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GLOBAL EXPERTS, LOCAL LEARNING

ACC Latin America Conference 2017

Arrhythmias and Clinical EP

Contemporary Management of Anticoagulant Therapies

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Saturday, June 24, 2017

11:15 a.m. to 12 p.m.

Disclosures

Relevant financial relationship(s) with industry

- I receive royalties for work licensed through Mayo Clinic to a privately held company for contributions related to the use of nerve signal modulation to treat central, autonomic and peripheral nervous system disorders, including pain. Mayo Clinic receives royalties and owns equity in this company. The company does not currently license or manufacture any drug or device in the medical field.
- Co-patent holder for technique to minimize coagulum formation during radiofrequency ablation
- Products or techniques related to the above disclosures are not being discussed in this presentation
- Pertains to inventions/startup companies that include Nevro, Aegis and the Phoenix Corp

Honoraria/Speakers

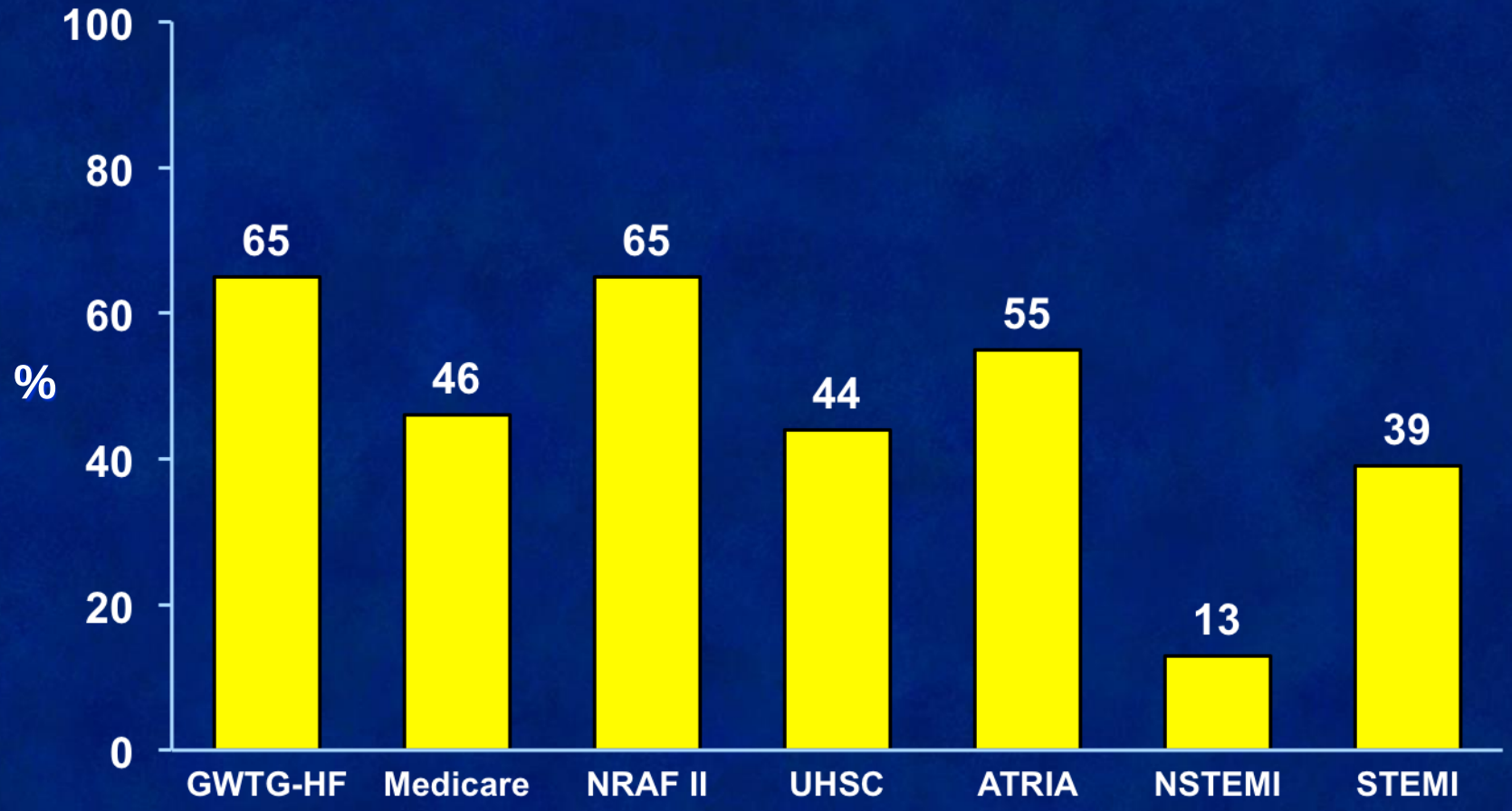
- Abiomed, Atricure, Biotronik, Blackwell Futura, Boston Scientific, Medtronic, Medtelligence Sanofi-aventis, Spectranetics, St. Jude, Zoll

