The Role of Oral Anticoagulants in Atrial Fibrillation: What You Need to Know Now

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Outline

- Atrial Fibrillation Overview
- Overview of New Oral Anticoagulants (OACs)
- Case Presentations
- New Anticoagulants on Horizon

Atrial Fibrillation Burden

- 1.5-2% of the developed population has atrial fibrillation (afib)
- Increased mortality
- 5-fold increase in stroke risk
- 3-fold increase in congestive heart failure

Stroke Risk Stratification

- $CHADS_2$
- CHA_2DS_2-VASC

The CHA_2DS_2VASc Index

Stroke Risk Score for Atrial Fibrillation

	Weight (points)
Congestive heart failure or LVEF ≤ 35%	1
Hypertension	1
Age > 75 years	2
Diabetes mellitus	1
Stroke/TIA/systemic embolism	2
Vascular disease (MI/PAD/Aortic plaque)	1
Age 65–74 years	1
Sex category (female)	1
Truly low risk	Score = 0

Lip GYH, Halperin JL. *Am J Med.* 2010; 123:484.

$CHADS_2$ -> CHA_2DS_2VASc

CHADS2 score	Patients (n = 1733)	Adjusted stroke rate %/ year
0	120	1.9
1	463	2.8
2	523	4.0
3	337	5.9
4	220	8.5
5	65	12.5
6	5	18.2

CHA2DS2-VASc score	Patients (n = 7329)	Adjusted stroke rate %/ year
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

From ESC AF Guidelines http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocumentLibrary/guidelines-af-FT.pdf

ESC Guidelines

Are We Anticoagulating Enough?

- Registry Data:
- Rowan et al: < 50% of patients with afib were anticoagulated.
- Kowey et al: 64% of patients with $CHADS_2$ 2 or greater were anticoagulated with warfarin

Rowan et al.
Kowey et al.

Why Not Anticoagulate?

- Fear of bleeding, esp gastrointestinal or intracranial
- Drug interactions
- Patient preference
- Difficulty regulating drug
- Fear of warfarin
- Lack of physician insight?

Oral Anticoagulants

- Vitamin K antagonists
- Direct Thrombin Inhibitor
- Factor Xa Inhibitors

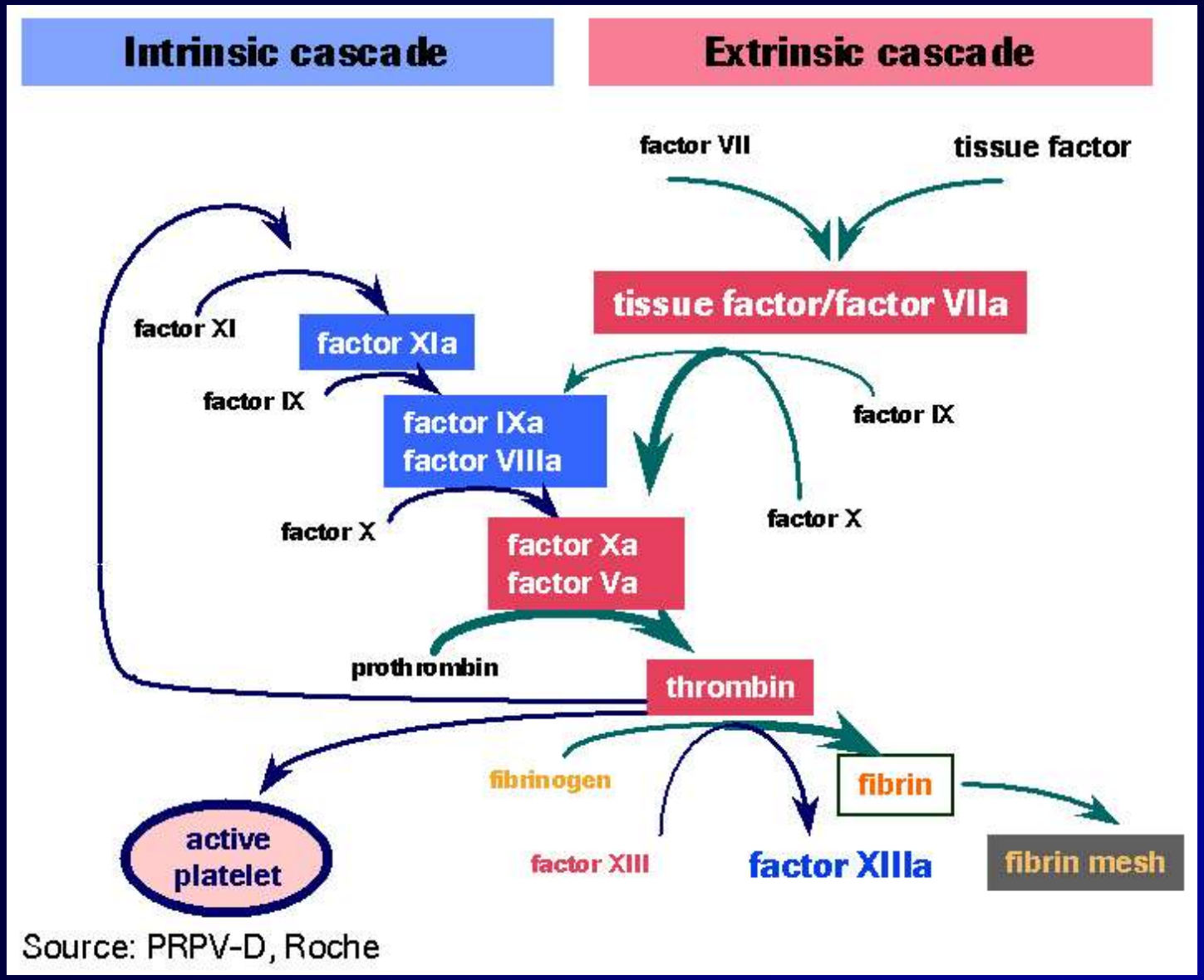
Table 1 Pharmacological Characteristics of Oral Direct Thrombin Inhibitors and Oral Direct Factor Xa Inhibitors in Phase III Clinical Development

