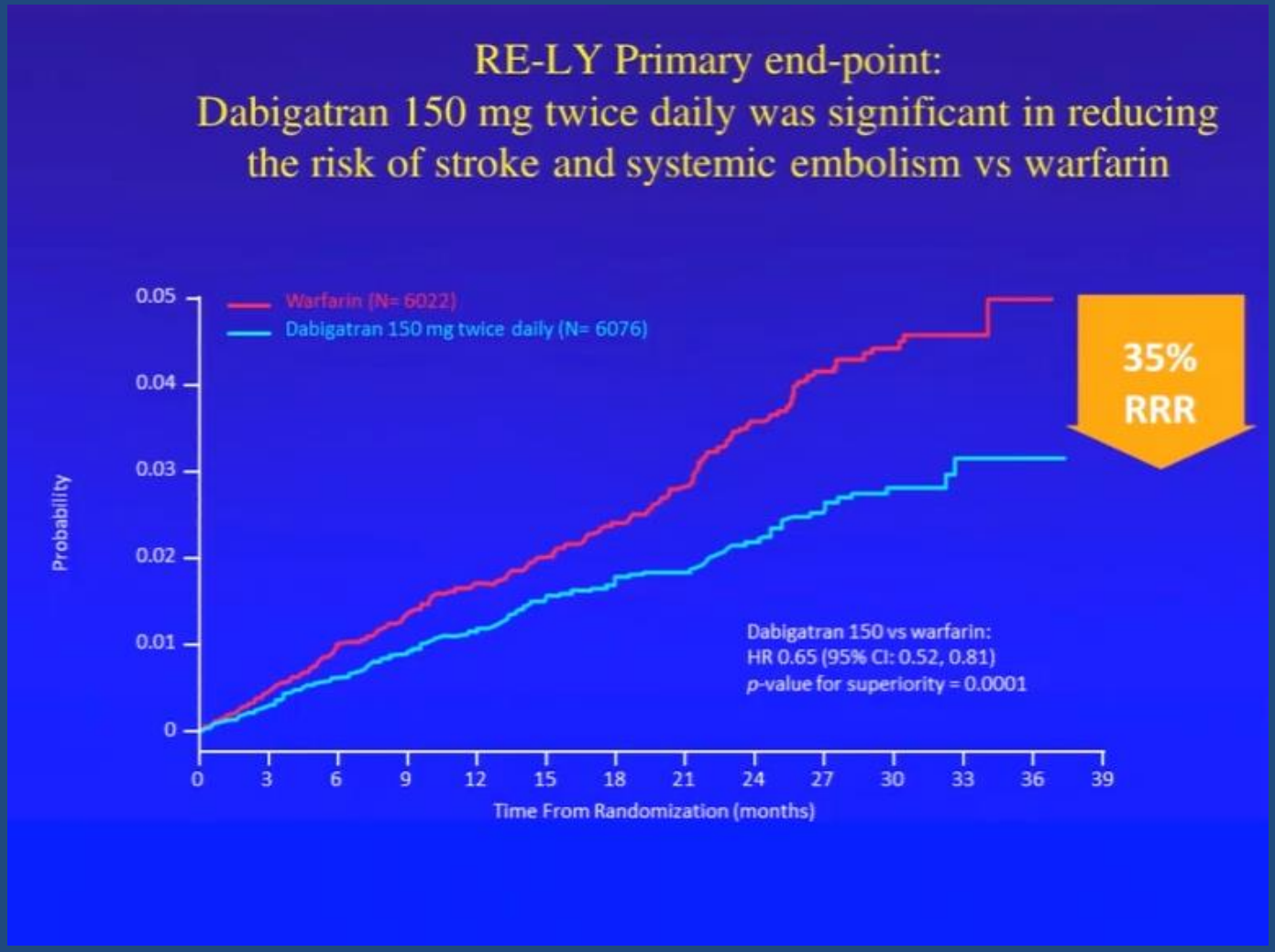
Feature	Warfarin	New OAC
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Interactions	Many	Few
Monitoring	Yes	No
Offset	Long	Shorter

Eikelboom and Weitz. Circulation 2010

Dose considerations

Characteristic	Rivaroxaban	Apixaban	Dabigatran
Target	Factor Xa		Thrombin
Prodrug	No		Yes
Bioavailability	80%		6%
Dosing	o.d. (b.i.d.)		b.i.d. (o.d.)
Half life	7-11 h		12-17 h
Renal	33% (66%)		80%
Monitoring	No		No
Interactions	3A4/P-gp		P-gp

Efficacy in 12000 patients



Overall Clinical Trial Program Comparison

INDICATION	Rivaroxaban (FXaI)		Dabigatran (DTI)	
VTEp THR	RECORD1 RECORD2	Superior Superior	RE-NOVATE RE-NOVATEII	Non-inferior Non-inferior
VTEp TKR	RECORD3 RECORD4	Superior Superior	RE-MODEL RE-MOBILIZE	Non-inferior **Failed**
SPAF	ROCKET-AF	Superior	RE-LY	Non-inferior (110mg) Superior (150mg)
DVT treatment	EINSTEIN DVT	Non-inferior	RECOVER RECOVERII	Non-inferior Results not yet available
PE treatment	EINSTEIN PE	Non-inferior		
Secondary prevention of VTE	EINSTEIN EXT	Superior to placebo	RE-MEDY RE-SONATE	Non-inferior to warfarin Superior to placebo
ACS add to anti Plt	ATLAS ACS 2	Significant reduction in primary endpoint	RE-DEEM (Phase 2)	Phase 3 trial not conducted
Medically ill	MAGELLAN	Non-inferior to enoxaparin Superior to placebo but **more bleeding**	Not conducted	N/A

Country for Regulatory Approval

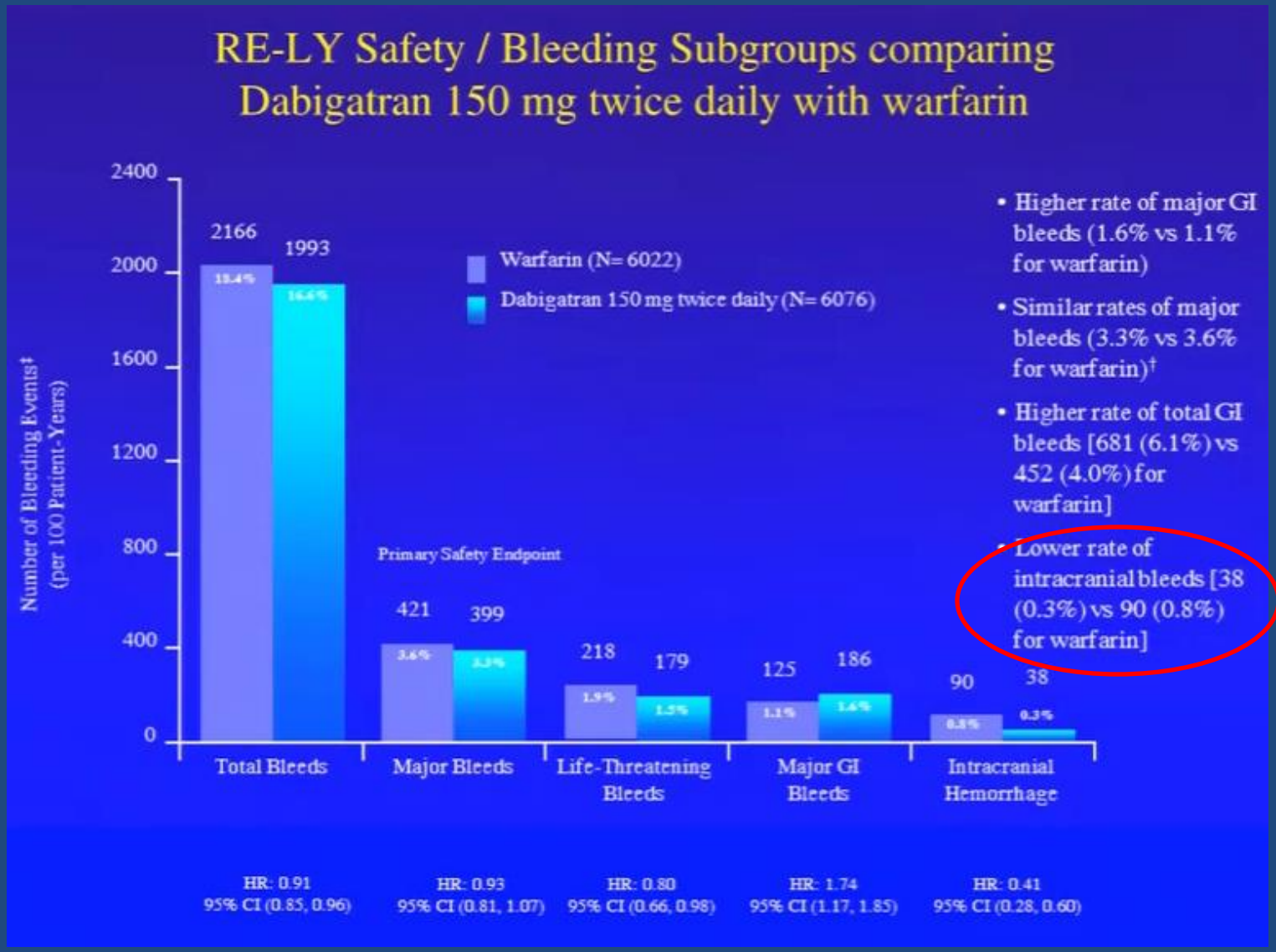
Indications	Europe (EU)		USA (FDA)		Hong Kong (DOH)	
	Rivaroxaban	Dabigatran	Rivaroxaban	Dabigatran	Rivaroxaban	Dabigatran
VTEp THR/TKR	Yes	Yes	Yes	No	Yes	Yes
SPAF	Yes	Yes	Yes	Yes	Yes	Yes
DVT treatment	Yes	No	Yes	No	Yes	No
PE treatment	Yes	No	Yes	No	Approval pending	No
Prevention of recurrent VTE	Yes	No	Yes	No	Yes	No
ACS	CHMP positive opinion in Mar, 2013	No	Submitted for approval in Dec, 2011	No	Submission subject to EU approval	No

European , Canadian, American guidelines: first line and PREFERRED over warfarin

1. What are NOAC?

- Specific inhibitors of single coagulation factor
- Oral fix-dose rapid action
- Will replace warfarin in long run
- $35 versus $3 per day
- No need x INR
- Pro warfarin: long safety data, patient interaction, miss dose, monitor and reversal.

Safety in 12000 patients



Lessons from Clinical Trials in Atrial Fibrillation

All of the new oral anticoagulants are at least as effective as warfarin and can be given without routine monitoring

All agents reduce the risk of intracranial bleeding

New agents produce about a 10% reduction in mortality

Mortality of bleeding
NOAC no different from VKA

Table 2. Mortality rates of intracranial hemorrhages by treatment arm and site in **RE-LY** trial

Type	Warfarin % (n/n)	Dabigatran 150 mg % (n/n)	Dabigatran 110 mg % (n/n)
All intracranial hemorrhages	36% (32/90)	35% (13/37)	41% (11/27)
Intracerebral hemorrhage	41% (19/46)	64% (7/11)	64% (9/14)
Subdural hemorrhage	28% (10/36)	21% (5/24)	20% (2/10)
Subarachnoid hemorrhage	38% (3/8)	50% (1/2)	0% (0/3)

How to prevent bleed?

- RELY trial 4591 surgeries (12000 pat)
- 7.8% were urgent OT
- no difference DB vs. VKA (but no refined data)
- For normal Cr Cl, 48hrs or 4 half lives (4 x13-18hr) hence <30ng/ml
- ROCKET-AF no data on rivaroxaban E-OT

Interaction with other anticoagulants

No need to bridge with LMWH, can give 12 hours after last dose

Change from warfarin: wait INR 2 or give Vitamin K10mg and start next day

Low Platelets: 50 is probably good enough
Aspirin compatible if indicated

To avoid bleeding

- Patient education to avoid overdose
- Adjust x Cr, age, indication and bleeding risks
- 4 $T_{1/2}$ before elective OT
- No need x absolute absence of drug for OT
- No need x absolute normal TT / FXa
- No need x prophylactic reversal for OT
- Nature of OT: neurosurgery, endoscopy
- Chinese bleed more and clot less

Chinese clot less?

Table I. Population studies of VTE across different ethnic groups in the USA.

