IHS WG on ACC

8th International Conference on Acute Cardiac Care

Jerusalem, Israel
June 16-18, 2013

Will Apixaban change practice in atrial fibrillation

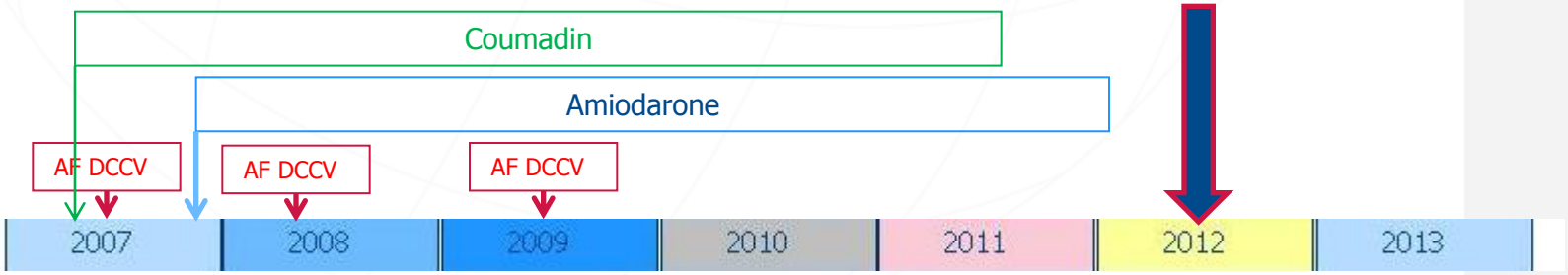
Luncheon Satellite Sponsored by Pfizer

Patient with high risk for bleeding

Prof. Amos Katz M.D
המרכז הרפואי ע"ש ברזילי, אשקלון
THE BARZILAI MEDICAL CENTER ASHKELON
מדינת ישראל
משרד הבריאות
affiliated to the Faculty of Health Sciences
Ben-Gurion University of The Negev
מסונף לפקולטה למדעי הבריאות
אוניברסיטת בן-גוריון בנגב

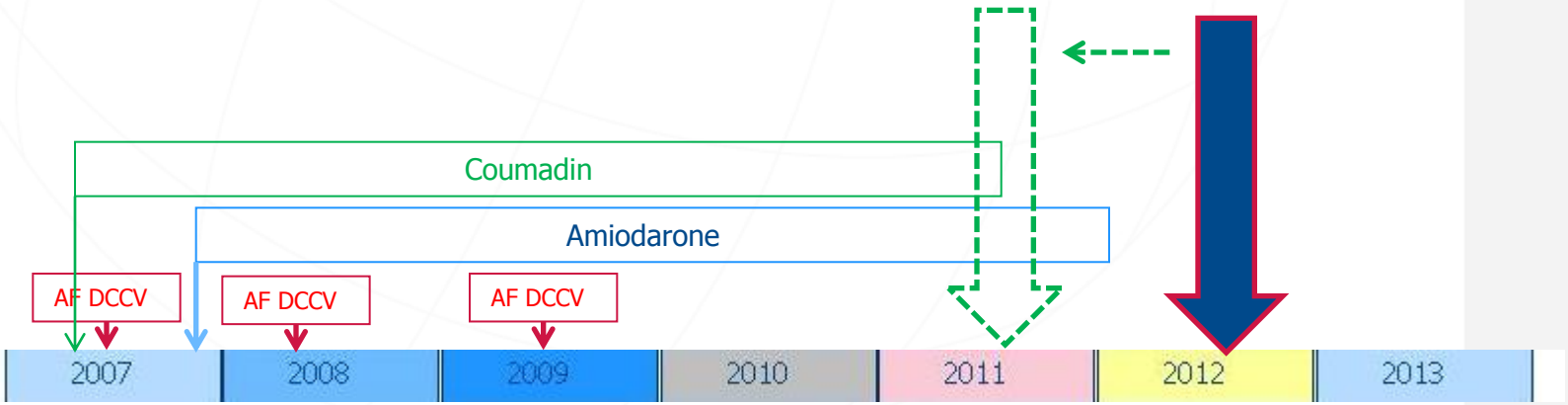
August 2012: patient background

- 67-year-old woman
- History of coronary artery disease
  - Coronary intervention; 12/2006 PCI BMS to RCA
  - Last Coronary angiography; 7/2011, patent RCA, D1 90%, conservative treatment
- Medical History:
  - Hypertension
  - T2 DM
  - Dyslipidemia
  - Lung bronchiectasis COPD
  - Obesity ; BMI=35
  - eGFR =55
- Diagnosis of AF since 2007
  - DC CV; 2007, 2008, 2009
  - Rx Amiodarone until 2012
  - Rx Coumadin until 2011

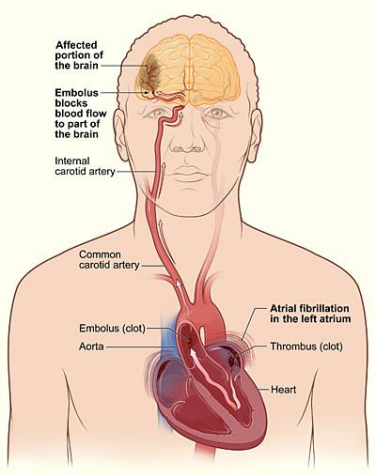


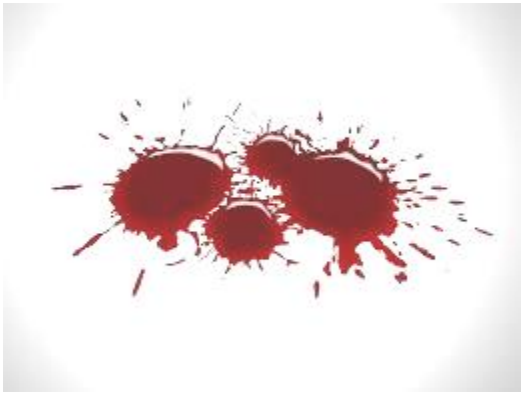
August 2011:

- August 2011 – labile INR [4.5-7]
- Major lung bleeding: hemoptysis
- Coumadin – stopped
- Medications:
  - Aspirin, Metformine, Valsartan, Rosuvastatin



Patient with high risk for bleeding





Efficacy:

All stroke (ischaemic + aemorrhagic)

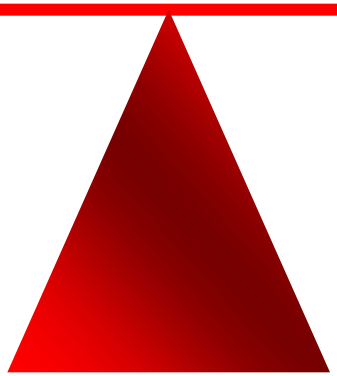
& systemic embolism

Safety:

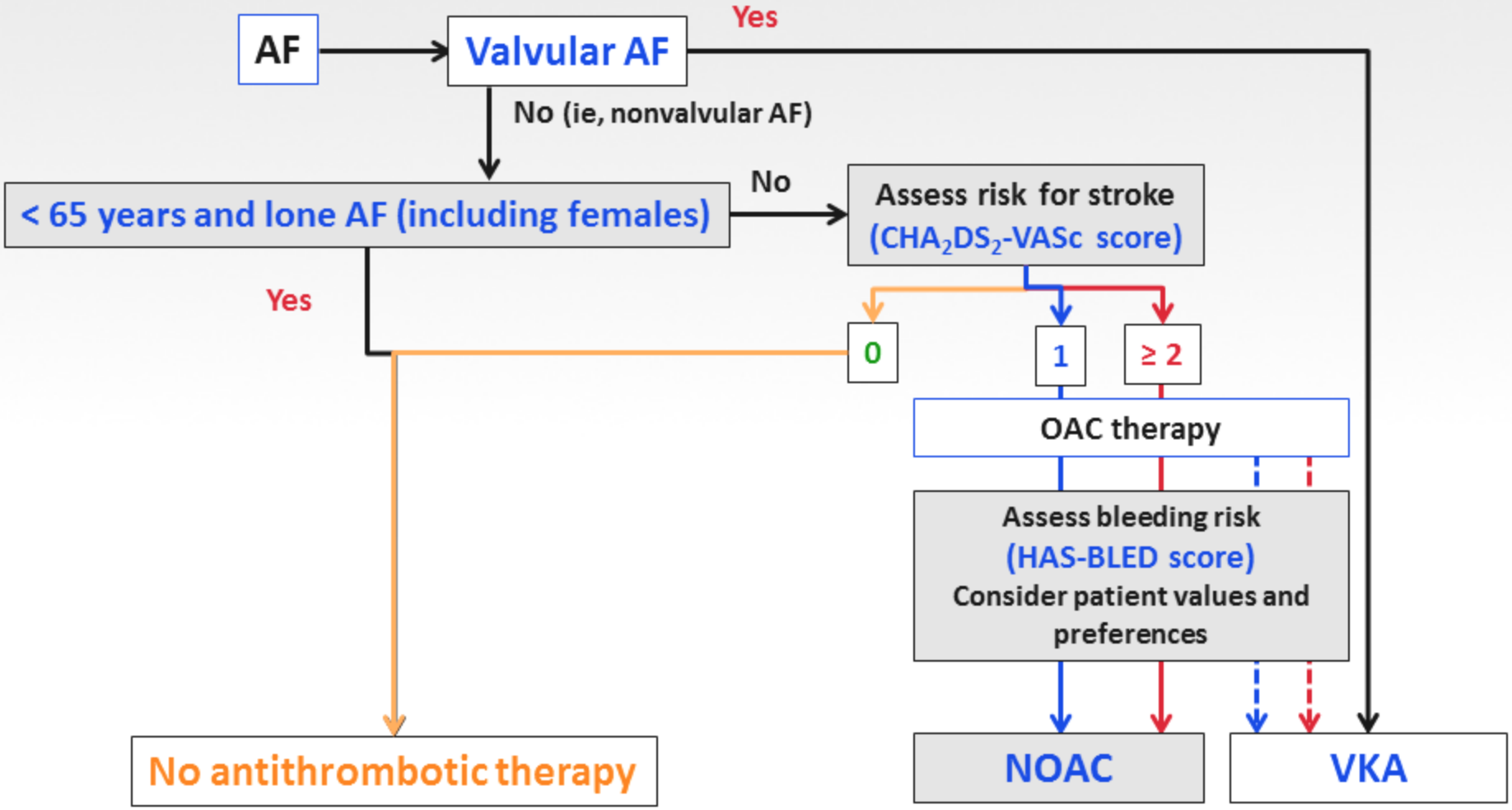
Bleeding events (major and minor)

Intracranial haemorrhage

MI, LFT, Death



Clinical Flowchart for OAC



Adapted from Camm AJ, et al. *Eur Heart J.* 2012;33(21):2719-2747.

