TCT AP-2015

Regimens for ACS and AF: What's the Best Choice?

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Duke Clinical Research Institute

From Thought Leadership to Clinical Practice

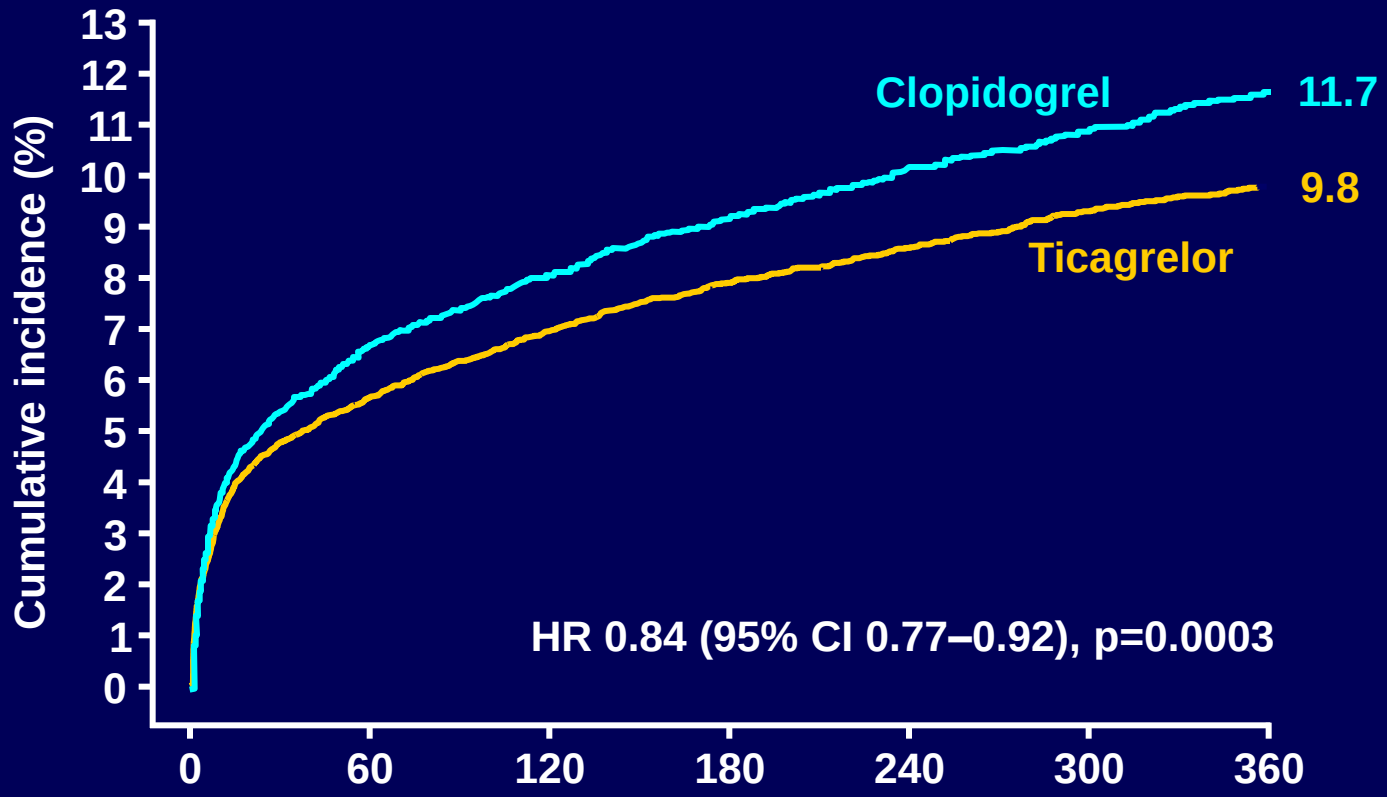
Disclosures

- Research Grants:
  Johnson and Johnson PRD – ROCKET AF
  NIH – PROMISE trial
  AHRQ – Comparative Effectiveness
- Advisory Board / Consultant: Ikaria, Cardiostem, Pleuristem, Bayer, Genzyme, Jansen, theheart.org, DukeTV.org, Ortho McNeil Jansen, Pleuristem
- Research Faculty at DCRI

What is our standard regimen for ACS care?

K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

PLATO



No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

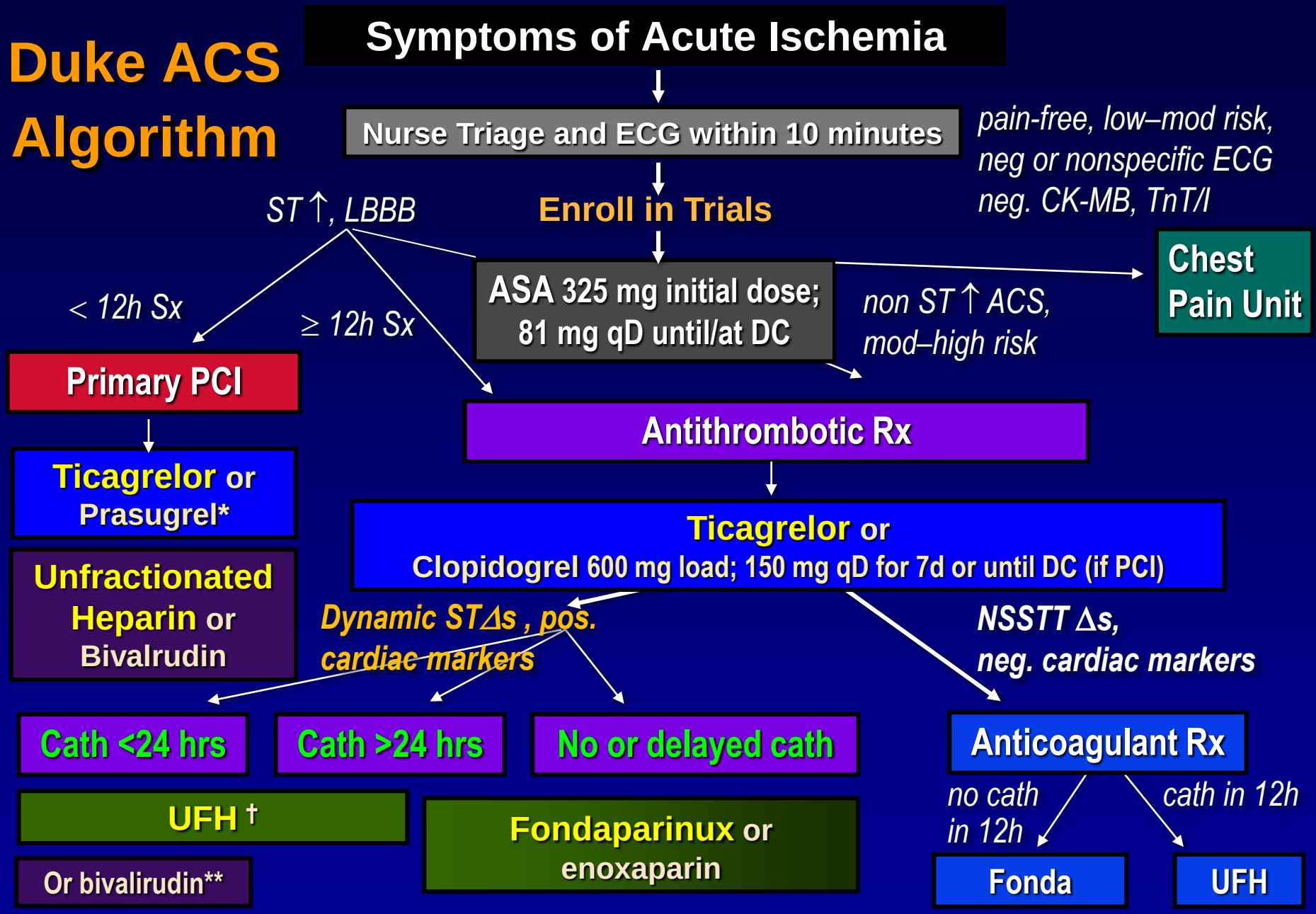
Hierarchical testing major efficacy endpoints

PLATO

All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (95% CI)	p value†
Primary objective, n (%)				
CV death + MI + stroke	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	<0.001
Secondary objectives, n (%)				
Total death + MI + stroke	901 (10.2)	1,065 (12.3)	0.84 (0.77–0.92)	<0.001
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	1,290 (14.6)	1,456 (16.7)	0.88 (0.81–0.95)	<0.001
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.005
CV death	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.22
Total death	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	<0.001

The percentages are K-M estimates of the rate of the endpoint at 12 months.