	Study population	White/ Caucasian	African American	Hispanic	Asian/Pacific Islander
Stein *et al* (2004b): number of subjects	2 490 000	2 641 000	440 000	–	21 000
All VTE (age adjusted rate/100 000 per year)		130	138	–	26, $P < 0{\cdot}0005$
DVT (age adjusted rate/100 000 per year)		104	107	–	22, $P < 0{\cdot}0005$
PE (age adjusted rate/100 000 per year)	612 000	36	40	–	7, $P < 0{\cdot}0005$
White *et al* (2005): number of subjects	21 002	16 015	1794	2216	612
Adjusted standardised incidence of all VTE/100 000		104	141, $P < 0{\cdot}0001$	55, $P < 0{\cdot}0001$	21, $P < 0{\cdot}0001$
Idiopathic VTE: number of events	5418	4209	426	588	116
Incidence of idiopathic VTE/100 000 (95% CI)		28 (27–29)	32 (29–35), $P = 0{\cdot}04$	15 (13–16), $P < 0{\cdot}0001$	6 (5–7), $P < 0{\cdot}0001$
Schneider *et al* (2006)	10 542				
PE Male (age adjusted rate/100 000)		36·47	53·64, $P < 0{\cdot}001$	–	–
PE Female (age adjusted rate/100 000)		37·97	61·53, $P < 0{\cdot}001$	–	–

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; 95% CI: 95% confidence interval; –, group not examined in study.

Roberts et al. Br J Haematol 2009

Less clotting genes?

Table VI. Prevalence of hereditary thrombophilia in the healthy population by ethnicity. Please refer to text for references.

	F5 R506Q	*F2* G20210A	AT deficiency	PS deficiency	PC deficiency
Europeans	8·8–15%	1·7–3%	0·02–0·15%	0·03–0·13%	0·2–0·4%
SE Asian	0	0	0·15%	1·12%	0·13%
UK blacks	–	0	0	2%*	4%*
African Americans	1·1–1·23%	<0·001%	–	–	–

	F5 R506Q	G20210A	AT deficiency	PS deficiency	PC deficiency
Europeans	20%	6·2%	1–3%	1–5%	3–5%
SE Asian	0	0	5·6%	18%*	8%
UK blacks	1·4%	0	0·7%†	2·8%†	4·2%†
African Americans	2·9%	1·1%	–	–	–

–, Data not available.

*Patients with unprovoked DVT.

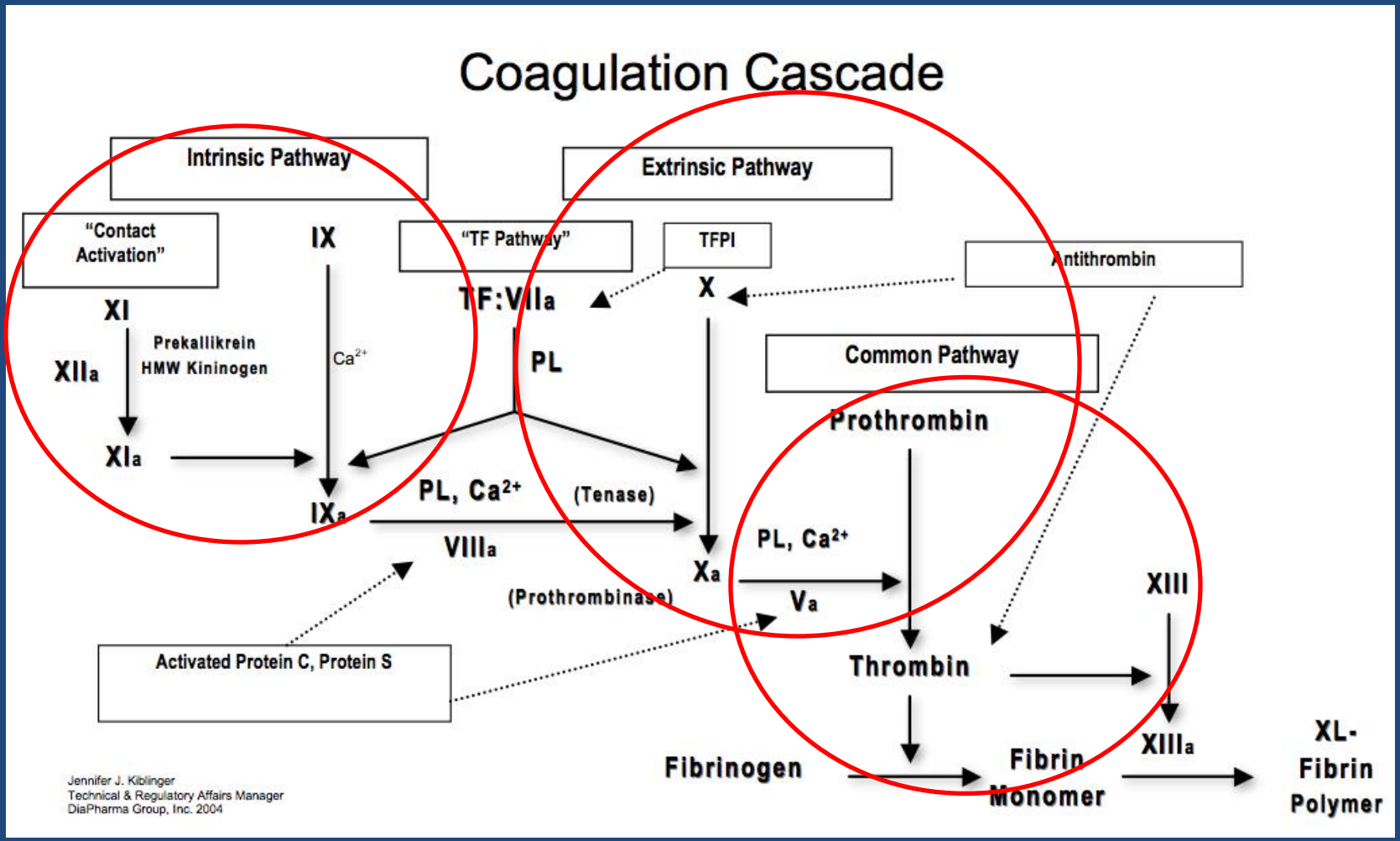
2. Risk of bleed vs Warfarin

- There will be risk of bleeding (no free lunch)
- Risks vary with age and indication, but either equivalent (MB) or less than warfarin (ICH)
- Bleeding outcome equivalent to warfarin
- Despite we seem to known VKA dosing, monitoring and reversal and seem not to know NOAC dosing, monitoring and reversal

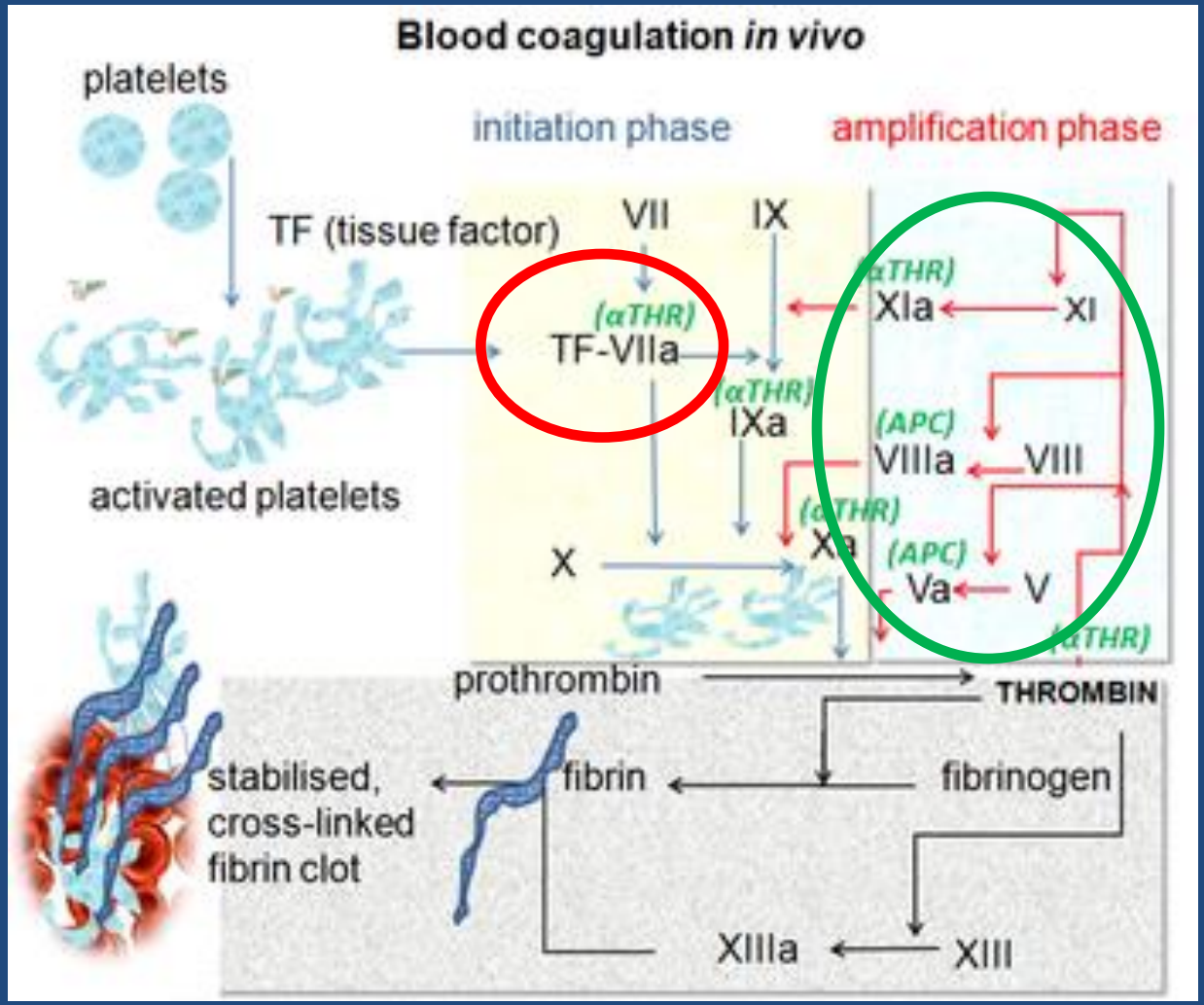
When and What from lab?

1. To identify mechanism of bleeding
2. To detect overdose
   - Renal / Liver impairment / Elderly
3. To determine the offset of activity
   - Pre-operative / thrombolysis for ischemic stroke
4. To monitor adherence
   - To distinguish treatment failure from non-adherence

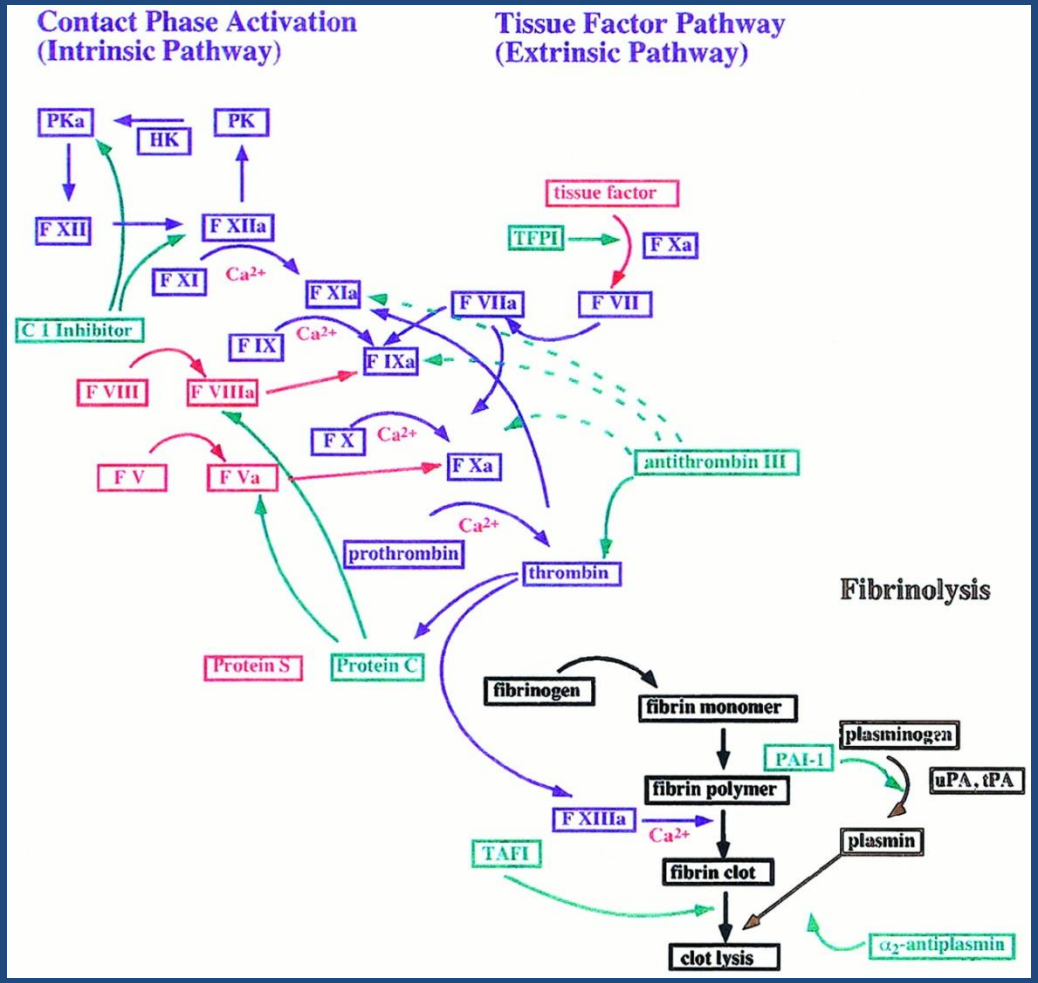
In vitro: test tube
Intrinsic / extrinsic PT/APTT/TT



