Anticoagulant Therapy

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Disclosures for Brian F. Gage, MD, MSc
(past 2 yrs)

Research Support	No conflicts of interest, but 1 grant pending
Consultation	No conflicts of interest
Employee	No conflicts of interest
Speakers Bureau	No conflicts of interest
Honoraria	No conflicts of interest
Scientific Advisory Board	No conflicts of interest

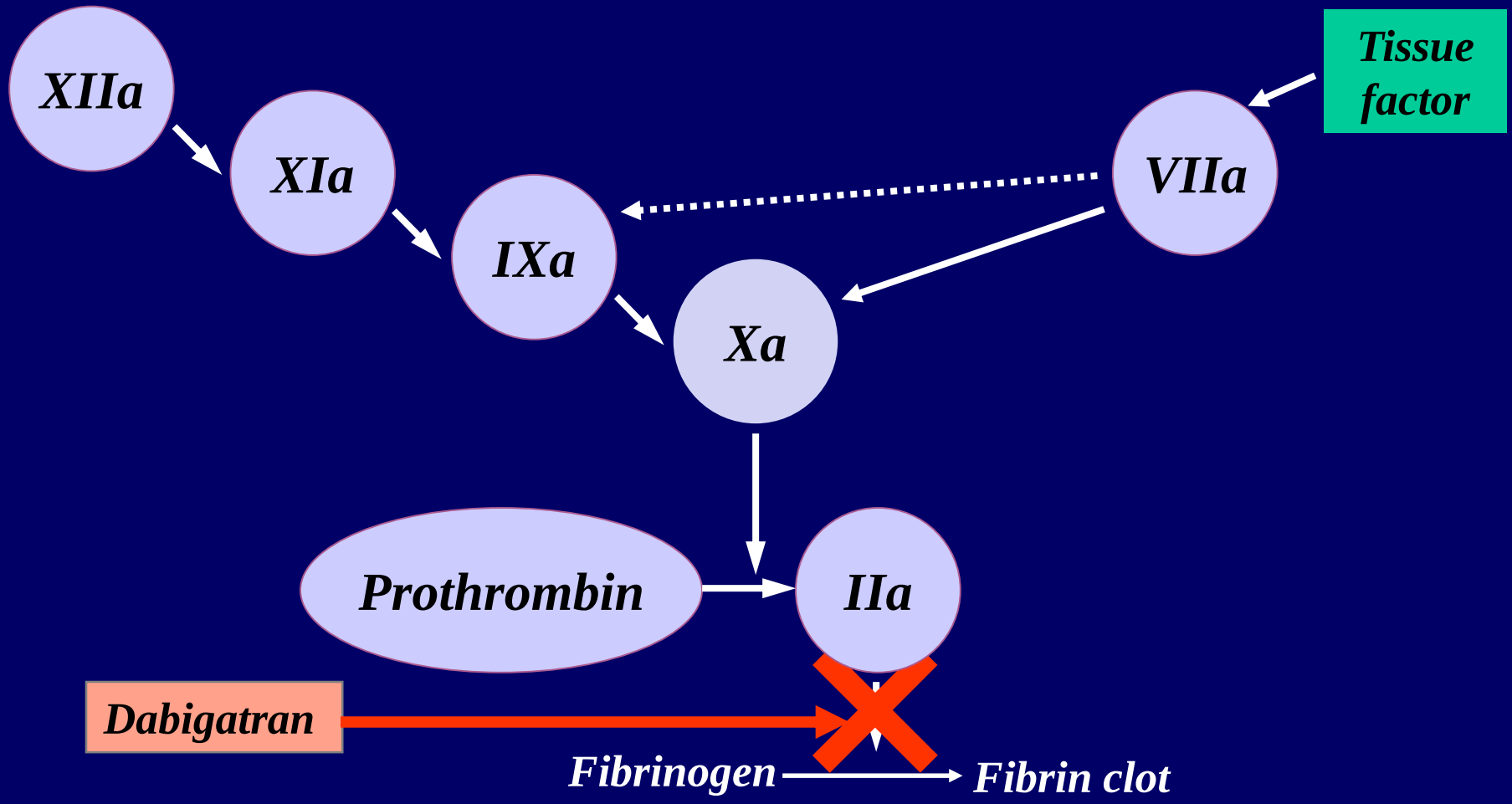
Objectives

- To prevent stroke in patients with atrial fibrillation (Afib)
- To prevent DVT/PE after arthroplasty or an initial event
- To use pharmacogenetics to improve the safety of warfarin therapy

DOACs: Direct Orally-Acting Anticoagulants

- Dabigatran (Pradaxa)
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- Edoxaban (Savaysa)
- Betrixaban (Bevyxxa)

Dabigatran (Pradaxa): Thrombin Inhibitor



Slide adapted from A. Turpie

RE-LY

The NEW ENGLAND JOURNAL of MEDICINE

VOL. 361 NO. 12

SEPTEMBER 17, 2009

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*

Hazard Ratio (HR) Was Similar in Countries with Top Quartile of INR Control

Quartiles of INR Control	150 mg dabigatran			Warfarin			
	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	HR (95% CI)
	Stroke and systemic embolism						
≤57·1%	1509	32	1·10	1504	54	1·92	0·57 (0·37–0·88)
57·1–65·5%	1526	32	1·04	1514	62	2·06	0·50 (0·33–0·77)
65·5–72·6%	1484	31	1·04	1487	45	1·51	0·69 (0·44–1·09)
>72·6%	1514	38	1·27	1509	40	1·34	0·95 (0·61–1·48)

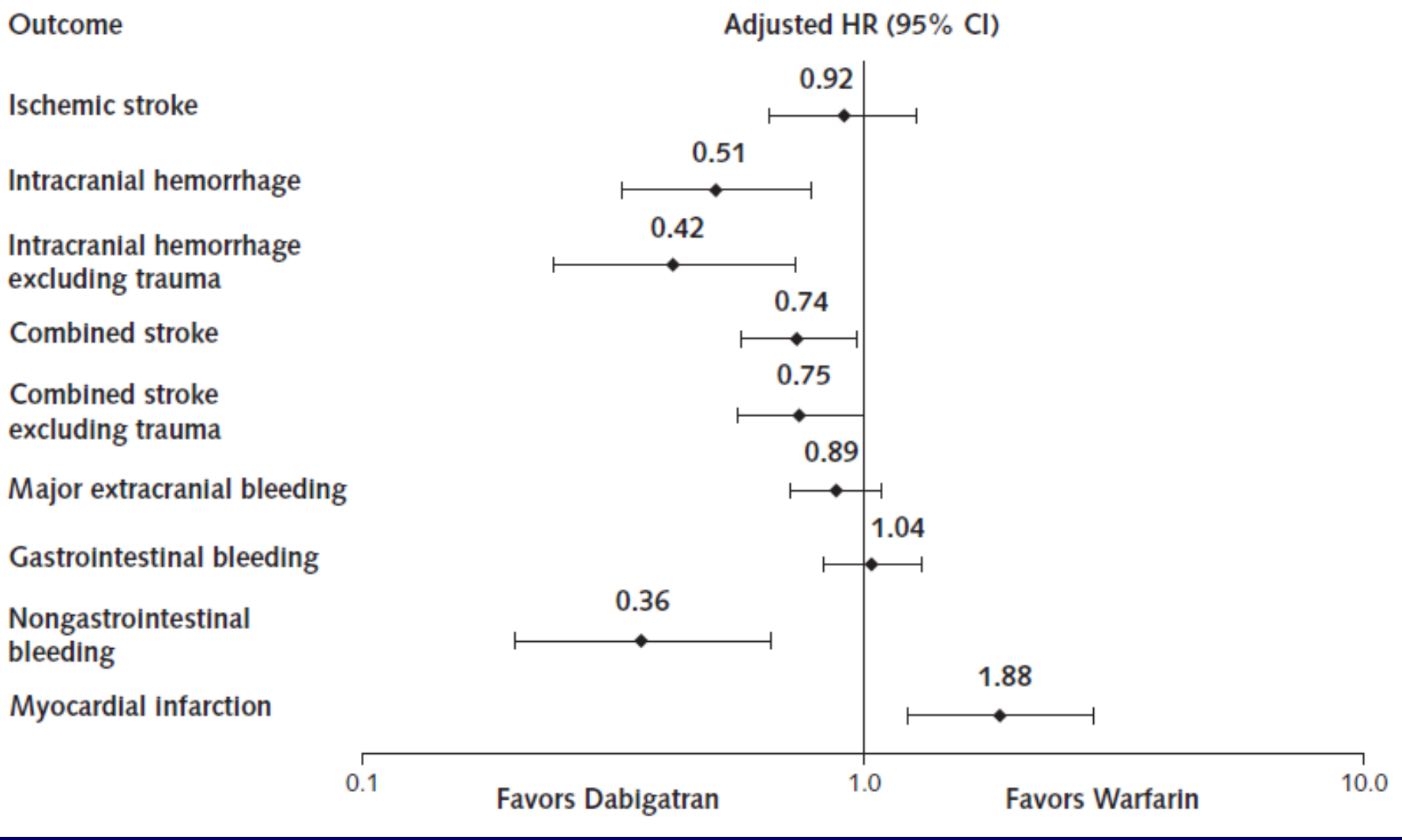
Wallentin L. et al. 2010 **Lancet**

Dabigatran in AF

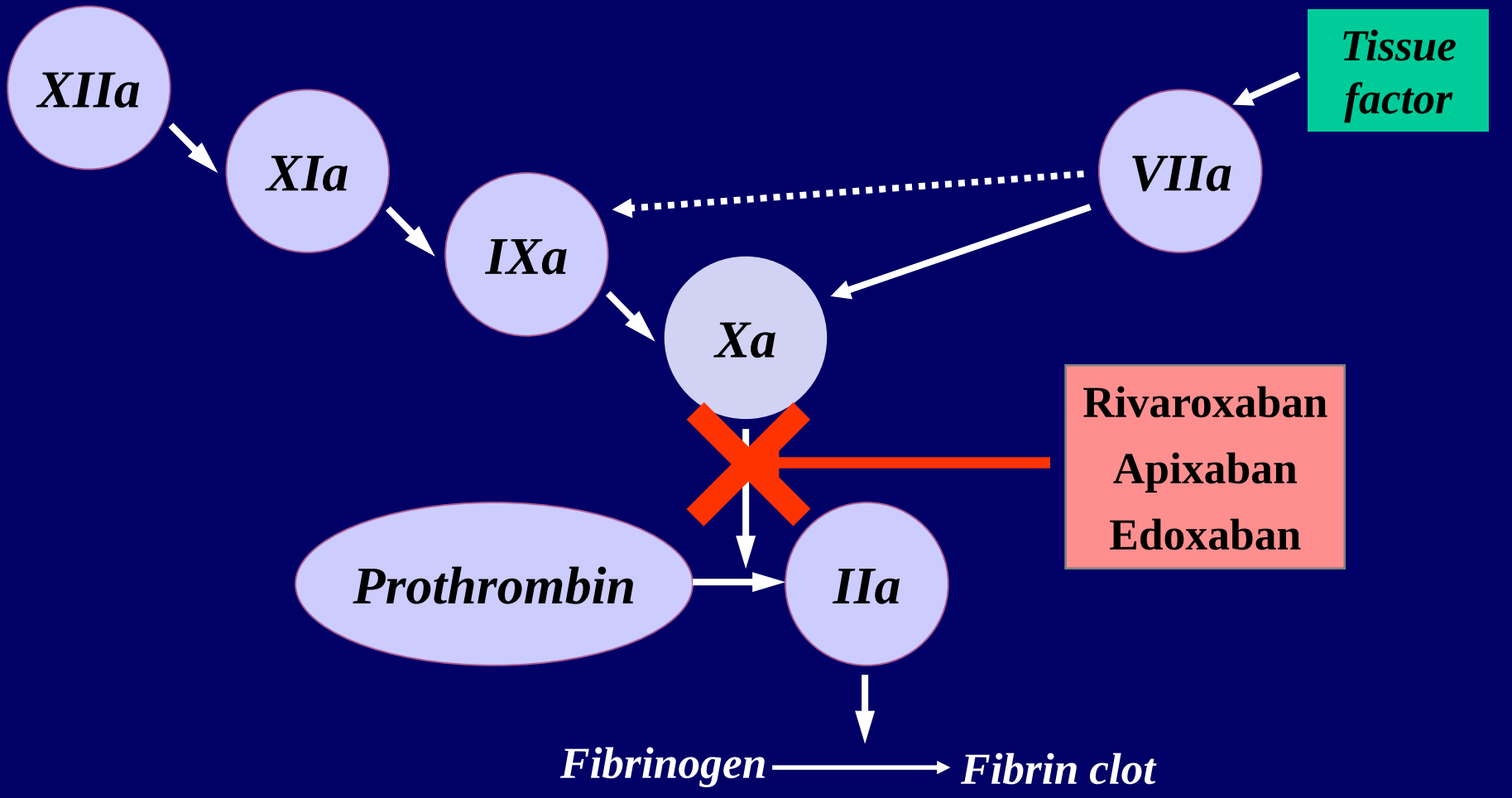
- 150 mg po bid was more effective than warfarin (unless INR control > 72.6%)
  - Fewer ICHs
  - Fewer ischemic strokes or TIAs
  - But more GIBs/dyspepsia and MIs than warfarin
- 110 mg po bid is not FDA-approved
  - Perhaps the safer dose in elderly, petite patients.
- 75 mg po bid is the FDA-approved dose in patients w/ eGFR 15-30 ml/min
  - Outcomes data lacking

A. Go et al. **Ann Intern Med** Nov 2017

propensity score–matched patients with atrial fibrillation receiving dabigatran and warfarin.



