New oral anticoagulants and haemorrhage

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'Too much to lose'
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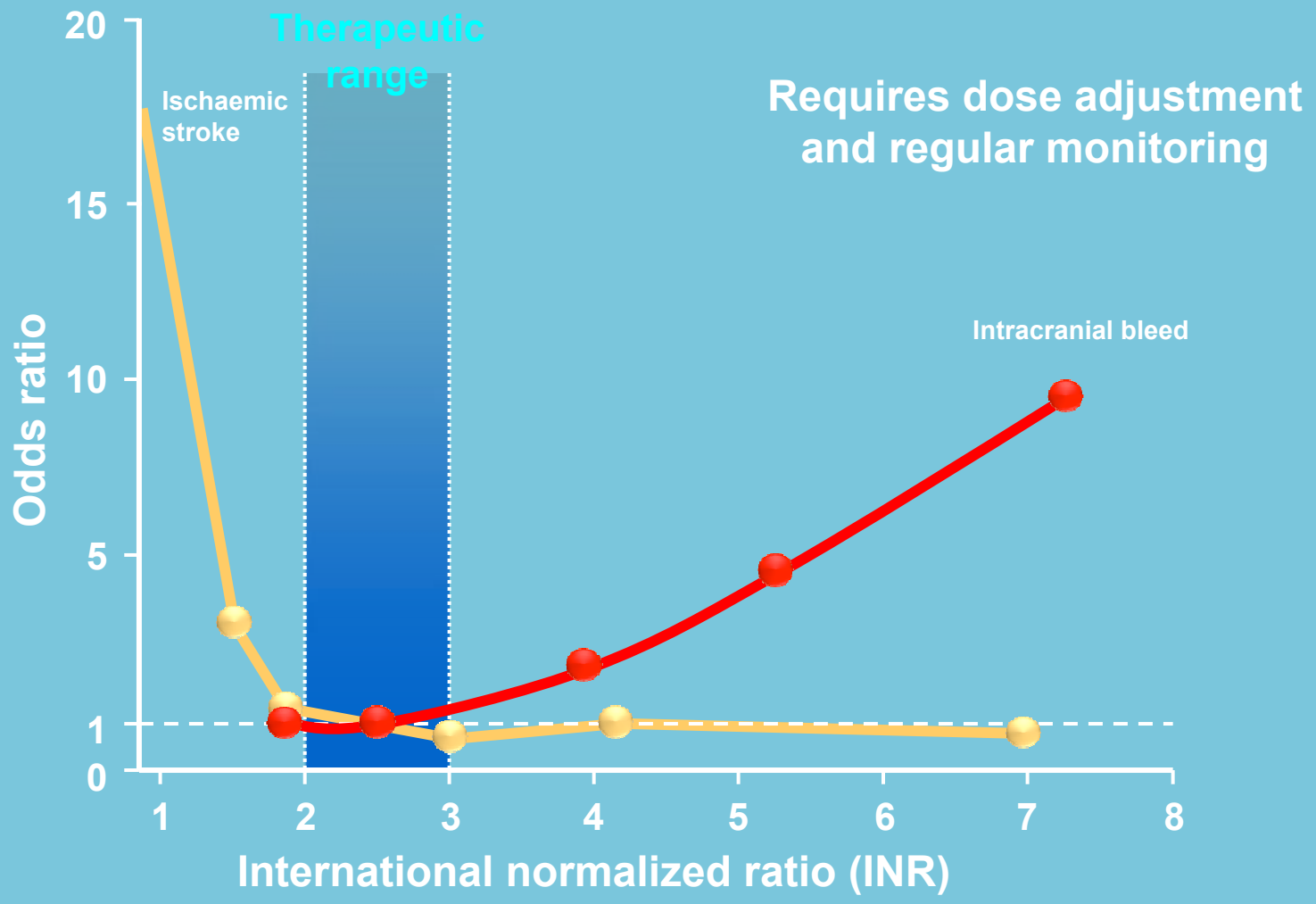
Disclosures/Conflicts of interest

- None to declare

The extent of the problem

- ≈1% of the UK population are anticoagulated with warfarin
  - 8% of individuals >80 years old
- The most frequent indication is stroke prevention in atrial fibrillation
  - 46% of patients with AF not prescribed warfarin (NICE, 2006)
  - Efforts to increase diagnosis of AF, perform risk assessment ($CHADS_2$), warfarin (not aspirin) anticoagulation in those at risk of stroke, QoF for general practice
- NICE guidance on indications for new oral anticoagulants
- Haemorrhagic risk of warfarin
  - 3.5%/yr major haemorrhage; 0.5%/yr ICH

Warfarin and its challenging therapeutic window



ACC/AHA/ESC guidelines: Fuster V *et al. Circulation* 2006;114:e257–e354.

Problems with warfarin

- Narrow therapeutic window
- Variable dosing: Inter- and intra-individual
- Unpredictable response therefore requires monitoring- inconvenience, cost
- Numerous interactions with other medications
- Influence of diet and alcohol

Advantages of warfarin

- Effective
- Cheap- £20 per annum (≈£300 pa)
- Familiar: support structure in place
- Monitored:
  - encourages better compliance
  - reminds patient and physician of anticoagulation
  - can adjust intensity if clinically indicated
- Long half-life
- Rapidly reversible/available antidote

Characteristics of the ideal anticoagulant

- Effective
- Oral administration
- Rapid onset and offset of action
- Wide therapeutic window
- Predictable response- fixed/weight-adjusted dose, well defined pharmacokinetics in renal or hepatic impairment, no monitoring required
- No food or drug interactions
- Effective antidote available
- Cheap

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New blood-thinning drug could stop 5,000 strokes a year

By JENNY HOPE

PUBLISHED: 00:00, 15 March 2012 | **UPDATED:** 10:25, 15 March 2012

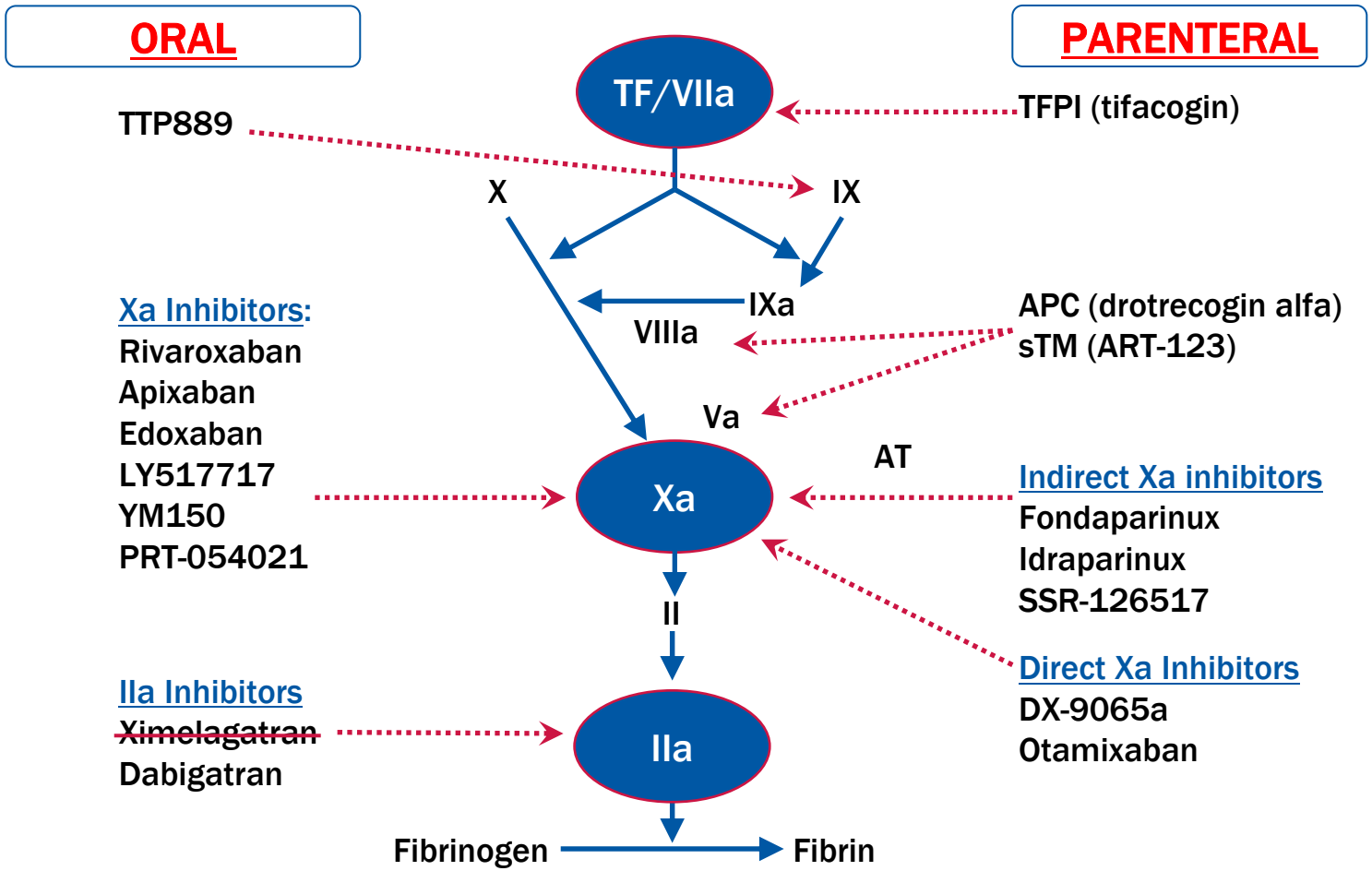
A blood-thinning drug has been given the go-ahead for use on the NHS in a move that is expected to revolutionise stroke prevention.