Estimation of Bleeding Risk

- Risk estimation tools

Pros
Validated
Reproducible
Easily learned

Cons
Limited variables
One-size fits all philosophy
Depend on the validity of the collected information

- Clinical judgment

Pros
Multivariable
Individualized
Flexible

Cons
Cannot be validated
Non reproducible
Time consuming

Bleeding risk scores

ATRIA		HAS-BLED		HEMORR$_2$HAGES	
Anaemia	3	**H**ypertension	1	**H**epatic or Renal disease	1 1
Severe renal disease	3	**A**bnormal Renal or Liver function	1 1	**E**thanol abuse	1
Age ≥75 yrs	2	**S**troke	1	**M**alignancy	1
Any prior hemorrhage	1	**B**leeding	1	**O**lder Age (>75 yrs)	1
Hypertension[3]	1	**L**abile INR	1	**R**educed platelet number or function	1
		Elderly (>65 yrs)	1	**R**ebleeding	2
		Drugs or Alcohol	1 1	**H**ypertension	1
				Anaemia	1
				Genetic factors	1
				Excessive fall risk	1
				Stroke	1

Singer et al. Ann Intern Med. 2009; 151: 297-305.
Gage et al Am Heart J. 2006; 151: 713-9.
Pisters et al Chest. 2010; 138: 1093-100.

Performance of the HEMORR$_2$HAGES, ATRIA, and HAS-BLED Bleeding Risk–Prediction Scores in Patients With Atrial Fibrillation Undergoing Anticoagulation

The AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) Study

Stavros Apostolakis, MD, PHD,* Deirdre A. Lane, PHD,* Yutao Guo, MD,* Harry Buller, MD, PHD,† Gregory Y. H. Lip, MD*

Comparing C Indexes

AUC analysis	Any Clinically Relevant Bleeding			Major Bleeding			Death		
	AUC Difference (95%CI)	z	p	AUC Difference (95%CI)	z	p	AUC Difference (95%CI)	z	p
HAS-BLED vs. HEMORR$_2$HAGES	0.04 (0.52 to 0.59)	2.95	**0.003**	0.04 (-0.03-0.12)	1.19	0.23	0.09 (-0.14 to -0.05)	4.33	**<0.0001**
HAS-BLED vs. ATRIA	0.09 (0.03 to 0.15)	3.14	**0.002**	0.04 (-0.06-0.14)	0.85	0.4	0.04 (-0.03 to 0.11)	1.17	0.2
ATRIA vs. HEMORR$_2$HAGES	-0.05 (-0.01 to 0.11)	-1.54	0.1	0.0 (-0.09-0.09)	0.04	0.97	0.05 (-0.12 to 0.02)	1.5	0.1

- Among the AMADEUS population, the HAS-BLED score performed better than either the HEMORR$_2$HAGES or ATRIA scores in predicting any clinically relevant bleeding.
- All tested bleeding scores performed less than modestly in predicting endpoints.

- European Society of Cardiology and
- Canadian guidelines.
- RCPE

JACC, 28 August 2012, Pages 861–867

Stroke risk Scores

CHADS2

	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	1
Diabetes	1
Stroke/TIA	2

$CHADS_2$	Stroke Rate (95% CI)*
6	**18.2** (10.5-27.4)
5	**12.5** (8.2-17.5)
4	**8.5** (6.3-11.1)
3	**5.9** (4.6-7.3)
2	**4.0** (3.1-5.1)
1	**2.8** (2.0-3.8)
0	**1.9** (1.2-3.0)

CHA2DS2 VASc

	Points
Congestive heart failure or LVEF ≤ 35%	1
Hypertension	1
Age ≥ 75 years	2
Diabetes	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

CHA_2DS_2VASc score	No. of patients (%)	Thromboembolism* per 100 person years at 1 year follow-up
0	6,369 (8.7)	**0.78**
1	8,203 (11.2)	**2.01**
2	12,771 (17.4)	**3.71**
3	17,371 (23.6)	**5.92**
4	13,887 (18.9)	**9.27**
5	8,942 (12.2)	**15.26**
6	4,244 (5.8)	**19.74**
7	1,420 (1.9)	**21.50**
8	285 (0.4)	**22.38**
9	46 (0.1)	**23.64**

a. Gage BF, et al. *JAMA*. 2001;285(22):2864-2870.
b. Lip GY, et al. *Am J Med*. 2010;123(6):484-488.

HAS - BLED

HAS-BLED Risk Criteria	Score
Hypertension	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (eg, age > 65 years)	1
Drugs or alcohol (1 point each)	1 or 2

HAS-BLED Total Score	N	Number of Bleeds	Bleeds per 100 Patient-Years*
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.5
6	2	0	0.0
7	0	–	–
8	0	–	–
9	0	–	–

**P* value for trend = .007

Pisters R, et al. *Chest.* 2010;138(5):1093-1100;
Camm AJ, et al. *Eur Heart J.* 2010; 31(19):2369-2429.

Recommendation for Assessment of Bleeding Risk

Recommendation	Class	Level
Assessment of bleeding risk is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin alone).	I	A
HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥ 3 indicates "high risk" and some caution and regular review is needed, following initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy.	IIa	A
Correctable factors for bleeding (eg, uncontrolled blood pressure, labile INRs if patient was on a VKA, concomitant drugs [aspirin, NSAIDs, etc.], alcohol, etc.) should be addressed.		B
Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed but should not be used on its own to exclude patients from OAC therapy.		B
Risk for major bleeding with antiplatelet therapy (with aspirin-clopidogrel combination therapy and—especially in the elderly—also with aspirin monotherapy) should be considered as being similar to OAC.	IIa	B

NSAIDs = nonsteroidal anti-inflammatory drugs

Camm AJ, et al. *Eur Heart J*. 2012;33(21):2719-2747.

August 2011:→ **August 2013**

- Major lung bleeding: hemoptysis
- Coumadin – stopped
- Medication: Aspirin
- CHADS2=2= 4% risk,
- CHA2DS2 VASc=5=15.2% risk
- HAS-BLED=4=8.7% risk

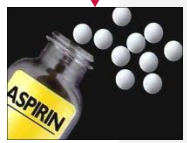
Patient background

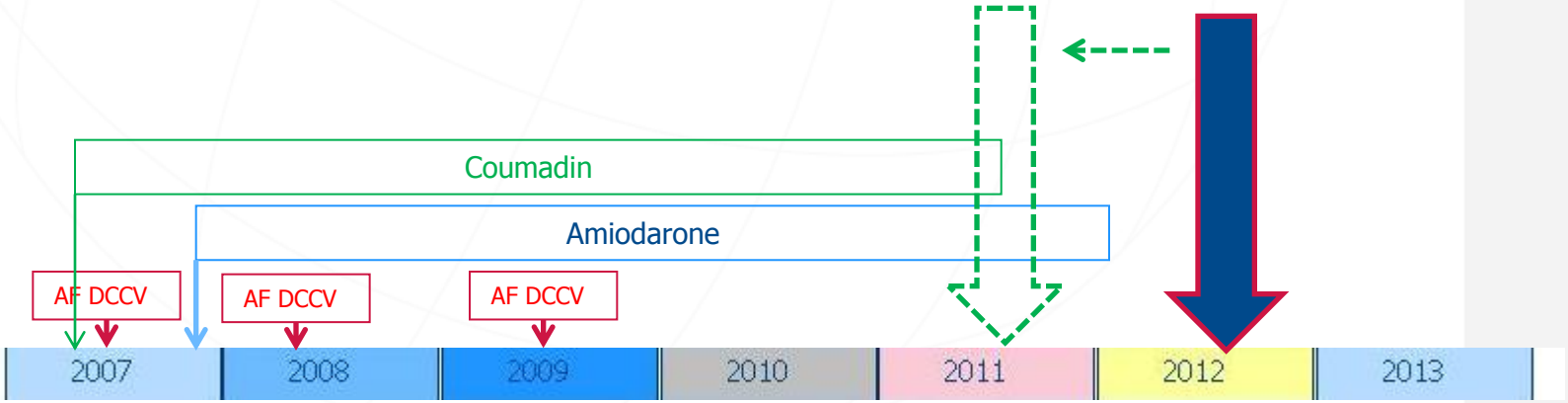
- 67-year-old woman
- CAD
- HT
- DM
- Diagnosis of AF

Xarelto rivaroxaban

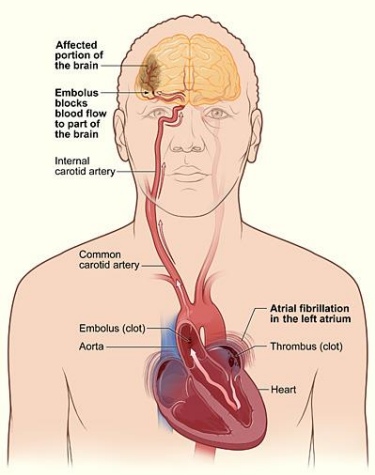
Pradaxa dabigatran etexilate

Clopidogrel





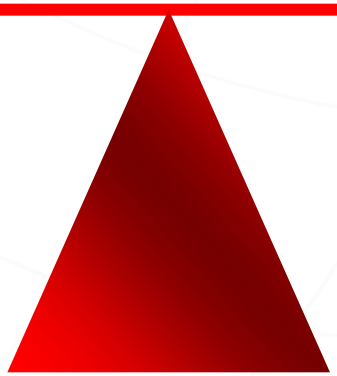
Patient with high risk for bleeding



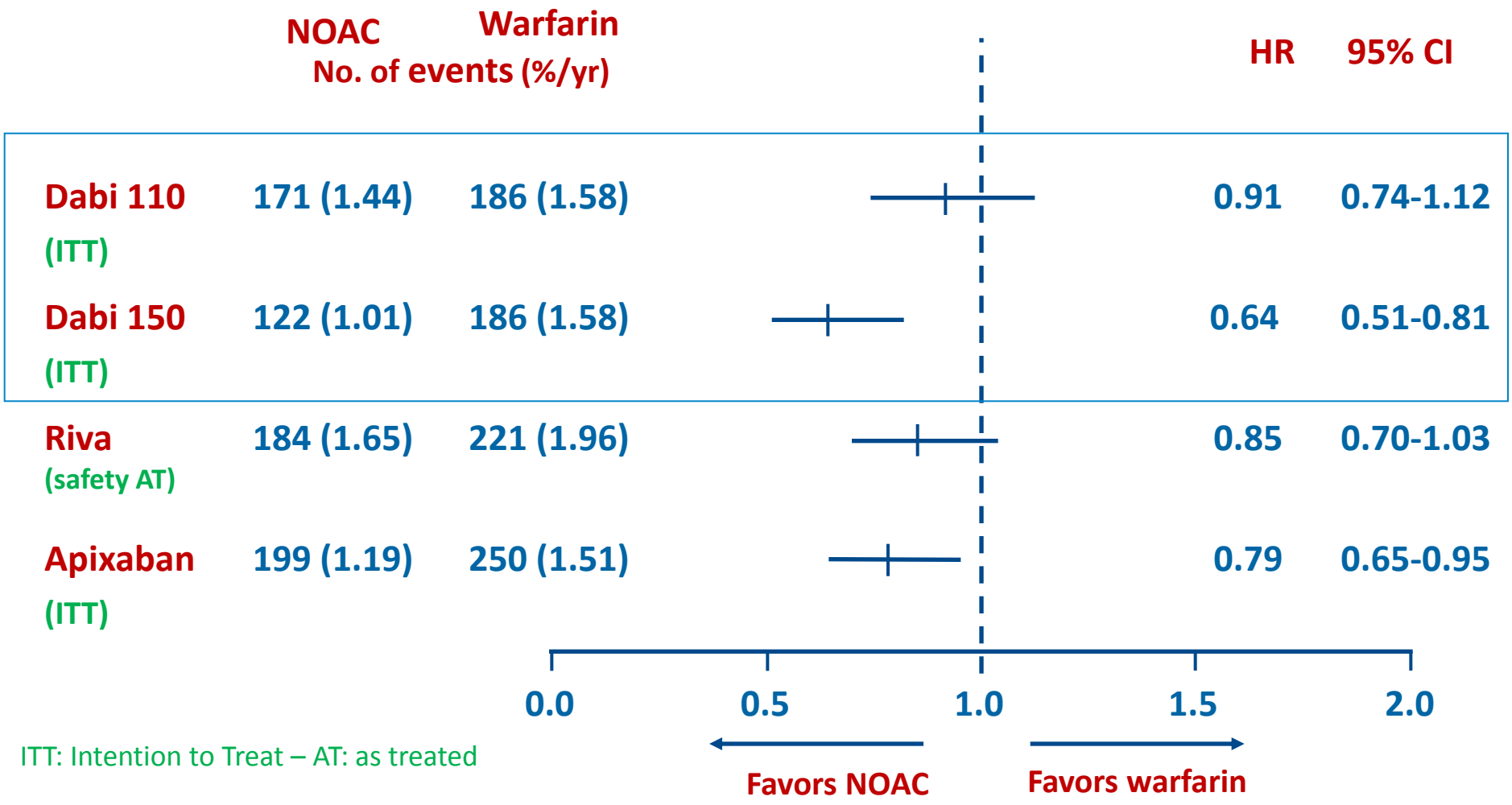
Efficacy:

All stroke (ischaemic + aemorrhagic)

& systemic embolism



Stroke or Systemic Embolism

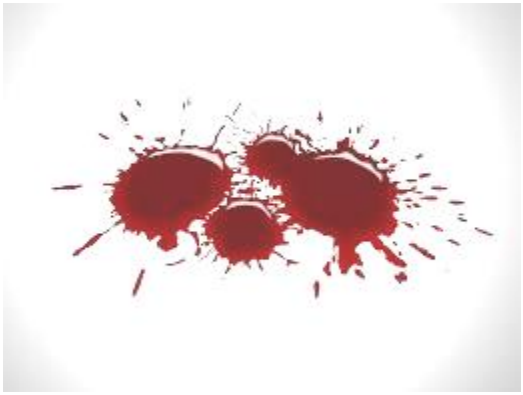


ITT: Intention to Treat – AT: as treated

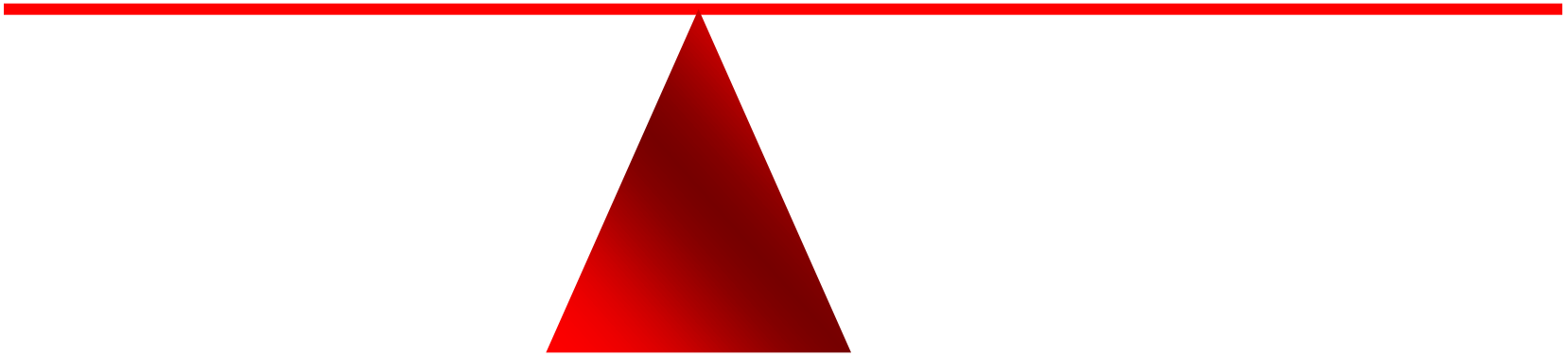
Not head to head comparison – For illustrative purposes only – adapted from references 1-4

1. Connolly et al. NEJM 2009; 361: 1139-51. 2. Connolly et al. NEJM 2010; 363: 1875-6.
3. Patel et al. NEJM 2011; 365: 883-91. 4. Granger et al. NEJM 2011; 365: 981-92.

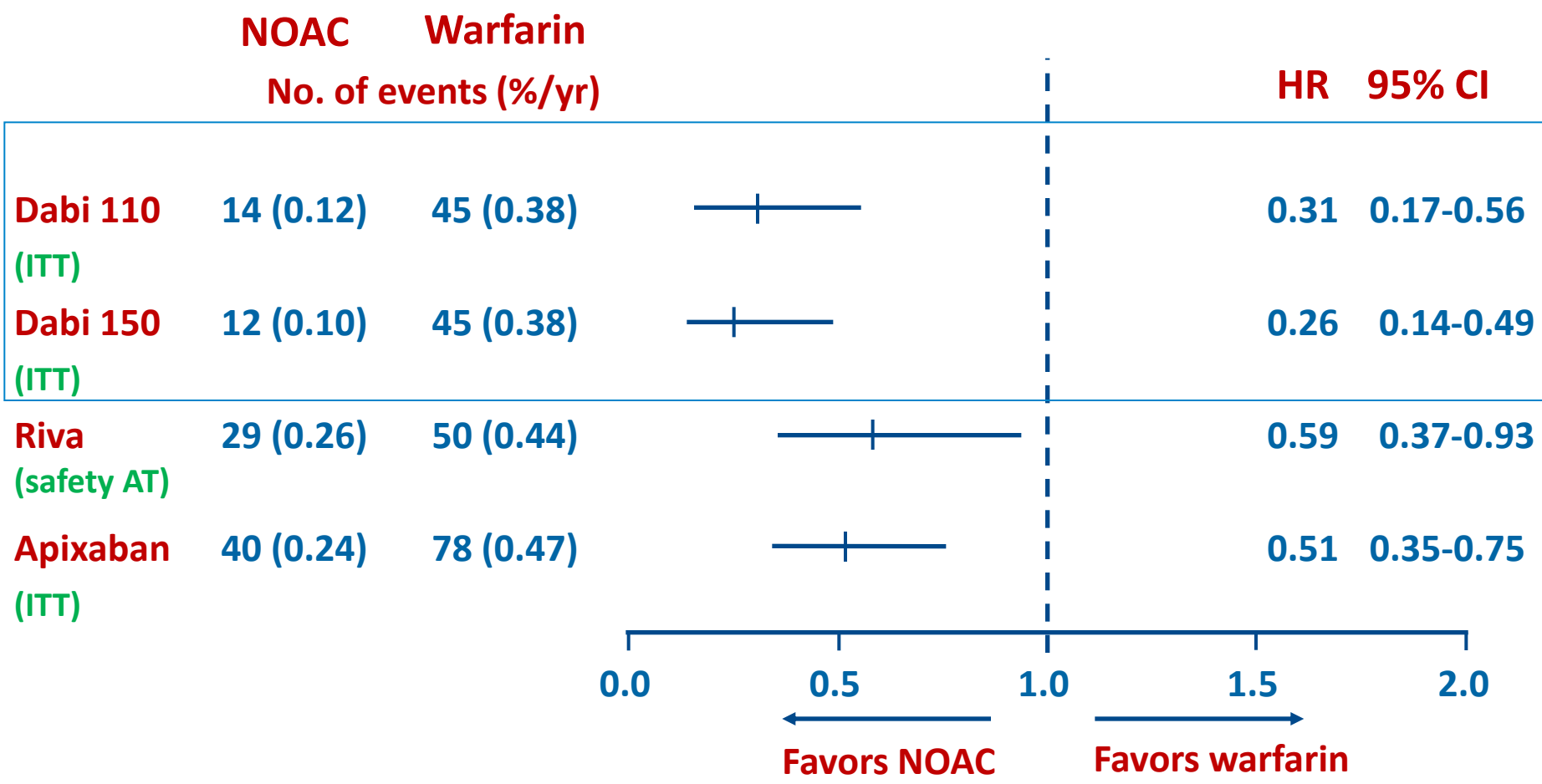
Patient with high risk for bleeding



Safety:
Bleeding events (major and minor)
Intracranial haemorrhage
MI, LFT, Death



Hemorrhagic Stroke

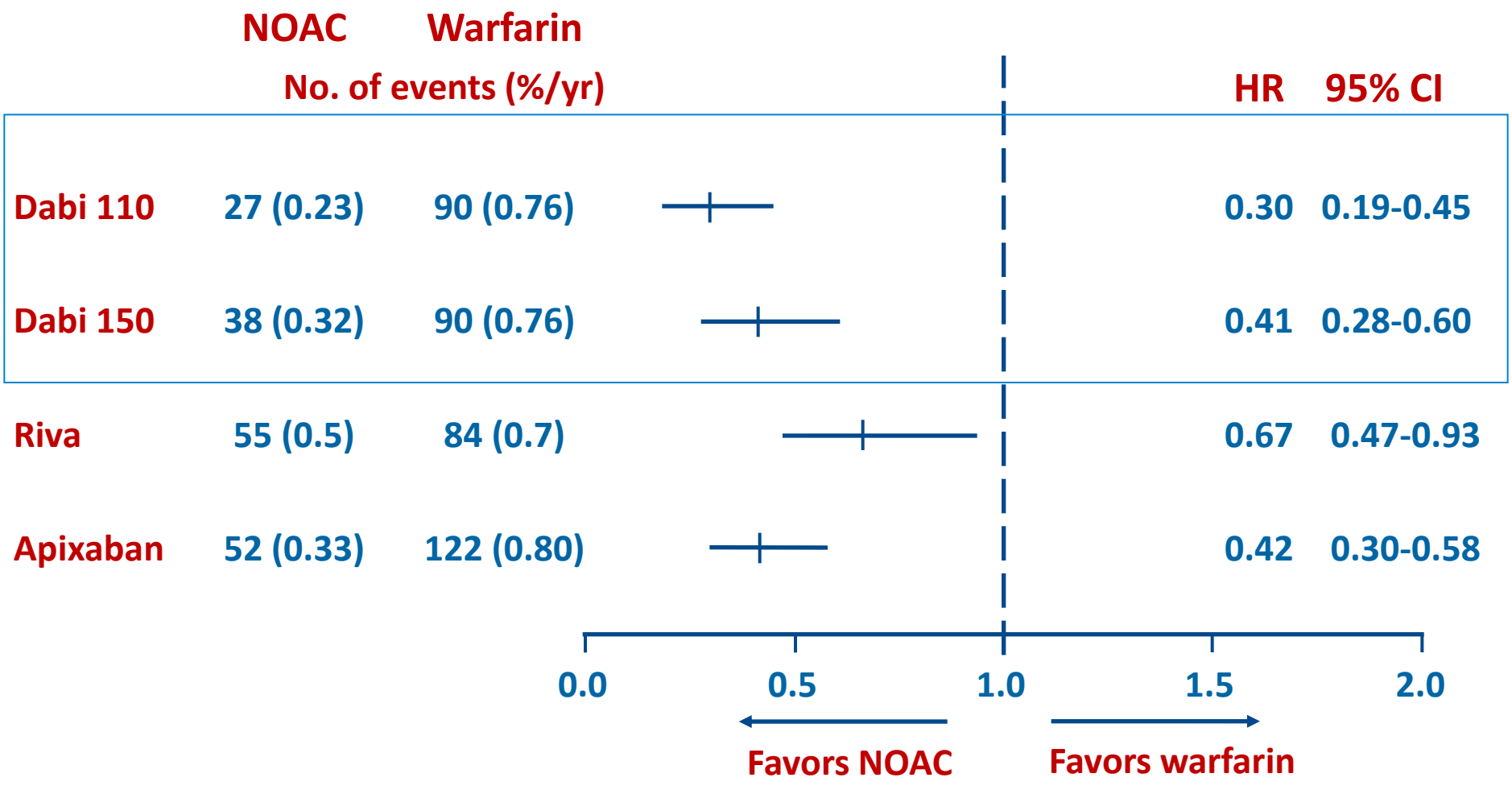


ITT: Intention to Treat – AT: as treated.