Oral Xa Inhibitors



Slide adapted from A. Turpie

ROCKET AF: Patel et al. NEJM 2011

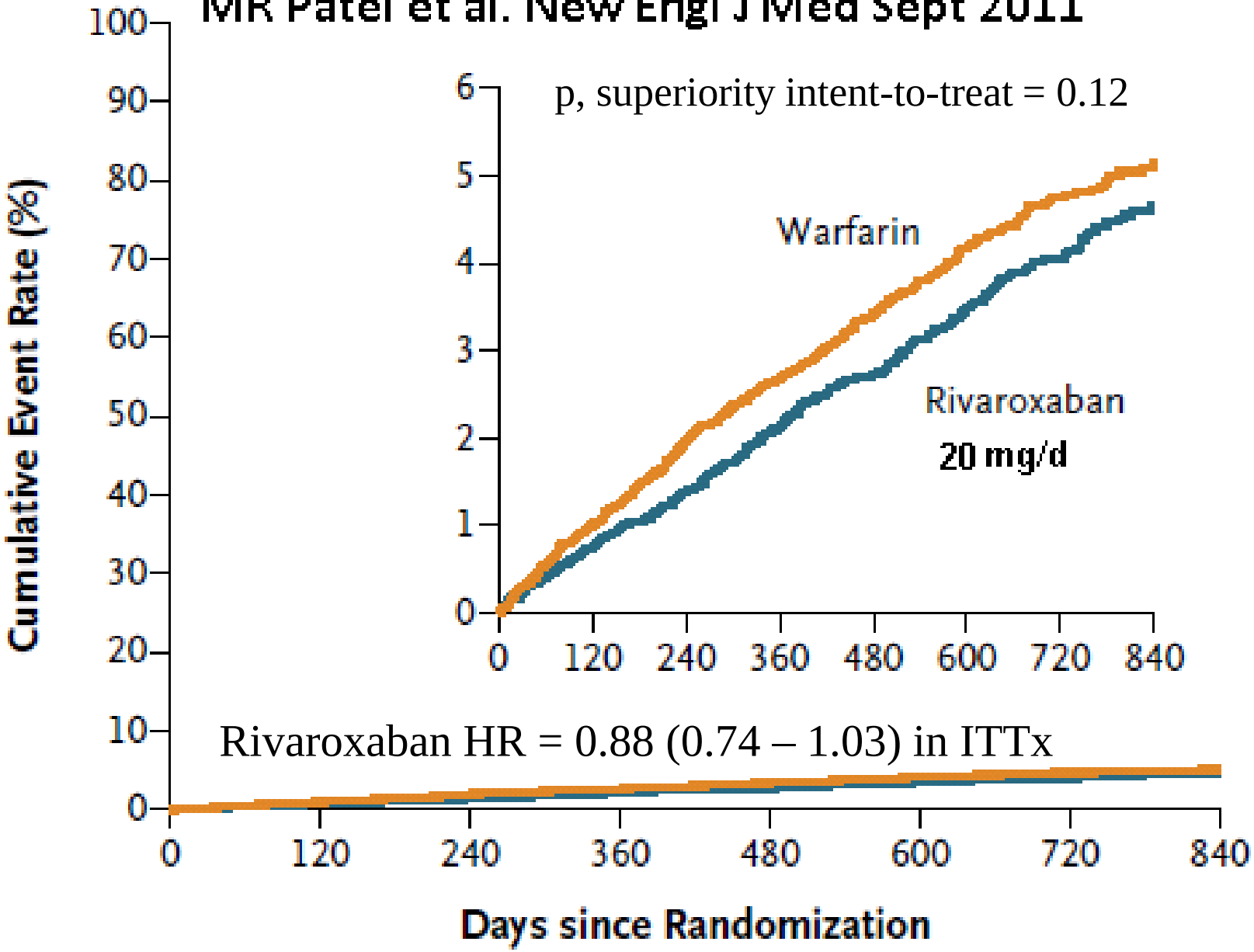
- Double-blind RCT ☺
- 14,264 patients with nonvalvular AF
- Rivaroxaban (Xarelto) daily dose of 20 mg vs. dose-adjusted warfarin
  - INR 2-3, TTR ~ 55% ☹
  - warfarin was monitored w/ a faulty POC device
- Primary analysis was non-inferiority, as-treated, for {stroke or systemic embolism}
- Patients: Mean $CHADS_2$ score = 3.5

Rivaroxaban (Xarelto)

- Fixed dose in ROCKET AF: 20 mg/d or
  - 15 mg/d in patients with a Cr Cl of 30 to 49 ml/min
  - Caution: initial dosing is different for VTE
- Half-life 9-13 hours in adults, but dosed qd
  - Avoid interruptions, which can lead to stroke

Stroke or systemic embolism in Rocket AF

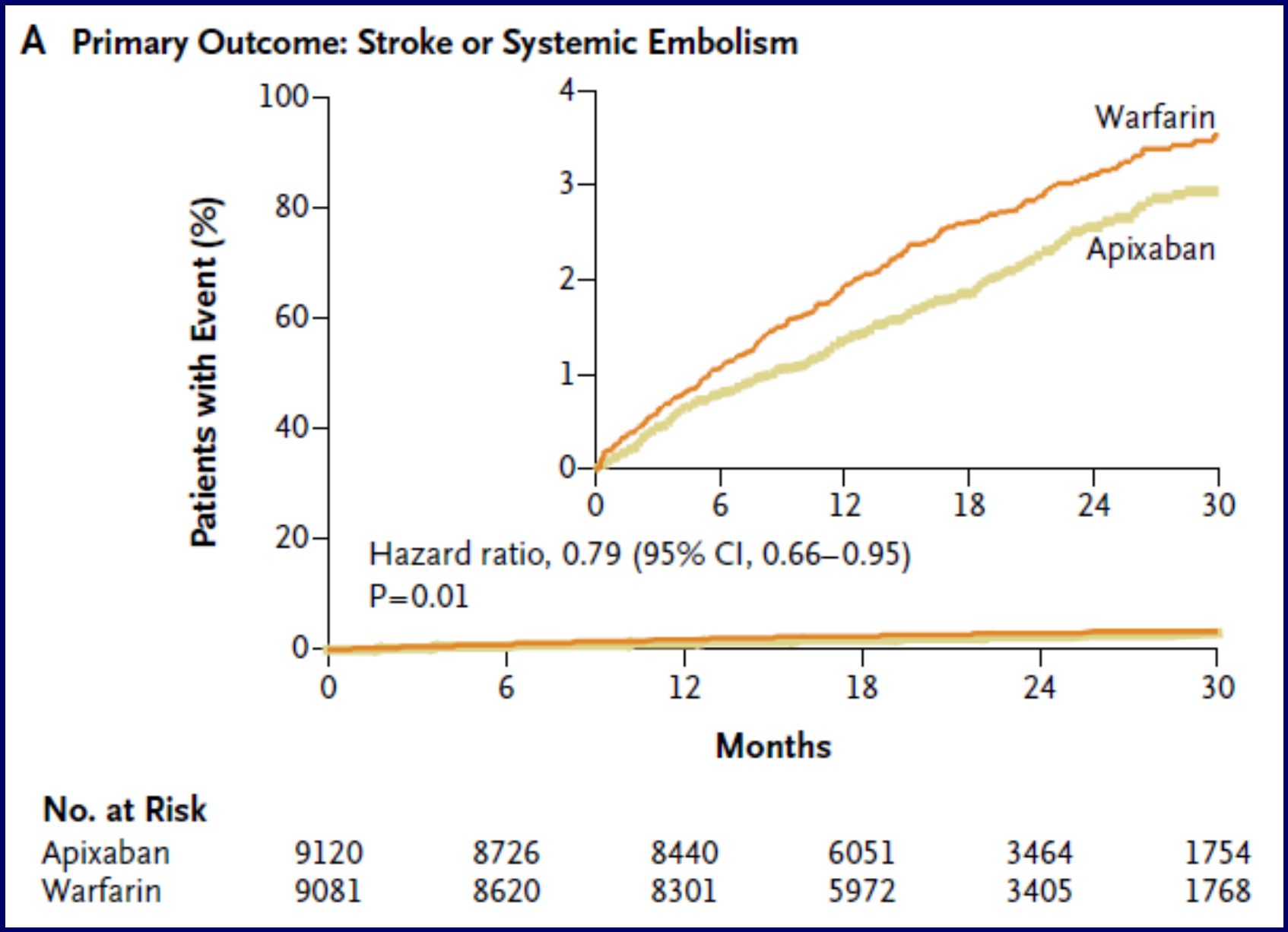
MR Patel et al. New Engl J Med Sept 2011



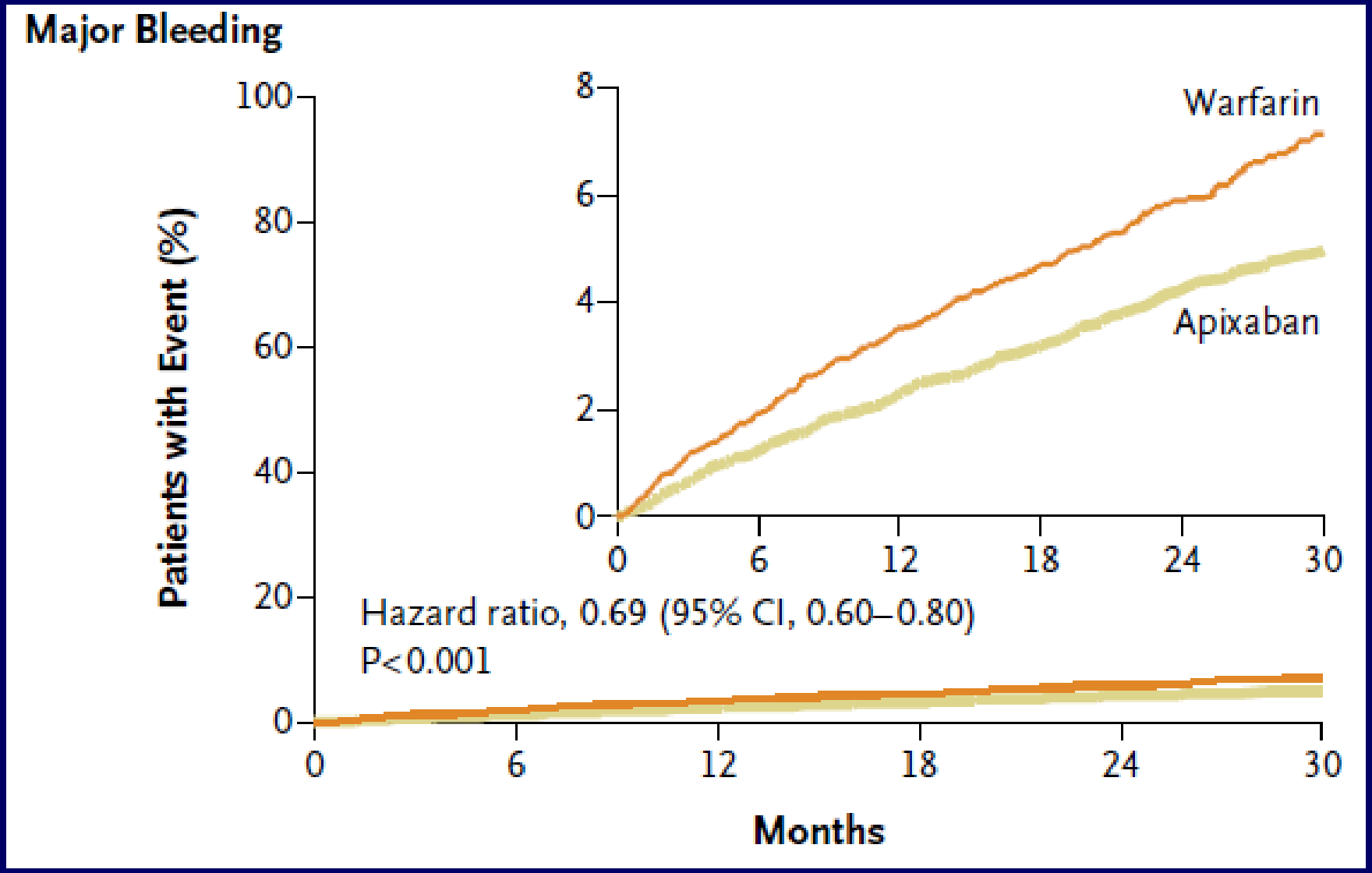
ARISTOTLE: Granger et al **NEJM** 2011

- Double-blind RCT ☺ of apixaban (Eliquis)
- 18,201 patients with nonvalvular AF
- Mean $CHADS_2$ score = 2.1
- Apixaban daily dose of 5 mg bid (2.5 mg CRI)
- vs. warfarin (INR 2-3, 66% TTR)
- Primary analysis was non-inferiority, for {ischemic or hemorrhagic stroke or systemic embolism}
  - I present p-values for superiority

