Aspirin on Top of $P2Y_{12}$ Inhibitors
Little Benefits, Possible Harm

"Drop Aspirin" Trial

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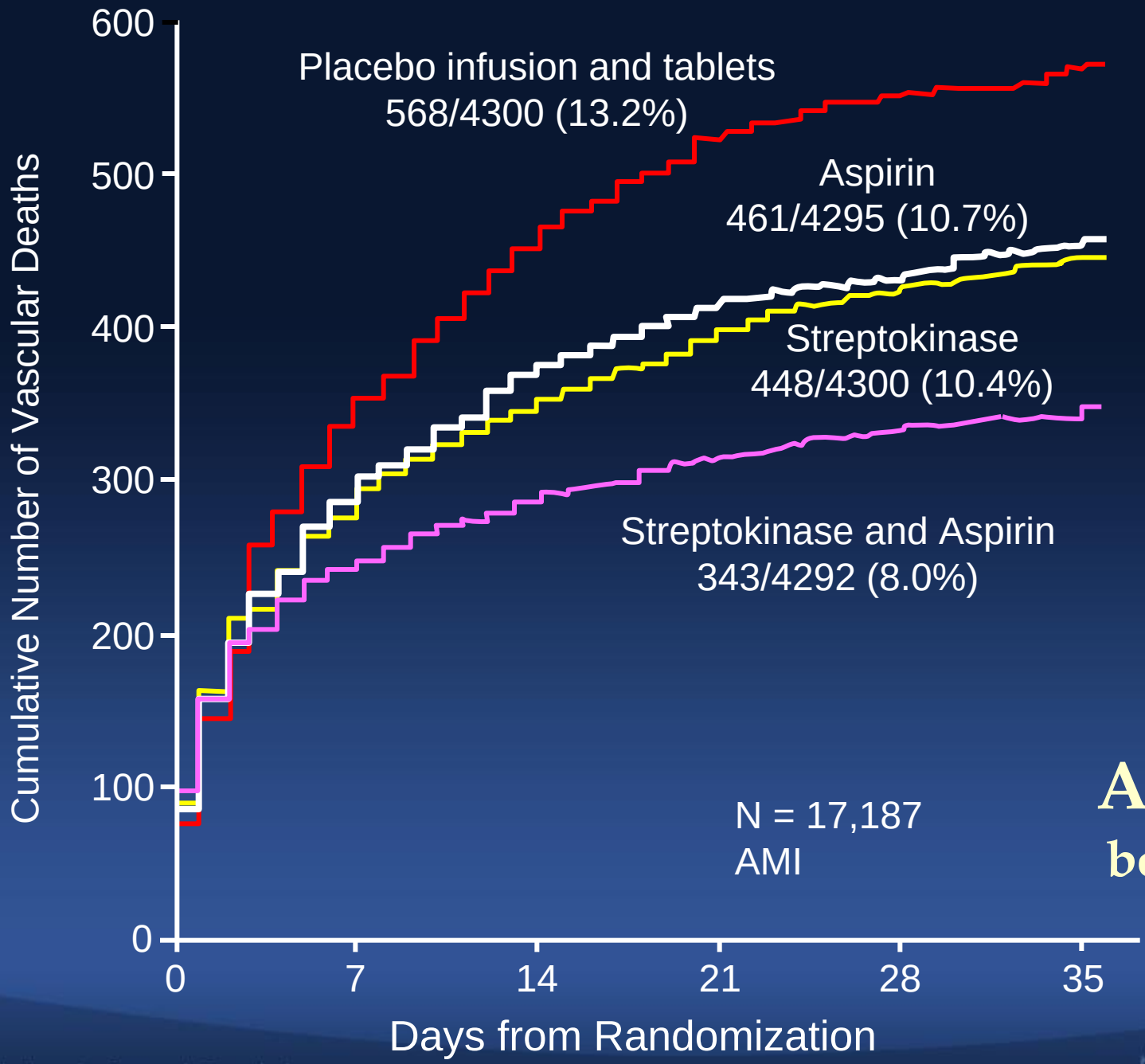
Presentation

- Aspirin Myth
- Why DAPT?: The Evidence So Far
- Stent Thrombosis: The Critical Period
- Conclusions

Why aspirin so popular?

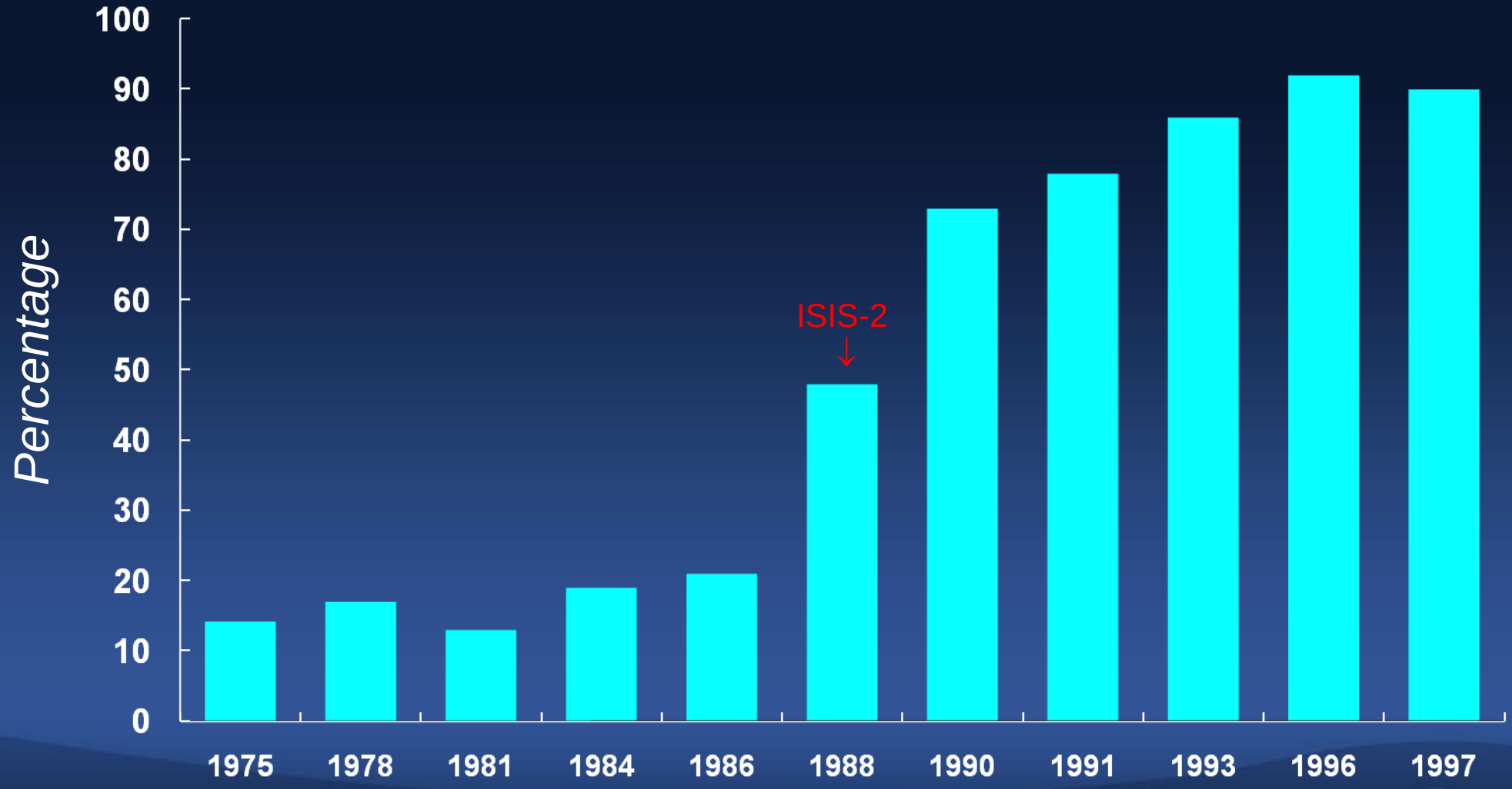
Aspirin in AMI (ISIS-2)



Aspirin should be initiated at ER.

Lancet 1988;2:349

Changes Over Time in The Use of Aspirin in Patients Hospitalized with AMI (1975 to 1997)



Am Heart J 2002;144:259

Wide Use, Little Evidence!