	Dabigatran Etexilate	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Oral bioavailability, %	6.5	80–100	50	62
Half-life, h	12–17	5–13	8–15	6–11
Renal elimination, %	85	66 (36 unchanged and 30 inactive metabolites)	27	50§
Time to maximum inhibition, h	0.5–2	1–4	1–4	1–2
Potential metabolic drug interactions	Inhibitors of P-gp:verapamil, reduce dose; dronedarone: avoid	Potent inhibitors of CYP3A4 and P-gp*: avoid	Potent inhibitors of CYP3A4 and P-gp*: avoid	Potent inhibitors of P-gp*: reduce dose
	Potent inducers of P-gp†: avoid	Potent inducers of CYP3A4‡ and P-gp: use with caution	Potent inducers of CYP3A4‡ and P-gp† use with caution	Potent inducers of P-gp†: avoid

*Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, itraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atanazavir). P-g inhibitors include verapamil, amiodarone, quinidine, and clarithromycin. †P-gp inducers include rifampicin, St. John's wort (*Hypericum perforatum*), carbamazepine, and phenytoin. ‡Potent CYP3A4 induce include phenytoin, carbamazepine, phenobarbital, and St. John's wort. §Of the absorbed drug.

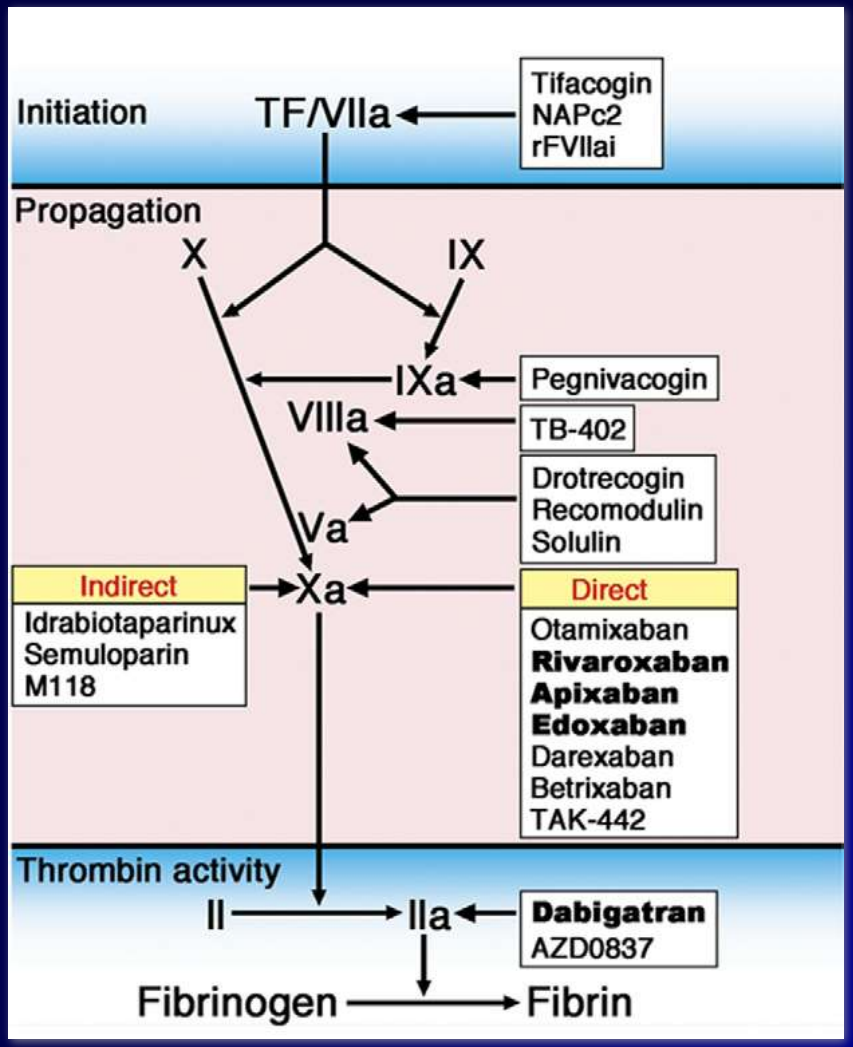
CYP = cytochrome P450 isoenzyme; F = factor; P-gp = P-glycoprotein.

De Caterina et al.



From Roche.com

Site of Action



From DeCaterina et al.

Case 1

- 83 yo woman presents to the hospital with coffee ground emesis, dizziness. Recent viral illness
- Hx of Afib, HTN, CKD 3

- Medications: Atenolol 50 mg daily, Dabigatran 150 mg bid, Spironolactone 25 mg daily, Aspirin 81 mg daily, Atorvastatin 20 mg daily

Case 1

- PE: HR 85 bpm, regular BP 92/50 mm Hg
- Appears pale, +orthostatics
- Labs: Hgb 7.1 g/dL, creat 3.1 mg/dl (nl 1.8), INR 2.6

Case 1 Discussion

- Was the use/dose of dabigatran appropriate?
- What does the INR tell us about the level of anticoagulation in this patient?