Not head to head comparison – For illustrative purpose only – adapted from references 1-4

1. Connolly et al. NEJM 2009; 361: 1139-51. 2. Connolly et al. NEJM 2010; 363: 1875-6.
3. Patel et al. NEJM 2011; 365: 883-91. 4. Granger et al. NEJM 2011; 365: 981-92.

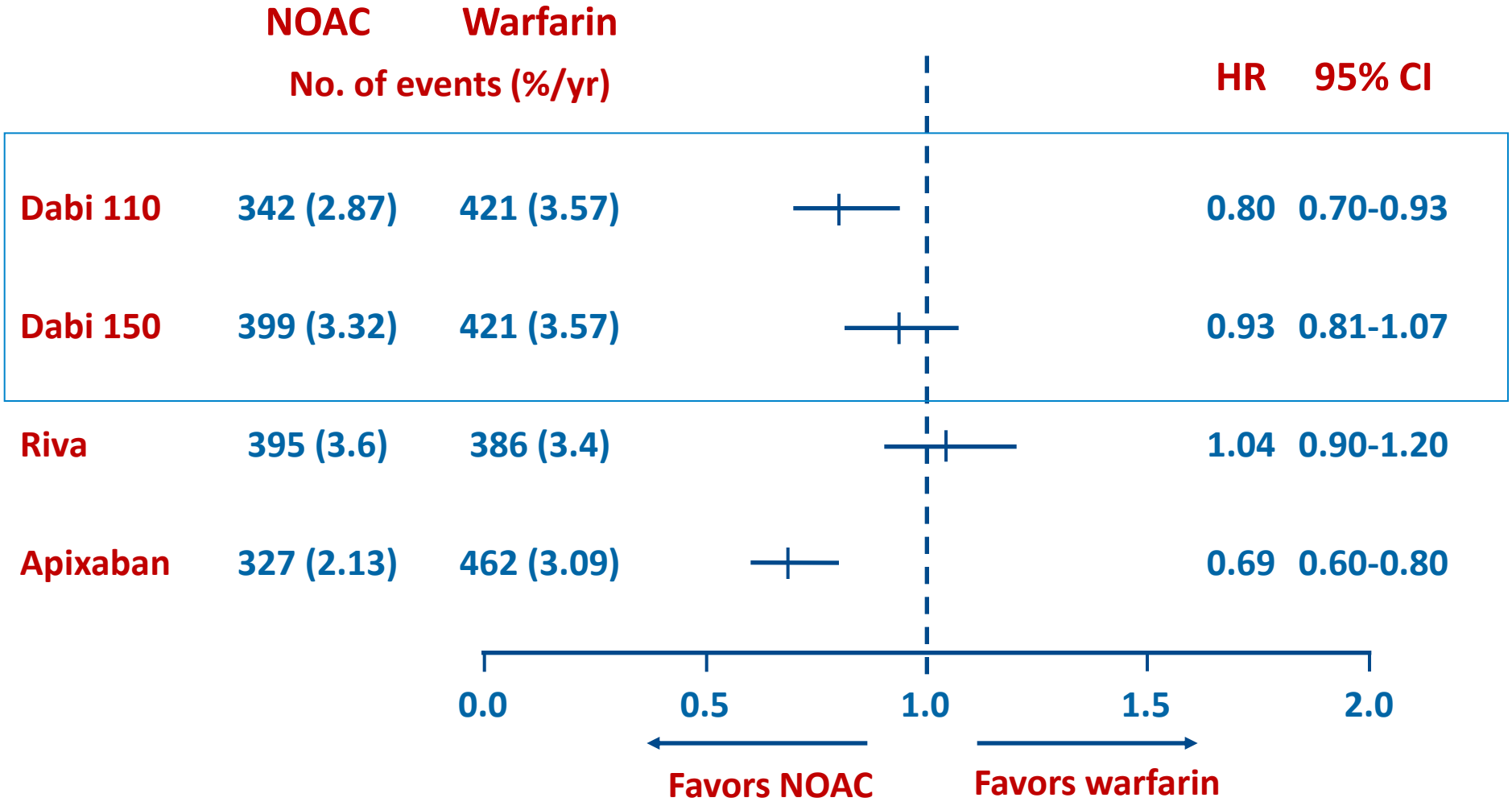
Intracranial Bleeding



Not head to head comparison – For illustrative purpose only – adapted from references 1-4

1. Connolly et al. NEJM 2009; 361: 1139-51. 2. Connolly et al. NEJM 2010; 363: 1875-6.
3. Patel et al. NEJM 2011; 365: 883-91. 4. Granger et al. NEJM 2011; 365: 981-92.

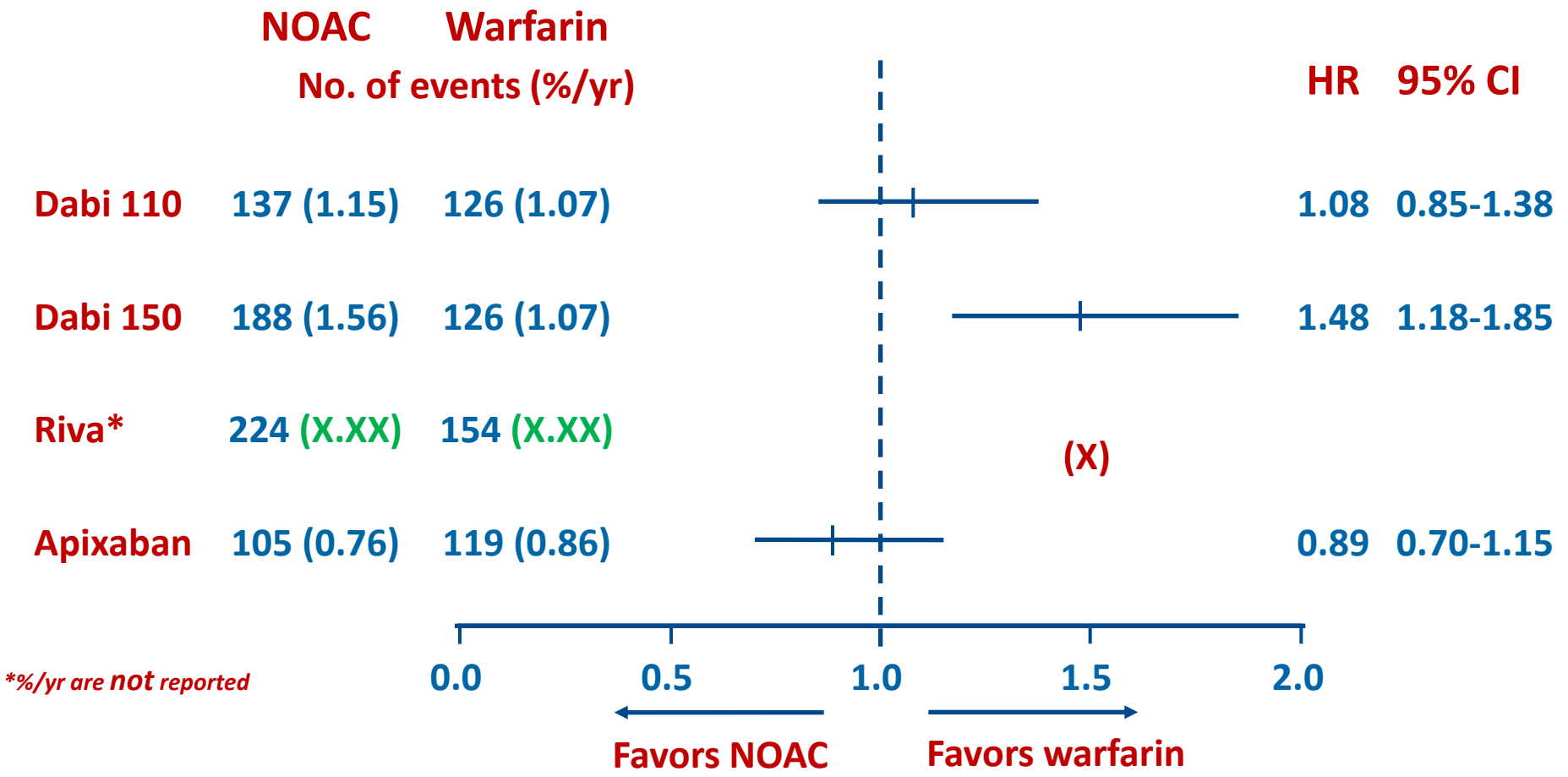
Major Bleeding



Not head to head comparison – For illustrative purpose only – adapted from references 1-4

1. Connolly et al. NEJM 2009; 361: 1139-51. 2. Connolly et al. NEJM 2010; 363: 1875-6.
3. Patel et al. NEJM 2011; 365: 883-91. 4. Granger et al. NEJM 2011; 365: 981-92.