Consulting

- Aegis, ATP, Nevro, Sanovas, Sorin Medical, FocusStart

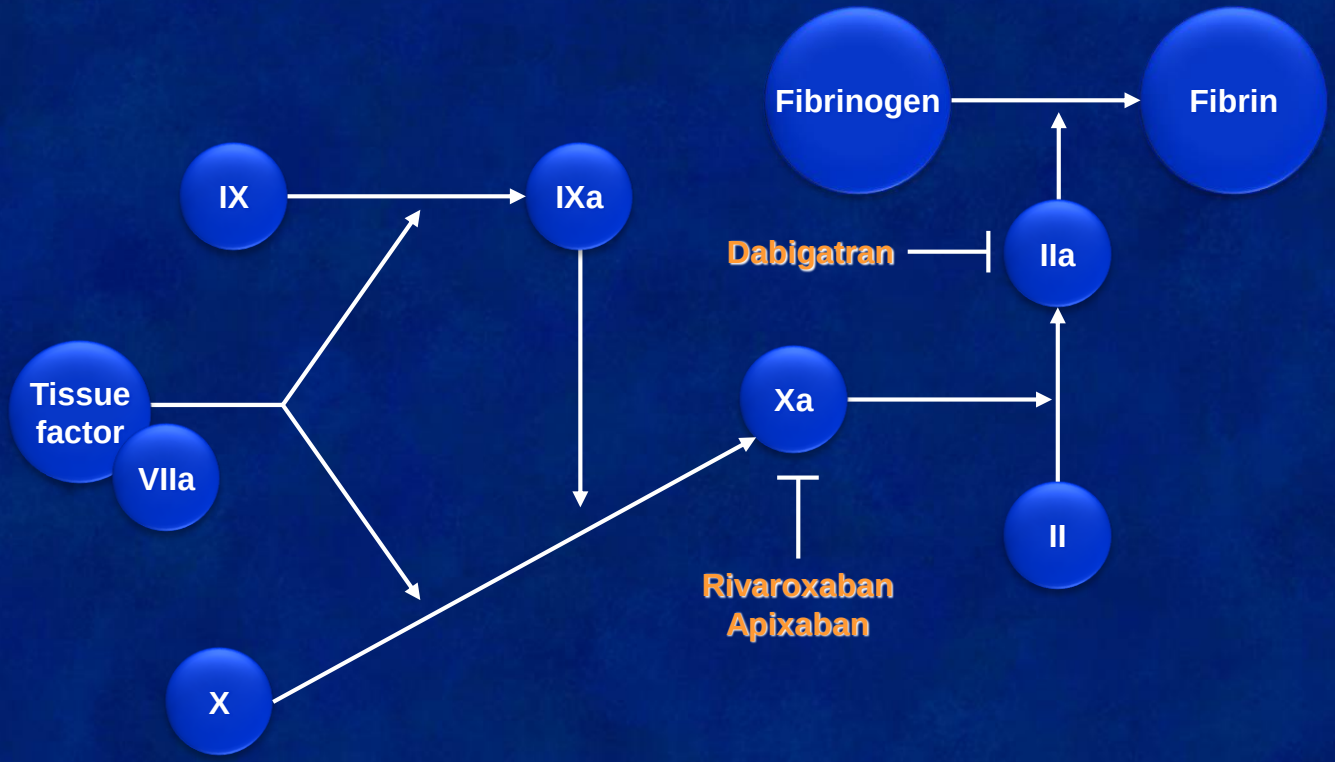
Warfarin Use in AF Patients With an Indication

How are We Doing in Practice?



Piccini et al: Curr Opin Cardiol 25:312, 2010

Targets in Anticoagulation Cascade for Novel Anticoagulants



Cove/Hylek: J Am Heart Assoc 2013:e000136 DOI: 10.1161/JAHA. 113.000136

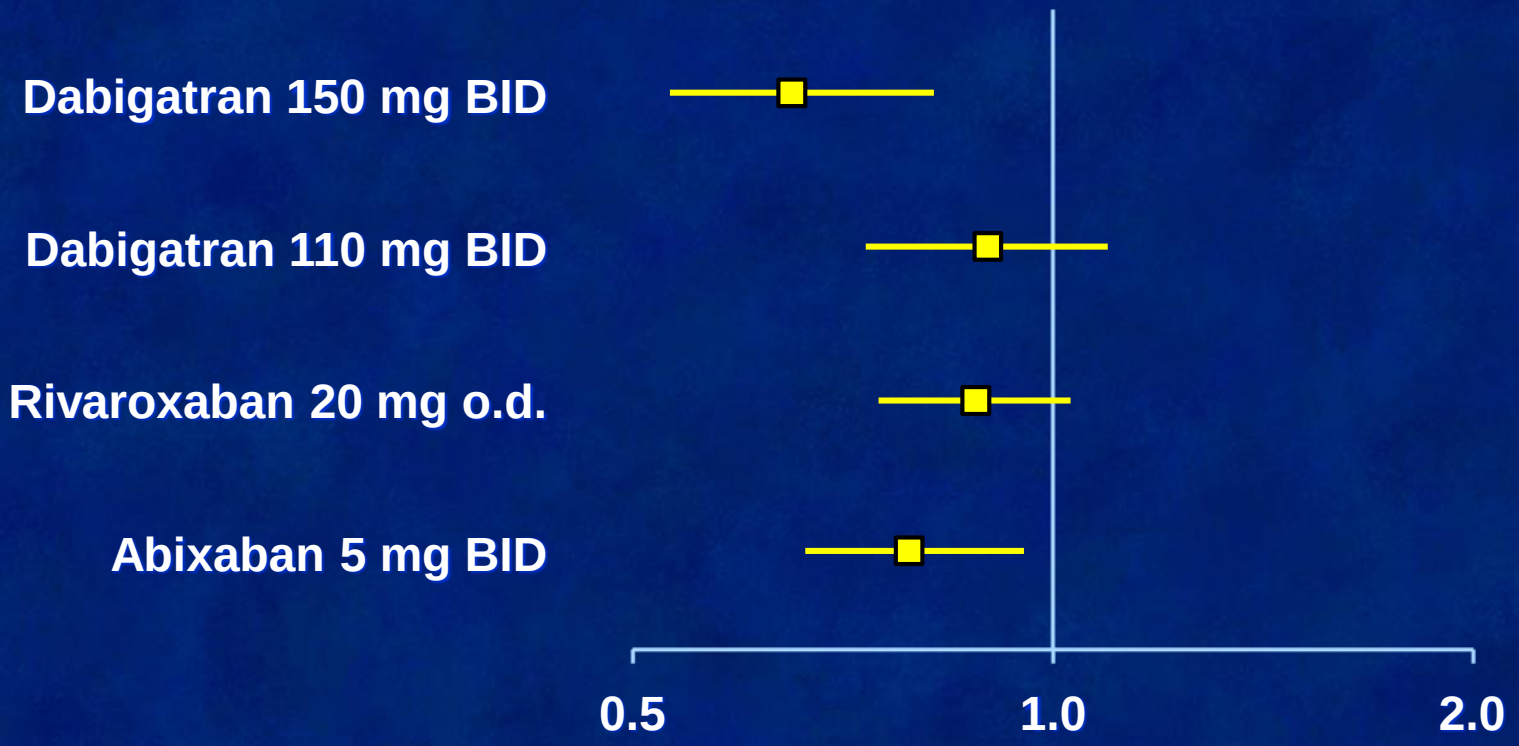
Phase III AF Trials

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose (mg) freq	150, 110 BID	20 (15*) QD	5 (2.5*) BID	60*, 30* QD
No.	18,113	14,266	18,206	>21,000
Design	PROBE	2 x blind	2 x blind	2 x blind
AF criteria	AF x 1 <6 mo	AF x 2 (≥1 in <30d)	AF or AFl x 2 <12 mo.	AF x 1 <12 mo.
VKA naïve (%)	50	38	43	Goal 40