The drug – the first anti-clotting agent to be developed in almost 60 years – could eventually replace warfarin, the most commonly used therapy, which is based on rat poison.

Almost a million patients suffering an irregular heartbeat could be eligible to take the new drug, called Pradaxa, which could prevent an additional 5,000 strokes a year.

www.dailymail.co.uk/tvshowbiz/article-2226577/Robbie-Savage-spotted-leaving-Michelle-Mones-house-early-hours-morning-Pride-Bri

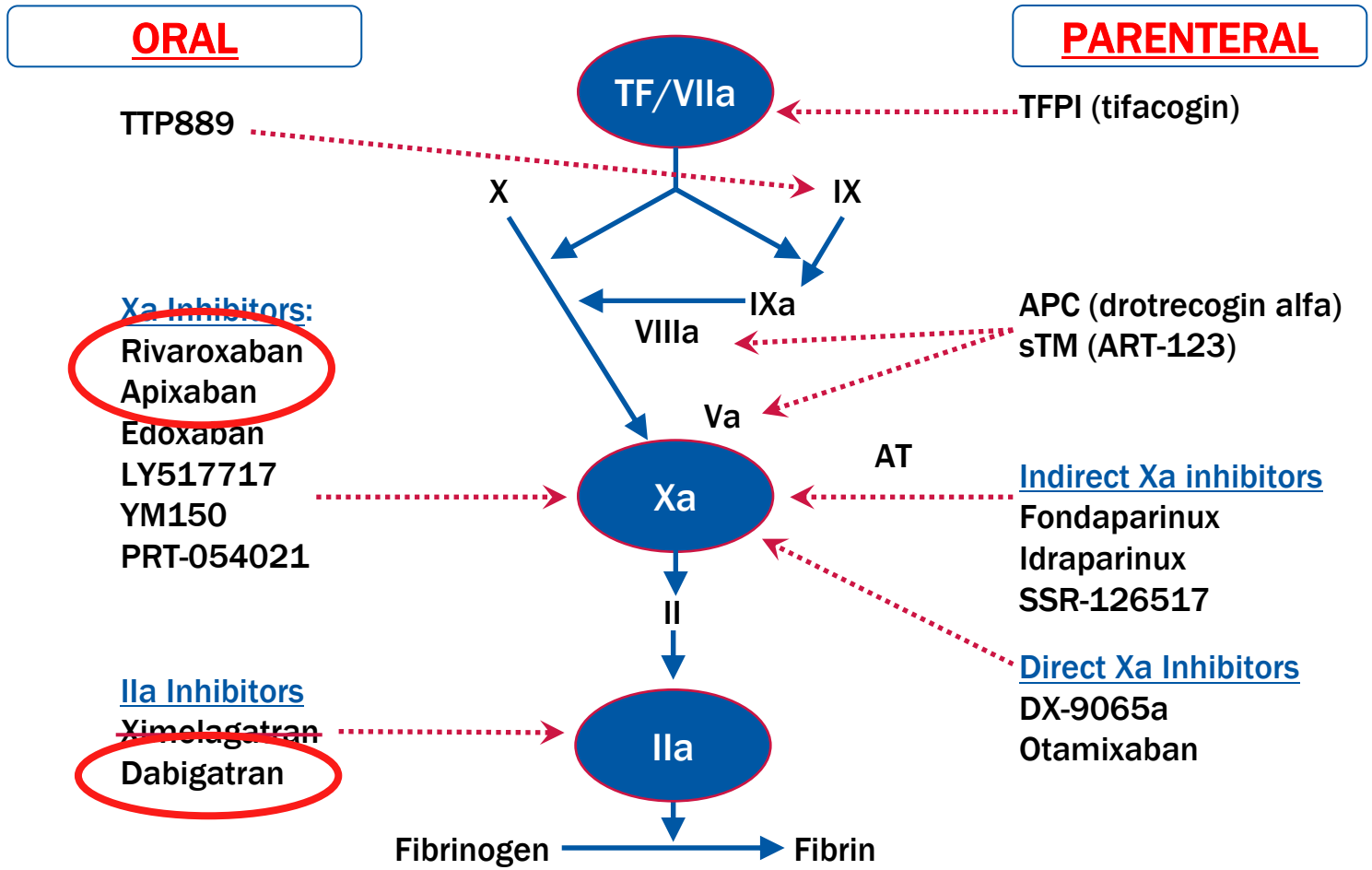
Targets of New Anticoagulant Agents



TF=tissue factor

Adapted from Weitz JI et al. *J Thromb Haemost.* 2005;3:1843-1853.

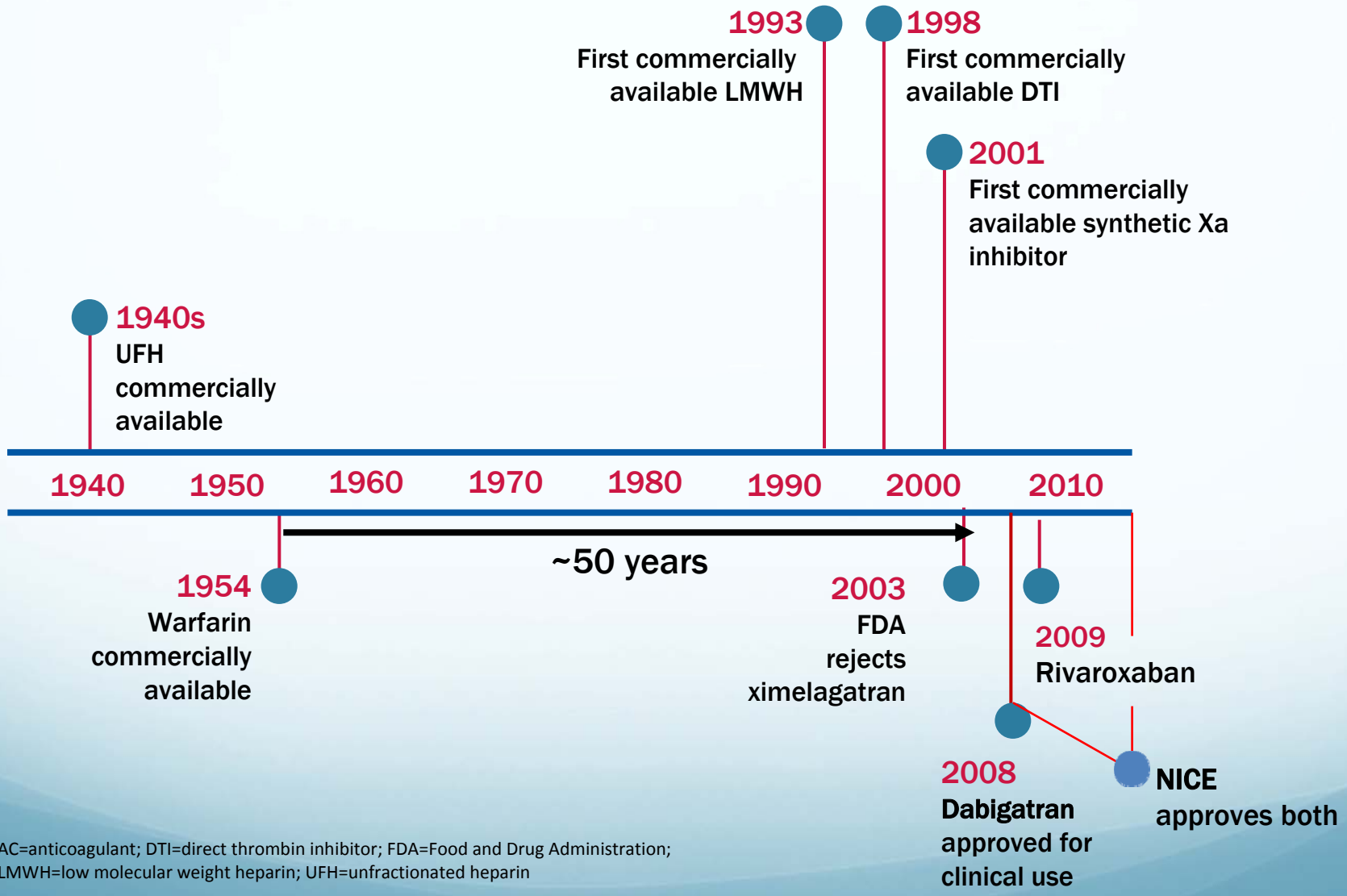
Targets of New Anticoagulant Agents



TF=tissue factor

Adapted from Weitz JI et al. *J Thromb Haemost.* 2005;3:1843-1853.