Duke ACS Algorithm



*Prasugrel for primary PCI (if no h/o TIA or stroke); †GP IIb/IIIa at time of PCI or if refractory ischemia; **Consider bivalirudin for cath <12 hours

What Agent should we use for Atrial Fibrillation?

Pivotal Warfarin-Controlled Trials
Stroke Prevention in AF

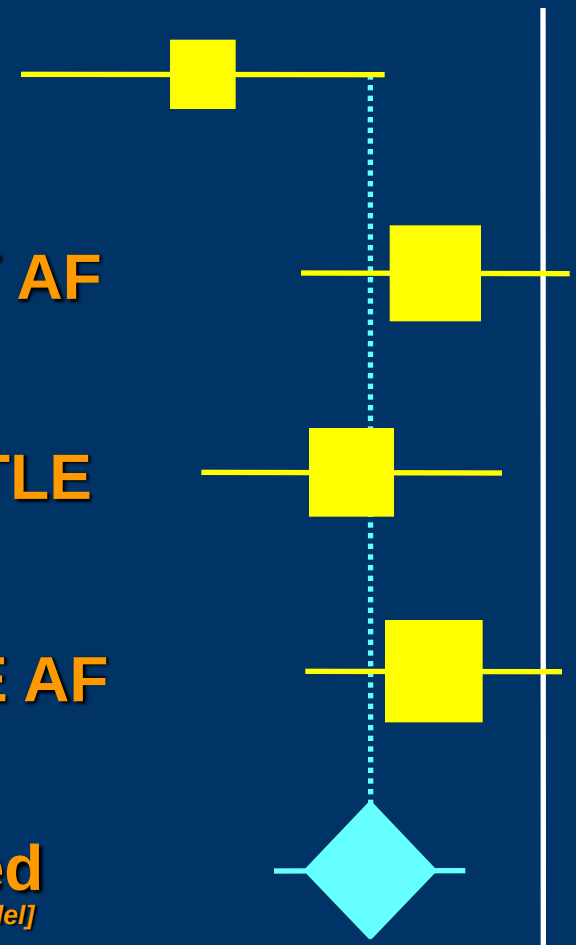
Warfarin vs. Placebo
2,900 Patients

NOACs vs. Warfarin
71,683 Patients

Adapted Ruff Meta-analysis
20113 Lancet

All NOACS: Stroke or SEE

Heterogeneity p=0.13



	Risk Ratio (95% CI)
RE-LY [150 mg]	0.66 (0.53 - 0.82)
ROCKET AF	0.88 (0.75 - 1.03)
ARISTOTLE	0.80 (0.67 - 0.95)
ENGAGE AF [60 mg]	0.88 (0.75 - 1.02)
Combined *[Random Effects Model]*	0.81 (0.73 - 0.91)

p=<0.0001

N=58,541

0.5 *Favors NOAC* 1 *Favors Warfarin* 2

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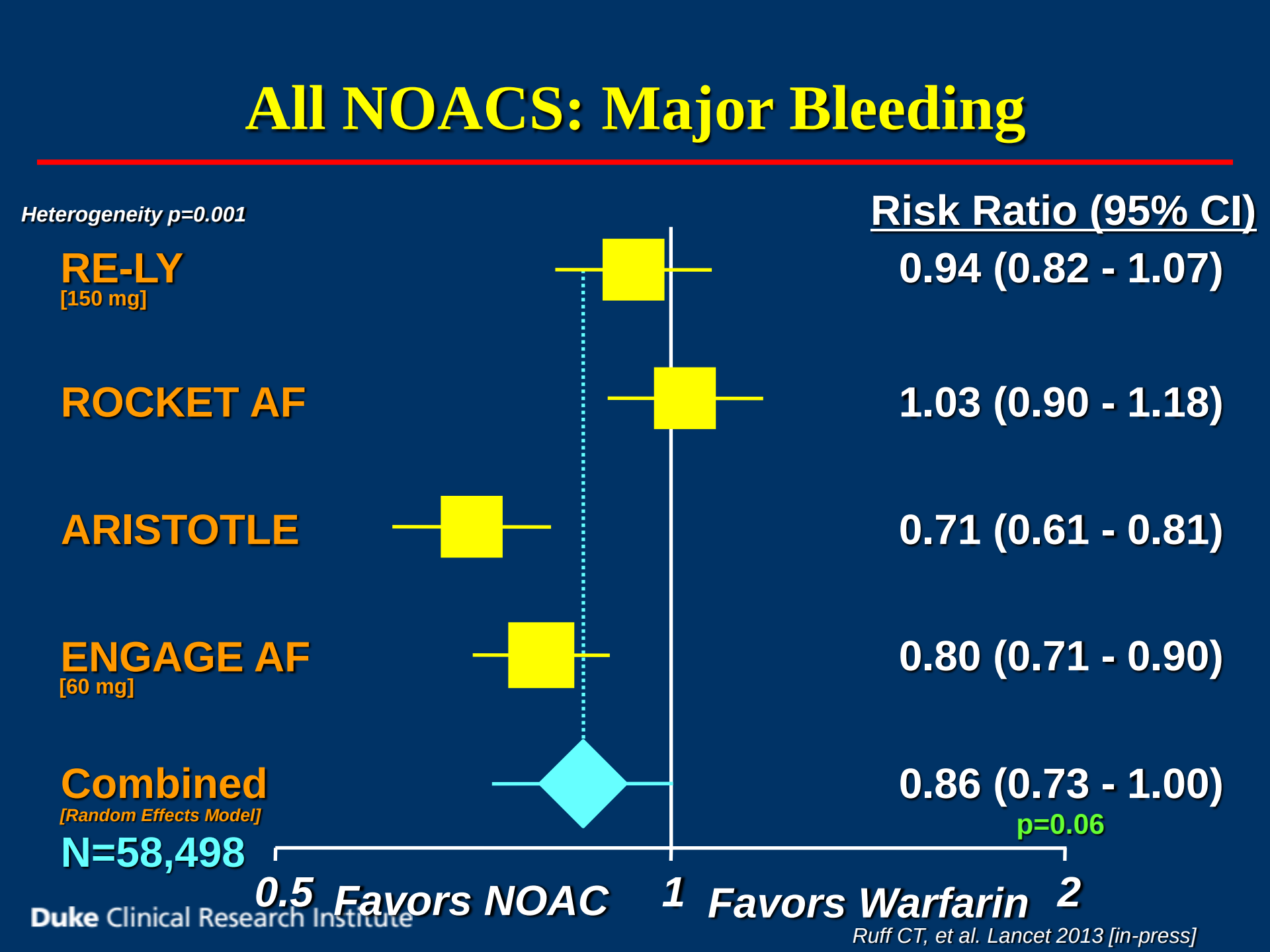
Ruff CT, et al. Lancet 2013]

