“Αντιπηκτικά και αντιαιμοπεταλιακά φάρμακα στον Καρδιολογικό Ασθενη”

Γεώργιος Σ. Γκουμάς MD, PhD, FESC

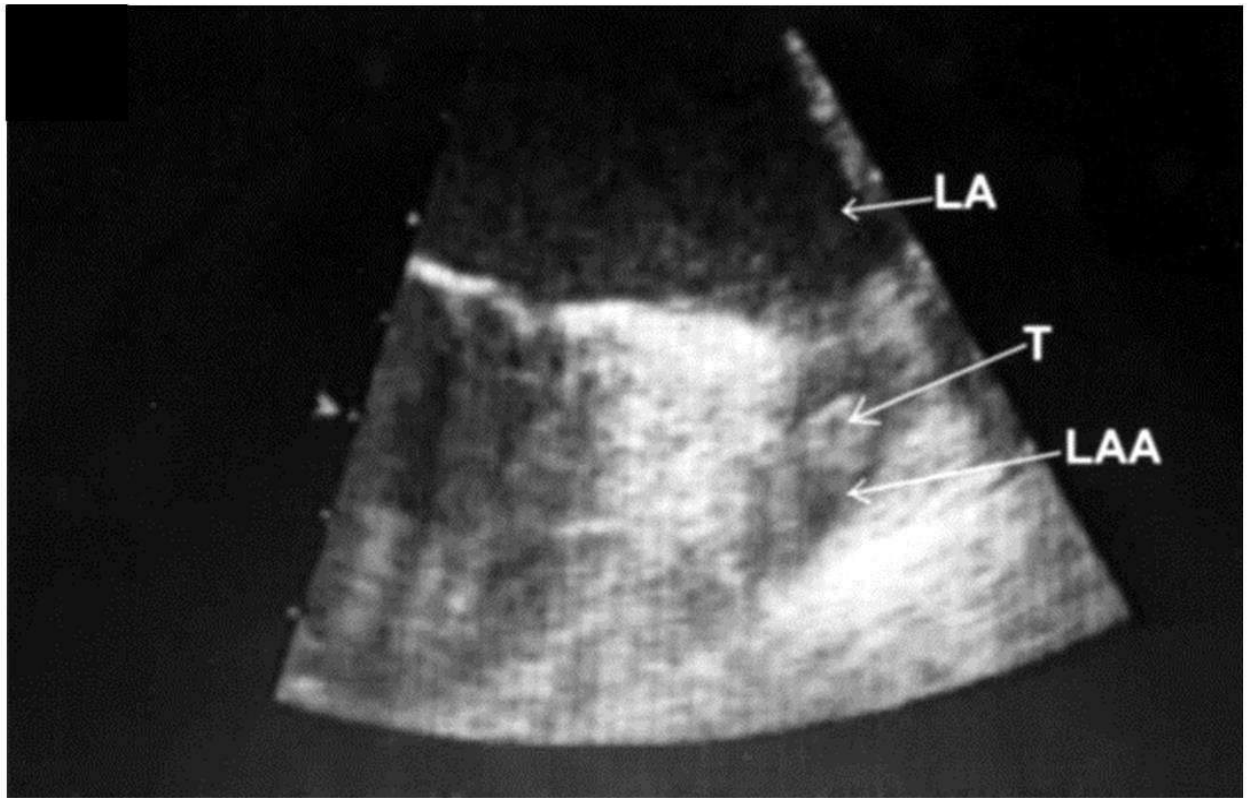
Αν. Διευθυντής Καρδιολογικής Κλινικής, Ευρωκλινική Αθηνών

ΔΗΛΩΣΗ ΣΥΓΚΡΟΥΣΗΣ ΣΥΜΦΕΡΟΝΤΩΝ

Τα προηγούμενα δύο χρόνια έχω λάβει τιμητικές αμοιβές ως σύμβουλος ή ομιλητής από τις ακόλουθες φαρμακευτικές εταιρείες:

SANOFI, MENARINI, GALENICA, ASTRAZENECA, VIANEX, PFIZER, BAYER

Transesophageal Echocardiography Depicting a Left Atrium Appendage Thrombus

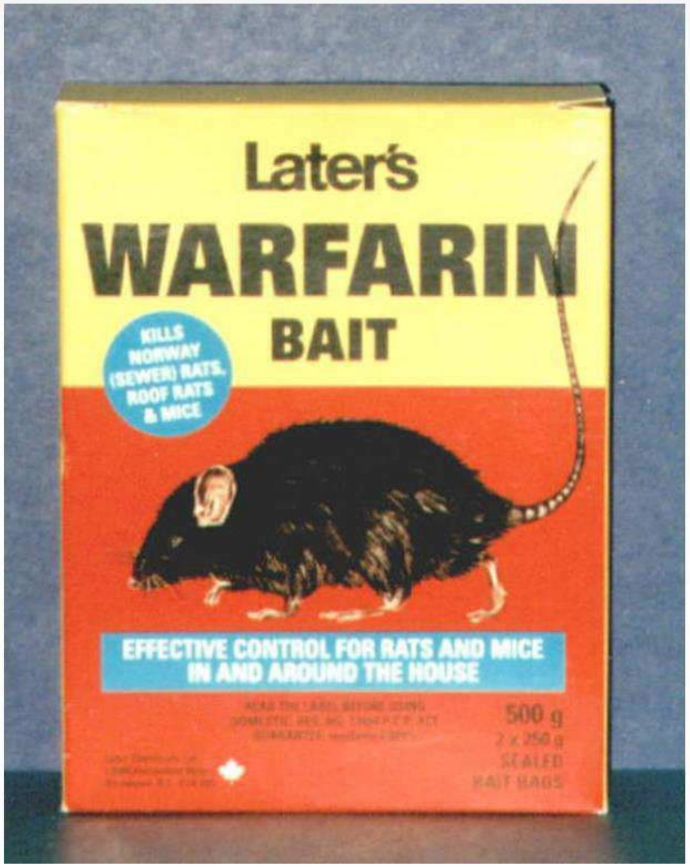


Parekh A, et al. *Circulation*. 2006;114:e513-e514.

1933 - A Dead Bull and Blood That Would Not Clot

Wisconsin
Alumni
Research
Foundation

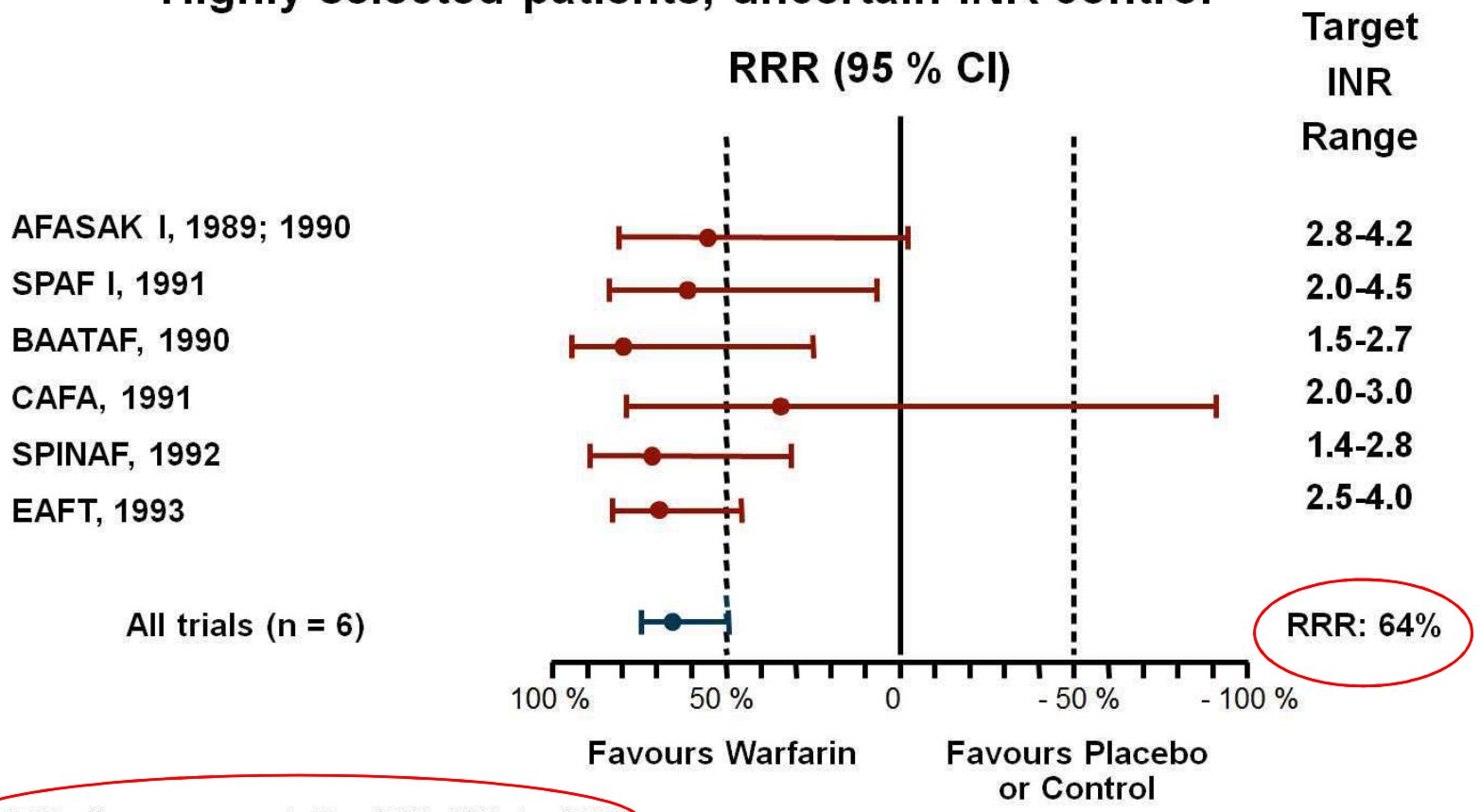
COUMARIN



"In 1941, Karl Paul Link successfully isolated the anticoagulant factor, which initially found commercial application as a rodent-killer. Warfarin is now one of the most widely prescribed medicines in the world."

VKA Therapy in AF

6 trials, 2900 patients with AF
Highly selected patients, uncertain INR control

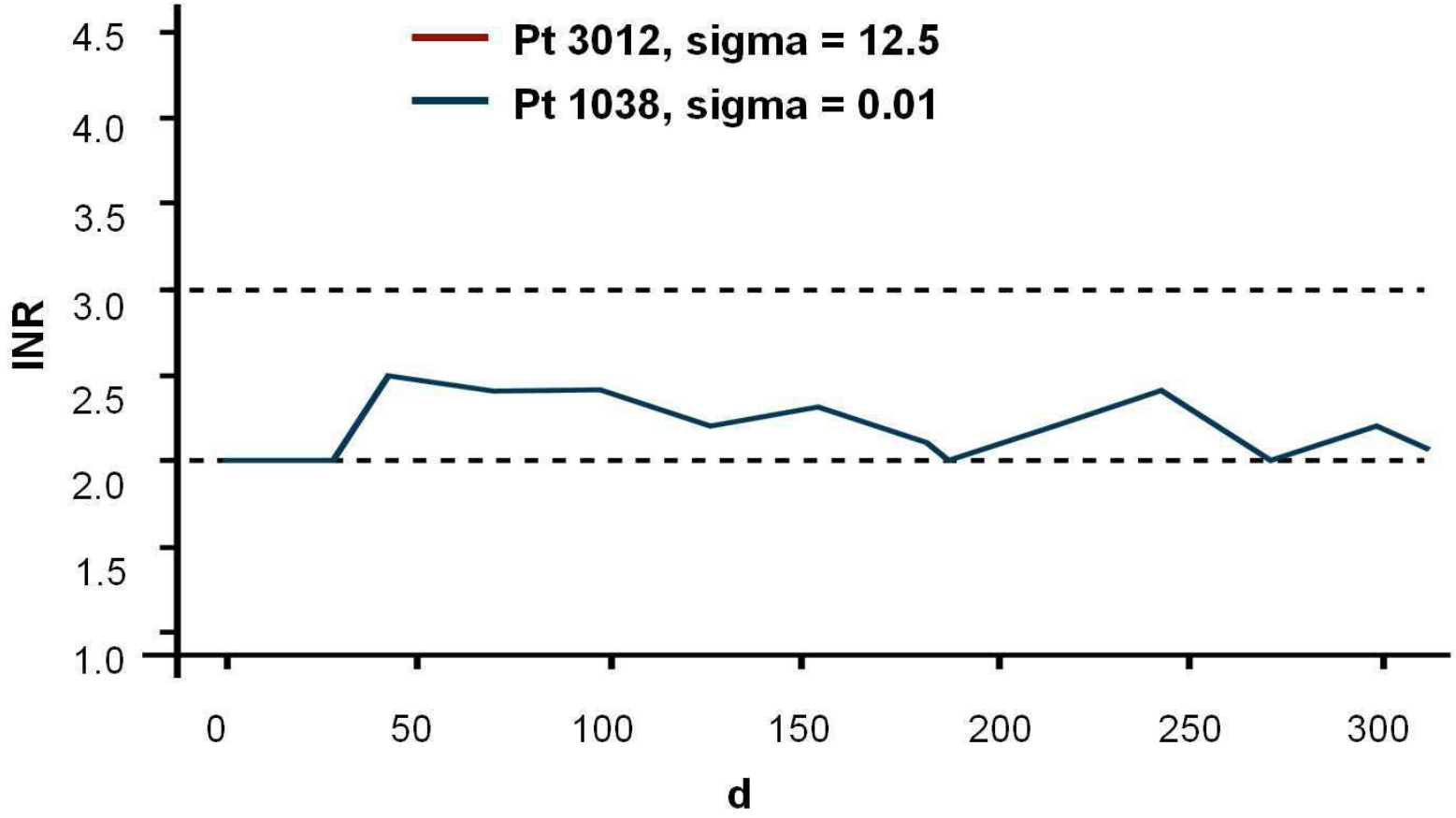


RRR all-cause mortality 26% (3% to 43%)
Absolute increase in risk of major ECH 0.3%/year

ECH = extracranial haemorrhage
RRR = relative risk reduction

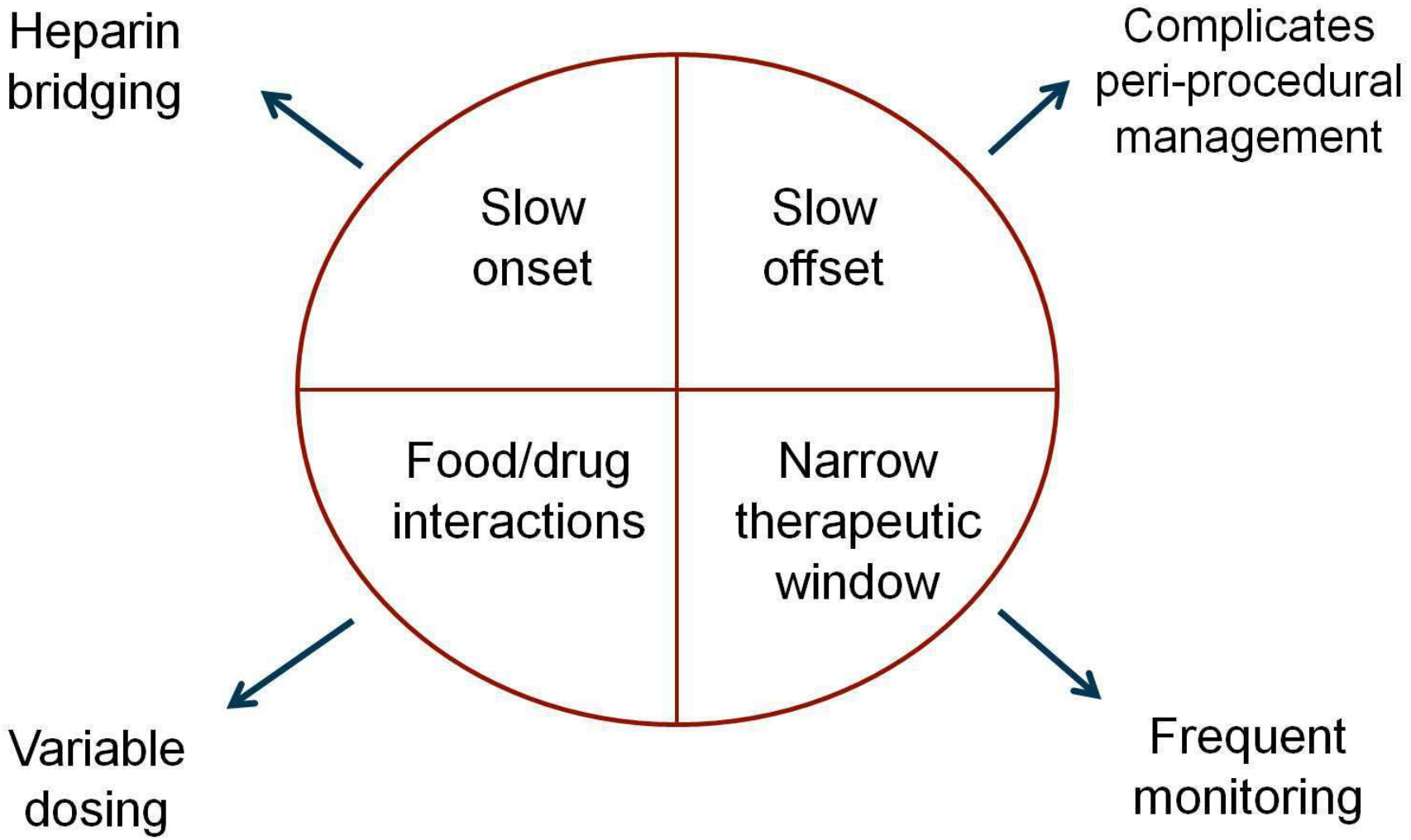
Adapted from Hart RG, et al. *Ann Intern Med.* 2007;146:857-867.[29]

Patient With Low INR Variability



Rose AJ, et al. *J Gen Intern Med*. 2007 Jul;22(7):997-1002

Limitations of Warfarin



Hazards of Warfarin

Medication	Annual National Estimate of Hospitalizations (N = 99,628)		Proportion of Emergency Department Visits Resulting in Hospitalization
Most commonly implicated medications	no.	% (95% CI)	%
Warfarin	33,171	33.3 (28.0-38.5)	46.2
Insulins	13,854	13.9 (9.8-18.0)	40.6
Oral antiplatelet agents	13,263	13.3 (7.5-19.1)	41.5
Oral hypoglycemic agents	10,656	10.7 (8.1-13.3)	51.8
Opioid analgesics	4778	4.8 (3.5-6.1)	32.4
Antibiotics	4205	4.2 (2.9-5.5)	18.3

Budnitz DS, et al. *N Engl J Med.* 2011;365:2002-2012.