Evolution of Anticoagulant Therapy

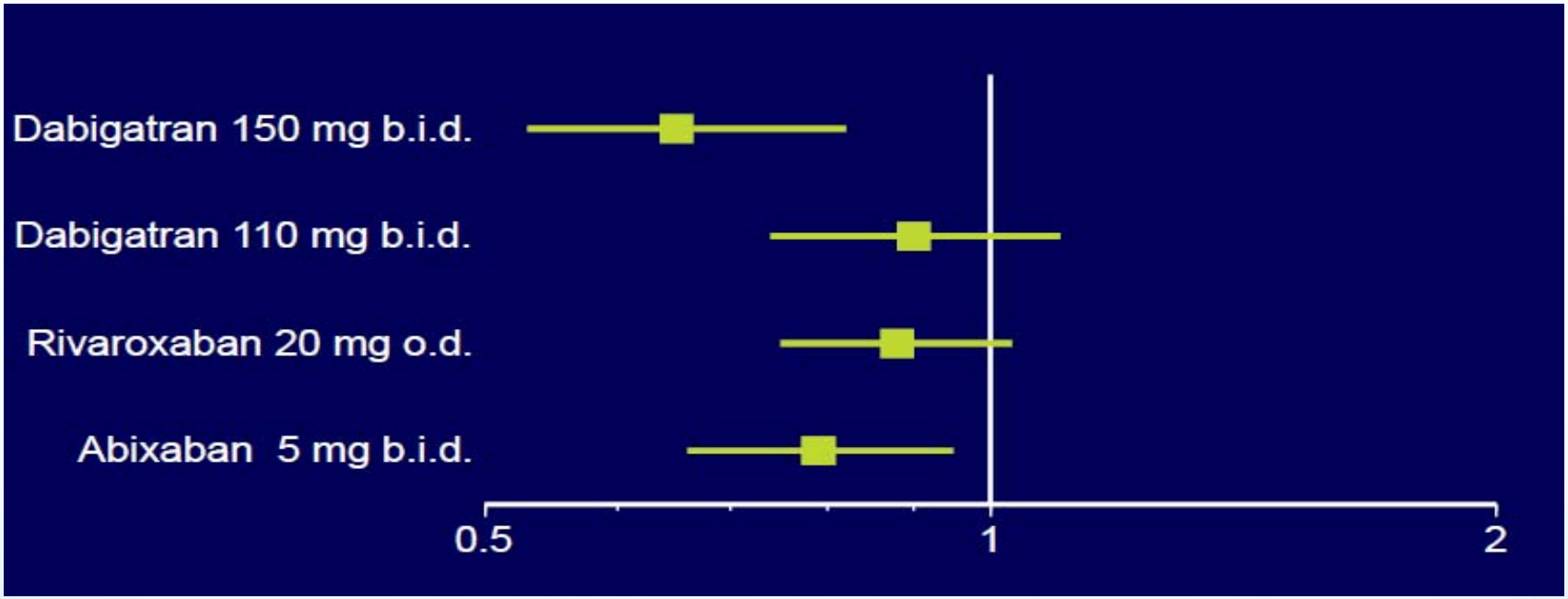


AC=anticoagulant; DTI=direct thrombin inhibitor; FDA=Food and Drug Administration; LMWH=low molecular weight heparin; UFH=unfractionated heparin

Overview of the most important Phase III randomized controlled trials involving the novel anti coagulants

	Atrial Fibrillation	DVT prevention	DVT treatment	ACS
Apixaban (Pfizer / BMS)	AVERROES ARISTOTLE	*Orthopaedic* ADVANCE 1 (49) ADVANCE-2 (50) ADVANCE-3 *Medical* ADOPT (NCT00457002) *Long-term secondary prevention* AMPLIFY-Ext (NCT00633893)	AMPLIFY (NCT00643201)	APPRAISE (54) APPRAISE-2 (NCT00831441)
Edoxaban (Daiichi Sankyo)	ENGAGE AF TIMI 48 (NCT00781391)		NCT00986154	
Dabigatran Etexilate (Boehringer Ingelheim)	Re-LY (13) RELY-ABLE (NCT00808067)	*Orthopaedic* RE-NOVATE (21) RE-MODEL (22) RE-MOBILIZE (69) *Long-term secondary prevention* RE-MEDY (NCT00329238) NCT00558259	RE-COVER (25) RE-COVER II (NCT00680186) RE-SONATE	RE-DEEM
Rivaroxaban (Bayer)	ROCKET-AF	*Orthopaedic* RECORD I (37) RECORD II (40) RECORD III (38) RECORD IV (39) *Medical* MAGELLAN (NCT00571649) *Long-term secondary prevention* EINSTEIN-Ext (42)	EINSTEIN-DVT (42) EINSTEIN-PE (NCT00439777)	ATLAS-TIMI 46 (43) ATLAS-TIMI 51 (NCT00809965)

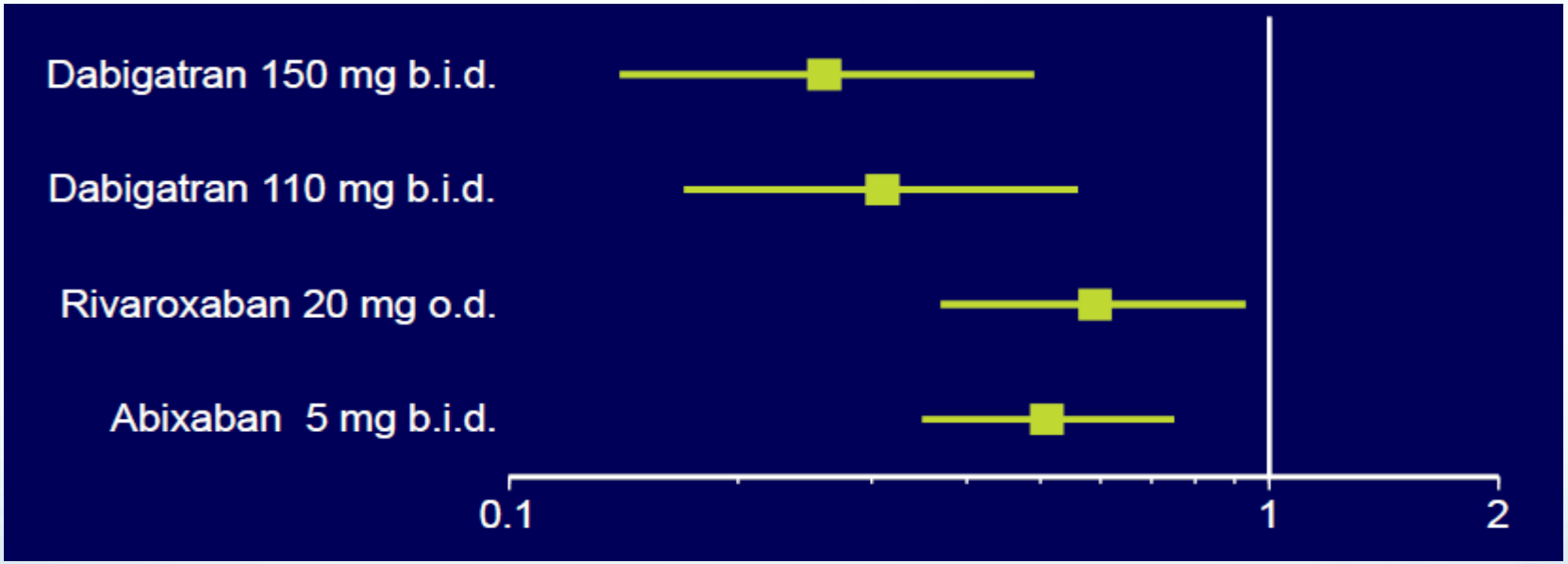
STROKE AND SYSTEMIC EMBOLISM



Favours other treatment

Favours warfarin

HAEMORRHAGIC STROKE



Favours other treatment

Favours warfarin

Most common adverse events

	Dabigatran 110 mg %	Dabigatran 150 mg %	Warfarin %
Any bleeding	14.74%	16.56%	18.37%
Dyspepsia*	11.8	11.3	5.8
Dyspnoea	9.3	9.5	9.7
Dizziness	8.1	8.3	9.4
Peripheral oedema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	5.2	6.2	5.9
Arthralgia	4.5	5.5	5.7
Back pain	5.3	5.2	5.6
Nasopharyngitis	5.6	5.4	5.6
Diarrhoea	6.3	6.5	5.7
Atrial fibrillation	5.5	5.9	5.8
Urinary tract infection	4.5	4.8	5.6
Upper respiratory tract infection	4.8	4.7	5.2

* Occurred more commonly on dabigatran $p<0.001$

1 Connolly SJ *et al. N Engl J Med* 2009;361:1139–1151.
2 SPC Pradaxa® 110 mg and 150 mg 2011.

Major bleeding and components

Characteristic	D 110 mg	D 150 mg	Warfarin	p-value 110 vs. W	p-value 150 vs. W
Number of patients (n)	6015	6076	6022		
Major bleeding	2.87	3.32	3.57	0.003	0.32
– Life threatening	1.24	1.49	1.85	<0.001	0.03
– Non-life threatening	1.83	2.06	1.92	0.65	0.39
– Gastrointestinal	1.15	1.56	1.07	0.52	0.001

Current licensed/NICE approved indications

	Stroke prevention in AF	VTE prevention (THR/TKR)	VTE treatment
Dabigatran	□	□	
Rivaroxaban	□	□	□
Apixaban		□	

Dabigatran etexilate (Pradaxa)

- Dabigatran: oral direct thrombin inhibitor
- Administered as a pro-drug
- Rapid onset of action- 2 hours
- Twice daily dosing
- Predictable and consistent anticoagulant effect- No requirement for routine coagulation monitoring
- No known dietary restrictions
- Few drug interactions
- 80% renal excretion
- Half-life- 13 hours (up to 30 hours in severe renal impairment)

Rivaroxaban (Xarelto)

- Rivaroxaban- oral direct factor Xa inhibitor
- Rapid onset of action- 2 hours
- Once daily dosing
- Predictable and consistent anticoagulant effect- No requirement for routine coagulation monitoring
- No known dietary restrictions
- Few drug interactions
- Liver (2/3rd)/Renal (1/3rd) excretion
- Half-life- 9 hours