Major Gastro-intestinal Bleeding



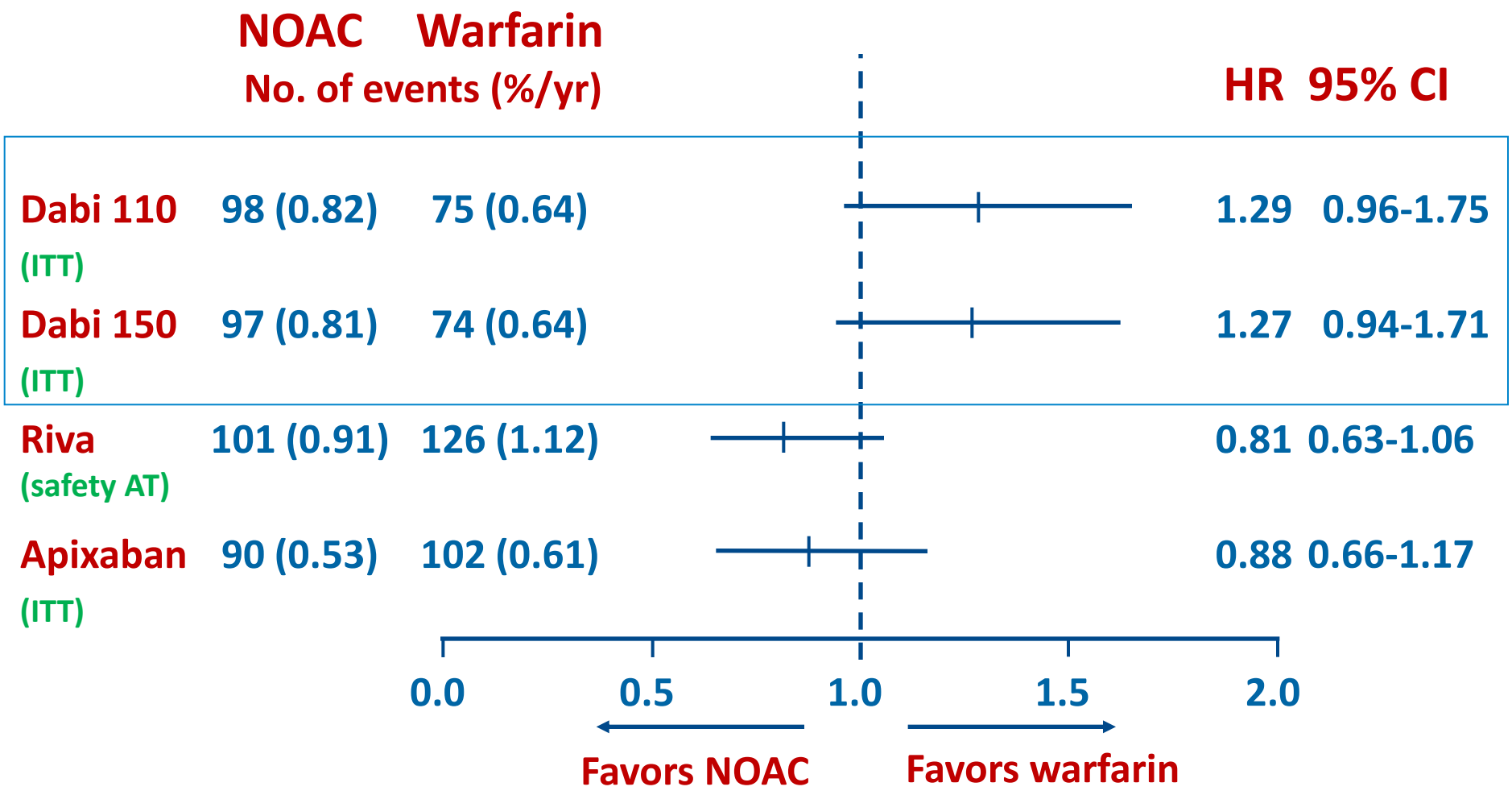
*%/yr are not reported

*p value given in the NEJM; HR not reported;

Not head to head comparison – For illustrative purpose only – adapted from references 1-4

1. Connolly et al. NEJM 2009; 361: 1139-51. 2. Connolly et al. NEJM 2010; 363: 1875-6.
3. Patel et al. NEJM 2011; 365: 883-91. 4. Granger et al. NEJM 2011; 365: 981-92.

Myocardial Infarction

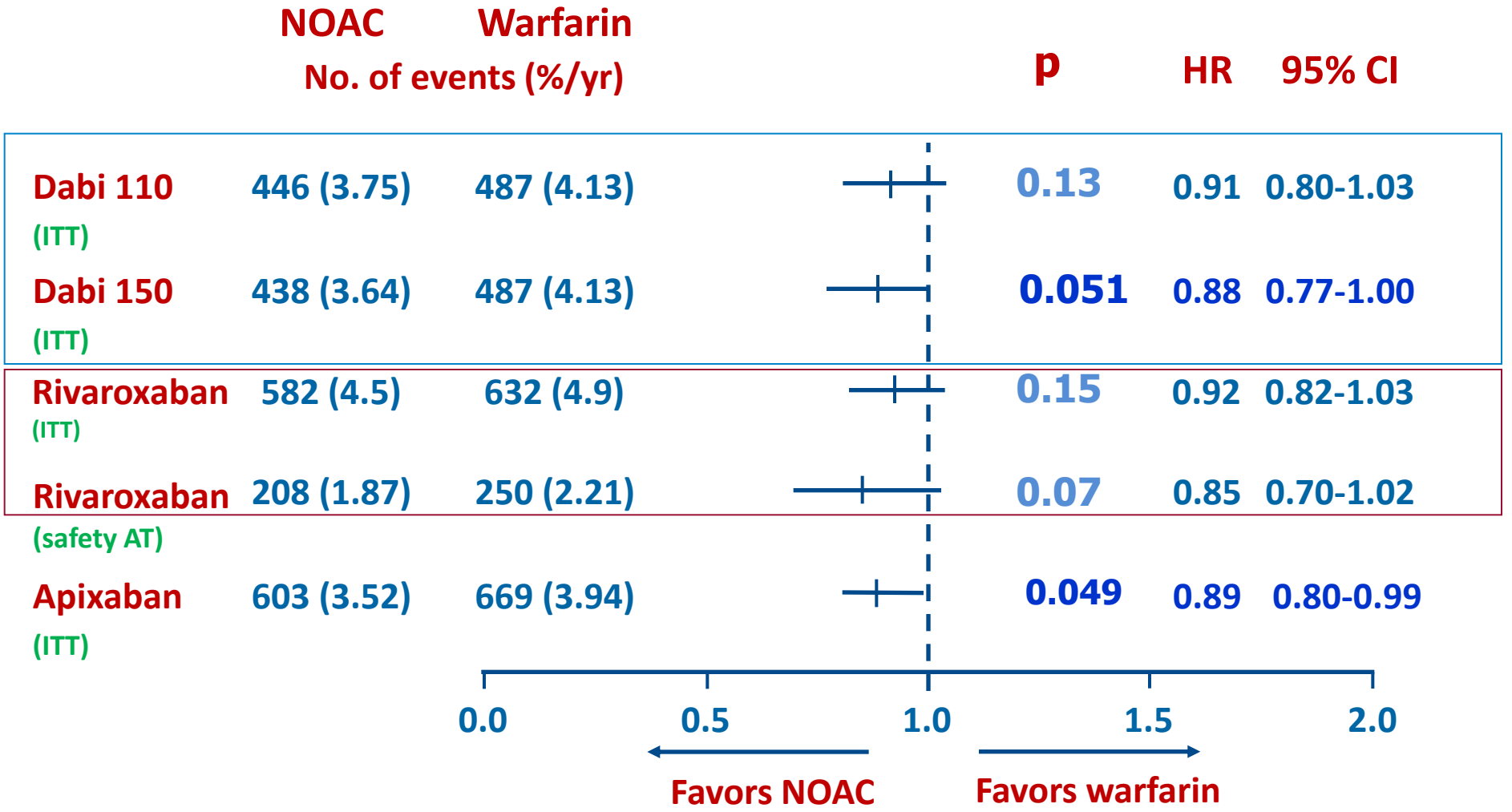


ITT: Intention to Treat – AT: as treated.

Not head to head comparison – For illustrative purpose only – adapted from references 1-4

1. Connolly et al. NEJM 2009; 361: 1139-51. 2. Connolly et al. NEJM 2010; 363: 1875-6.
3. Patel et al. NEJM 2011; 365: 883-91. 4. Granger et al. NEJM 2011; 365: 981-92.

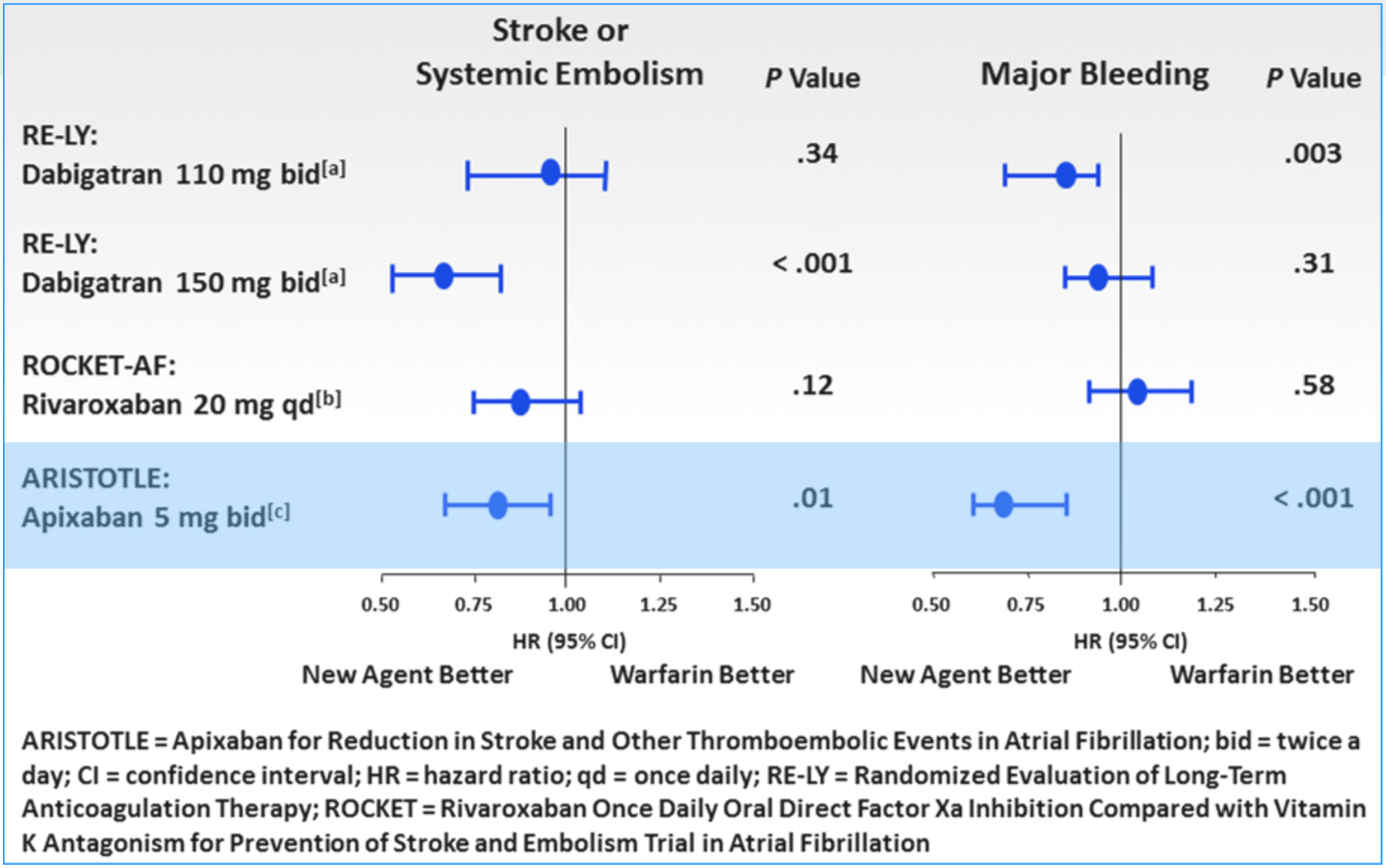
Death From Any **Cause** –Total Mortality



Not head to head comparison – For illustrative purpose only – adapted from references 1-4

1. Connolly et al. NEJM 2009; 361: 1139-51. 2. Connolly et al. NEJM 2010; 363: 1875-6.
3. Patel et al. NEJM 2011; 365: 883-91. 4. Granger et al. NEJM 2011; 365: 981-92.