*Dose adjusted in pt with ↓drug clearance: **Max of 10% with $CHADS_2$ score = 2 and no stroke/TIA/SEE: PROBE = prospective, randomized, open-label, blinded end point evaluation: VKA = vitamin K antagonist

New Anticoagulant Therapies Compared to Warfarin

Stroke or Systemic Embolism



Connolly et al: NEJM 2009; Patel et al:NEJM, 2011; Granger et al: NEJM, 2011

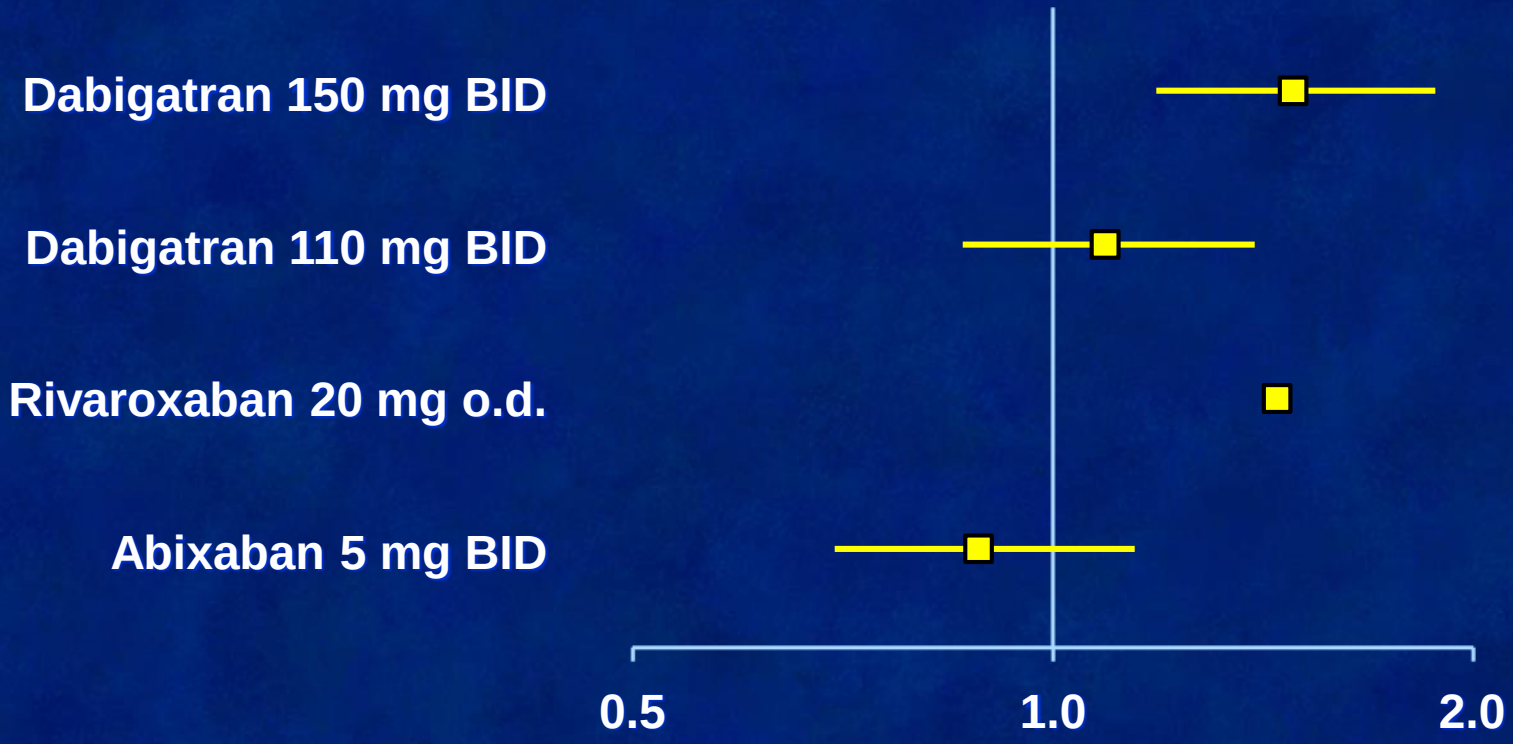
Intracerebral Hemorrhage
The Worst Complication of Antithrombotic Therapy

- >10% of intracerebral hemorrhages (ICH) occur in patients on antithrombotic therapy
- Aspirin increases the risk by ~40%
- Warfarin (INR 2-3) *doubles* the risk to 0.3-0.6%/year
- ICH during anticoagulation is catastrophic (~50% mortality in most studies)
- In anticoagulated patients with AF, concomitant antiplatelet therapy is the most important modifiable independent risk factor for ICH