ARISTOTLE RESULTS

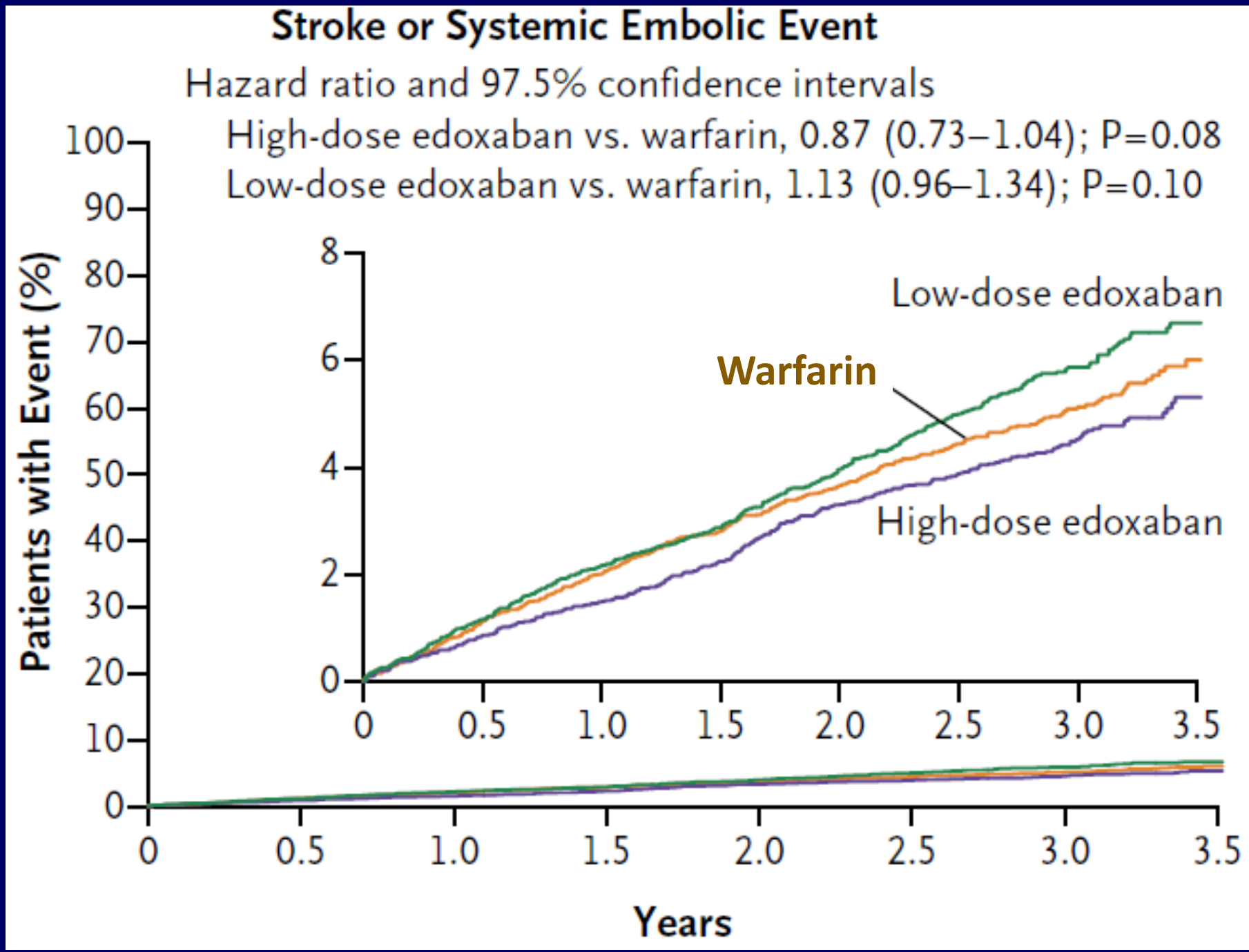


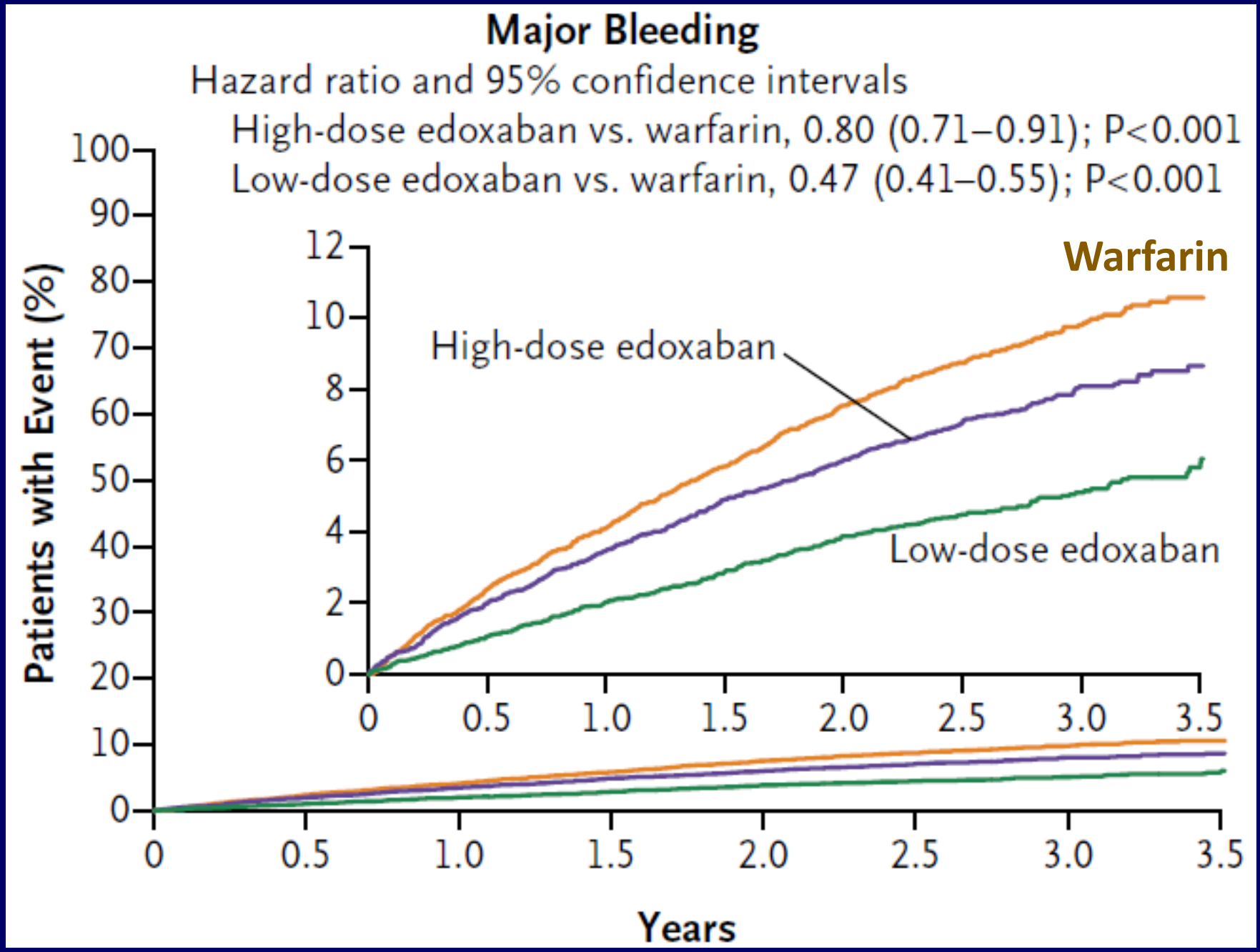
Apixaban also Reduced Major Bleeding Despite Good Warfarin Dosing (66% time in range)

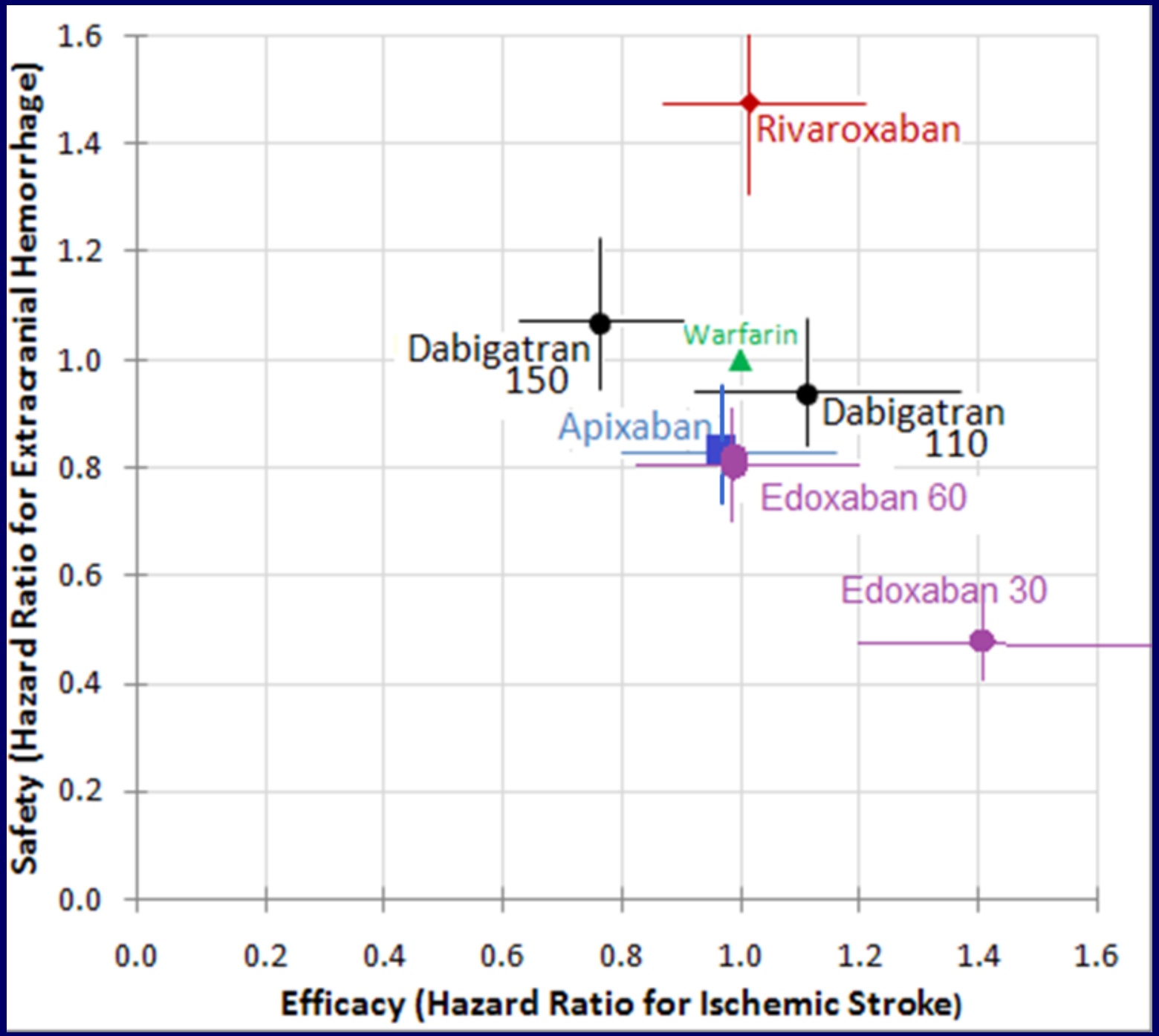


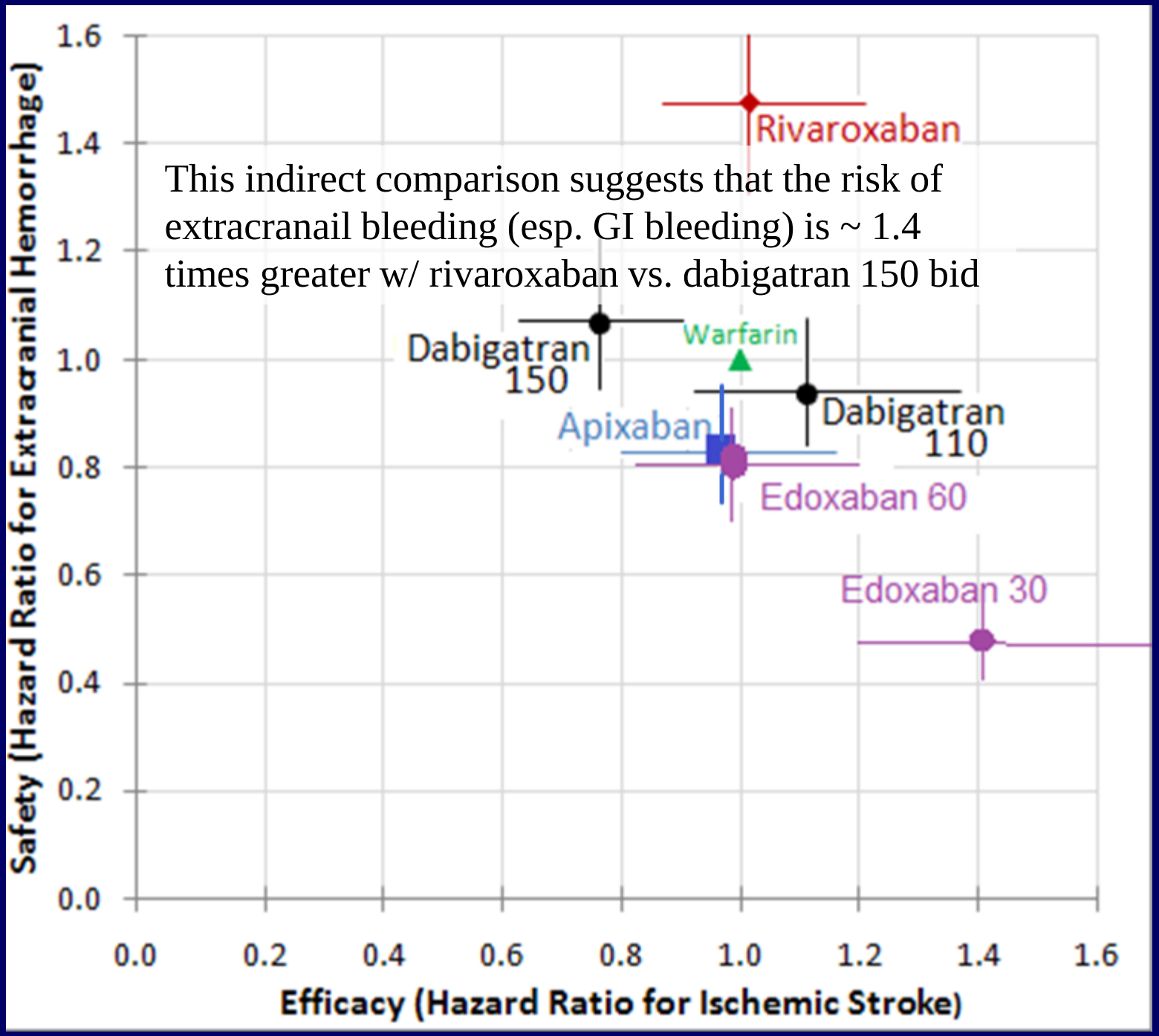
ENGAGE AF-TIMI 48: Giugliano et al. **NEJM** 2013

- Double-blind RCT ☺ of edoxaban (Savaysa)
- 21,105 patients with nonvalvular AF
- Mean $CHADS_2$ score = 2.8
- Edoxaban daily doses of 30 or 60 mg/d vs. warfarin (INR 2-3, 65% TTR)
- Primary analysis was non-inferiority, for {ischemic or hemorrhagic stroke or systemic embolism}


Stroke or Systemic Embolic Event
Hazard ratio and 97.5% confidence intervals
High-dose edoxaban vs. warfarin, 0.87 (0.73–1.04); P=0.08
Low-dose edoxaban vs. warfarin, 1.13 (0.96–1.34); P=0.10
Patients with Event (%)
100
90
80
70
60
50
40
30
20
10
0
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Years
8
6
4
2
0
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Low-dose edoxaban
Warfarin
High-dose edoxaban


Major Bleeding
Hazard ratio and 95% confidence intervals
High-dose edoxaban vs. warfarin, 0.80 (0.71–0.91); P<0.001
Low-dose edoxaban vs. warfarin, 0.47 (0.41–0.55); P<0.001
Warfarin
High-dose edoxaban
Low-dose edoxaban
Patients with Event (%)
Years
0
10
20
30
40
50
60
70
80
90
100
0
2
4
6
8
10
12
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5


Safety (Hazard Ratio for Extracranial Hemorrhage)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
Efficacy (Hazard Ratio for Ischemic Stroke)
Rivaroxaban
Warfarin
Dabigatran 150
Dabigatran 110
Apixaban
Edoxaban 60
Edoxaban 30


This indirect comparison suggests that the risk of extracranail bleeding (esp. GI bleeding) is ~ 1.4 times greater w/ rivaroxaban vs. dabigatran 150 bid
Rivaroxaban
Dabigatran 150
Warfarin
Dabigatran 110
Apixaban
Edoxaban 60
Edoxaban 30
Safety (Hazard Ratio for Extracranial Hemorrhage)
Efficacy (Hazard Ratio for Ischemic Stroke)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6

FDA's Comparison of Dabigatran vs. Rivaroxaban for Afib:

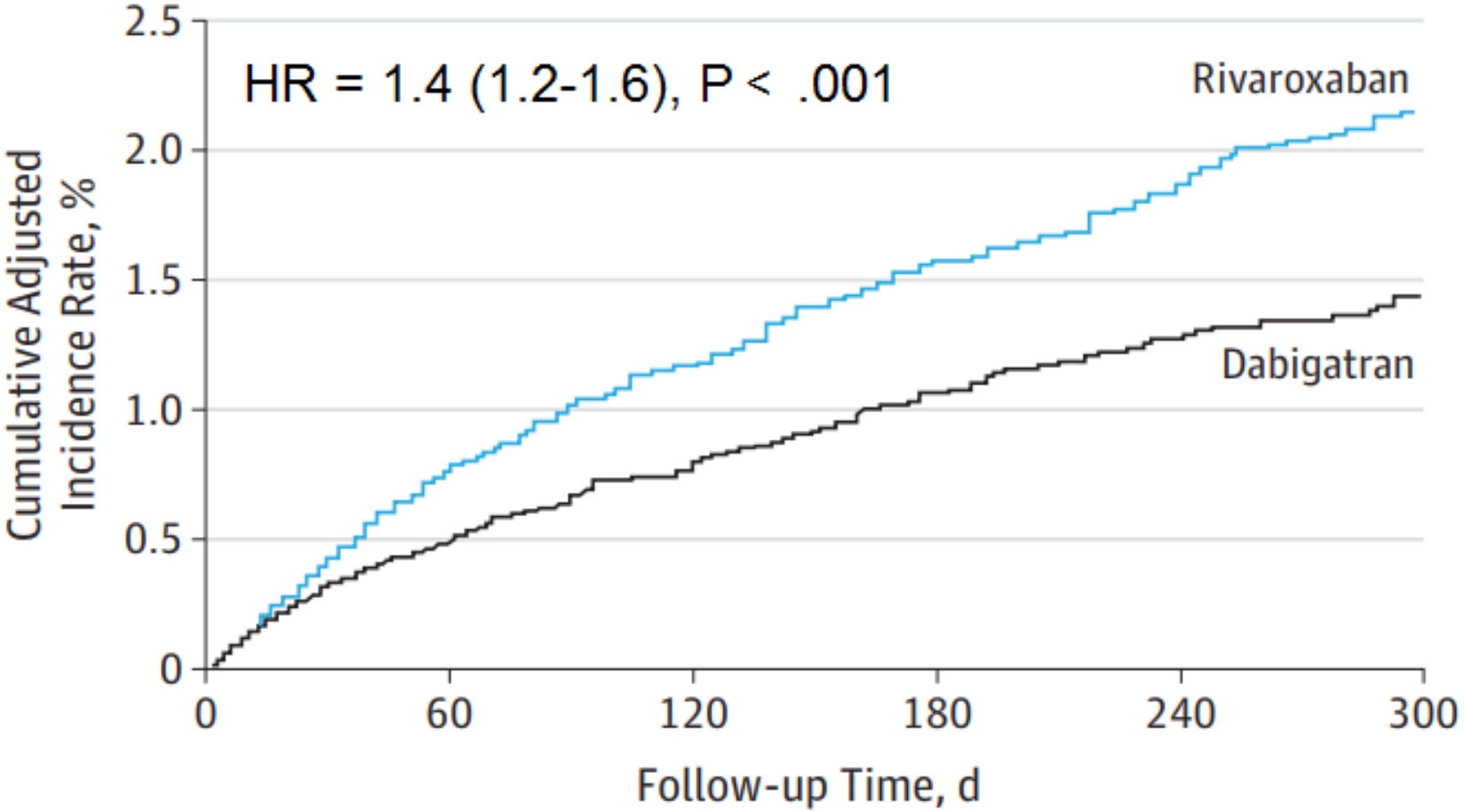
JAMA Internal Medicine | Original Investigation

Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Ya-Hui Hsueh, PhD; Rima Izem, PhD; Mary Ross Southworth, PharmD; Yuqin Wei, MS; Jiemin Liao, MA; Margie R. Goulding, PhD; Katrina Mott, MHS; Yoganand Chillarige, MPA; Thomas E. MaCurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMSc

- Retrospective new-user cohort study
- 118,891 Medicare patients with nonvalvular AF
- who initiated dabigatran 150 mg bid or rivaroxaban 20 qd

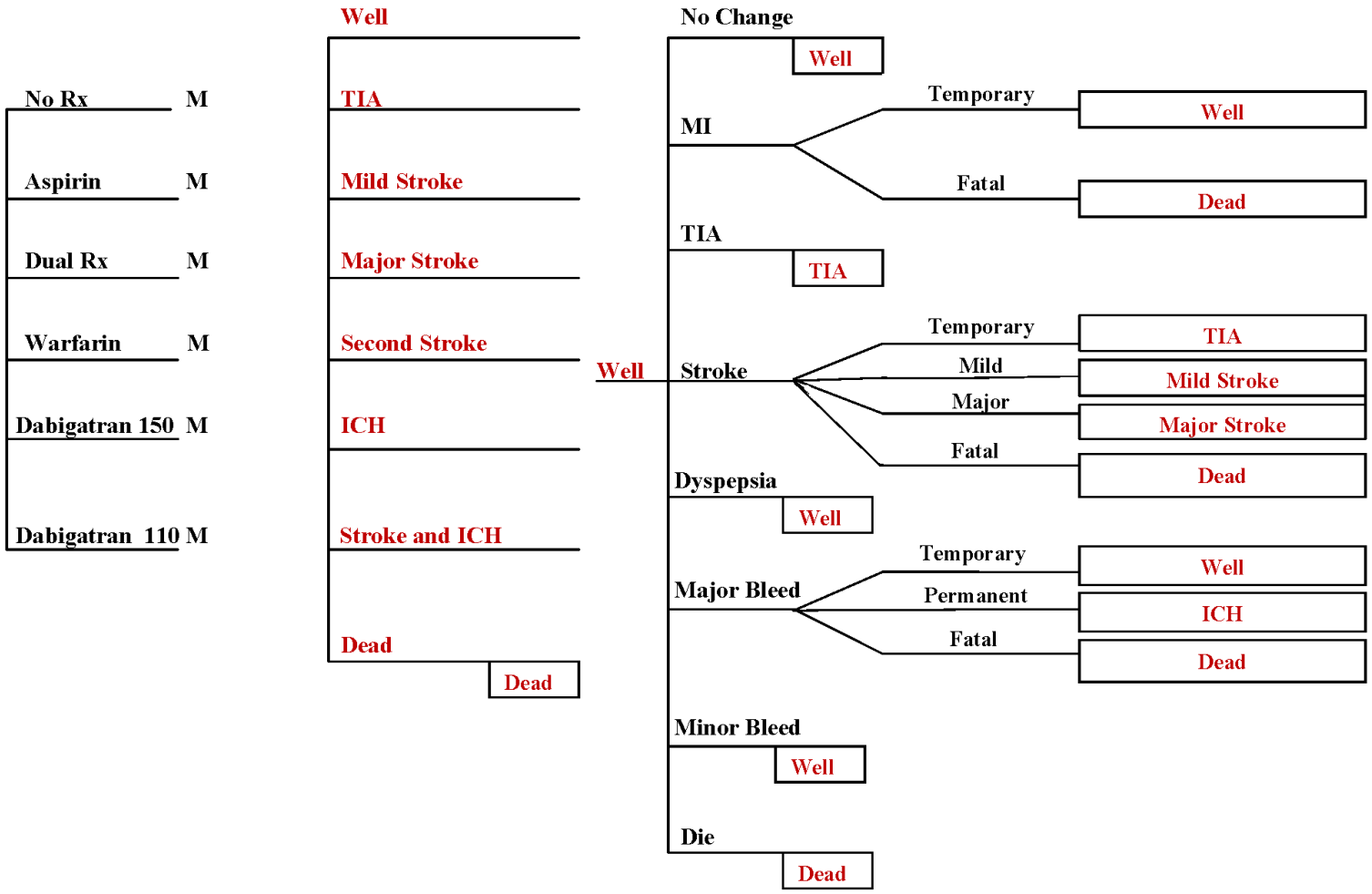
C Major gastrointestinal bleeding



D.J. Graham et al. JAMA Int Med 2016

Weighted No. at risk						
Dabigatran	52 264	26 729	13 355	9236	6156	4384
Rivaroxaban	66 630	35 707	19 527	12 947	8511	5753

Decision Tree To Estimate QALYs in Chronic AF



Shah S, Gage B. *Circulation* 2011

AF Stroke Risk Stratification $CHADS_2$

We calculated $CHADS_2$ by assigning points for the presence of each major risk factor for stroke in AF:

Congestive heart failure (1 point)
Hypertension (1 point)
Age > 75 years (1 point)
Diabetes mellitus (1 point)
Stroke or transient ischemic attack (2 points)

Gage B, Waterman A, Shannon W. et al. JAMA. 2001;285:2864-70

HEMORR$_2$HAGES Risk Factors	Definition
Hepatic (1) or ESRD (1)	Cr clearance < 30 ml/min
Ethanol use (1)	EtOH abuse
Malignancy (1)	Metastatic cancer
Older (age > 75) (1)	> 75 years
Reduced platelet count (1) or fcn (1)	Platelets < 75,000 ASA, clopidogrel, or NSAID
Re-Bleeding (2)	Prior bleeding
HTN, uncontrolled (1)	SBP $\geq$ 160
Anemia (1)	Hct < 30
Genetic factors (1)	CYP2C9*2, CYP2C9*3, etc.
Elevated risk of fall (1)	Alzheimer's, Parkinson's, etc.
Stroke (1)	Prior ischemic stroke

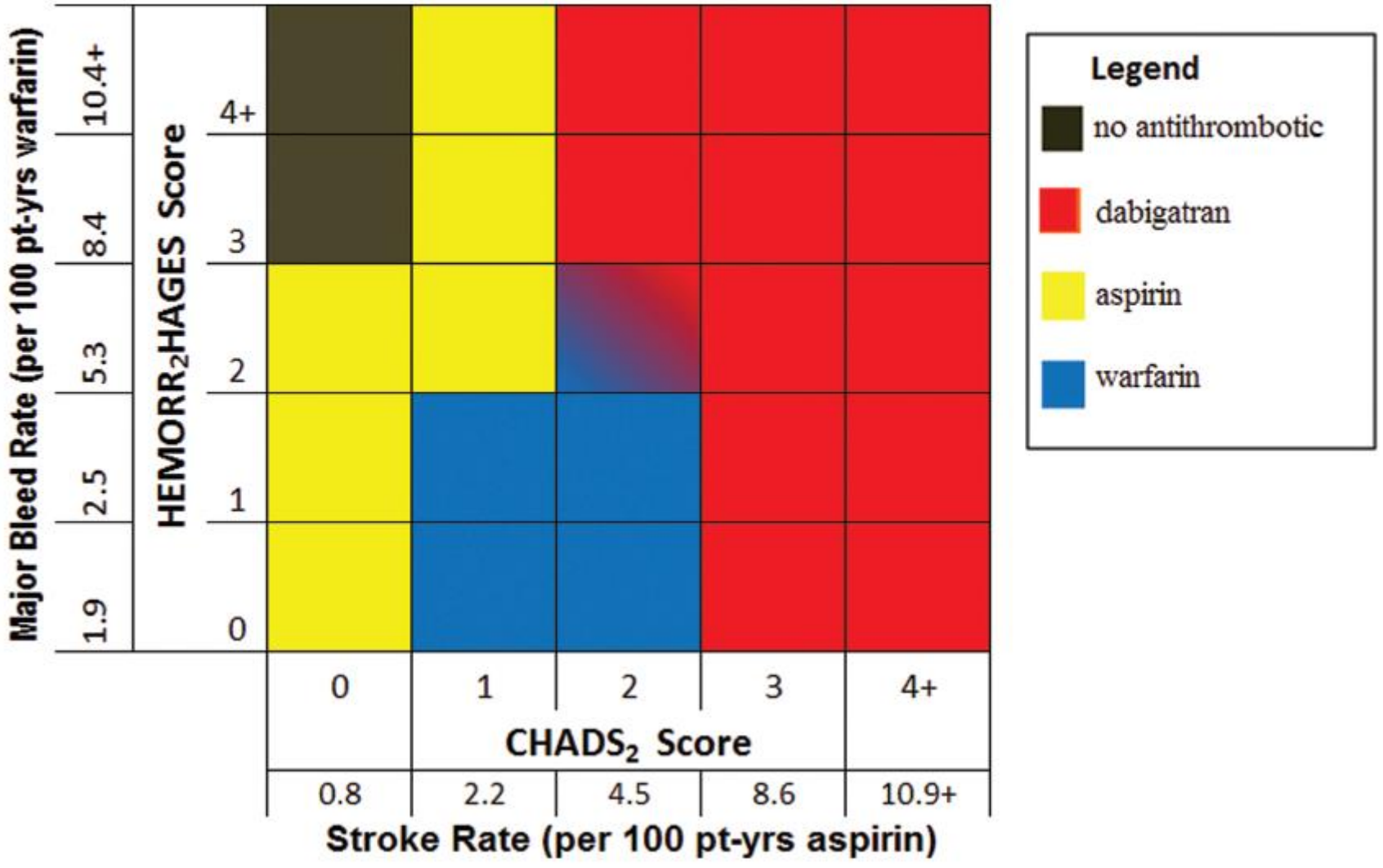
HEMORR$_2$HAGES Score Predicted Bleeding in NRAF

HEMORR$_2$HAGES Score	N	N of Bleeds	Bleeds per 100 pt-yrs warfarin (95% CI)
0	209	4	1.9 (0.6-4.4)
1	508	11	2.5 (1.3-4.3)
2	454	20	5.3 (3.4-8.1)
3	240	15	8.4 (4.9-13.6)
4	106	9	10.4 (5.1-18.9)
≧ 5	87	8	12.3 (5.8-23.1)