NOACs Trials



ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; bid = twice a day; CI = confidence interval; HR = hazard ratio; qd = once daily; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

a. Connolly SJ, et al. *N Engl J Med*. 2009;361(12):1139-1151.
b. Patel MR, et al. *N Engl J Med*. 2011;365(10):883-891.
c. Granger C, et al. *N Eng J Med*. 2011;365(11):981-992.

August 2013:

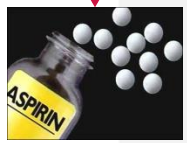
- Major lung bleeding: hemoptysis
- Coumadin – stopped
- Medication: Aspirin
- CHADS2=2= 4% risk, CHA2DS2 VASc=5=15.2% risk
- HAS-BLED=4=8.7% risk

My recommendation:
Start Apixaban 5mg bid
- Best efficacy / safety balance

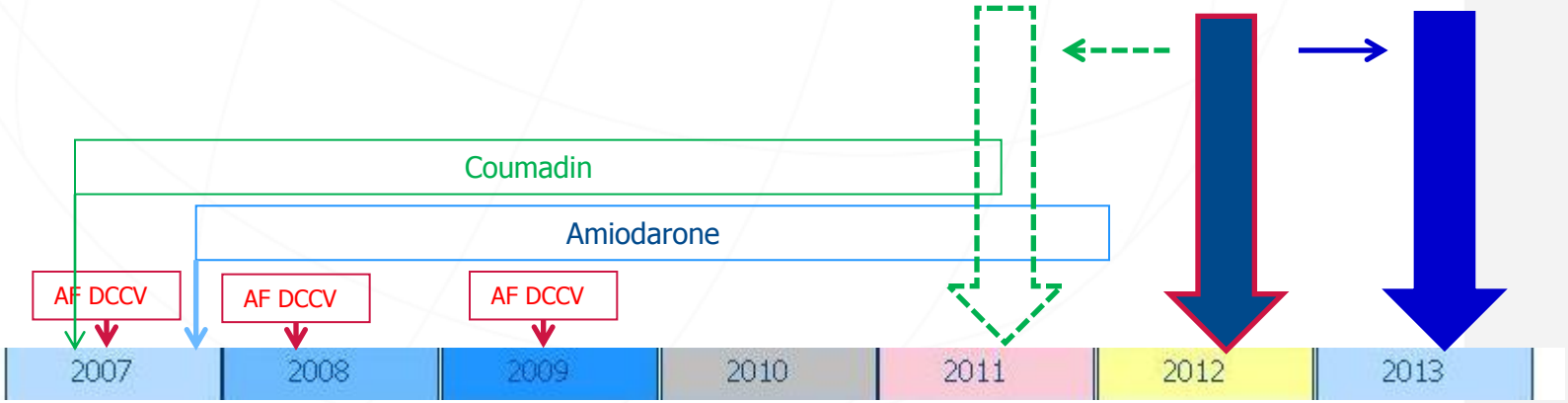
Xarelto rivaroxaban

Pradaxa dabigatran etexilate

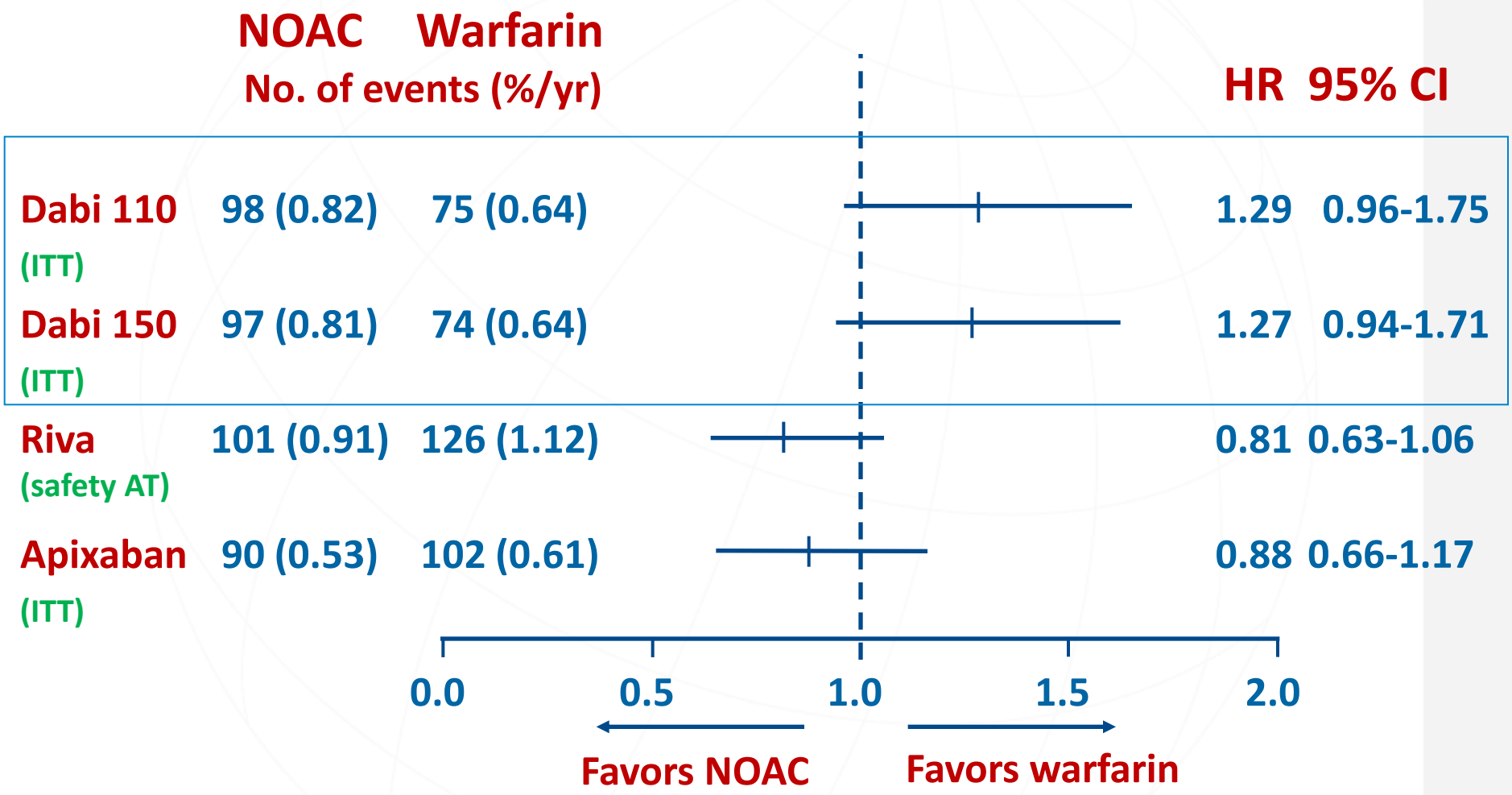
Clopidogrel



APPRISE 2



Myocardial Infarction



ITT: Intention to Treat – AT: as treated.

Not head to head comparison – For illustrative purpose only – adapted from references 1-4

1. Connolly et al. NEJM 2009; 361: 1139-51. 2. Connolly et al. NEJM 2010; 363: 1875-6.
3. Patel et al. NEJM 2011; 365: 883-91. 4. Granger et al. NEJM 2011; 365: 981-92.

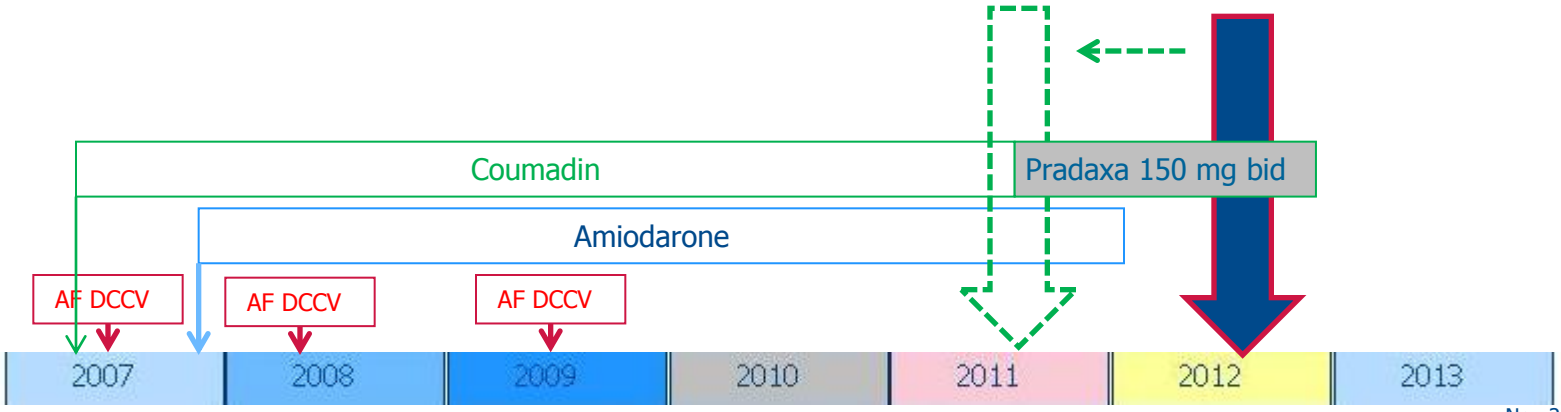
August 2011:

- Major lung bleeding: hemoptysis
- Coumadin – stopped
- Medication: Aspirin
- CHADS2=2= 4% risk, CHA2DS2 VASc=5=15.2% risk
- HAS-BLED=4=8.7% risk