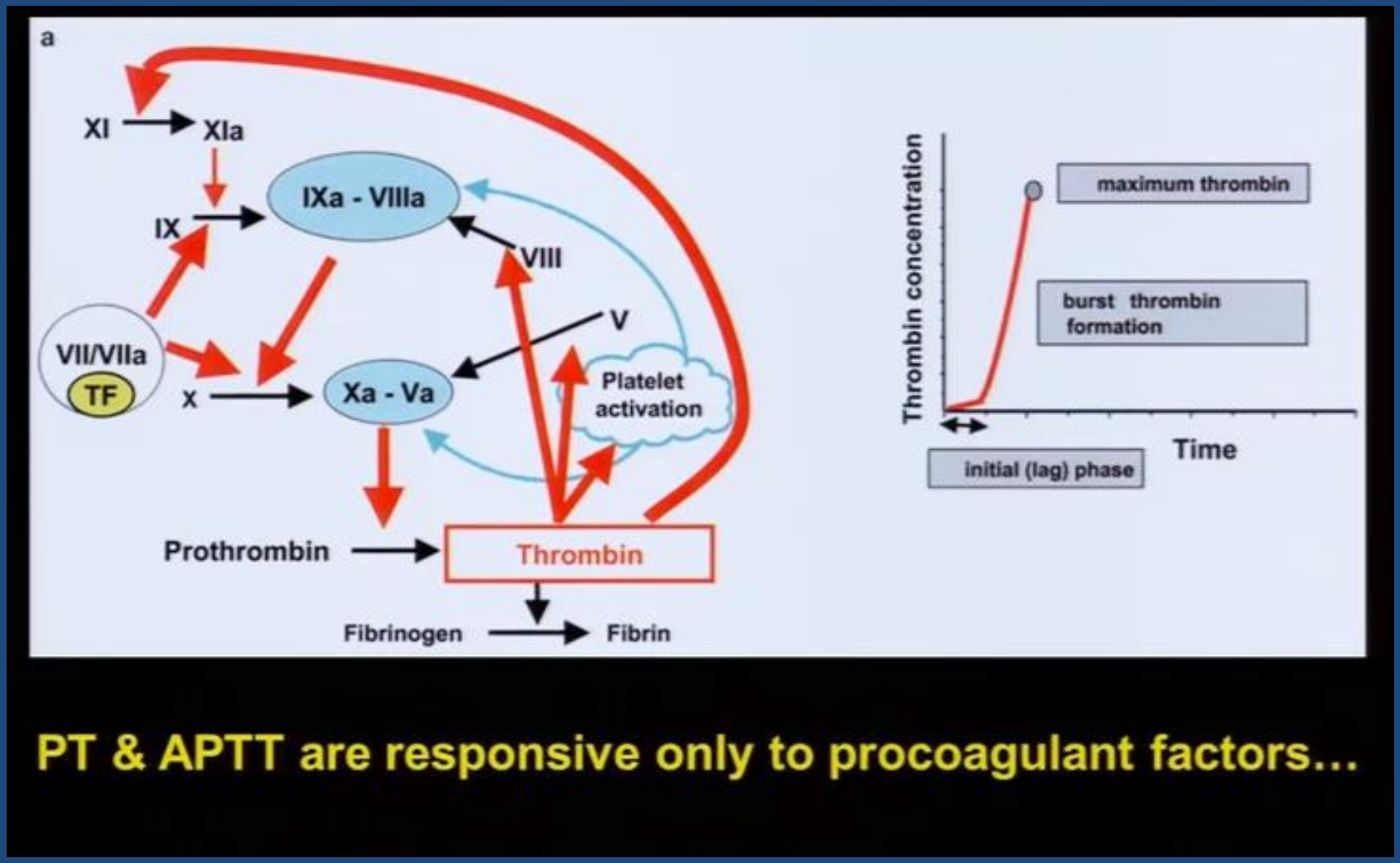
In vivo: blood vessels
no pathways no clotting times



Coagulation vs. Anti-coagulation
Fibrinolysis vs. Anti-fibrinolysis

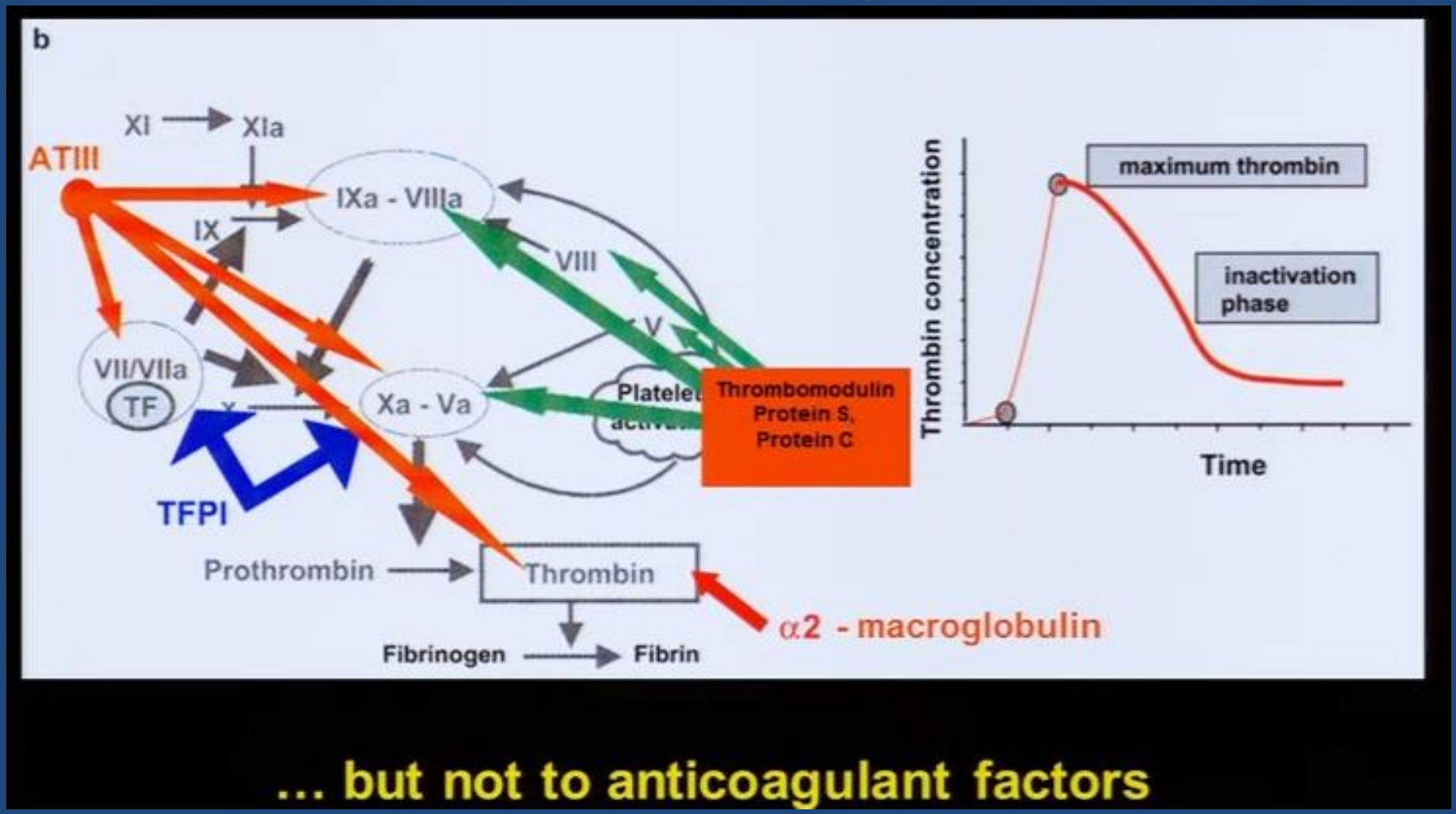


Real time
Thrombin Generation Assay



PT & APTT are responsive only to procoagulant factors…

Shows that same INR variable thrombin generation



What can we monitor?

Laboratory Detection of DTIs and FXa Inhibitors

- **Global assays (APTT, PT, TT):**
  - Responsiveness of different reagents varies significantly
  - Tend to be too sensitive, too insensitive, or fail to show the appropriate dose response
- **Measuring Direct FXa inhibitors using the PT**
  - Too much variability in results in seconds depending on anticoagulant agent and reagent used
- **Measuring Dabigatran with the APTT**
  - Responsiveness of different reagents varies
  - There is a non linear dose response
  - There are no published data correlating APTT to clinical outcome
  - APTT value *can be normal* despite therapeutic dabigatran levels*
  - A normal TT indicates that minimal or no dabigatran is present

*Hawes E, Adcock D, et al. Submitted for publication

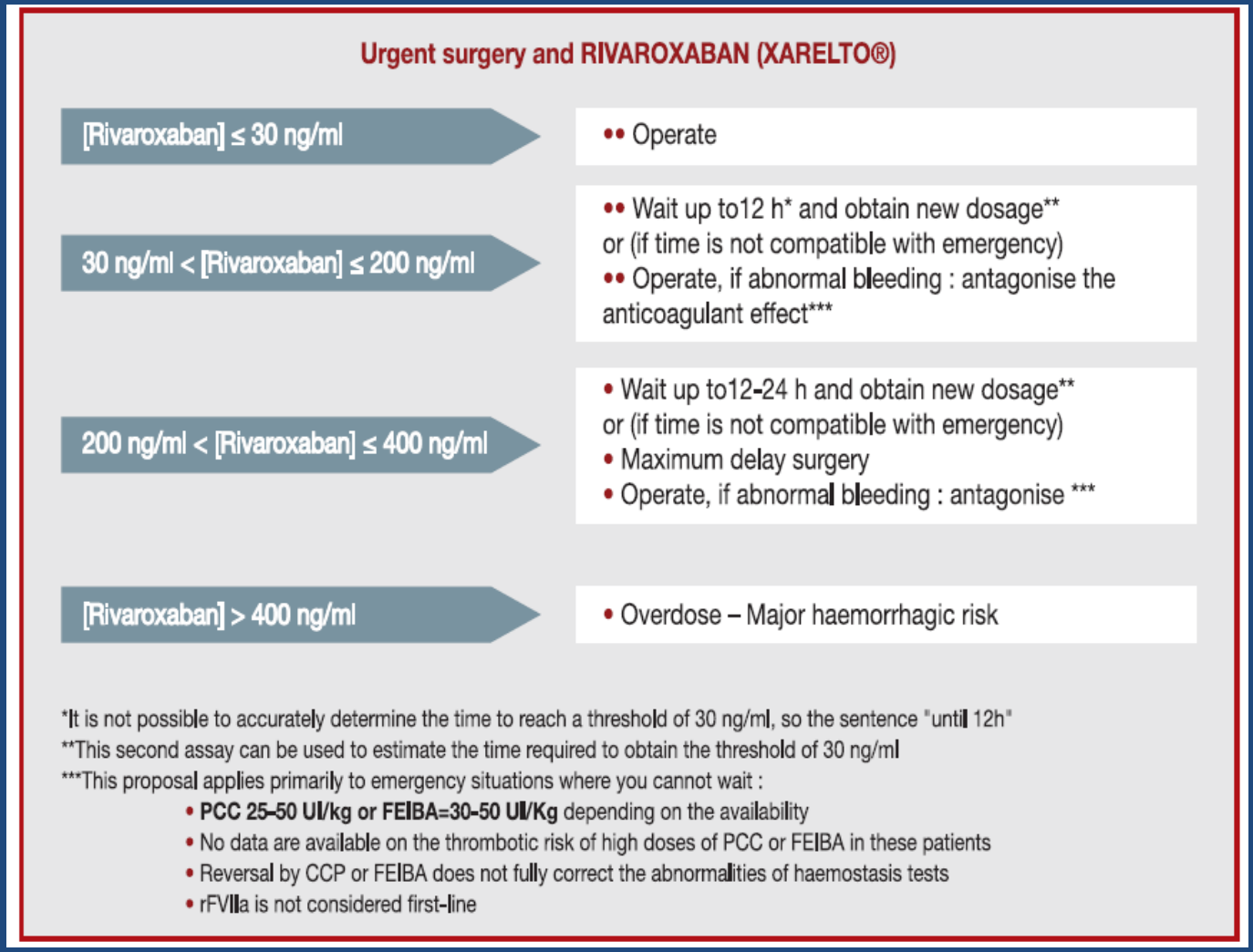
Anticoagulant	How to monitor
Coumadin	INR
Heparin	PTT, anti-factor Xa
LMW heparin	Anti-factor Xa if needed
Fondaparinux	Anti-factor Xa if needed
Rivaroxaban	Anti-factor Xa if needed
Dabigatran	Thrombin time to test for residual drug. Dilute thrombin time to assess extent of anticoagulation or test for residual drug.