All NOACS: Major Bleeding

Heterogeneity p=0.001



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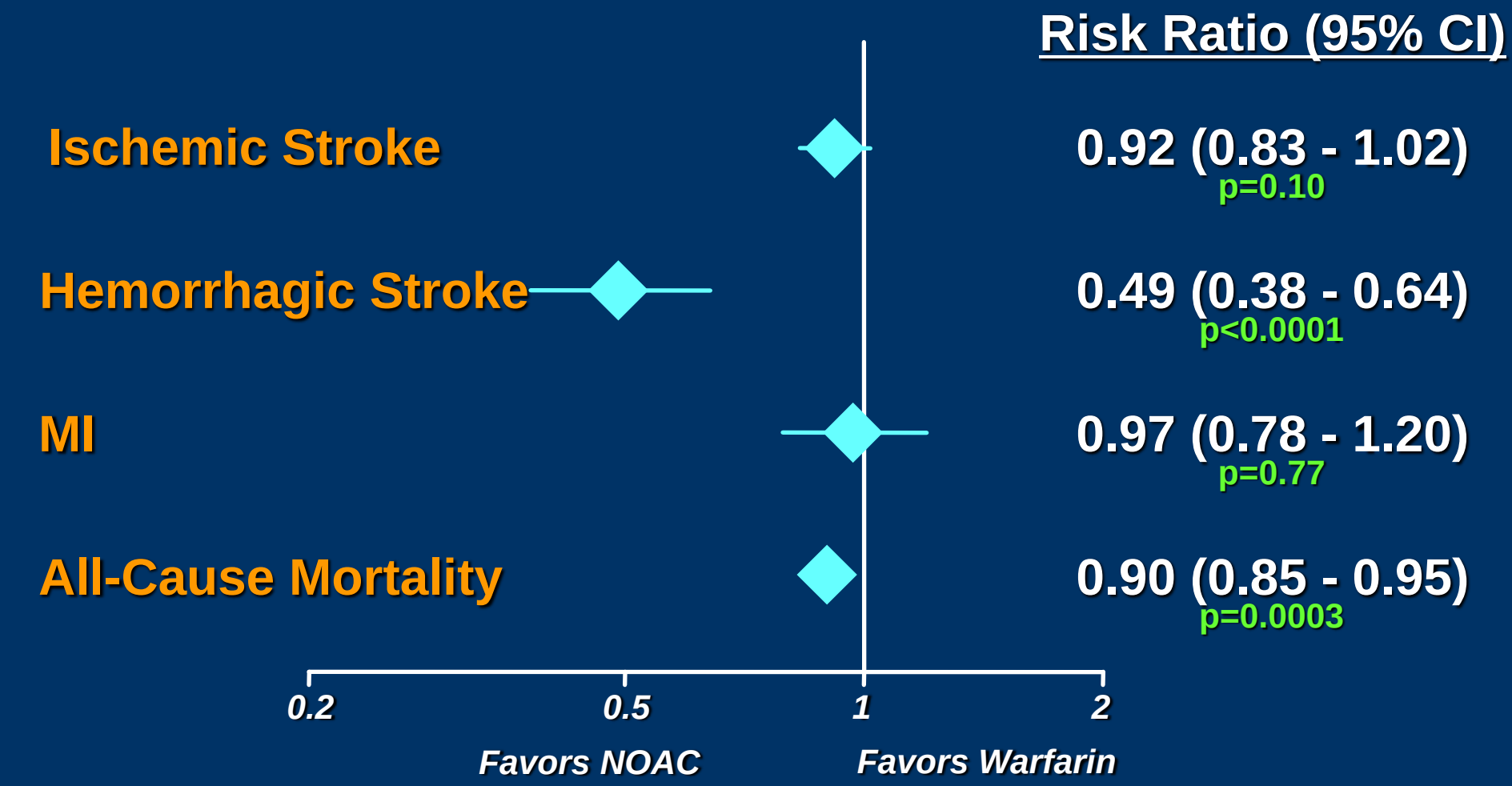
Ruff CT, et al. Lancet 2013 [in-press]

Secondary Efficacy Outcomes



Heterogeneity p=NS for all outcomes

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Ruff CT, et al. Lancet 2013 [in-press]

Which Agent in AF patients?

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

Outline

- What about patients with AF and ACS – which agents should we use?

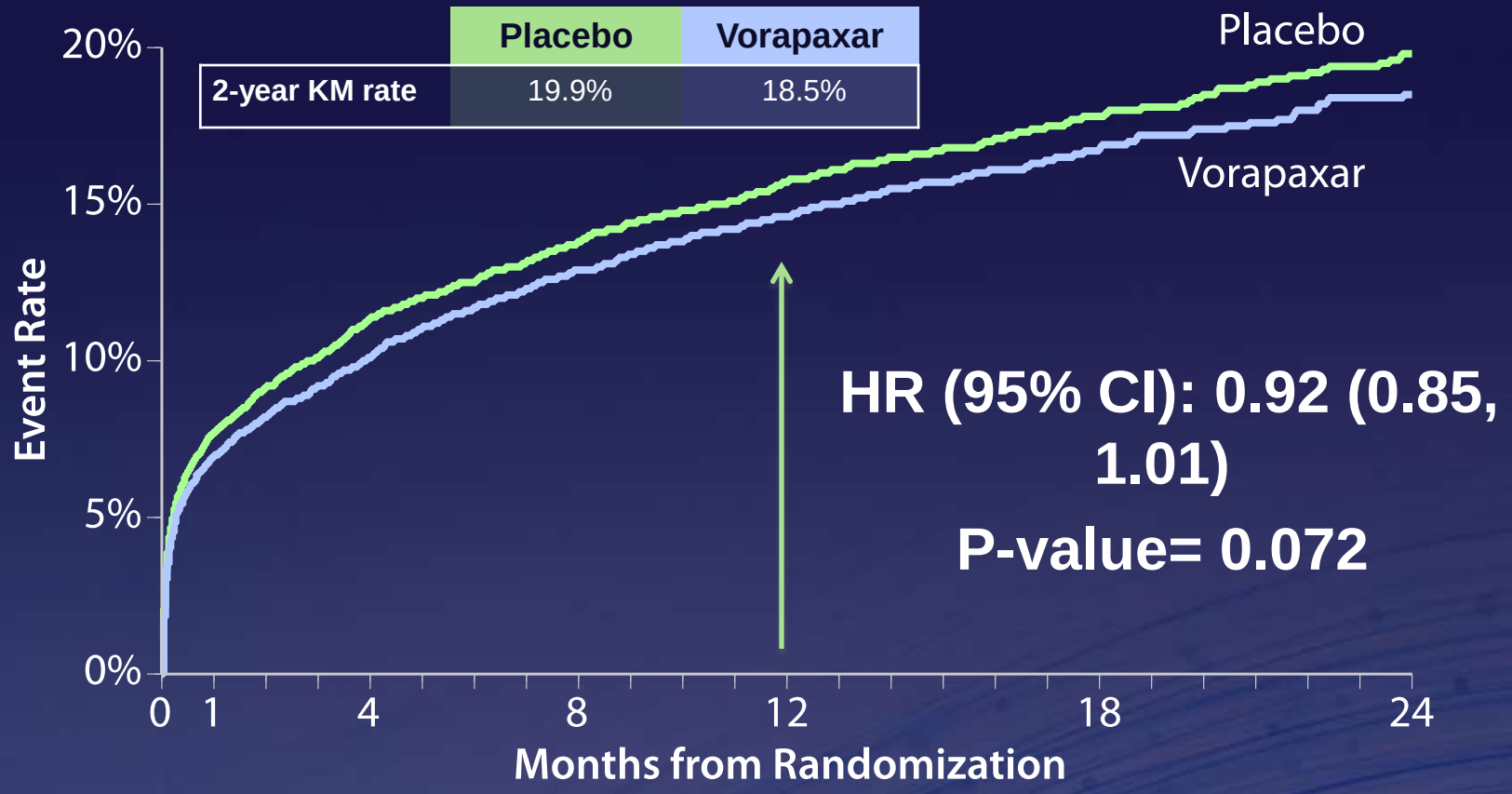
Unmet Need

- Despite years of incremental benefits with novel therapeutics – we still have adverse outcomes in ACS patients