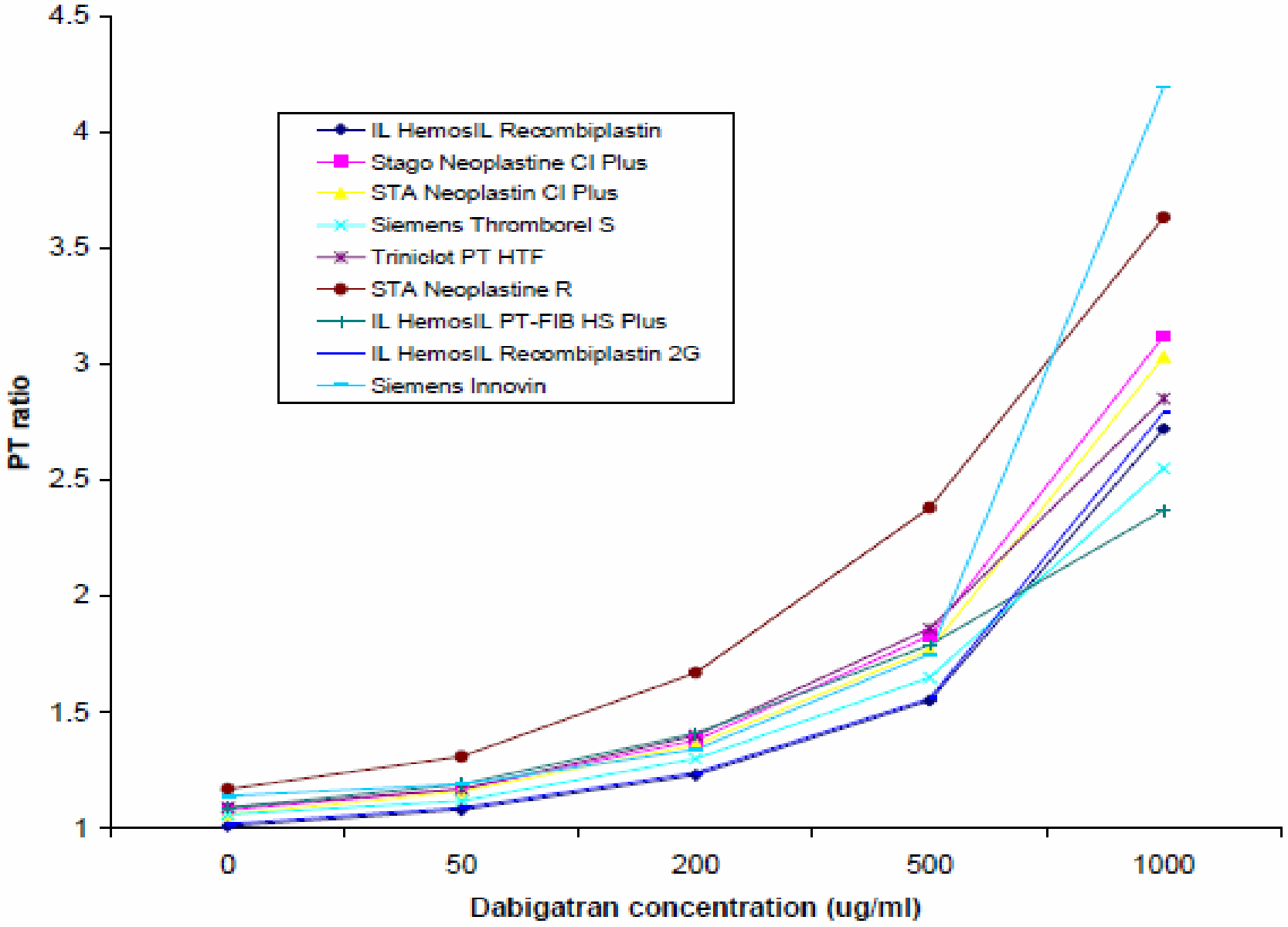
Limitations of the new oral anticoagulants

- Efficacy
- Potency
- Short half-life
- Cost (≈£800 pa)
- Monitoring

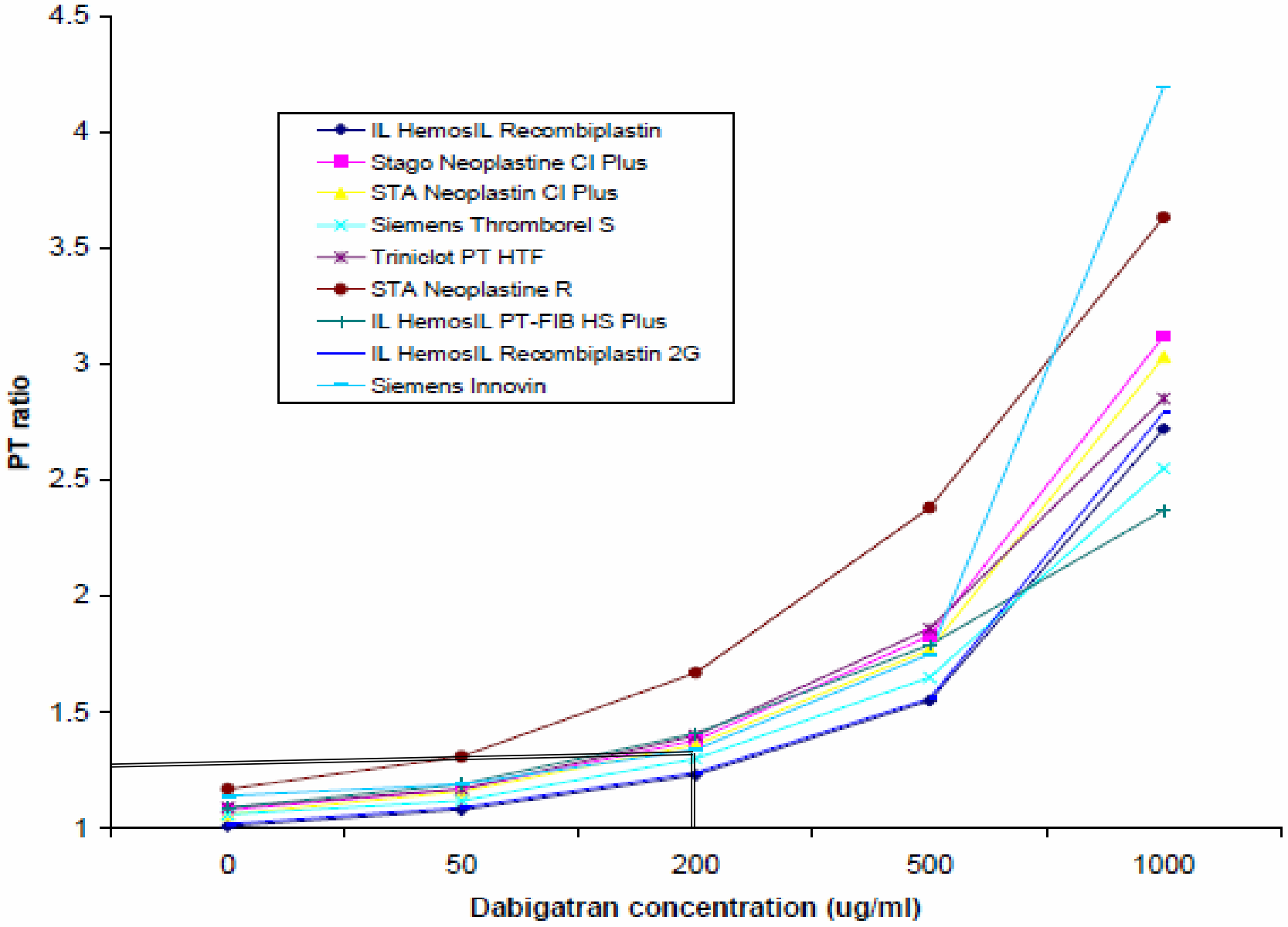
Monitoring of the new oral anticoagulants

- Monitoring during anticoagulant therapy is required to:
  - Assess compliance
  - Assess treatment failure
  - Titrate to lower/higher levels of anticoagulation
  - Detect accumulation in renal/liver impairment
  - Assess drug levels in a patient with haemorrhage, need for urgent surgery or overdose