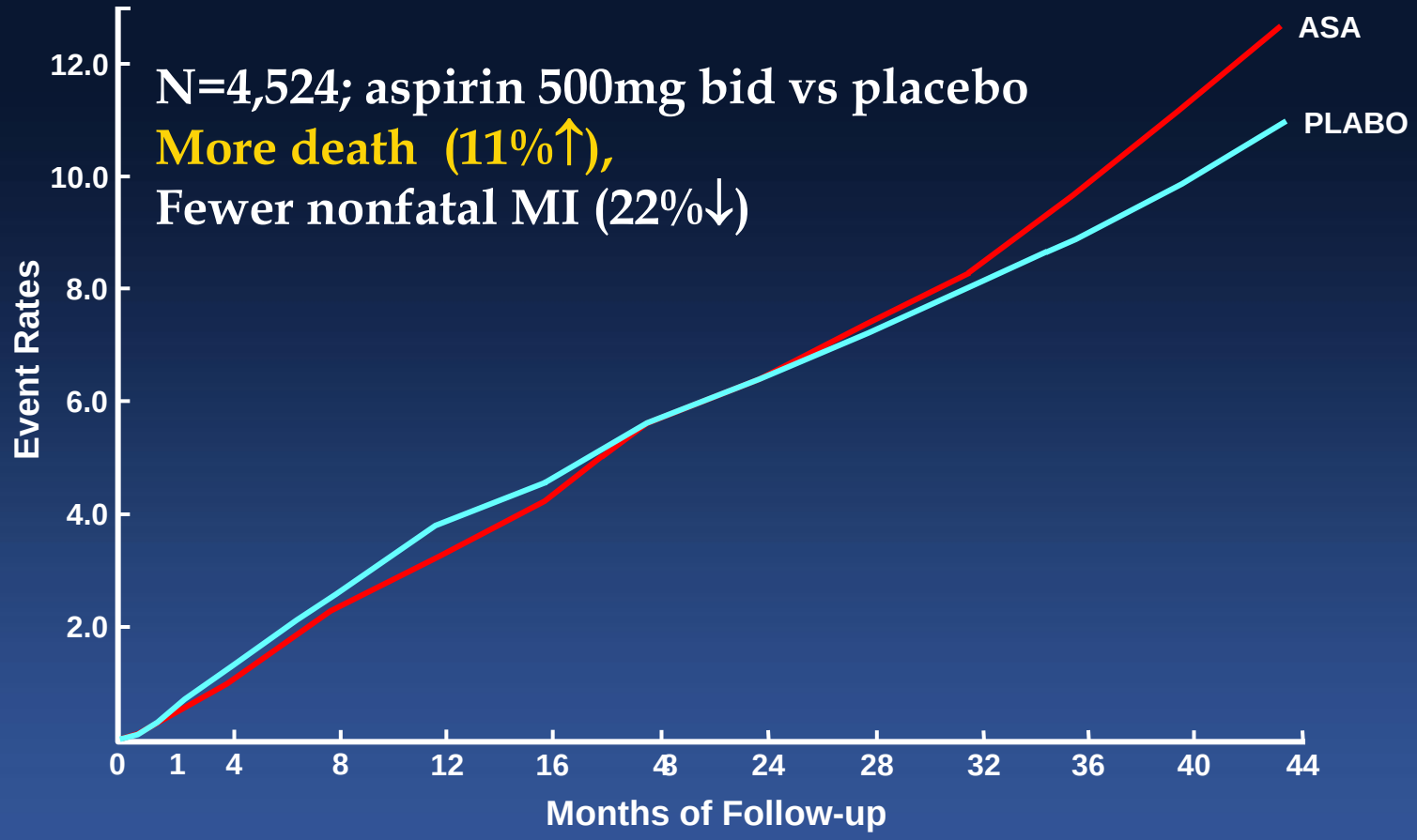
The Forgotten Studies

Publication bias
in meta-analysis

No Background Statin!

The Aspirin Myocardial Infarction Study (AMIS)

The Largest Long-term F/U Study



Routine use of aspirin after myocardial infarction is not recommended.

Circulation 1980;62:V-79

Prevention of Pulmonary Embolism and DVT with Aspirin: Pulmonary Embolism Prevention Trial

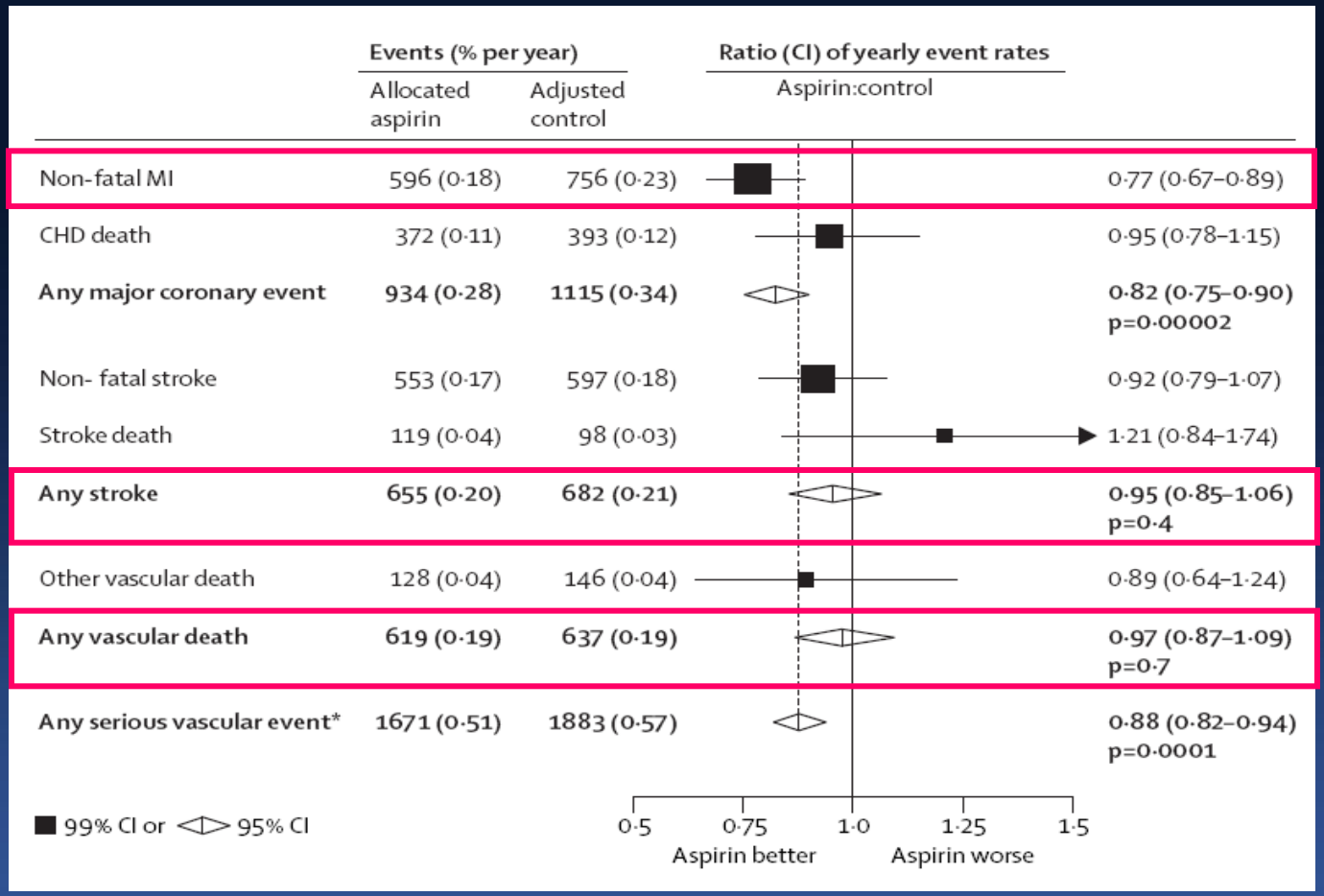
Event	Aspirin (n=6679)	Placebo (n=6677)	Hazard ratio (95% CI)*
Non-fatal vascular events			
Deep-vein thrombosis	69	97	0·71 (0·52–0·97)
Pulmonary embolism	28	38	0·74 (0·45–1·21)
Venous thromboembolism†	87	122	0·71 (0·54–0·94)
Myocardial infarction	36	23	1·57 (0·93–2·65)
Stroke	34	30	1·13 (0·69–1·85)
Vascular death			
Pulmonary embolism	18	43	0·42 (0·24–0·73)
Ischaemic heart disease	69	56	1·23 (0·87–1·75)
Stroke	20	19	1·05 (0·56–1·97)
Heart failure	66	55	1·20 (0·84–1·72)
Other vascular cause	16	31	0·52 (0·28–0·94)
Unknown cause‡	46	48	0·96 (0·64–1·44)
All vascular deaths	235	252	0·93 (0·78–1·11)
Non-vascular death			
Pneumonia or bronchitis	114	126	0·90 (0·70–1·17)
Other non-vascular cause	98	83	1·18 (0·88–1·58)
All non-vascular deaths	212	209	1·01 (0·84–1·23)
All deaths up to day 35§	447	461	0·97 (0·85–1·10)

Aspirin 160 mg for 35 days: ↓36% of pulmonary embolism of symptomatic DVT after hip surgery

Lancet 2000;355:1295

Aspirin in Primary Prevention

Individualised Approach



Antithrombotic Trialists' Collaboration
Lancet 2009;373:1849

- Primary endpoints
  - all negative (except 1)
- ICH 32%↑ (1.0-1.75)
- Major extracranial bleeding 54%↑ (1.3-1.82)

0.06% /y ↓CV outcome
0.03% /y ↑major bleed

NICE guideline: Aspirin is not licensed for the primary prevention of vascular events. If aspirin is used in primary prevention, the balance of benefits & risks should be considered for each individual.

Aspirin ad Infinitum
for Prevention It Really Works?

FDA has not approved aspirin for use in primary prevention.

International guidelines have started to recommend withdrawal of aspirin.