Primary Endpoint

CV Death, MI, Stroke, Hospitalization for Ischemia, Urgent Revascularization

TRA·CER

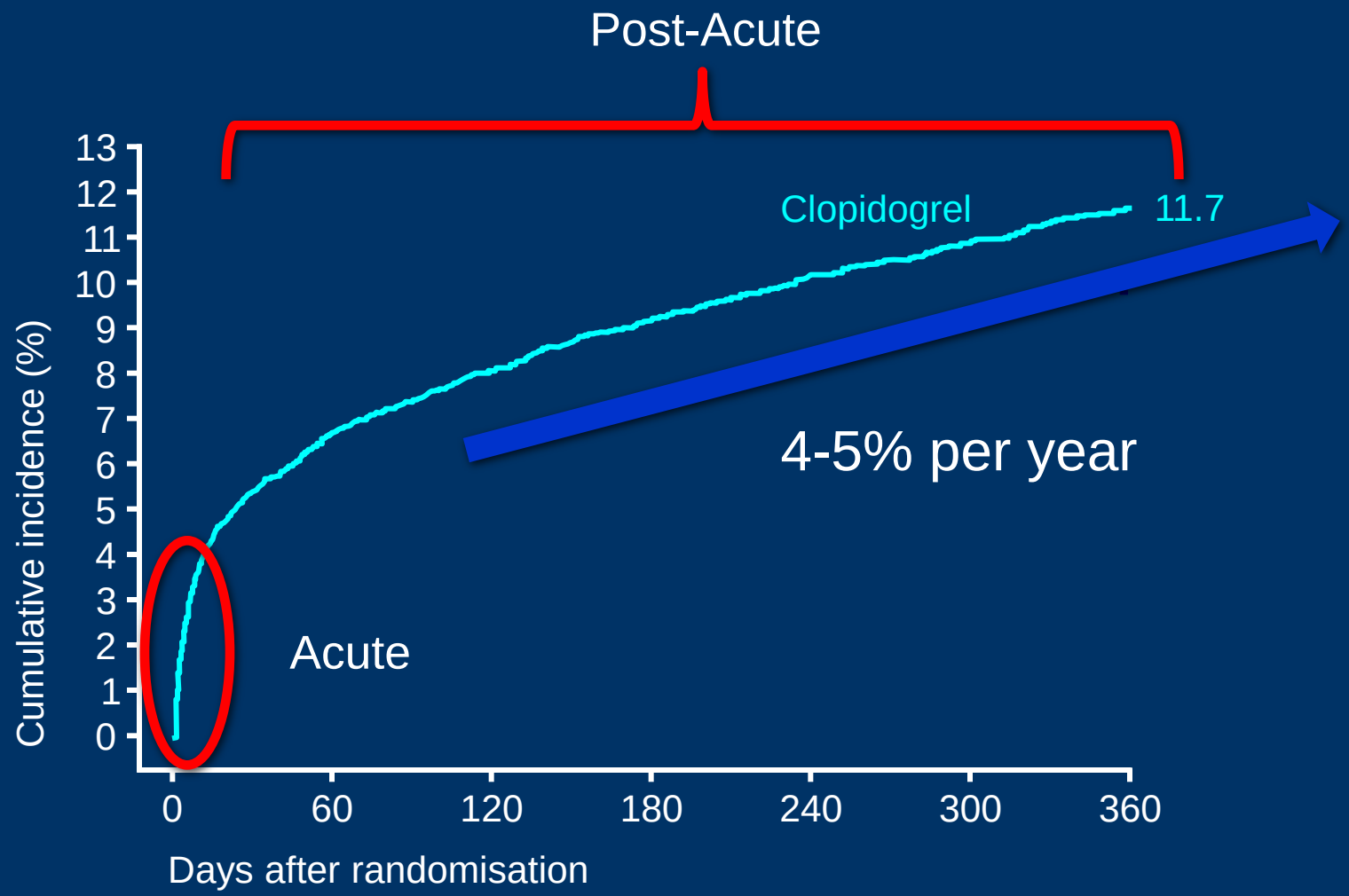


No. at risk							
Placebo	6471	5844	5468	5121	3794	2291	795
Vorapaxar	6473	5897	5570	5199	3881	2318	832

PLATO

Primary Efficacy Endpoint

CV Death, MI, Stroke



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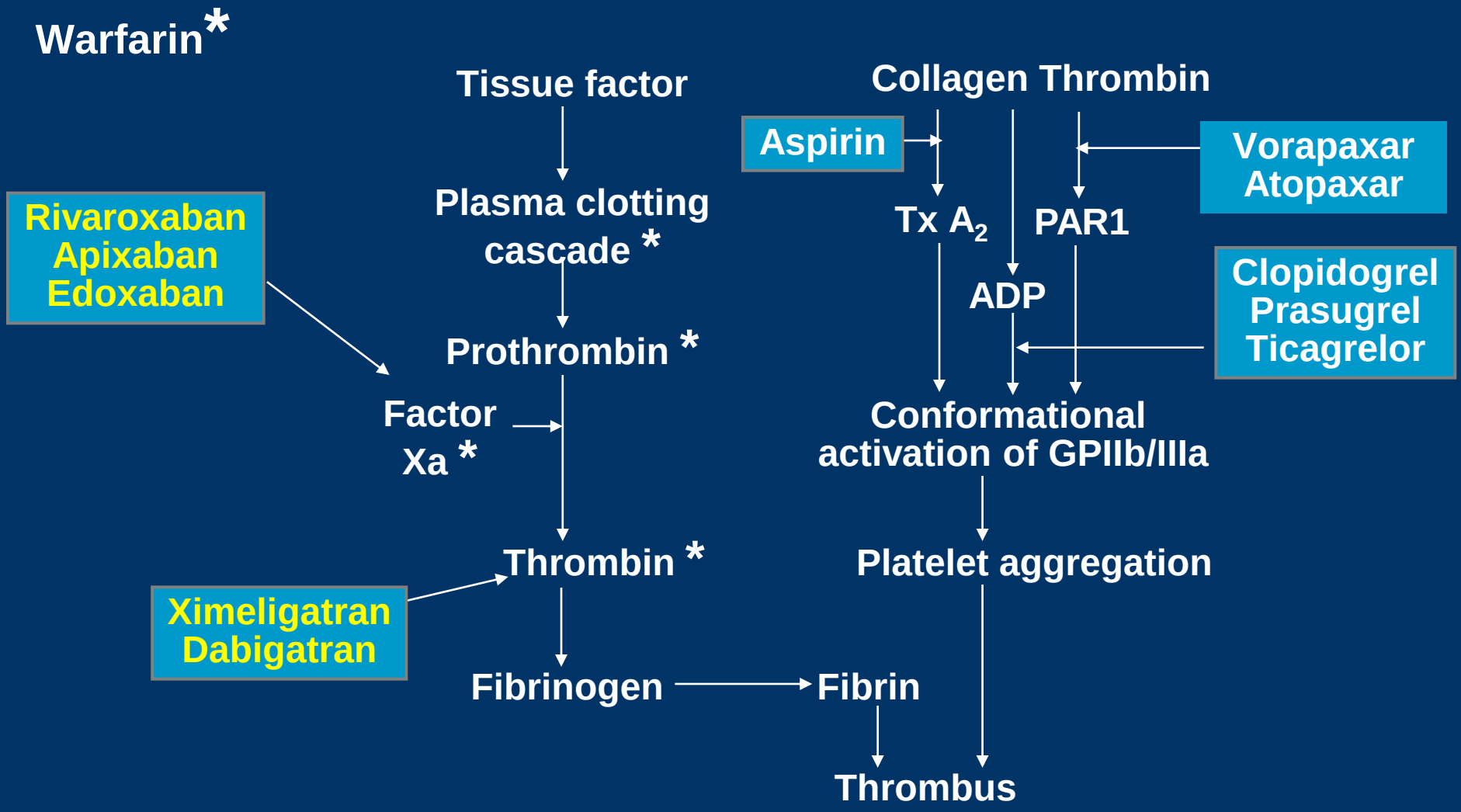
Wallentin NEJM 2009;361:1045-57