Gage BF et al. Am Heart J 2006

Shah and Gage

Cost-Effectiveness of Dabigatran

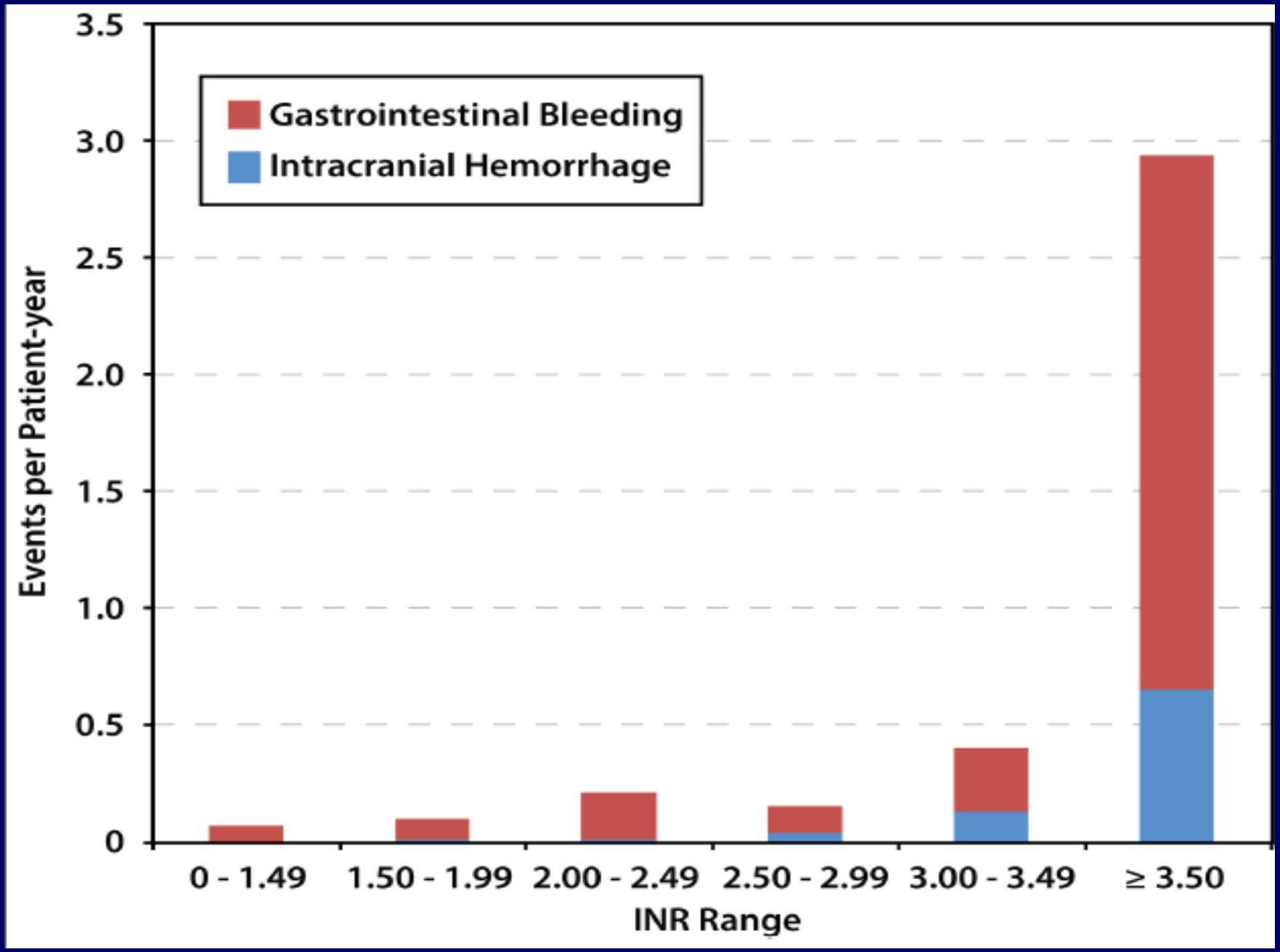


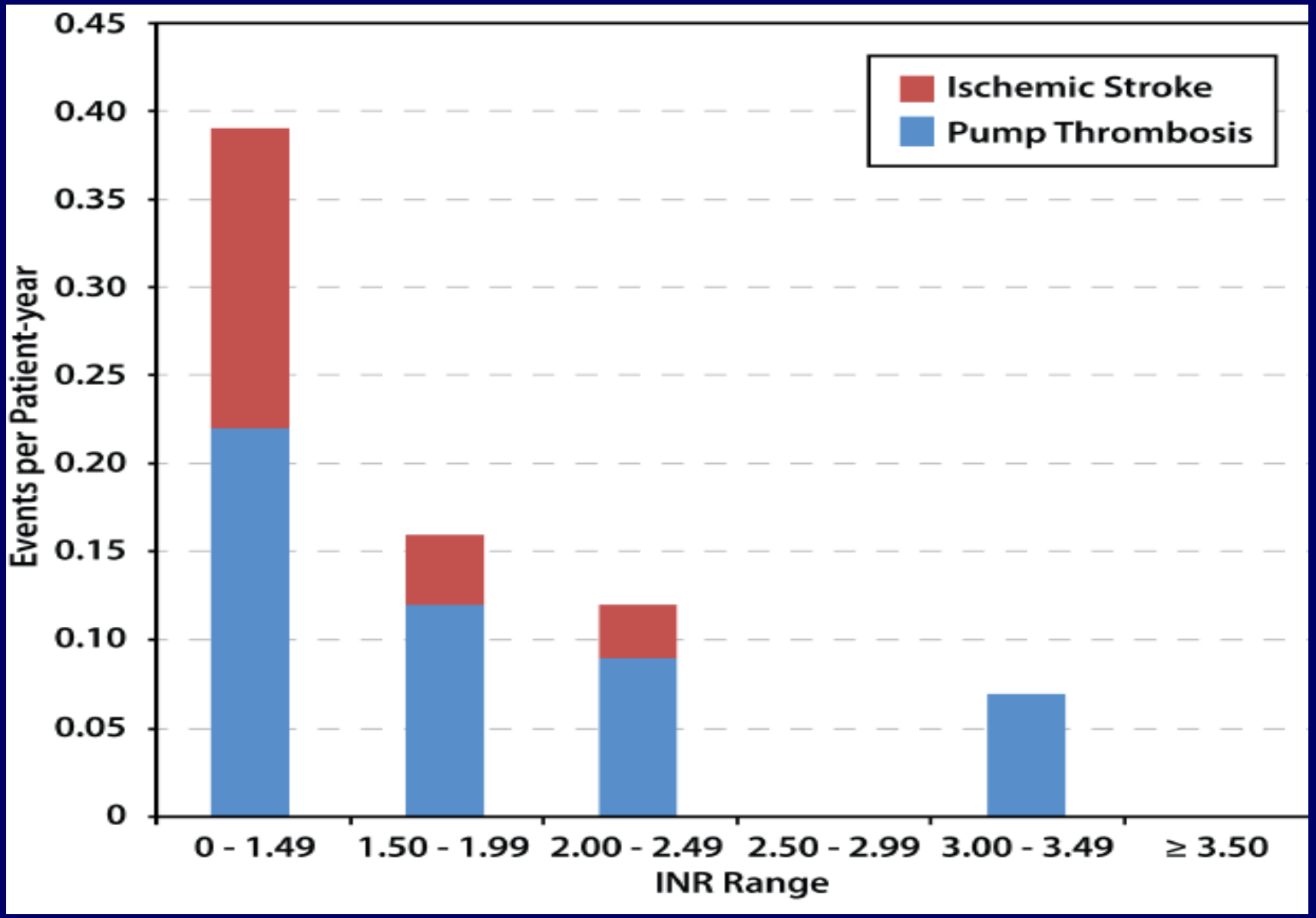
When To Avoid DOACs in AF

- Patients doing well on warfarin
- Patients with poor adherence
  - Longer half life of warfarin is better here
- Recent ICH
  - Avoid all anticoagulants (esp. warfarin)
- Recent ACS: avoid dabigatran
- Cr clearance < 30 ml/min
- Indigent patients w/out Medicaid
- Mechanical valve, LVAD

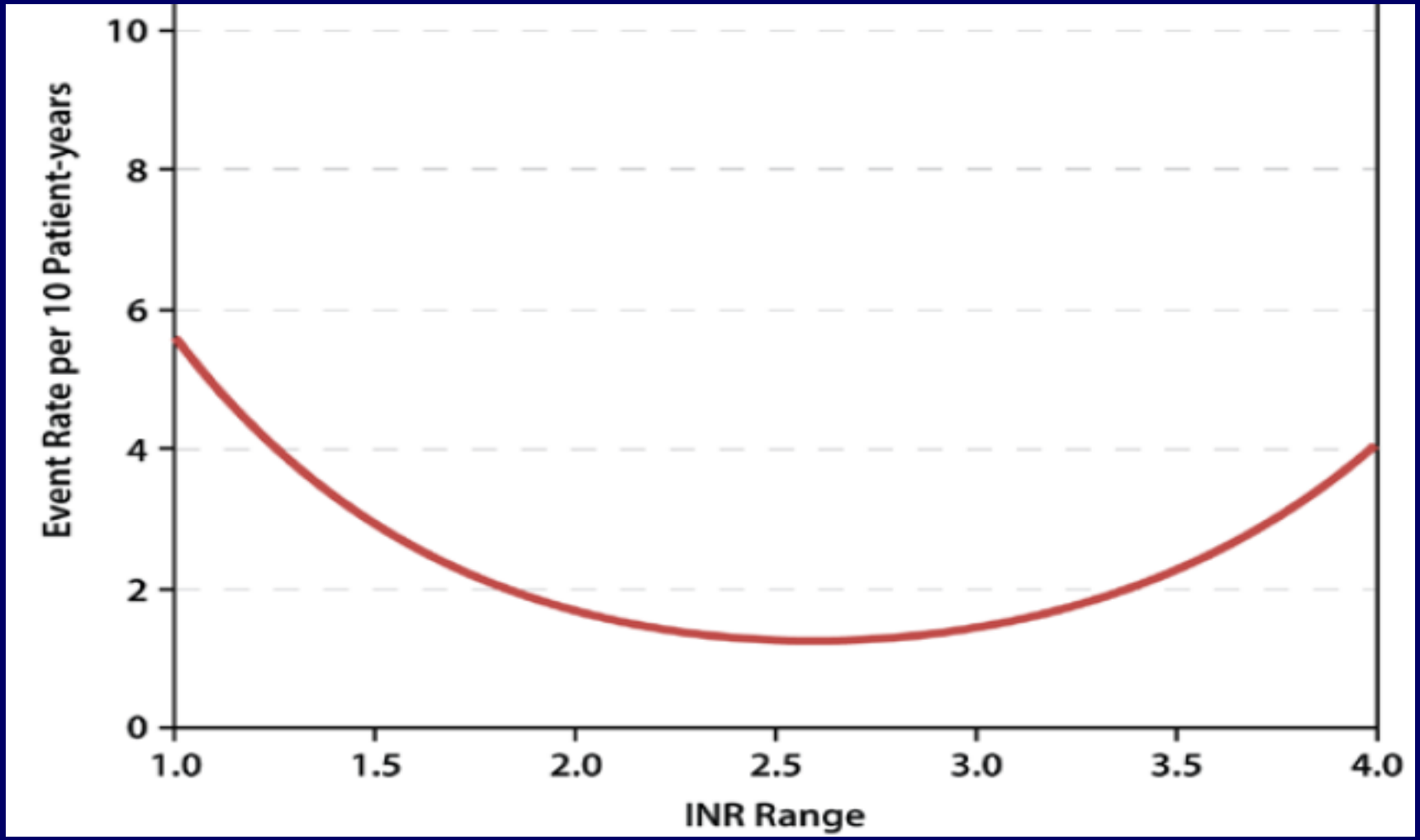
What INR to Target in Patients with Left Ventricular Assist Devices (LVAD)?

- Study by Nassif, LaRue et al. **Circulation Heart Failure** 2016
  - Poisson models analyzed 10,927 INRs to determine INR-specific rates of adverse events.


Gastrointestinal Bleeding
Intracranial Hemorrhage
Events per Patient-year
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
0 - 1.49
1.50 - 1.99
2.00 - 2.49
2.50 - 2.99
3.00 - 3.49
≥ 3.50
INR Range


Ischemic Stroke
Pump Thrombosis
Events per Patient-year
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0 - 1.49
1.50 - 1.99
2.00 - 2.49
2.50 - 2.99
3.00 - 3.49
≥ 3.50
INR Range

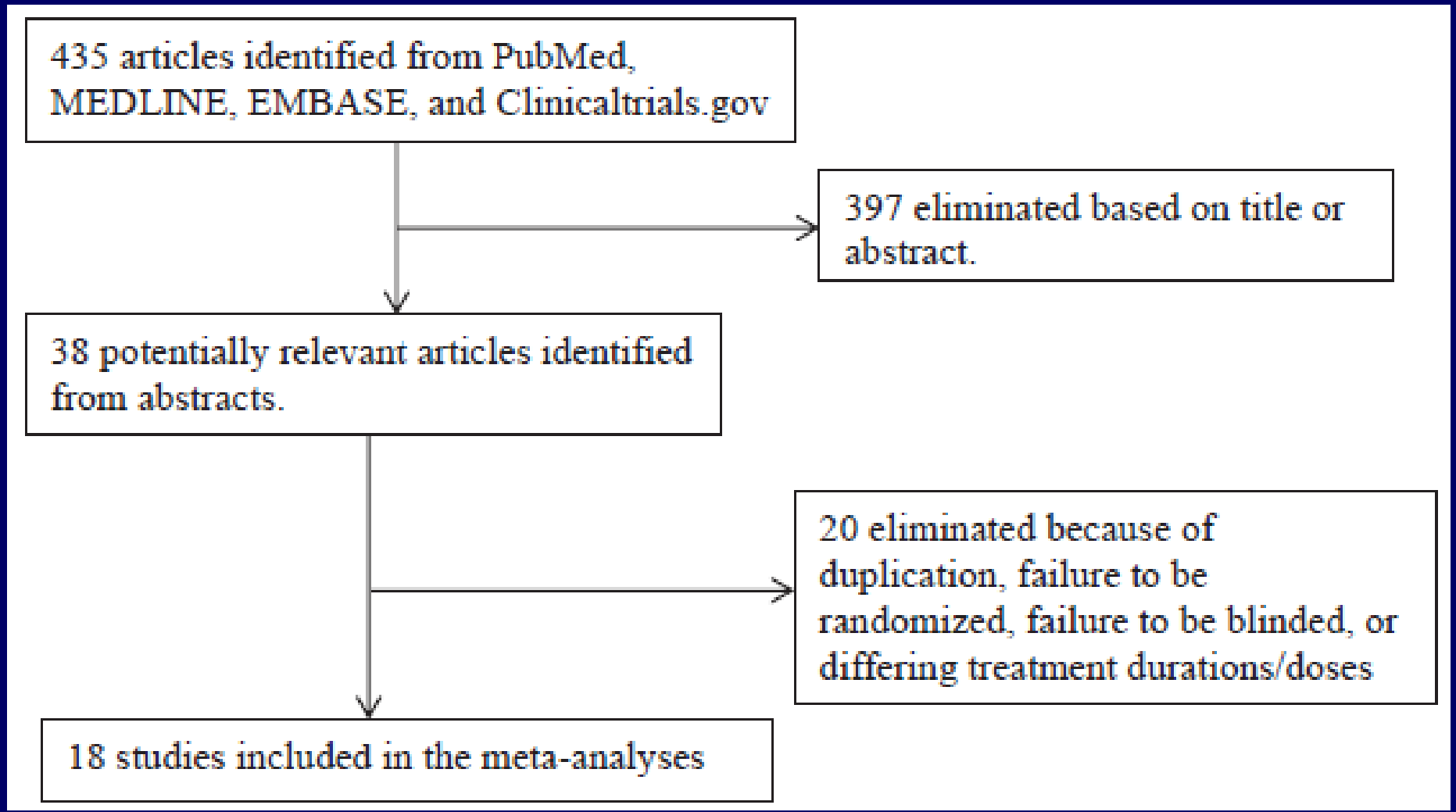
INR ~2.6 Minimized Events in LVADs (events weighted by their mortality)

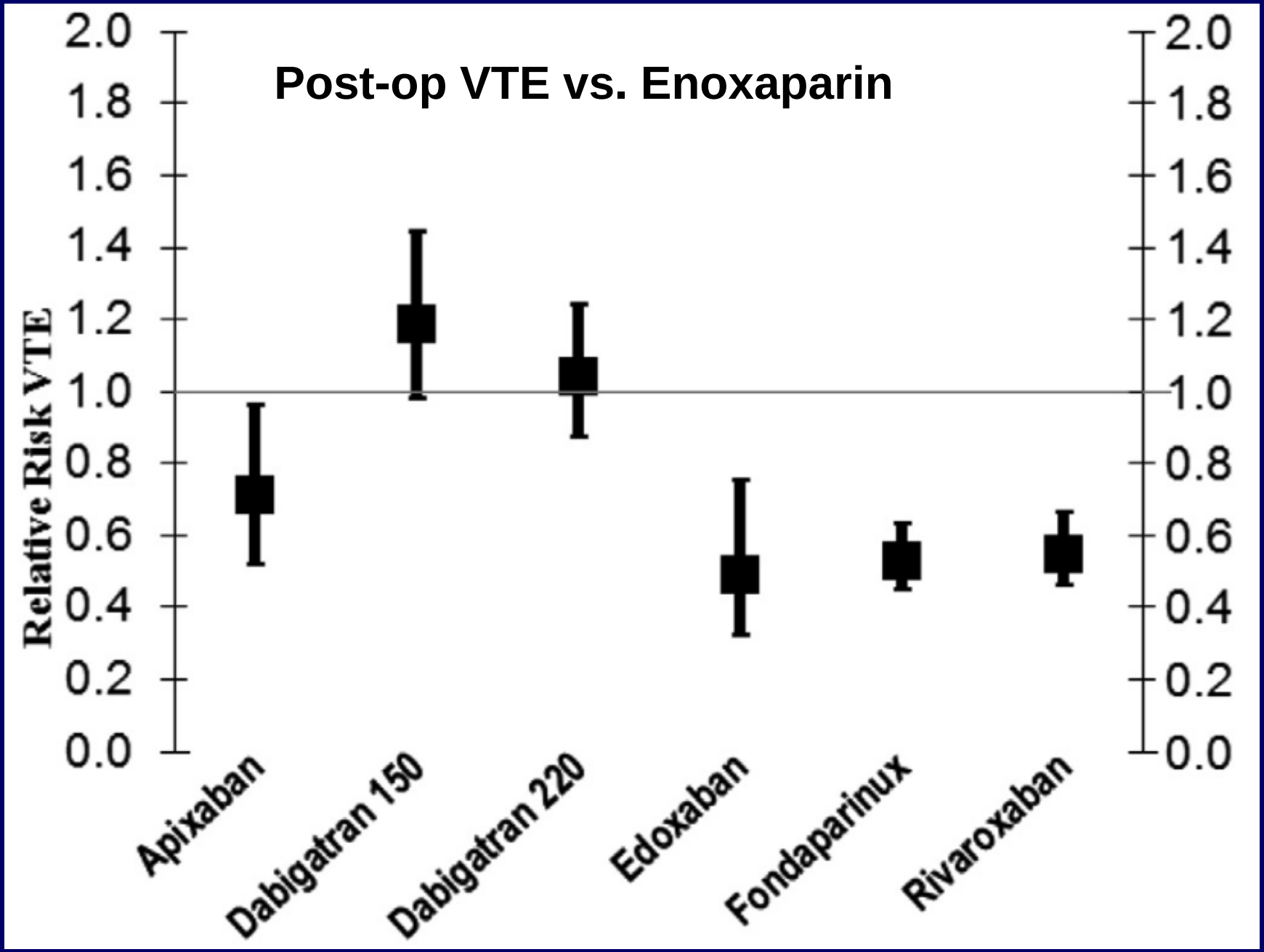


Patients Undergoing Major Orthopedic Surgery: Total Hip Arthroplasty (THA), Total Knee Arthroplasty (TKA), Hip Fracture Surgery (HFS) (ACCP 2012)

… recommend use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular-weight heparin, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin, adjusted-dose vitamin K antagonist, aspirin (all Grade 1B), or an intermittent pneumatic compression device (Grade 1C).