RE-LY Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

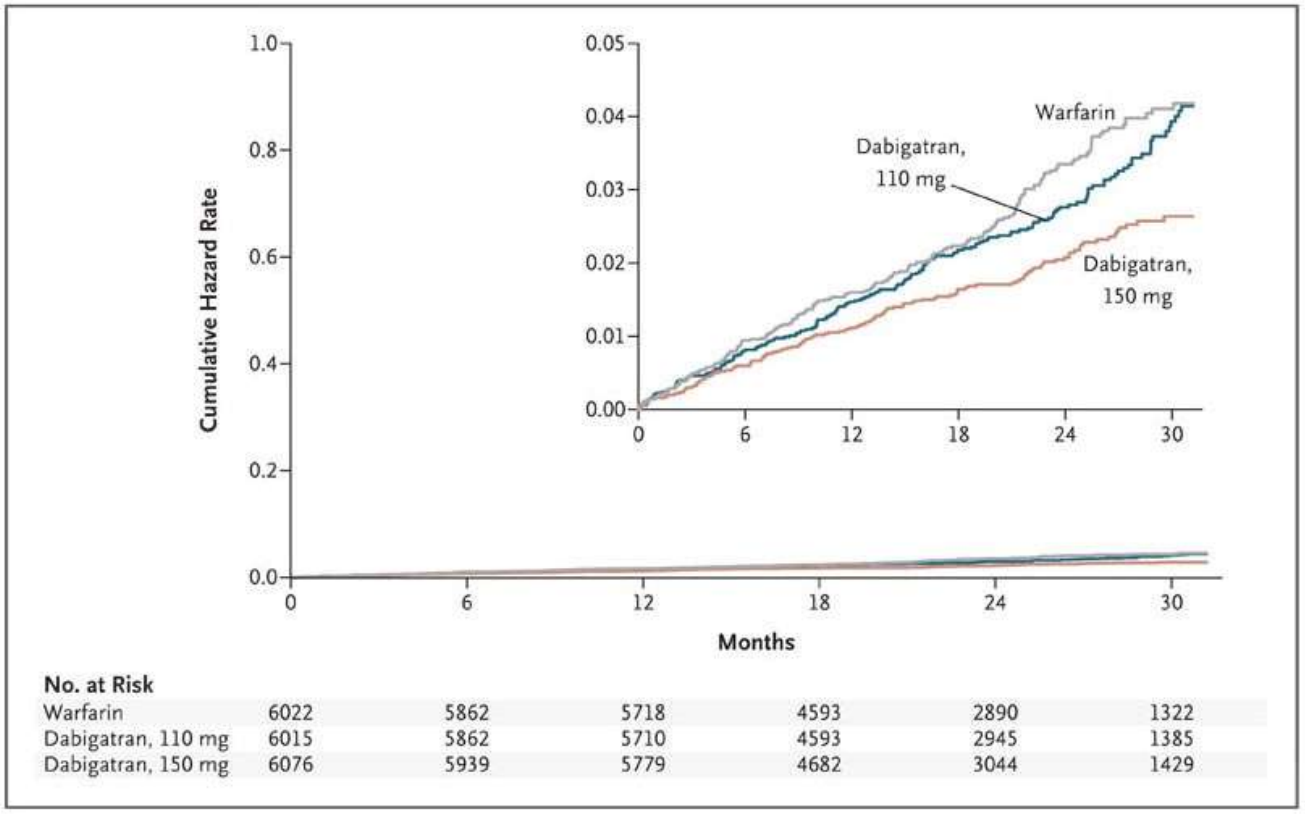
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

RE-LY

- Warfarin vs 110 mg bid dabigatran vs 150 mg bid dabigatran
- Primary outcome was stroke or systemic embolism

Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Connolly SJ et al. N Engl J Med 2009;361:1139-1151.

RE-LY Results

- Dabigatran 150 mg bid superior to warfarin with respect to primary outcome (110 mg dose was noninferior)
- No increase in major bleeding of 150 mg dose (110 mg dose less bleeding)
- Significant decrease in hemorrhagic stroke with both dabigatran doses
- Trend in improved mortality with both doses vs. warfarin

RE-LY Results

- Dabigatran 150 mg bid higher risk of GI bleed and increased risk of myocardial infarction

Table 2. Efficacy Outcomes, According to Treatment Group.

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58–0.91)	0.005
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001	0.70 (0.56–0.89)	0.003
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001	0.85 (0.39–1.83)	0.67
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03	0.69 (0.54–0.88)	0.002
Nondisabling stroke	60	0.50	44	0.37	69	0.58	0.86 (0.61–1.22)	0.40	0.62 (0.43–0.91)	0.01	0.72 (0.49–1.07)	0.10
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005	0.70 (0.53–0.94)	0.02
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048	1.02 (0.76–1.38)	0.88
Pulmonary embolism	14	0.12	18	0.15	11	0.09	1.26 (0.57–2.78)	0.56	1.61 (0.76–3.42)	0.21	1.27 (0.63–2.56)	0.50
Hospitalization	2311	19.4	2430	20.2	2458	20.8	0.92 (0.87–0.97)	0.003	0.97 (0.92–1.03)	0.34	1.06 (1.00–1.12)	0.04
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04	0.94 (0.79–1.11)	0.44
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority, unless otherwise indicated. The modified Rankin scale (on which scores can range from 0 [no neurologic disability] to 5 [severe disability], with 6 indicating a fatal stroke) was used to categorize stroke: nondisabling stroke was defined by a score of 0 to 2, and disabling or fatal stroke, a score of 3 to 6.

Dabigatran (Pradaxa©)

- Direct Thrombin Inhibitor
- Pro-drug, best absorbed in an acidic environment
- Renally cleared
- $T_{1/2}$ = 12 hrs
- 85% can be dialyzed
- Peak Effect 2-3 h

Dabigatran Dosing

- FDA recommendation based on GFR:

1. GFR >30 mL/min→ 150 mg bid
2. GFR 15-30 mL/min→75 mg bid
3. GFR < 15 mL/min→ cannot recommend use

Measuring Effect of Dabigatran

- INR is not accurate and should not be checked!!
- ECT (ecarin clotting time) and TT (thrombin time) can be measured.
- Activated Partial Thromboplastin Time (aPTT) approximation. ~ 2 x control when therapeutic
- Activated clotting time (ACT) is affected, though therapeutic range not studied

Dabigatran

- No antidote available
- Activated Prothrombin Complex Concentrates may be used to some effect
- Fresh Frozen Plasma (FFP) not typically helpful

Case 1

- GFR at baseline ~27mL/min, reduced to 14 mL/min. 75 mg bid dosing more appropriate
- The patient was transfused 2 units pRBCs
- Vitamin K 10 mg
- EGD-gastritis, no active bleeding
- Dabigatran discontinued, warfarin started.

Case 2

- 70 year old man desires atrial fibrillation ablation

- Paroxysmal afib
- HTN
- Remote cardiac stent

- Medications: amiodarone 200 mg daily, aspirin 81 mg daily, carvedilol 6.25 mg bid, rosuvastatin 20 mg qhs, lisinopril 10 mg daily, dabigatran 150 mg bid

- How should his anticoagulation be managed perioperatively?