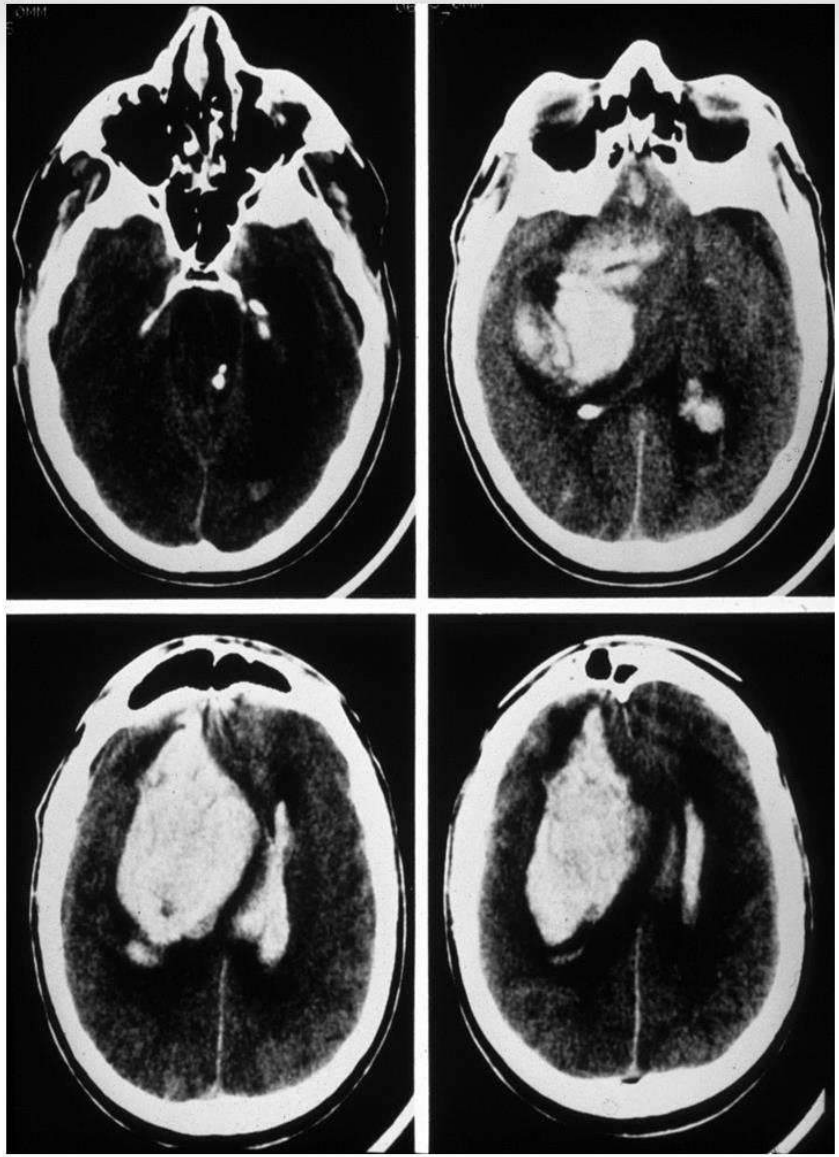
Hazards of Warfarin

Therapeutic Category and Adverse Event Manifestation	Annual National Estimate of Hospitalizations, % (95% CI)	Proportion of Emergency Department Visits Resulting in Hospitalization, %
Hematologic agents		
Intracranial hemorrhage	5.6 (2.1-9.1)	99.7
Hemoptysis	2.0 (1.1-2.8)	73.6
Gastrointestinal hemorrhage	40.8 (29.9-51.7)	84.7
Genitourinary hemorrhage	4.7 (3.2-6.2)	42.4
Epistaxis	6.1 (4.3-8.0)	10.6
Skin or wound hemorrhage	6.8 (4.5-9.1)	24.5
Other type of hemorrhage	5.3 (2.7-8.0)	27.5
Elevated INR, abnormal laboratory values, or drug toxicity not otherwise described	23.7 (16.8-30.6)	59.5

Budnitz DS, et al. *N Engl J Med*. 2011;365:2002-2012.

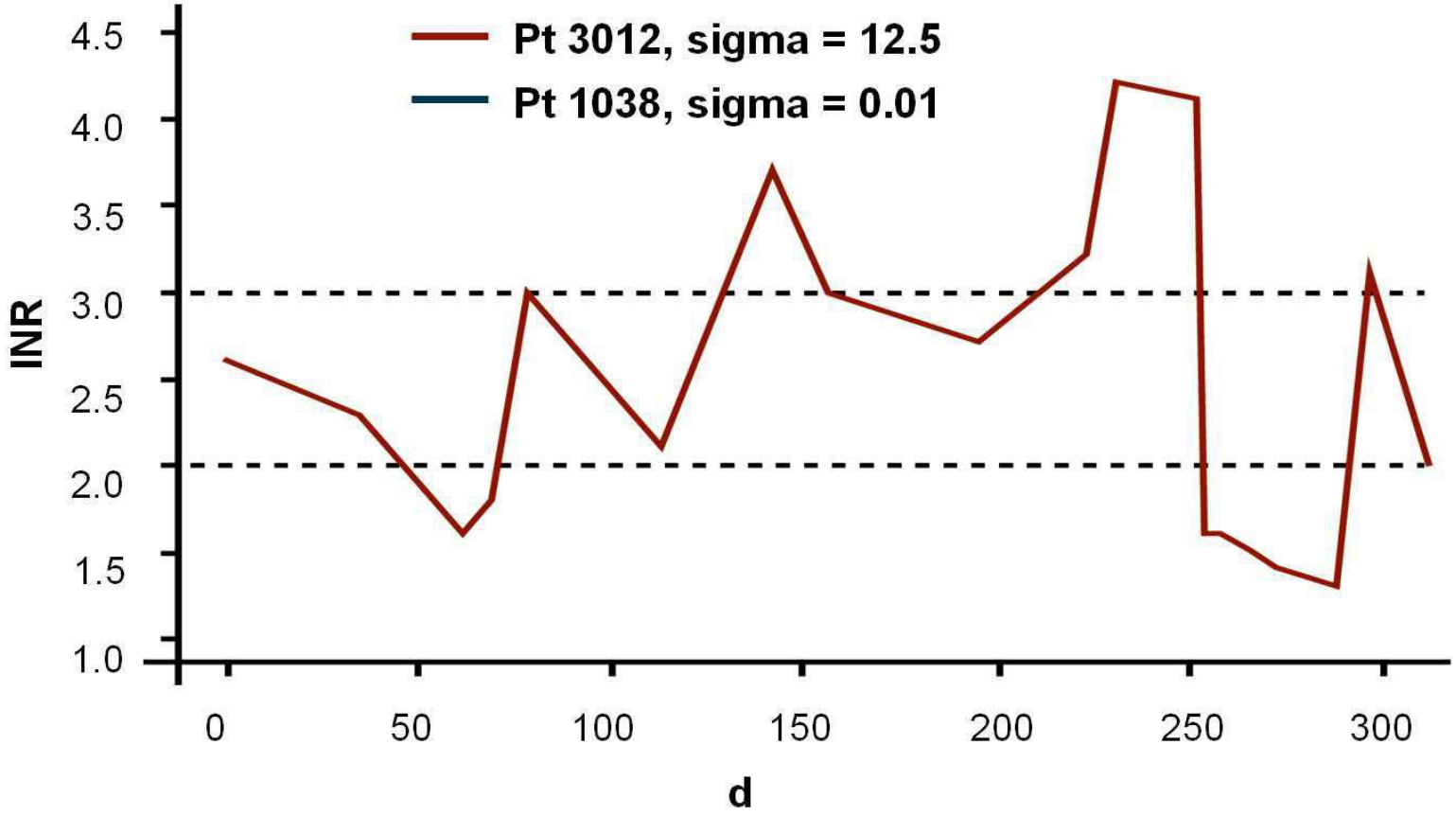
ICH on Warfarin

- OR age ≥ 80 years
  2.8 (1.3 to 5.8)
  P < .001
- 2/3 occur with an INR in 2.0-3.0 range
- 46% mortality
- 17% major deficit



Hylek EM, et al. *Ann Intern Med*. 1994;120:897-902.

Patient With High INR Variability



Rose AJ, et al. *J Gen Intern Med*. 2007 Jul;22(7):997-1002

BAFTA: Role of Aspirin?

Primary Analysis

End point	Warfarin	Aspirin	Hazard Ratio (95% CI)	NNT
Fatal or nonfatal disabling stroke or significant arterial embolism (% annum)	1.8	3.8	0.48 (0.28–0.80)	50

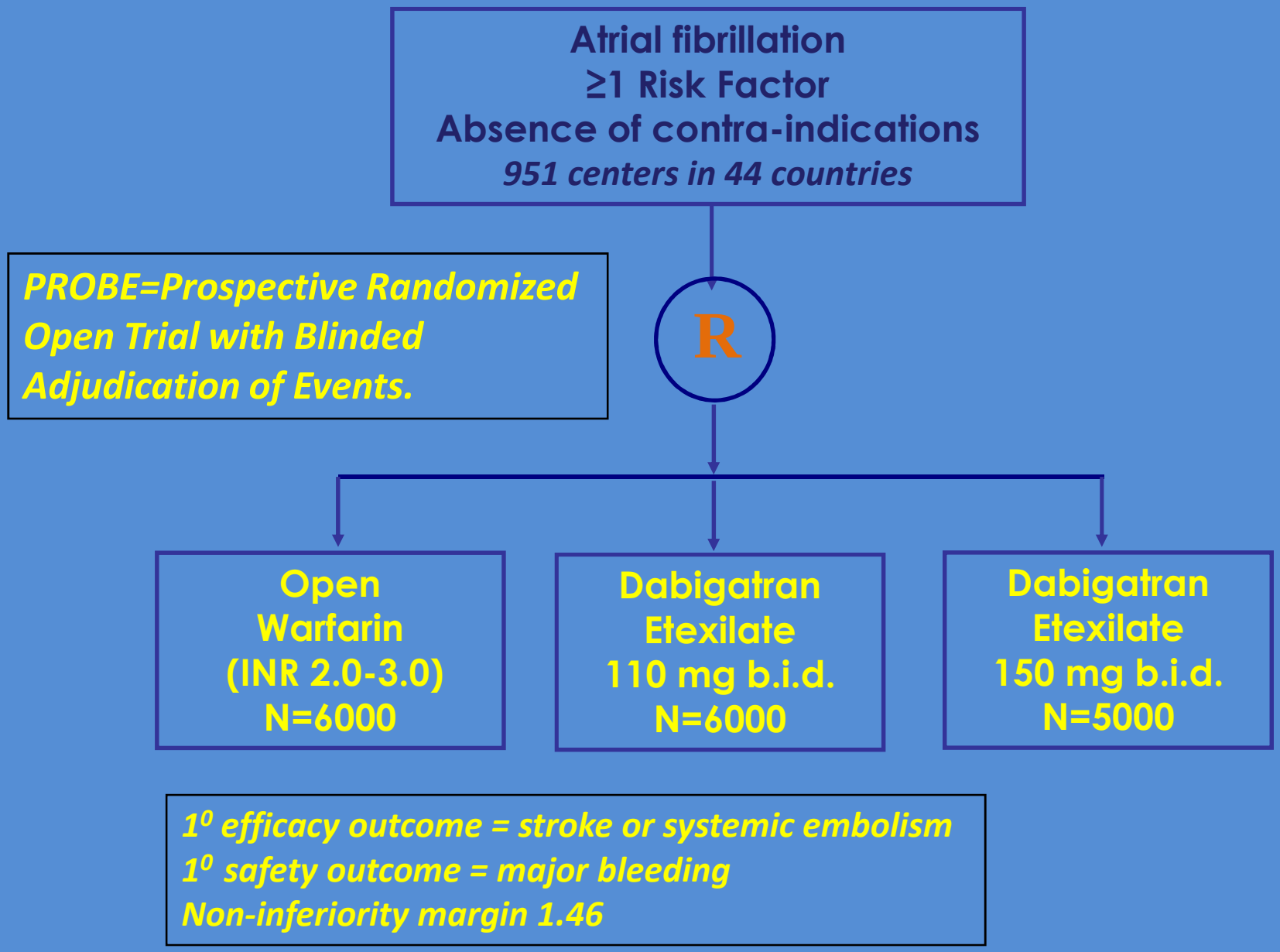
Mant J, et al. *Lancet*. 2007;370:493-503.

BAFTA: Role of Aspirin?
Bleeding Complications With Warfarin vs Aspirin in AF Patients > 75 Years

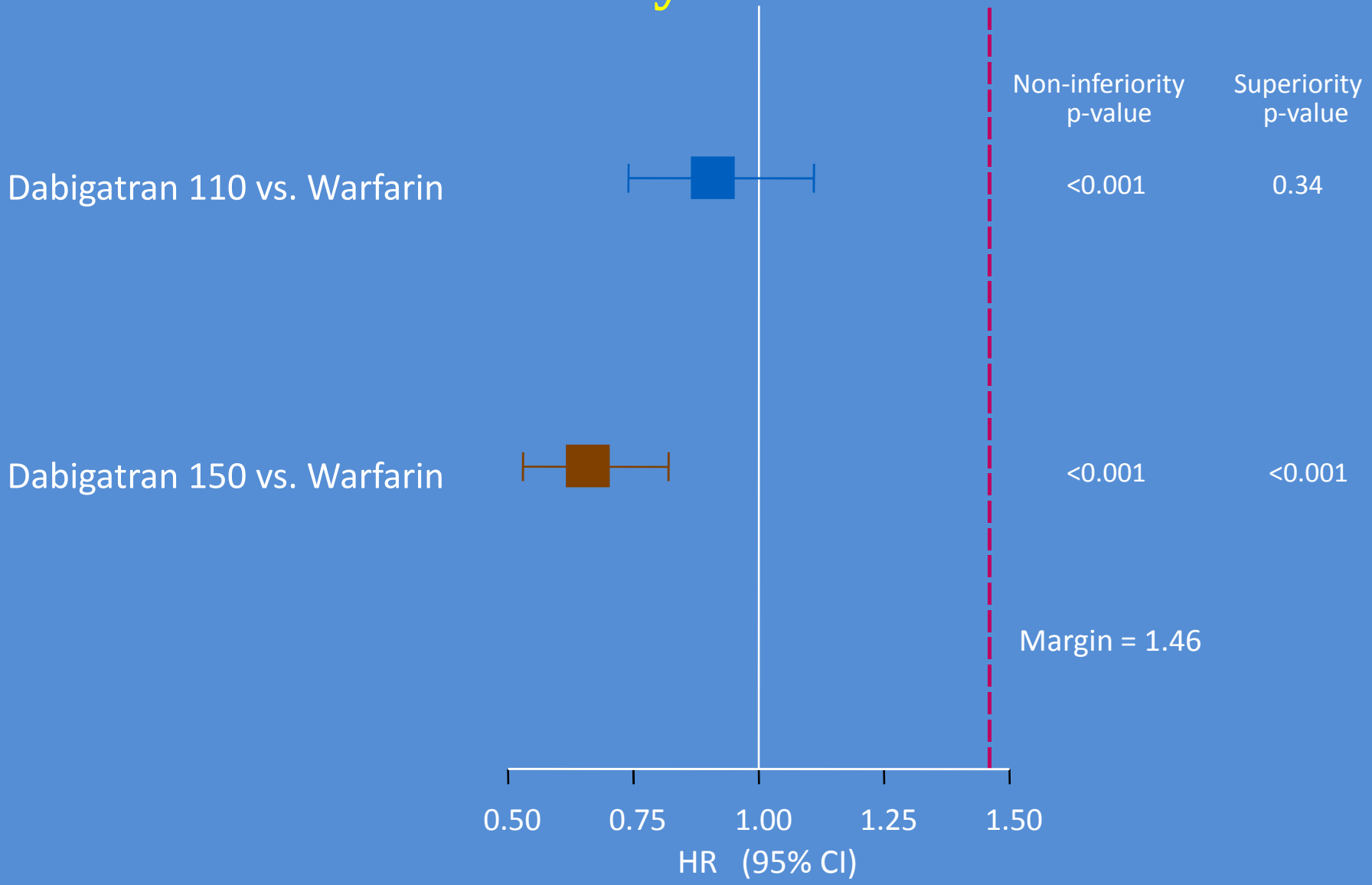
End point	Warfarin	Aspirin	Hazard ratio (95% CI)
Major extracranial hemorrhage, % annum	1.4	1.6	0.87 (0.43-1.73)
All major hemorrhages, % annum	1.9	2.2	0.96 (0.53-1.75)

Mant J, et al. *Lancet*. 2007;370:493-503.

