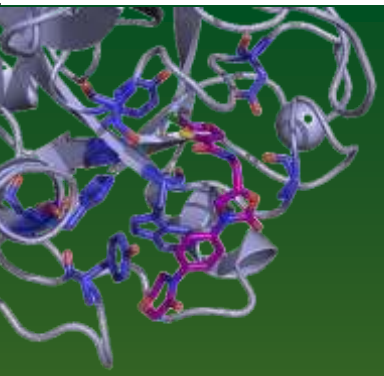

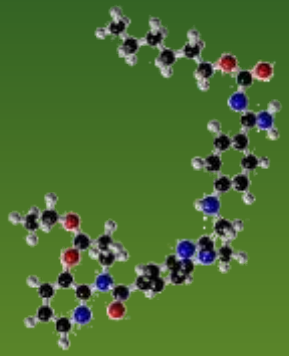

HELIOS Kliniken
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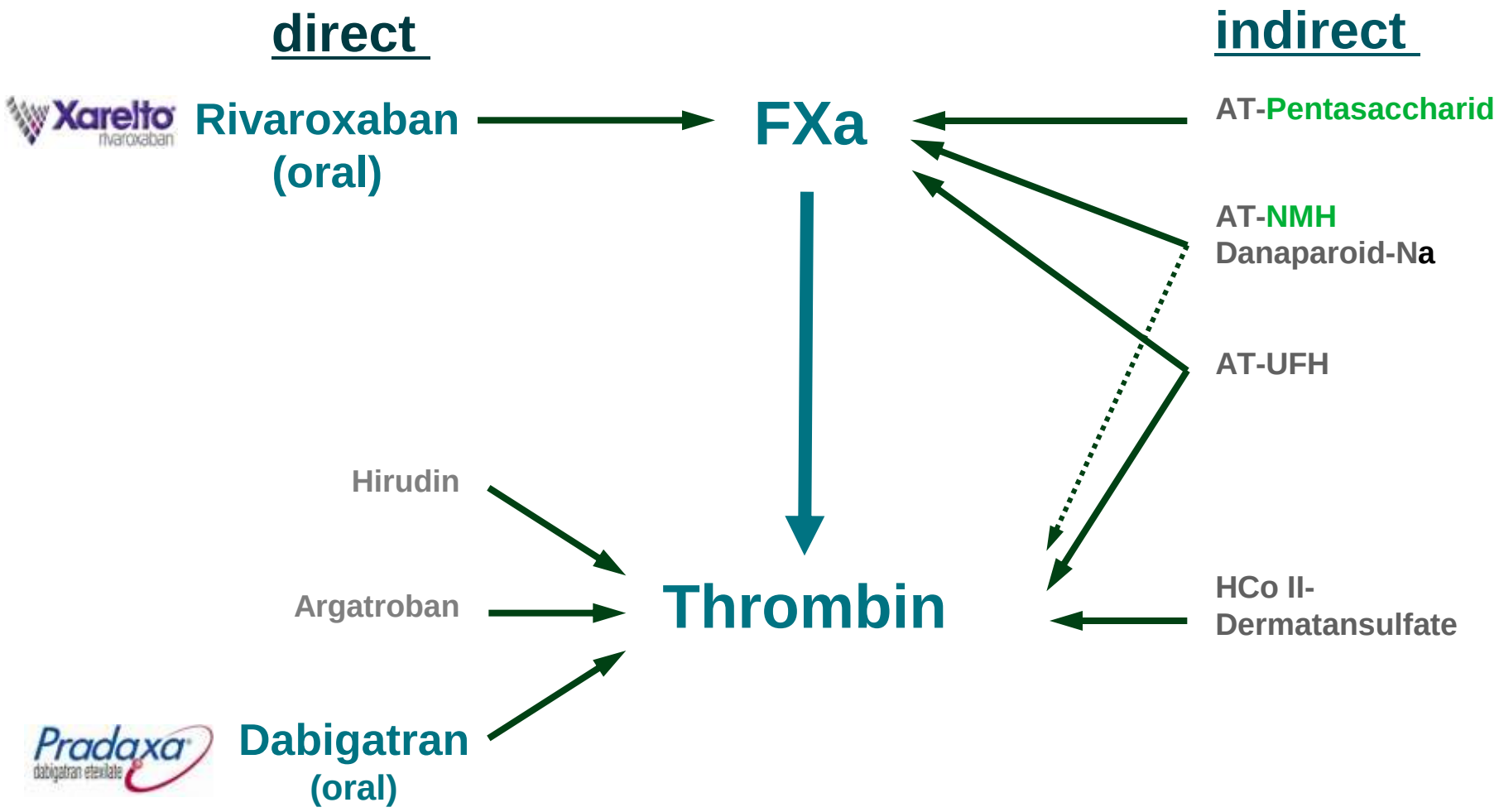
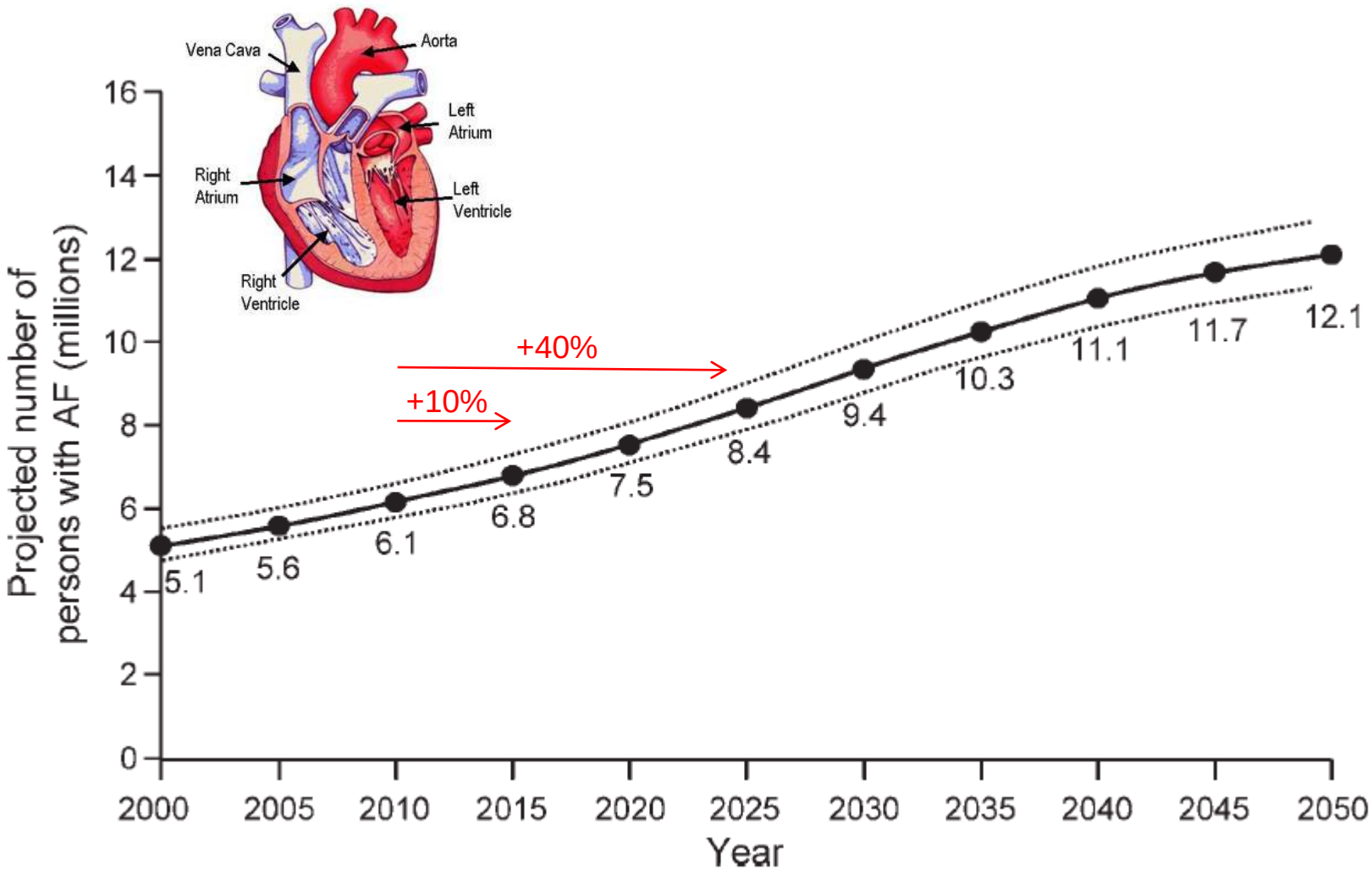
Desired tests for monitoring new anticoagulation drugs