Nature Clinical Practice Cardiovascular Medicine 2006;3:234-235

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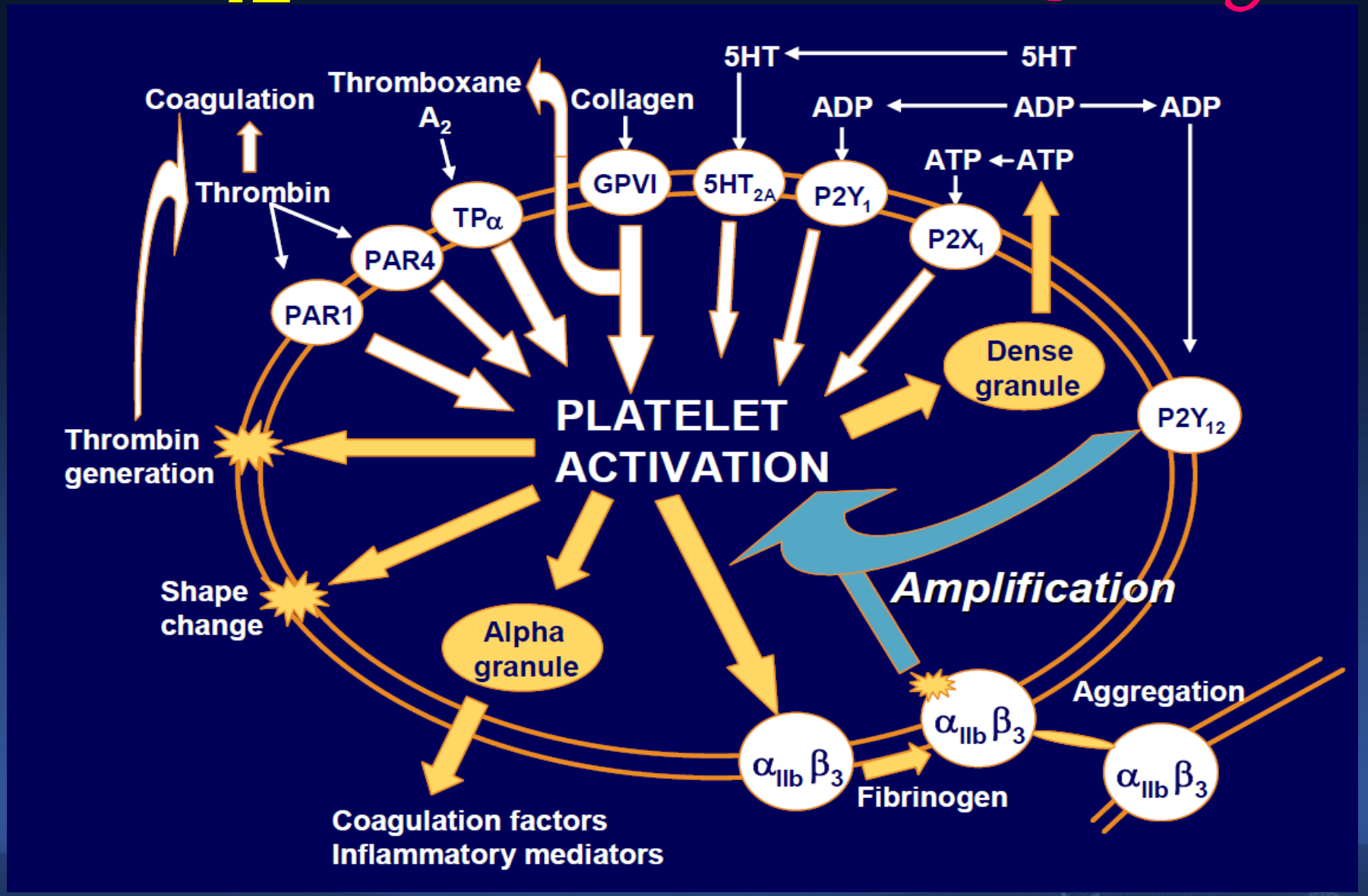
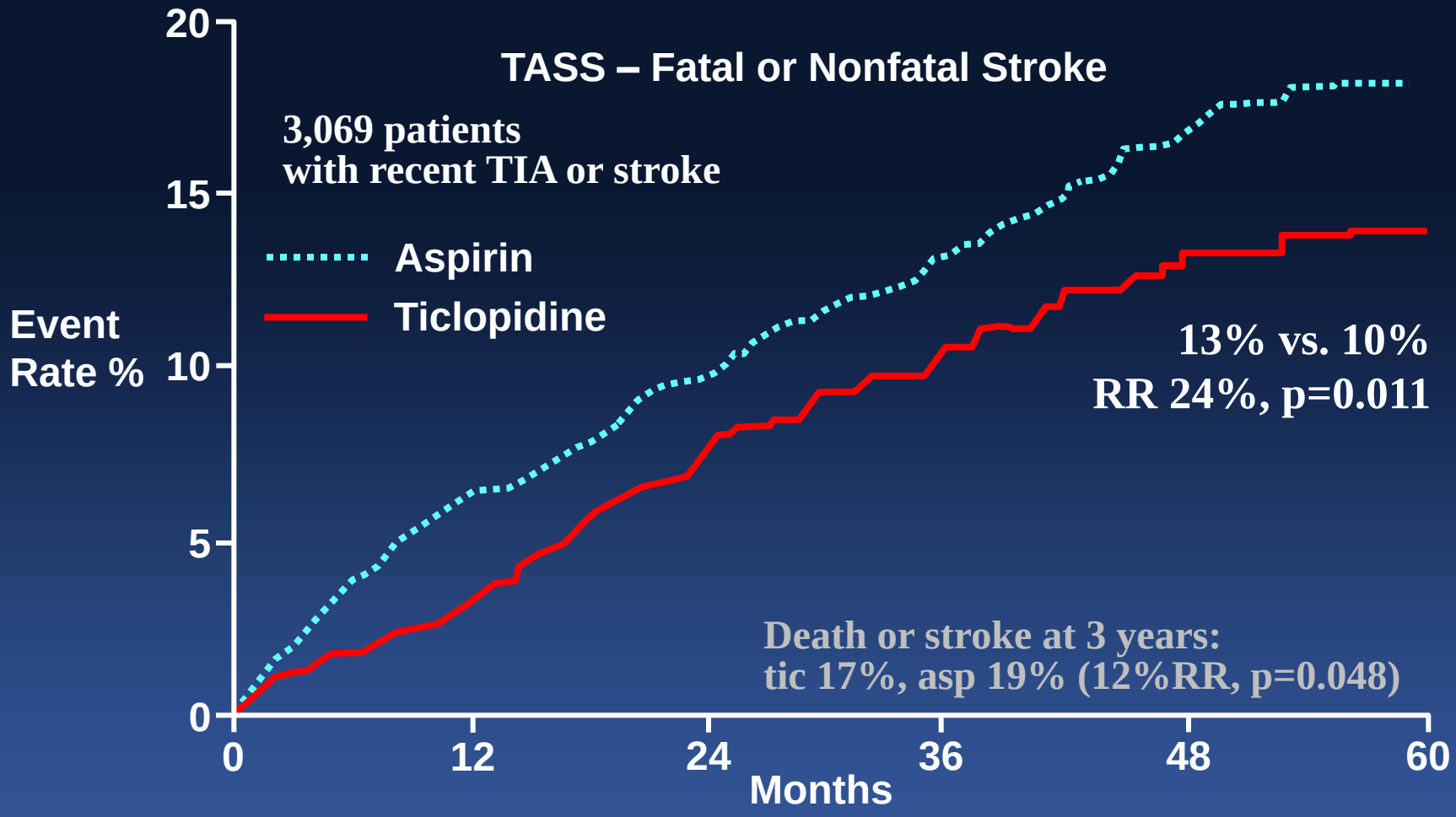
$P2Y_{12}$ Inhibitor on top of Aspirin

$P2Y_{12}$ Receptor: A Key Player



JCI 2004;113:340; Curr Pharm Des 2006;12:1255; Circulation 2010;121:171

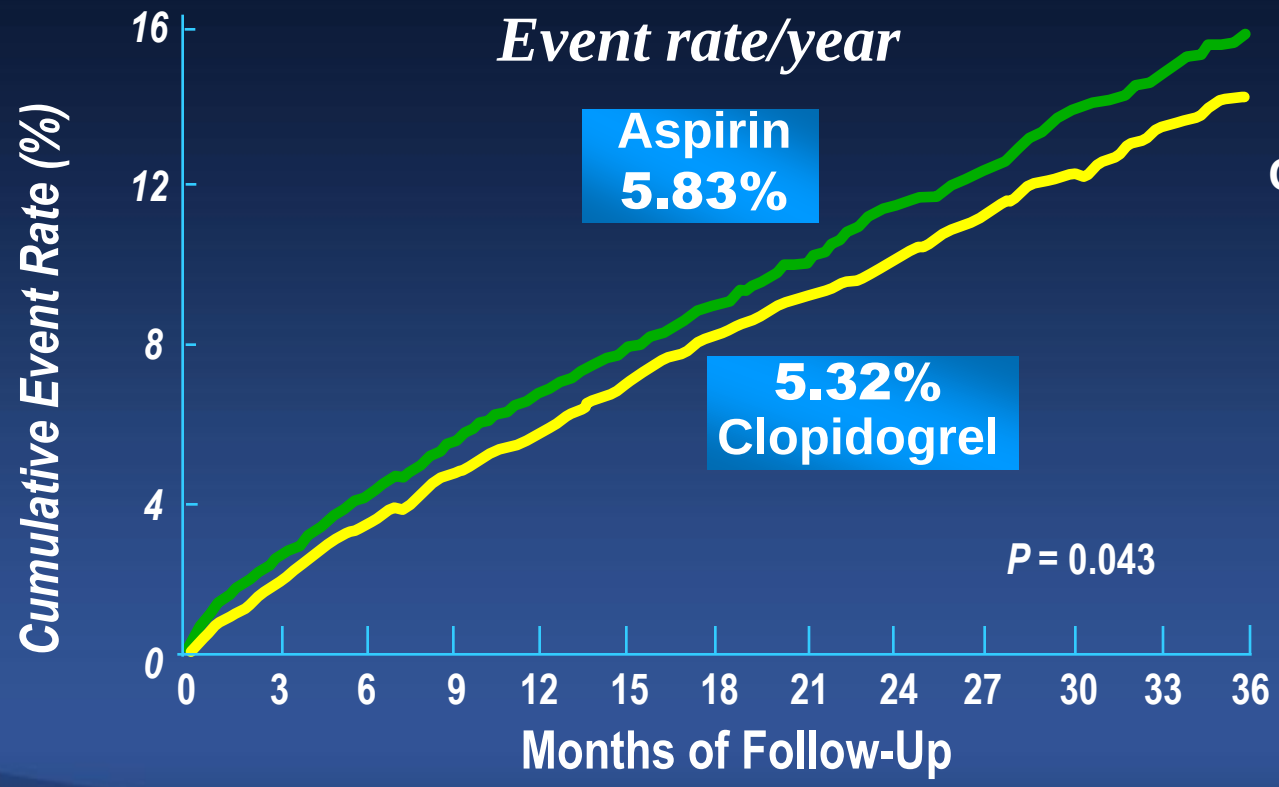
TASS Aspirin vs. Ticlopidine



Ticlopidine was more effective than aspirin (650mg po bid) in preventing Strokes in this population, although the risk of side effects were greater.