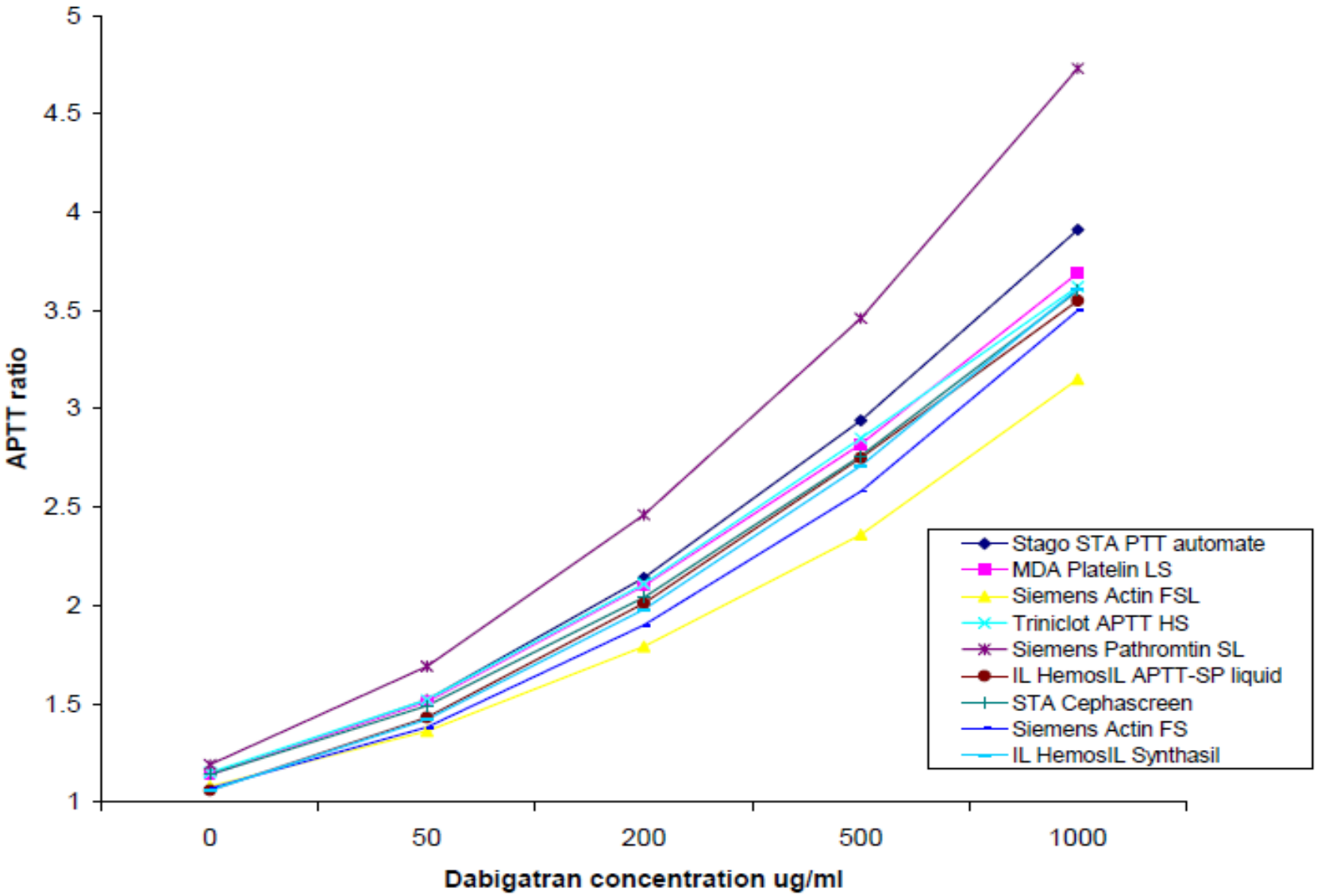
Median PT ratio against dabigatran concentration



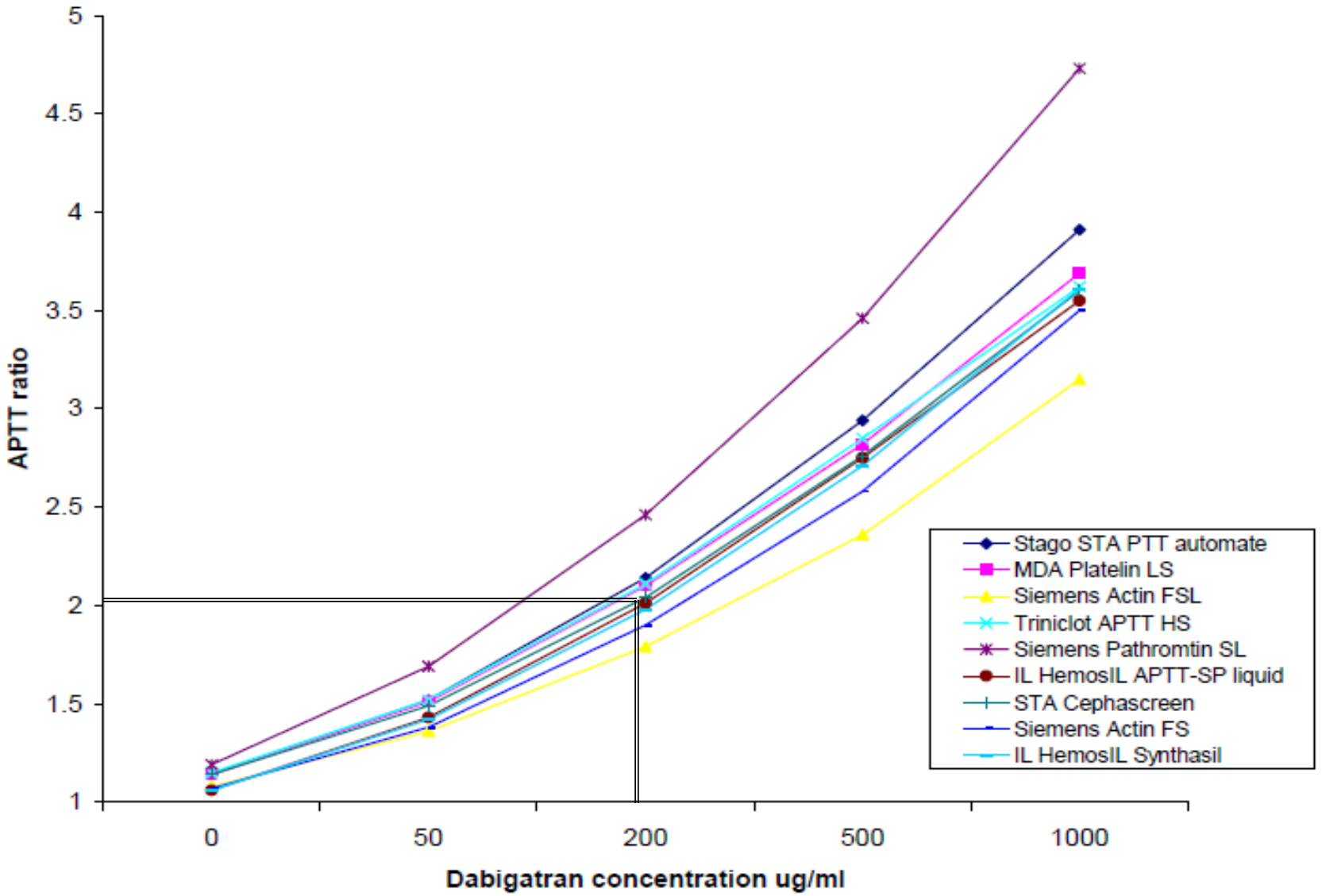
Median PT ratio against dabigatran concentration



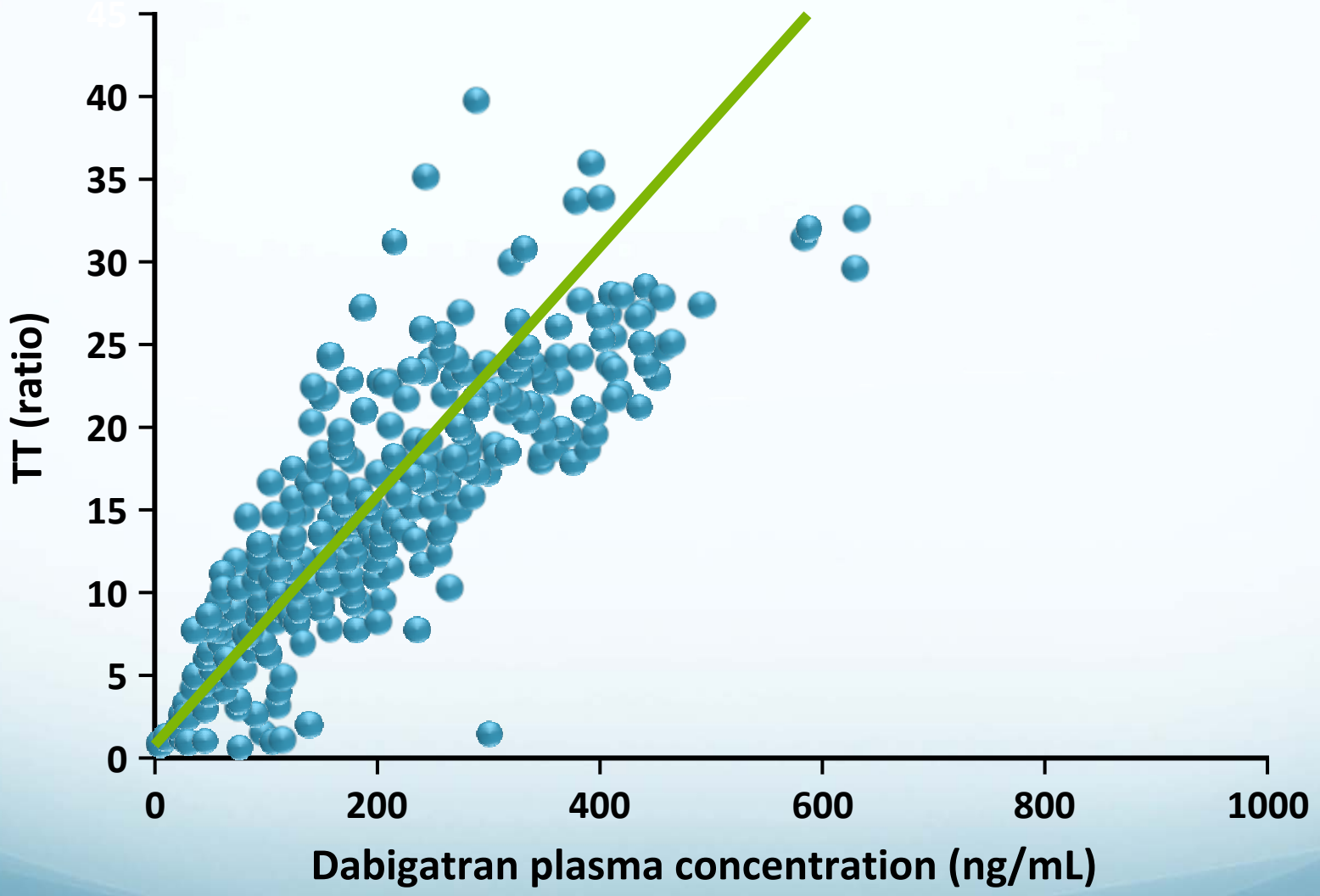
Median APTT ratio against dabigatran concentration