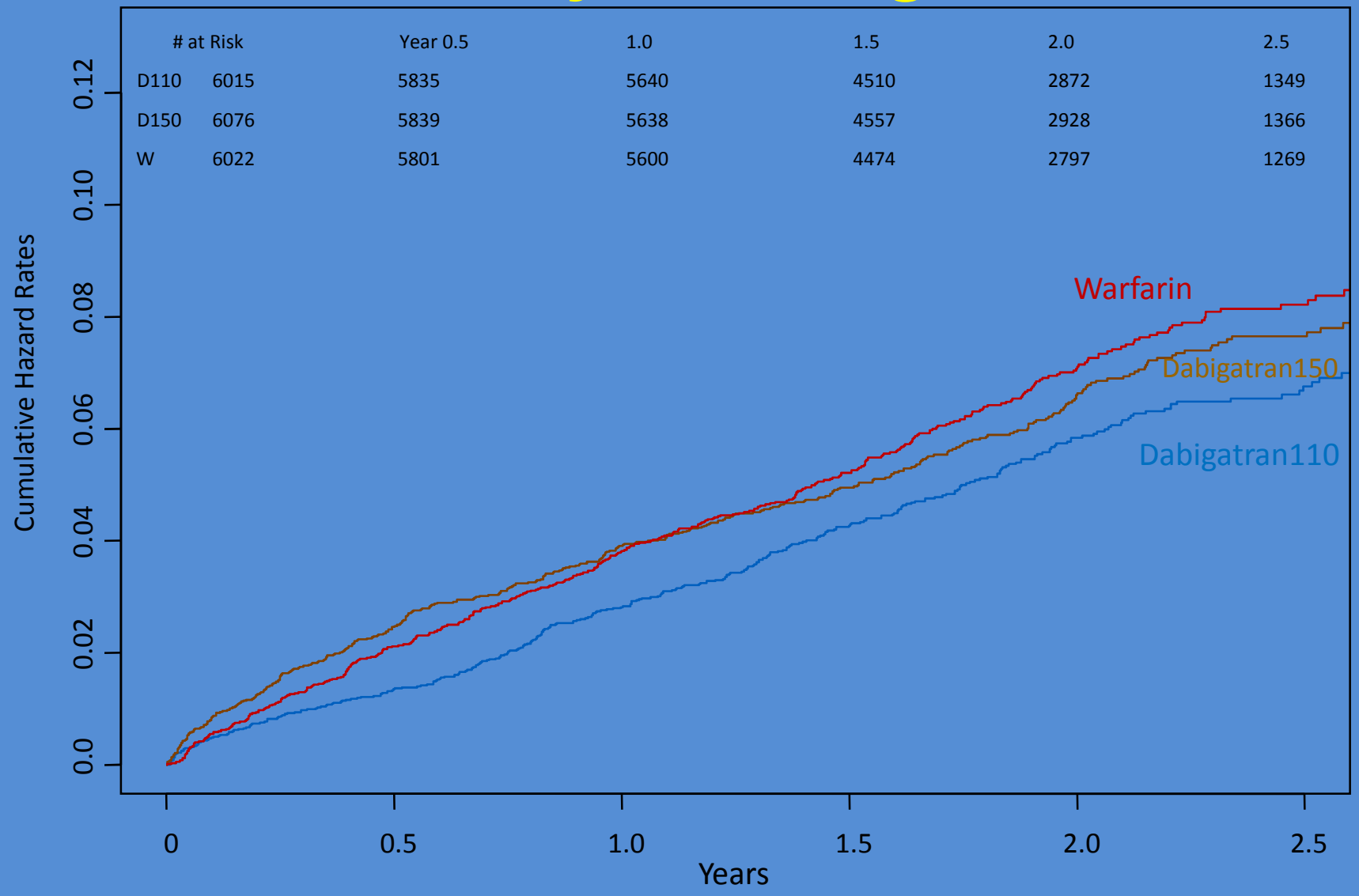
RE-LY: Study design



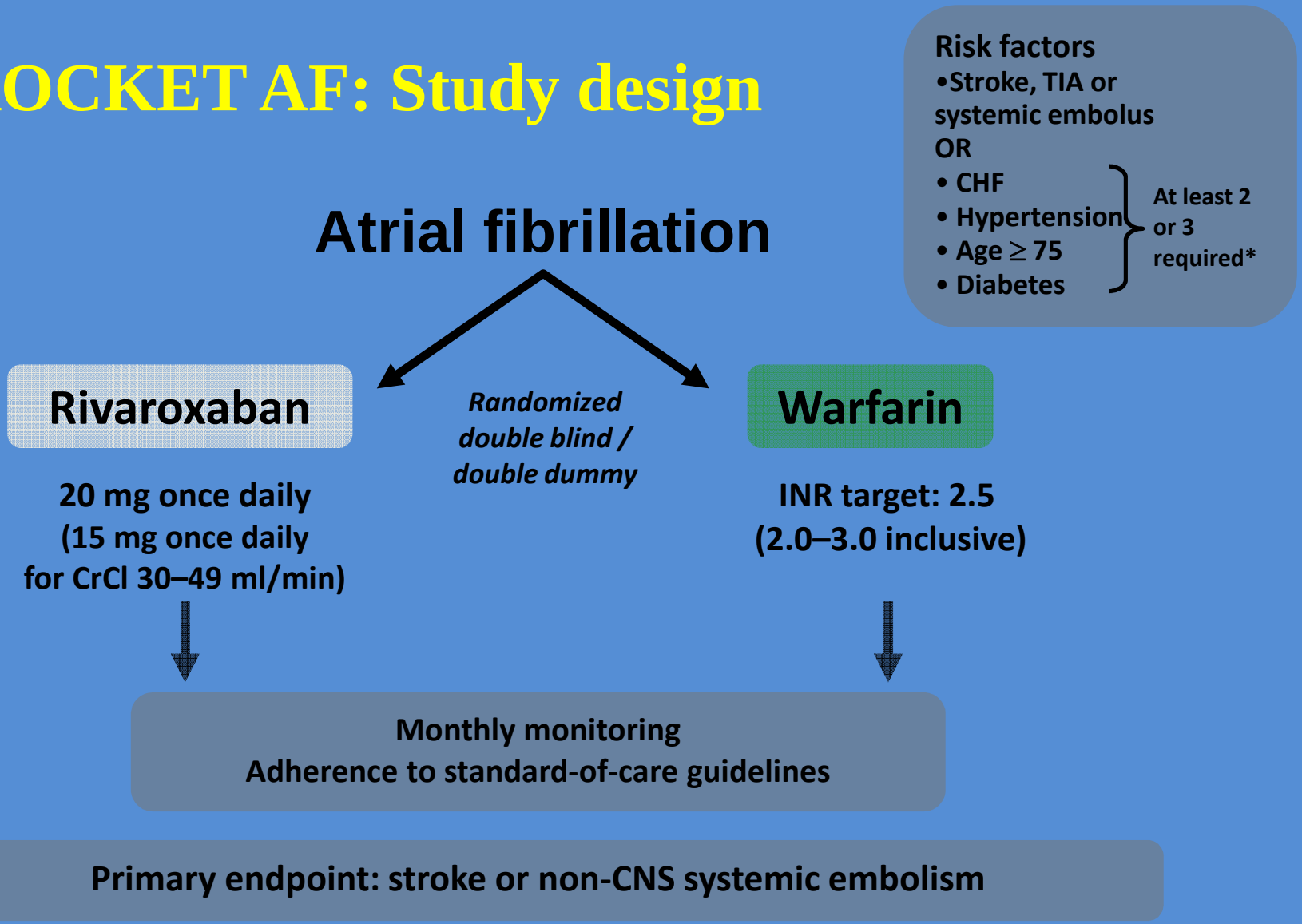
The RE-LY Study: Primary Outcome



The RE-LY Study: Major Bleeding



ROCKET AF: Study design



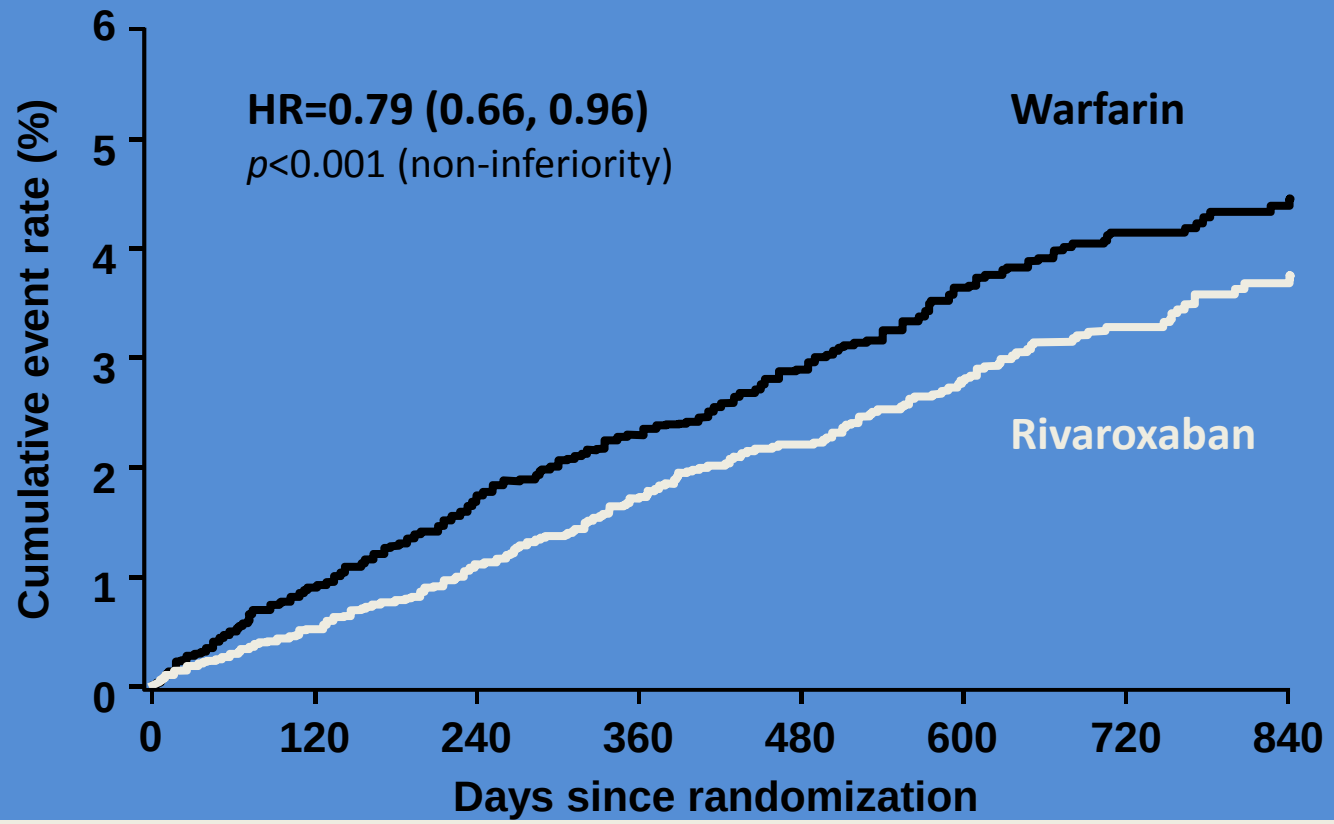
*Enrolment of patients without prior stroke, TIA or SE and only two factors capped at 10%

Patel MR *et al. N Engl J Med* 2011;365:883–891

ROCKET AF

ROCKET AF: primary efficacy endpoint

Stroke or systemic embolism



Number of subjects at risk								
Rivaroxaban	6,958	6,211	5,786	5,468	4,406	3,407	2,472	1,496
Warfarin	7,004	6,327	5,911	5,542	4,461	3,478	2,539	1,538

Per-protocol population – as treated

Patel MR *et al. N Engl J Med* 2011;365:883–891

ROCKET AF

ROCKET AF: Primary Safety Outcomes

	Rivaroxaban	Warfarin		
	Event Rate or N (Rate)	Event Rate or N (Rate)	HR (95% CI)	P-value
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
≥2 g/dL Hgb drop	2.77	2.26	1.22 (1.03, 1.44)	0.019
Transfusion (> 2 units)	1.65	1.32	1.25 (1.01, 1.55)	0.044
Critical organ bleeding	0.82	1.18	0.69 (0.53, 0.91)	0.007
Bleeding causing death	0.24	0.48	0.50 (0.31, 0.79)	0.003
Intracranial Hemorrhage	55 (0.49)	84 (0.74)	0.67 (0.47, 0.94)	0.019
Intraparenchymal	37 (0.33)	56 (0.49)	0.67 (0.44, 1.02)	0.060
Intraventricular	2 (0.02)	4 (0.04)		
Subdural	14 (0.13)	27 (0.27)	0.53 (0.28, 1.00)	0.051
Subarachnoid	4 (0.04)	1 (0.01)		

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

ARISTOTLE: Study design

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomized
double blind,
double dummy
(n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

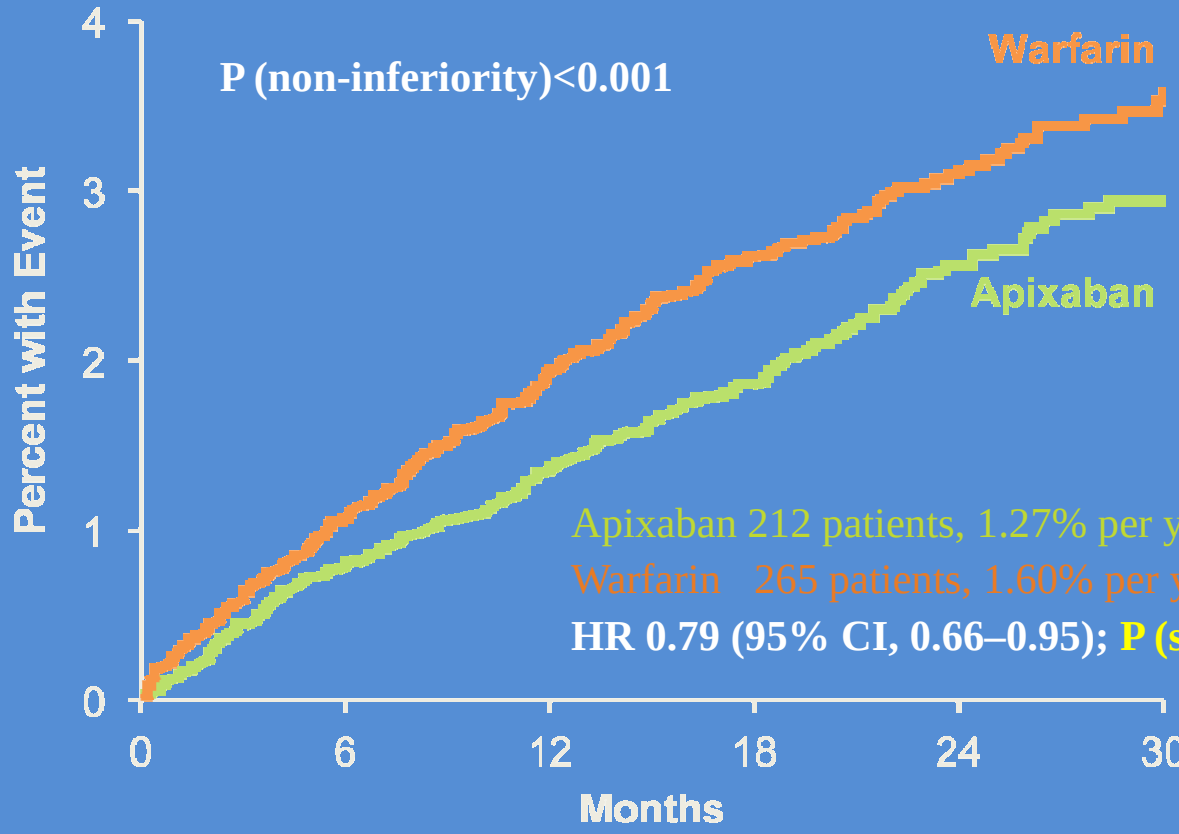
Warfarin/warfarin placebo adjusted by INR/sham INR
based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

ARISTOTLE Study: Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



21% RRR

Apixaban 212 patients, 1.27% per year

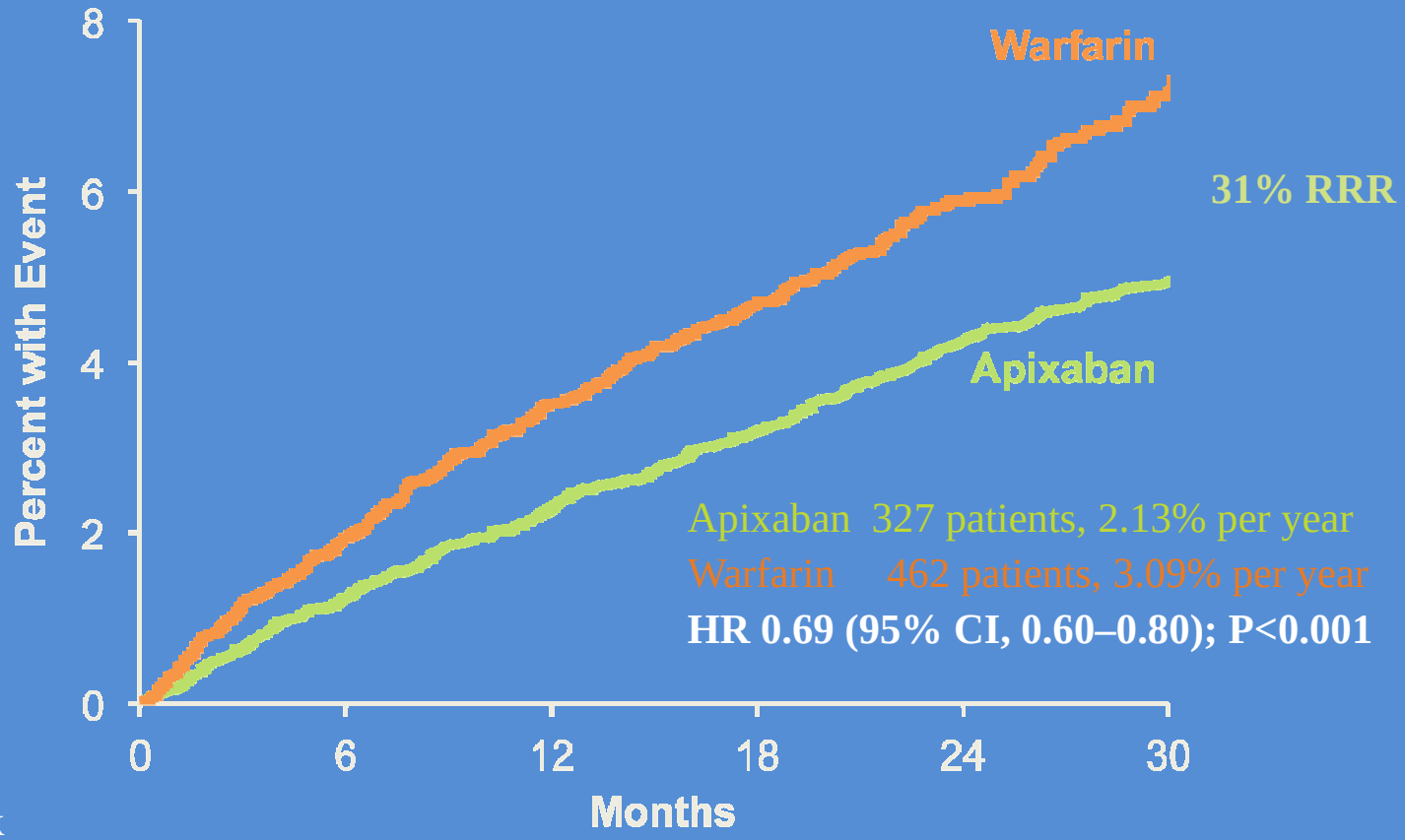
Warfarin 265 patients, 1.60% per year

HR 0.79 (95% CI, 0.66–0.95); P (superiority)=0.011

No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

Aristotle Study:
Major Bleeding

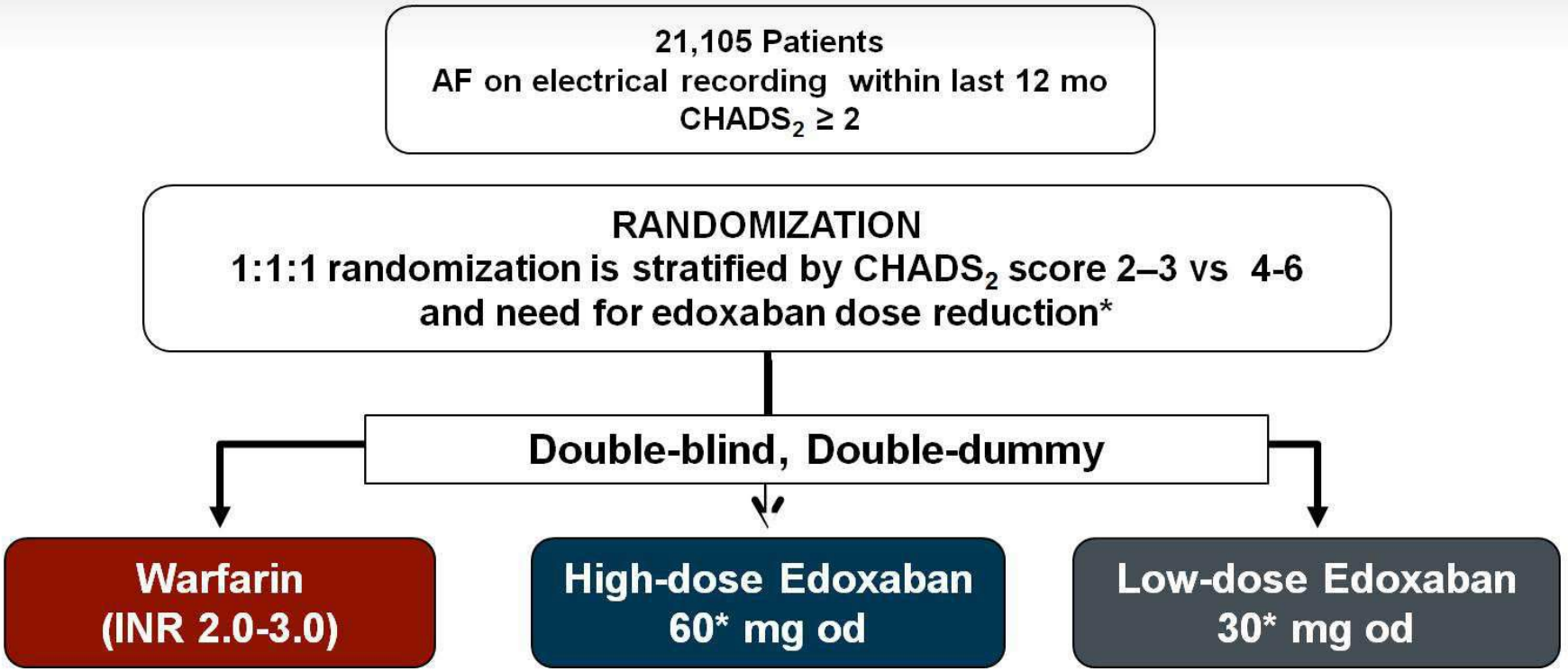
ISTH definition



No. at Risk						
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

Study Design

Engage AF TIMI-48 Study



*Dose reduced by 50% if
- CrCl 30-50 mL/min
- weight ≤ 60 kg
- strong P-gp inhibitor

1º Efficacy EP = Stroke or SEE
2º Efficacy EP = Stroke or SEE or CV mortality
1º Safety EP = Major Bleeding (ISTH criteria)

Noninferiority
Upper 97.5% CI
RR, 1.38

CI = confidence interval CrCl = creatinine clearance;
ISTH=International Society on Thrombosis and Haemostasis
P-gp = P-glycoprotein; SEE=systemic embolic event

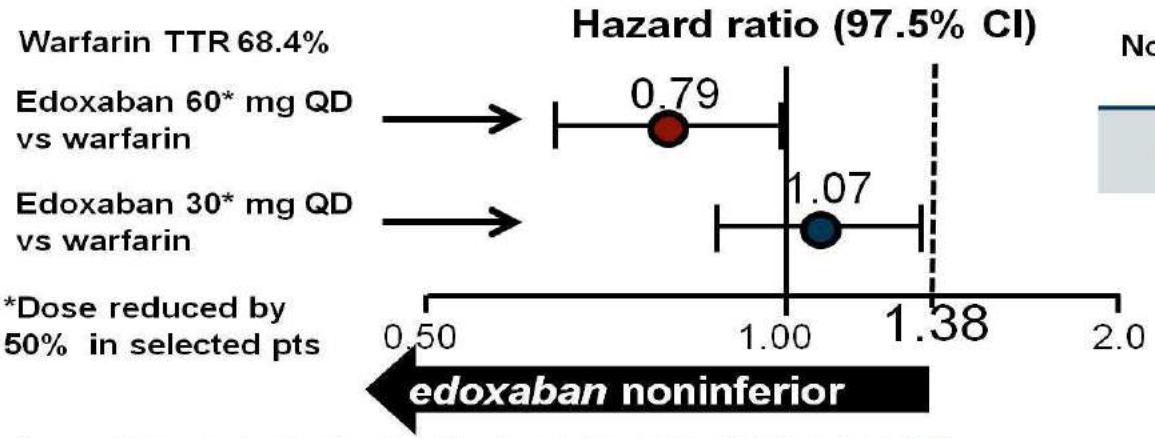
Ruff CT, et al. *Am Heart J.* 2010; 160:635-641.