Hart RG et al: Stroke 36:1588, 2005
Hart RG et al: Stroke 43:1511, 2012

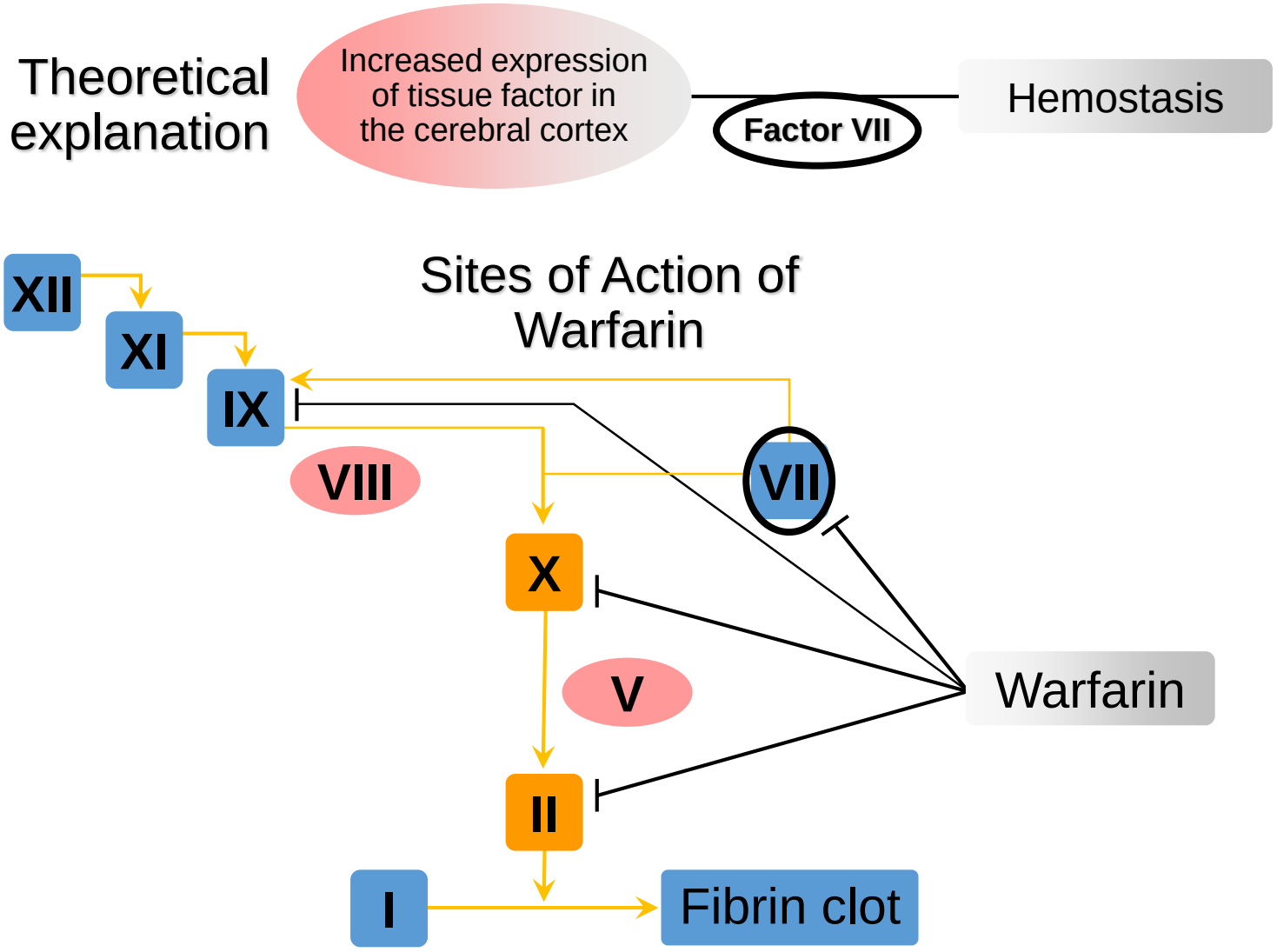
New Anticoagulant Therapies Compared to Warfarin

Gastrointestinal Bleeding



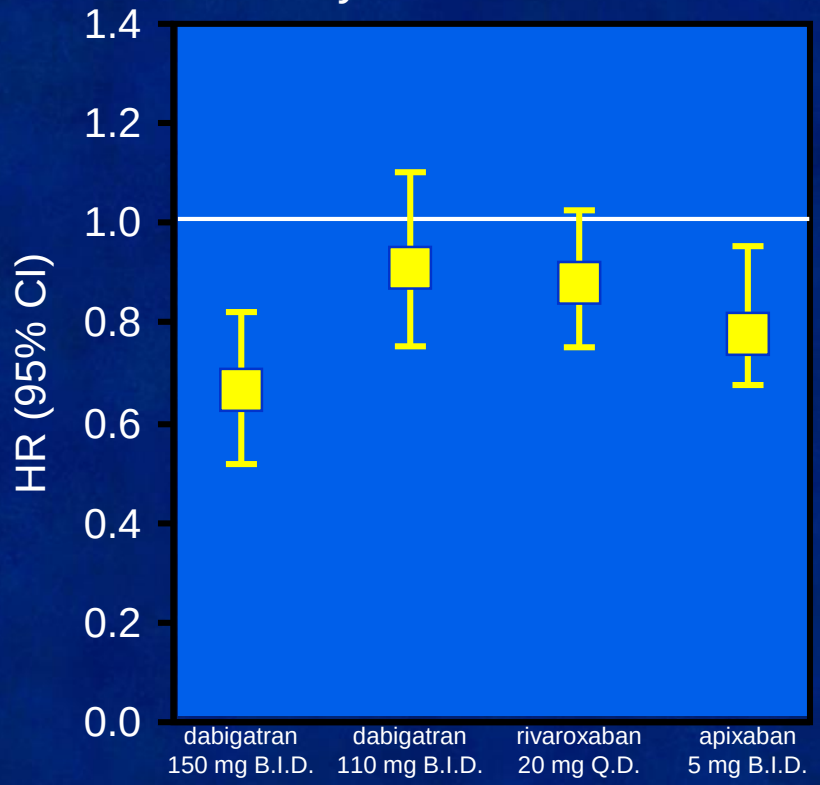
Connolly et al: NEJM 2009; Patel et al:NEJM, 2011; Granger et al: NEJM, 2011