Median APTT ratio against dabigatran concentration

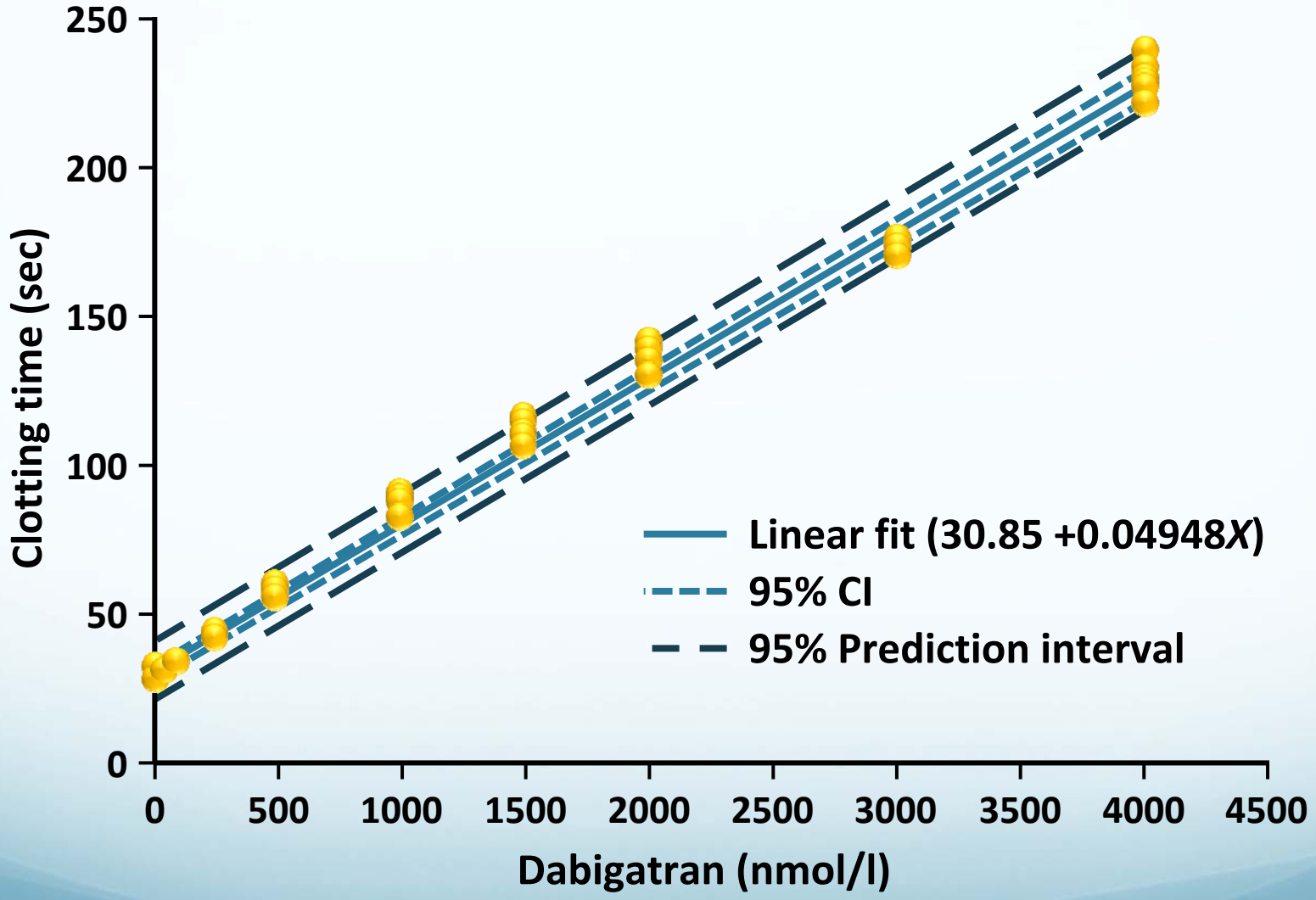


Thrombin time



Stangier *et al. Br J Clin Pharmacol* 2007;64:292–303

Hemoclot® thrombin time assay



Stangier J. *Blood Coagul Fibrinolysis* 2012; 23:138–143

Effect of the new oral anticoagulants on basic coagulation screening

- **Dabigatran** *van Ryn et al, Thromb Haemost 2010*
  - PT/INR- Insensitive
  - APTT- Qualitative
  - TT- Too sensitive
  - Hemoclot TT- Quantitative
  - If TT and APTT are normal, no anticoagulant effect is present
- **Rivaroxaban** *Hillarp et al, JTH 2011*
  - PT/INR- Qualitative, variable sensitivity
  - APTT- Poor sensitivity
  - TT- Insensitive
  - Anti-Xa activity- Can be used to monitor, need to use drug-specific calibrants
  - If PT or APTT are abnormal, an anticoagulant effect is likely to be present

Limitations of the new oral anticoagulants

- Efficacy
- Potency
- Short half-life
- Cost (≈£800 pa)
- Unable to monitor
- Reversibility/Lack of an antidote

Reversibility of the new oral anticoagulants using bypassing agents

- **Dabigatran**
  - PCC showed some clinical effect in a rabbit trauma model
  - Activated PCC (FEIBA) and rFVIIa effective in rat tail bleeding model
  - rFVIIa improved APTT and reduced bleeding in animal models at high doses
- **Rivaroxaban**
  - rFVIIa partially reversed reduced thrombin generation in an *in vitro* model
  - APCC and rFVIIa partially effective in a baboon animal model
  - PCC and rFVIIa reversed laboratory coagulopathy but not bleeding in a rabbit trauma model

Circulation

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Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