Indirect monitor calibrated tests

- Dabigatran
  - Hemoclot thrombin inhibitor assay
    - TAT 2 – 4 hours (non-batch)
    - HKS&H test charge HK$ 1,570
- Rivaroxaban
  - Anti-FXa assay using rivaroxaban calibrators
    - TAT 2 – 4 hours (non-batch)
    - HKS&H test charge: HK$ 1,195

- BUT no absolute safety e.g. neurosurgery
- Other causes of prolongation (heparin contamination / DIC / afibrinogenemia)
- may change with rescue use of PCC /PCC / FVIIa.

Drug level guide to OT (30/200/400)



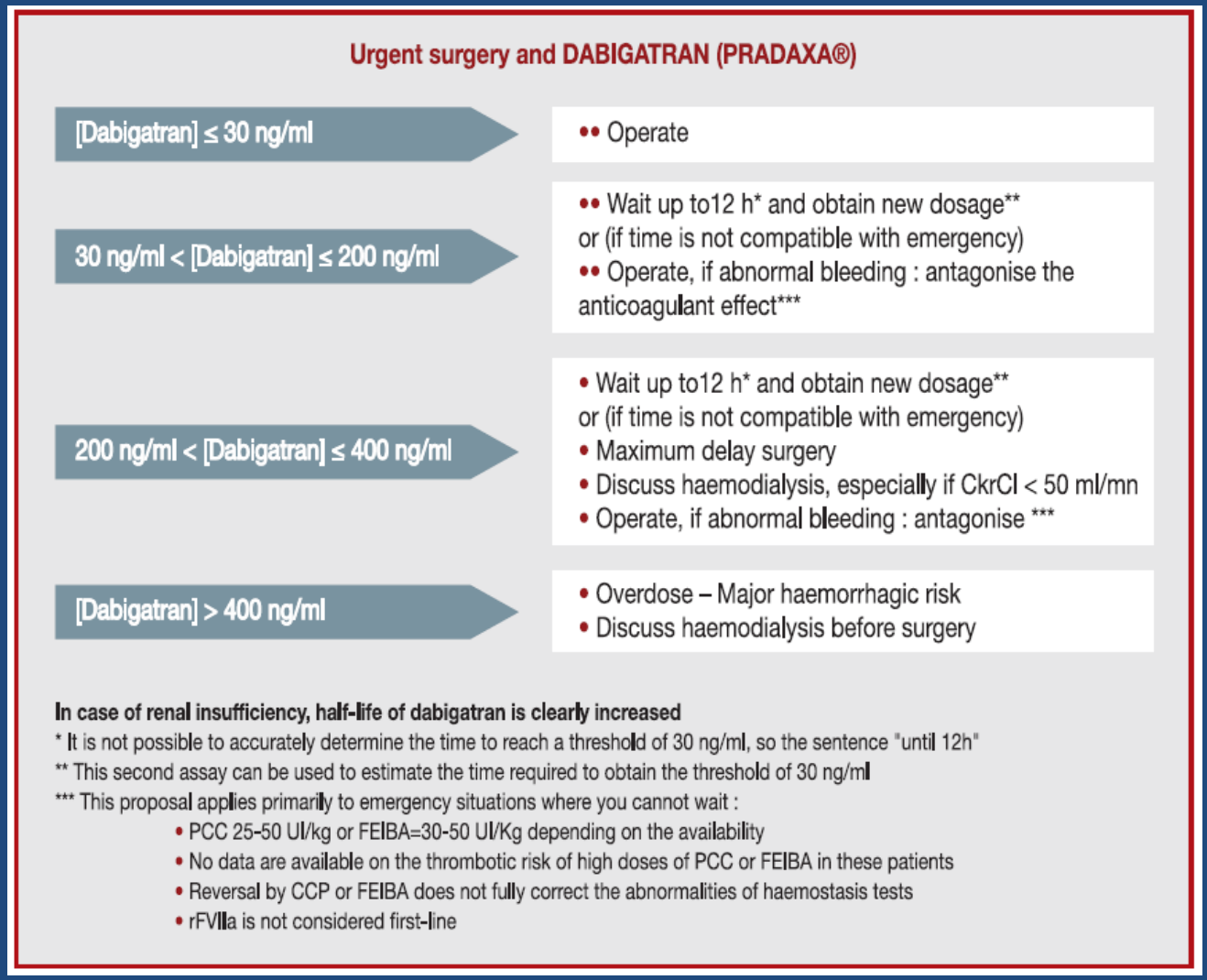
Urgent surgery and RIVAROXABAN (XARELTO®)

[Rivaroxaban] ≤ 30 ng/ml	•• Operate
30 ng/ml < [Rivaroxaban] ≤ 200 ng/ml	•• Wait up to12 h* and obtain new dosage** or (if time is not compatible with emergency) •• Operate, if abnormal bleeding : antagonise the anticoagulant effect***
200 ng/ml < [Rivaroxaban] ≤ 400 ng/ml	• Wait up to12-24 h and obtain new dosage** or (if time is not compatible with emergency) • Maximum delay surgery • Operate, if abnormal bleeding : antagonise ***
[Rivaroxaban] > 400 ng/ml	• Overdose – Major haemorrhagic risk

*It is not possible to accurately determine the time to reach a threshold of 30 ng/ml, so the sentence "until 12h"
**This second assay can be used to estimate the time required to obtain the threshold of 30 ng/ml
***This proposal applies primarily to emergency situations where you cannot wait :

- **PCC 25–50 UI/kg or FEIBA=30–50 UI/Kg** depending on the availability
- No data are available on the thrombotic risk of high doses of PCC or FEIBA in these patients
- Reversal by CCP or FEIBA does not fully correct the abnormalities of haemostasis tests
- rFVIIa is not considered first-line

Drug level guide to OT (30/200/400)



Urgent surgery and DABIGATRAN (PRADAXA®)

[Dabigatran] ≤ 30 ng/ml	•• Operate
30 ng/ml < [Dabigatran] ≤ 200 ng/ml	•• Wait up to12 h* and obtain new dosage** or (if time is not compatible with emergency) •• Operate, if abnormal bleeding : antagonise the anticoagulant effect***
200 ng/ml < [Dabigatran] ≤ 400 ng/ml	• Wait up to12 h* and obtain new dosage** or (if time is not compatible with emergency) • Maximum delay surgery • Discuss haemodialysis, especially if CkrCl < 50 ml/mn • Operate, if abnormal bleeding : antagonise ***
[Dabigatran] > 400 ng/ml	• Overdose – Major haemorrhagic risk • Discuss haemodialysis before surgery

In case of renal insufficiency, half-life of dabigatran is clearly increased

* It is not possible to accurately determine the time to reach a threshold of 30 ng/ml, so the sentence "until 12h"

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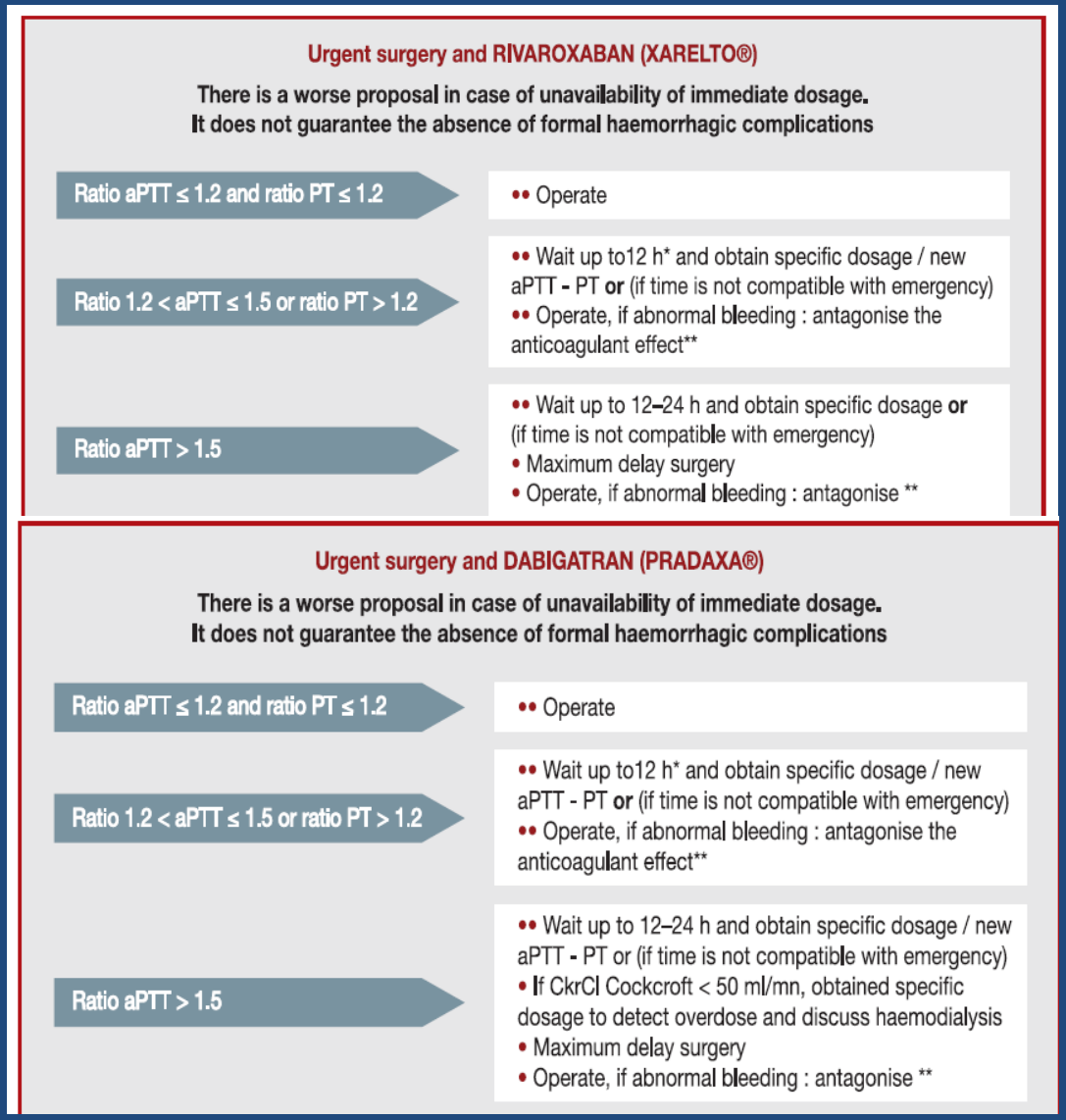
- PCC 25-50 UI/kg or FEIBA=30-50 UI/Kg depending on the availability
- No data are available on the thrombotic risk of high doses of PCC or FEIBA in these patients
- Reversal by CCP or FEIBA does not fully correct the abnormalities of haemostasis tests
- rFVIIa is not considered first-line

Jungle version: use at own risk (1.2/1.5)



Urgent surgery and RIVAROXABAN (XARELTO®)

There is a worse proposal in case of unavailability of immediate dosage.
It does not guarantee the absence of formal haemorrhagic complications

Ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2	•• Operate
Ratio 1.2 < aPTT ≤ 1.5 or ratio PT > 1.2	•• Wait up to12 h* and obtain specific dosage / new aPTT - PT **or** (if time is not compatible with emergency) •• Operate, if abnormal bleeding : antagonise the anticoagulant effect**
Ratio aPTT > 1.5	•• Wait up to 12–24 h and obtain specific dosage **or** (if time is not compatible with emergency) • Maximum delay surgery • Operate, if abnormal bleeding : antagonise **

Urgent surgery and DABIGATRAN (PRADAXA®)

There is a worse proposal in case of unavailability of immediate dosage.
It does not guarantee the absence of formal haemorrhagic complications

Ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2	•• Operate
Ratio 1.2 < aPTT ≤ 1.5 or ratio PT > 1.2	•• Wait up to12 h* and obtain specific dosage / new aPTT - PT **or** (if time is not compatible with emergency) •• Operate, if abnormal bleeding : antagonise the anticoagulant effect**
Ratio aPTT > 1.5	•• Wait up to 12–24 h and obtain specific dosage / new aPTT - PT or (if time is not compatible with emergency) • If CkrCl Cockcroft < 50 ml/mn, obtained specific dosage to detect overdose and discuss haemodialysis • Maximum delay surgery • Operate, if abnormal bleeding : antagonise **

3. How to guide ourselves

- From the phase III mega-trials, treatment level between 30-200 and <30ng/ml probably safe
- Timing of last dose, and coagulation tests are rough guides only.
- Sought hematopathologist advice x test interpretations
- Clot based assays are indirect estimates and repeat testing to<30ng/ml is best
- Save blood first (2 vials of citrate to lab or in fridge)

BLEED!