Dirk Peetz, Nov 12th, 2010

New oral anticoagulants
Modes of action



Prevalence of atrial fibrillation (US)
Prognosis 2010 → 2050



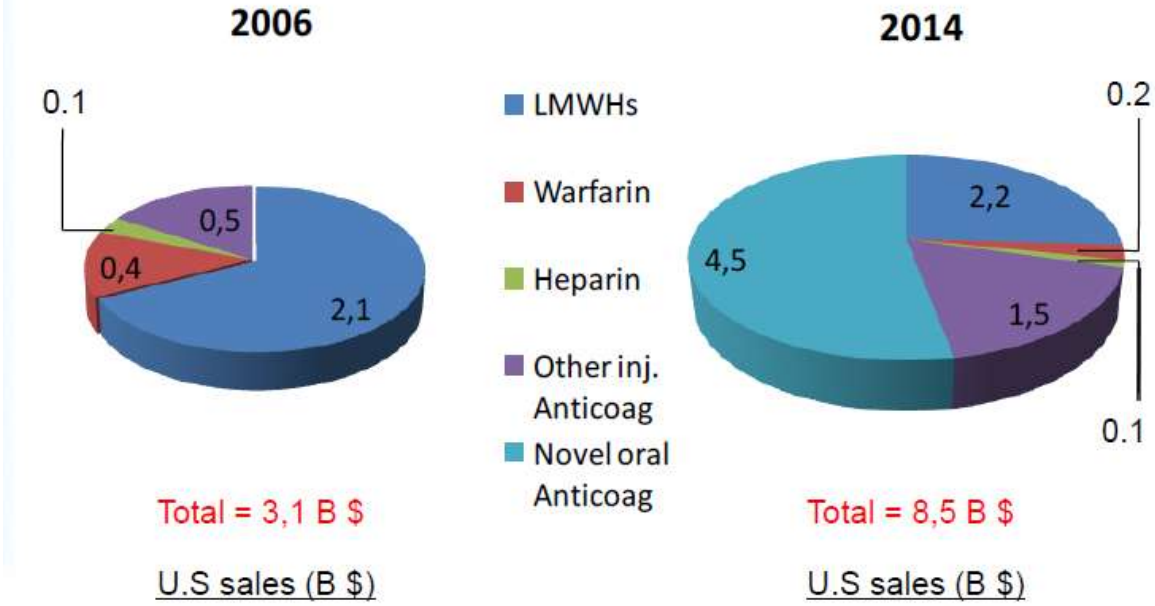
Turpie AGG. European Heart Journal (2007) 29, 155–165

Rivaroxaban
Estimated business volume 2009-2015 (million €)

	2009	2010	2011	2012	2013	2014	2015
RECORD (VTE prev)	50	120	250	350	400	420	450
ROCKET (AF)			300	1200	2200	3100	4000
EINSTEIN (VTE treat)			80	180	300	550	800
MAGELLAN (VTE prev hosp patients)				250	350	650	850
ATLAS (ACS 2nd prev)					30	80	120
TOTAL	50	120	630	1980	3280	4800	6220

BNP Paripas – Bayer presentation 2009

Anticoagulants
Market development 2006-2014



JNJ Investor relations – Bayer Präsentation 2009

New oral anticoagulants - Dabigatran
Approval

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From Heartwire

[heartwire]

FDA Will Be in Dabigatran's Corner at Next Monday's Advisory Panel Meeting

Steve Stiles

Authors and Disclosures

Physician Rating: (9 Votes) Rate This Article:

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September 16, 2010 (Silver Spring, Maryland) — With all the buzz surrounding the oncoming wave of possible new oral anticoagulants, one might think they have the potential for dramatically simplifying the care of a huge and growing population of patients. And actually, that's true. Food and Drug Administration documents released today suggest that the agency will recommend to its Cardiovascular and Renal Drugs Advisory Committee on September 20 that one of those anticipated replacements for venerable but troublesome **warfarin**, **dabigatran etexilate** (Boehringer Ingelheim) should be approved for the prevention of stroke in patients with atrial fibrillation (AF) [1].

RELATED ARTICLES

- RE-LY: Post Hoc Analysis Confirms Benefit of Dabigatran Relative to Warfarin at All INR Levels
- New Approaches for Stroke Prevention in Atrial Fibrillation
- Warfarin Use in AF Is Unrelated to Stroke, Bleeding Risk: Study

New oral anticoagulants - Dabigatran
Approval

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From Heartwire > Alerts, Approvals and Safety Changes > Approvals

heartwire

FDA Approves Dabigatran for Stroke Prevention, Embolism in AF Patients

Shelley Wood

Authors and Disclosures

Physician Rating: ★★★★★ (22 Votes) Rate This Article: ☆☆☆☆☆

Print This Email this Share

October 20, 2010 (Silver Spring, Maryland)— Late Tuesday, Boehringer Ingelheim announced that the US **FDA** has approved **dabigatran** (Pradaxa) for the prevention of stroke and systemic embolism in patients with atrial fibrillation [1].

As previously reported by **heartwire** , an advisory panel in September voted 9 to 0 to recommend that the oral antithrombin be approved. The drug will be available in two doses: 150 mg twice daily and, for a small subset with severe renal impairment, 75 mg twice daily. Debates about the approved dosing have already begun (see the discussion in the **heartwire** forum).

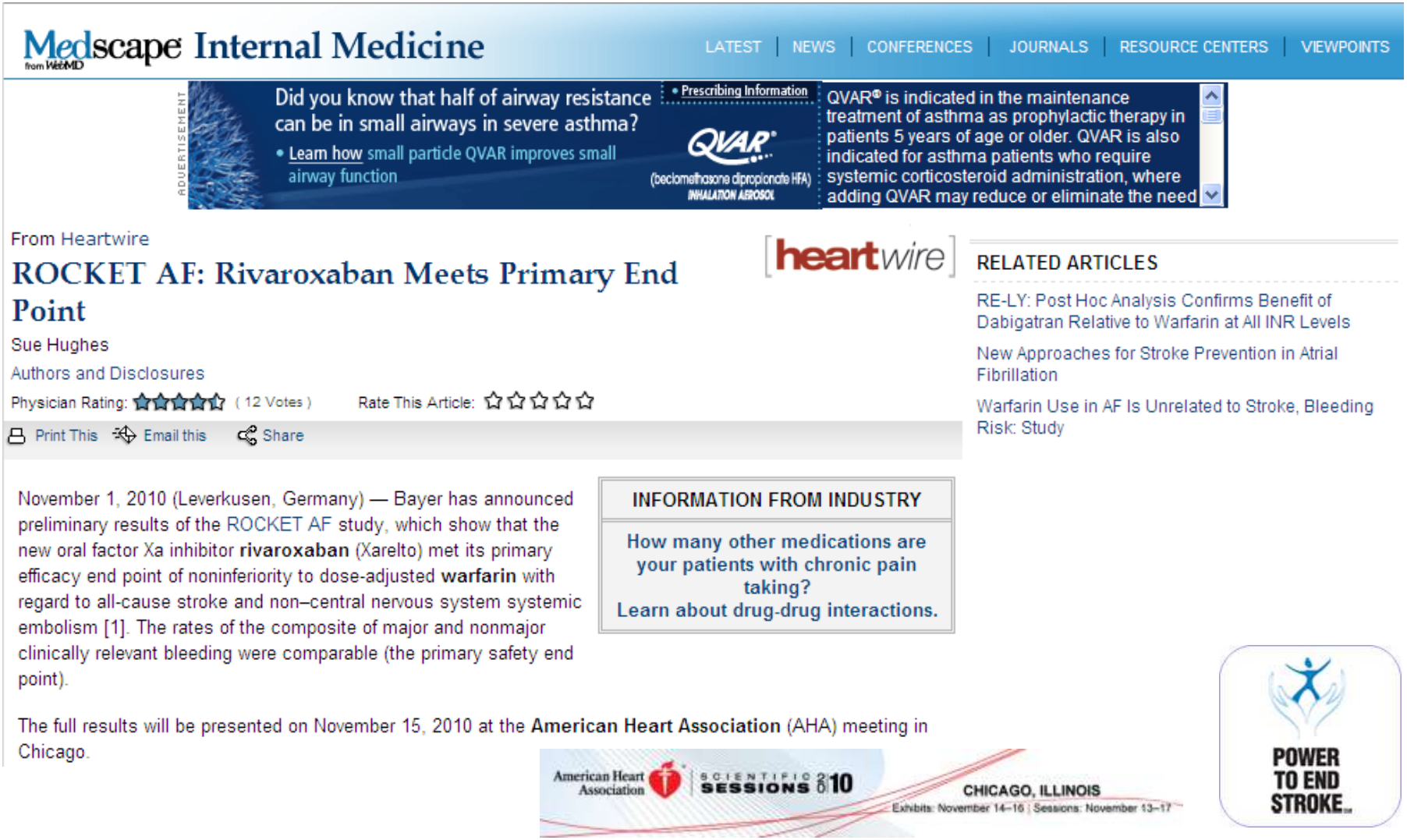
RELATED ARTICLES

RE-LY: Post Hoc Analysis Confirms Benefit of Dabigatran Relative to Warfarin at All INR Levels

New Approaches for Stroke Prevention in Atrial Fibrillation

New oral anticoagulants - Rivaroxaban

What's about rivaroxaban



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From Heartwire

heartwire

ROCKET AF: Rivaroxaban Meets Primary End Point

Sue Hughes

Authors and Disclosures

Physician Rating: ★★★★★ (12 Votes) Rate This Article: ☆☆☆☆☆

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November 1, 2010 (Leverkusen, Germany) — Bayer has announced preliminary results of the ROCKET AF study, which show that the new oral factor Xa inhibitor **rivaroxaban** (Xarelto) met its primary efficacy end point of noninferiority to dose-adjusted **warfarin** with regard to all-cause stroke and non–central nervous system systemic embolism [1]. The rates of the composite of major and nonmajor clinically relevant bleeding were comparable (the primary safety end point).