CAPRIE Aspirin vs. Clopidogrel

19,185 patients with atherosclerotic disease



Aspirin

Clopidogrel

8.7%*
Overall Relative Risk Reduction

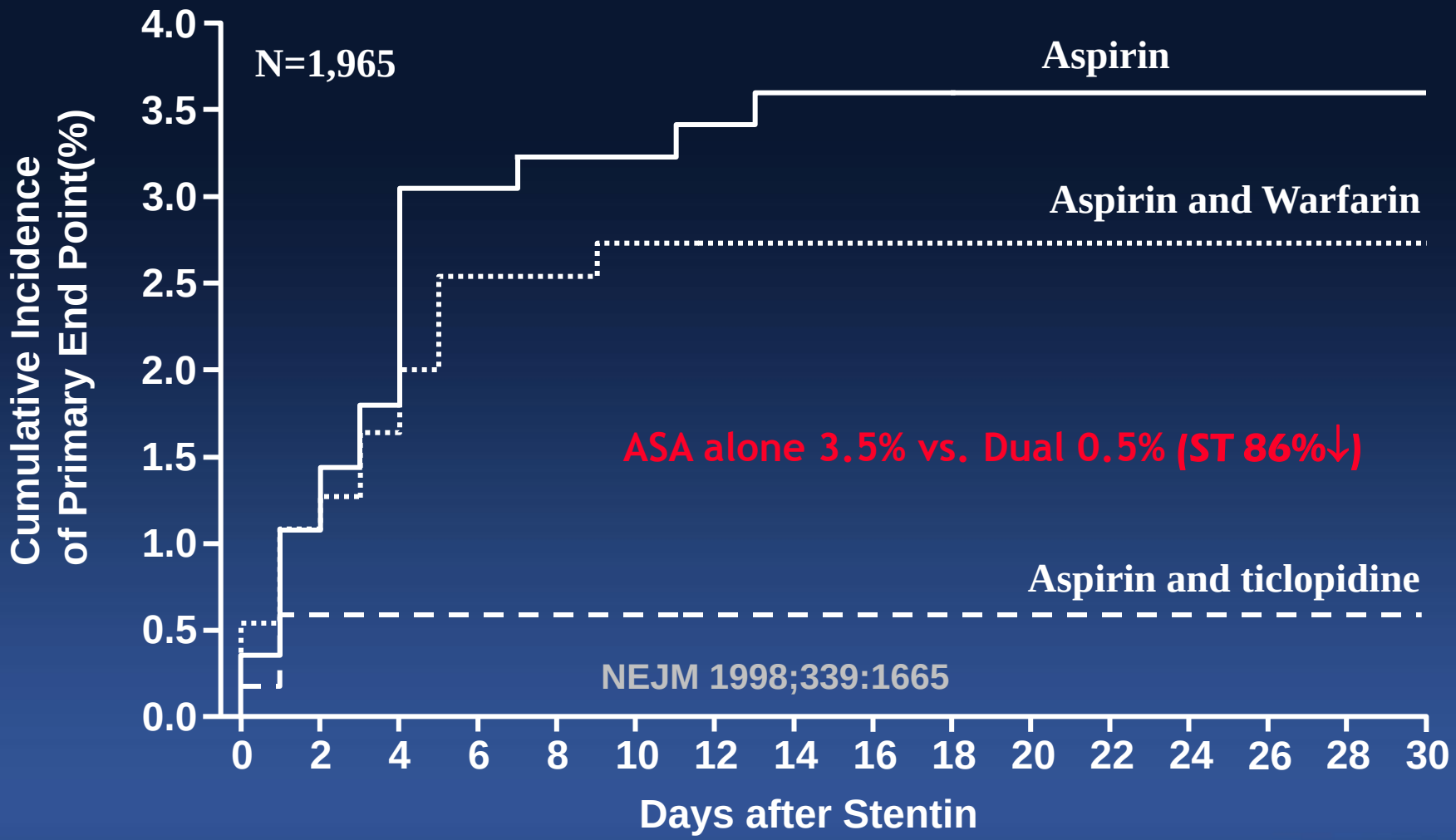
No major safety differences

	Aspirin	Plavix
Any bleed	9.28%	9.27%
ICH	0.49%	0.35%
GI bleed*	2.66%	1.99%

**p<0.05*

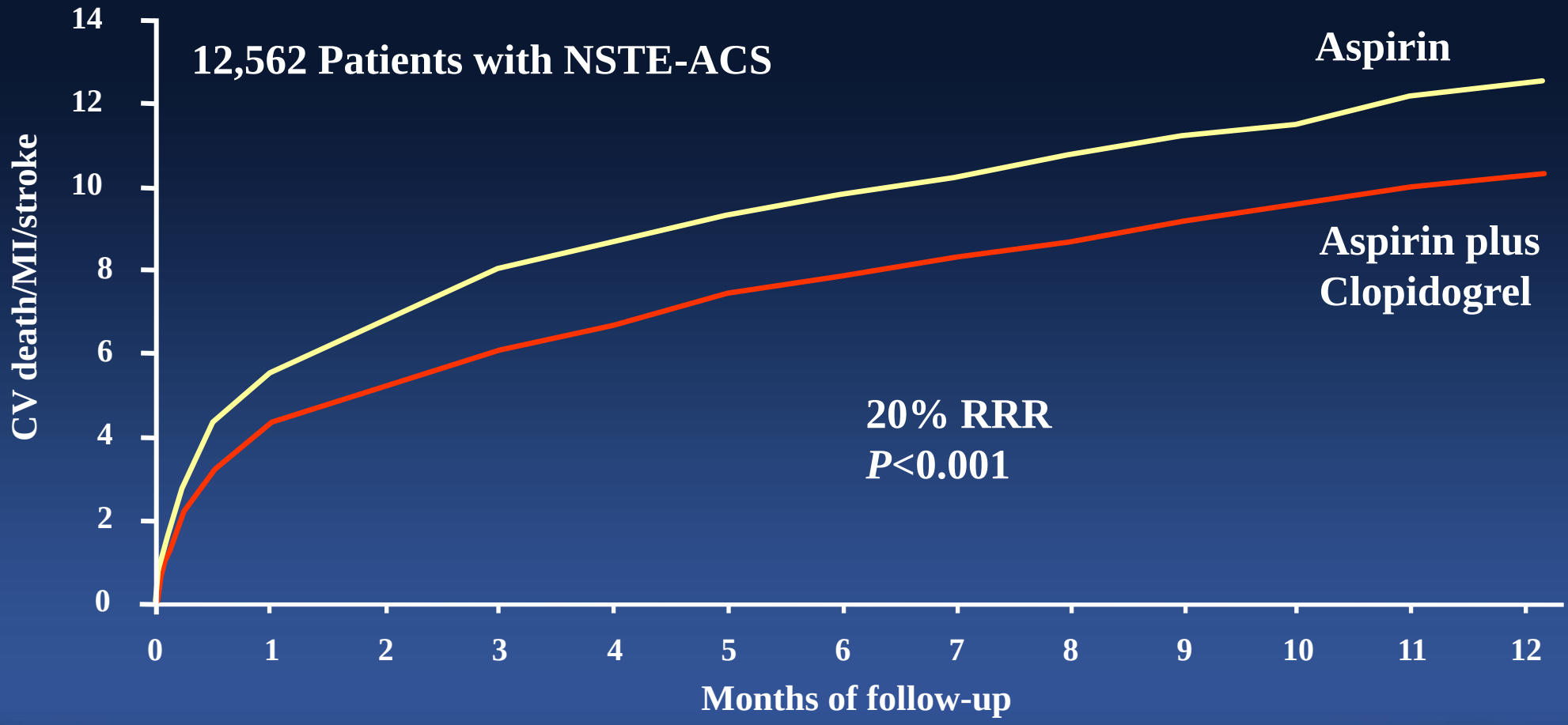
Lancet 1996;348:1329

STARS Aspirin vs. Aspirin plus Clopidogrel



After coronary stenting, aspirin & ticlopidine should be considered for the prevention of the serious complication of stent thrombosis.

CURE Aspirin vs. Aspirin plus Clopidogrel



N Eng J Med 2001;345:494-502

Landmark Clopidogrel Trials

So Luxurious …

Clinical End-Point Trials: "The Proven Clopidogrel Trials"

CAPRIE, CLASSICS, CURE, CREDO, CARESS, CLARITY, COMMIT, MATCH, CARESS, FASTER, CHARISMA, CASPAR, ACTIVE-A, OASIS-7, GRAVITAS…

PLATO: Clopiodgrel vs Ticagrelor

Absolute mortality reduction

PLATO: 1.4%
thrombolysis vs. placebo: ~2%
primary angioplasty vs. thrombolysis: ~2%
tPA vs. Streptokinase (2002 NICE):
death (HR1.0), MI (HR0.86), stroke (HR1.37)

$P2Y_{12}$ Inhibitor on top of Aspirin?

… up to 1 year

Yes, it clearly works!