Feasibility and Safety of Dabigatran Versus Warfarin for Periprocedural Anticoagulation in Patients Undergoing Radiofrequency Ablation for Atrial Fibrillation

Results From a Multicenter Prospective Registry

- Multicenter (8) Observational Study
- 290 pts (half uninterrupted coumadin, half dabigatran)
- Dabigatran dose 150 mg bid
- Warfarin target INR 2-3.5

- Dabigatran stopped am of procedure and restarted 3 hrs post hemostasis
- Transesophageal echo performed day of procedure on dabigatran pts but not warfarin patients
- Similar baseline characteristics

Results

- Trend toward increased thromboembolic events in dabigatran group
- Higher risk of major bleeding rate, total bleeding rate, and composite of bleeding and thromboembolic complications in the dabigatran group

Table 3 Comparison of Complications Between Patients on Dabigatran and Warfarin

Safety Endpoints	Dabigatran (n = 145)	Warfarin (n = 145)	Total (N = 290)	p Value
Major bleeding complications	9 (6)	1 (1)	10 (3)	0.019
Periprocedural pericardial tamponade	6 (4)	1 (1)	7 (2)	0.12
Late pericardial tamponade	3 (2)	0 (0)	3 (1)	0.25
Minor bleeding complications	12 (8)	8 (6)	20 (7)	0.35
Groin hematoma	6 (4)	5 (3)	11 (4)	0.76
Pericardial effusion without tamponade	6 (4)	4 (3)	10 (3)	0.75
Total bleeding complications	20 (14)	9 (6)	29 (10)	0.031
Embolic complications (CVA/TIA)	3 (2)	0 (0)	3 (1)	0.25
Composite of bleeding and embolic complications	23 (16)	9 (6)	32 (11)	0.009

Values are n (%).

CVA = cerebrovascular accident; TIA = transient ischemic attack.

Concerns

- Dabigatran not held long enough prior to procedure
- Interaction between unfractionated heparin and dabigatran
- FFP given to reverse dabigatran
- Timing of reinitiation of dabigatran

Our Experience

- Holding coumadin
- Hold dabigatran 48 hours prior to procedure.

Case 3

- 75 year old woman with newly diagnosed afib.

- Recent drug-eluting stent to LAD (3 weeks prior), HTN, DM, obese, nl renal function

Case 3

- Medications: carvedilol 12.5 mg bid, aspirin 325 mg daily, clopidogrel 75 mg daily, simvastatin 40 mg qhs, diabetic meds

- Asymptomatic. Ventricular rate between 60-80 bpm at rest

Case 3

- Should this woman receive anticoagulation?
- Which anticoagulant would be best?

Case 3

- $CHADS_2$ = 3 (5.9% annual stroke risk)
  CHA_2DS_2-VASc = 6 (9.8% annual stroke risk)

Case 3

- ACC/AHA/ESC guidelines: “triple” therapy in PCI patients with afib as a IIb recommendation (Level of Evidence C)

Aka “Proceed with Caution”

Case 3

- Which anticoagulant to use?

What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting?
WOEST Trial

- European Study
- Randomized Controlled Trial- 573 pts
- VKA + clopidogrel 75 mg daily + ASA 80 mg daily
- VKA + clopidogrel 75 mg daily

WOEST Trial

- 1 yr followup (35% BMS, 65% DES)
- Primary endpoint all TIMI bleeding

WOEST Trial

- Dual therapy (clopidogrel + VKA) significantly reduced all TIMI bleeding (driven by minimal and minor)
- No difference in intracranial bleeding
- Trend toward reduced death, stroke, MI, instent thrombosis in dual therapy

Case 3

- Which anticoagulant?
- Only data to date involve VKA

Case 4

- 66 y/o Female
- Paroxysmal Atrial Fibrillation
  - Symptomatic
- HTN
- DM
- MV Repair 5 years ago
- No history of GI bleeding

Case 4

- Meds:
  - Glucophage
  - Lisinopril
  - ASA 81
- NKDA
- Hb 13, Cr=1.1
- EF=60%
- LA size 4.5 cm

Case 4

- CHADS-2 = 2
- CHADS-VASc= 4
- HAS-BLED = 2

Case 4

- Choice?

Case 4

- Reminder

Case 4

- Reminder

AF category due to aging or development of cardiac abnormalities such as enlargement of the left atrium (LA. Then, the risks of thromboembolism and mortality rise accordingly. By convention, the term "nonvalvular AF" is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.

Case 4

- Reminder

AF category due to aging or development of cardiac abnormalities such as enlargement of the left atrium (LA. Then, the risks of thromboembolism and mortality rise accordingly. By convention, the term "nonvalvular AF" is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.

Case 4

- Reminder

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PRADAXA is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

XARELTO (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Case 5

50 y/o Female

- Paroxysmal Atrial Fibrillation
- HTN

Involved in a MVA

Multiple rib fractures

Hemothorax – chest tube

Intubated

Case 5

- Meds:
  - Dabigatran 150 mg bid
  - Metoprolol 50 mg po bid

- NKDA
- Hb 8 (12), Cr=1.3 (0.9), INR 1.3
- EF=60%
- LA size 4.0 cm

Case 5

- HR 110 (afib)
- BP 80/40
- Intubated
- Abdomen is distended
- Continued output from chest tube

Case 5

- Next step?