The full results will be presented on November 15, 2010 at the **American Heart Association** (AHA) meeting in Chicago.

RELATED ARTICLES

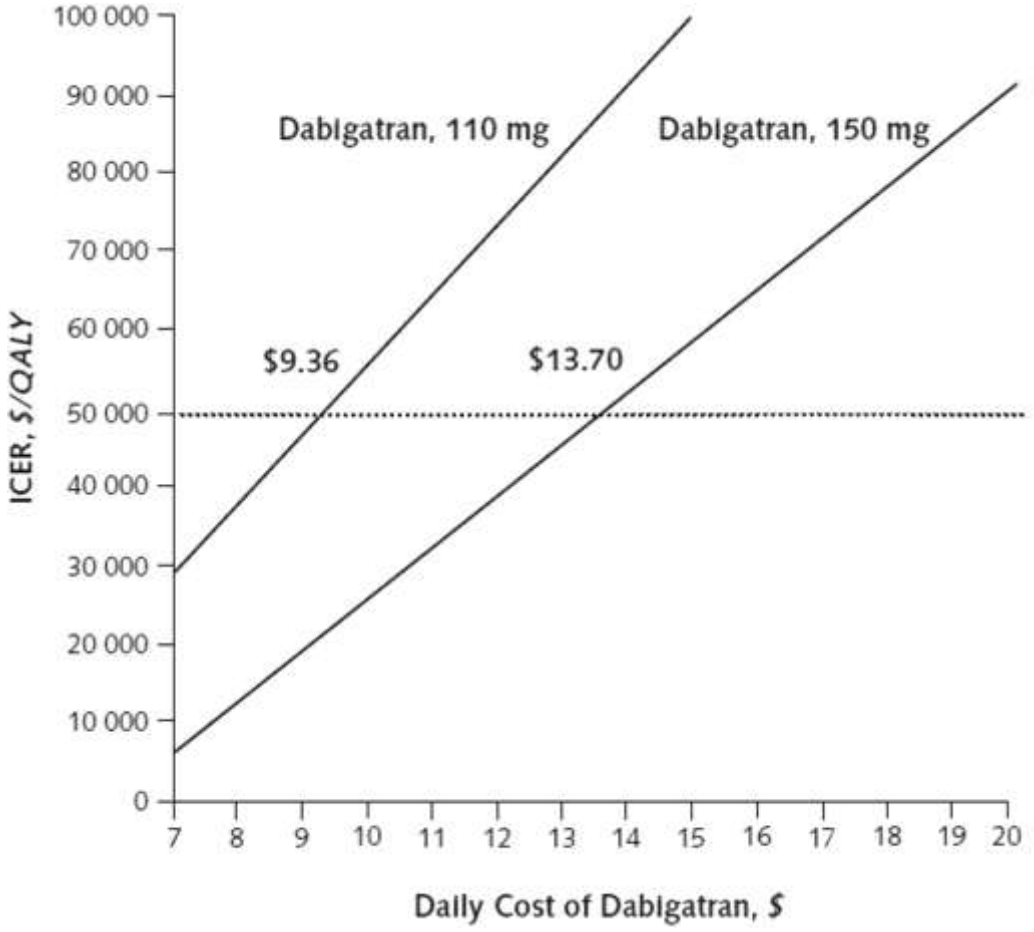
RE-LY: Post Hoc Analysis Confirms Benefit of Dabigatran Relative to Warfarin at All INR Levels

New Approaches for Stroke Prevention in Atrial Fibrillation

Warfarin Use in AF Is Unrelated to Stroke, Bleeding Risk: Study

New oral anticoagulants - Dabigatran

Cost effectiveness – Stroke prevention in atrial fibrillation



Total costs:

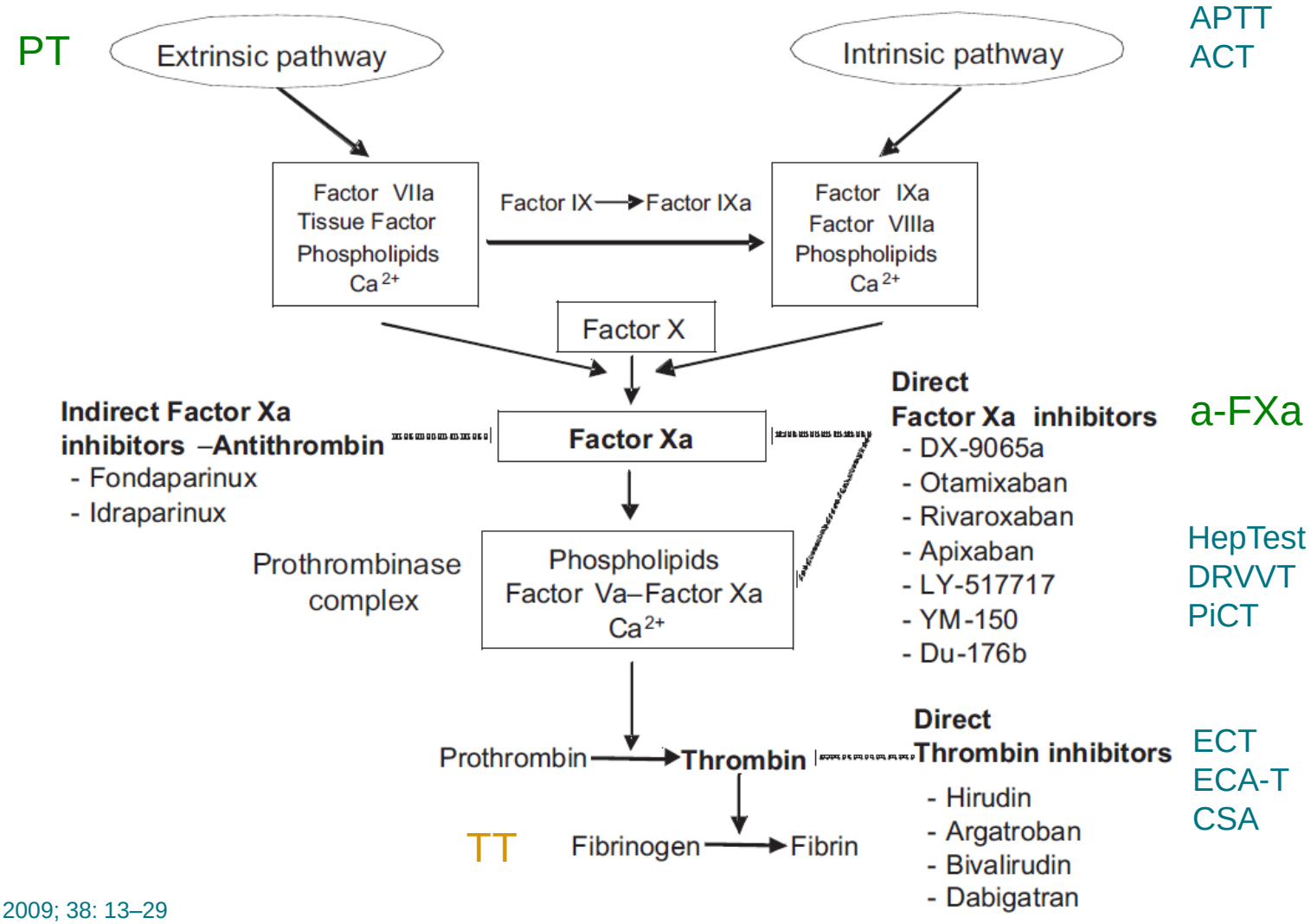
Warfarin	$143 193
Low-dose dabigatran	$164 576
High-dose dabigatran	$168 398