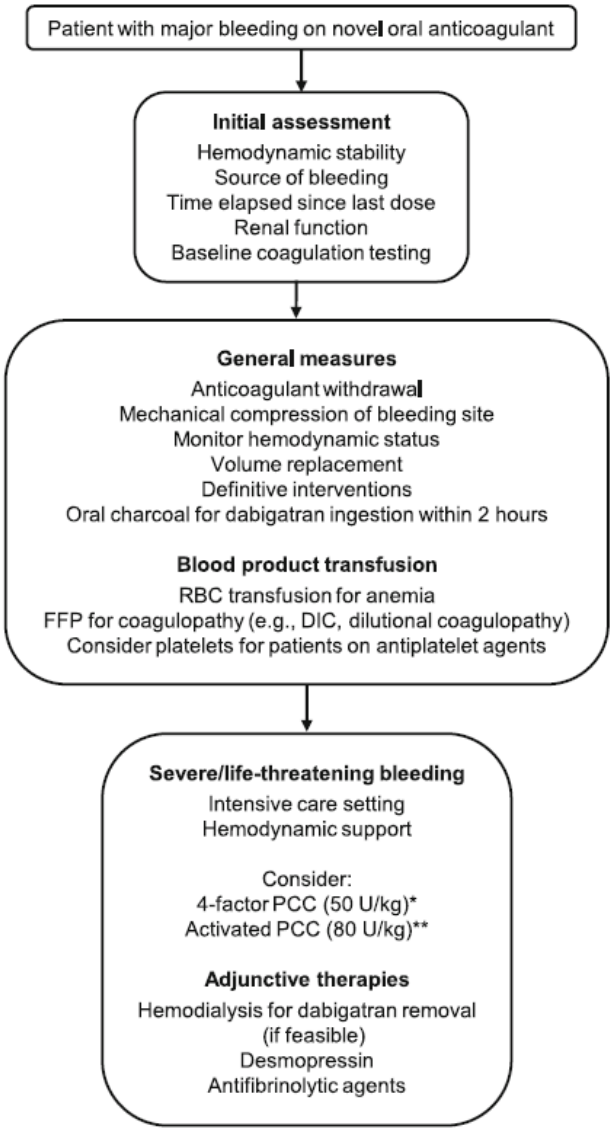


Table 2 Definition of serious or potentially serious bleeding with vitamin K antagonists, according to the French Health Authority [27].

Serious or potentially serious bleeding in the context of treatment with a VKA is defined by the presence of at least one of the following criteria

- Externalized bleeding uncontrollable by conventional procedure
- Haemodynamic instability
  - SBP < 90 mmHg or
  - 40 mmHg decrease in SBP compared with usual or
  - Mean arterial pressure < 65 mmHg or
  - Signs of shock
- Need for urgent haemostatic surgery, interventional radiology, endoscopy
- Need for blood transfusion
- Threatening or functional location
  - Intracranial or intraspinal haemorrhage
  - Retro-orbital and intraocular bleeding
  - Haemothorax, haemoeritoneum and retroperitoneum, haemopericardium
  - Deep muscular haematoma and/or compartment syndrome
- Acute gastrointestinal bleeding
- Haemarthrosis

SBP: systolic blood pressure; VKA: vitamin K antagonist.

Antidotes

- Humanized monoclonal Ab fragment Fab vs dabigatran,(aDabi-Fab) monkey / rat tail bleed
- Plasma derived and recombinant Xa (pd-Xa and r-Xa, r-Antidote PRT064445) lack catalytic and membrane binding domains. Rabbit laceration model, also ok x heparin / LMWH

Extreme measures

- Hemodialysis remove 55-65% DB after 1-4hr
- Successful in urgent Heart Transplant case
  (Wanek et al Ann Pharmacotherapy 2012 46:e21)
- Oral activated charcoal within 2 hrs adsorb 99% DB. Please consider use within 4hrs
- Successful in 57 yr-old 11.25g DB (970ng/ml)
  Woo et al J Med Toxicol 2013 9:192-5.

Specific factor deficiency = hemophilia

ORIGINAL ARTICLE

A synopsis of current haemophilia care in Hong Kong

CME

WY Au 區永仁
Vincent Lee 李偉生
Bonnie Kho 許紫珊
Alvin SC Ling 凌紹祥
Desmond Chan 陳振榮
Eric YT Chan 陳日東
Godfrey CF Chan 陳志峯
Winnie WW Cheung 張永慧
CW Lau 劉靜華

Objective To provide a synopsis of current haemophilia care in Hong Kong.

Design Retrospective survey.

Setting All haematology units of the Hospital Authority in Hong Kong.

Patients All patients with haemophilia A and haemophilia B.

Results To date, there were 222 mild-to-severe haemophilia patients (192 type A, 30 type B) under regular public care in Hong Kong

W. Y. Au · C. C. K. Lam · W. C. Cheung · Y. L. Kwong

Two novel factor X gene mutations in a Chinese family with factor X deficiency

CASE REPORT

Successful treatment of acquired factor VIII inhibitor with cyclosporin

W. Y. AU,* C. C. K. LAM† and Y. L. KWONG*

CASE REPORT

Living donor liver transplantation for hepatitis C related hepatocellular carcinoma in a haemophilia A patient

W. Y. AU,* C. L. LIU,† C. M. LO,† S. T. FAN† and C. K. LAM‡
*Departments of *Medicine; †Surgery; and ‡Pathology, Queen Mary Hospital, University of Hong Kong, Hong Kong, China*

Reversal strategies

Table 5. Reversal strategies and pharmacologic characteristics of the currently available anticoagulants[1,32,45,49]

Anticoagulants	Elimination half-life ($T_{1/2}$)	Target	Recommended laboratory assay	Reversal strategies and potential approaches to enhancing hemostasis*
VKAs	Acenocoumarol: 6-8 h Phenprocoumarol: 90-140 h Warfarin: 36-48 h	Vitamin K epoxide reductase (synthesis of factors II, VII, IX, X)	PT, INR	Vitamin K PO/IV, PCC, activated PCC, FFP
Dabigatran	14-17 h (80% renal excretion)	Factor IIa	Hemodot	PCC, activated PCC, recombinant factor VIIa
Rivaroxaban	9-15 h (33% renal excretion)	Factor Xa	Anti–factor X	PCC, activated PCC, recombinant factor VIIa
Apixaban	9-14 h (25% renal excretion)	Factor Xa	Anti–factor X	PCC, activated PCC, recombinant factor VIIa

FFP, fresh frozen plasma; INR, international normalized ratio; IV, intravenous; PCC, prothrombin complex concentrate; PO, by mouth; PT, prothrombin time; VKAs, vitamin K antagonists.

*The new oral anticoagulants lack a specific antidote and reversal agents are of unproven efficacy.

Give factor to overcome factor inhibition

Factor derivatives: Fresh frozen plasma FFP, prothrombin complex concentrates (PCC / impure FIX) activated prothrombin complex concentrates (aPCC), recombinant activated factor VII (rFVIIa)

Survey : 221 US surgeons 73% will try to reverse dabigatran in ICH

Choice of agents PCC 61%, FFP 53%, rFVIIa 24%, HD 24%, Plt 7%.

PROTHROMBIN COMPLEX CONCENTRATE THERAPY FOR WARFARIN ASSOCIATED INTRACRANIAL HAEMORRHAGE

PCC FIRST PROTOCOL TREATMENT FORM

A&E,MEDICAL and NS DEPARTMENT QUEEN ELIZABETH HOSPITAL

Patient Gum Label

- ***Please ensure PT/INR/APPT and Type & Screen had been checked and send urgently to the lab***
- ***Please contact haematology lab to trace INR result if intracranial haemorrhage is confirmed in CT brain***

INDICATIONS

1. Currently on Warfarin	1. Yes / No
2. Intracranial Haemorrhage noticed in CT brain:	2. Yes / No
● Intracerebral haemorrhage	☐
● Subdural haemorrhage	☐
● Subarachnoid haemorrhage	☐
3. <24 hours after onset of neurological symptoms/signs, **OR**	3. Yes / No
>24 hours after onset of Sx/Sign **with progression on presentation**	Yes / No

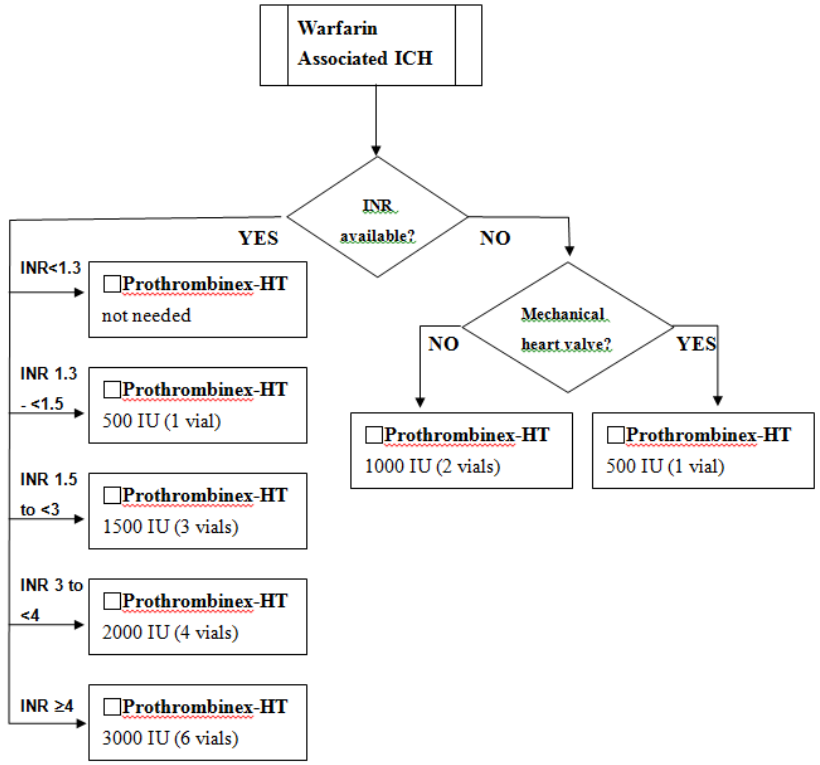
Note: *If **all** of the above are yes, proceed to **CONTRAINDICATIONS.***
If not, patient is not indicated.

CONTRAINDICATIONS for STAT PCC Rx

1. Any known history of DVT or PE	1. Yes / No
2. Known LA/LV clots	2. Yes / No
3. Known Antiphospholipid Antibody Syndrome/Protein C/S/Antithrombin III def.	3. Yes / No
4. Suspected to have ischeamic stroke with haemorrhagic transformation or minimal subdural haematoma	4. Yes / No
5. Suspected to have intracranial calcification instead of ICH	5. Yes / No
6. Suspected to have disseminated intravascular coagulation (DIC)	6. Yes / No
7. Others: (please specify) _____	7. Yes / No

Patient decided **INDICATED** for **STAT** Prothrombinex-HT Therapy	Yes/ No

If **STAT** Prothrombinex-HT Therapy not indicated: Admit to Ward immediately and inform Medical Officer of the receiving ward for urgent attention of the patient in order to initiate the appropriate Warfarin reversal therapy.