Case 5

- Next step?
  - FFP

Case 5

- Next step?
  - FFP
  - Hematology Consult

Case 5

- Why are we comfortable with warfarin?
  - INR
- We can reverse it
  - Vitamin K
  - FFP

Case 5

- Dabigatran
  - Prolongs PTT and PT/INR
  - No reversal agent
  - Hemodialysis
    - Low protein binding
    - 60% removed in 2-3 hours
      - Limited data
  - Relatively short half life

Case 5

- Rivaroxaban
  - No reversal agent
  - Hemodialysis
    - 95% protein bound
    - No effect
  - Consider
    - Prothrombin complex concentrate
    - Activated prothrombin complex concentrate
    - Recombinant Factor VIIa
    - Limited data

Case 5

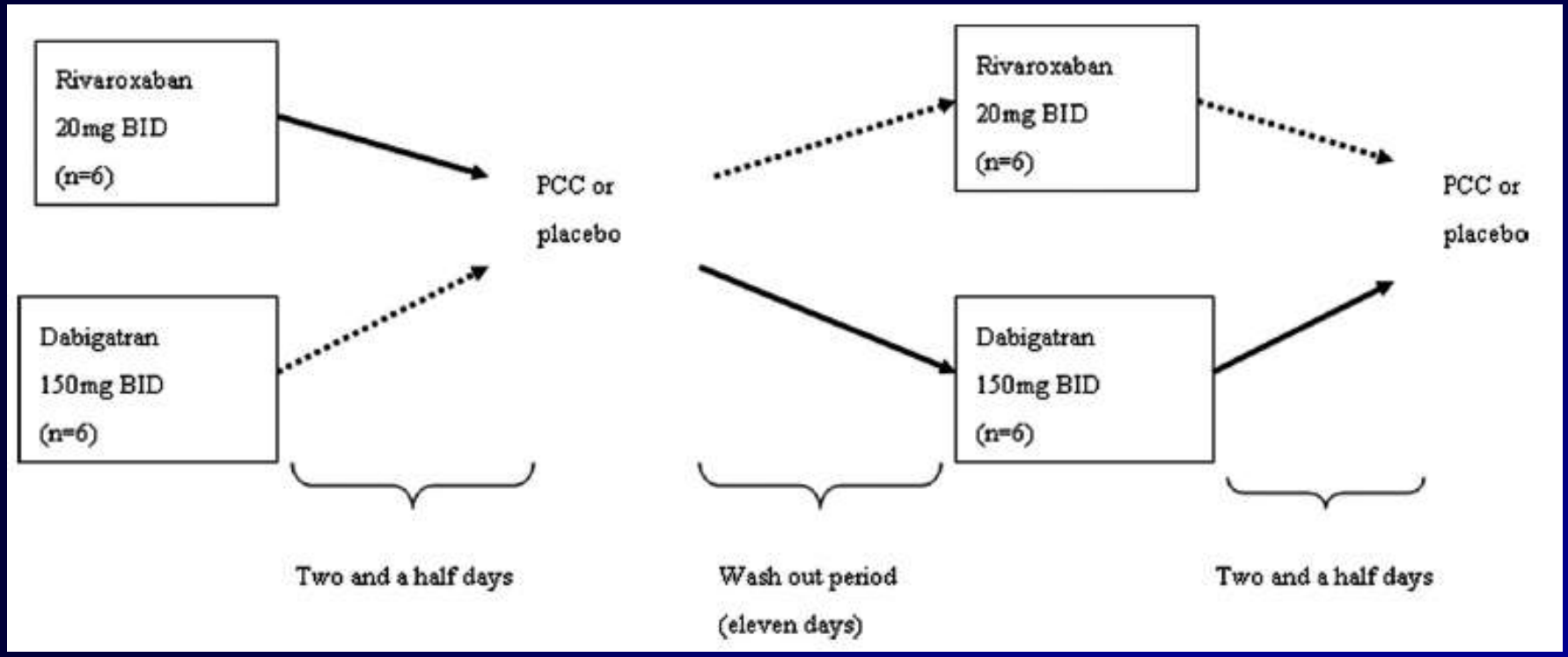
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc;
Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

Circulation:2011;124: 1573-1579

Case 5



Circulation:2011;124: 1573-1579

Case 5

- Observations
  - Rivaroxaban
    - PT was significantly prolonged
    - Immediately normalized
  - Dabigatran
    - PTT and ECT was significantly prolonged
    - No effect

Circulation:2011;124: 1573-1579

Case 5

- Decision
  - Wait
  - Supportive Care
  - 2 U PRBC
  - OR next day
  - Full recovery

Case 6

76 y/o Female

- Persistent Atrial Fibrillation
- HTN

Elective cardioversion

Dabigatran for 2 months

Case 6

- Meds:
  - Dabigatran 150 mg bid
  - Diltiazem 240 mg bid
  - Amiodarone 200 mg daily
- NKDA
- Cr = 1.1
- Cr Clearance > 50
- EF=60%
- LA size 3.7 cm

Case 6

- Compliant with medication
- Daughter confirms

Case 6

- Compliant with medication
- Daughter confirms
- Successful cardioversion
  - 100J

Case 6

- CVA
  - <24 hours later
  - Hemorrhagic

Case 6

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Dabigatran Versus Warfarin in Patients With Atrial Fibrillation : An Analysis of Patients Undergoing Cardioversion

Rangadham Nagarakanti, Michael D. Ezekowitz, Jonas Oldgren, Sean Yang, Michael Chernick, Timothy H. Aikens, Greg Flaker, Josep Brugada, Gabriel Kamenský, Amit Parekh, Paul A. Reilly, Salim Yusuf and Stuart J. Connolly

Case 6

- RE-LY Trial
  - Cardioversion on randomized treatment permitted
    - 1983 cardioversions performed
- TEE was encouraged but not mandatory
  - Dabigatran 110 mg 25%
  - Dabigatran 150 mg 24%
  - Warfarin 13%
- Stroke and systemic embolism rates similar
  - Between 3 medication groups
  - Between TEE and non-TEE

Circulation 2011;123:131-136

Case 6

XARELTO® (rivaroxaban) tablets

Few patients in ROCKET AF underwent electrical cardioversion for atrial fibrillation. The utility of XARELTO for preventing post-cardioversion stroke and systemic embolism is unknown.

Case 7

70 y/o Female

- Paroxysmal Atrial Fibrillation
- HTN
- DM
- Dronedarone x 1 year
- Dabigatran x 6 months

Case 7

- Previous visit (6 months ago)
- Cr = 1.4
- EF=60%
- LA size 4.2 cm
- Sinus rhythm

Case 7

- Today's visit
- Reports no episodes of atrial fibrillation
- HR 70, BP 130/60
- Weight: 90 kg
- Cr = 1.6
- Sinus rhythm

Case 7

- Changes?