What are possible options for improvement?

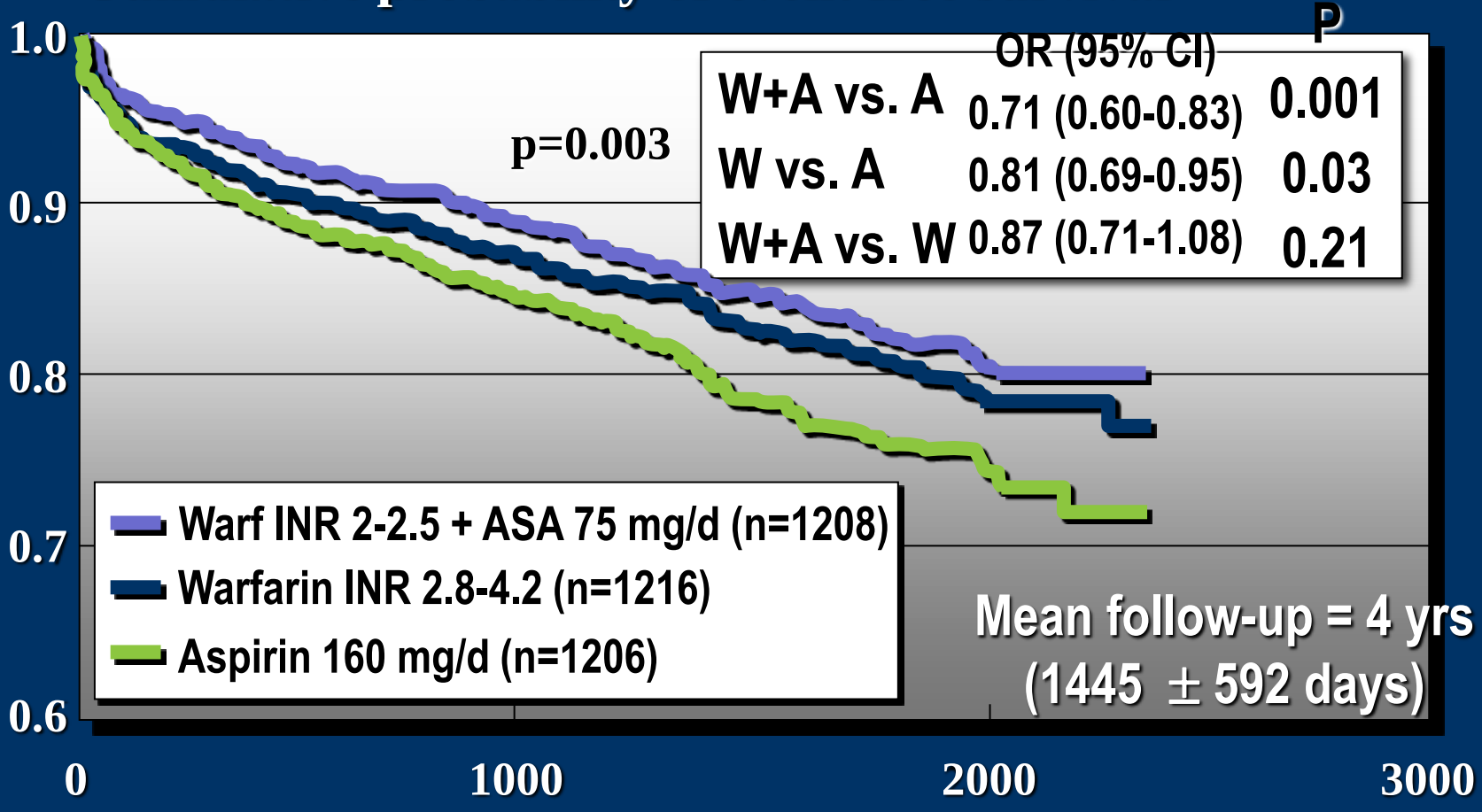
Post-ACS Antithrombotic Therapy
Multiple Targets



WARIS-II Death, Reinfarction, Stroke

Post-MI <75 years, randomization before discharge in 20 Norwegian hospitals

Cumulative probability of event free survival



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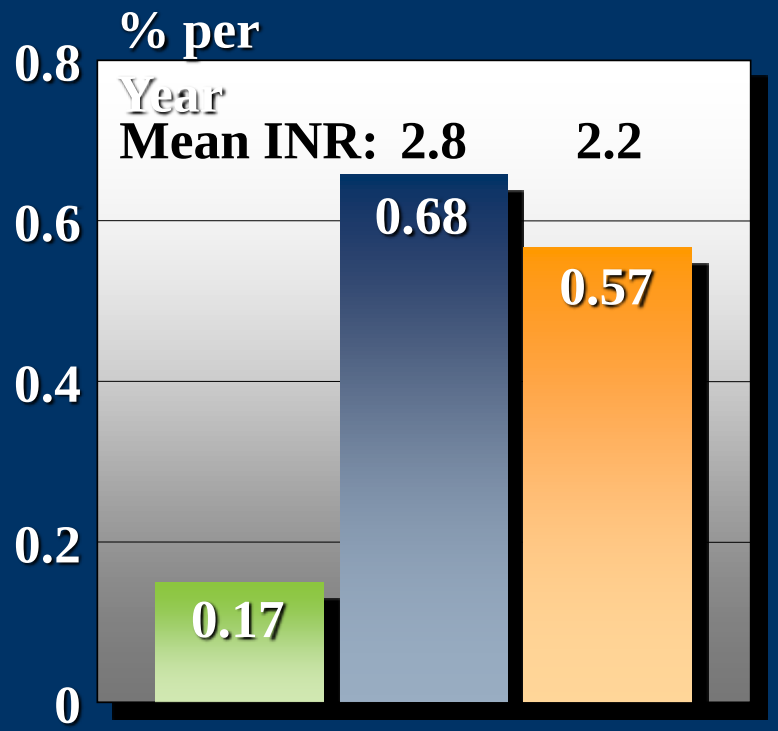
Hurlen et al *N Engl J Med* 2002;347:969-74