Engage AF TIMI-48 Study

Primary Efficacy End Point (Stroke/SEE) mITT Population While on Treatment

Noninferiority Analysis: Edoxaban vs Warfarin

Treatment	N	n	Incidence, %/yr	HR (97.5% CI)	*P* for non-inferiority
Warfarin (median TTR 68.4%)	7012	232	1.50	-	-
Edoxaban 60* mg QD	7012	182	1.18	0.79 (0.63–0.99)	< .0001
Edoxaban 30* mg QD	7002	253	1.61	1.07 (0.87–1.31)	.005



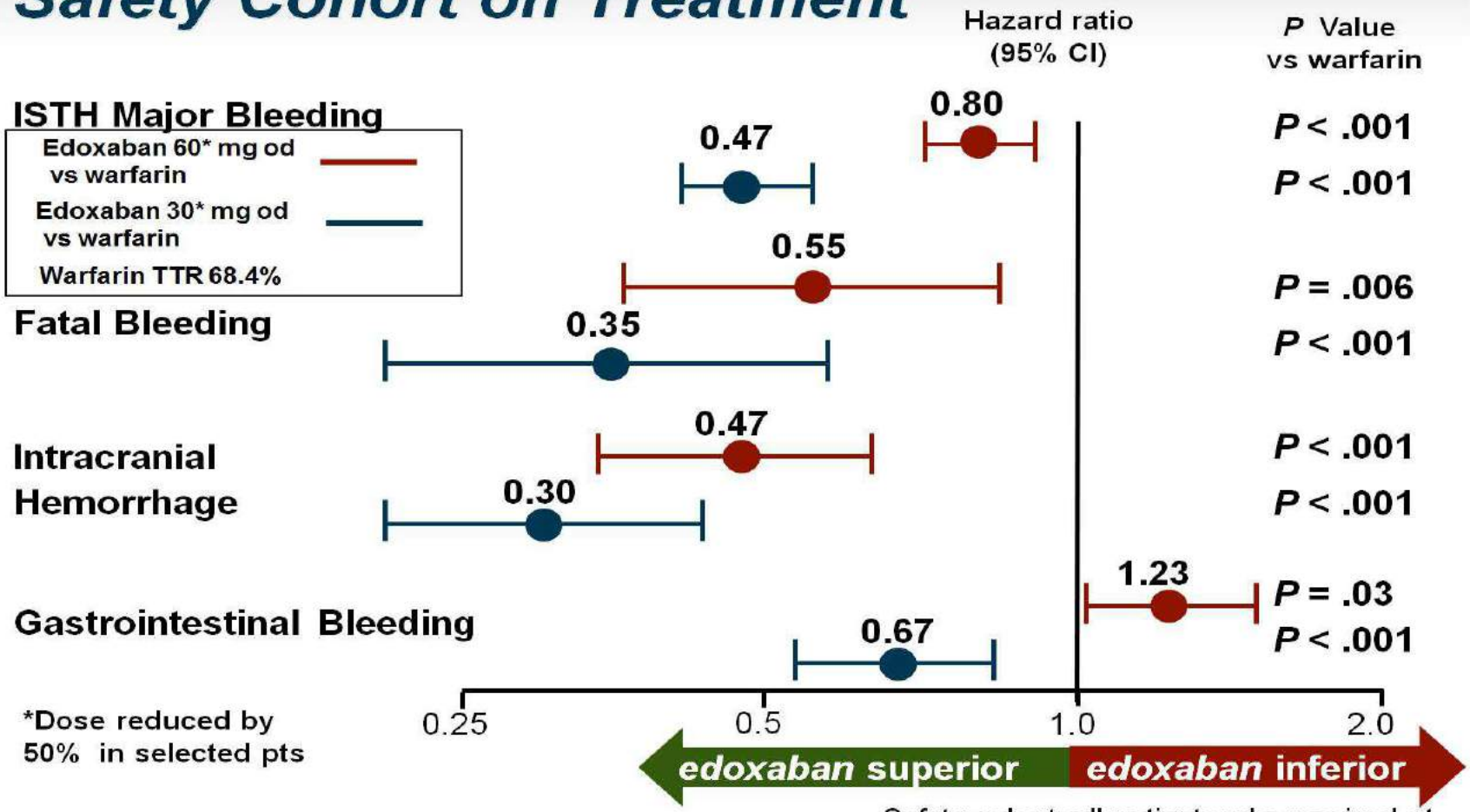
Non-inferiority *P* Values	Superiority *P* Values
P < .0001	*P* = .017
P = .005	*P* = .44

Giugliano RP, et al. *N Engl J Med*. 2013; 369:2093-2104.[17]

Engage AF TIMI-48 Study

Main Safety Results

Safety Cohort on Treatment



Safety cohort=all patients who received at least 1 dose by treatment actually received

Giugliano RP, et al. *N Engl J Med*. 2013; 369:2093-2104.[17]

Rates of Intracranial Bleeding

ARISTOTLE[a]	Apixaban (n = 9088)	Warfarin (n = 9052)	*P* Value
%/yr	0.33	0.80	< .001

RE-LY[b]	Dabigatran 110 mg (n = 6015)	Dabigatran 150 mg (n = 6076)	Warfarin (n = 6022)	
Rate/yr, %	0.2	0.3	0.7	<.001

ROCKET AF[c]	Rivaroxaban (n = 7111)	Warfarin (n = 7125)	
%	0.8	1.2	.02

a. Granger CB, et al. *N Engl J Med*. 2011;365:981-992.
b. Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151.
c. Patel MR, et al. *N Engl J Med*. 2011;365:8838-8891.

Novel Oral Anticoagulants in Atrial Fibrillation and Intracranial Bleeding

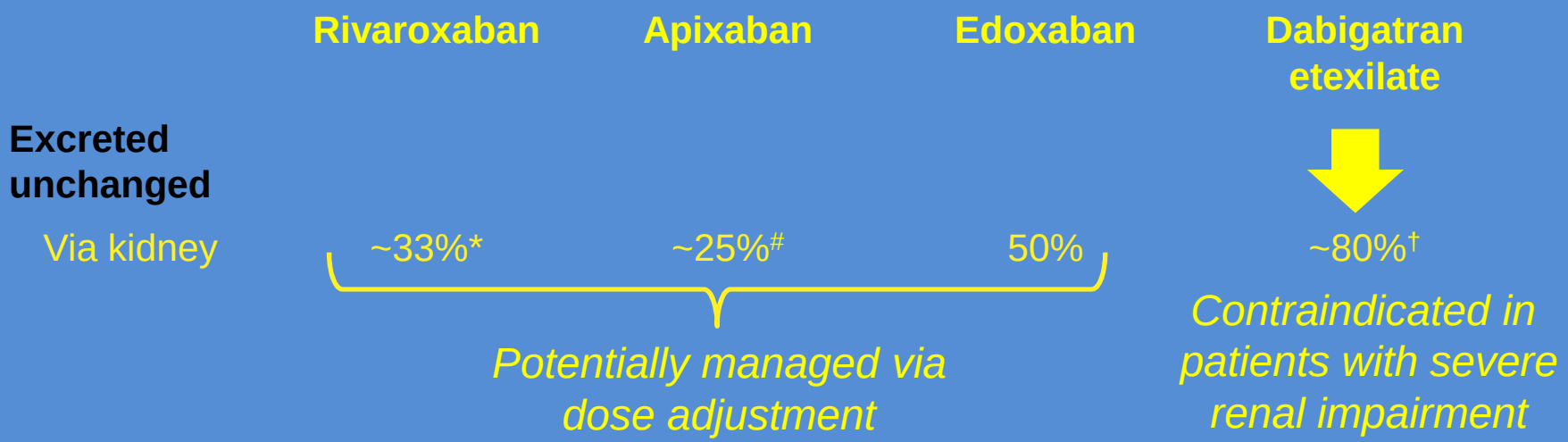
The lower risk of hemorrhagic stroke associated with all four novel anticoagulants suggests that

there is a specific risk associated with warfarin

possibly related to its inhibition of multiple coagulation factors or interaction between warfarin and tissue factor VIIa complexes in the brain

NOAC therapy in patients with renal impairment

NOAC are partially cleared via the renal route but not all rely on this route to the same extent

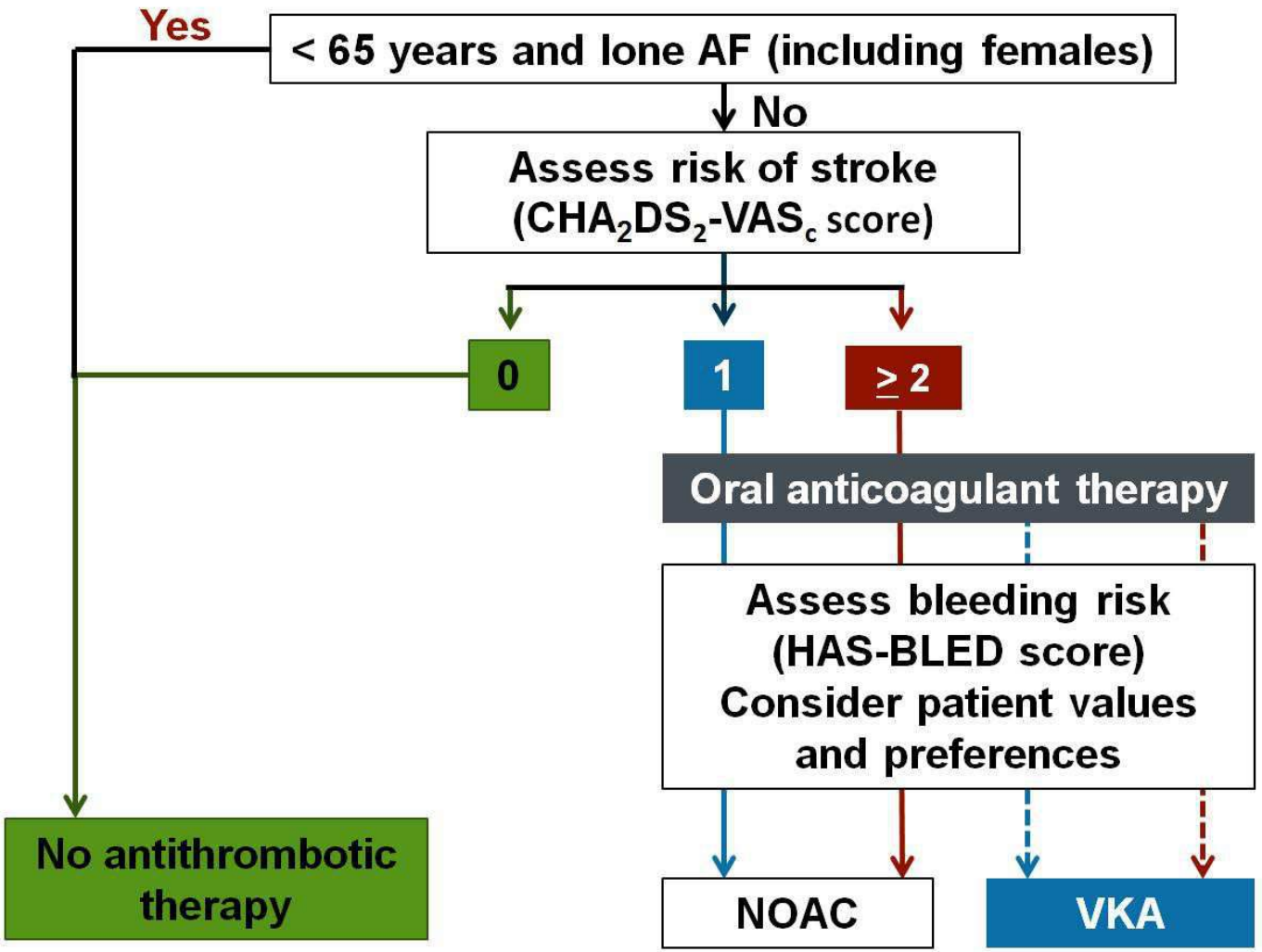


*Additional 33% cleared renally after metabolic degradation to inactive drug

Table 3 Interpretation of coagulation assays in patients treated with different NOACs

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12–24 h after ingestion	12–24 h after ingestion	12–24 h after ingestion[9]	16–24 h after ingestion
PT	Cannot be used	Cannot be used	Prolonged but no known relation with bleeding risk[5,9]	Prolonged: may indicate excess bleeding risk but local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	At trough: >2x ULN suggests excess bleeding risk	Cannot be used	Prolonged but no known relation with bleeding risk[9]	Cannot be used
dTT	At trough: >200 ng/ml or >65 s: excess bleeding risk	Cannot be used	Cannot be used[10]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	No data yet	Quantitative;[10] no data on threshold values for bleeding or thrombosis	Quantitative; no data on threshold values for bleeding or thrombosis
ECT	At trough: ≥3 × ULN: excess bleeding risk	Not affected	Not affected	Not affected

ESC 2012 Updated Guidelines for AF



Camm AJ, et al. *Europace*. 2012;14:1385-1413.

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary

Table 5. Summary of Recommendations for Prevention of Thromboembolism in Patients With AF

Recommendations	COR	LOE	References
Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences	I	C	N/A
Antithrombotic therapy selection based on risk of thromboembolism	I	B	(64-67)
CHA_2DS_2-VASc score recommended to assess stroke risk	I	B	(68-70)
Warfarin recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis	I	B	(71-73)
With prior stroke, TIA, or CHA_2DS_2-VASc score ≥2, oral anticoagulants recommended. Options include:			
• Warfarin	I	A	(68-70)
• Dabigatran, rivaroxaban, or apixaban	I	B	(74-76)
With warfarin, determine INR at least weekly during initiation and monthly when stable	I	A	(77-79)
Direct thrombin or factor Xa inhibitor recommended, if unable to maintain therapeutic INR	I	C	N/A
Re-evaluate the need for anticoagulation at periodic intervals	I	C	N/A
Bridging therapy with LMWH or UFH recommended with a mechanical heart valve if warfarin is interrupted. Bridging therapy should balance risks of stroke and bleeding	I	C	N/A
Without a mechanical heart valve, bridging therapy decisions should balance stroke and bleeding risks against the duration of time patient will not be anticoagulated	I	C	N/A
Evaluate renal function prior to initiation of direct thrombin or factor Xa inhibitors, and re-evaluate when clinically indicated and at least annually	I	B	(80-82)
For atrial flutter, antithrombotic therapy is recommended as for AF	I	C	N/A

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary

Table 5. Summary of Recommendations for Prevention of Thromboembolism in Patients With AF

With nonvalvular AF and CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy	IIa	B	(80, 81)
With CHA_2DS_2-VASc score ≥2 and end-stage CKD (CrCl <15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation	IIa	B	(82)
With nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered	IIb	C	N/A
With moderate-to-severe CKD and CHA_2DS_2-VASc scores of ≥2, reduced doses of direct thrombin or factor Xa inhibitors may be considered	IIb	C	N/A
For PCI,* BMS may be considered to minimize duration of DAPT	IIb	C	N/A
Following coronary revascularization in patients with CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel concurrently with oral anticoagulants, but without aspirin	IIb	B	(83)
Direct thrombin, dabigatran, and factor Xa inhibitor, rivaroxaban, are not recommended with AF and end-stage CKD or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits	III: No Benefit	C	(74-76, 84-86)
Direct thrombin inhibitor, dabigatran, should not be used with a mechanical heart valve	III: Harm	B	(87)

Warfarin -- Modern Role

Standard of Care for the Following Patient Groups

- Warfarin with monitoring should be the standard of care if
  - There is a risk of nonadherence
  - Renal impairment is present
  - The patient has ACS ± angioplasty ± stent (DES)
  - A mechanical heart valve is in situ
  - The patient has hypertrophic cardiomyopathy
  - The patients are children or adolescents
  - A drug that has an antidote is preferred
  - The patient is intolerant to the new drugs
  - Cost is an issue

Hell is an atherosclerotic artery with severe plaque and a thrombus partially occluding the lumen

Θνησιμότητα στα Οξέα Στεφανιαία Σύνδρομα στην Ελλάδα: Η μελέτη HELIOS (2005-2006)

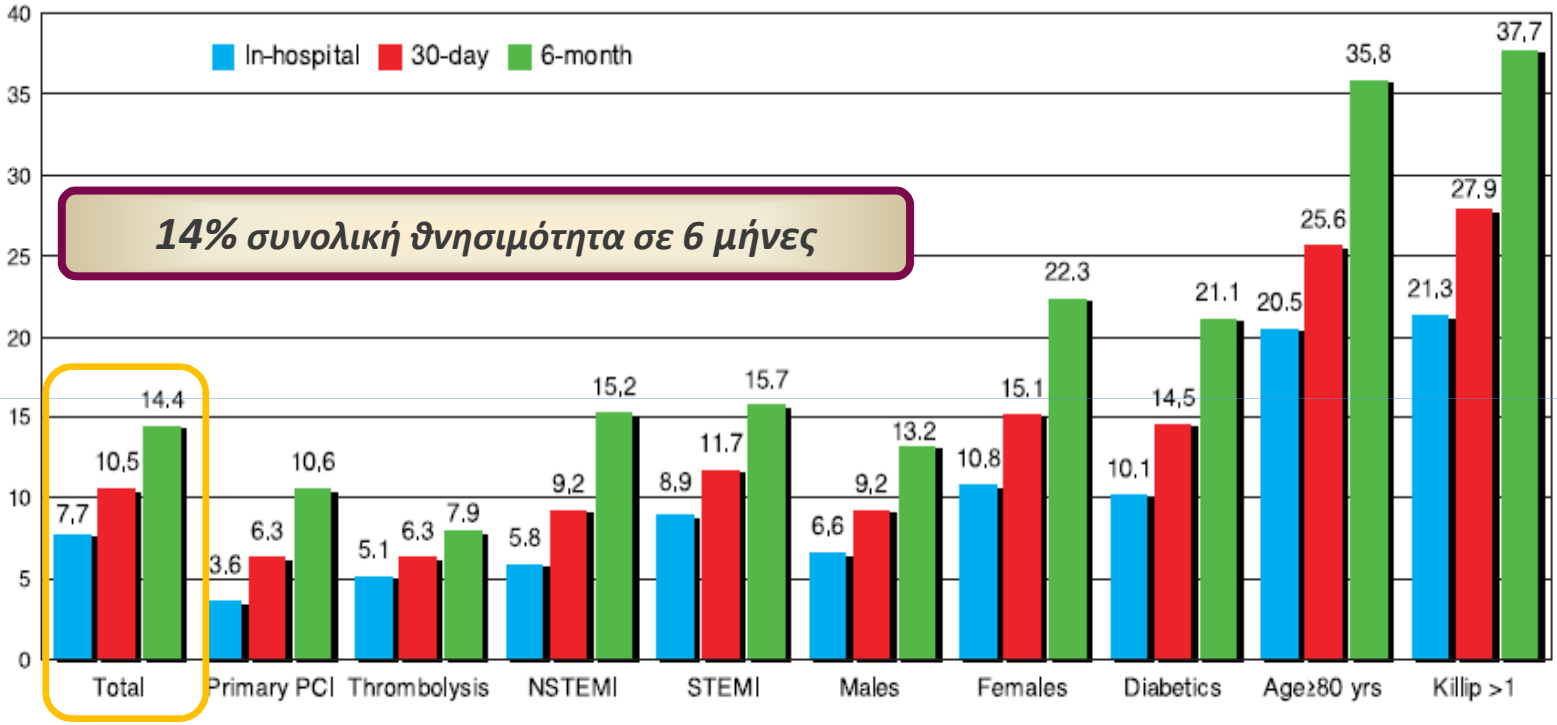
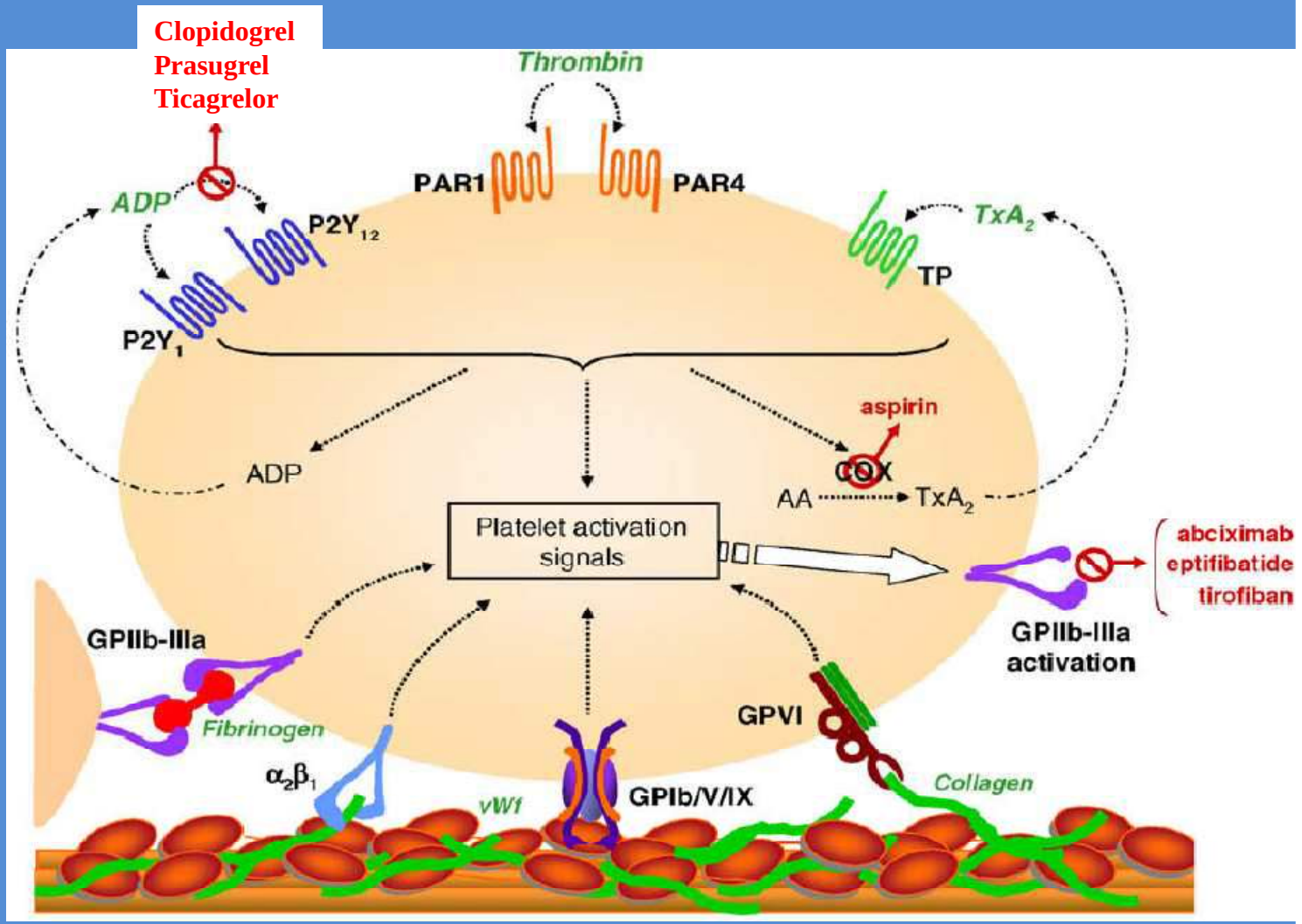