Freeman J V et al. Ann Intern Med doi:10.1059/0003-4819-154-1-201101040-00289

New oral anticoagulants
Need for monitoring

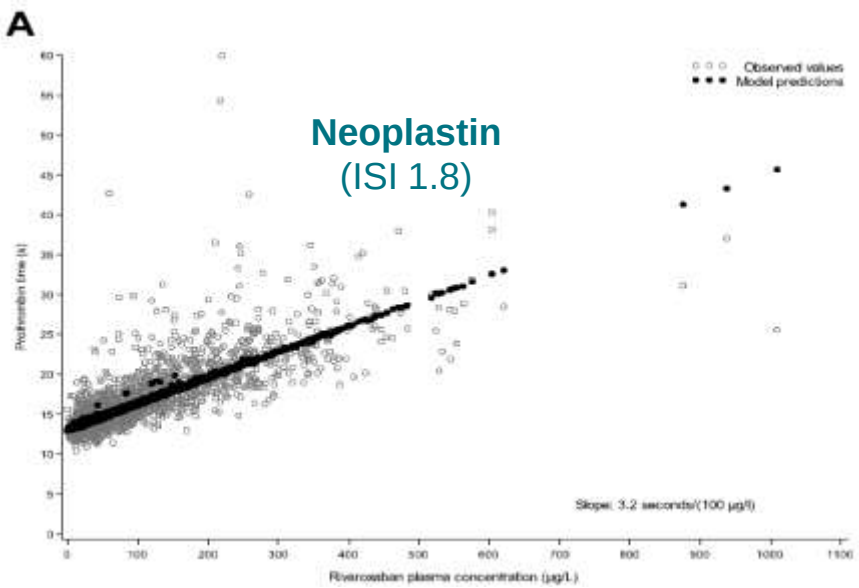
1. Hemorrhagic or thromboembolic event during treatment
2. Compliance
2. Low body weight
3. Obese patients
4. Pediatric patients
5. Renal impairment
6. Hepatic impairment
7. Overdose

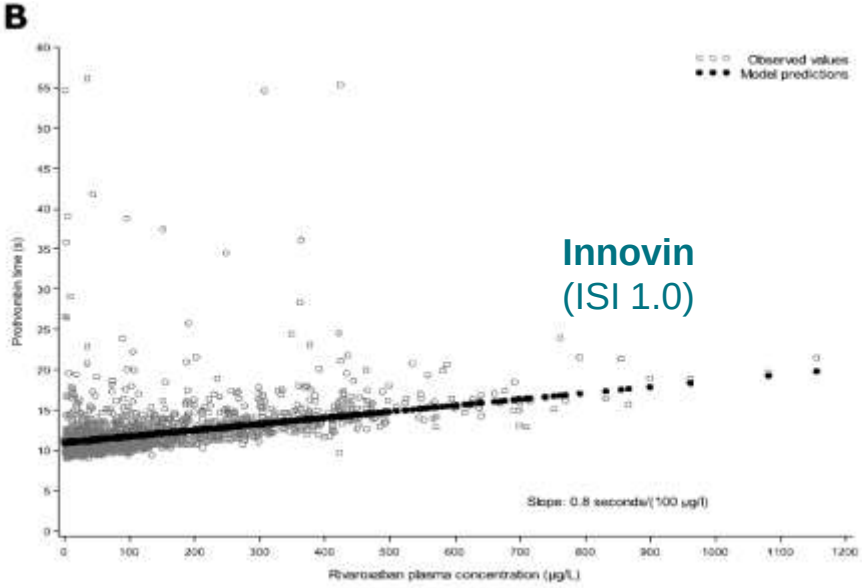
New oral anticoagulants
Therapeutic Drug Monitoring



Haas S. VASA 2009; 38: 13–29

Rivaroxaban
Therapeutic Drug Monitoring



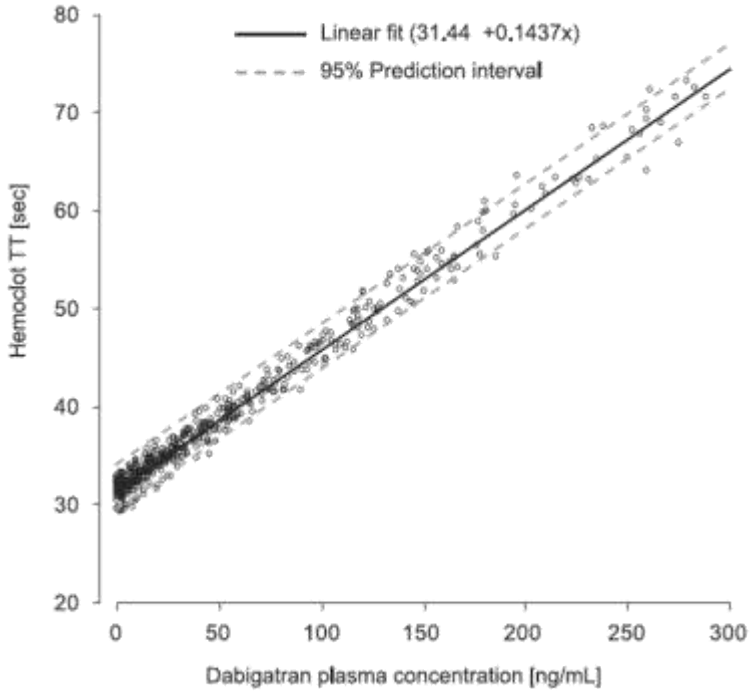


2010: change in strategy of Bayer → anti-factor Xa-activity for monitoring

Mueck W et al. Thromb Haemost 2008; 100: 453–461

Dabigatran
Accumulation in Renal Failure - TDM

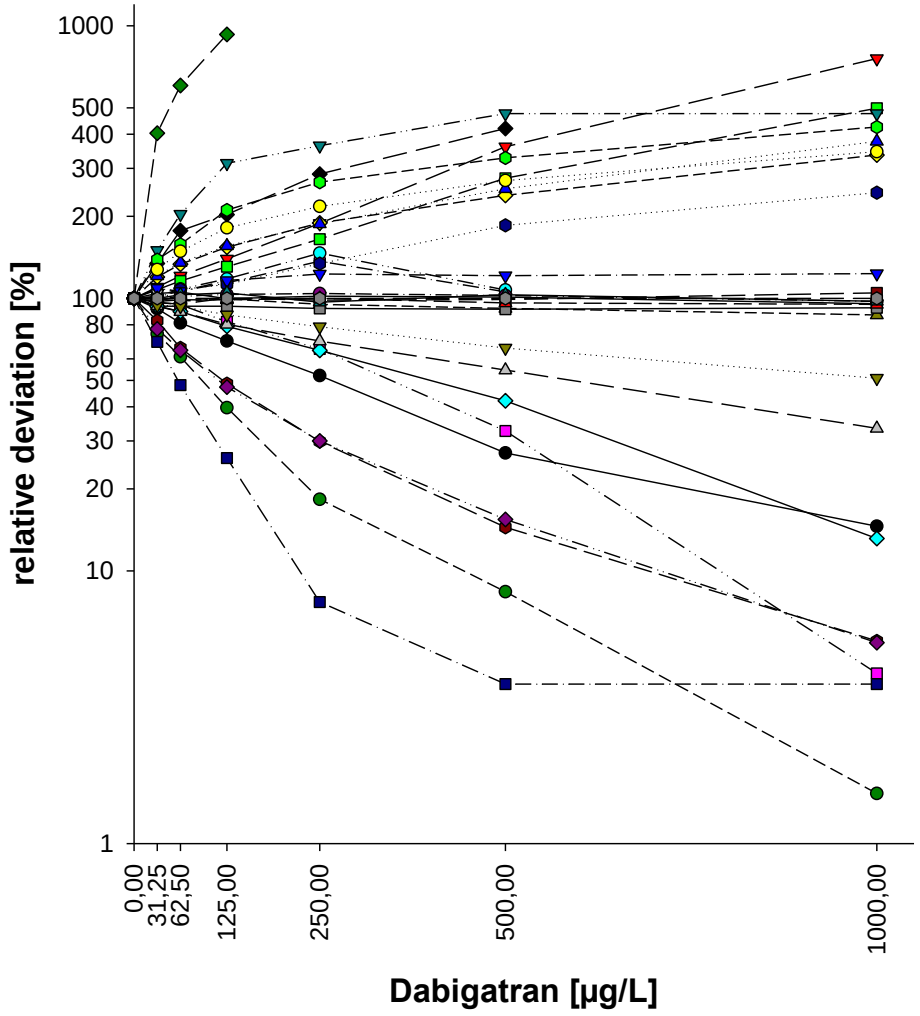
Renal function	C_{max} (ng/mL)	Ratio[a]	Maximum ECT (s)	Ratio[a]	Maximum aPTT (s)	Ratio[a]
Normal	100		55.2		47.4	
Mild impairment	140	1.4	77.4	1.40	54.2	1.14
Moderate impairment	180	1.8	108	1.95	61.9	1.31
Severe impairment	240	2.4	183	3.32	78.3	1.65