Aspirin
on top of
$P2Y_{12}$ inhibitor

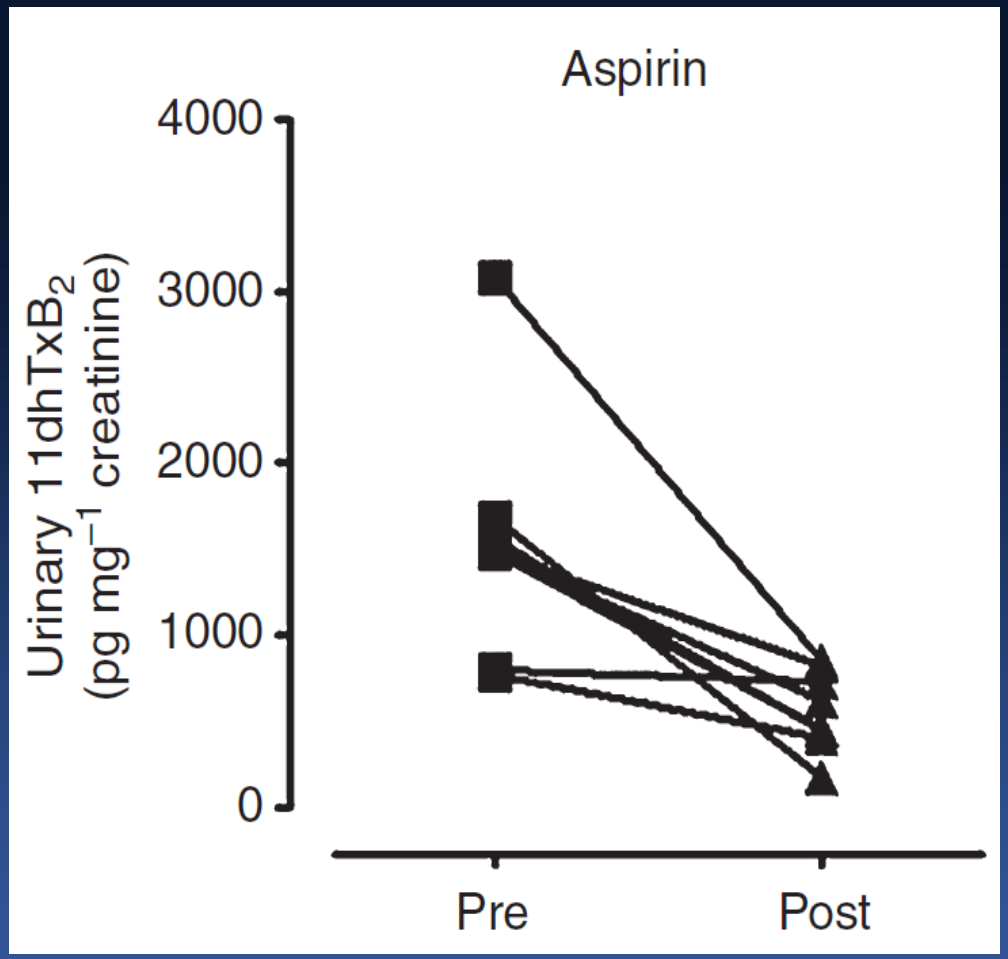
Why? Aspirin "The Default Therapy"

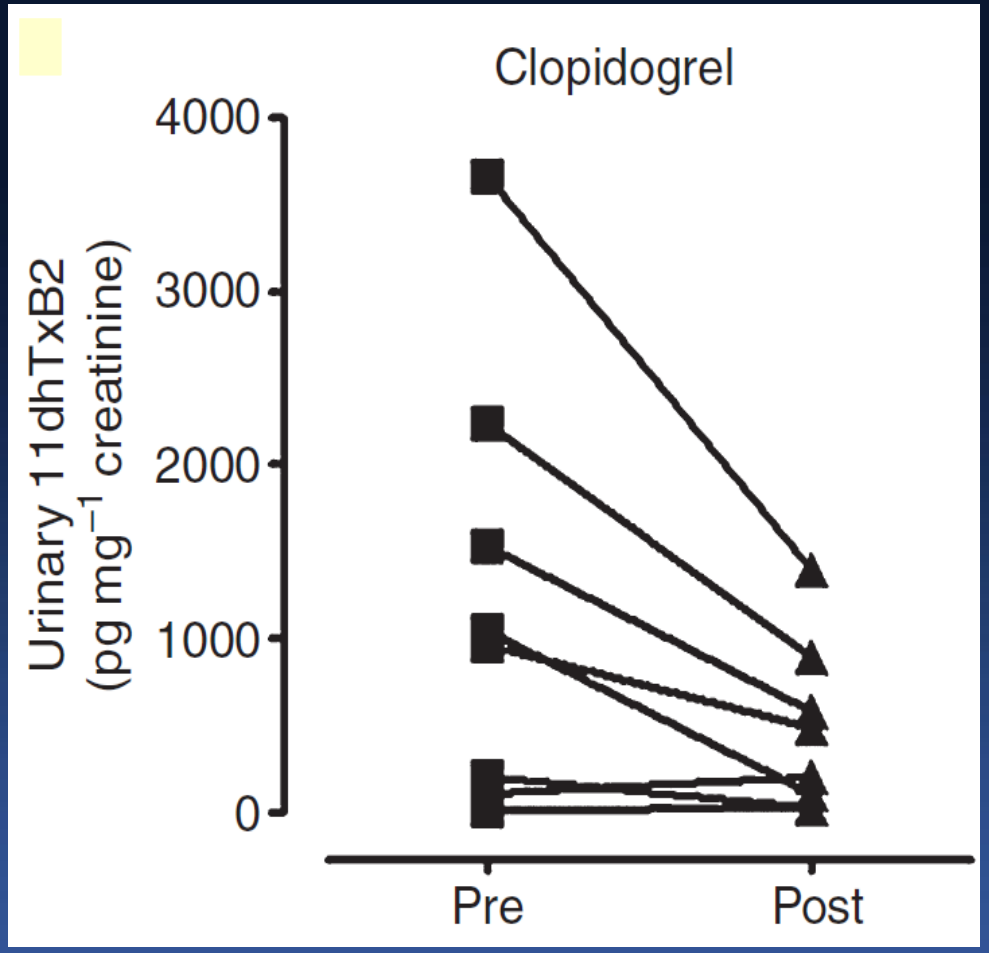
- **Aspirin after ISIS-2 trial:**
  - from 1 month's evidence to a lifelong tablet.
  - It appears unethical for aspirin not to be included in antiplatelet regimens.

- **Basic assumption of DAPT:**
  - will independently inhibit the TXA_2-dependent and $P2Y_{12}$ receptor-dependent pathways of platelet activation, and thus have additive effects on inhibition of platelet function.

Platelet Function Test

Reduction of platelet thromboxane A2 production ex vivo and in vivo by clopidogrel therapy



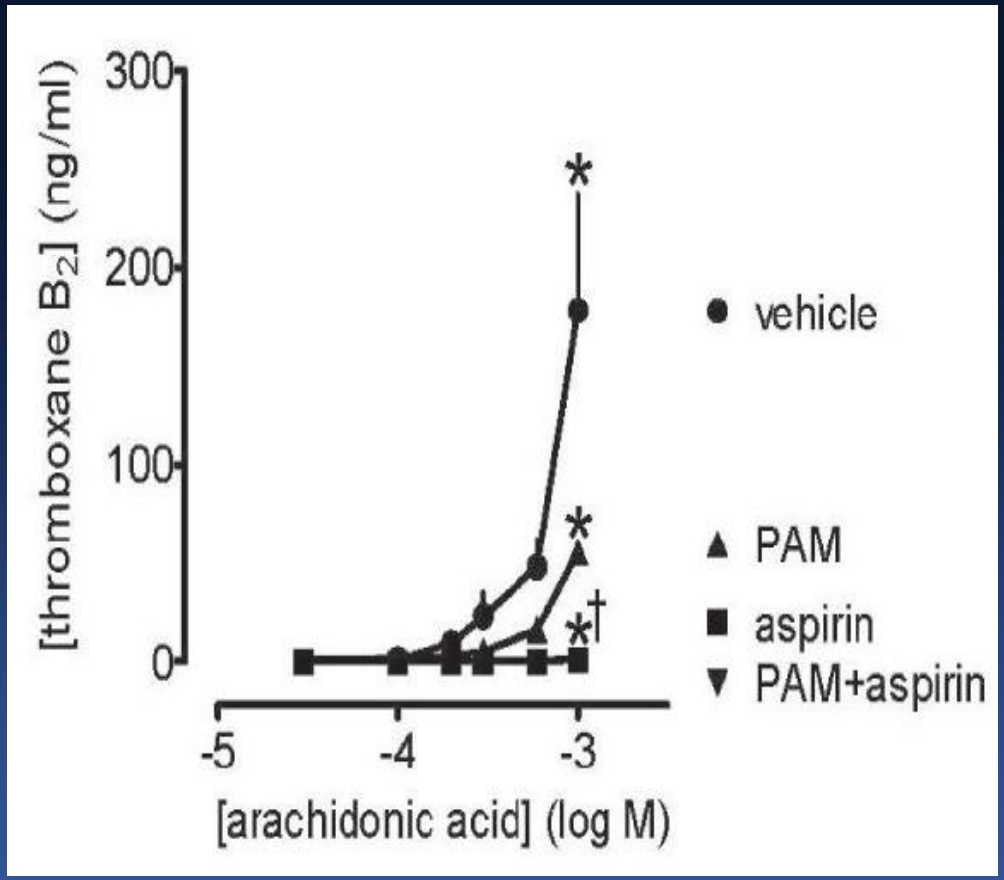


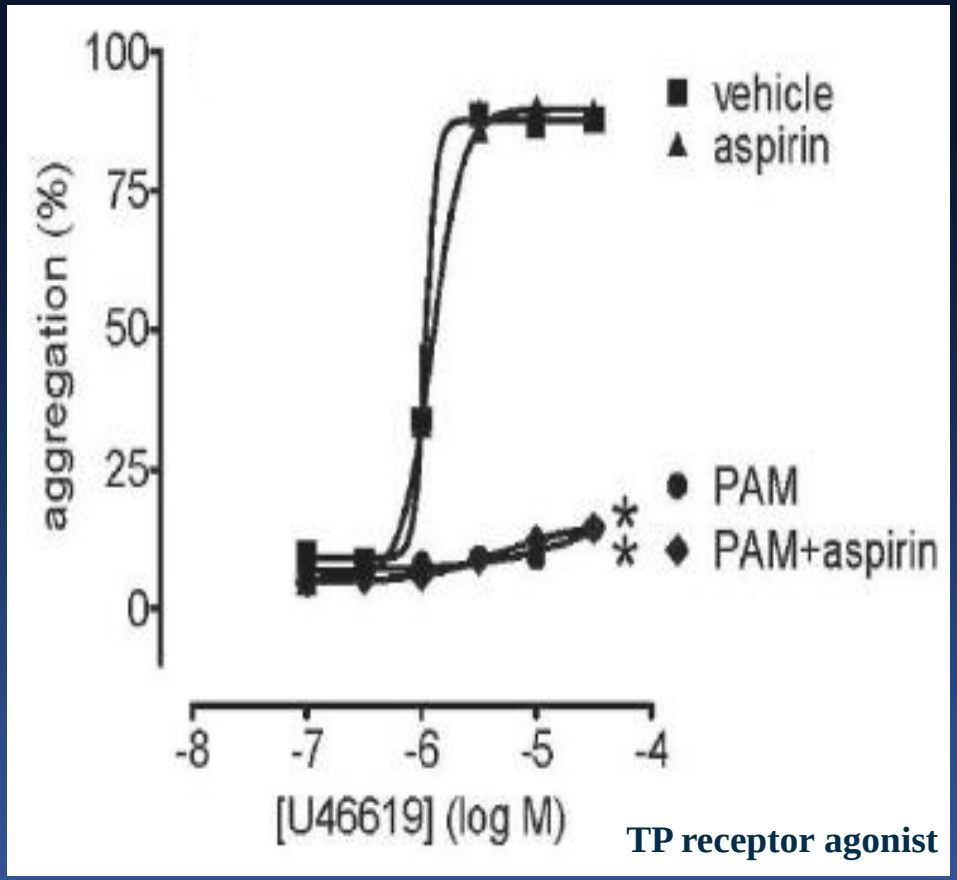
clopidogrel reduced urinary 11-dh-TXB_2 to the same extent with aspirin, raising questions regarding the co-administration of aspirin and $P2Y_{12}$ receptor antagonists.