Does Warfarin Predispose to Bleeding

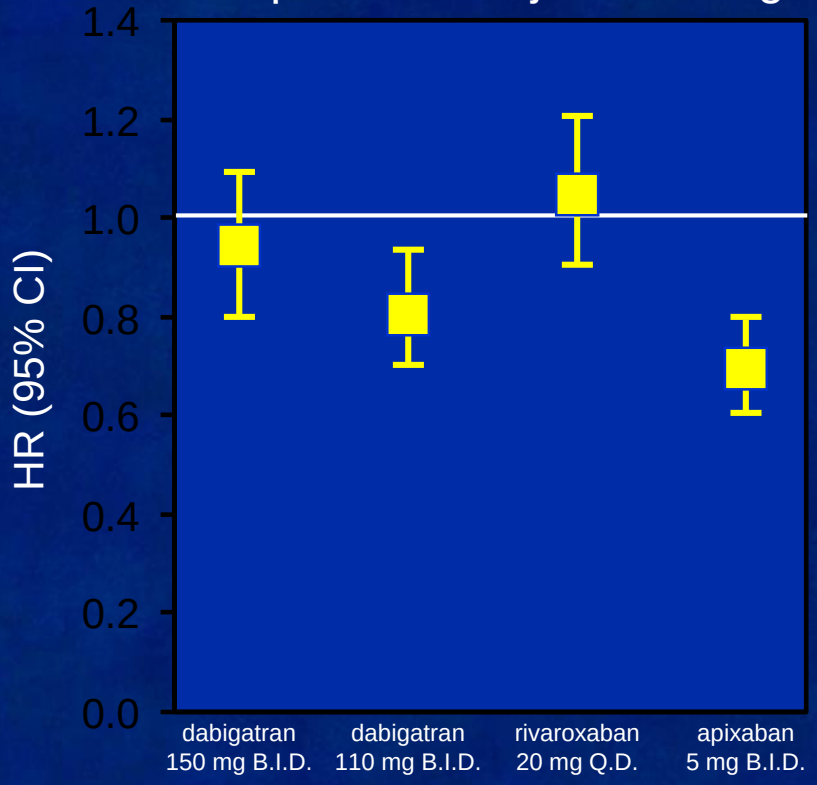


Indirect Comparison of Efficacy and Safety

Comparable Primary Efficacy Endpoints on Stroke or Systemic Embolism



Comparable Primary Safety Endpoints of Major Bleeding



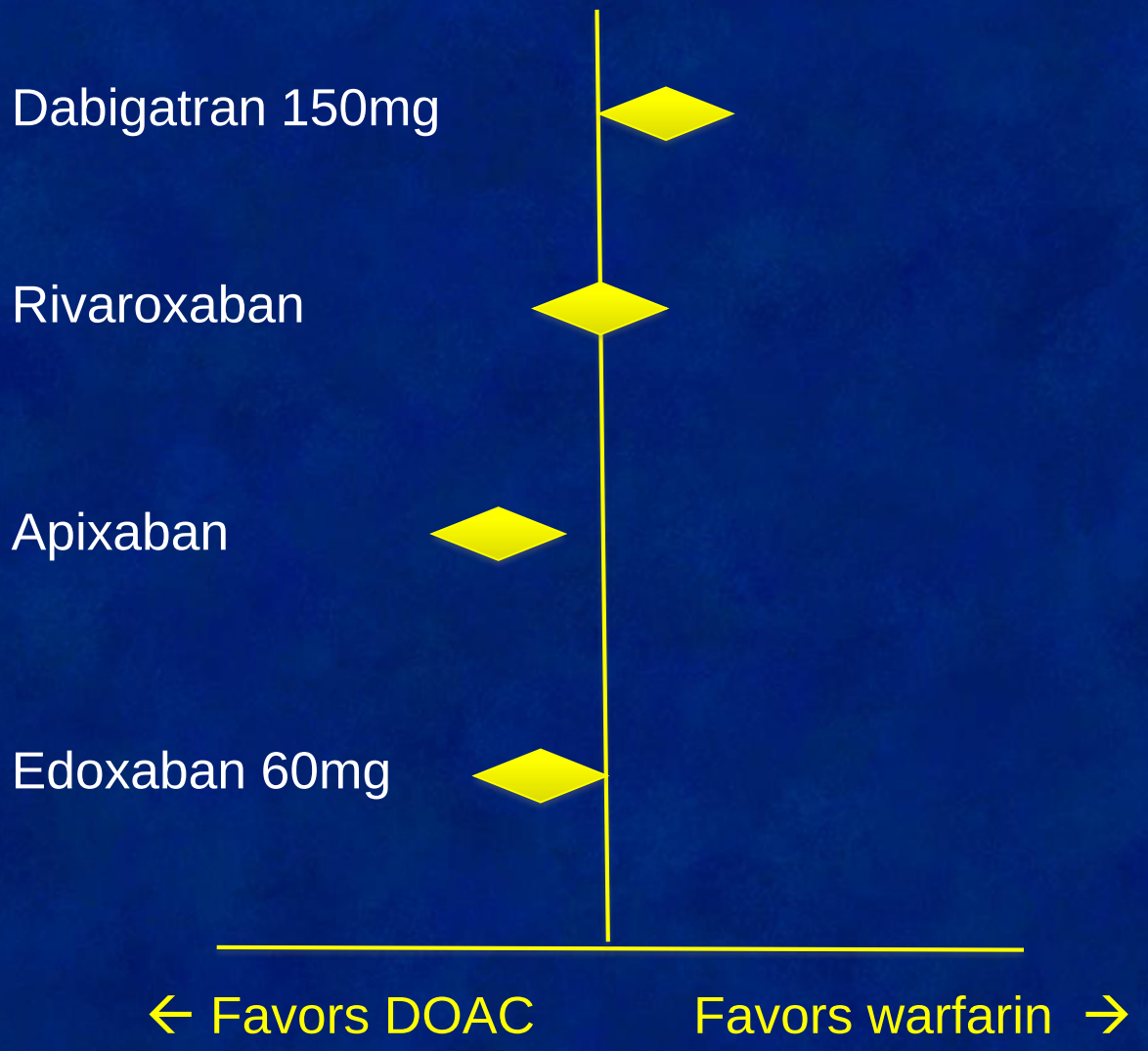
De Caterina, JACC 2012

Which Agent?

- Largest RRR of ischemic stroke: **dabigatran**
- Largest renal elimination: **dabigatran**
- One daily dosing: **rivaroxaban / edoxaban**
- Well established dosing for high risk patients with modest renal insufficiency: **rivaroxaban**
- Single dose with reduction in stroke and reduction in major bleeding: **apixaban**
- Least expensive: **warfarin**

Risk of major bleeding in the elderly

: meta-analysis of all major RCTs



Manuj Sharma et al. Circulation. 2015

Renal Function and Dabigatran

Estimated Pharmacokinetic Parameters of Dabigatran by Renal Function

Renal function	CrCl mL/min	Increase in AUC	Increase in C_{max}	$T_{1/2}$ hr
Normal	80	1x	1x	13
Mild	50	1.5x	1.1x	15
Moderate	30	3.2x	1.7x	18