Xarelto rivaroxaban

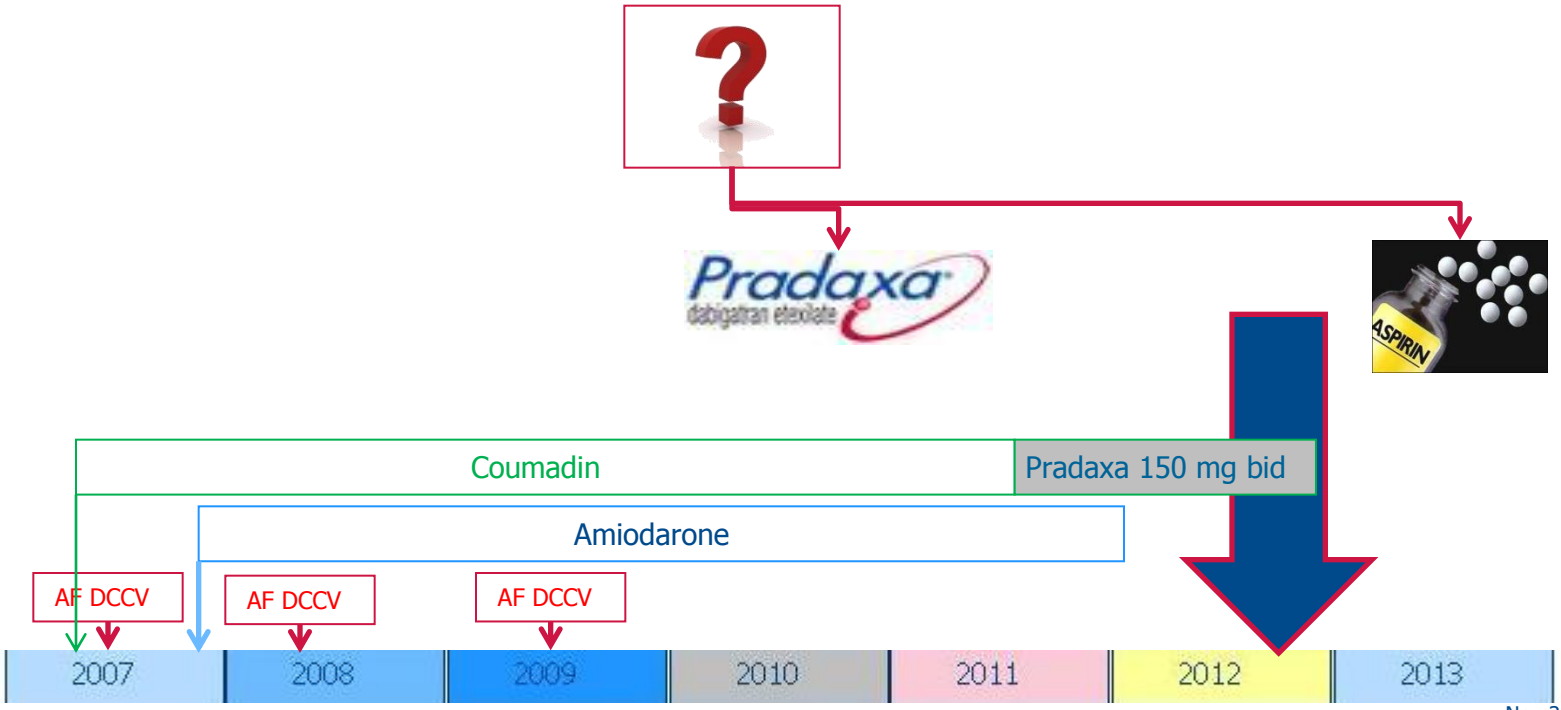
Pradaxa dabigatran etexilate

Clopidogrel



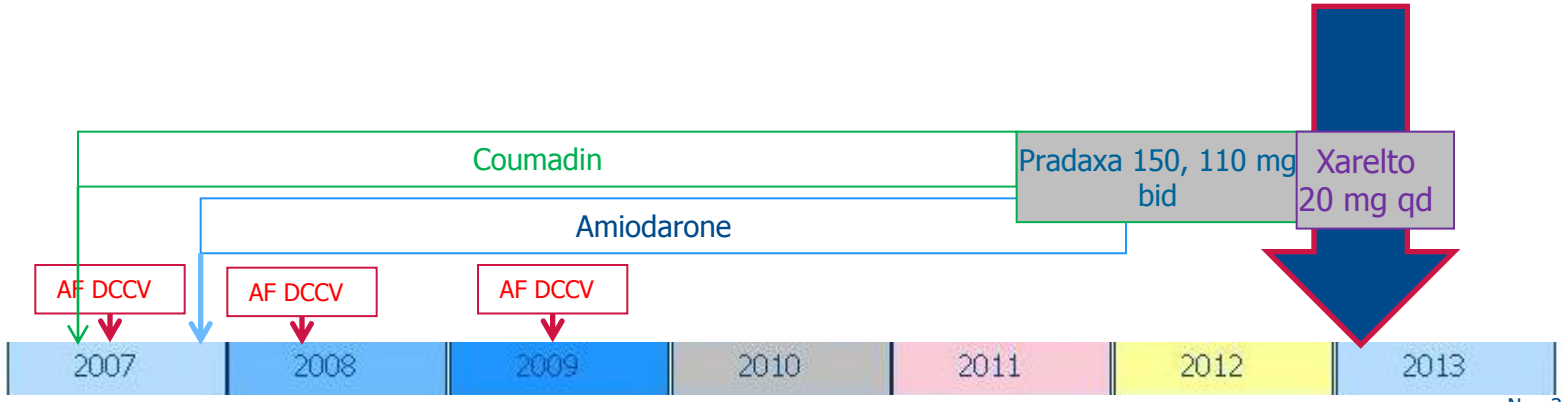
August 2012 → December 2012

- Amiodarone – Lung toxicity
- Sotalol - Failure
- Persistent AF fast V rate
- Preparation for PVI (ablation)
  - **TEE LA thrombus X 2**
- DDDR pacemaker → Total AV J Ablation



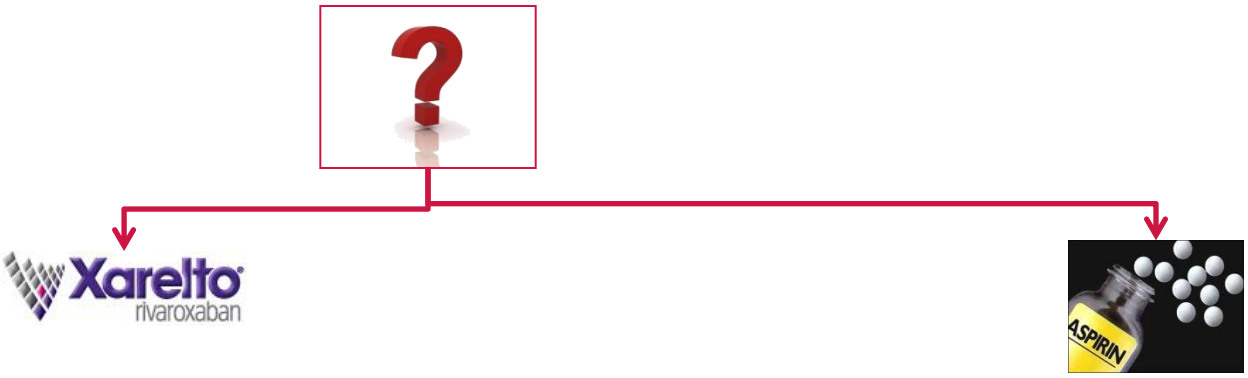
January 2013

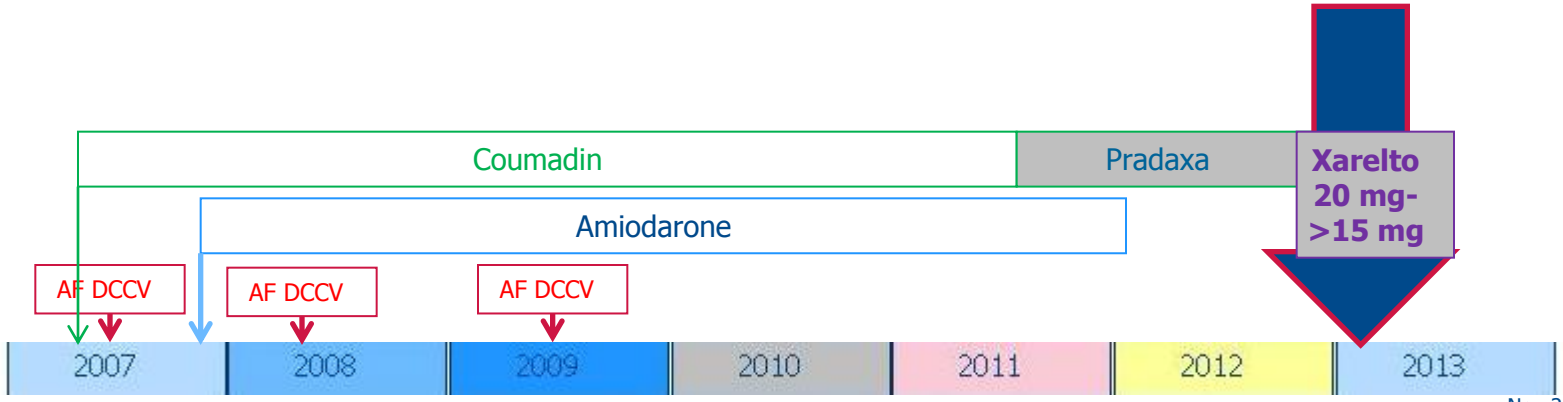
- Persistent AF fast V rate
- Preparation for PVI (ablation)
  - **TEE LA thrombus**
- DDDR pacemaker → Total AV J Ablation
- Hemoptysis
- Skin rash
- Dyspepsia



April 2013

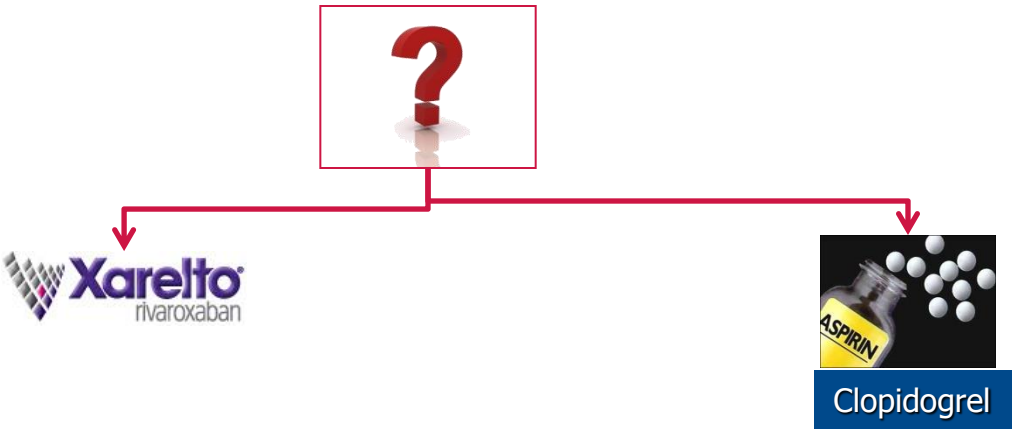
- Persistent AF fast V rate
- Preparation for PVI (ablation)
  - **TEE LA thrombus**
- DDDR pacemaker → Total AV J Ablation
- Hemoptysis