J Thromb Haemost 2010;8:613

Platelet Function Test

In The Presence Of Strong P2Y12 Receptor Blockade, Aspirin Provides Little Additional Inhibition Of Platelet Aggregation





TP receptor agonist

PAM (prasugrel active metabolite) inhibits the formation of TXA2 and TXA2-driven platelet aggregration. Platelet inhibition by DAPT is not greater than that produced by high levels of P2Y12 receptor blocker.

J Thromb Haemost 2011;9:552

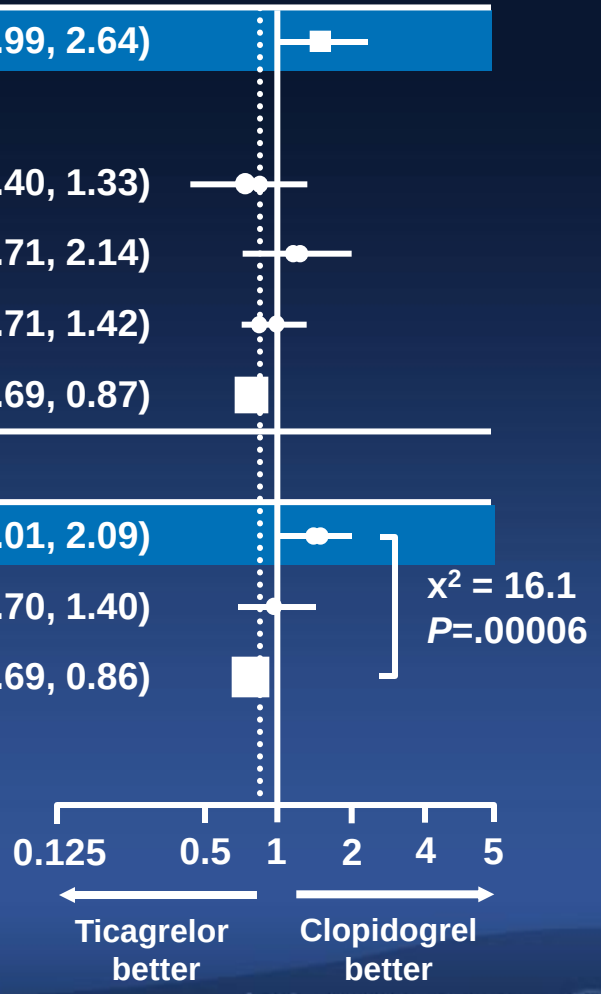
ADAPT-DES: Aspirin Resistance (1 Year Outcome)

VerifyNow test	Def/prob ST (n=70)	No def/prob ST (n=8,513)	P
Aspirin ARU	426 ± 58	419 ± 55	0.30
- ARU ≥ 550	7.2%	5.6%	0.54
P2Y12 Base	305 ± 60	310 ± 58	0.56
P2Y12 PRU	234 ± 97	188 ± 97	<0.0001
- PRU > 208	65.2%	42.5%	0.0002
- PRU ≥ 230	53.6%	34.9%	0.001
P2Y12 % Inhibition	24.8 ± 27.0	40.1 ± 28.2	<0.0001
- Inhibition ≤ 11%	44.9%	19.9%	<0.0001
IIb/IIIa PAU	194 ± 56	193 ± 54	0.92

Aspirin resistance was unrelated to ST, MI or death, but may be related to bleeding (HR0.65, p=0.04), questioning the utility of aspirin in pts with DES.

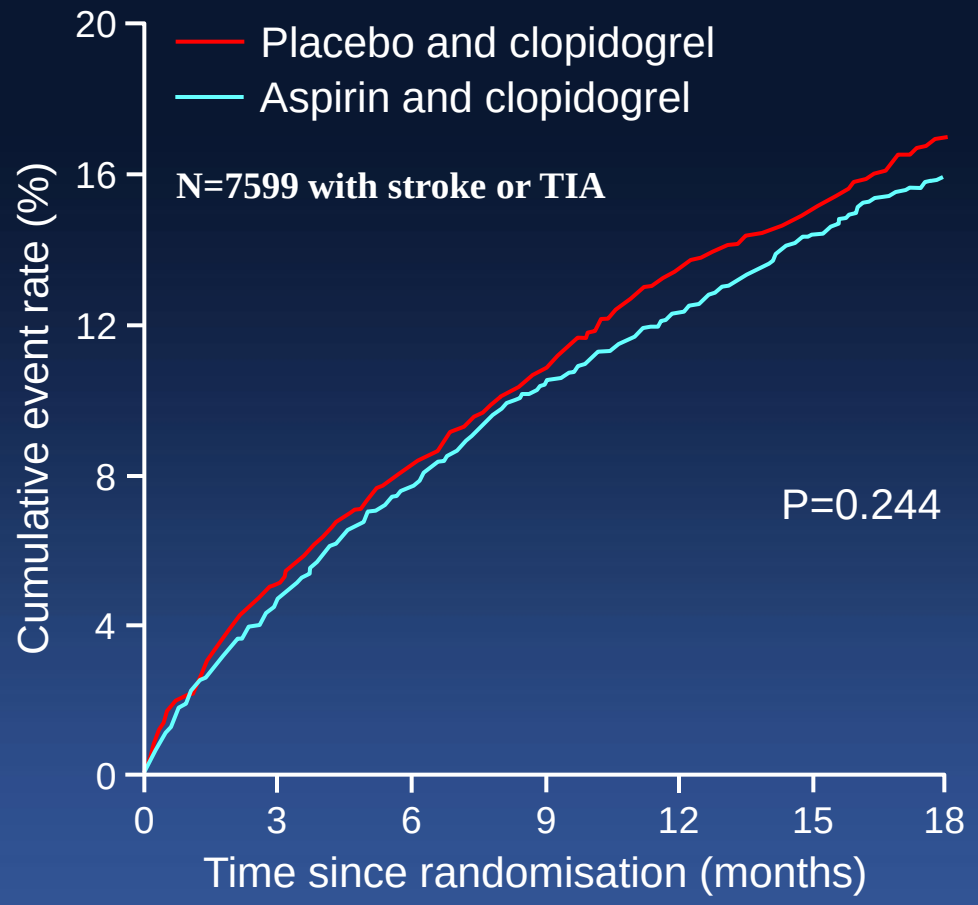
PLATO Trial: "Aspirin Hypothesis"

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥ 300	324	40	352	27	1.62 (0.99, 2.64)
	> 100 - < 300	22	2	16	2	
	≤ 100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥ 300	140	28	140	23	1.23 (0.71, 2.14)
	> 100 - < 300	503	62	511	63	1.00 (0.71, 1.42)
	≤ 100	7449	546	7443	699	0.78 (0.69, 0.87)
Overall						
	≥ 300	464	68	492	50	1.45 (1.01, 2.09)
	> 100 - < 300	525	64	527	65	0.99 (0.70, 1.40)
	≤ 100	7733	565	4406	723	0.77 (0.69, 0.86)



MATCH: "Drop Aspirin"