Stangier J. Clin Pharmacokinet 2008; 47 (5): 285-295

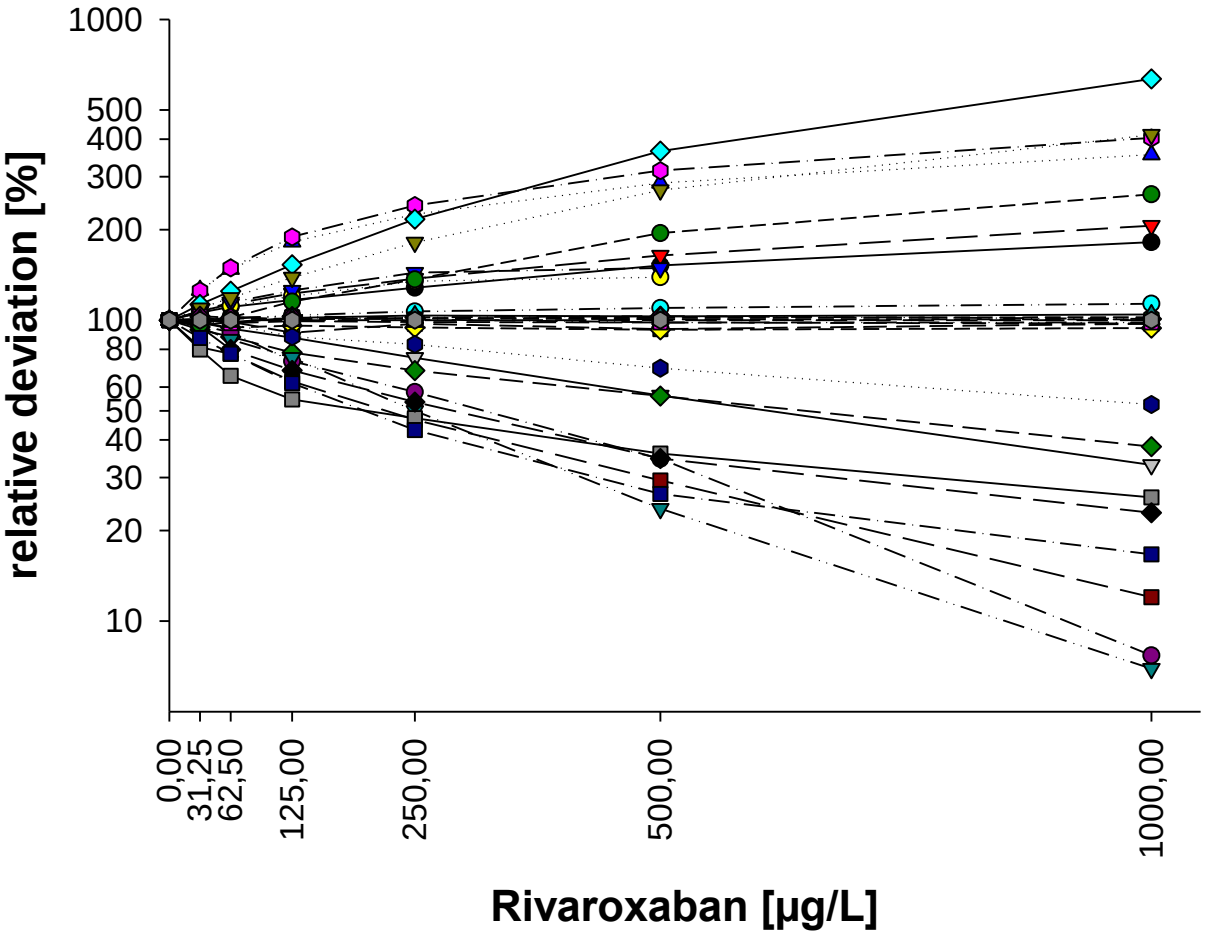
New oral anticoagulants - Dabigatran

Influence on coagulation assays



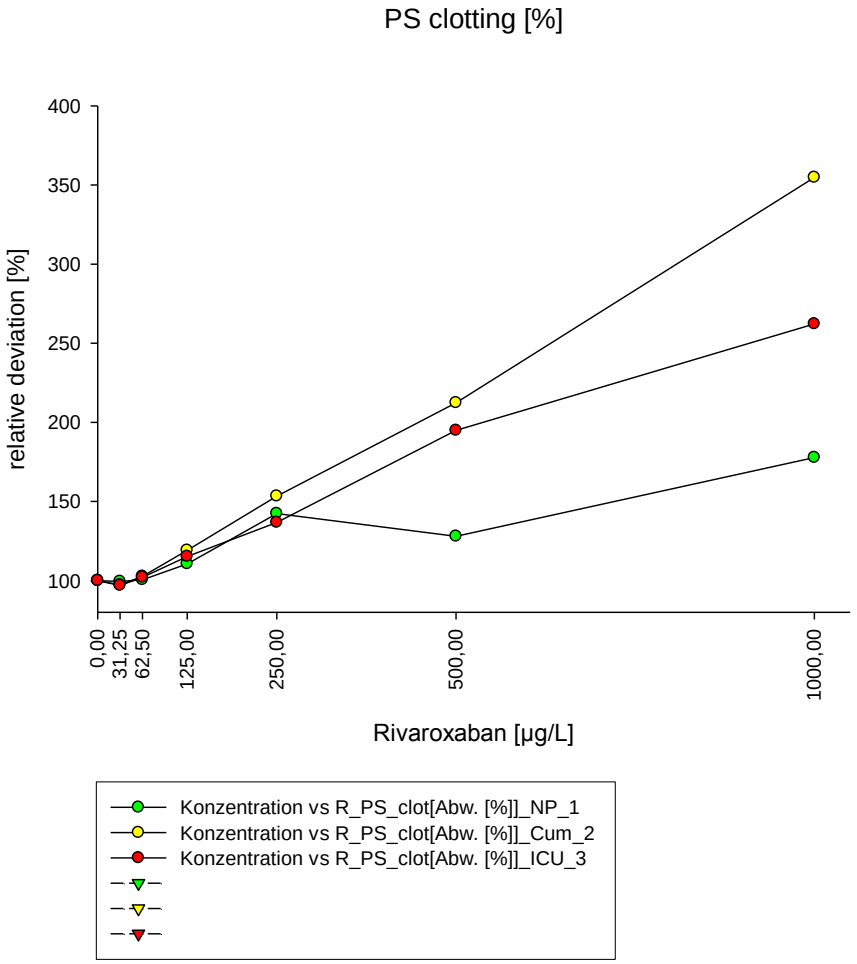
New oral anticoagulants - Rivaroxaban

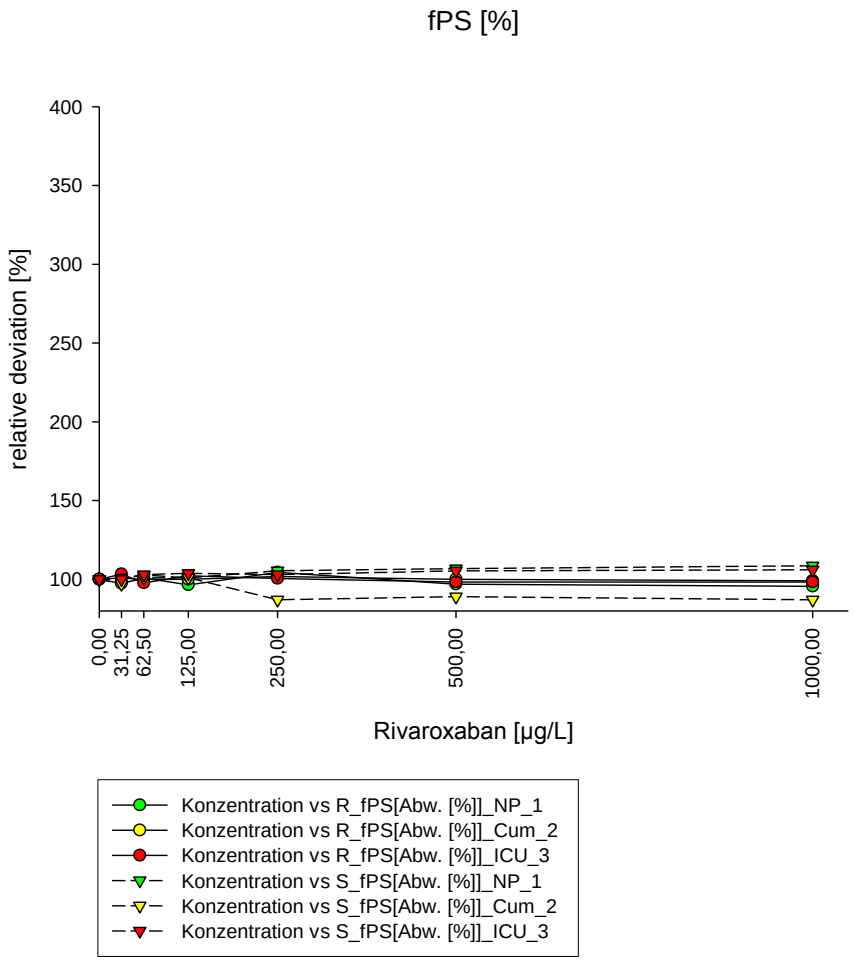
Influence on coagulation assays



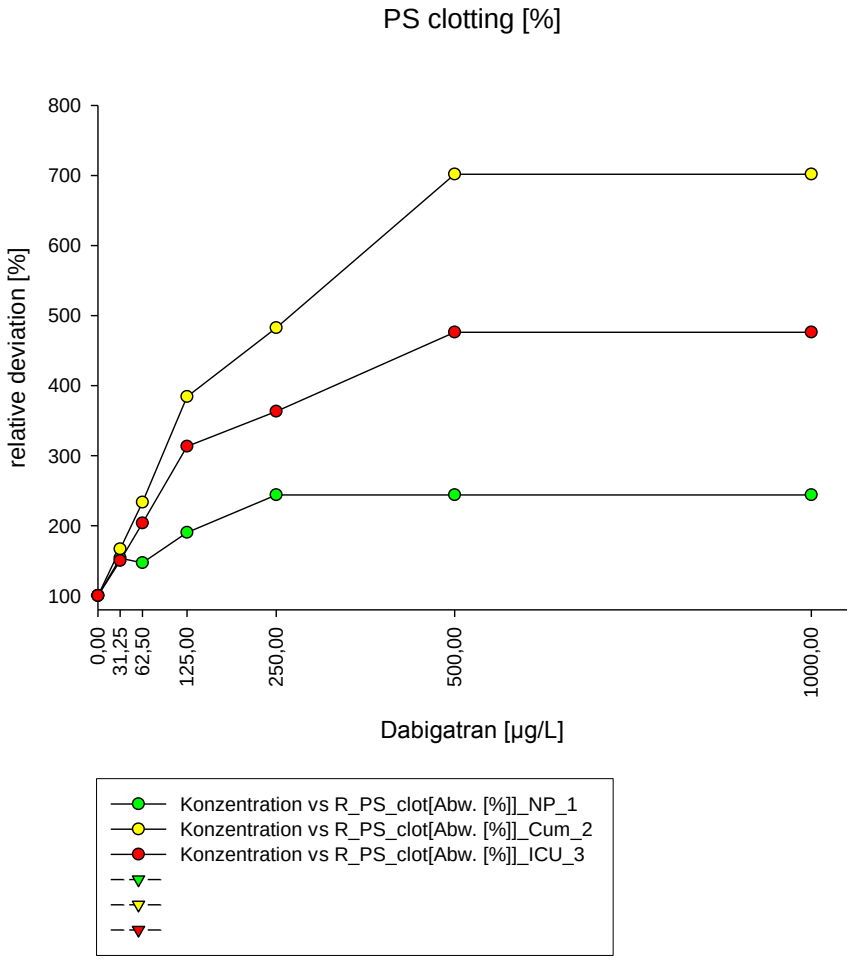
New oral anticoagulants - Rivaroxaban

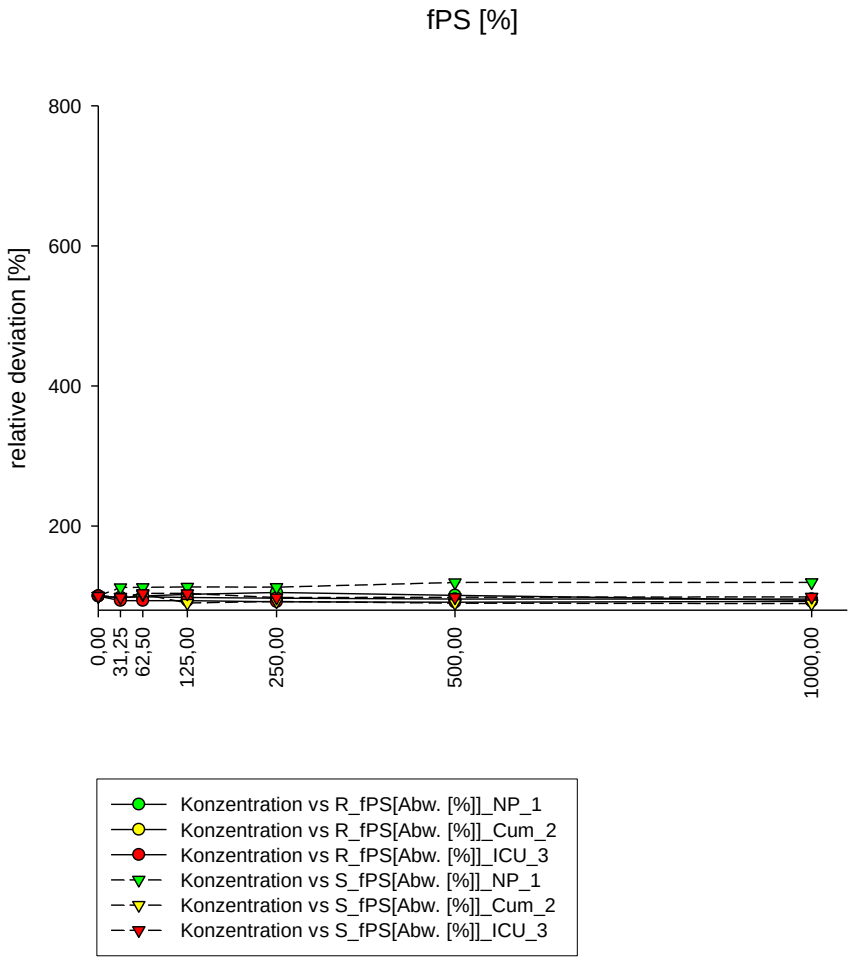
Influence on coagulation assays