Case 7

- Creatinine Clearance
- 6 months ago
  - 53 mL/min
- Today's visit
  - 46.5 mL/min
- Cockcroft-Gault Equation
  - eCrCl = (140-age)*(wt in kg)/(72 * Cr (mg/dL)
    - Multiply by 0.85 if Female

Case 7

- CrCl >30 ml/min 150 mg po bid
- CrCl 15-30 ml/min 75 mg po bid

Case 7

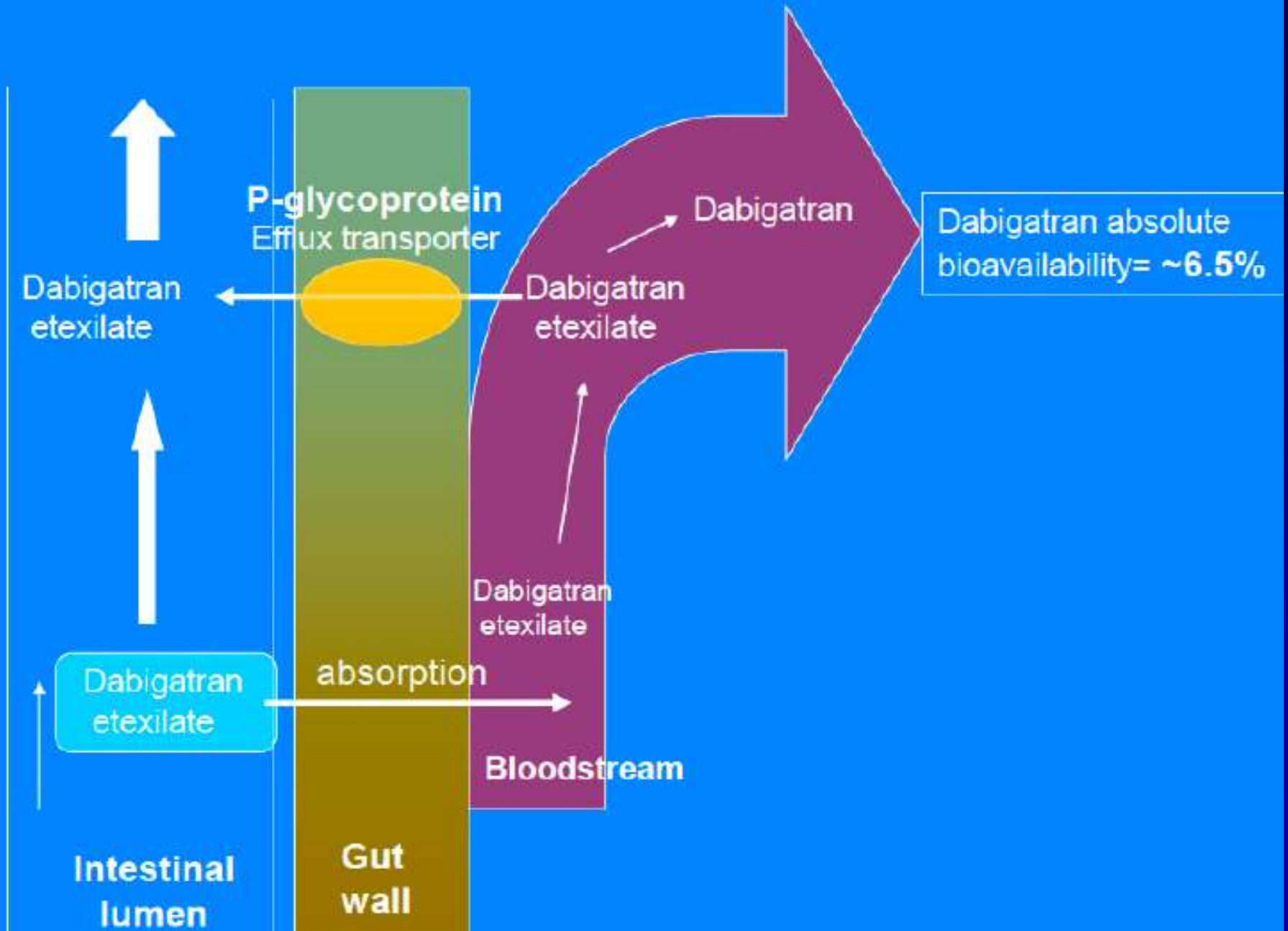
- CrCl >30 ml/min 150 mg po bid
- CrCl 15-30 ml/min 75 mg po bid

- Dronedarone
  - CrCl 30-50 ml/min 75 mg po bid
  - Also applies to ketoconazole

Case 7

- Dronedarone
  - Inhibits p-glycoprotein transport

Dabigatran etexilate as P-glycoprotein substrate



Case 7

- Inhibitors of p-glyocprotein transport
  - Dronedarone
  - Amiodarone
  - Verapamil
  - Ketoconazole
  - Clarithromycin
  - Quinidine
- Inducers of p-glycoprotein transport
  - Rifampin

Case 7

In patients with moderate renal impairment (CrCl 30-50 mL/min), consider reducing the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole. The use of P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) does not require a dose adjustment of PRADAXA. These results should not be extrapolated to other P-gp inhibitors *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

- "In patients with moderate renal impairment (Cr Cl 30-50 mL/min) consider reducing the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole"
- "The use of P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) does not require a dose adjustment of Pradaxa"

Case 7

- Rivaroxaban
  - Metabolized 2/3 liver, 1/3 kidneys
  - Substrate of Cytochrome P450 3A4 and p-glycoprotein
  - Affected by inhibitors and inducers
  - Ketoconazole (inhibits both)
  - Clarithromycin (inhibits both)
  - Ritonovir (inhibits both)
  - Rifampin (induces both)

Case 7

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan), which cause significant increases in rivaroxaban exposure that may increase bleeding risk.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort).