Figure 3. Unadjusted in-hospital, 30-day and 6-month mortality rates in relation to selected clinical prognostic predictors. PCI – percutaneous coronary intervention; NSTEMI – non-ST elevation myocardial infarction; STEMI – ST-segment elevation myocardial infarction.

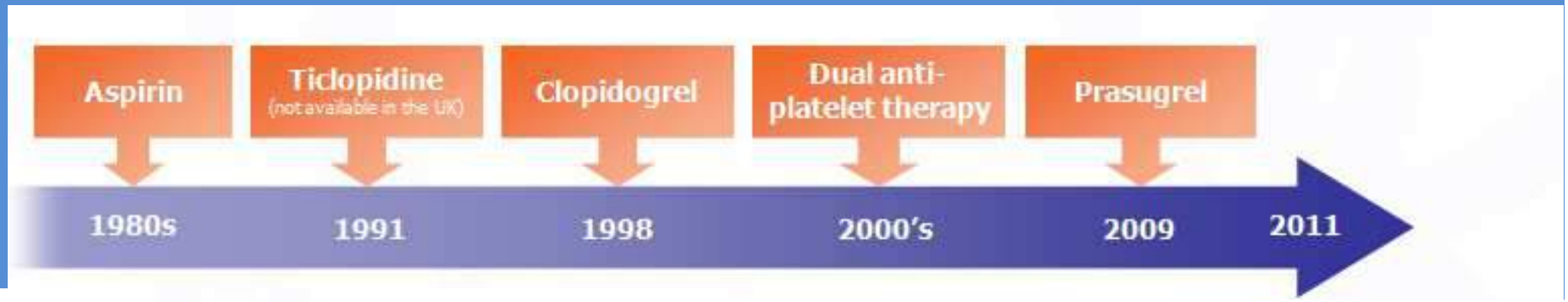
N=1840 ασθενείς με οξύ έμφραγμα του μυοκαρδίου

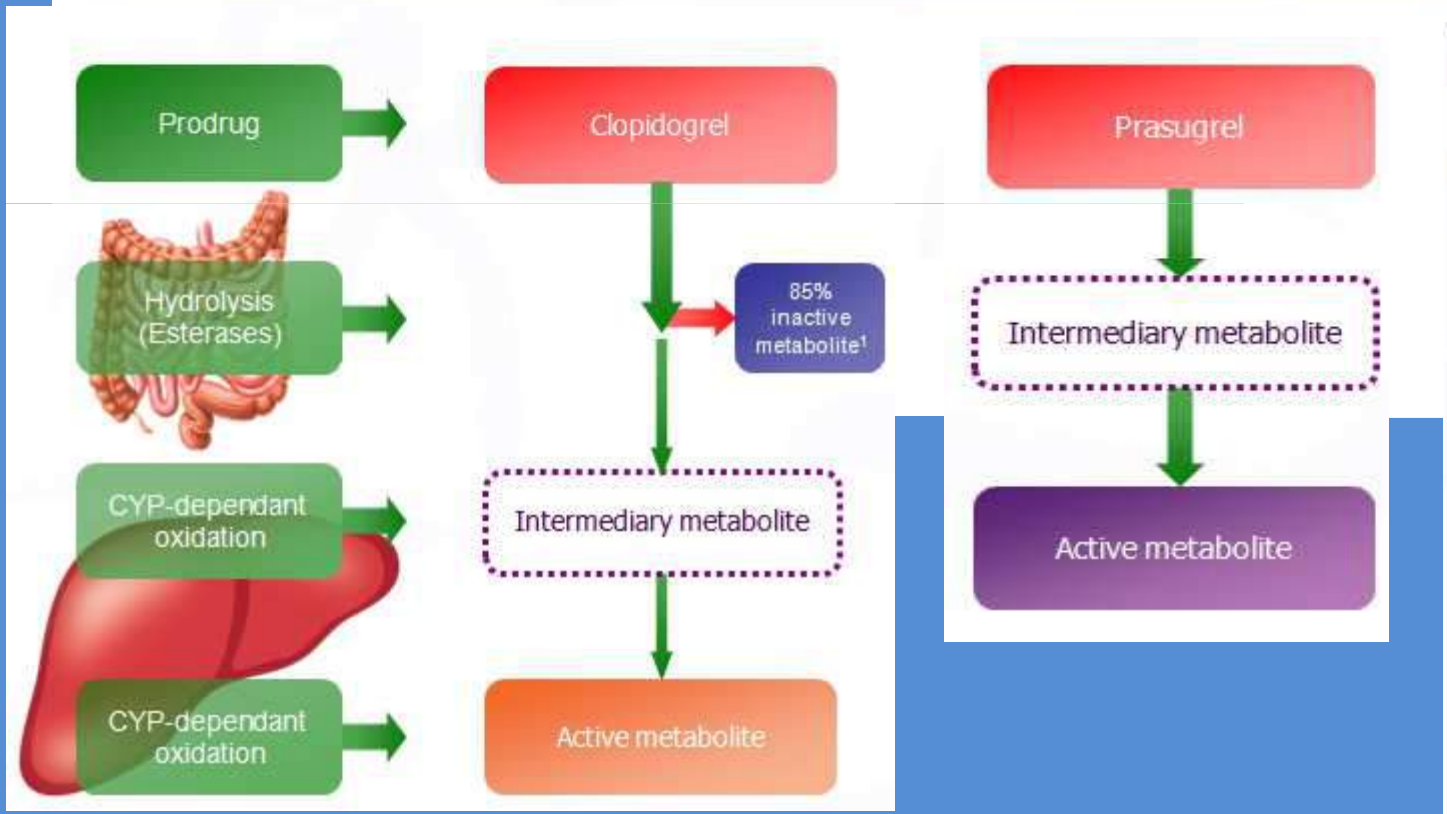
Andrikopoulos G, et al. Hellenic J Cardiol. 2007;48:325-34.

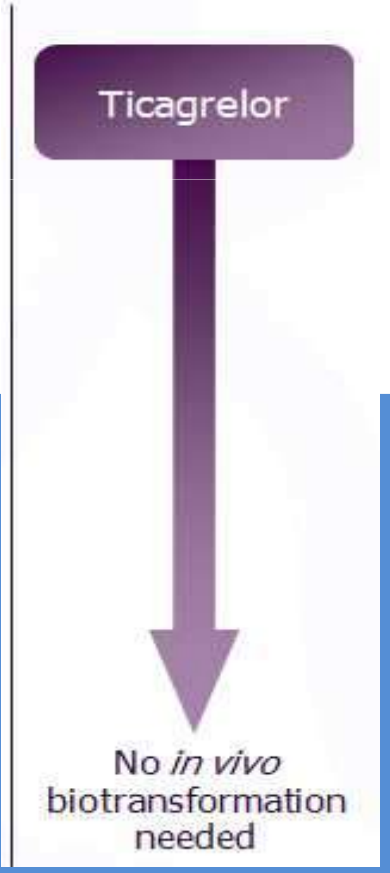
Mechanisms of platelet activation and mode of action of existing antiplatelet therapies



The evolution of antiplatelet therapy in acute coronary syndromes







Treatment guidelines: Timing of antiplatelet therapy in STEMI

- While pre-hospital initiation of oral antiplatelet treatment is not recommended specifically, the 2012 ESC STE-ACS guidelines acknowledge that it is common practice in Europe[Steg 2012]
  - Early administration may be preferable to achieve early efficacy
- The new ESC/EACTS guidelines recommend initiation of DAPT at first medical contact* in STEMI primary PCI[Kolh 2014]

STEMI with primary PCI	Class	Level	Evidence
Initiate DAPT at first medical contact** and maintain treatment for 12 months unless excessive bleeding risk*	I	A*/B**	• PLATO • TRITON • CURRENT-OASIS 7

*The point at which the patient is either initially assessed (12-lead ECG) by a paramedic or physician or other medical personnel in the pre-hospital setting, or the patient arrives at the hospital emergency department, and therefore often in the outpatient setting

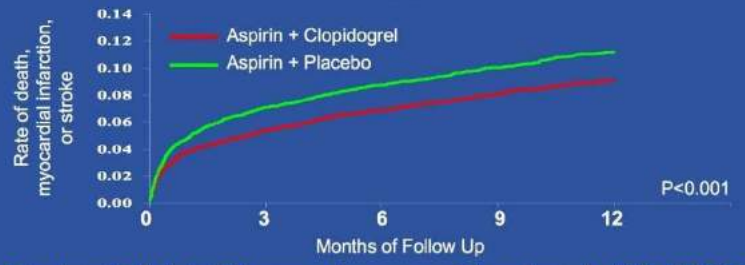
Steg G et al. Eur Heart J 2012;33:2569–2619

.Kolh P et al. Eur Heart J August 29 2014; DOI:10.1093/eurheart/ehu278 [Epub ahead of print]

Clopidogrel Evidence: Secondary Prevention

Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) Trial

12,562 patients with a NSTE-ACS randomized to daily aspirin (75-325 mg) or clopidogrel (300 mg load, 75 mg thereafter) plus aspirin (75-325 mg) for 9 months

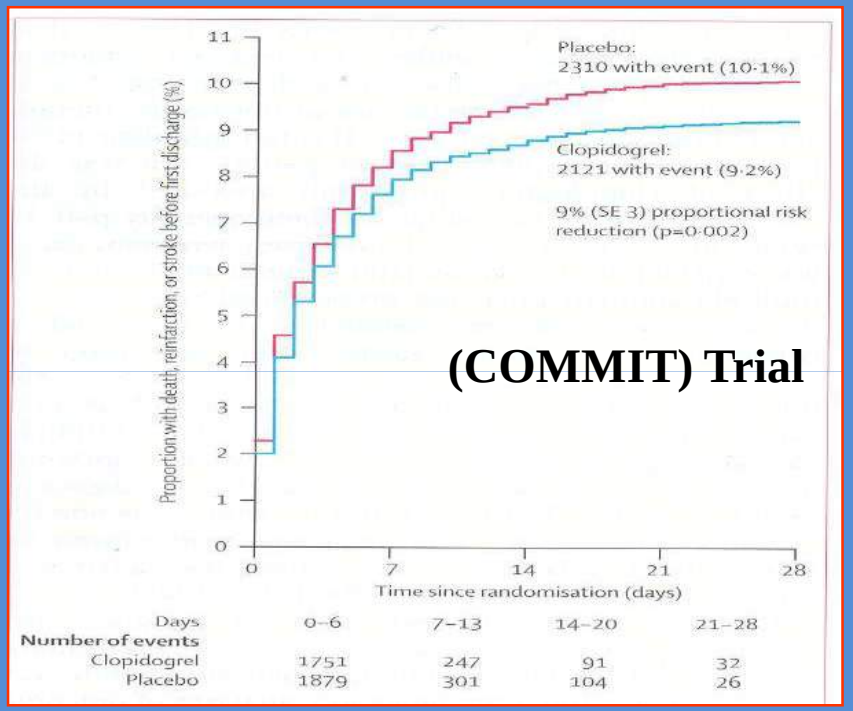


Dual antiplatelet therapy is more efficacious in NSTE-ACS

NSTE-ACS=Non ST-segment elevation acute coronary syndrome

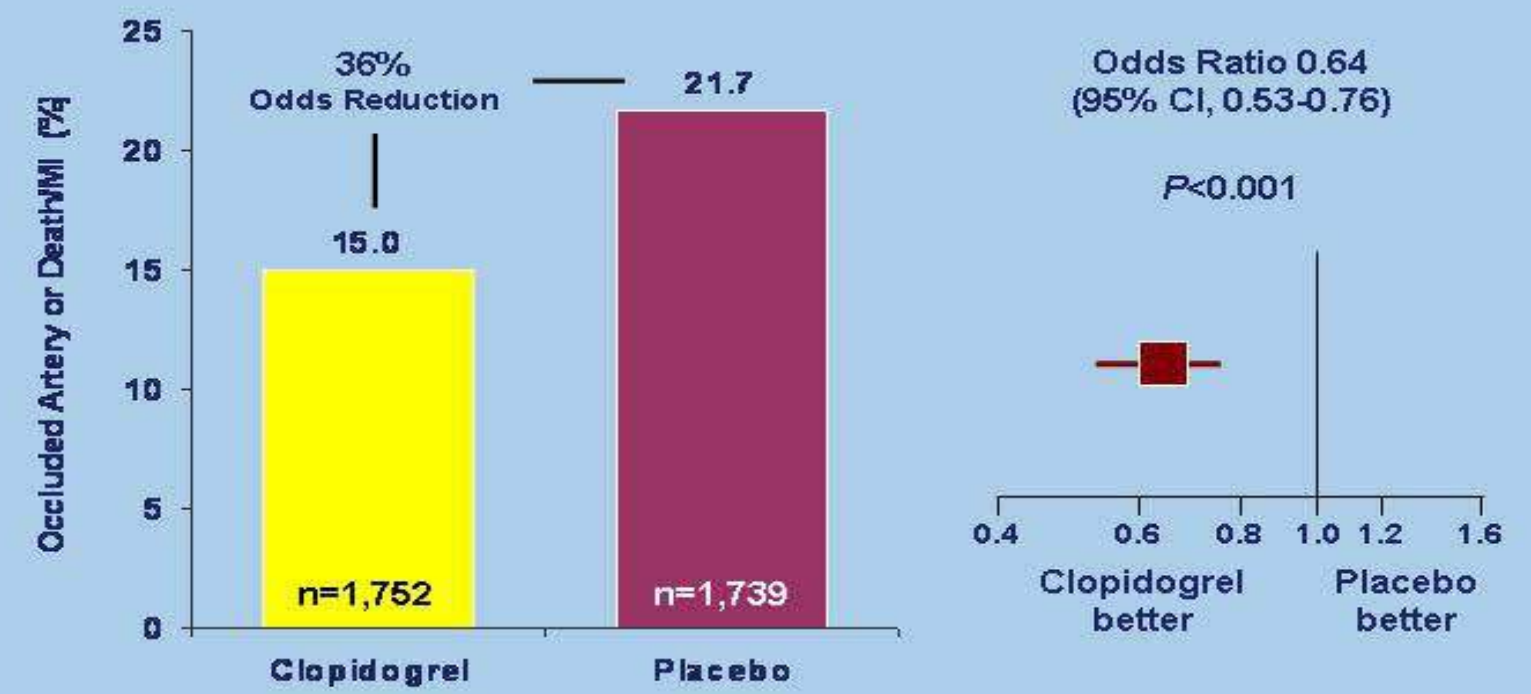
The CURE Trial Investigators. *NEJM* 2001;345:494-502

11



(COMMIT) Trial

CLARITY-TIMI 28: Primary Endpoint: Occluded Artery (or Death/MI through Angio/HD)

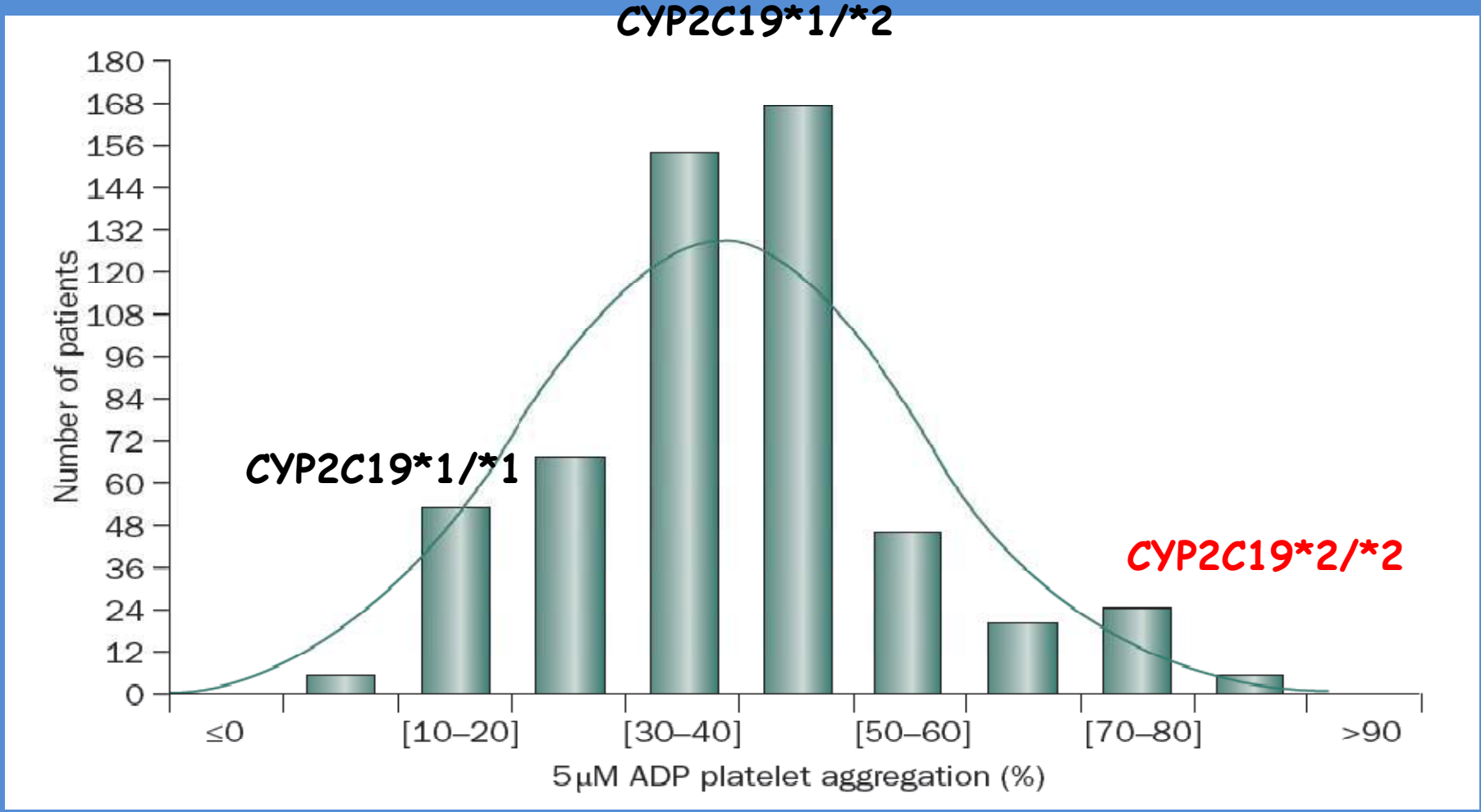


HD=hospital discharge
MI=myocardial infarction

Sabatine MS, et al. *N Engl J Med.* 2005;352:1179-1189.