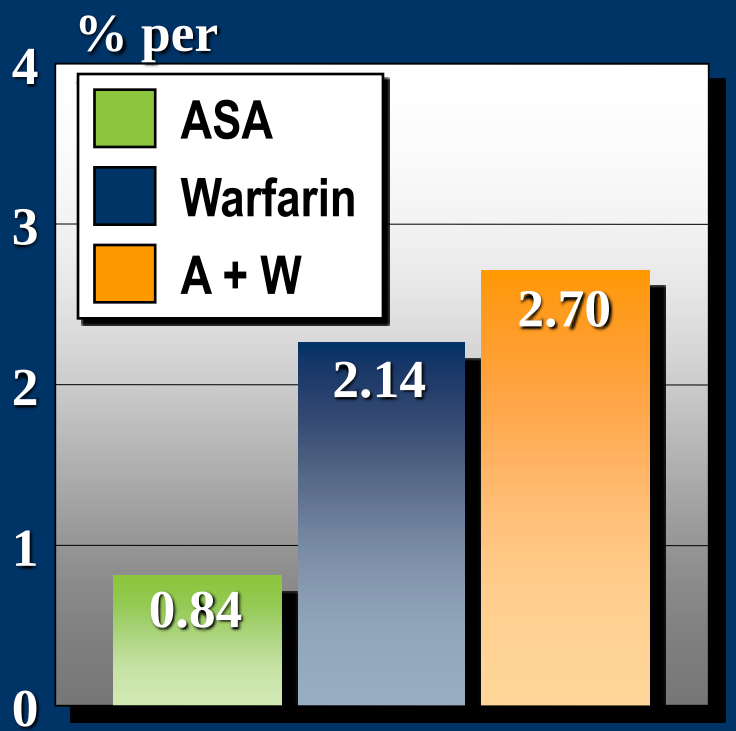
WARIS-II

Hemorrhage

Major Bleeding



Minor Bleeding



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Hurlen et al *N Engl J Med* 2002;347:969-74

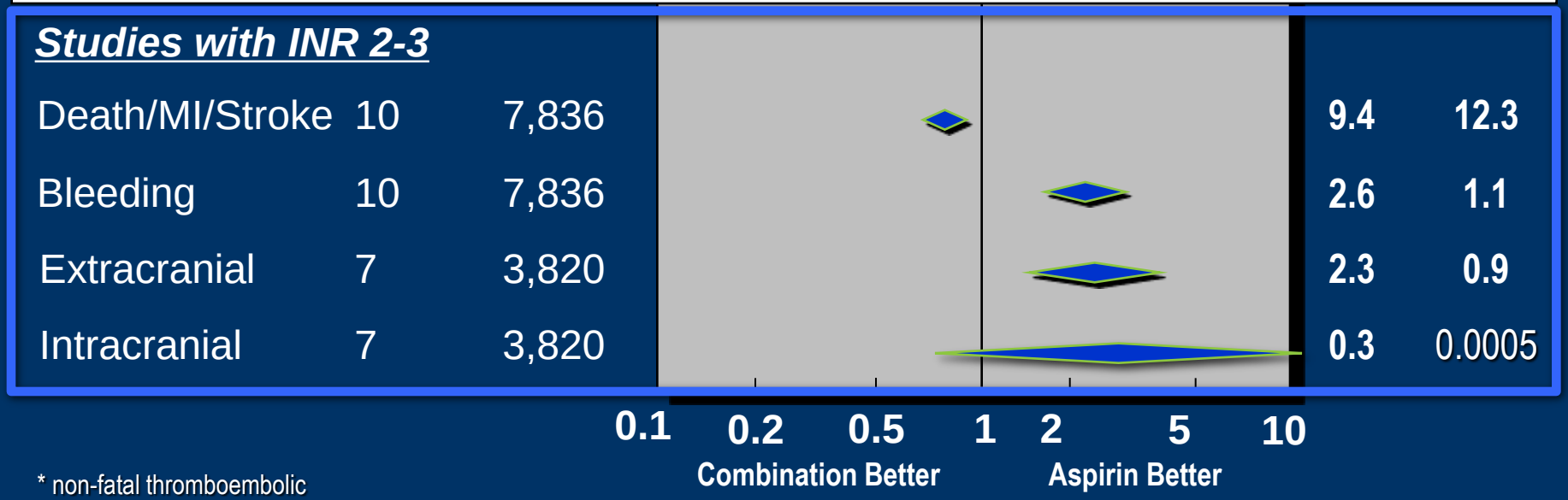
Warfarin After Acute Coronary Syndrome

Studies with INR 2-3

Non-fatal thromboembolic stroke: 0.6% vs. 1.5%; OR 0.43 (0.27-0.70), p=0.0007 NNT=100

Non-fatal myocardial infarction: 4.7% vs. 5.6%; OR 0.70 (0.52-0.95), p=0.0003 NNT=50