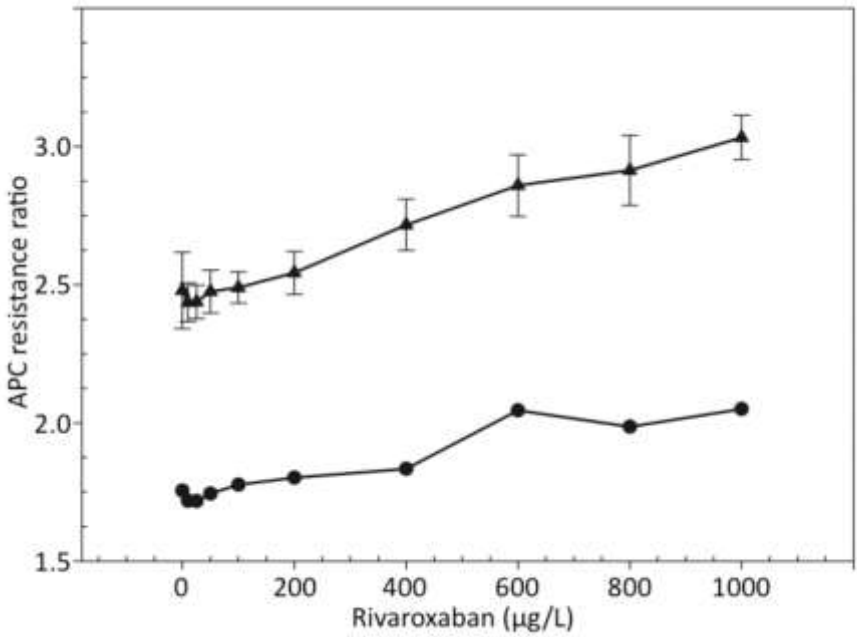
New oral anticoagulants - Dabigatran
Influence on coagulation assays



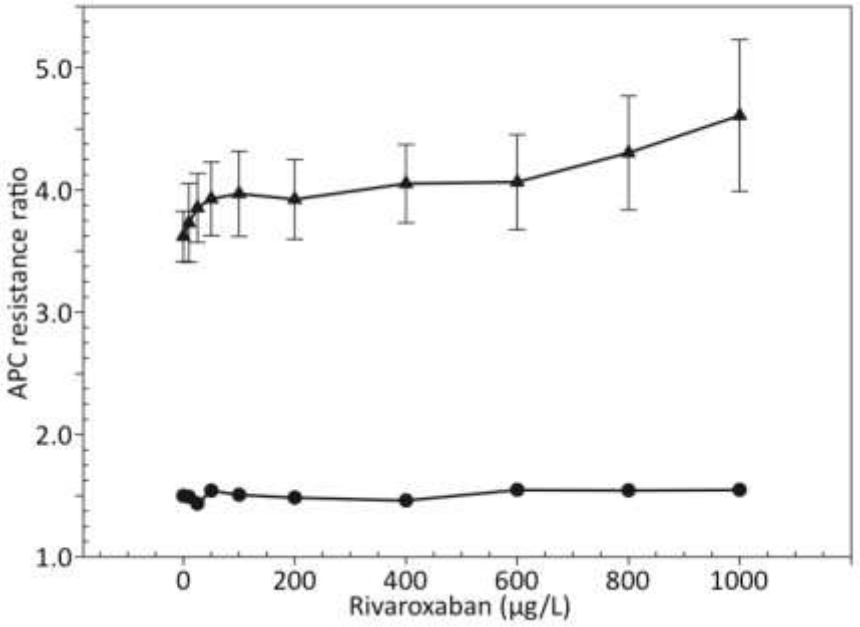


New oral anticoagulants - Rivaroxaban
Influence on coagulation assays

APTT-based assay
(Coatest APC Resistance V)



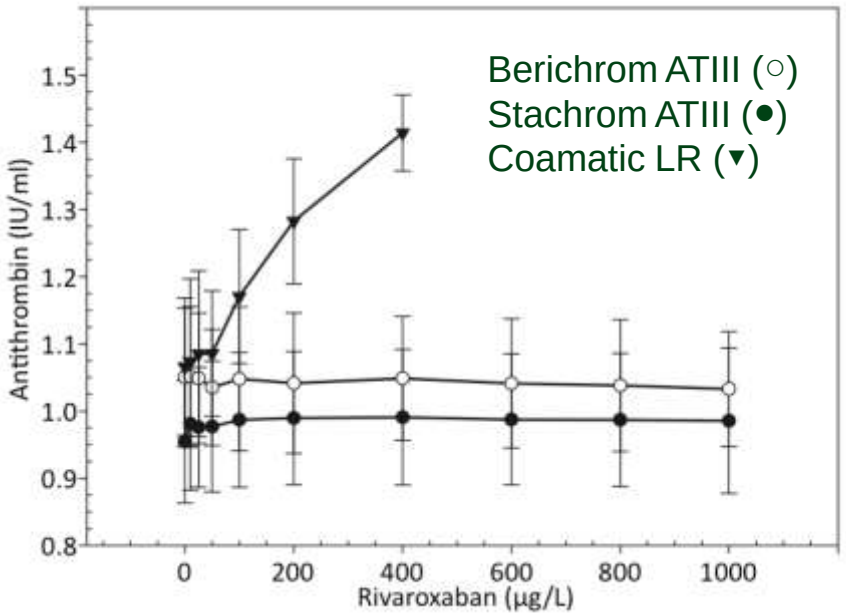
Activation at the prothrombinase level
(Pefakit APC Resistance Factor V Leiden)



Normal phenotype (▲)
APC-resistant phenotype (●).