Selection process for trials included in meta-analyses (B. Venker et al. 2017)




Post-op VTE vs. Enoxaparin
Relative Risk VTE
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Apixaban
Dabigatran 150
Dabigatran 220
Edoxaban
Fondaparinux
Rivaroxaban

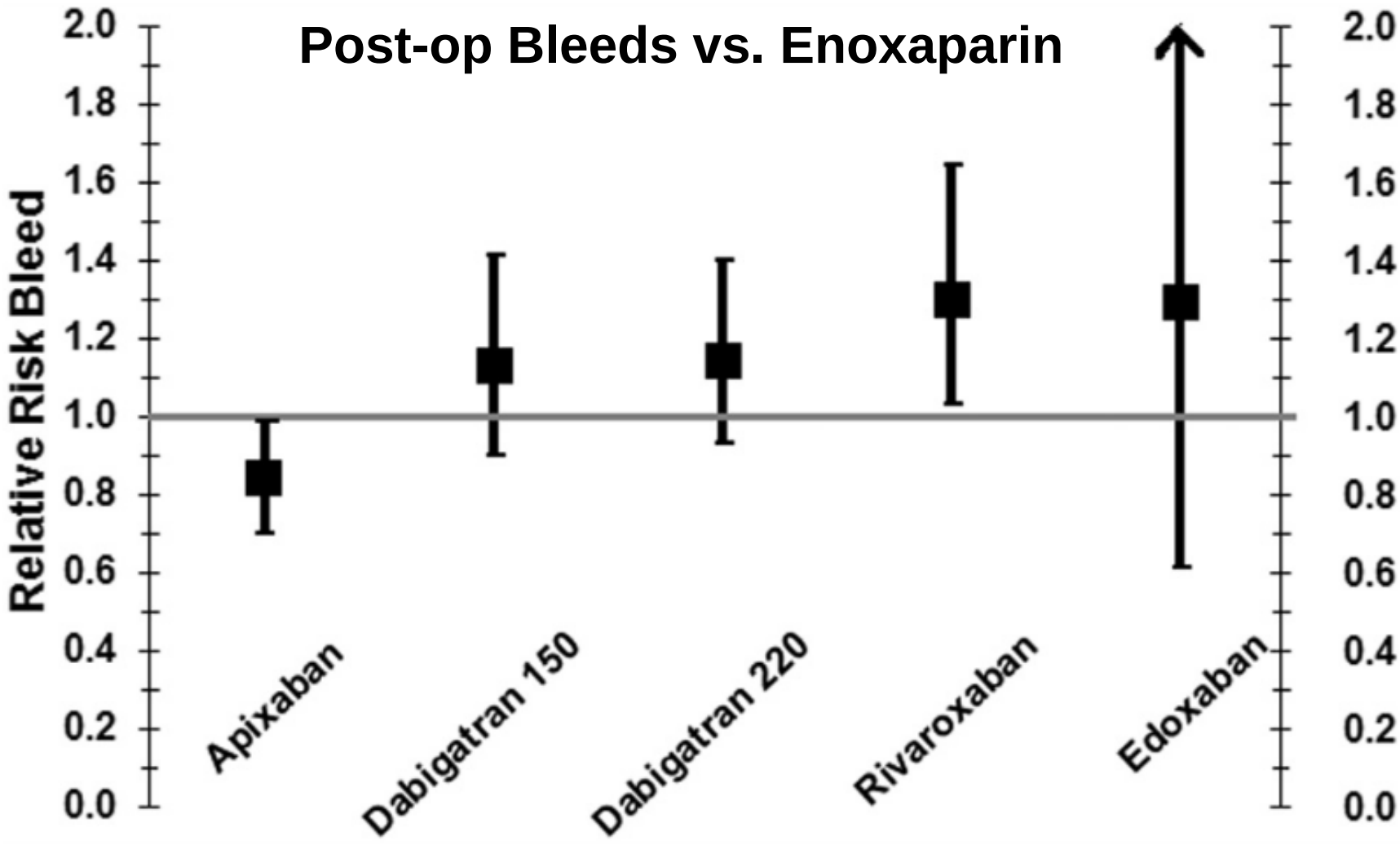


Fig. 3. Pooled RR of major/clinically relevant bleeding for newer anticoagulants compared to enoxaparin.

Brian's Recommendation's for TKA, TKA

1 month of: LWMH, apixaban, warfarin, or ASA; or 5 days of rivaroxaban followed by ASA

Rivaroxaban if prior VTE

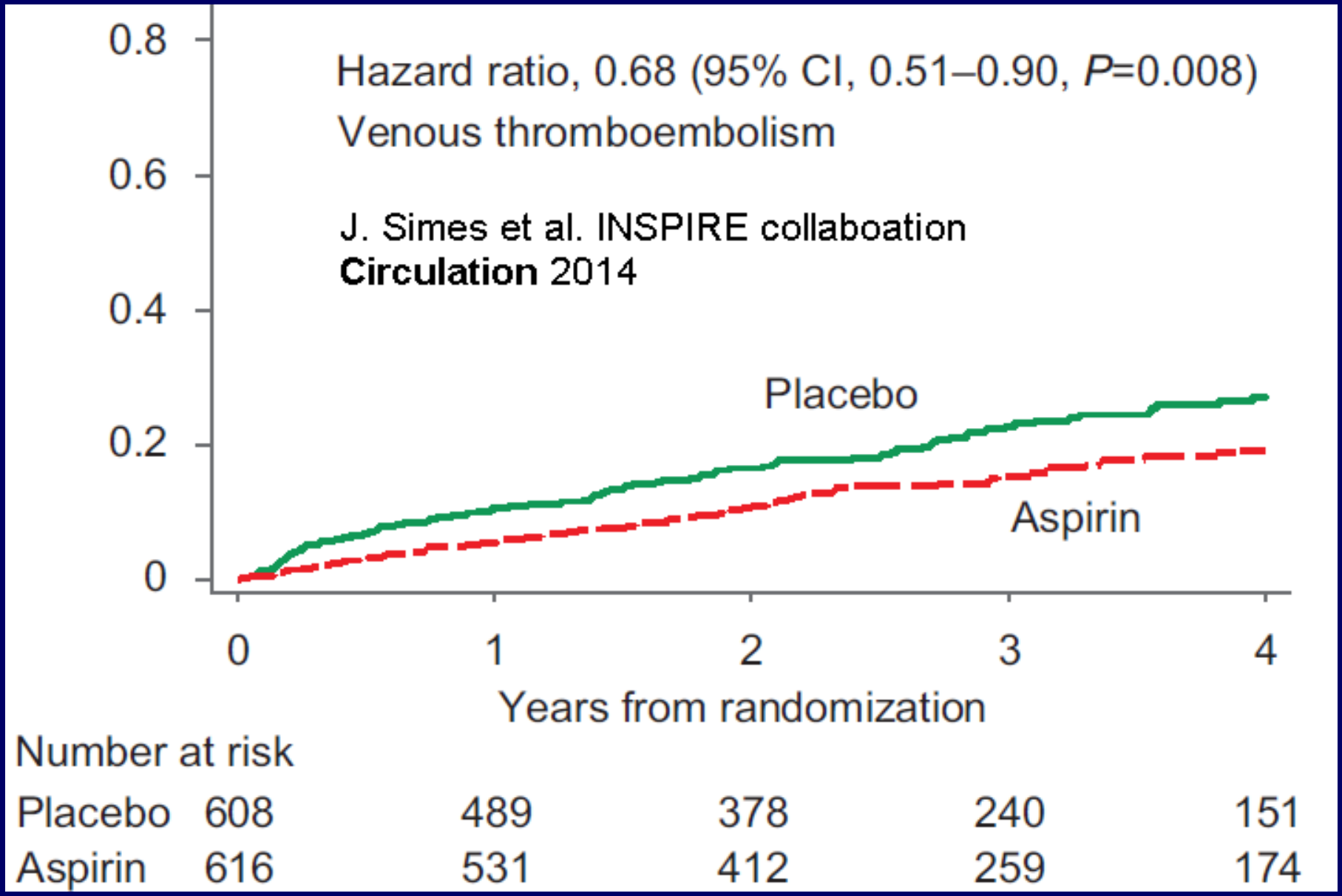
Esp. if using ASA (e.g. low VTE risk), combine with intermittent pneumatic compression.

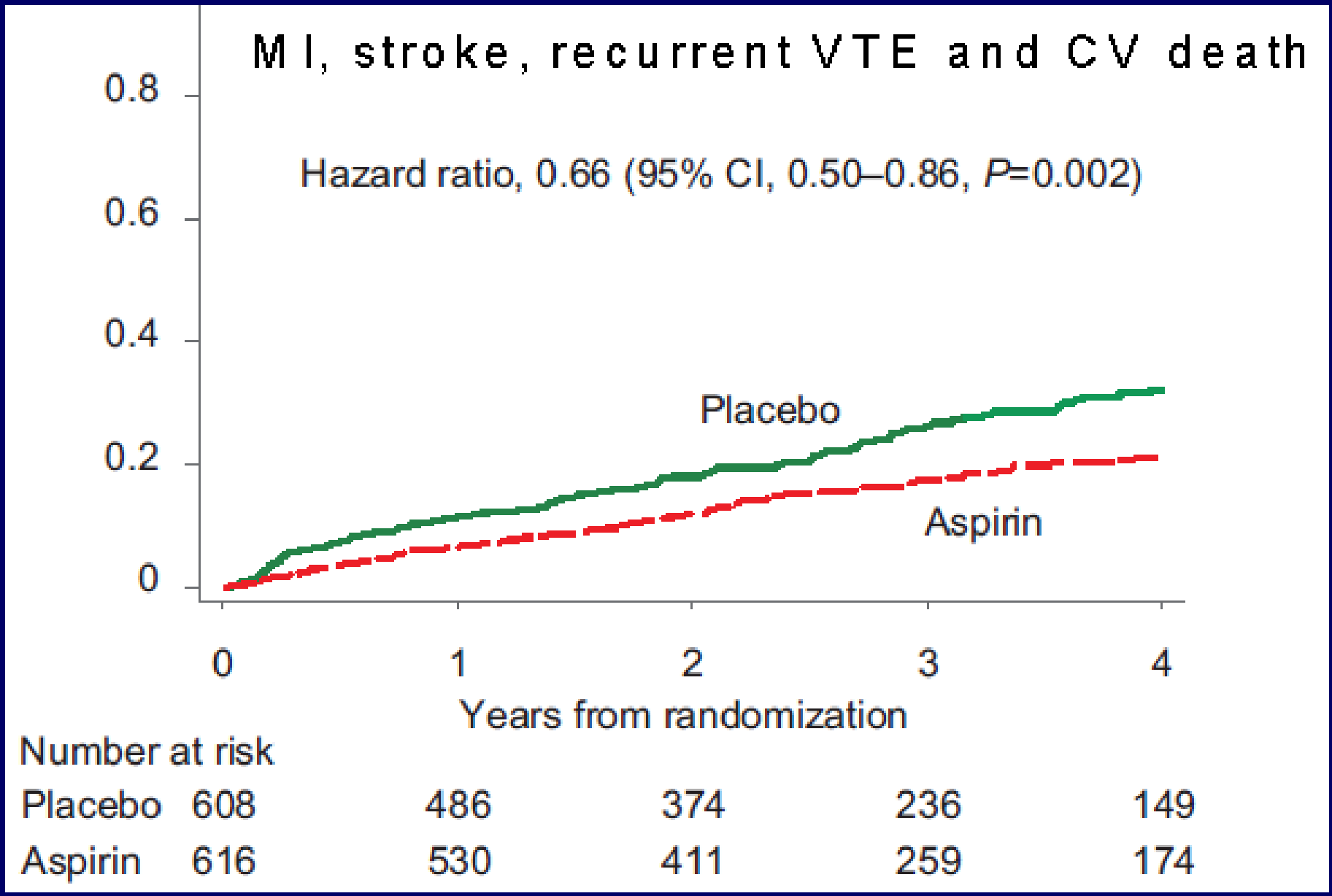
Antithrombotic Therapy for VTE Tx: CHEST Guideline 2016

- For VTE w/out CA: DOACs
  - e.g. apixaban 10 mg bid x 7 days, then 5 mg bid
- Exceptions:
  - VKA if Cr Cl < 30 mL/min
  - LMWH if cancer
- Duration AC post provoked VTE: 3-months, then ASA
- Duration AC post unprovoked VTE: 6+ months.

Aspirin for the Prevention of Recurrent VTE?