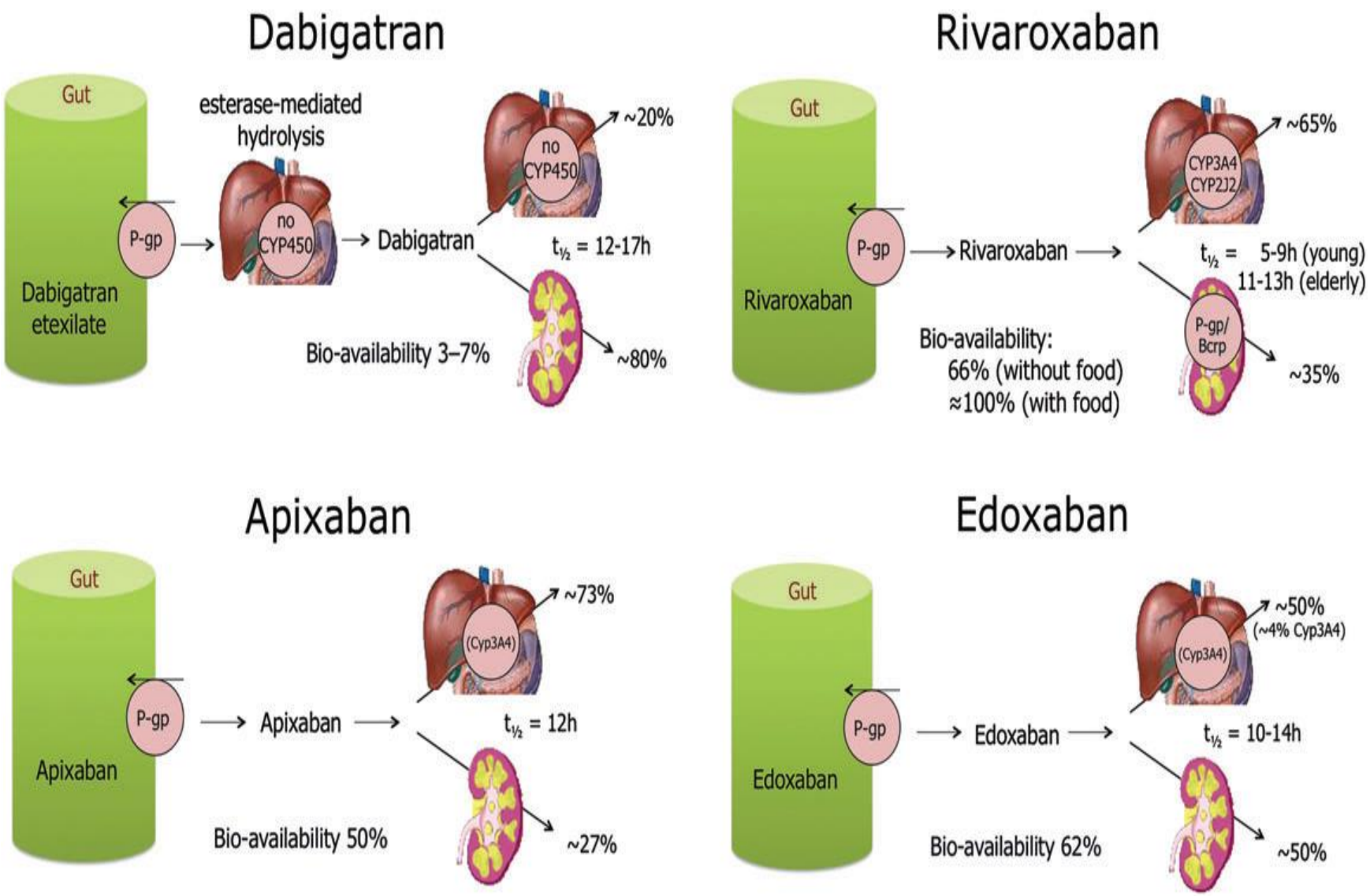
Dabigatran FDA package insert

Renal Function and Novel Drugs

- RE-LY, ROCKET excluded patients with eGFR<30, ARISTOTLE eGFR <25
- Dabigatran is 80% renally eliminated; riva, apixaban and edoxaban are around 30%
- Renal impairment is independent risk factor for stroke, for bleeding, for death
- 150 mg bid of dabigatran should be used cautiously in elderly (>80 y/o) and with renal impairment (< ~40 ml/min)
- Riva should be used at 15 mg/d with CrCL <50
- Apixaban should be used at 2.5 mg