plateletNEWS.org
Breakthrough platelet information and education

Pharmacogenetics of “Clopidogrel resistance”



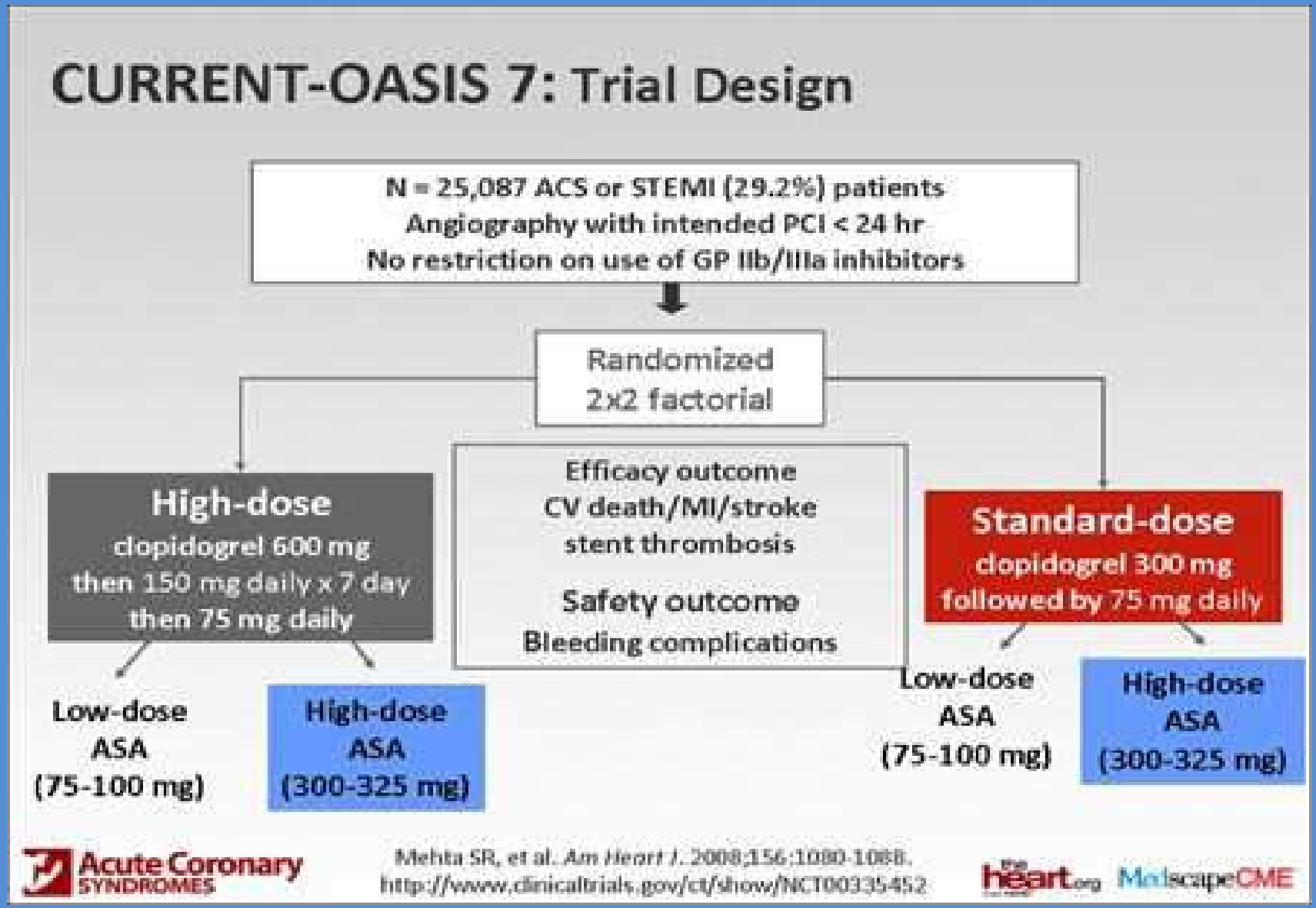
Good metabolizer Intermediate metabolizer Poor metabolizer

Clopidogrel: Black-Box Warning

DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

- Effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19
- Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following ACS or PCI than patients with normal CYP2C19 function
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

CURRENT-OASIS 7: Trial Design



Acute Coronary SYNDROMES

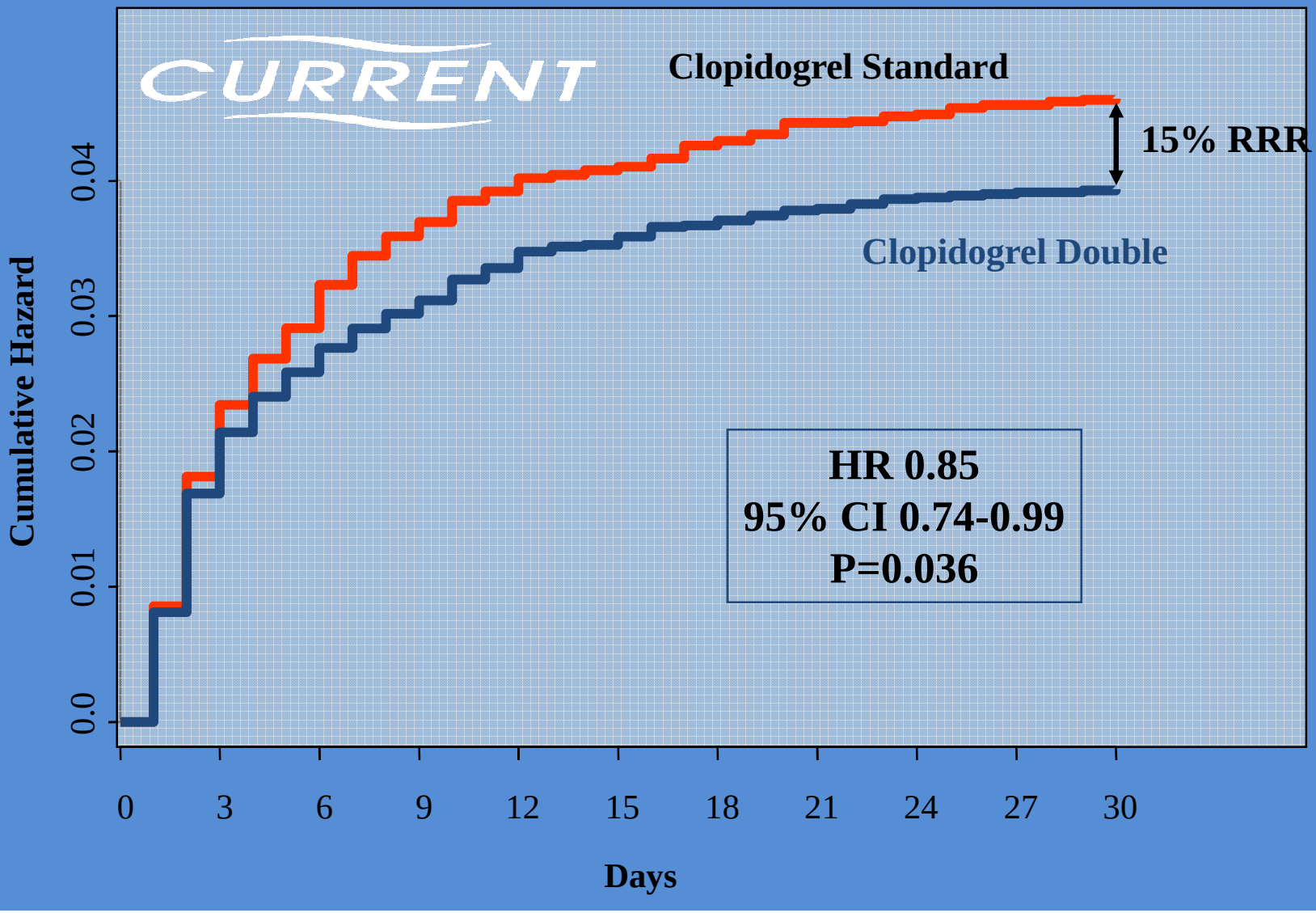
Mehta SR, et al. *Am Heart J*. 2008;156:1080-1088.
http://www.clinicaltrials.gov/ct/show/NCT00335452

theheart.org MedscapeCME

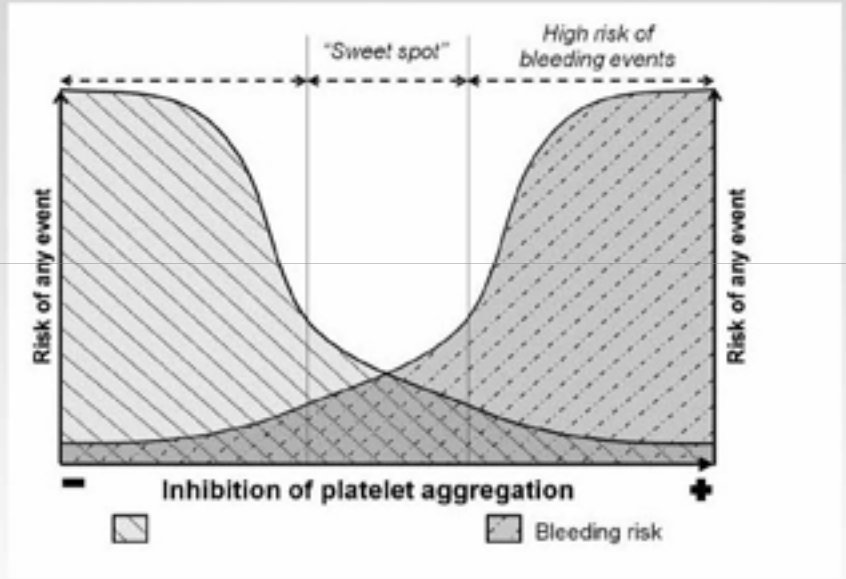
CURRENT-OASIS 7

Clopidogrel: Double vs Standard Dose in PCI Patients

Primary Outcome: CV Death, MI or Stroke



Inhibition of Platelet Aggregation: "Sweet Spot"



Large-scale studies are needed to identify this therapeutic window

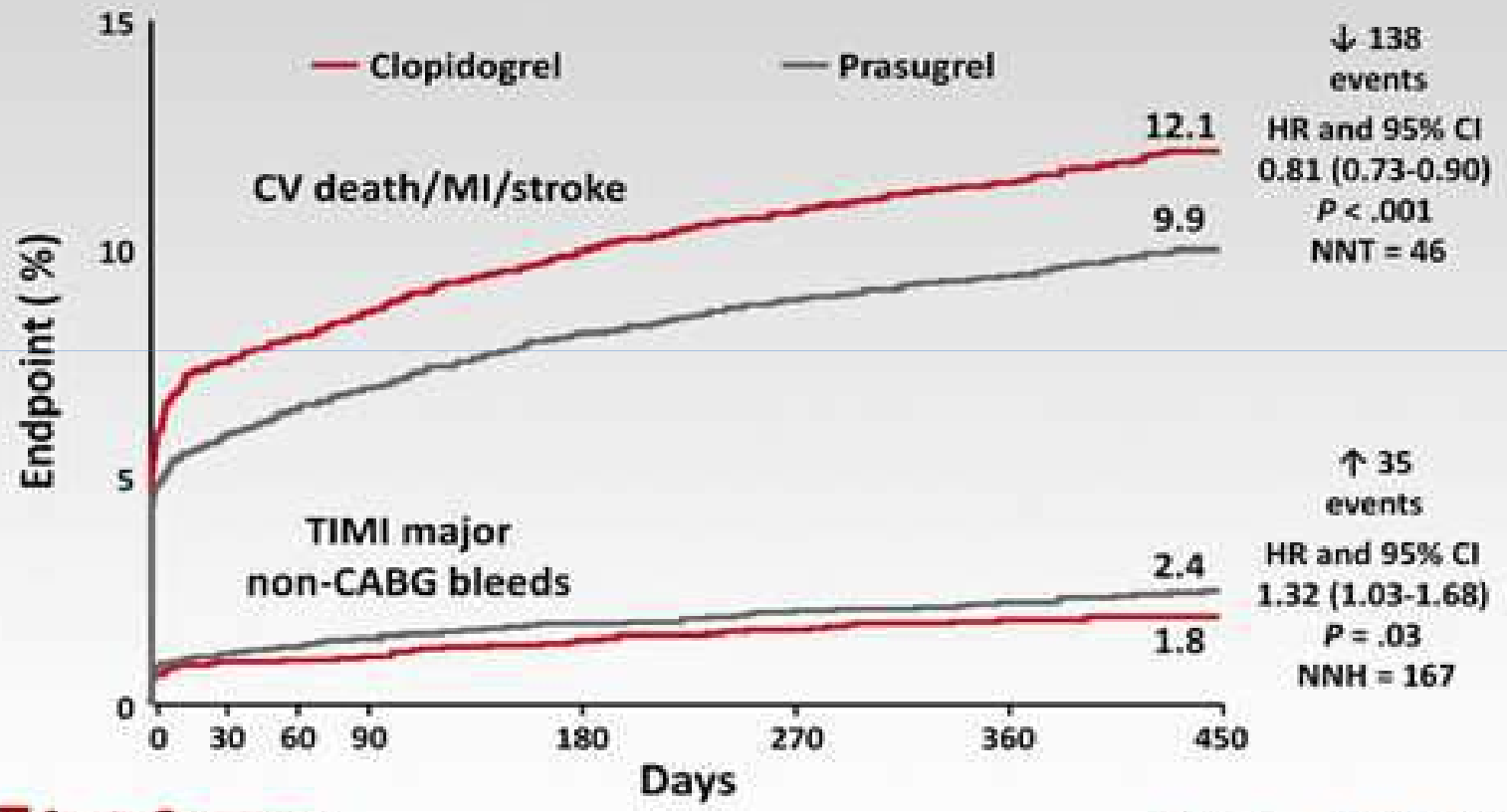
Acute Coronary SYNDROMES

Ferreiro JL, et al. *Thromb Haemost*. 2010;103:250-256.
Reproduced with permission.

theheart.org MedscapeCME

TRITON-TIMI 38: Prasugrel

Primary endpoint: CV death/MI/stroke; TIMI non-CABG bleeding

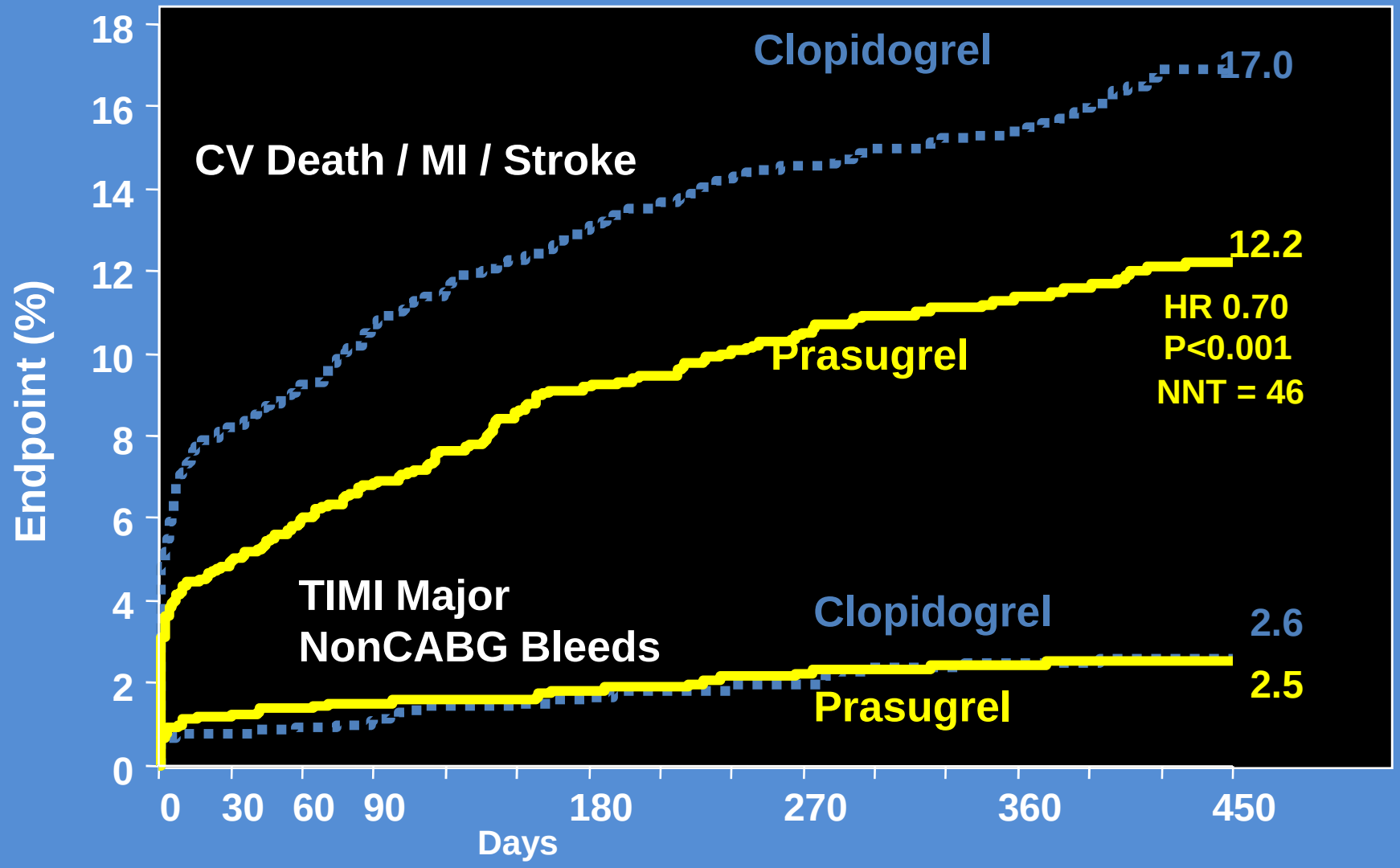


Acute Coronary SYNDROMES

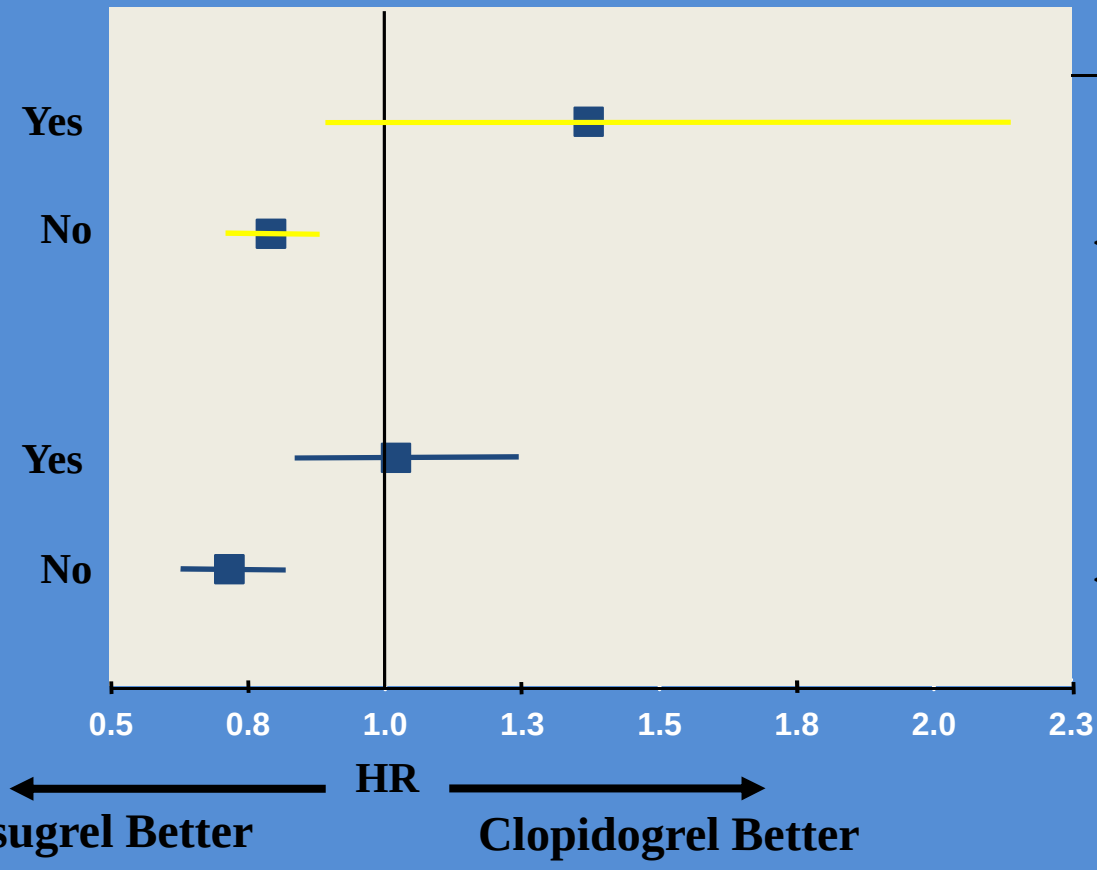
Wiviott SD et al. *N Engl J Med.* 2007;357:2001-2015.