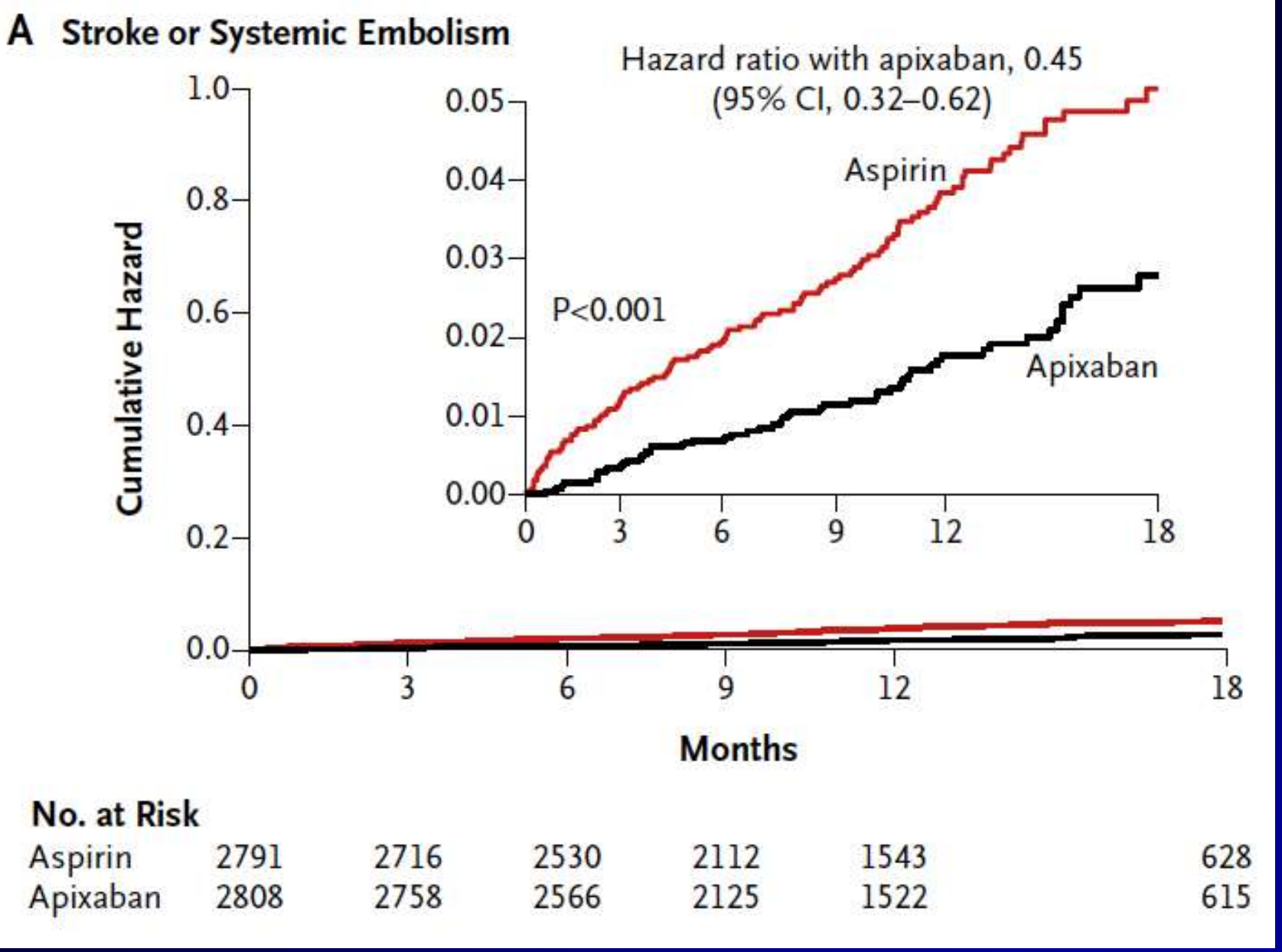
Apixaban

- Factor Xa inhibitor
- 87% protein bound
- 25% elimination renal
- 55% elimination fecal
- Primarily metabolized Cyp 3A4/5
- Half life 8-15 hours
- BID

Apixaban

- AVERROES
  - 5599 patients
  - Apixaban 5 mg bid vs ASA 81-324 mg qd
  - Primary outcome – Stroke/systemic embolism
  - Early termination
    - 51 events Apixaban (1.6%/year)
    - 113 events ASA (3.7%/year)
  - No significant difference in major bleed or ICH