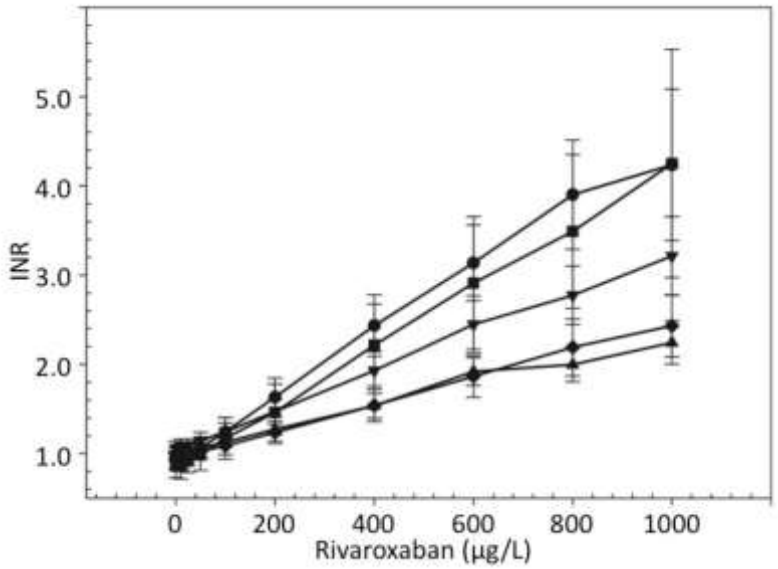
Hillarp A et al. JTH 2010 (ahead of print - doi: 10.1111/j.1538-7836.2010.04098.x

New oral anticoagulants - Rivaroxaban
Influence on coagulation assays

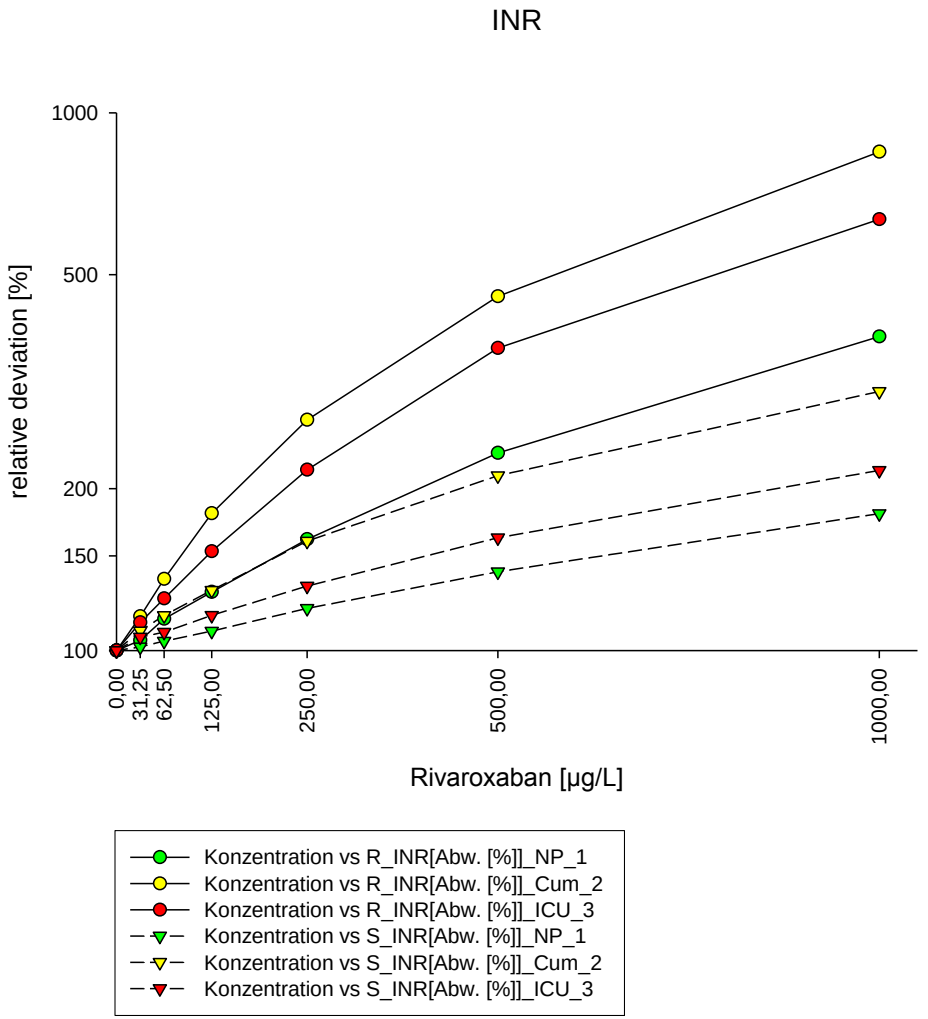


Hillarp A et al. JTH 2010 (ahead of print - doi: 10.1111/j.1538-7836.2010.04098.x

New oral anticoagulants - Rivaroxaban
Influence on coagulation assays



STA-Neoplastine (●),
RecombiPlastTin 2G (▼)
Technoplastin HIS (■)
Thromborel S (♦)
Dade Innovin (▲).



Hillarp A et al. JTH 2010 (ahead of print - doi: 10.1111/j.1538-7836.2010.04098.x

New oral anticoagulants
Influence on coagulation assays

Antikoagulans	Dosierung	PTT[4]	TPZ[4]		TZ	Fibrinogen[4]		AT		D-Dimere	vWF:Ag
			%	INR		derived	Clauss	IIa	Xa		
Argatroban (Argatra®)	Prophylaxe[2]	↑/↑↑	↓	↑↑[5]	↑↑↑	↑	↓	↔/↑	↔	↔	↔
	Therapie	↑↑	↓↓	↑↑↑[5]	↑↑↑	↑↑	↓↓	↑	↔	↔	↔
Lepirudin (Refludan®, Revasc®)	Prophylaxe[2]	↑/↑↑	↔/↓	↑[5]	↑↑↑	↔/↑	↔/↓	↔/↑	↔	↔	↔
	Therapie	↑↑	↓	↑↑[5]	↑↑↑	↑	↓	↑	↔	↔	↔
Dabigatran[1] (Pradaxa®)	Prophylaxe	↑/↑↑	↓	↑	↑↑↑	↔	↔	↔/↑		↔	↔
	Therapie[3]	↑↑	↓↓	↑↑	↑↑↑	↑	↔/↓	↑		↔	↔
Fondaparinux (Arixtra®)	Prophylaxe	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Therapie	↔/↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Rivaroxaban[1] (Xarelto®)	Prophylaxe	↔/↑	↓	↑	↔	↔/↑	↔	↔	↑	↔	↔
	Therapie[3]	↑	↓↓	↑↑	↔	↑	↔	↔		↔	↔

[1] *Ausmaß der Beeinflussung hängt von Zeitspanne zwischen Tabletteneinnahme und Blutentnahme ab; Tabellenwert entspricht Ausmaß für Peakspiegel*
[2] *keine Zulassung für Prophylaxe; Angaben für Einsatz im klinischen Alltag außerhalb der Zulassung*
[3] *bisher keine Zulassung zur Therapie thromboembolischer Ereignisse; Angaben für Einsatz außerhalb der Zulassung*
[4] *Ausmaß der Beeinflussung von PTT, TPZ und Fibrinogen hängt vom jeweils eingesetzten Reagenz ab*
[5] *INR-Beeinflussung unter gleichzeitiger Vit. K-Antagonisten-Therapie deutlich stärker ausgeprägt*