- **INSPIRE combined raw data from two trials of low-dose ASA: ASPIRE & WARFASA.**

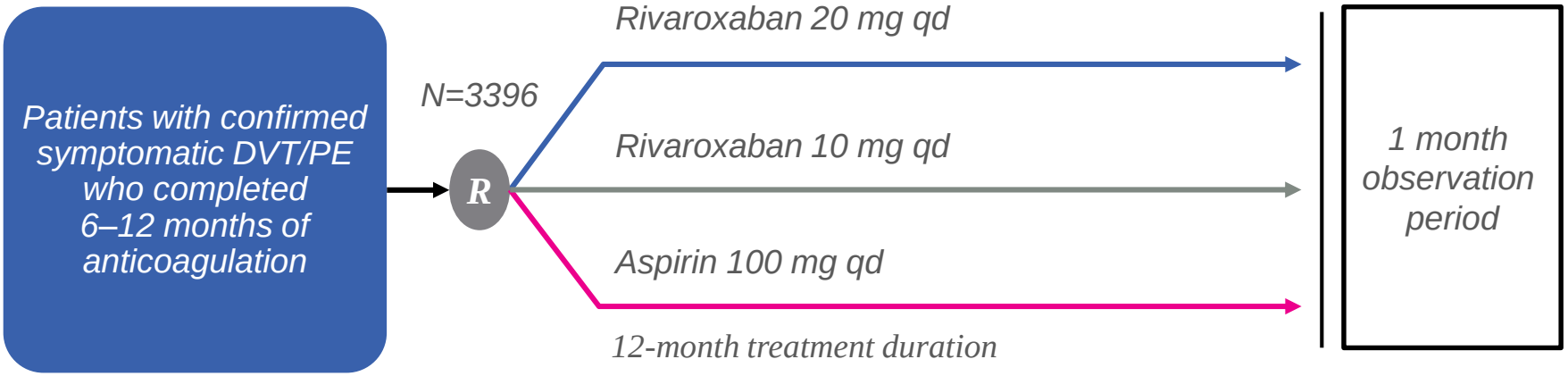

Hazard ratio, 0.68 (95% CI, 0.51–0.90, P=0.008)
Venous thromboembolism
J. Simes et al. INSPIRE collaboation
Circulation 2014
Placebo
Aspirin
0.8
0.6
0.4
0.2
0
0
1
2
3
4
Years from randomization
Number at risk
Placebo 608 489 378 240 151
Aspirin 616 531 412 259 174



J. Simes et al. for INSPIRE ***Circulation*** *2014*

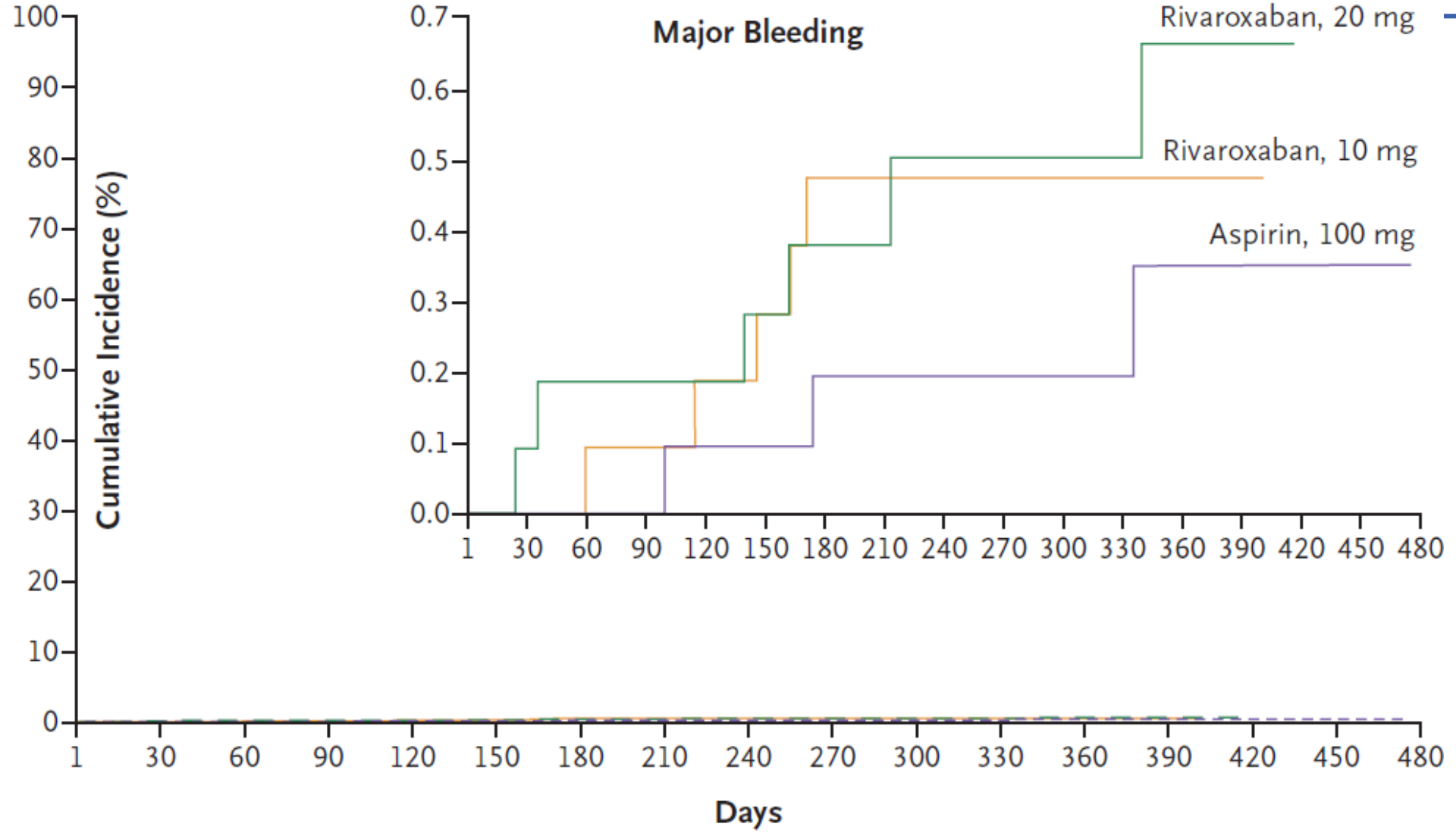
EINSTEIN CHOICE Study Design

- Aim: Compare the efficacy and safety of once daily rivaroxaban (20 or 10 mg) with aspirin (100 mg) in VTE patients who completed 6 to 12 months of treatment and with equipoise regarding the need for extended anticoagulation
- Randomized, double-blind, event-driven, superiority study

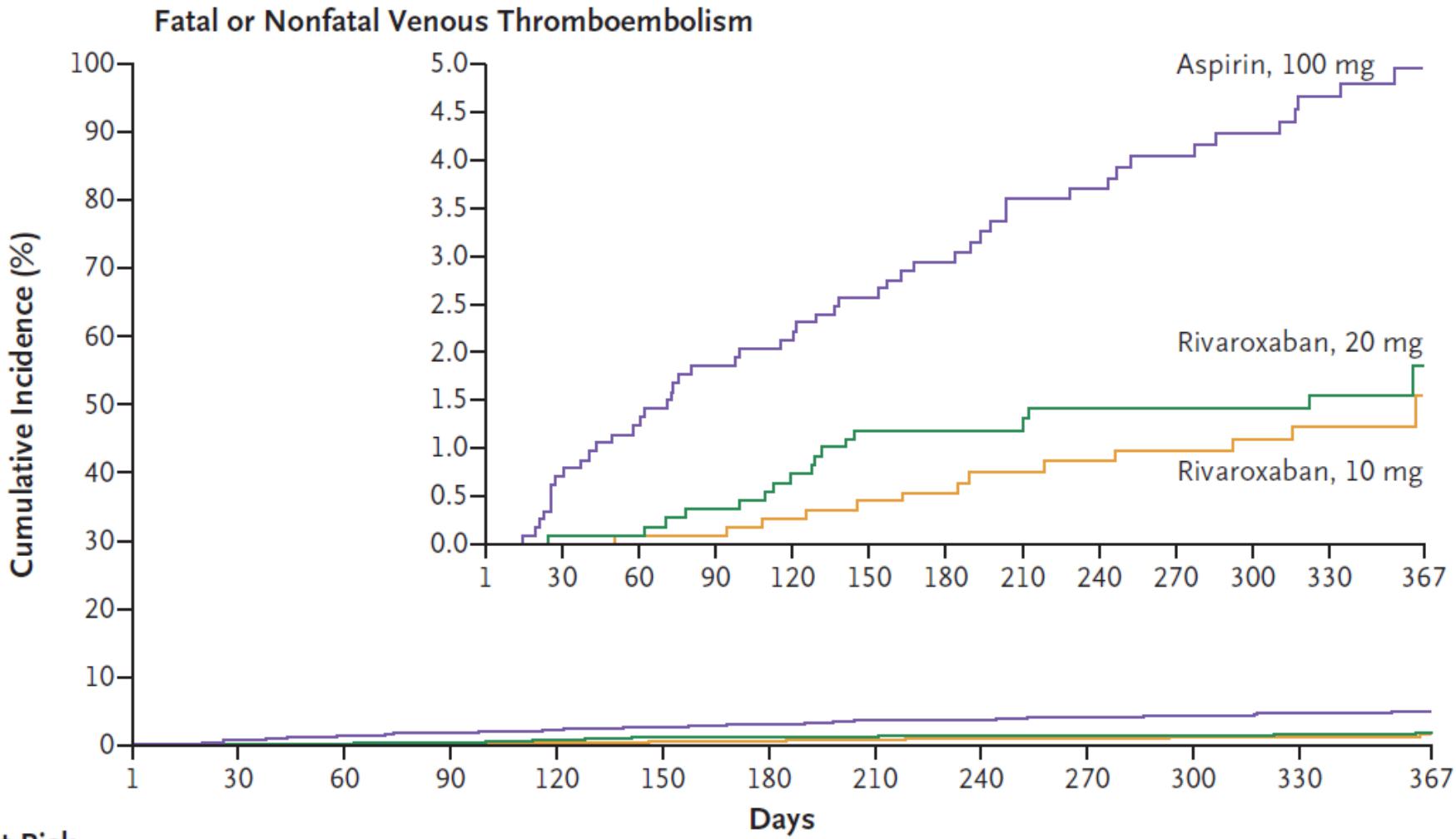


Weitz JI et al. Thromb Haemost 2015;114:645–50

Major Bleeding in EINSTEIN CHOICE:



Recurrent VTE in EINSTEIN CHOICE

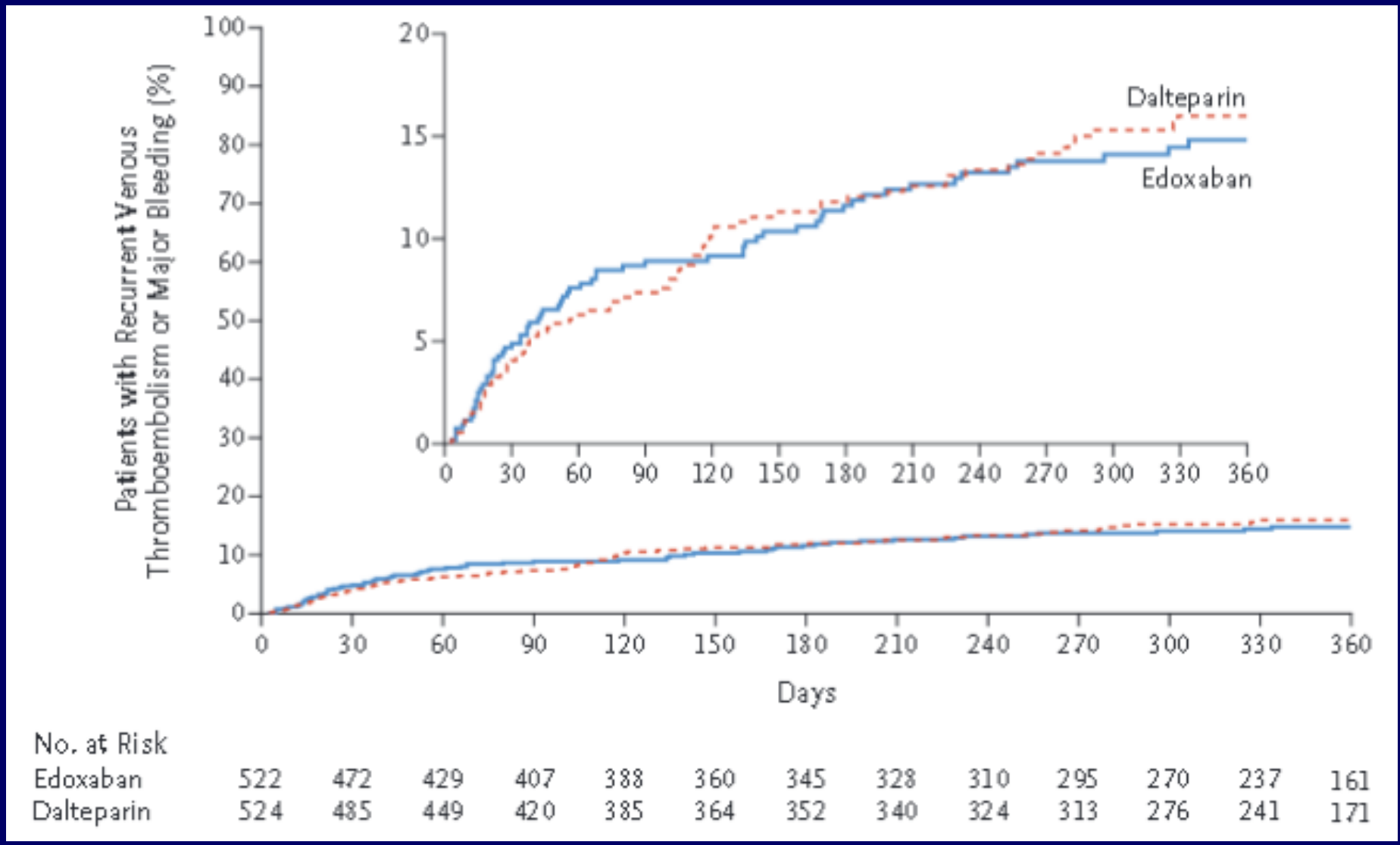


No. at Risk

Riva, 20 mg	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Riva, 10 mg	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspir	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

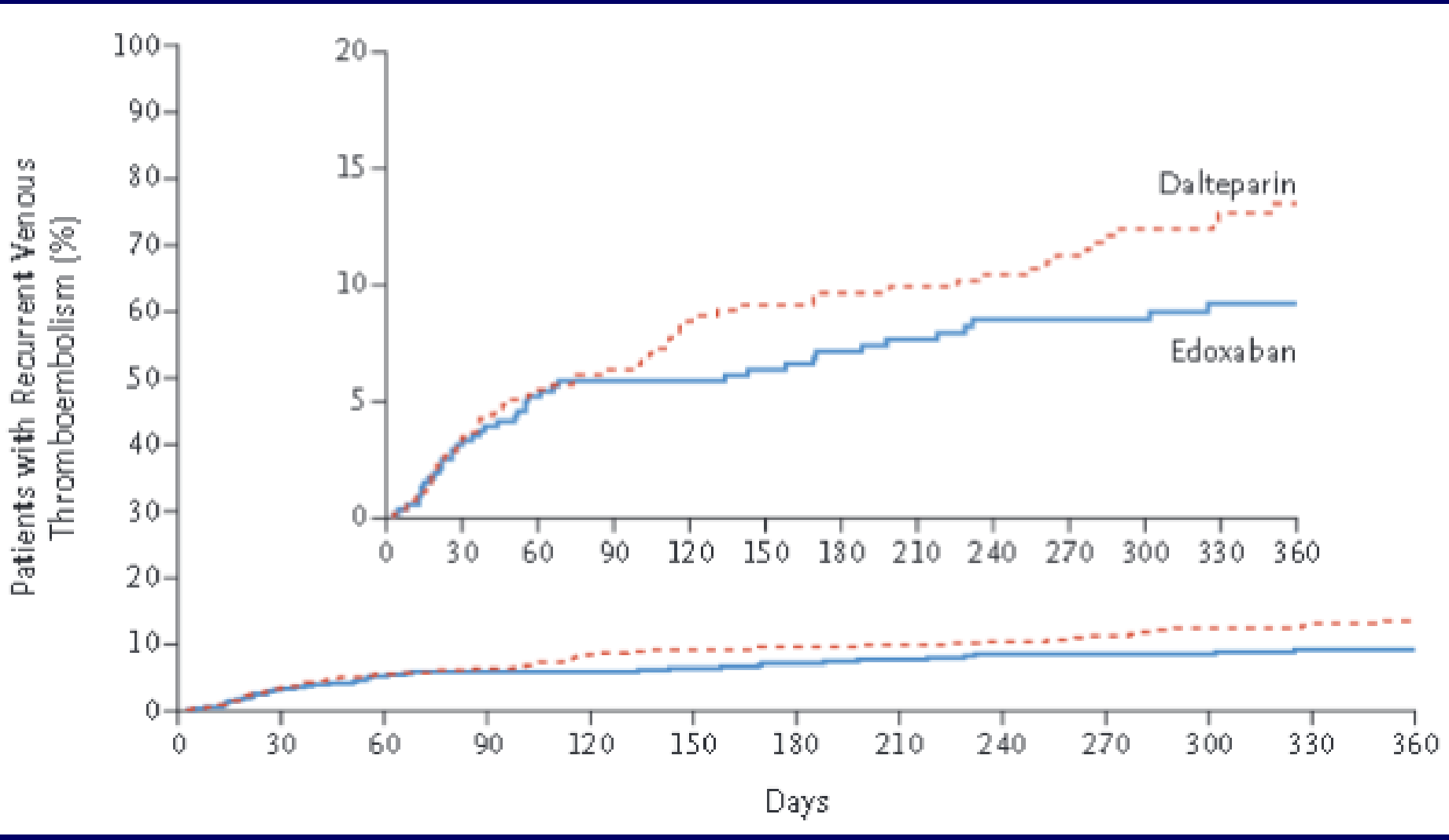
CA-Associated VTE

- See the Hokusai VTE Cancer Trial:
- http://www.nejm.org/doi/full/10.1056/NEJMoa1711948#t=article