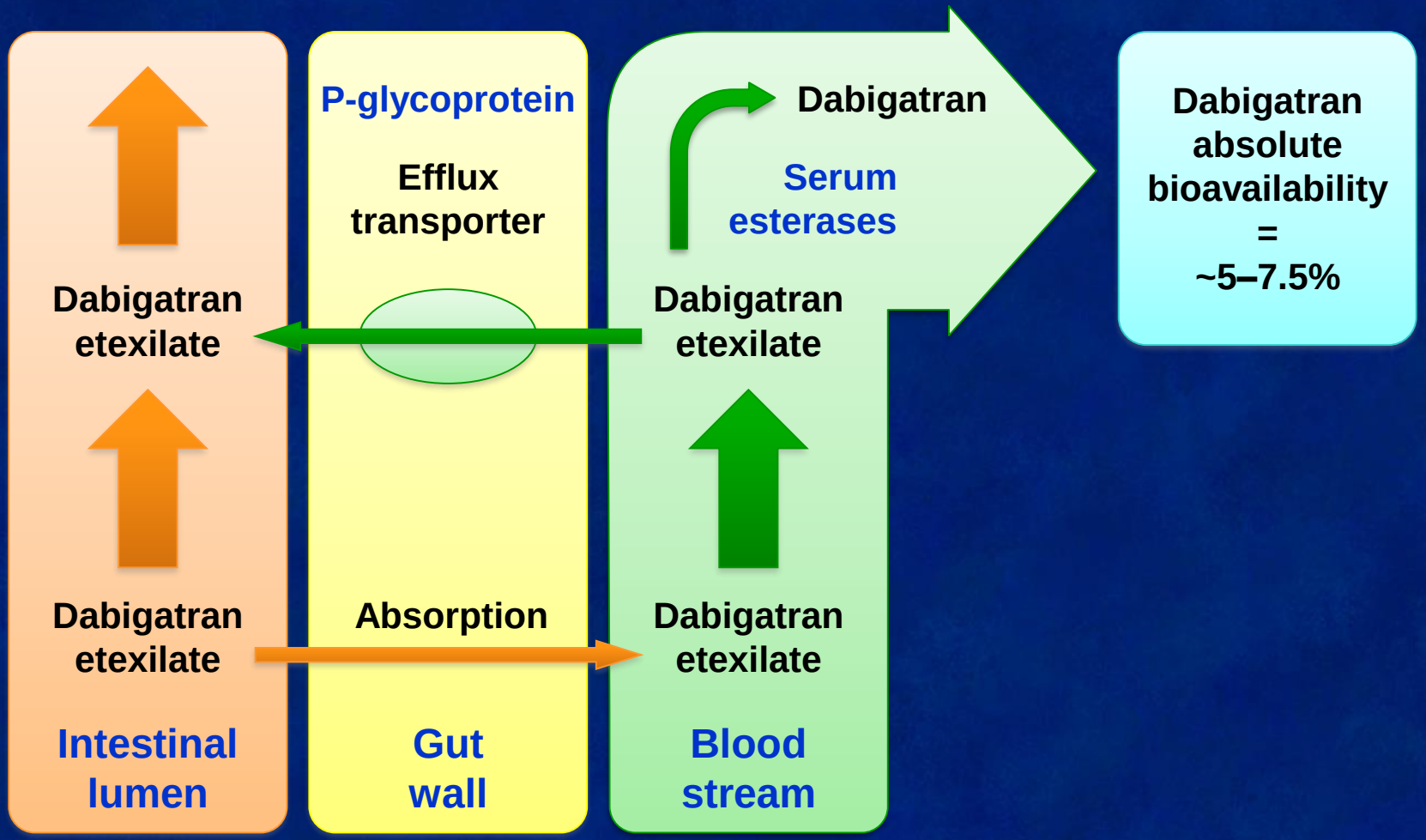
Recommendations	Class	Level
Where dabigatran is prescribed, a dose of 150 mg bid should be considered for most patients in preference to 110 mg bid with the latter dose recommended in •Elderly patients, age ≥80 •Concomitant use of interacting drugs (eg verapamil) •High bleeding risk (HAS-BLED score ≥3) •Moderate renal impairment (CrCl 30-49 mL/min)	IIa	B
Where rivaroxaban is being considered, a dose of 20 mg od should be considered for most patients in reference to 15 mg o.d. with the latter dose recommended in •High bleeding risk (HAS-BLED score ≥3) •Moderate renal impairment (CrCl 30-49 mL/min)	IIa	C
Baseline and subsequent regular assessment of renal function by (CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2-3 times per year	IIa	B
NOACs (dabigatran, rivaroxaban and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min)	III	A

EHJ 33:2719, 2012



Heidbuchel et al Europace (2015) 17, 1467–1507

Dabigatran as P-glycoprotein Substrate



Effect on NOAC Plasma Levels from D-D Interactions and Recommendations

	Via	Dabigatran (%)	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp weak CYP3A4	+18	No data	No effect	No effect
Digoxin	P-gp	No effect	No data	No effect	No effect
Verapamil	P-gp weak CYP3A4	+12-180 reduce dose take together	No data	+53 (SR) reduce dose	minor effect use with caution if CrCL: 15-50 ml/min
Diltiazem	P-gp weak CYP3A4	No effect	+40	No data	minor effect use with caution if CrCL: 15-50 ml/min
Quinidine	P-gp	+50	No data	+80 reduce dose	+50
Amiodarone	P-gp	+12-60	No data	No effect	minor effect use with caution if CrCL: 15-50 ml/min
Dronedarone	P-gp weak CYP3A4	+70-100	No data	+88 reduce dose	No data yet

Not recommended/contraindicated | Reduce dose if 2 factors or more | Reduce dose | No data yet

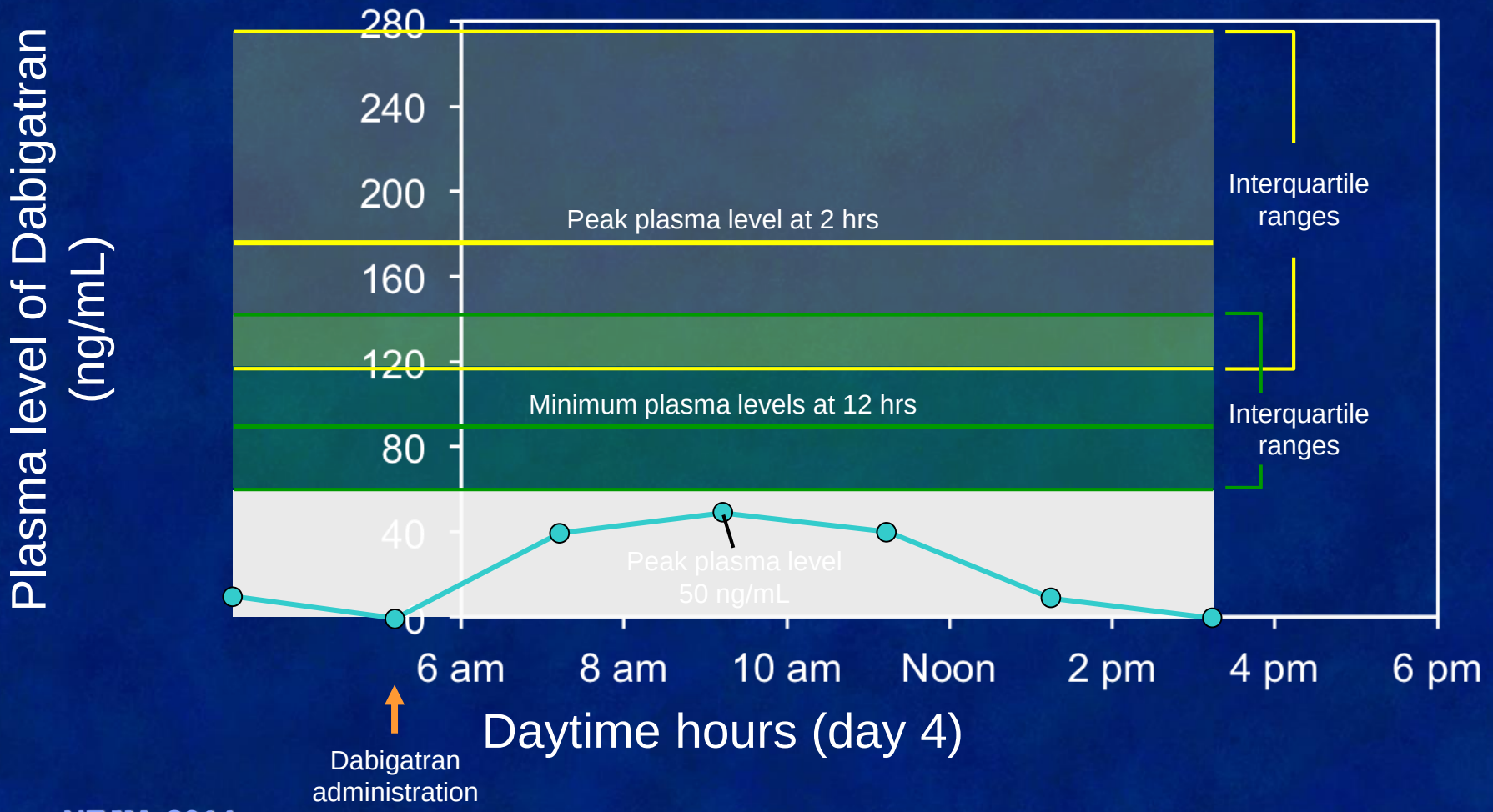
Heidbuchel et al: Europace, 2013 (in press)