Circulation published online September 6, 2011

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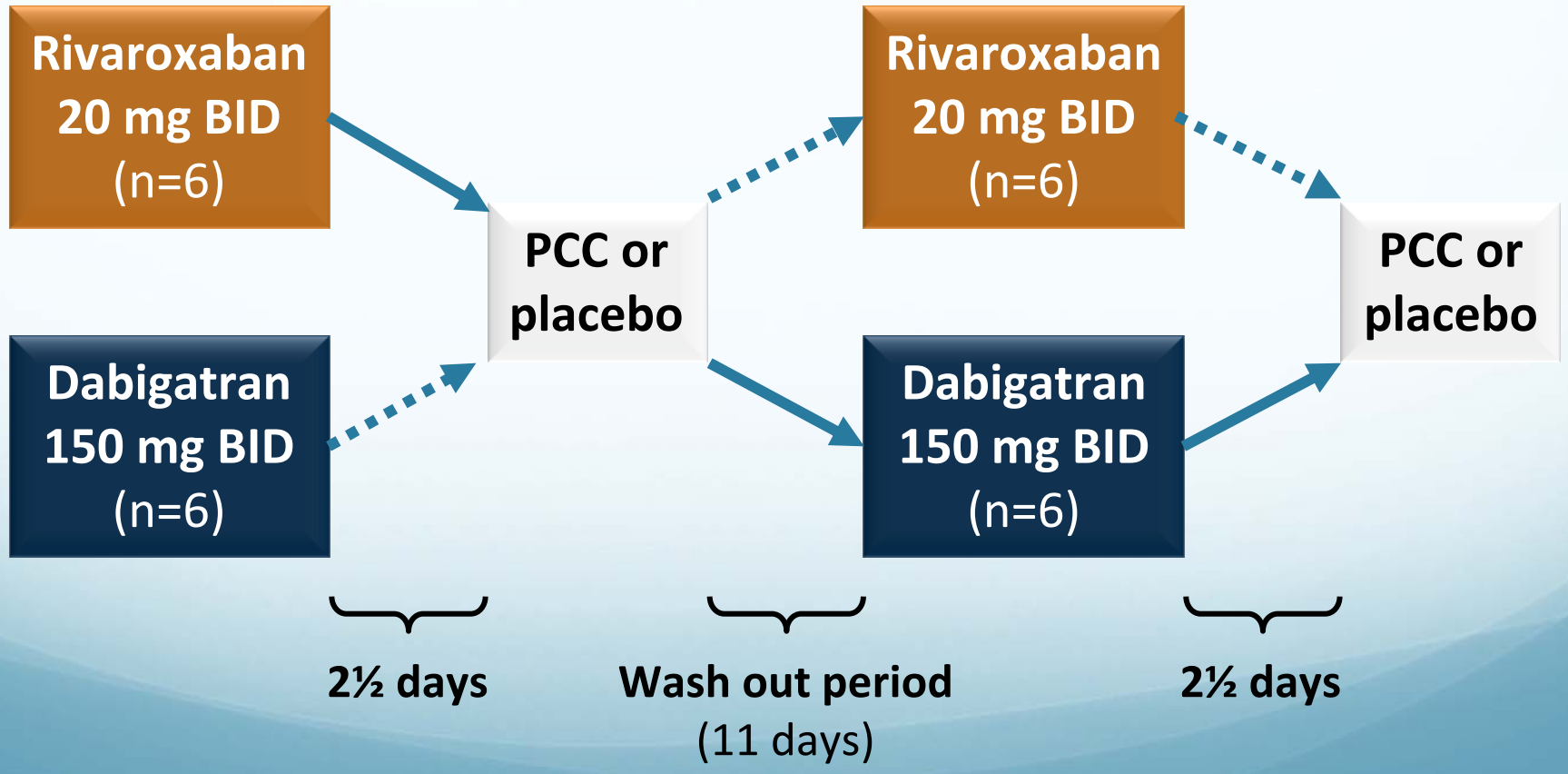
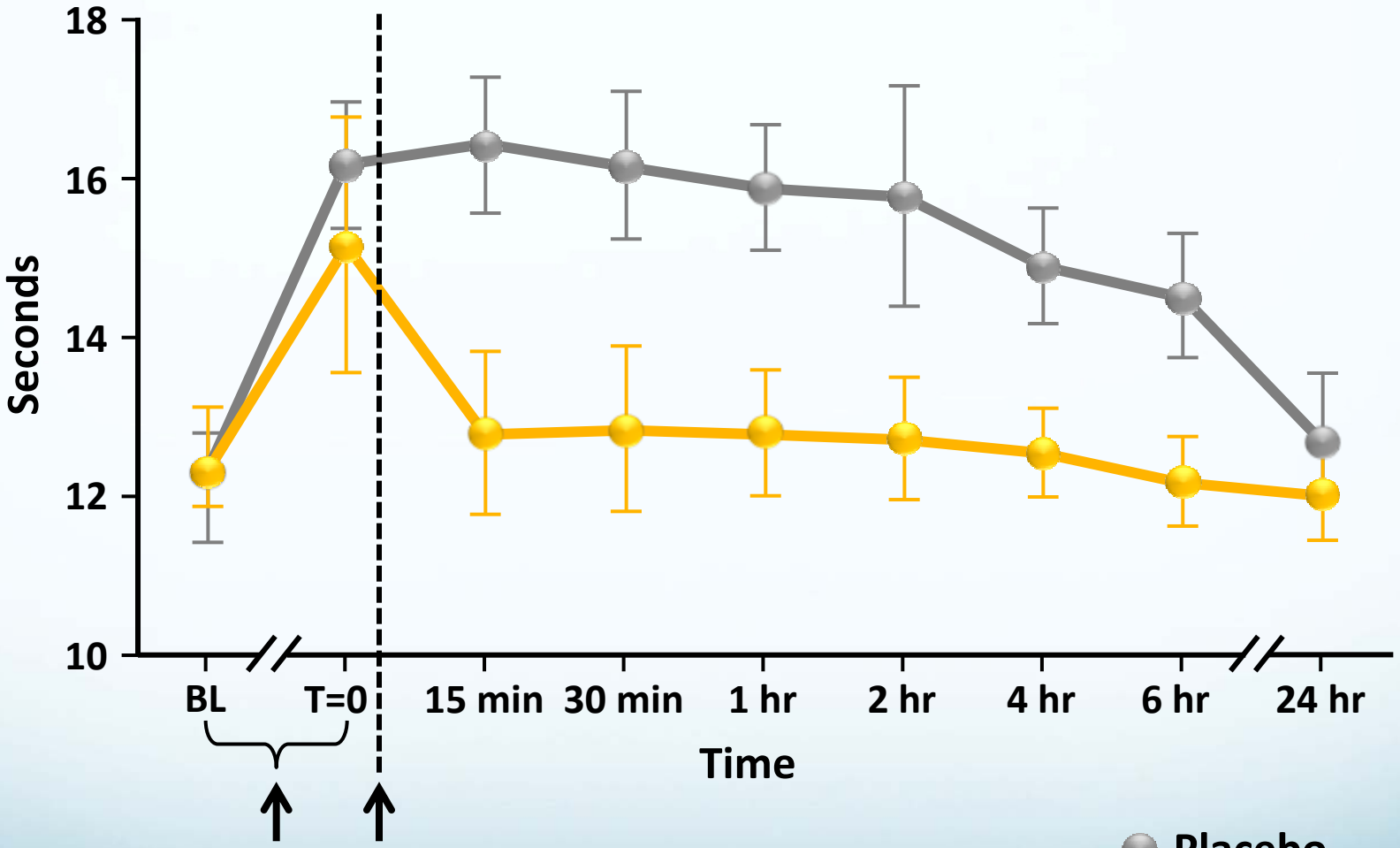
Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate

A randomized, double-blind, placebo-controlled, crossover trial with healthy male subjects (n=12)



Eerenberg *et al. Circulation* 2011

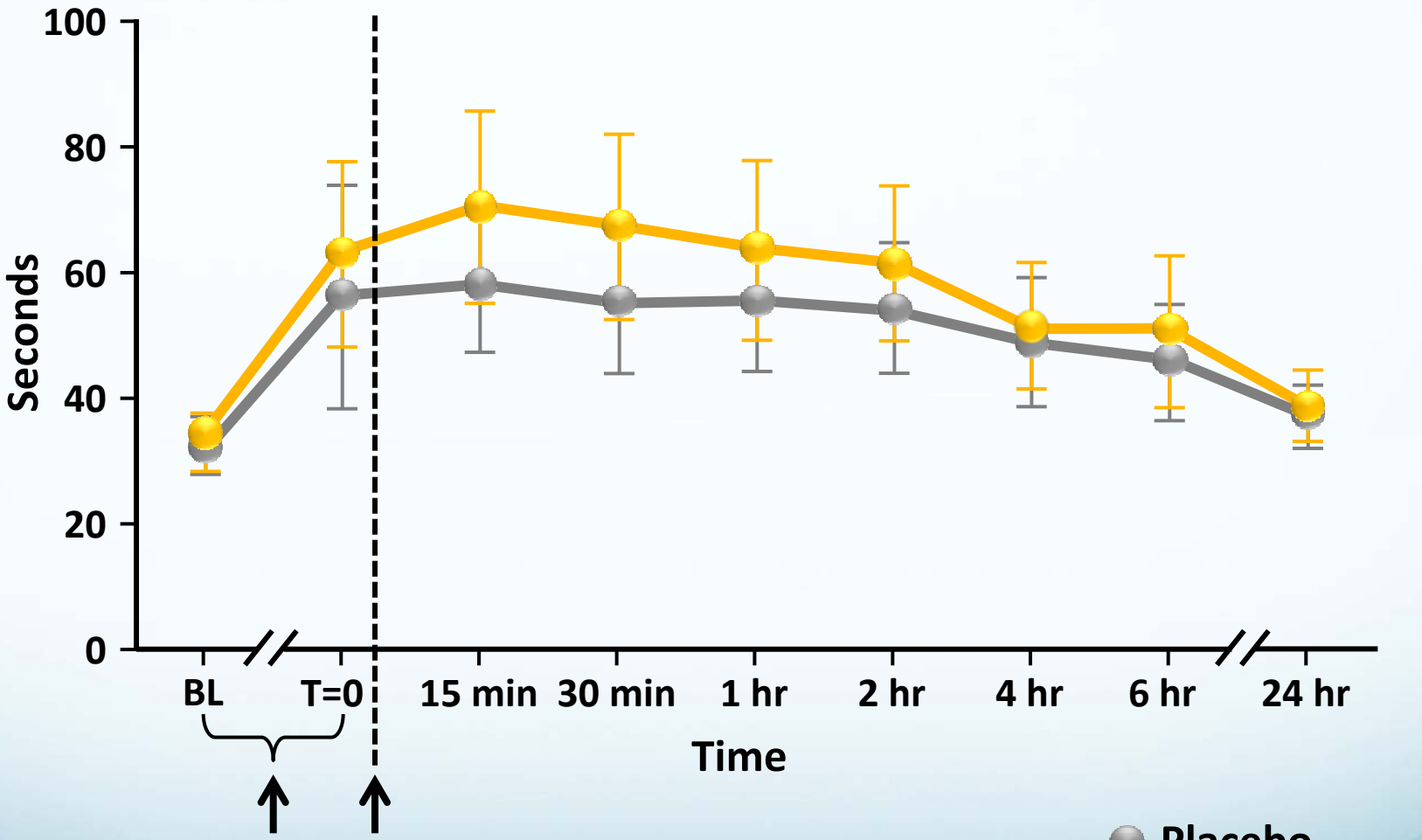
Reversal of rivaroxaban monitored by PT



Rivaroxaban 20 mg BID for two and a half days

PCC or placebo infusion

Reversal of dabigatran monitored by aPTT

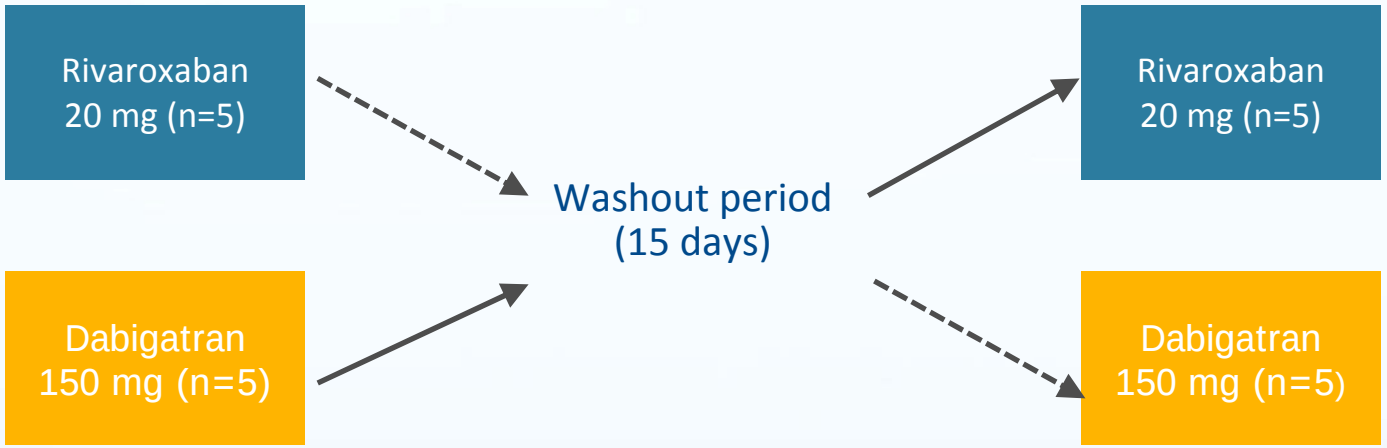


Dabigatran 150 mg BID for two and a half days

PCC or placebo infusion

Reversal of dabigatran and rivaroxaban activity by coagulation factor concentrates