theheart.org Medscape EDUCATION

TRITON TIMI-38:
Diabetic Subgroup



TRITON-TIMI 38: Primary Endpoint (CVD/MI/Stroke) Subgroup Post-hoc Analyses



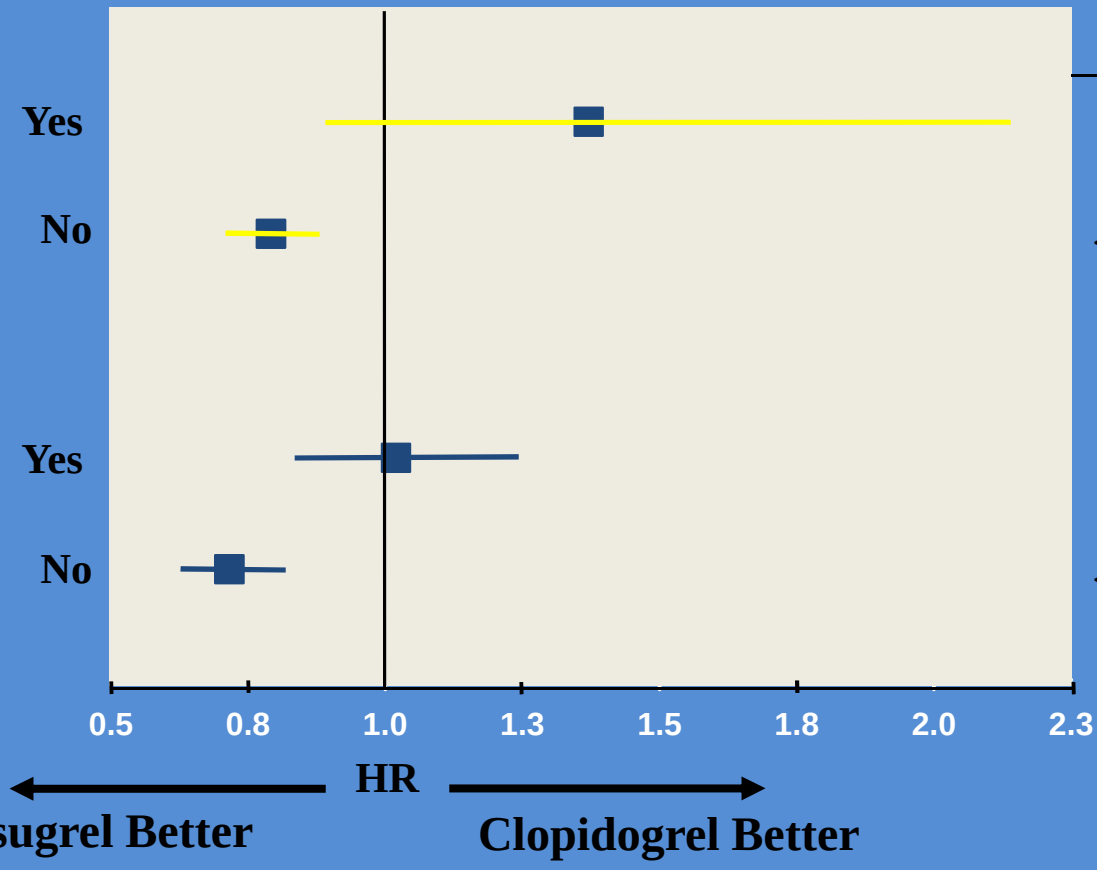
		P* value	P** interaction
History of stroke or TIA	Yes	0.15	-
	No	<0.001	0.02
Any of the following:			
Age ≥75 y, Body wt. <60 kg, History stroke/TIA	Yes	0.83	-
	No	<0.001	0.008

*Tests HR=1.0 within subgroups
**Tests equality HR between subgroups

CVD=Cardiovascular death; MI=Myocardial Infarction; HR=Hazard Ratio; TIA=Transient Ischemic Attack

Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

TRITON-TIMI 38: Primary Endpoint (CVD/MI/Stroke) Subgroup Post-hoc Analyses



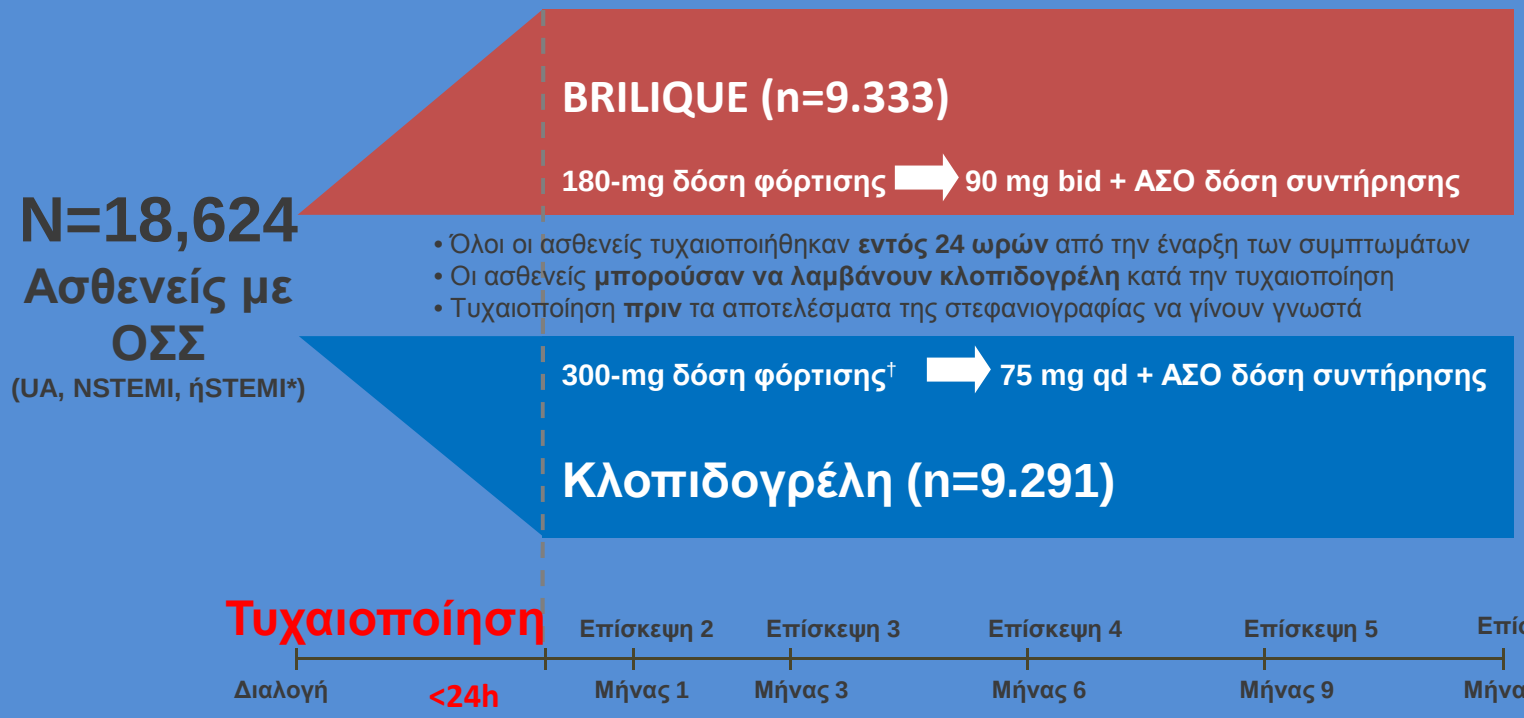
		P* value	P** interaction
History of stroke or TIA	Yes	0.15	-
	No	<0.001	0.02
Any of the following:			
Age ≥75 y, Body wt. <60 kg, History stroke/TIA	Yes	0.83	-
	No	<0.001	0.008

*Tests HR=1.0 within subgroups
**Tests equality HR between subgroups

CVD=Cardiovascular death; MI=Myocardial Infarction; HR=Hazard Ratio; TIA=Transient Ischemic Attack

Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

PLATO: Σχεδιασμός της Μελέτης



Κύριο τελικό σημείο Αποτελεσματικότητας:
Συνδυασμός ΚΑ θανάτου, ΕΜ (εξαιρουμένου του σιωπηρού ΕΜ), ή εγκεφαλικού

Κύριο τελικό σημείο Ασφάλειας:
Συνολικά μείζονα αιμορραγικά συμβάντα κατά PLATO‡

Αρχική Πρόθεση Θεραπείας
- Φαρμακευτικά (28%)
- Επεμβατικά (72%)

* Ασθενείς με STEMI που προγραμματίστηκαν για πρωτογενή PCI τυχαιοποιήθηκαν, ωστόσο, μπορεί τελικά να μην υπεβλήθησαν σε αυτή

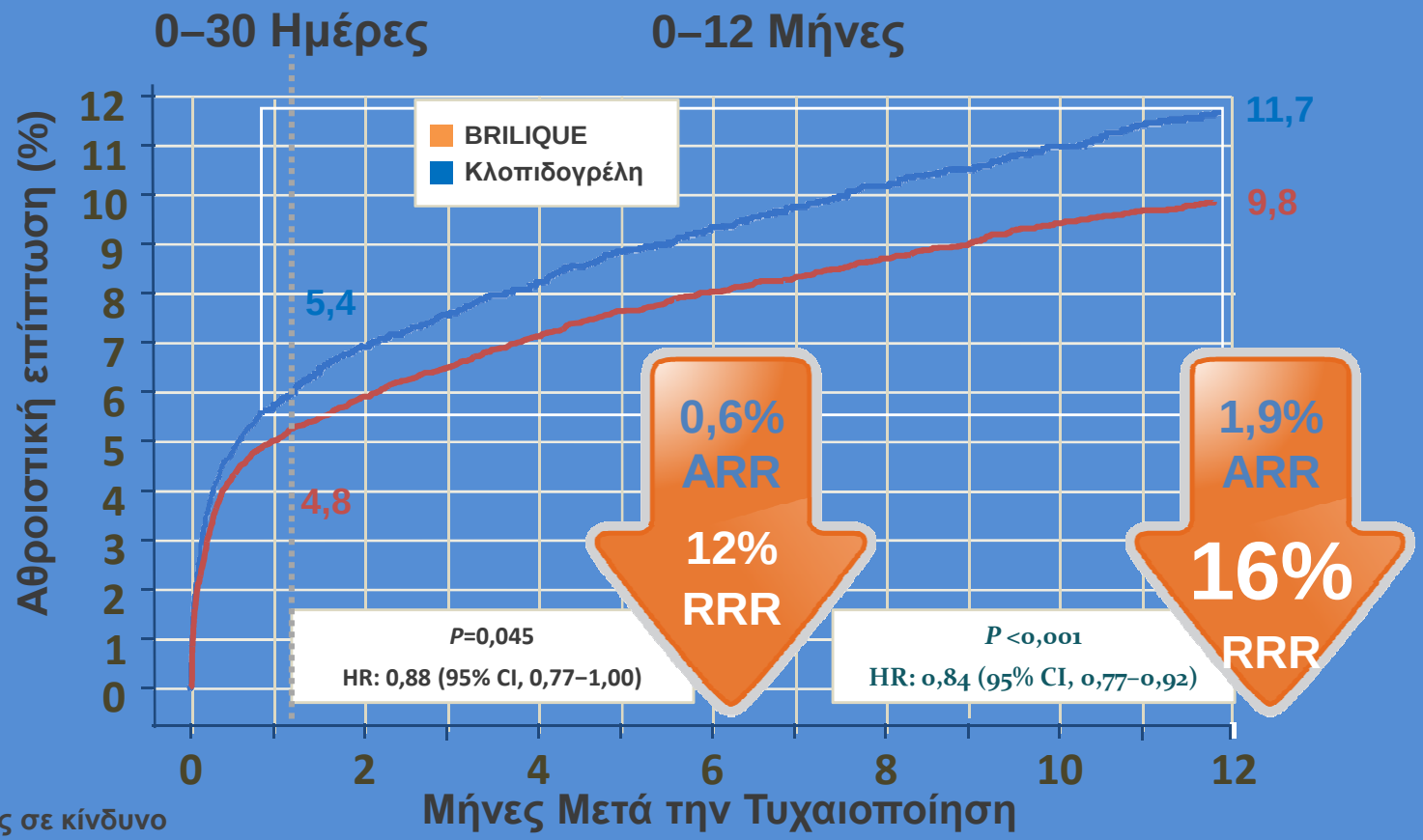
† Δόση φόρτισης κλοπιδογρέλης των 300 mg επετράπη σε ασθενείς που δεν είχαν λάβει πριν κλοπιδογρέλη, με επιπλέον 300 mg να επιτρέπονται σε περίπτωση που το κρίνει ο ερευνητής.

‡ Η μελέτη PLATO επέκτεινε τον ορισμό της μείζονος αιμορραγίας ώστε να είναι πιο περιεκτικός σε σύγκριση με προηγούμενες με μελέτες με ασθενείς ΟΣΣ. Το κύριο τελικό σημείο ασφάλειας ήταν η πρώτη εμφάνιση οποιουδήποτε μείζονος αιμορραγικού επεισοδίου.

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.
James S, et al. *Am Heart J*. 2009;157:599–605.

ΕΜ = Έμφραγμα του μυοκαρδίου
ΑΣΟ = Ακετυλοσαλυκικό οξύ

PLATO:Κύριο τελικό σημείο (Συνδυασμός ΚΑ θανάτου, ΕΜ ή Εγκεφαλικού)



Ασθενείς σε κίνδυνο							
BRILIQUE	9.333	8.628	8.460	8.219	6.743	5.161	4.147
Κλοπιδογρέλη	9.291	8.521	8.362	8.124	6.650	5.096	4.047

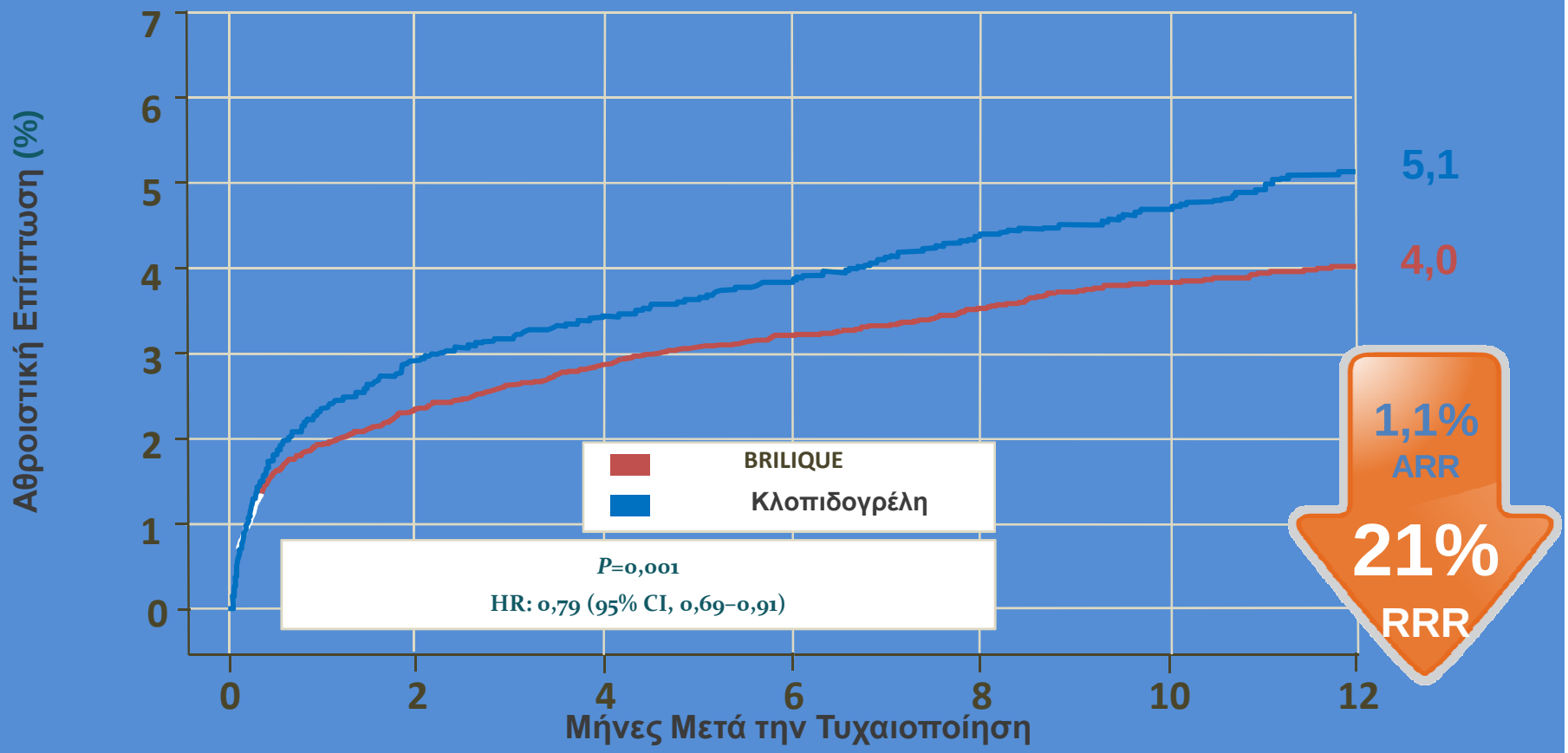
Και οι 2 ομάδες λάμβαναν ΑΣΟ. NNT στο 1 έτος

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

ARR = Absolute Risk Reduction = μείωση απόλυτου κινδύνου
RRR = Relative Risk Reduction = μείωση σχετικού κινδύνου

HR = Hazard Ratio

PLATO: Καρδιαγγειακός θάνατος



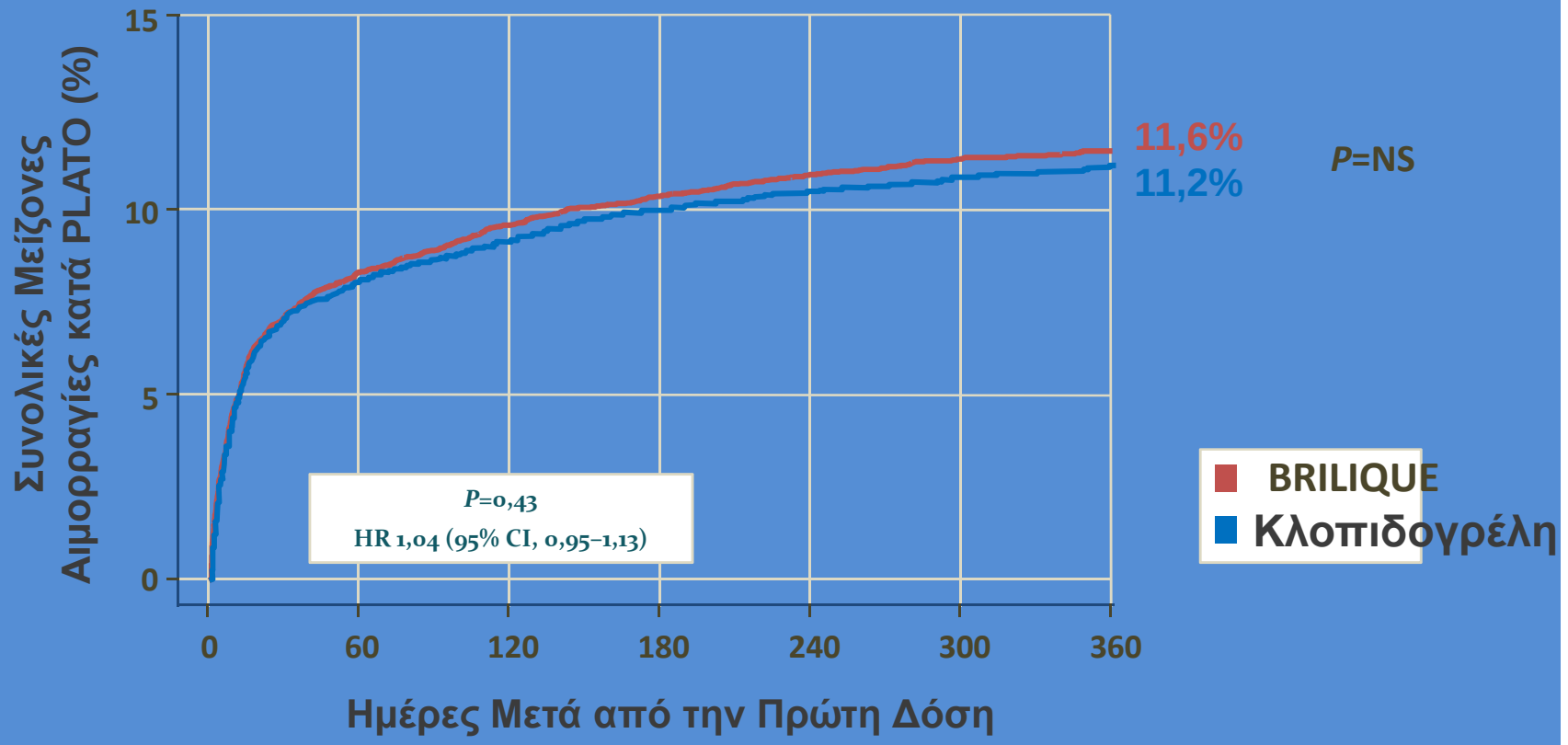
Και οι δύο ομάδες λάμβαναν ΑΣΟ

ARR = Absolute Risk Reduction = μείωση απόλυτου κινδύνου
RRR = Relative Risk Reduction = μείωση σχετικού κινδύνου

HR = Hazard Ratio

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.
Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057. Supplement.
BRILIQUE: Περίληψη Χαρακτηριστικών του Προϊόντος, 2013.