CV death/MI/stroke/readmission



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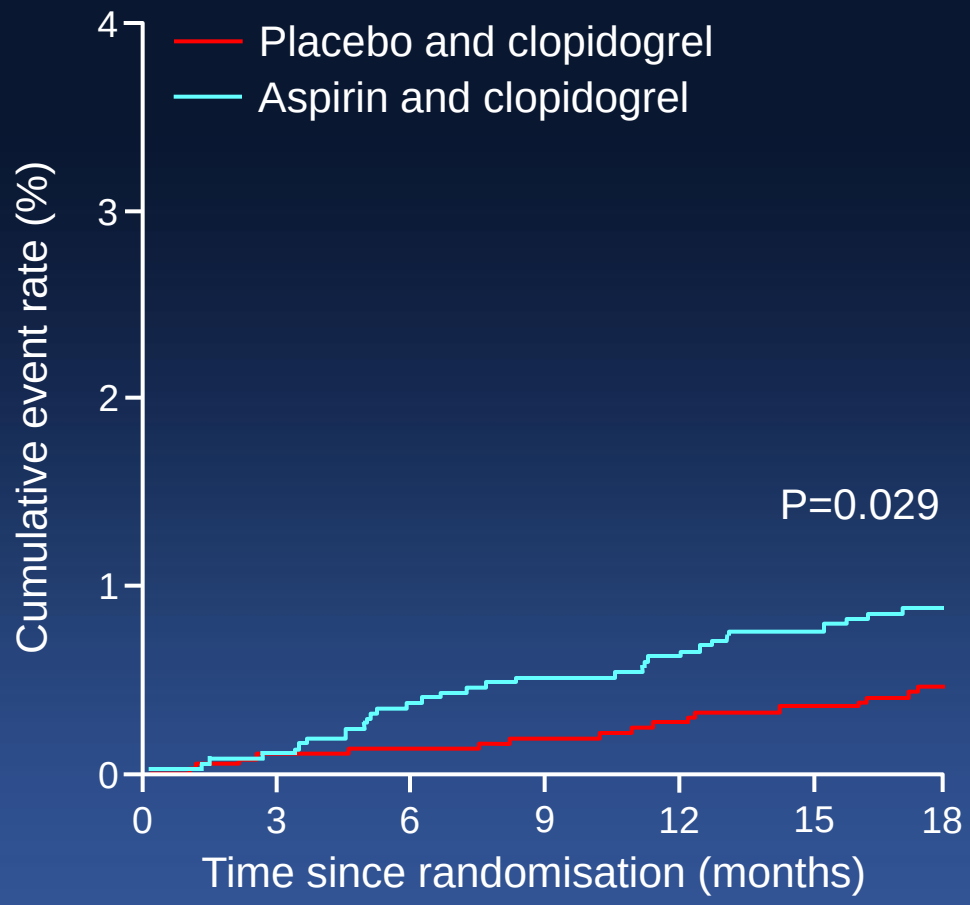
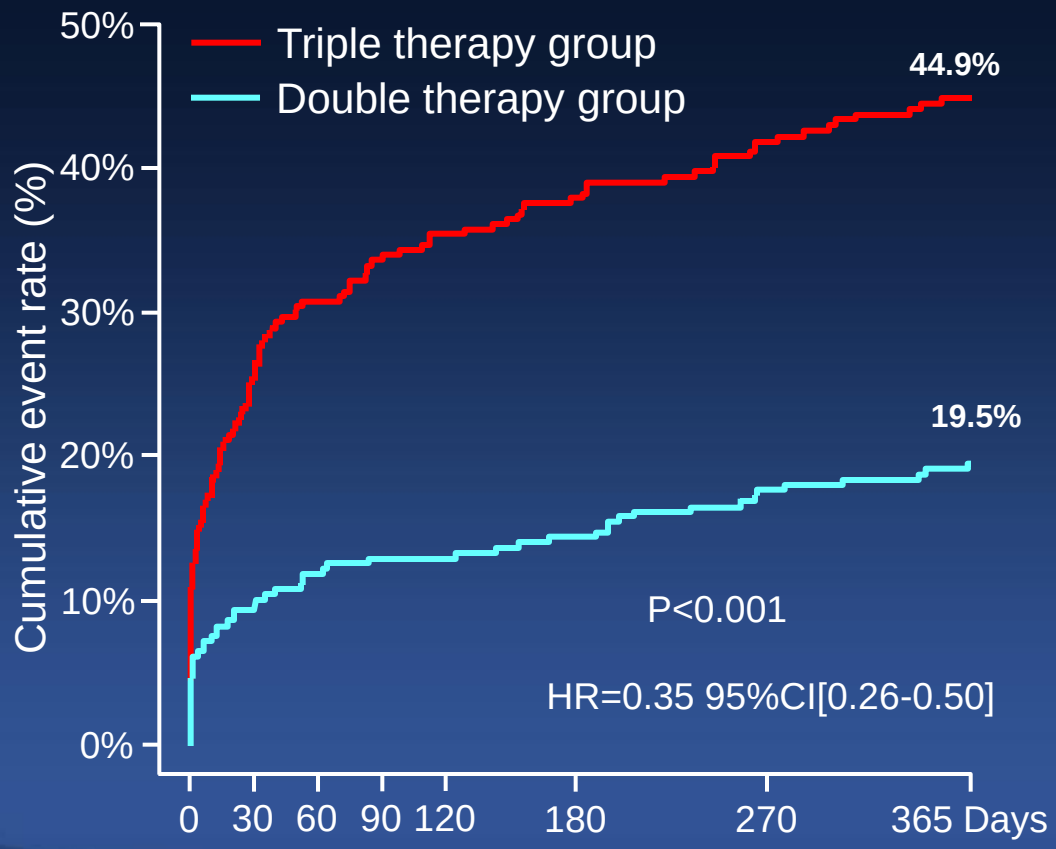


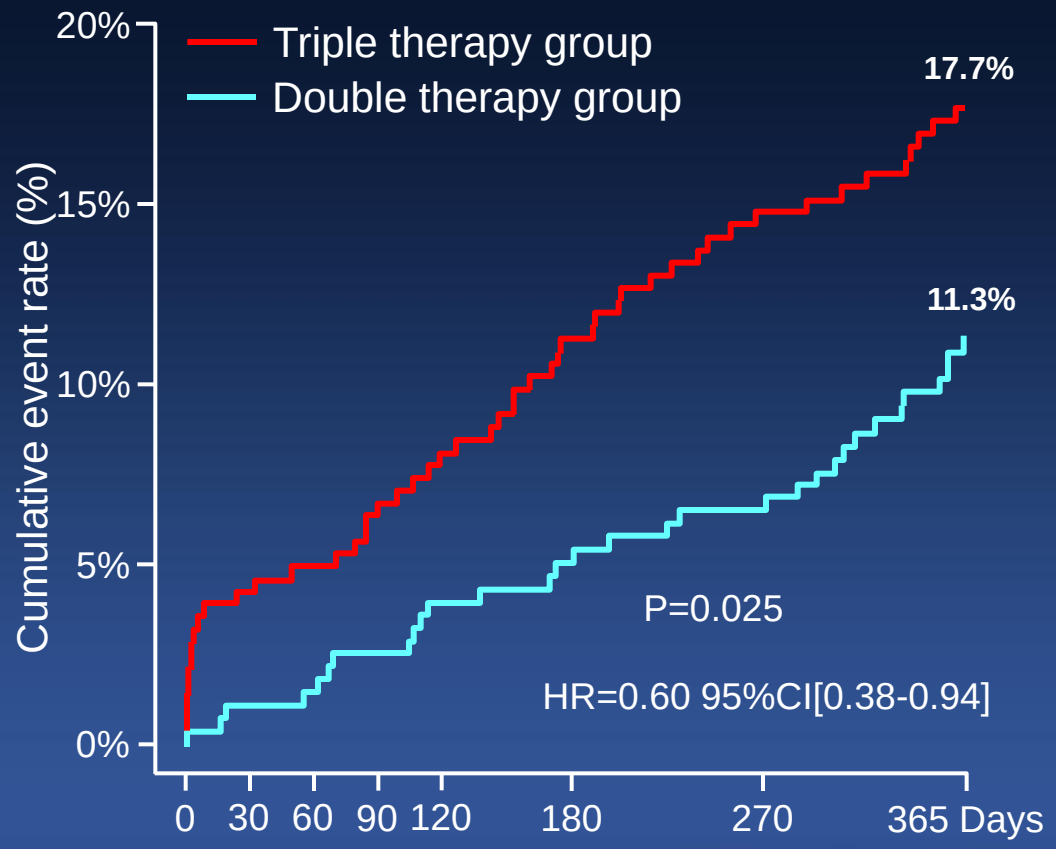
Adding aspirin to clopidogrel in high-risk patients with recent ischemic stroke or transient ischaemic attack is associated with a non-significant difference in reducing major vascular events. However, the risk of life-threatening or major bleeding is increased by the addition of aspirin.

WOEST: "Drop Aspirin"

573 pts with AF undergoing stent implantation (BMS~30%), 1 y F/U



TIMI Bleeding



Death/MI/stroke/ST/TVR

Aspirin on top of P2Y12 Inhibitor?

It's time *... doubtful & unclear*
to check a real value!