NEJM 2011; 364:806-17

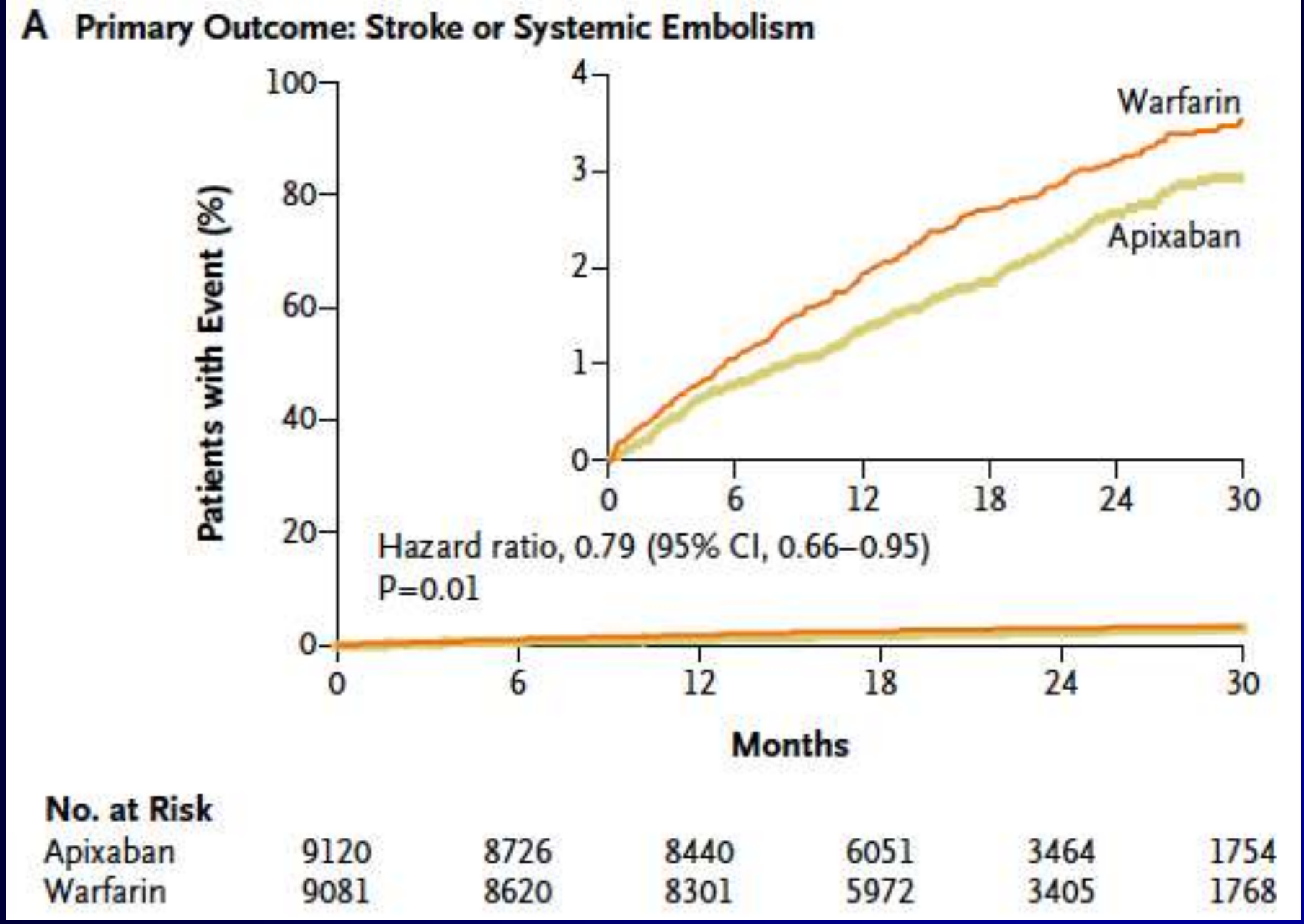


NEJM 2011; 364:806-17

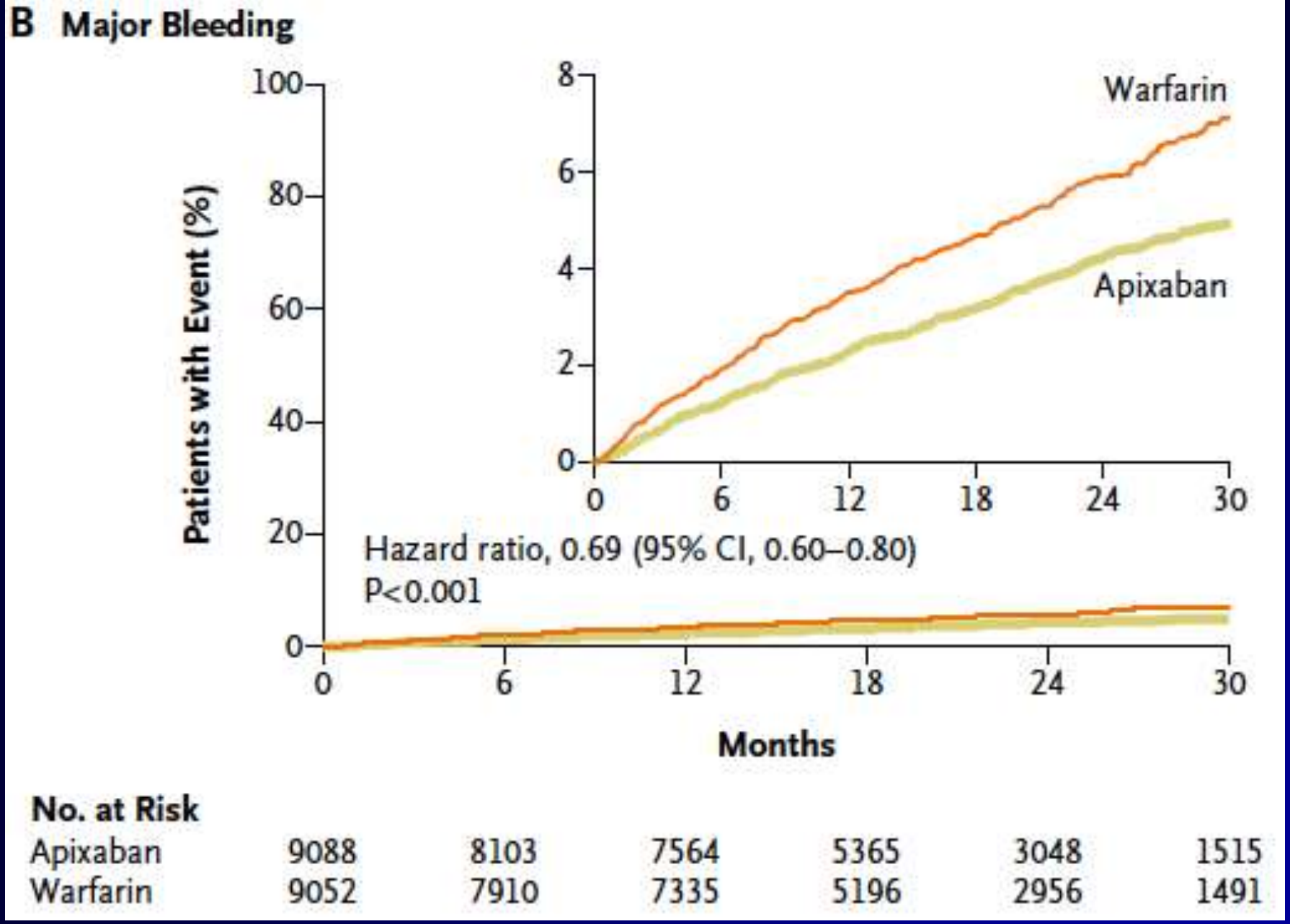
Apixaban

- ARISTOTLE
  - 18,201 patients
  - Apixaban 5 mg bid vs Warfarin
  - Primary outcome
    - Ischemic or hemorrhagic stroke/systemic embolism
    - Apixaban – 1.27%/year
    - Warfarin – 1.6%/year
  - Major bleed
    - Apixaban –2.13%/year
    - Warfarin – 3.09%/year

NEJM 2011; 365: 981-92



NEJM 2011; 365: 981-92



NEJM 2011; 365: 981-92

Thank you!