PLATO:Συνολικές μείζονες αιμορραγίες



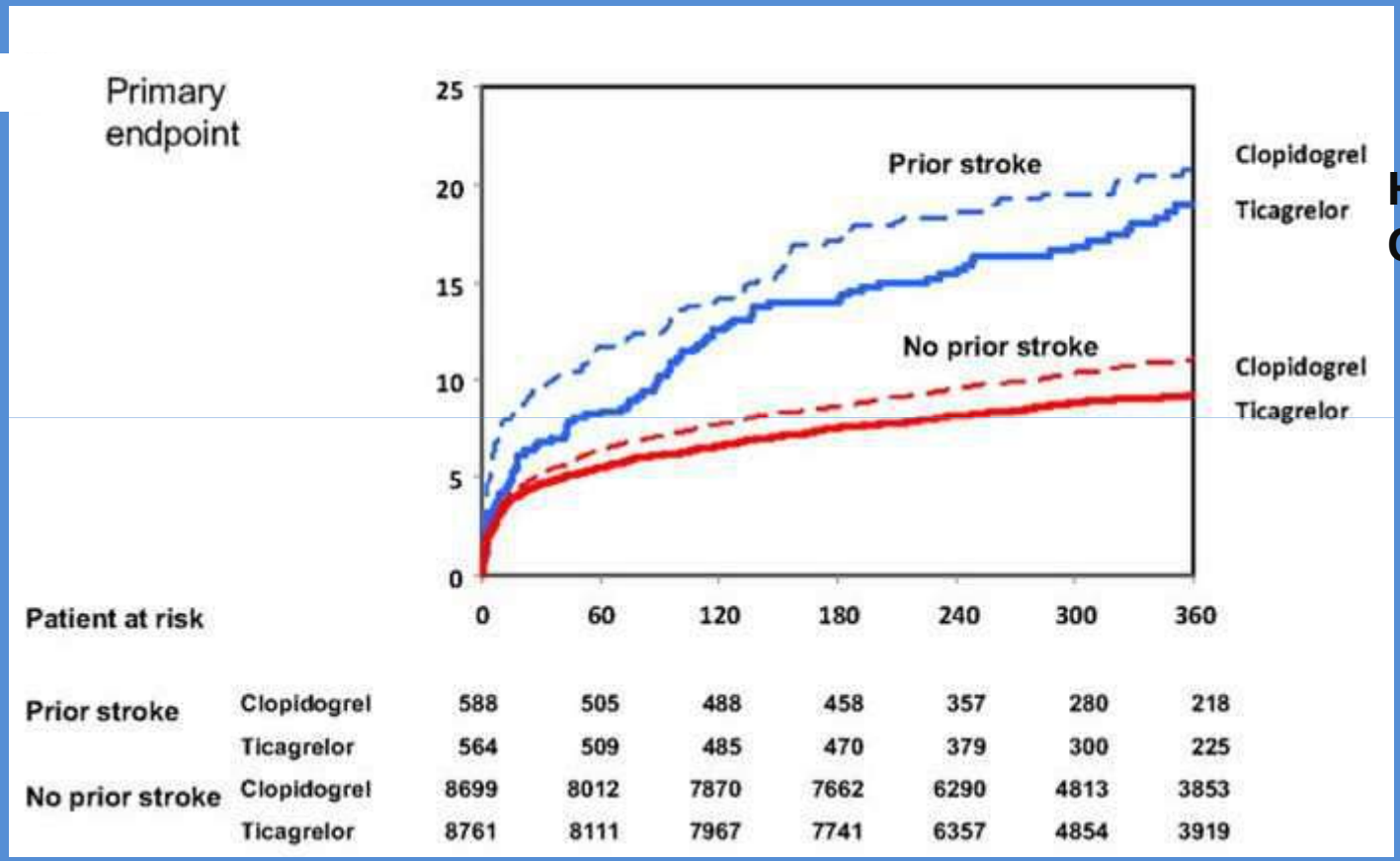
7.246	6.826	6.545	5.129	3.783	3.433
7.305	6.930	6.670	5.209	3.841	3.479

Και οι δυο ομάδες θεραπείας έλαβαν ΑΣΟ

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

NS = Non Significant

Ασθενείς με ιστορικό προηγούμενου εγκεφαλικού επεισοδίου (ή παροδικού ισχαιμικού επεισοδίου) Κύριο Τελικό Σημείο Αποτελεσματικότητας



RRR: 13%

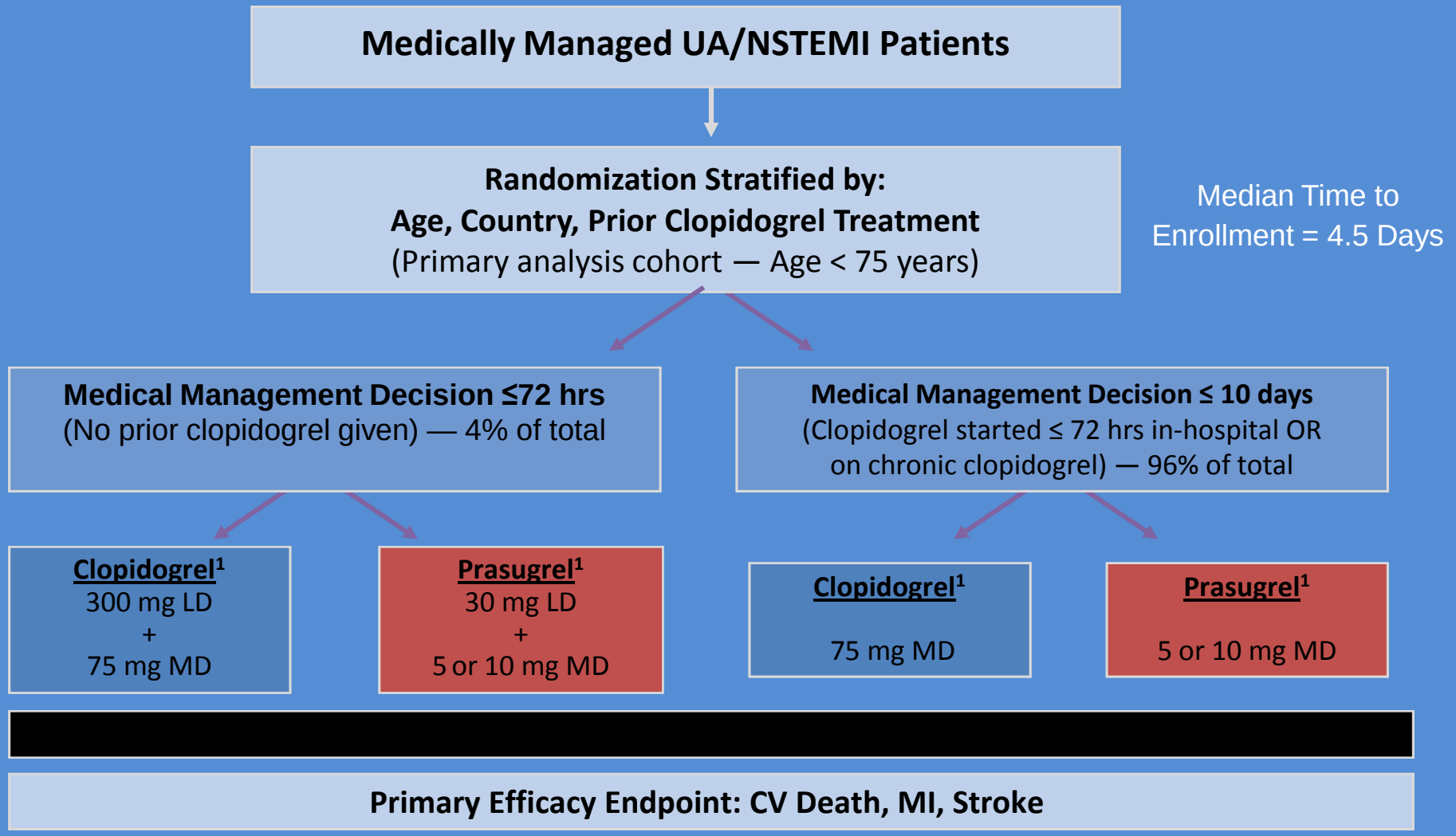
HR 0.87 (95% CI: 0.66-1.13)

P interaction = 0.84

Το BRILIQUE έχει αντένδειξη σε ασθενείς με ιστορικό αιμορραγικού εγκεφαλικού.

James SK, et al. *Circulation.* 2012;125:2914-2921

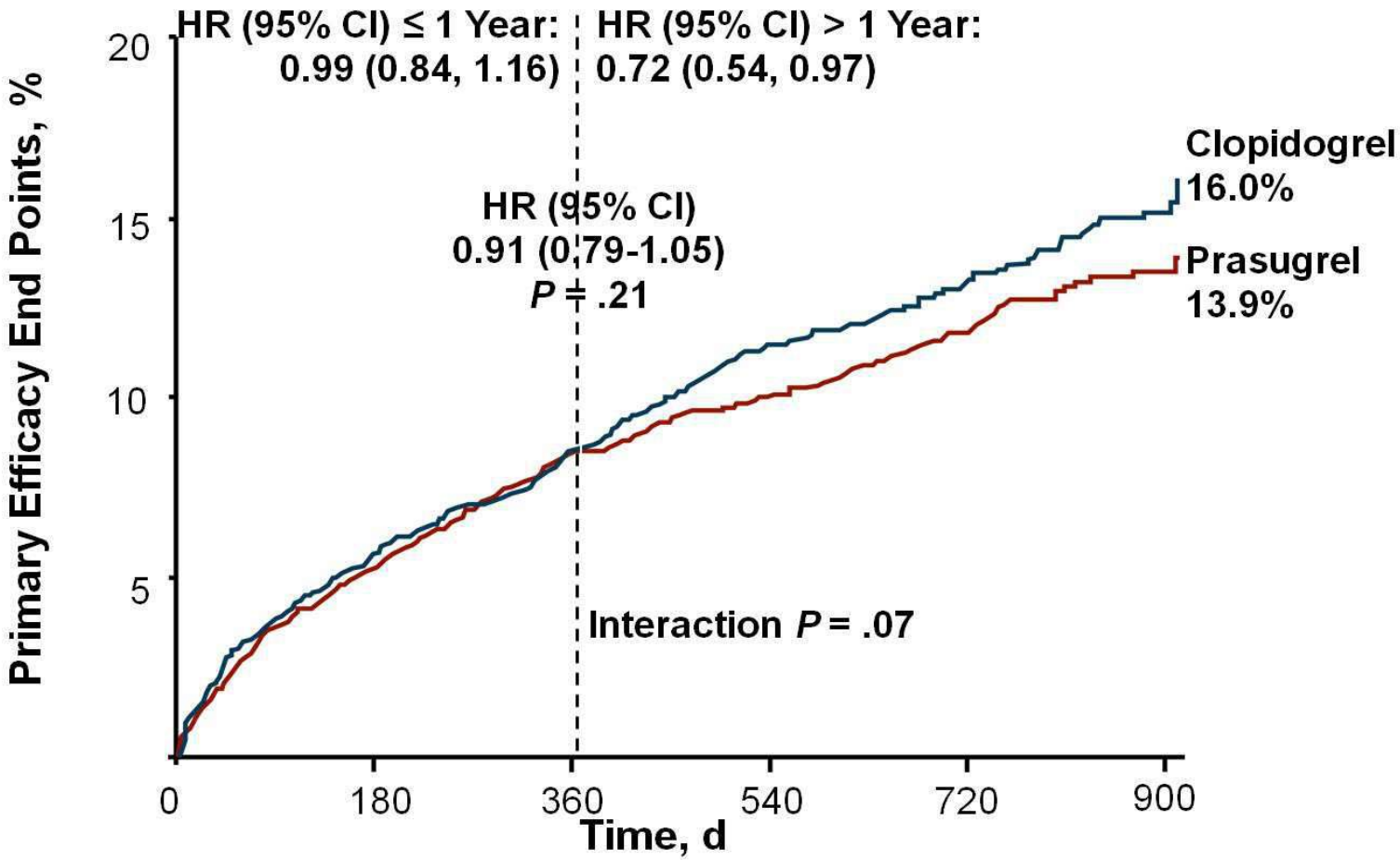
TRILOGY ACS: Study Design



1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 years, 5 mg MD of prasugrel was given. Adapted from Chin CT et al. *Am Heart J* 2010;160:16-22.e1.

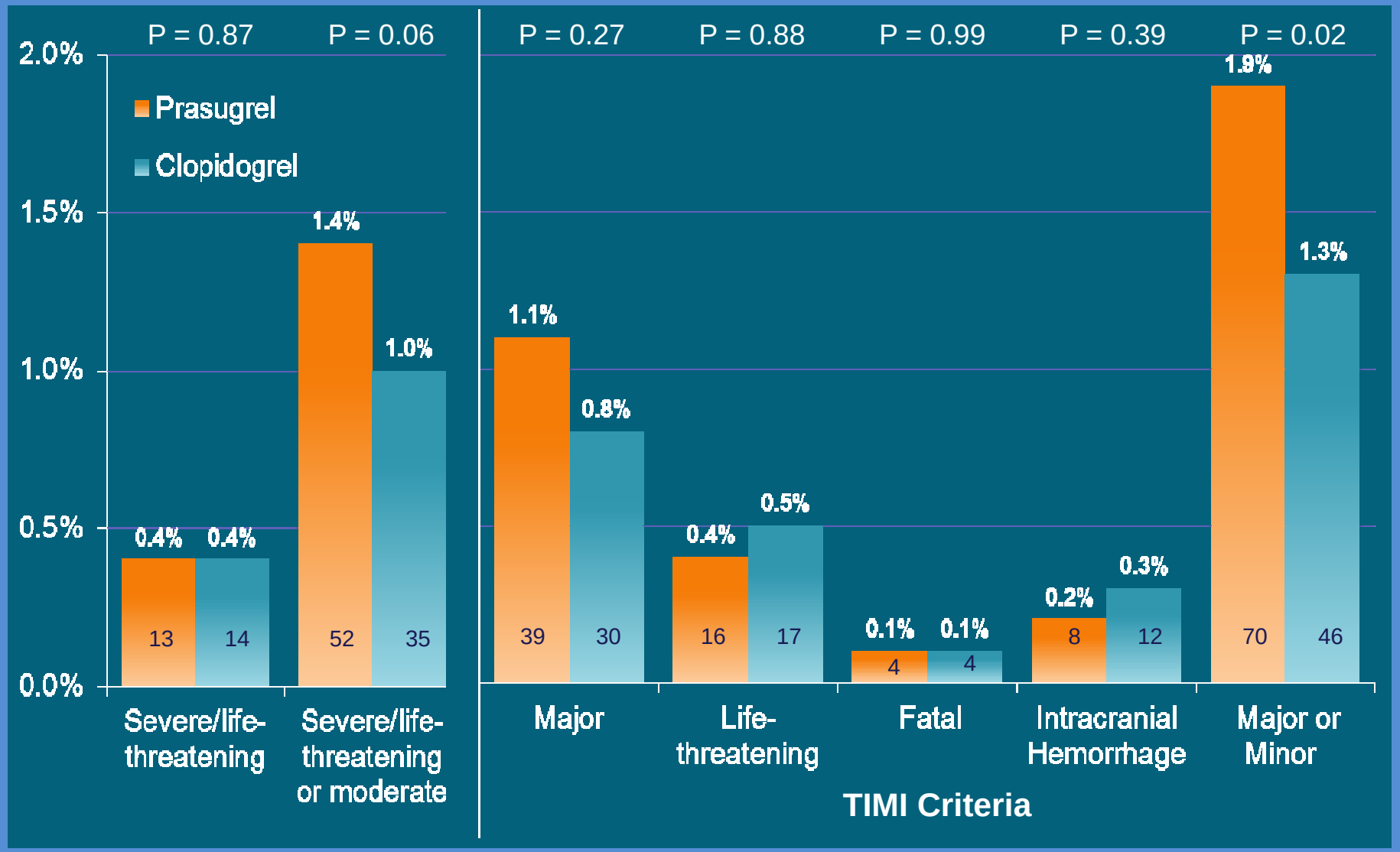
TRILOGY-ACS

Primary Efficacy End Point to 30 Months (Age < 75 years)



Roe MT, et al. *N Engl J Med*. 2012;367:1297-1309.[24]

TRILOGY ACS:
Incidence of Bleeding Outcomes



European Heart Journal (2012) **33**, 2569–2619
doi:10.1093/eurheartj/ehs215

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

Table 12 Periprocedural antithrombotic medication in primary percutaneous coronary intervention

Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy			
Aspirin oral or i.v. (if unable to swallow) is recommended	I	B	133, 134
An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A	135, 136
• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 years.	I	B	109
• Ticagrelor.	I	B	110
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C	-
GP IIb/IIIa inhibitors should be considered for bailout therapy if there is angiographic evidence of massive thrombus, slow or no-reflow or a thrombotic complication.	IIa	C	-
Routine use of a GP IIb/IIIa inhibitor as an adjunct to primary PCI performed with unfractionated heparin may be considered in patients without contraindications.	IIb	B	137–141
Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.	IIb	B	127, 128, 137, 142
Options for GP IIb/IIIa inhibitors are (with LoE for each agent):			
• Abciximab		A	137
• Eptifibatide (with double bolus)		B	138, 139
• Tirofiban (with a high bolus dose)		B	140, 141

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Recommendations	Class [a]	Level [b]
Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids).	I	A
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naive patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[c]	I	B
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	IIb	B
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B
In patients pre-treated with $P2Y_{12}$ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.	IIa	B
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C

Hamm W. Ch. et al European Heart Journal 2011 Dec;32(23):2999-3054