ADMINISTRATION

1. Start Prothrombinex-HT _____ vials Slow injection: 3ml per min	1. Time_____
2. GCS after treatment	2. E:___ V:___ M:____
3. BP after treatment	3. BP: _____

*Note: After completion of the injection, proceed to **WARD ADMISSION***

2.1 Implementation Date
1st July 2012

2.2 Criteria to start Prothrombinex-HT at A&E level:

- Prothrombinex-HT slow injection (over 3 mins) can be given if **intracerebral haemorrhage, subdural haemorrhage or subarachnoid haemorrhage** are noticed in the urgent CT brain.
- In the following rare situation in which the prothrombotic risk of prothrombinex-HT may be significant and potentially outweigh its expected benefit, it should not be given and the patient should be immediately transferred to ward for further management and the case should be handed over to the medical officer directly:
  - History pointed to ICH onset more than 24 hrs (e.g. patient with sudden onset of focal weakness > 24 hrs ago, static in severity, attended A&E afterward with CT brain performed > 24 hrs from onset of focal weakness)
  - Difficulties in differentiating between ICH vs calcification
  - Patient with acute DVT/ pulmonary embolism
  - Patient with known LA/LV clots
  - Patient with known antiphospholipid antibody syndrome or Protein C/Protein S/Antithrombin III deficiency

2.3 Key Logistics in A&E Department

- Book urgent CT by informing CT scan room via pre-admission CT brain protocol for acute stroke patient (effective 1 Jan 2006) OR urgent CT brain protocol for selected patients on warfarin (effective 1 Feb 2011)
- Perform blood tests including PT/APTT/INR and Type & screen immediately, contact haematology laboratory for immediate analysis of the specimen.
- Escort patients to CT room by A&E physician and A&E nurse.
- Review the CT films +/- with radiologist (if performed during office hour) to look for intracranial haemorrhage.
- If ICH/SAH/SDH is identified, transfer the patient back to A&E, **check whether INR result is available or not, follow the Prothrombinex-HT dosage guide to start the treatment accordingly to the INR result or empirically accordingly to the protocol if INR result is not yet available.** (see Protocol for Urgent Reversal of Warfarin Effect in Intracranial Haemorrhage for details)
- After Prothrombinex-HT is given, the patient is immediately transferred to ward. ***Medical officer***

Prothrombin complex concentrates PCC

Licensed x hemophilia B prophylaxis and treatment & Factor II VII IX X deficiency
Warfarin reversal (plus Vit K)

Prefer over FFP (ACCP 2012, FDA approved)

1. 80% correction in one hr.,
2. Improved survival for early use vs FFP
3. Less volume TRALI infection hypersensitivity
4. 500 unit in 20ml vs. (FFP 220ml has 220 units) No thawing or cross match

Beriplex® P/N Coagulation factor and thrombo-inhibitor content

	Content per ml after reconstitution	Content per 250 vial	Content per 500 vial
Total protein	6 – 14 mg/ml	60–140 mg	120–280 mg
Factor II	20 – 48 IU/ml	200–480 IU	400–960 IU
Factor VII	10 – 25 IU/ml	100–250 IU	200–500 IU
Factor IX	20 – 31 IU/ml	200–310 IU	400–620 IU
Factor X	22 – 60 IU/ml	220–600 IU	440–1200 IU
Protein C	15 – 45 IU/ml	150–450 IU	300–900 IU
Protein S	13 – 26 IU/ml	130–260 IU	260–520 IU

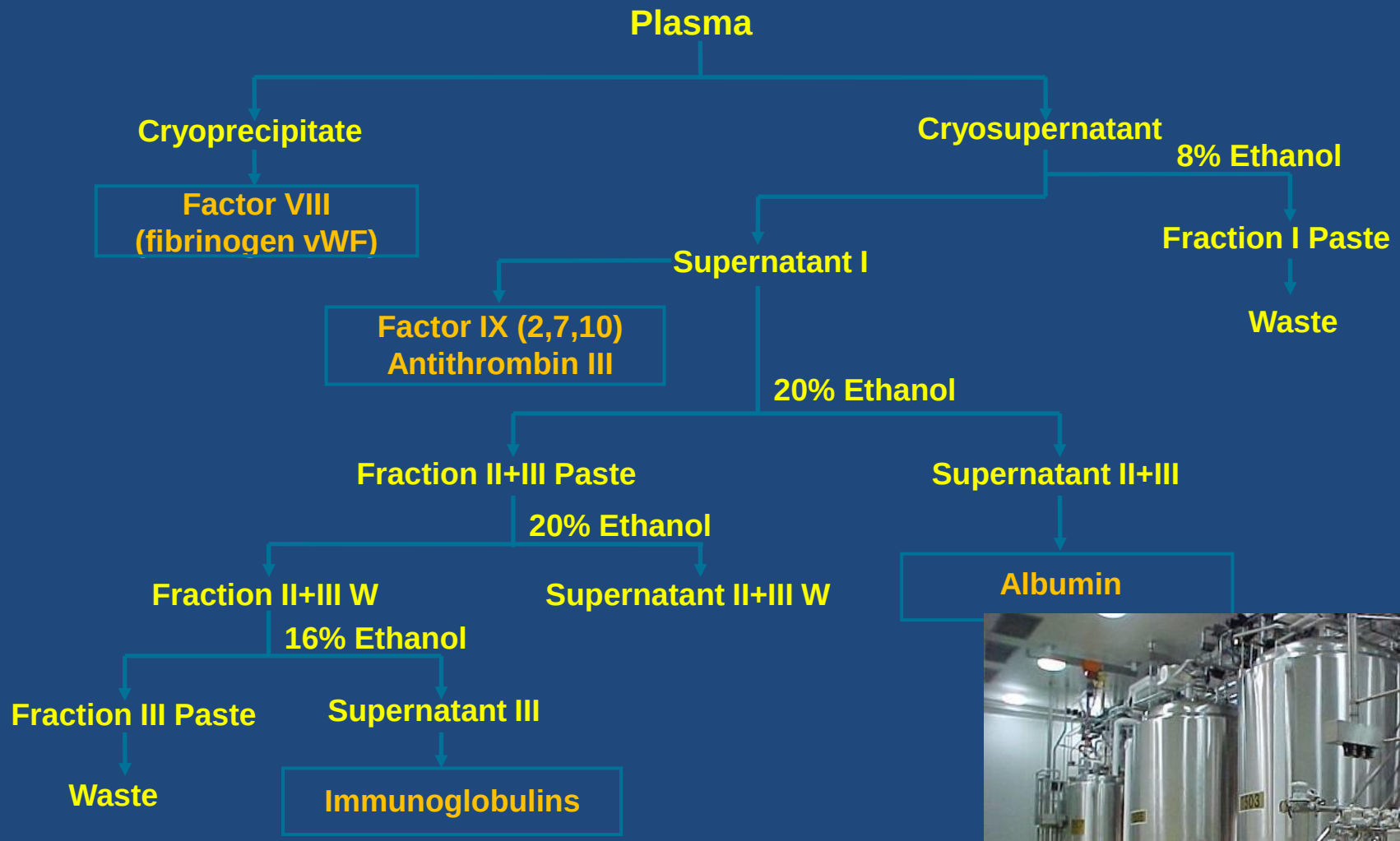
BeriplexSlideBackground

The specific activity of Factor IX is 2.5 IU per mg total protein.

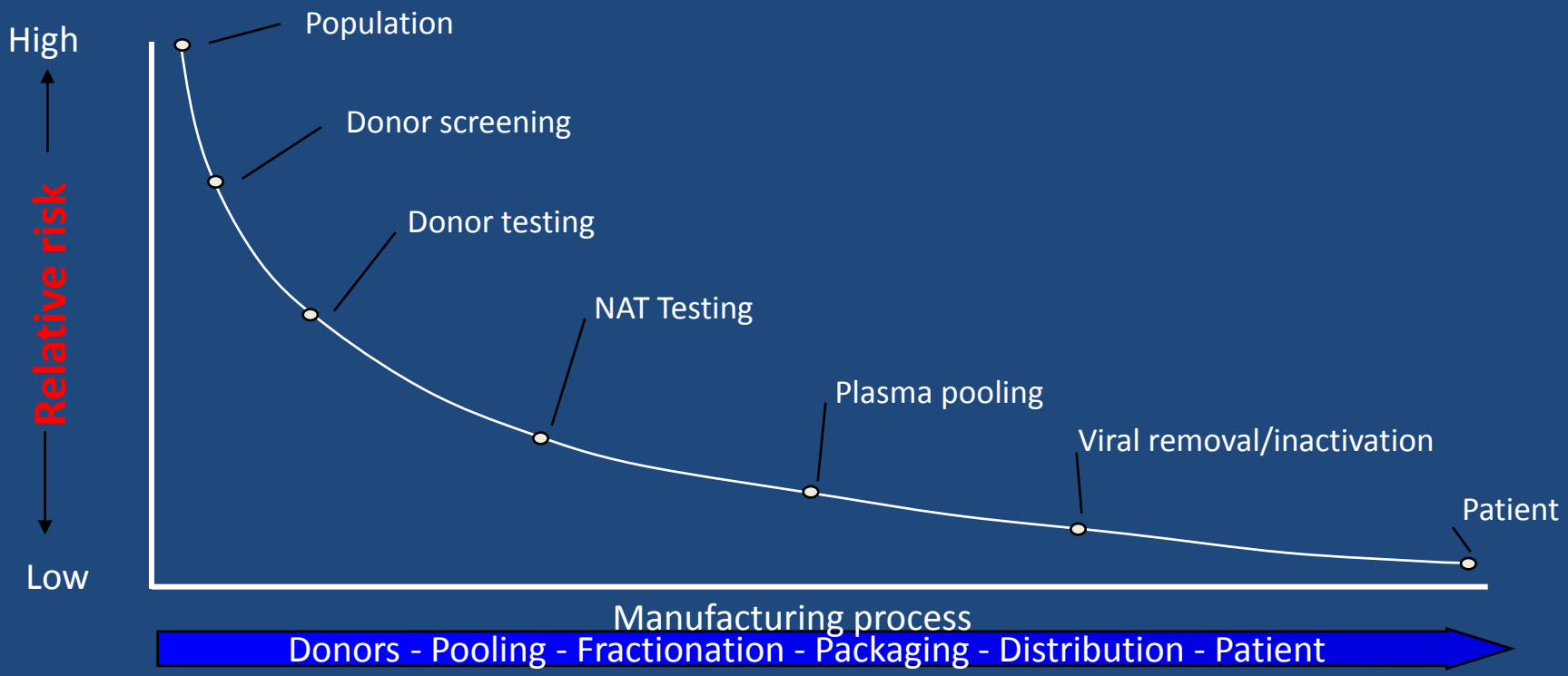
Beriplex P/N

Plasma products: limited supply

Cohn Fractionation Process



Plasma products: viral safety



Thalassaemia Hemophilia Care Summit 2010 2012

Dear Medical and Nursing colleagues,

This is a patient with **HAEMOPHILIA**. Bleeding complication in such patient can be serious, excruciatingly painful or even life-threatening. It can be controlled with **Factor Replacement Therapy**. Appropriate **intravenous factor infusion as early as possible** is recommended in case of pain or symptoms suggestive of bleeding. Please refer to the table below for the suggested dose of factor required, and consider paging the Adult or Pediatric hematologist named below for further advice. The factors are available in the emergency fridge of the Dept. of A&E. We thank you for your swift action to save this patient from unnecessary suffering and possible possibly life-threatening events.