- Randomized, crossover, *ex vivo* study in healthy male volunteers (n=10)
- Blood samples collected immediately before and 2 h after one dose of oral anticoagulant



•Haemostatic agents tested *ex vivo*:
- –PCC (Kanokad: 0.25, 0.5, and 1 U/mL),
- –rFVIIa (NovoSeven: 0.5, 1.5, and 3 µg/mL),
- –Activated PCC (FEIBA: 0.25, 0.5, 1, and 2 U/mL)

Marlu R et al. Thromb Haemost 2012;108:217–24

Management of bleeding or urgent need for surgery

- **General measures:**
  - Stop the drug
  - Document timing of last dose, estimate elimination half-life
  - Check FBC, coagulation screen, creatinine, G+S
  - Correct haemodynamic compromise
  - Defer surgery if able
  - Control haemorrhage:
    - Mechanical compression
    - Surgical/radiological intervention

Management of bleeding or urgent need for surgery

- **Specific measures:**
  - Dabigatran
    - Oral activated charcoal if last dose <2 hours previously
    - Consider haemodialysis/haemofiltration (≈60% removed within 2 hours)- guided by normalisation of APTT
  - Rivaroxaban
    - Oral activated charcoal may remove unadsorbed drug
    - Haemodialysis/haemofiltration unhelpful- 95% protein bound

Management of bleeding or urgent need for surgery

- **Pharmacological measures:**
  - Antifibrinolytics- Tranexamic acid, oral/IV/topical
  - PCC: May be helpful for rivaroxaban, ?unhelpful for dabigatran
  - rFVIIa
  - APCC (FEIBA)

PATIENT RECEIVING DABIGATRAN THERAPY: HAEMORRHAGE PATHWAY

STOP: Dabigatran

Coagulation screen to include APTT (and thrombin time) ,+/- Hemoclot TT
[Important to document time of last dose of dabigatran]
Full blood count and renal function (eGFR or CrCl)

APTT (and TT) normal: dabigatran levels low / absent

APTT normal (but TT) prolonged: dabigatran levels low

APTT (and TT) prolonged

Dabigatran anticoagulant effect maybe present (consider oral charcoal if dabigatran ingestion <2 hours)

MILD BLEED

- Mechanical compression
- Tranexamic Acid
  - oral 25 mg/kg
  - or i.v. 10 mg/kg
- Delay next dabigatran dose and review indication for anticoagulation

Continues to bleed

MAJOR BLEED

Maintain BP and Urine Output
(dabigatran 80% renal excretion)

- Optimise tissue oxygenation
- Control haemorrhage
  - Mechanical compression
  - Surgical / radiological intervention
- Tranexamic Acid (1g i.v.)
- Red cell transfusion
  - Aim Hb > 7 g/dl
- Platelet transfusion
  - Aim Plt > 50 x 10^9/l or
  - If CNS bleed aim Plt > 100 x 10^9/l
- Identify bleeding source e.g. surgery, endoscopy, interventional radiology

LIMB / LIFE THREATENING BLEED

If considering haemostatic agent discuss with haematologist

FEIBA / PCC / rFVIIa*

Haemodialysis

May reduce dabigatran plasma concentration by 50% with 4 hours

Major Bleed: Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome
(Schulman et al J Thromb Haemost 2010; 3:692-694)

PATIENT RECEIVING DABIGATRAN THERAPY: EMERGENCY SURGERY PATHWAY

STOP: Dabigatran

Coagulation screen to include APTT (and thrombin time) ,+/- Hemoclot TT
[Important to document time of last dose of dabigatran]
Full blood count and renal function (eGFR or CrCl)

→ APTT (and TT) normal: dabigatran levels low / absent
APTT normal (but TT) prolonged: dabigatran levels low

APTT (and TT) prolonged → Inform Surgeon and Anaesthetist

Dabigatran anticoagulant effect maybe present (consider oral charcoal if dabigatran ingestion <2 hours *and* anaesthetist / surgeon agrees)

Maintain BP and Urine Output (dabigatran 80% renal excretion) → IF ACTIVE BLEEDING

- Optimise tissue oxygenation
- Control of haemorrhage
  - Compression
  - Surgical intervention
  - Tranexamic Acid (1g i.v.)
- Red Cell transfusion
  - Aim Hb > 7 g/dl
- Platelet transfusion
  - Aim Plt > 50 x 10^9/l or
  - If CNS bleed aim Plt > 100 x 10^9/l

Discuss with surgeon feasibility of delaying surgery

SURGICAL DELAY ≥12 HOURS

Refer to elective surgery table 1

Risk of bleeding dependent on
- Time since last dabigatran dose
- Type of surgery
- Renal function / eGFR

SURGICAL DELAY ≥4–12 HOURS

Consider Haemodialysis

Or

IMMEDIATE SURGERY

If considering haemostatic agent discuss with haematologist

FEIBA / PCC / rFVIIa*

Regional anaesthesia (spinal / epidural) is considered to be contrai-indicated

Elective surgery discontinuation rules for dabigatran before invasive or surgical procedure

Renal function	Estimated half-life	Stop dabigatran before elective surgery	
CrCL ml/min	Hours	Major surgery or high risk bleeding ◊	Non-major surgery or standard risk #
≥80	~ 13	2 days before	24 hour before
≥50 <80	~ 15	2–3 days before	1–2 days before
≥30 <50	~ 18	4 days before	2–3 days before

◊ Examples of major surgery / high bleeding risk: cardiothoracic surgery, neurosurgery, major abdominal or pelvic surgery, major orthopaedic surgery; insertion of cardiac pacemaker / defibrillator

Examples of non-major surgery / standard risk: uncomplicated laparascopic procedure, cardiac catheterisation, ablation therapy

PATIENT RECEIVING DABIGATRAN THERAPY: OVERDOSE PATHWAY

STOP: Dabigatran

Coagulation screen to include APTT (and thrombin time) ,+/- Hemoclot TT
[Important to document time of last dose of dabigatran]
Full blood count and renal function (eGFR or CrCl)

APTT (and TT) normal: dabigatran levels low / absent

APTT normal (but TT) prolonged: dabigatran levels low

Repeat APTT (and TT) after 2 hours

APTT (and TT) prolonged

Dabigatran anticoagulant effect maybe present
(consider oral charcoal if dabigatran ingestion <2 hours)

Repeat APTT (and TT) 12 hourly until normal

Maintain BP and Urine Output
(dabigatran 80% renal excretion)

Review reason for overdose and indication for anticoagulation

Is patient bleeding?

YES

NO

Haemodialysis may reduce dabigatran plasma concentration by 50% with 4 hours

Refer to dabigatran haemorrhage protocol

Limitations of the new oral anticoagulants

- Efficacy
- Potency
- Short half-life
- Cost (≈£800 pa)
- Unable to monitor
- Reversibility/Lack of an antidote
- Accumulation in renal failure

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

- **FDA: July 2011**

Pradaxa (dabigatran etexilate mesylate): Drug Safety Communication - Safety Review of Post-Market Reports of Serious Bleeding Events

Posted 12/07/2011

- **MHRA: December 2011**

Drug Safety Update

Latest advice for medicines users

Dabigatran (Pradaxa▼): risk of serious haemorrhage—need for renal function testing

Article date: December 2011

Summary

A number of cases of serious and fatal haemorrhage have been reported in elderly patients with renal impairment who were receiving dabigatran. Renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min)

Dose reduction in renal impairment

	Normal renal function/mild renal impairment	Moderate renal impairment (CrCl 30-50ml/min)	Severe renal impairment (CrCl 15-30ml/min)	Hepatic impairment
Dabigatran	Standard dose	Dose ↓	Not recommended	Standard dose
Rivaroxaban	Standard dose	Dose ↓	Dose ↓	Not recommended
Apixaban	Standard dose	Standard dose	Dose ↓	Use with caution

Conclusions

- New oral anticoagulant agents show great promise
- Exercise caution regarding their lack of reversibility and reduced safety in renal/hepatic impairment
- Safe prescribing is crucial
- Future research should address:
  - Laboratory monitoring
  - Antidotes
  - Response to bypassing agents
- Collection of data regarding bleeding events