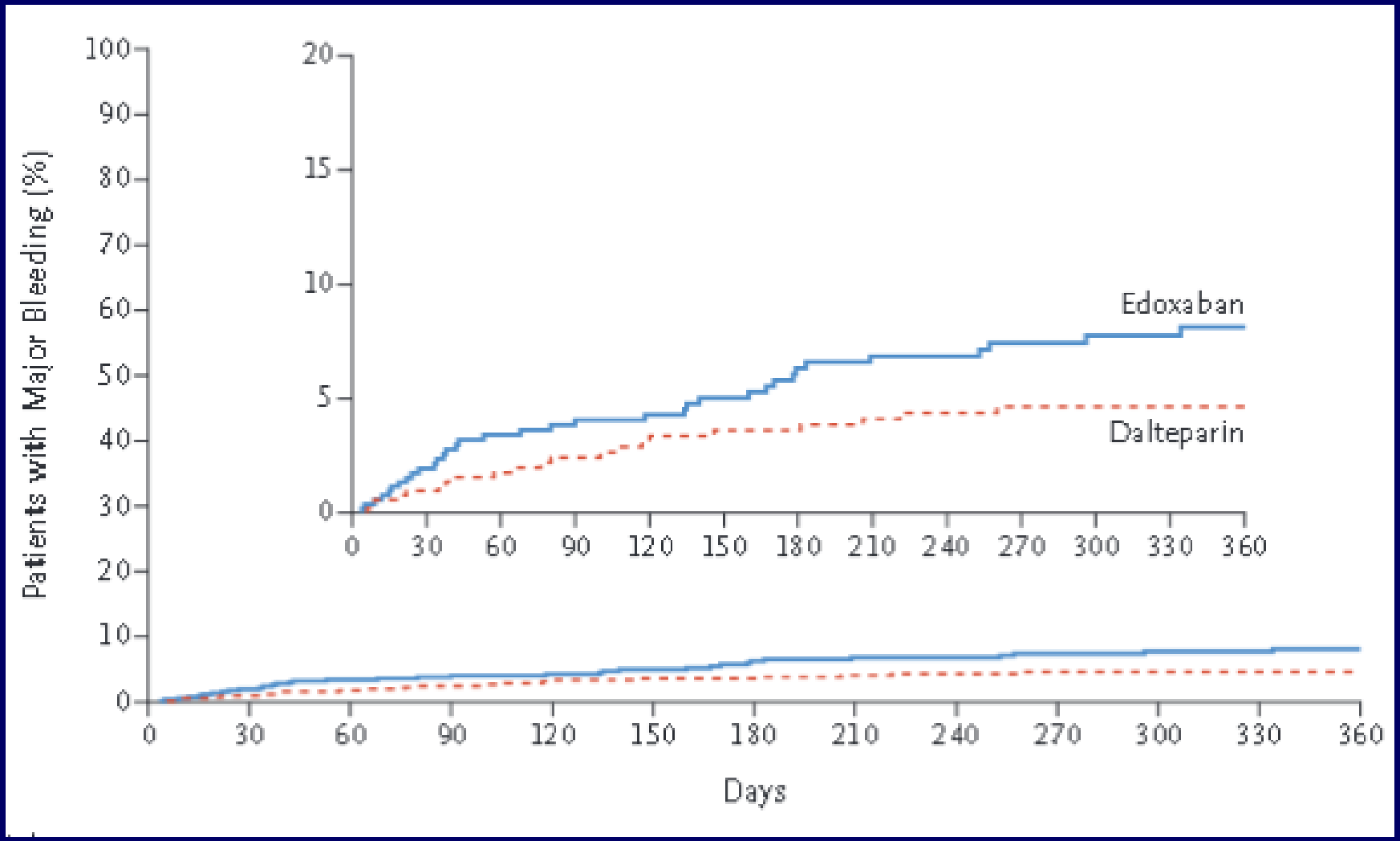


No. at Risk													
Edoxaban	522	472	429	407	388	360	345	328	310	295	270	237	161
Dalteparin	524	485	449	420	385	364	352	340	324	313	276	241	171

VTE Recurrence: Lower w/ Edoxaban?



Major Bleeding: Lower w/ Dalteparin

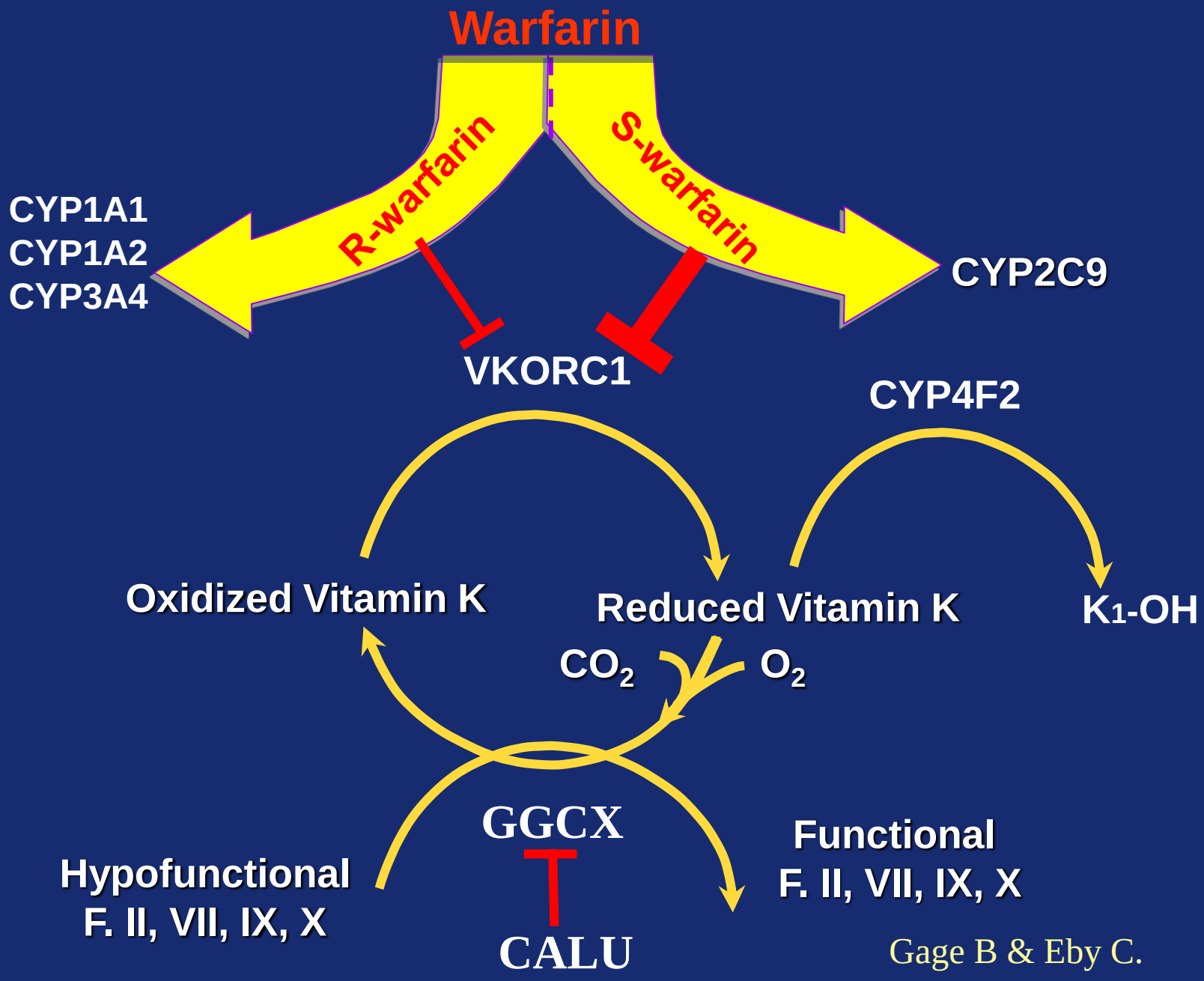


Genetics Informatics Trial (GIFT) of Warfarin Therapy for DVT Prevention

- Hypothesis: Pharmacogenetic dosing of warfarin therapy decreases the rate of adverse events vs. clinical-algorithm dosing

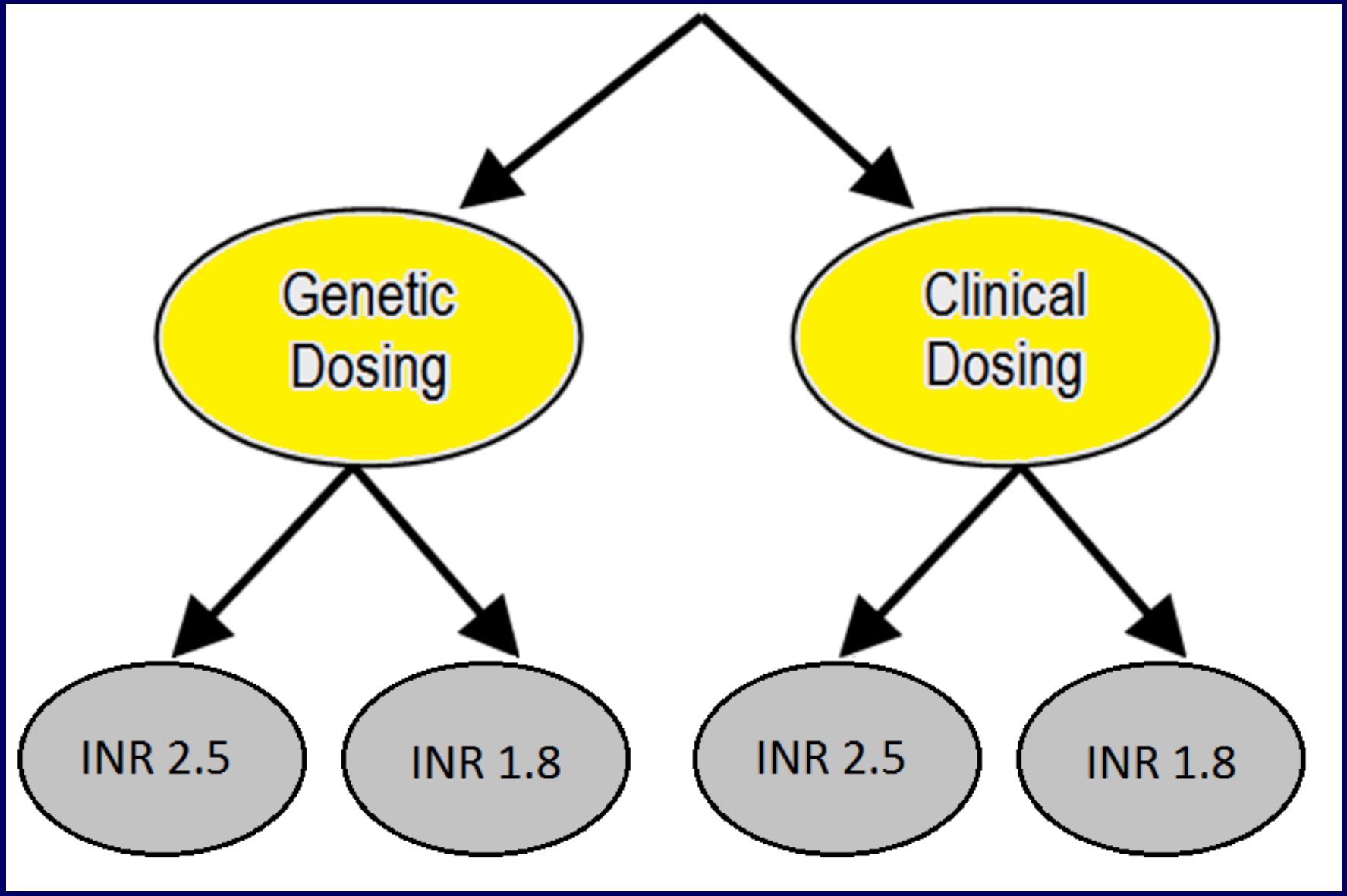
- What primary outcome would you use?

- Whom would you enroll?



Gage B & Eby C.
Pharmacogenomics J. 2004

2 x 2 Factorial Design



Randomization & Double Blinding

- Randomized 1:1 to genetic vs. clinical dosing
  - stratified by arthroplasty site, self-identified race, and center: HSS, Intermountain Healthcare, Rush, University of Utah, UT Southwestern, and WUSTL
- Participants and study personnel were blind to study arm and genotype, but not to warfarin dose

Primary Results (N = 1597)

Endpoint	Genotype Group, N = 808, % (N)	Clinical Group, N = 789, % (N)	P-value
Major bleed (days 1-30)	**0.25% (2)**	**1.01% (8)**	**0.062**
INR ≥ 4 (days 1-30)	**6.9% (56)**	**9.8% (77)**	**0.041**
VTE (days 1-60)	**4.1% (33)**	**4.8% (38)**	**0.48**
Death (days 1-30)	**0.0% (0)**	**0.0% (0)**	**1.00**
Total	10.8% (87)	14.7% (116)	0.018

Genetic dosing reduced the relative risk of adverse outcomes by 27% (RR=0.73; 95% CI: 0.56 – 0.95).

Secondary Outcome: Percentage of Time in the Therapeutic Range (PTTR) During Days 4-28 of Warfarin Therapy

Analyses	Genotype-Group		Clinical Group		Mean Difference	
	N	PTTR	N	PTTR	(95% CI)	P Value
Overall	803	54.7	785	51.3	3.4 (1.1, 5.8)	0.004
High-risk	321	55.5	333	48.4	7.0 (3.4, 10.6)	0.0002
Stratified by Target INR						
Target 2.5 (2.0-3.0)	399	56.2	389	50.4	5.8 (2.5, 9.1)	0.0006
Target 1.8 (1.5-2.1)	404	53.3	396	52.1	1.1 (-2.2, 4.5)	0.51

Anticoagulant Therapy

- AF: dabigatran if high risk of stroke; otherwise apixaban, warfarin, or ASA.
- Arthroplasty: LMWH, apixaban, warfarin, ASA + IPC devices; (rivaroxaban if high risk)
- Post-VTE: DOAC (if eGFR > 30 and no CA)
  - Extended therapy w/ low-dose DOAC (e.g. rivaroxaban 10 mg/d or apixaban 2.5 mg bid) is almost as safe as low-dose ASA.
- Pharmacogenetic dosing of warfarin reduced high INRs after arthroplasty