Yours truly,

連錫營
Dr SY Lin
Medicine, UCH

陳振榮
Dr Desmond Chan
Pediatrics, UCH

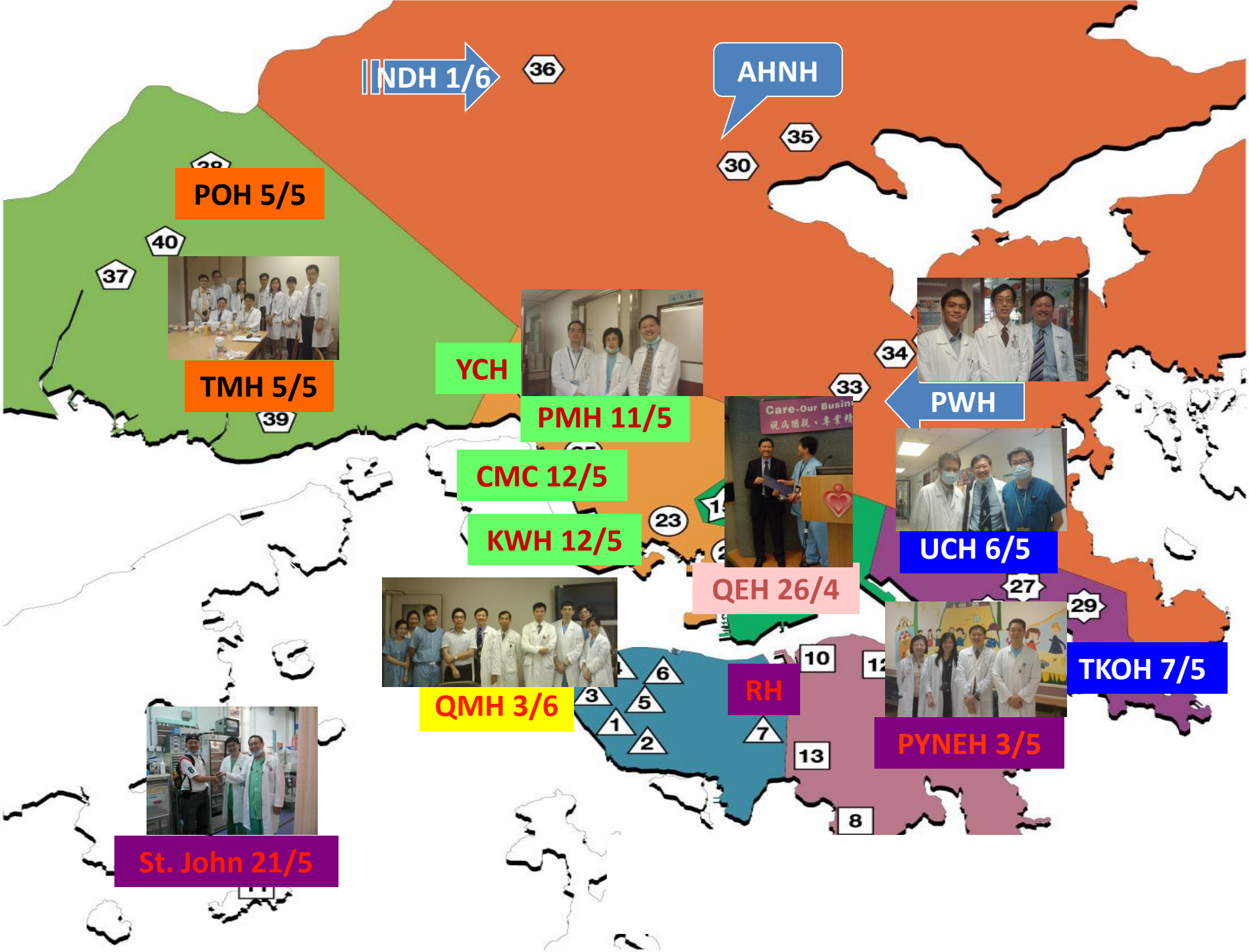
The dosage below is expected to bring the factor level up to about 50% in severe haemophilia.

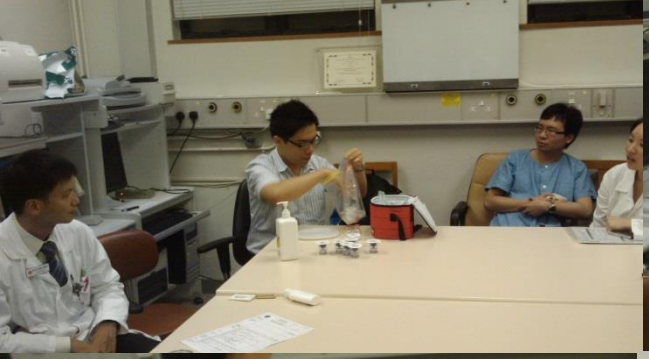
	Hemophilia A	Hemophilia B
Factor (dosage)	Factor VIII (~25units/kg) 1 vial ~ 250 units	Factor IX (~40units/kg) 1 vial ~ 500 units
< 10 kg	≤1 vial	≤1 vial
10 – < 20 kg	2 vials	1 vial
20 – < 30 kg	3 vials	2 vials
30 – < 40 kg	4 vials	3 vials
40 – < 50 kg	5 vials	4 vials
50 – < 60 kg	6 vials	5 vials
≥ 60 kg	≥ 6 vials (1 vial/10 kg **rounding up**)	≥ 5 vials

Double dose in case of life threatening bleeding.

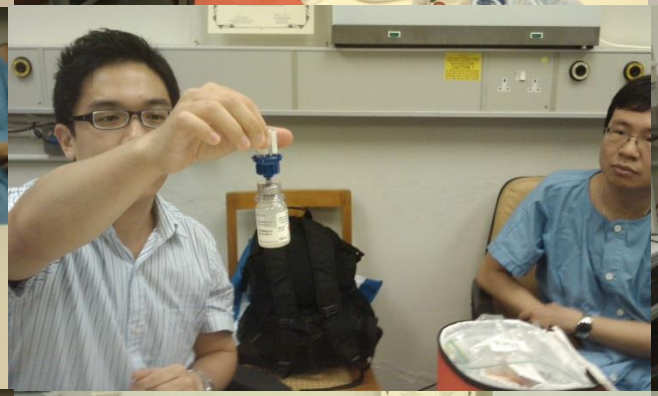
*There are 11 patients in Hong Kong with inhibitors (antibody to Factor VIII or Factor IX) may need by-passing agent (Novoseven, FEIBA or Prothrombinex) to stop bleeding. ASK the patient and CALL the Adult or Paediatric hematologist.

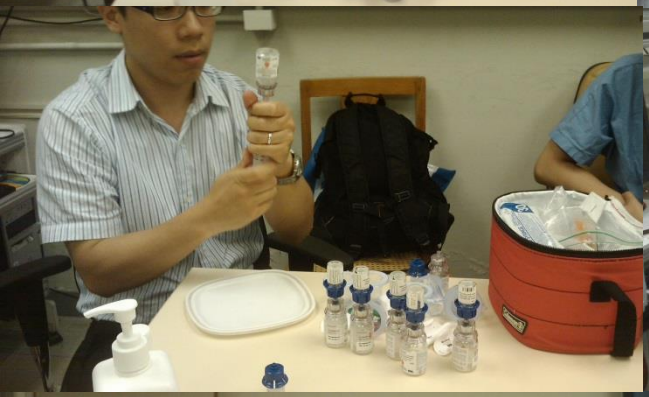
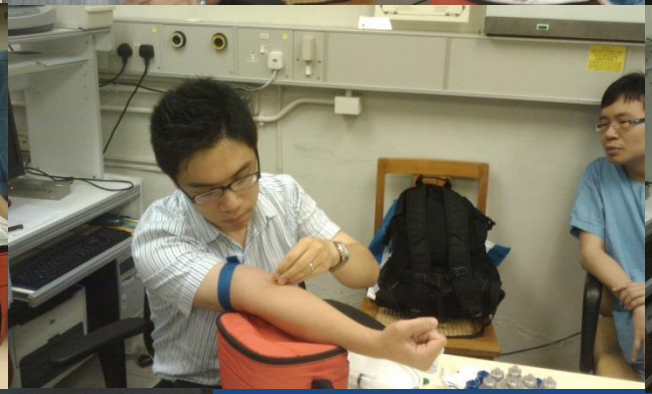
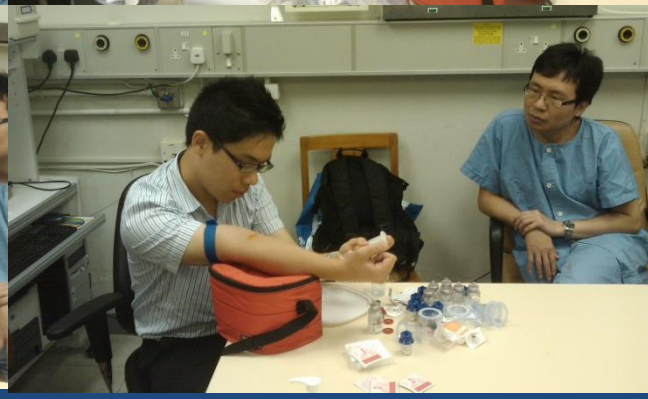
Factor first is official HA A&E policy as of 4 June 2010


NDH 1/6
AHNH
POH 5/5
TMH 5/5
YCH
PMH 11/5
CMC 12/5
KWH 12/5
PWH
UCH 6/5
QEH 26/4
QMH 3/6
RH
TKOH 7/5
PYNEH 3/5
St. John 21/5

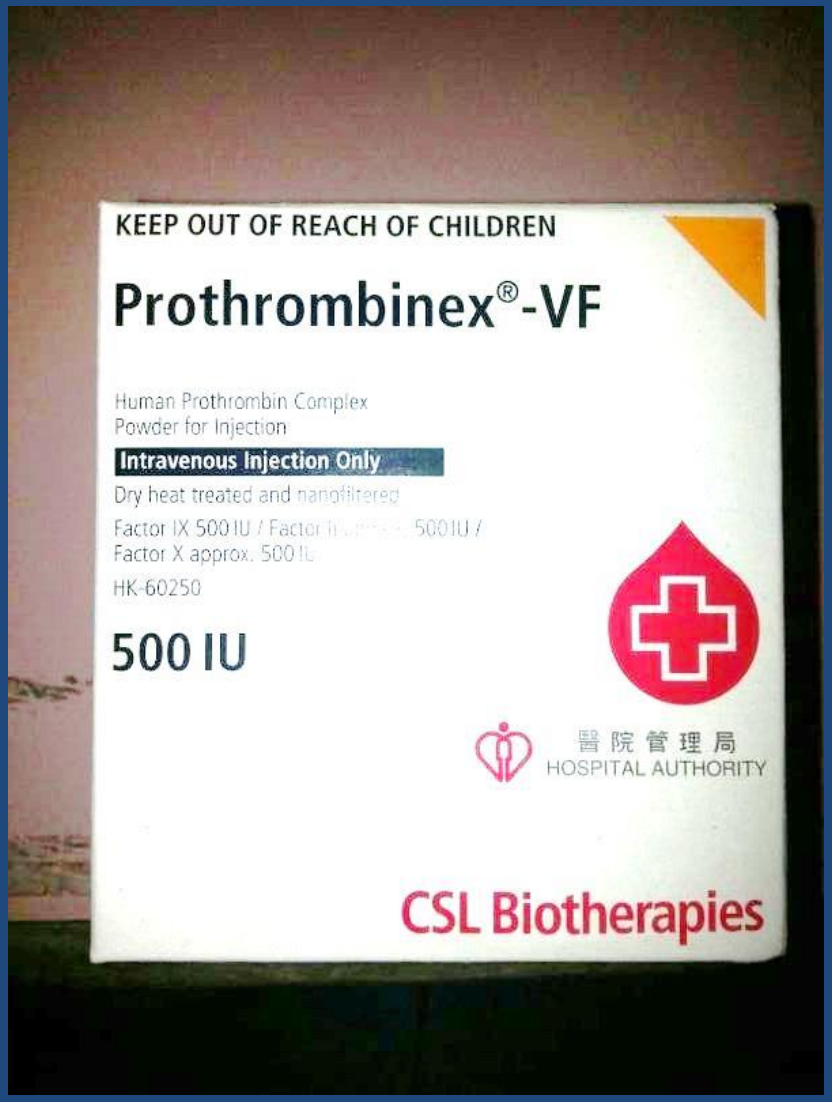







Many thanks for
A and E support


KEEP OUT OF REACH OF CHILDREN
Prothrombinex®-VF
Human Prothrombin Complex
Powder for Injection
Intravenous Injection Only
Dry heat treated and nanofiltered
HK-60250
500 IU
醫院管理局
HOSPITAL AUTHORITY
CSL Biotherapies


MonoFIX®-VF
Factor IX
500 IU
HK 44456
HOSPITAL AUTHORI
CSL LIMITED
45 POPLAR ROAD
PARKVILLE VIC 3052
AUSTRALIA
CSL

Quest for pure product may become a problem

	2010	2011	2012	2013 to date
PTX	80%	63%	56%	46%
MonoFIX	20%	37%	44%	54%

This data based on the quantities released to HA hospitals from HKRCBTS.