All-cause mortality: 2.8% vs. 2.9%; OR 0.99 (0.81-1.22), p=0.95



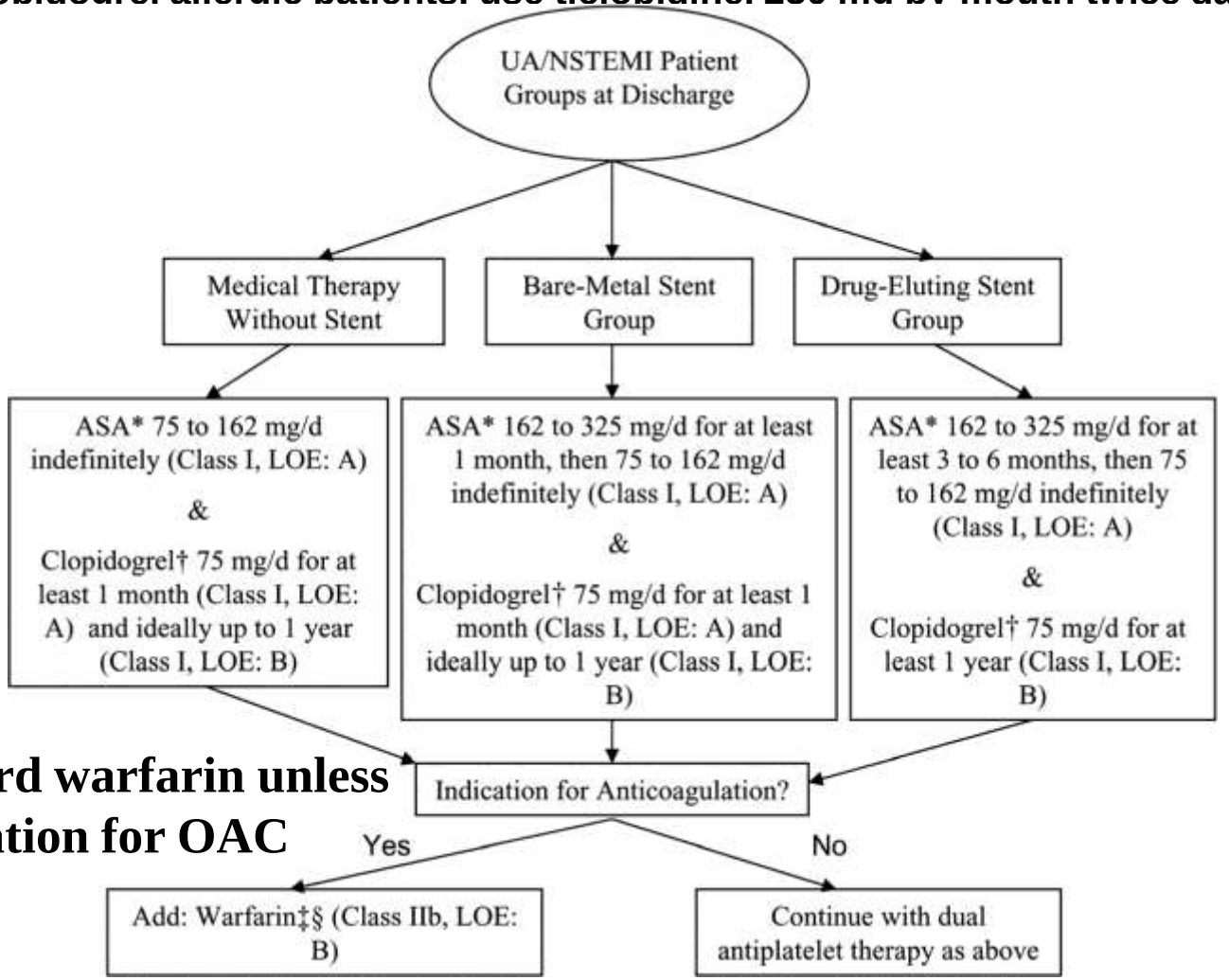
* non-fatal thromboembolic

Warfarin efficacy at the Bleeding risk

- NNH for any bleed ~ 78
- NNH for ICH ~ 660

Risk versus benefit

Long-Term Antitcoagulant Therapy at Hospital Discharge After UA/NSTEMI. *For aspirin (ASA) allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization. †For clopidogrel allergic patients, use ticlopidine, 250 mg by mouth twice da...



No standard warfarin unless indication for OAC

Anderson J L et al. Circulation 2011;123:e426-e579

American Heart Association
Learn and Live

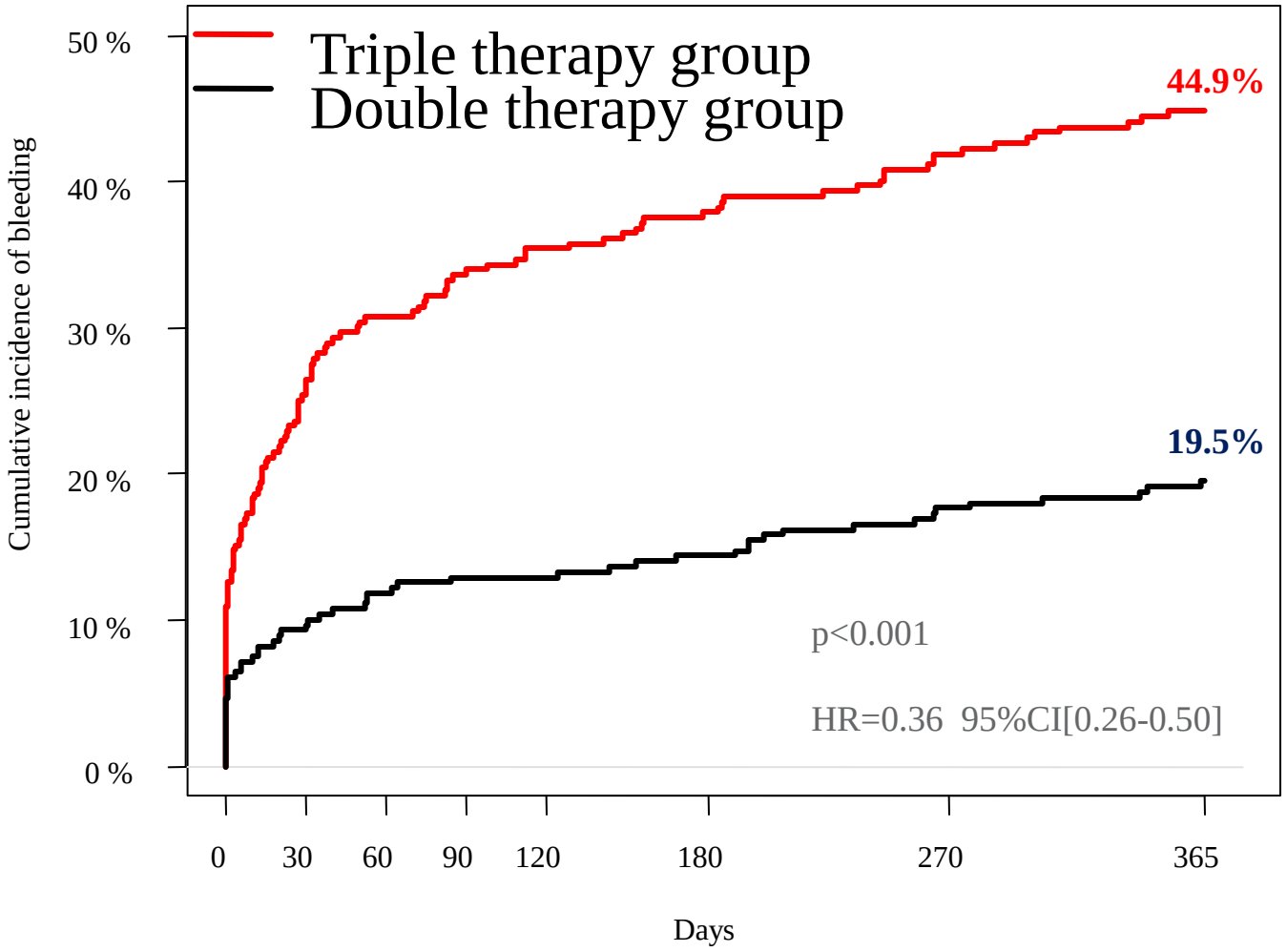
The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting

Willem Dewilde, Tom Oirbans, Freek Verheugt, Johannes Kelder, Bart De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius Heestermans, Marije Vis, Saman Rasoul, Kaioum Sheikjoesoef, Tom Vandendriessche, Carlos Van Mieghem, Kristoff Cornelis, Jeroen Vos, Guus Brueren, Nicolien Breet and Jurriën ten Berg

The WOEST Trial= **W**hat is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing (clinicaltrials.gov NCT00769938)