New oral anticoagulants
Influence on coagulation assays

Antikoagulans	Dosierung	PTT[4]	TPZ[4]		TZ	Fibrinogen[4]		AT		D-Dimere	vWF:Ag
			%	INR		derived	Clauss	IIa	Xa		
Dabigatran[1] (Pradaxa®)	Prophylaxe	↑/↑↑	↓	↑	↑↑↑	↔	↔	↔/↑		↔	↔
	Therapie[3]	↑↑	↓↓	↑↑	↑↑↑	↑	↔/↓	↑		↔	↔
Rivaroxaban[1] (Xarelto®)	Prophylaxe	↔/↑	↓	↑	↔	↔/↑	↔	↔	↑	↔	↔
	Therapie[3]	↑	↓↓	↑↑	↔	↑	↔	↔		↔	↔

Antikoagulans	Dosierung	Einzelfaktoren (clotting)[4]								Faktor XIII	
		II	V	VII	VIII	IX	X	XI	XII	chromo	immun
Dabigatran[1] (Pradaxa®)	Prophylaxe	↔	↓	↔/↓	↓↓	↓↓	↔/↓	↓↓	↓↓	↓	↔
	Therapie[3]	↔/↓	↓↓	↓	↓↓↓	↓↓↓	↓	↓↓↓	↓↓/↓↓↓	↓↓↓	↔
Rivaroxaban[1] (Xarelto®)	Prophylaxe	↔	↔/↓	↔/↓	↓	↓/↓↓	↔/↓	↓	↓	↔	↔
	Therapie[3]	↓	↓↓	↓↓	↓↓	↓↓/↓↓↓	↓/↓↓	↓↓/↓↓↓	↓↓	↔	↔

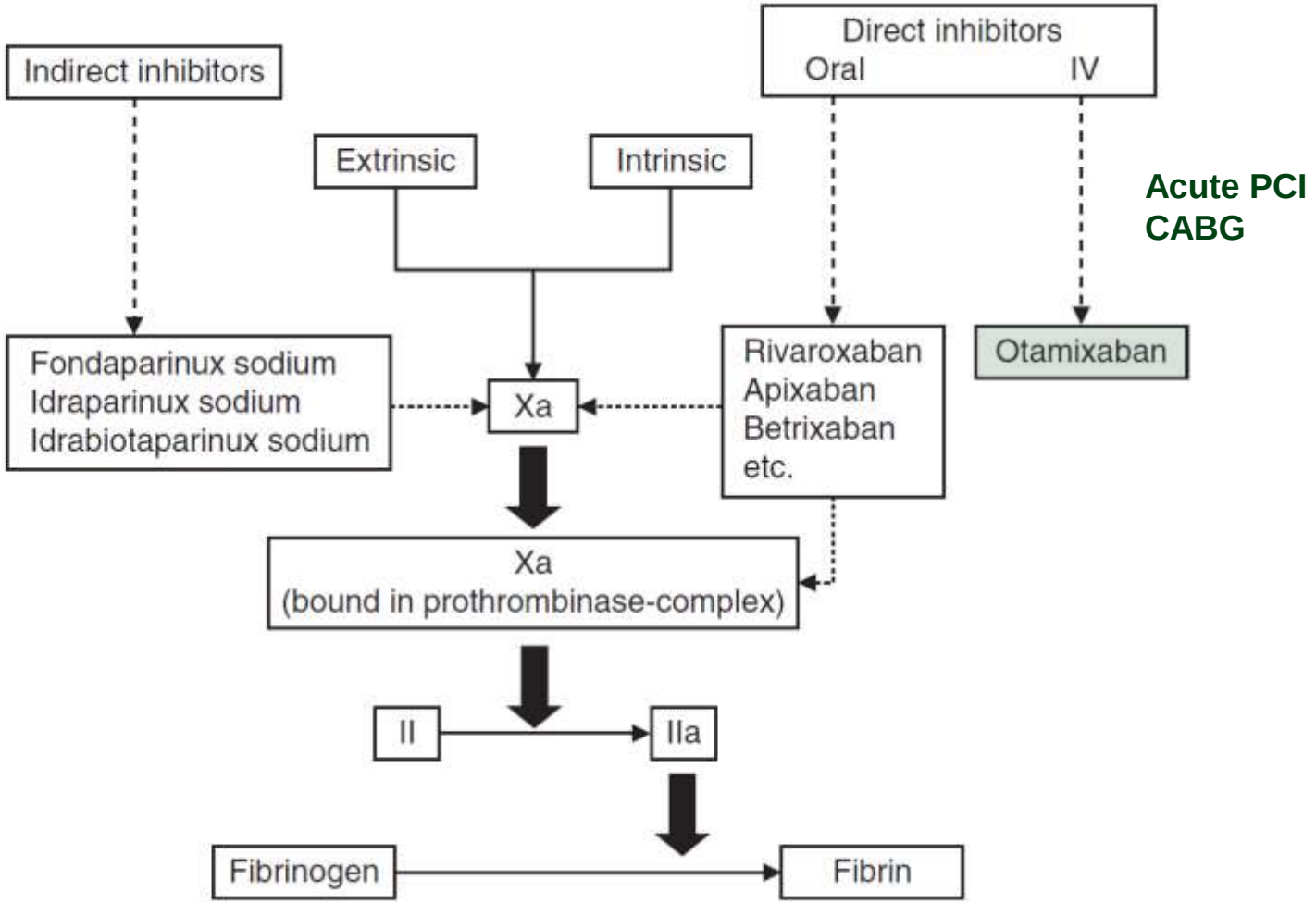
[1] *Ausmaß der Beeinflussung hängt von Zeitspanne zwischen Tabletteneinnahme und Blutentnahme ab; Tabellenwert entspricht Ausmaß für Peakspiegel*

[3] *bisher keine Zulassung zur Therapie thromboembolischer Ereignisse; Angaben für Einsatz außerhalb der Zulassung*

[4] *Ausmaß der Beeinflussung von PTT, TPZ und Fibrinogen hängt vom jeweils eingesetzten Reagenz ab*

[4] *Ausmaß der Beeinflussung der Einzelfaktorenbestimmung abhängig vom jeweils eingesetzten PTT-Reagenz (Faktor VIII, IX, XI, XII) bzw. Thromboplastin (Faktor II, V, VII, X)*

New oral anticoagulants
Need for monitoring



Desired tests
Conclusions

- **Monitoring**

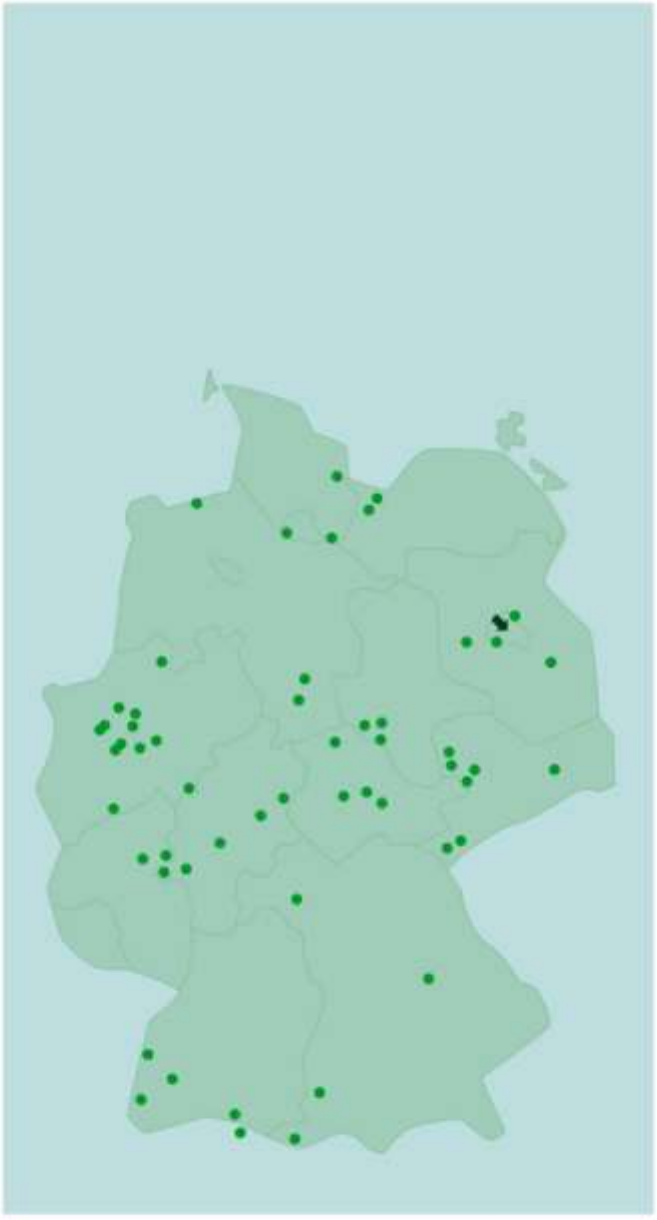
  Real drug levels:
  → HPLC-MS/MS *- in future: easy and cheap (?)*
  → chromogenic assays

  Real in-vivo effect:
  → impossible *(?)*
  → surrogate markers

- **Coagulation disorders**

  Real factor levels:
  → immunoassays
  → chromogenic assays

  Real activity in-vivo:
  → coagulation assays resembling in-vivo situation



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Thanks for your attention!

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