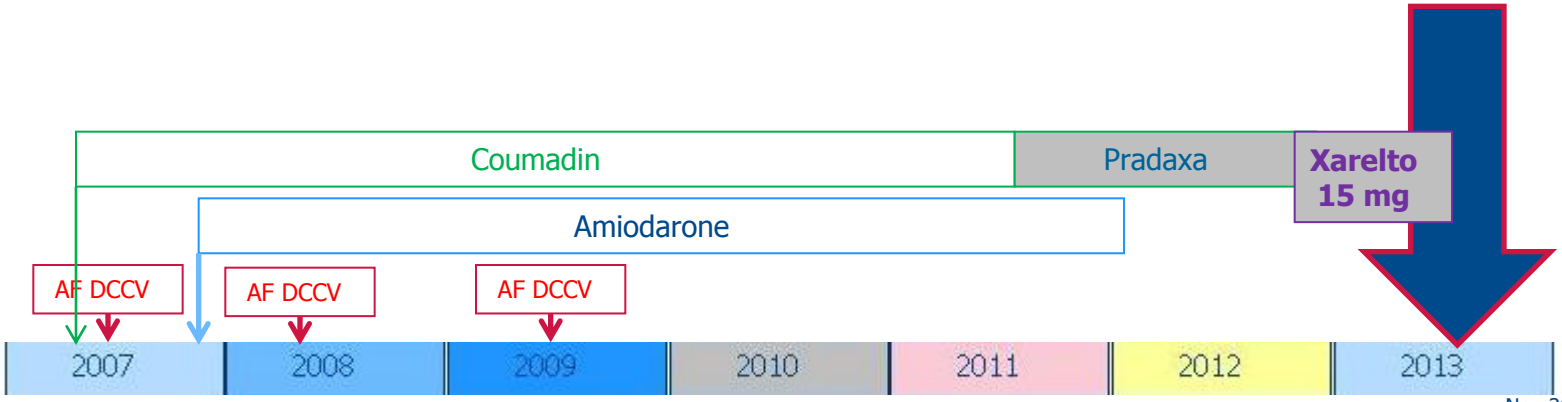




June 2013

- No Hemoptysis
- Anterior wall MI
  - PPCI to LAD



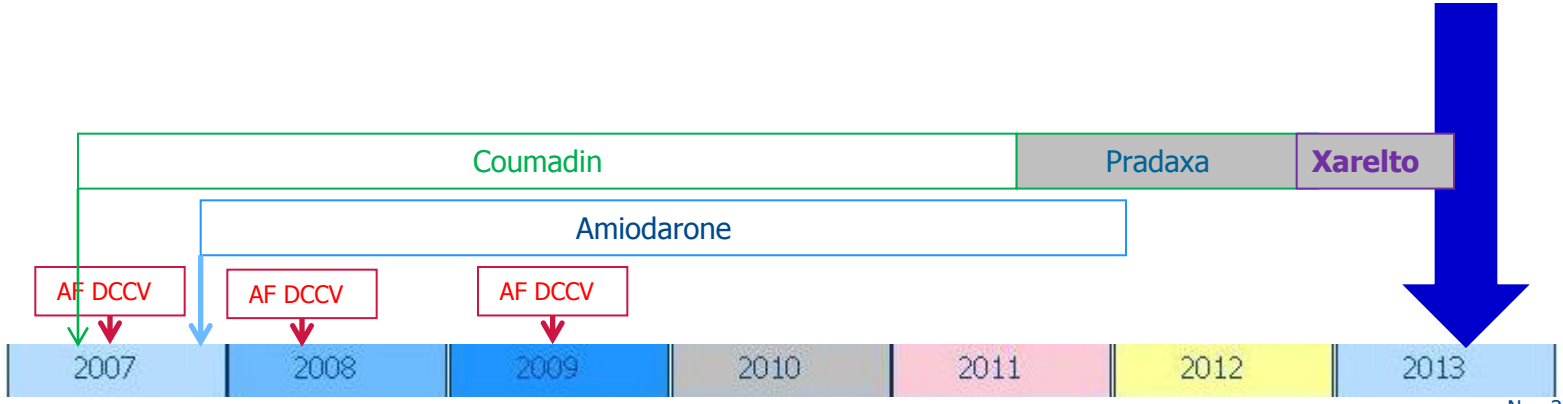


Nov 2012

Hypothetical 2013: pre MI

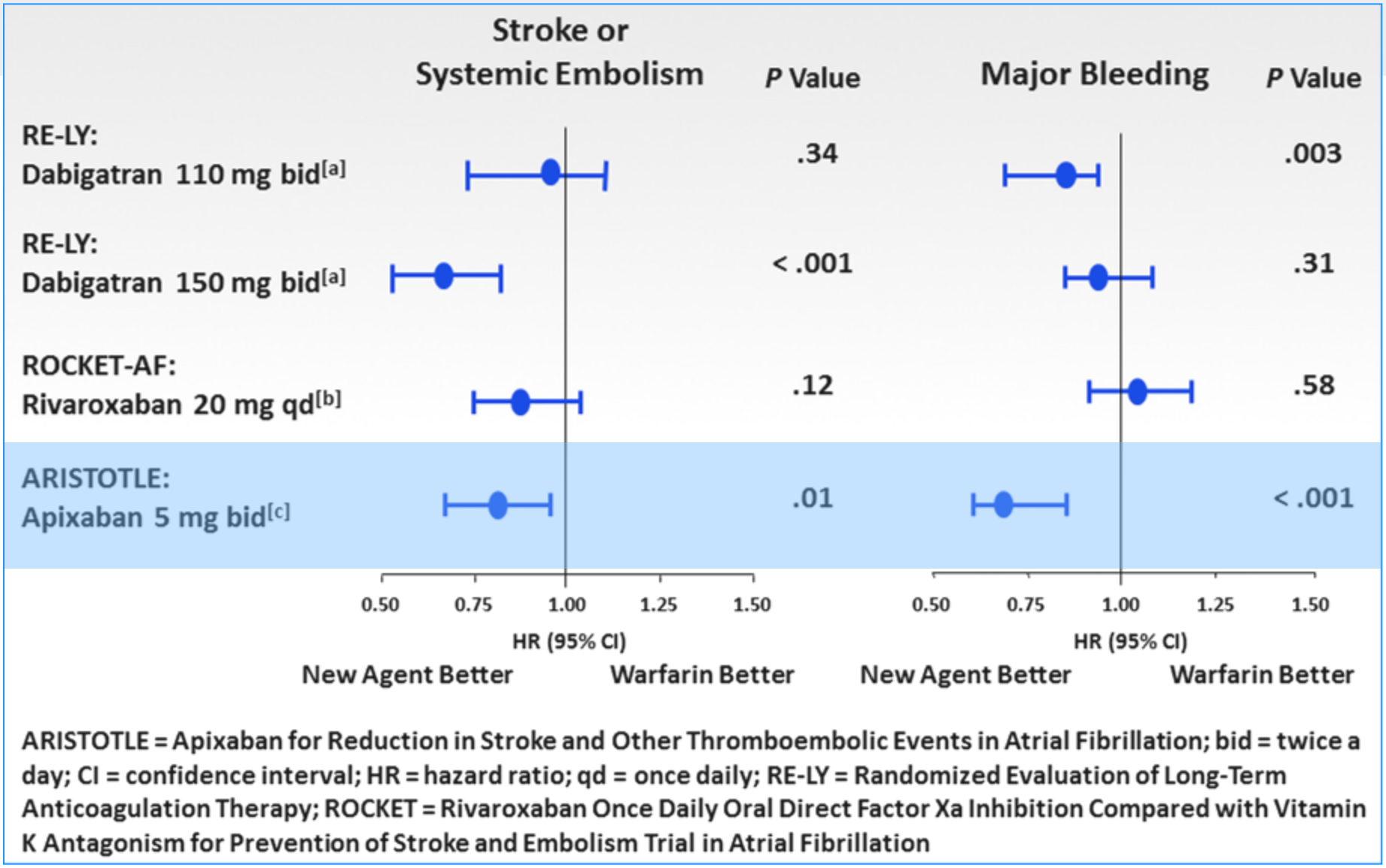
My recommendation:
Start Apixaban 5mg bid

- Best efficacy / safety balance



Nov 2012

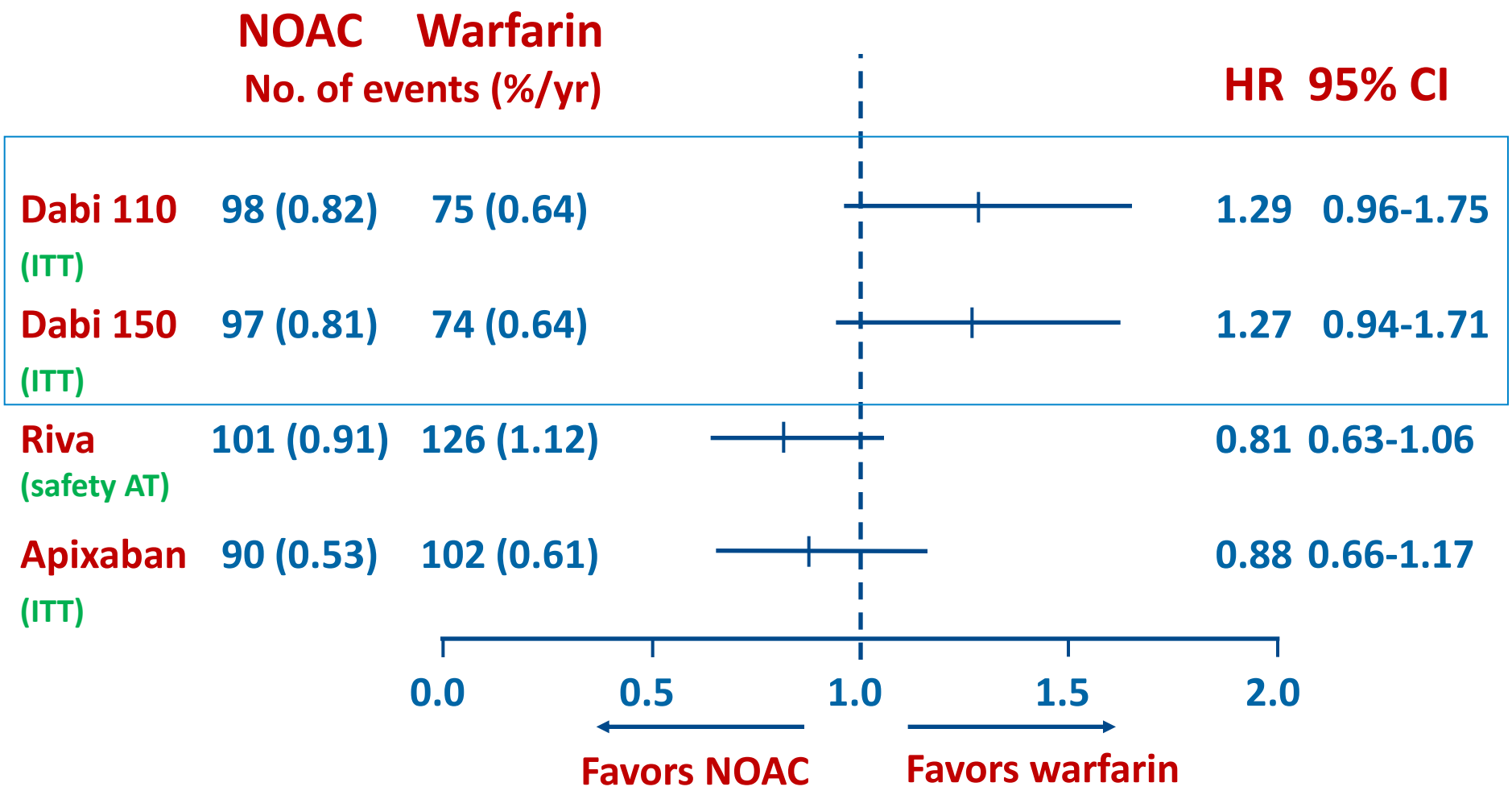
NOACs Trials



ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; bid = twice a day; CI = confidence interval; HR = hazard ratio; qd = once daily; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

a. Connolly SJ, et al. *N Engl J Med*. 2009;361(12):1139-1151.
b. Patel MR, et al. *N Engl J Med*. 2011;365(10):883-891.
c. Granger C, et al. *N Eng J Med*. 2011;365(11):981-992.

Myocardial Infarction



ITT: Intention to Treat – AT: as treated.

Not head to head comparison – For illustrative purpose only – adapted from references 1-4

1. Connolly et al. NEJM 2009; 361: 1139-51. 2. Connolly et al. NEJM 2010; 363: 1875-6.
3. Patel et al. NEJM 2011; 365: 883-91. 4. Granger et al. NEJM 2011; 365: 981-92.