ZIEKENHUIS ST ANTONIUS

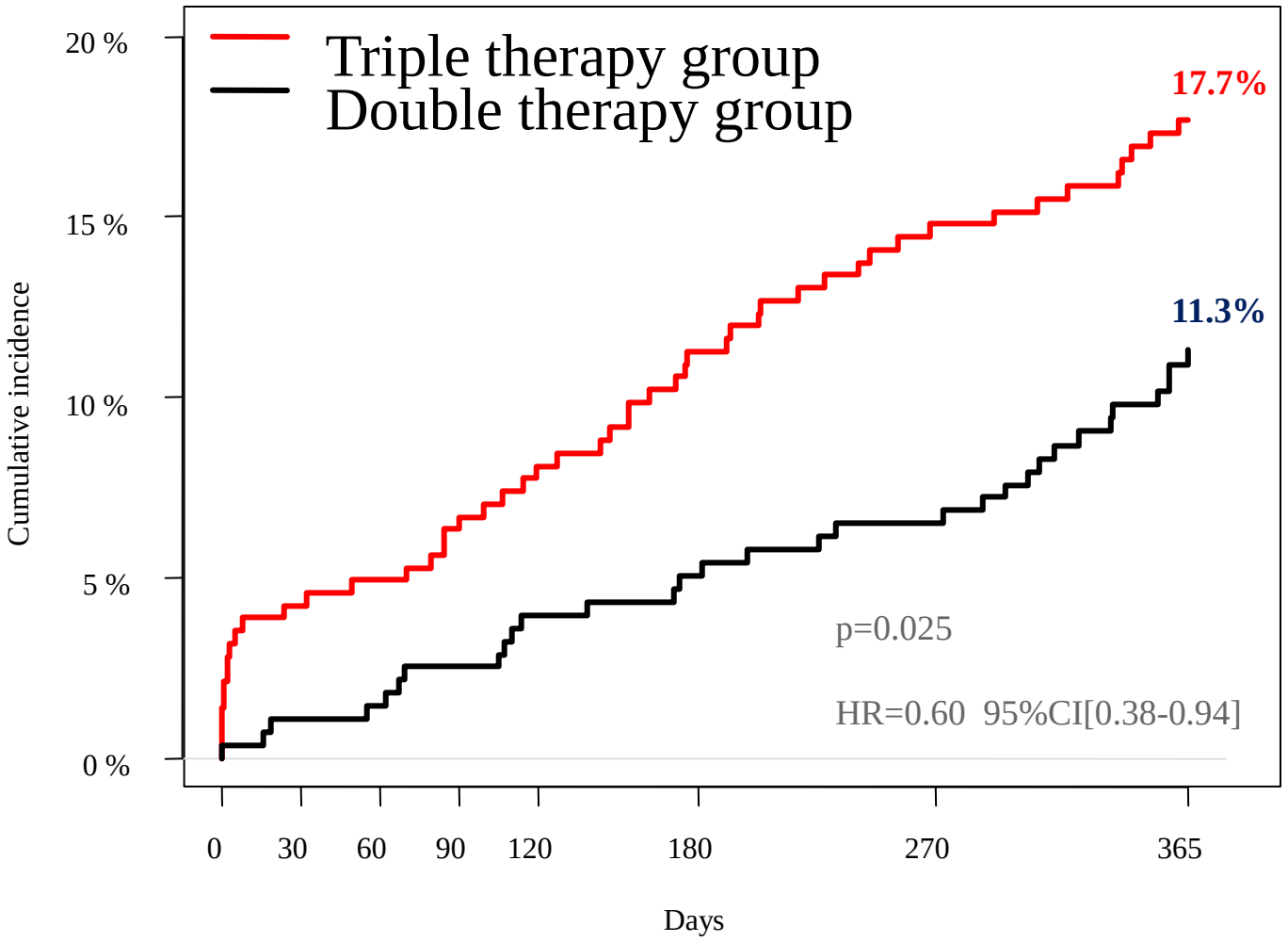
Primary Endpoint: Total number of TIMI bleeding events



n at risk:	284	210	194	186	181	173	159	140
	279	253	244	241	241	236	226	208

ZIEKENHUIS ST ANTONIUS

Secondary Endpoint (Death, MI,TVR, Stroke, ST)



n at risk:	284	272	270	266	261	252	242	223
	279	276	273	270	266	263	258	234

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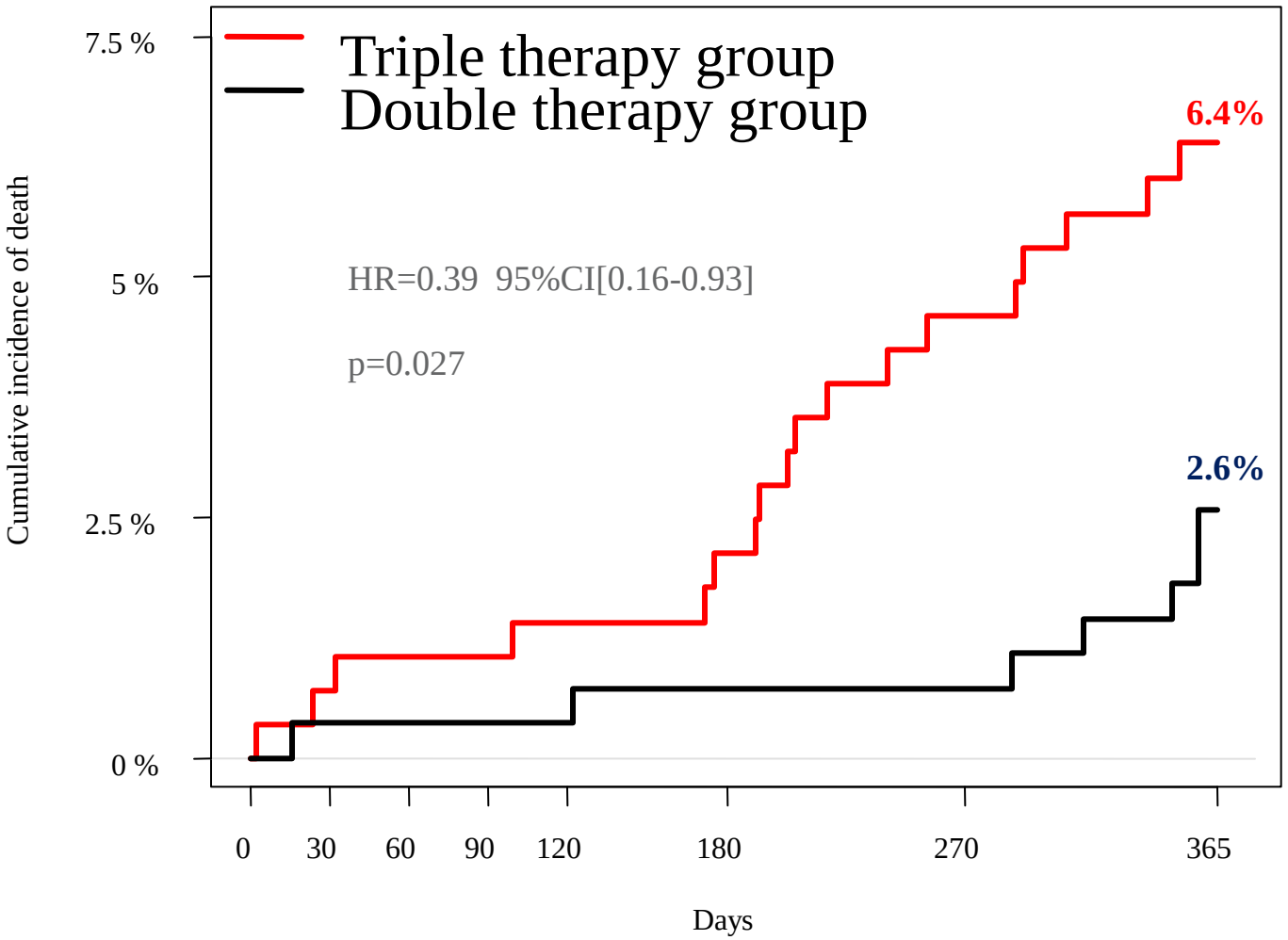
All-Cause Mortality



n at risk:								
	284	281	280	280	279	277	270	252
	279	278	276	276	276	275	274	256

ZIEKENHUIS ST ANTONIUS

Conclusions

- No significant data or benefit with warfarin when compared to bleeding risk in ACS
- Warfarin for ACS with AF – latest data might drop aspirin
- Given unmet need – high event rates
  - Double or triple therapy studies with novel anti-coagulants warranted
  - Pioneer AF – Rivaroxaban / RE-Dual PCI - Dabigatran