PCC for NOAC reversal

For NOAC reversal PCC (50U/kg, 7 vials) higher than VKA reversal (20U/kg) but lower than severe hemophilia bleed (100U/kg)
1.8% thrombosis (hi dose and liver ds, never seen in Chinese hemophilia B)
4-factor PCC Beriplex (Europe Canada)
3-factor PCC Prothrombinex (USA HK HA $500)
DO NOT USE MONOFIX OR MONONINE (pd or recombinant Factor IX only)
Need supplement FFP or rFVII 15-30 for 3-F?
Latest studies no difference between the two

Activated aPCC or Factor Eight Inhibitor Bypass Activity

Licensed indication for hemophilia with inhibitors (50-100 U/kg q12) $7980 per vial
Same as PCC but with activated factors (esp FVII) during freeze dry process
For NOAC reversal FEIBA 30-50 U/kg (3.5 vials)
Dosage is half that of hemophilia
Reported success vs. Dabigatran in cardiac ablation with FEIBA q8h
Thrombosis 4-8 per 10^5 doses 80% with thrombotic factors
Usage change the coagulation prolife
May need repeat depend on clinical scenario
(Dager et al Crit Care Med 2013 41:e42-6)

Table 1. Factor and Clotting Components in FEIBA [z]

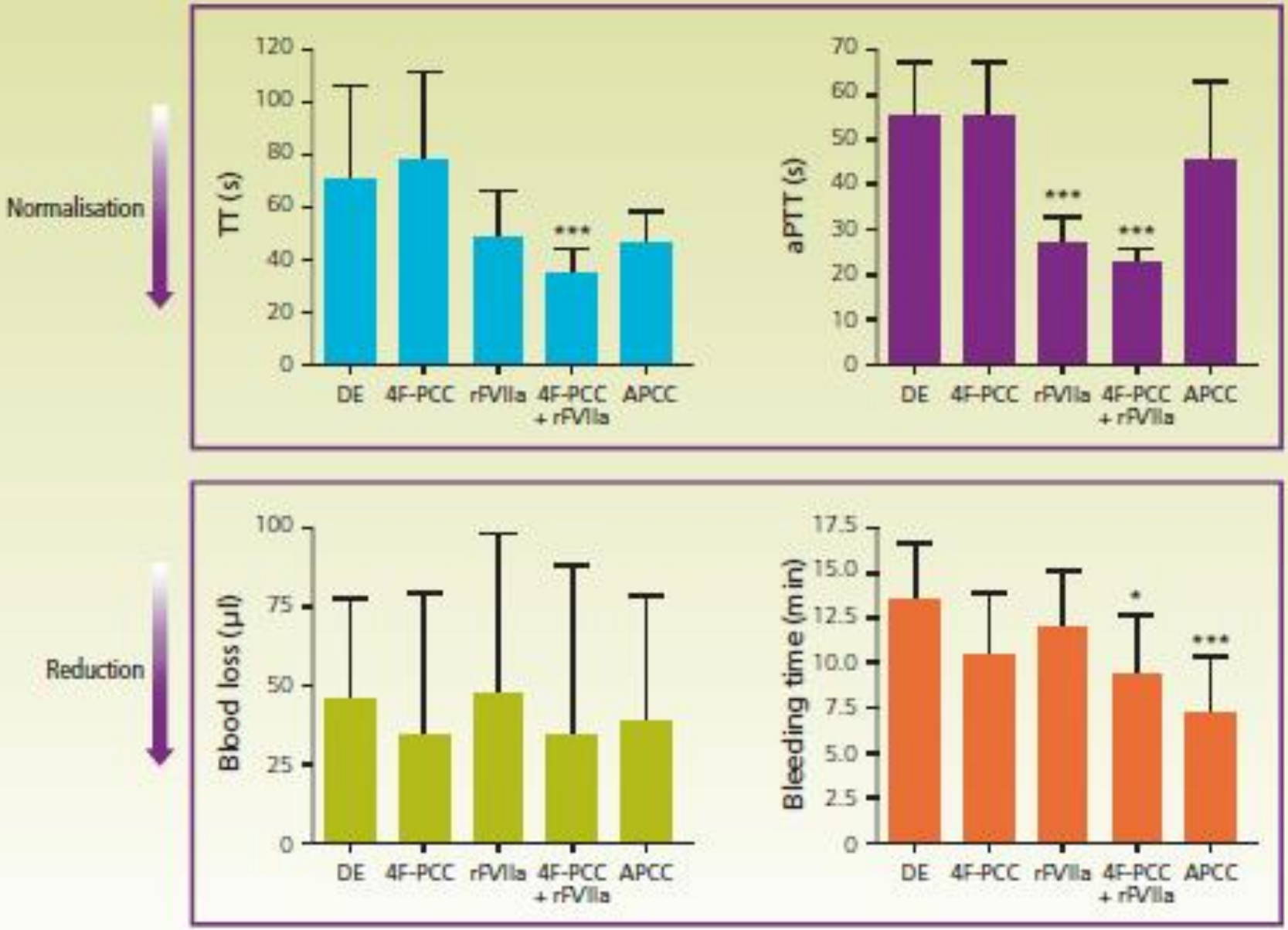
Component	Units per unit of FEIBA	+/- SD
II	1.3	0.3
VII	0.9	0.1
IX	1.4	0.1
X	1.1	0.2
Protein C	1.1	0.2
Thrombin	0.01	0.004
VIIa	1.5	0.2
IXa	≥ 0.0006	N/A
Xa	0.06	0.002

Recombinant activated factor VII Novoseven

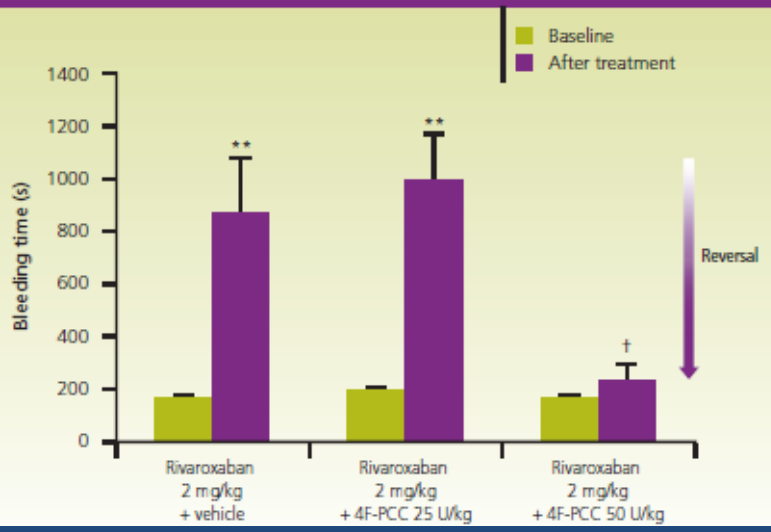
Licensed indication for hemophilia with inhibitor and for FVII deficiency
Off labeled Used x ICH, peripartum hemorrhage, liver transplant and trauma
Also in severe thrombocytopenia and Plt function disorders
One vial 1mg (90ug /kg, 6 vials) $9900
rVIIa reported ineffective in Dabigatran epidural
rFVII poorly effective In some animal models

(Trummees et al Spine 201214:E863-5.)
(Zhou et al, Stroke 2011;42: 3594-9, experimental ICH, Godier et al, Anesthesiology 2012;

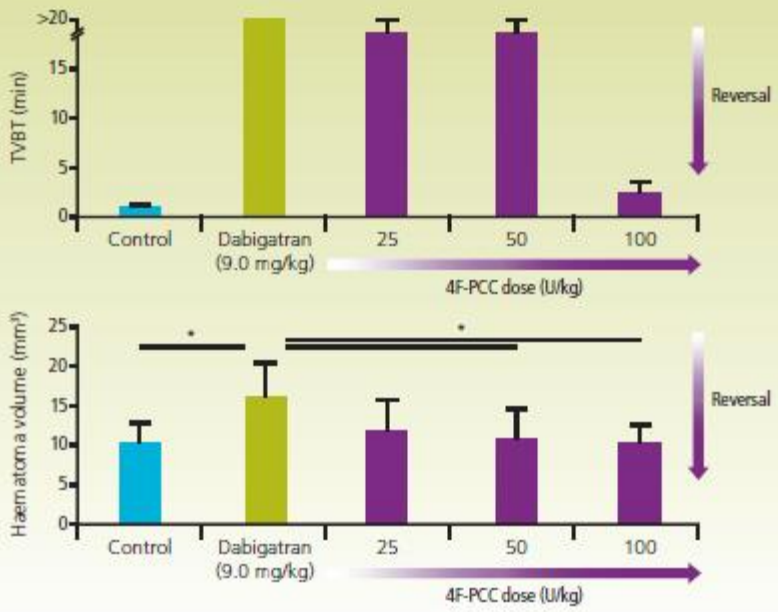
Reversal of the anticoagulation effects of dabigatran by 4F-PCC



4F-PCC reversal of the anticoagulant of rivaroxaban



4F-PCC reversal of the anticoagulant effects of dabigatran



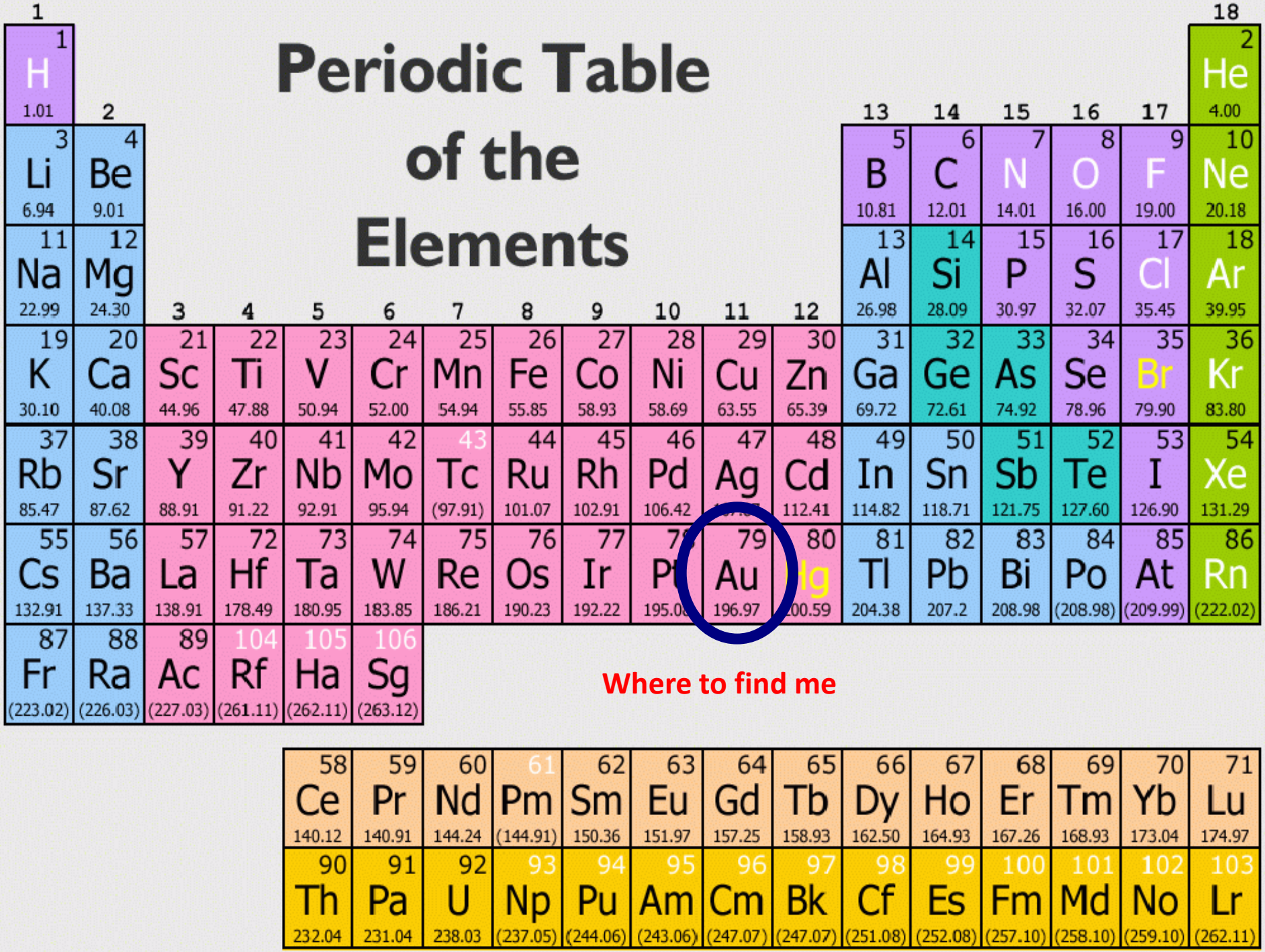
4. Use of reversal agents

- Dabigatran: FEIBA 30-80/kg preferred
- Rivaroxaban: 4-PCC 25-50/kg preferred
- 50U/kg use intraoperative postoperative at lower dose.
- If ICH IOH then PCC or FEIBA q8hr
- If <30ng/ml not needed
- Case reports are biased
- In vitro studies / animal models / volunteer in vivo volunteers all non-realistic and end points are arbitiary
- there will never be clinical RCT data

Conclusions

1. Less ICH than VKA. Not more complex in terms of dosing, monitoring and reversal
2. Rational dosing less iatrogenic bleeding
3. Laboratory monitoring available (not everywhere, in doubt call hematopathologist)
4. Reversing agents available (not everywhere, in doubt call hematologist)

Periodic Table of the Elements



Where to find me