Transitioning Between Anticoagulants

From warfarin to DOAC

Apixaban	Rivaroxaban	Dabigatran
Stop warfarin & start apixaban when INR <2	Stop warfarin & start rivaroxaban when INR <3	Stop warfarin & start dabigatran when INR <2

Ischemic Stroke in an Obese Patient Receiving Dabigatran



Breuer: NEJM, 2014

How to Monitor

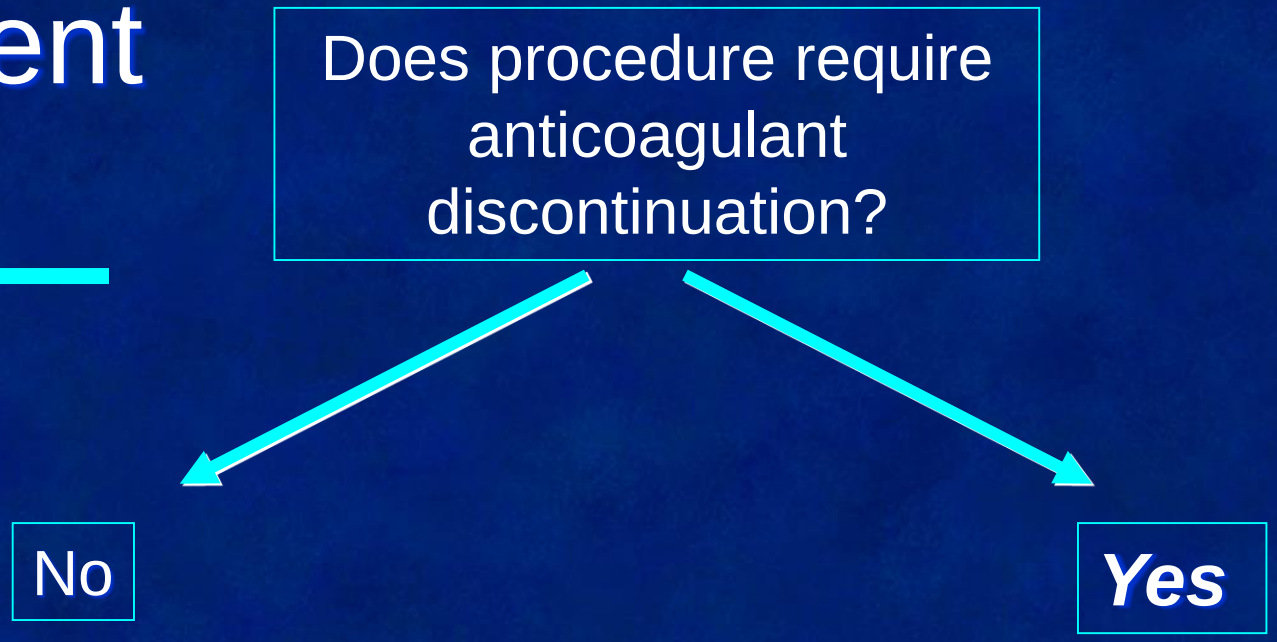
- Dabigatran
  - dTT
  - Ect
- Xa Inhibitors
  - Measurement of levels
    - Anti-Xa activity – STA-Rotachrom, Biochem
  - PT and aPTT prolonged

Managing Bleeding

- Novel OACs have less fatal bleeding than warfarin
- No specific antidote
  - Idarucizumab
  - Apirazine
- ***Not*** dialyzable
  Protamine and Vitamin K does ***not*** reverse
- Prothrombin complex concentrates reverse ± 30-50%

Levi et al: 2013; Mehta et al: 2012

Management Decisions



Mayo Approach:
Until we have more experience, we suggest ***discontinuation of direct factor inhibitors*** prior to ***most invasive procedures***.

In Which Patients is Warfarin Preferred ?

- Mechanical valves
- LV thrombi
- Rheumatic mitral valve disease

Pt with severe renal impairment (CrCl <30 mL/min)

Stable INR and no bleeding

Easy access to anticoagulation clinic
and home INR monitoring

Noncompliant pt
- INR as a monitoring tool
- Adherence to bid dosing?

Drug costs
- Uncovered pt
- Need for societal economic analyses

Good Candidates for New Oral A/C

Patients unwilling to take Warfarin after thorough discussion

New patients naïve to Warfarin

- Age <75 yrs
- Compliant
- Preserved renal function

Compliant pts with unstable INR on Warfarin

Patients not taking Dronedarone, Amiodarone, Verapmil, Quinidine

Non-compliance is not an indication

Conclusions

- Compared to warfarin, the novel oral anticoagulants are at least as good at preventing stroke, have half the rate of ICH, have 10% lower mortality, and are easier to use

- But many practical issues are important in their safe use, including
  - Adjusting for renal dysfunction
  - Understanding how to measure their effect
  - Understanding how to manage procedures
  - Understanding how to manage bleeding
  - Avoiding aspirin without clear indication

- Having protocols in place to guide rational use of the novel drugs is a high priority