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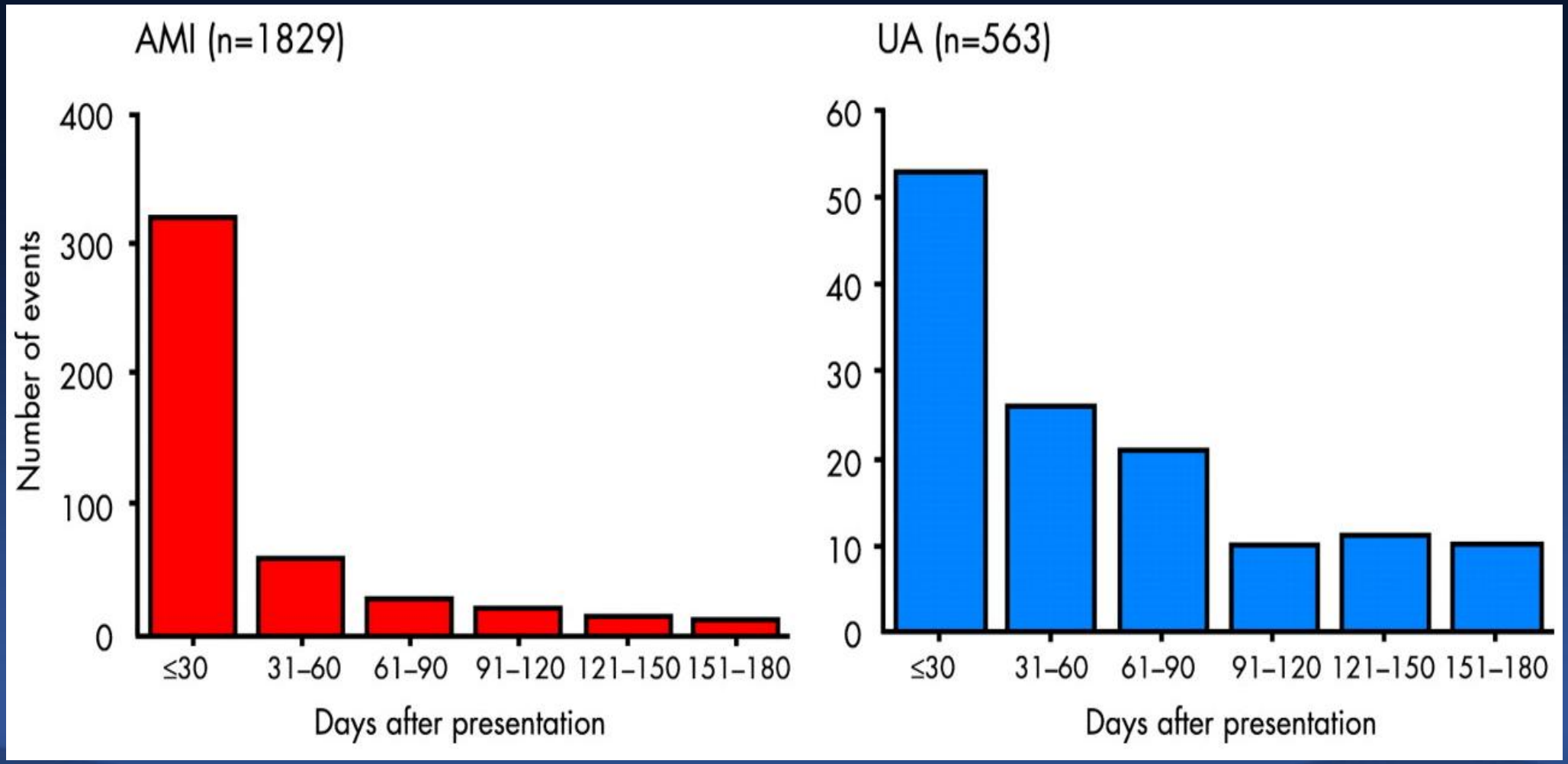
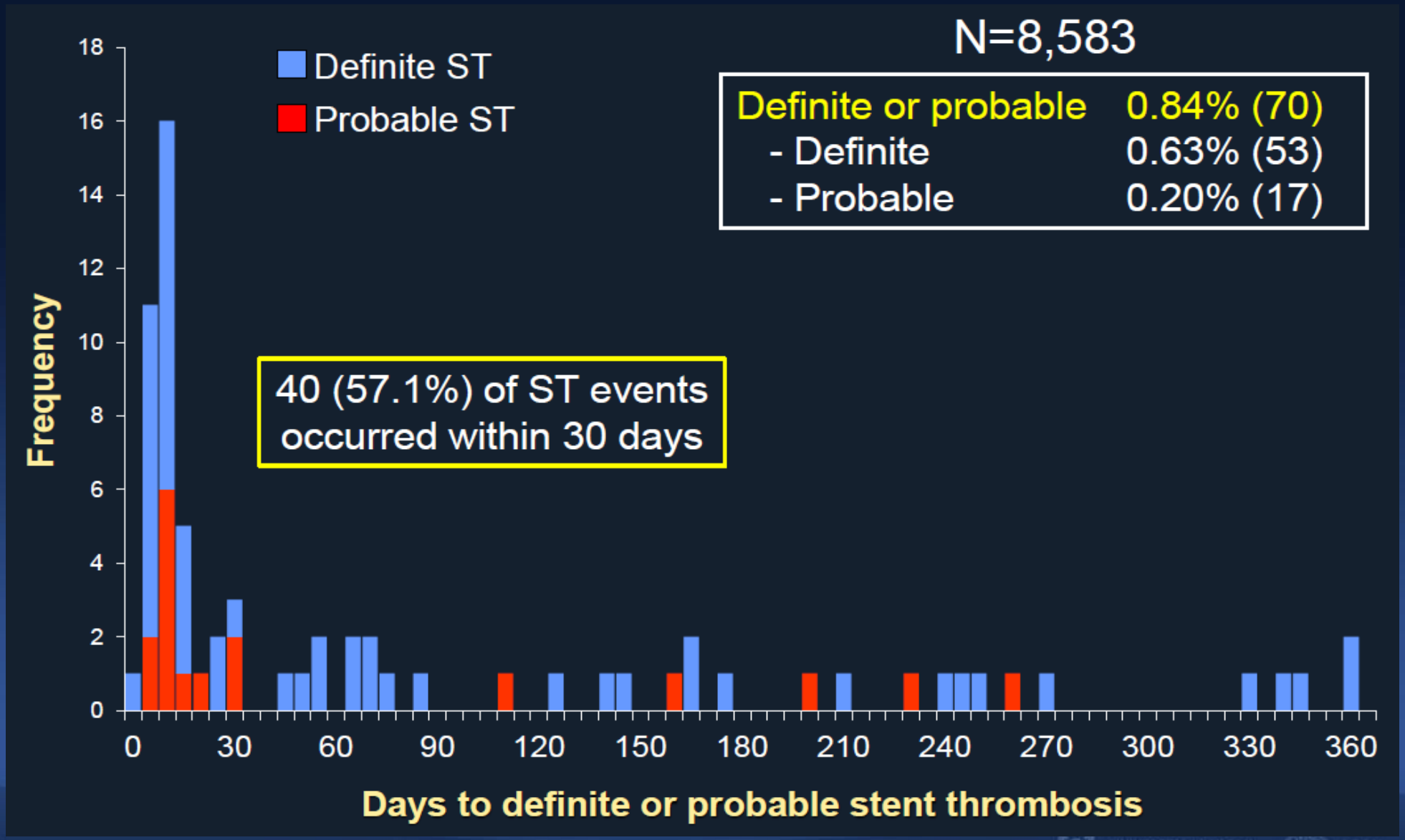
Recurrent Events after ACS



Heart 2003;89:1268-1272

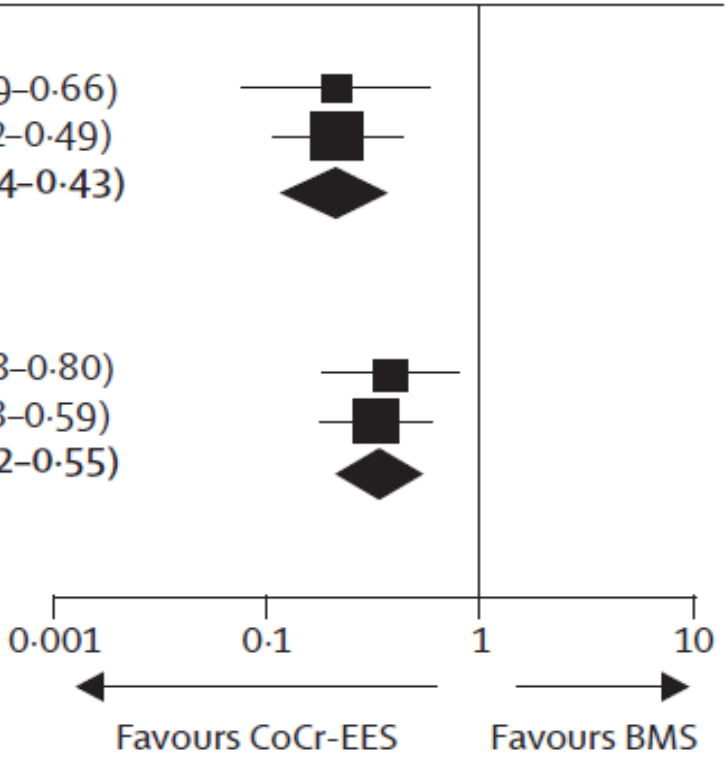
ADAPT-DES: Time to First Stent Thrombosis



NEW DES: Safer than BMS

Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis

	log (odds ratio)	SE	Weight	Odds ratio IV, random, 95% CI
(A) Definite thrombosis				
Direct estimate	–1·427	0·519	32·4%	0·24 (0·09–0·66)
Indirect estimate	–1·421	0·359	67·6%	0·24 (0·12–0·49)
Total (95% CI)			**100·00%**	**0·24 (0·14–0·43)**
Test for overall effect Z=4·82 (p<0·00001)				
(B) Definite or probable thrombosis				
Direct estimate	–0·968	0·377	39·4%	0·38 (0·18–0·80)
Indirect estimate	–1·122	0·304	60·6%	0·33 (0·18–0·59)
Total (95% CI)			**100·00%**	**0·35 (0·22–0·55)**
Test for overall effect Z=4·48 (p<0·00001)				



Lancet 2012 ;379:1392-1402

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Can We Omit Aspirin?

- **Challenge the traditional belief:**
  In an individual receiving a $P2Y_{12}$ inhibitor, TXA_2-dependent pathways of plt activation are markedly blunted, leading us to the question of what would be the net effect of added aspirin?

- **Non-platelet side effects of aspirin:**
  - increase the risk of GI trouble (~15% of UGI bleeding, ↑3.8 fold), leading to poor compliance.
  - inhibit COX in the vascular endothelium, reducing the release of PGI2.

GLOBAL-LEADERS: "Drop Aspirin"

Largest ever clinical trial involving a drug-eluting stent is announced

Plans for a new trial were announced yesterday at EuroPCR by Patrick W. Serruys. The GLOBAL LEADERS trial will compare two different anti-platelet strategies in patients who have received a drug eluting stent (DES) with an abluminally coated biodegradable polymer.

GLOBAL LEADERS is an investigator-driven trial supported by Biosensors and AstraZeneca and aims to enrol around 16,000 patients from an "all-comers" population to compare the effectiveness of two different pharmaco-intervention strategies. All patients will receive BioMatrix Flex, and then be randomised to either a study treatment strategy of one month's aspirin (ASA) plus the novel anti-platelet therapy ticagrelor, followed by 23 month's ticagrelor monotherapy; or a reference treatment strategy of 12 month's dual anti-platelet therapy (ASA plus ticagrelor for ACS patients; ASA plus clopidogrel for elective patients), followed by 12 month's ASA monotherapy. Recruitment is due to commence by the end of this year in what will be the largest ever randomised clinical trial involving a DES. Patients will be followed up for two years. This latest plan for the trial represents an evolution in the concept, protocol, management and support of GLOBAL LEADERS as announced at EuroPCR last year, which it supersedes and replaces.

GLOBAL LEADERS is being independently designed, implemented and analysed by the study investigators, led by Patrick W. Serruys (Erasmus Medical Center, Rotterdam, Netherlands), Stephan Windecker(University Hospital, Bern, Switzerland) and Marco Valgimigli (University of Ferrara, Italy).