האם יש חשיבות למתן מעכבי GPIIb/IIIa בחולים עם STEMI בעידן של מעכבי טסיות פומיים פוטנטיים ? נגד

פרופ' אלי לב

מנהל היחידה לצנתורי לב

בית חולים השרון, מרכז רפואי רבין

אוניברסיטת ת"א

OUTLINE

- Pharmacodynamic considerations
- Clinical data regarding the current role of GP IIb/IIIa inhibitors in patients with STEMI:

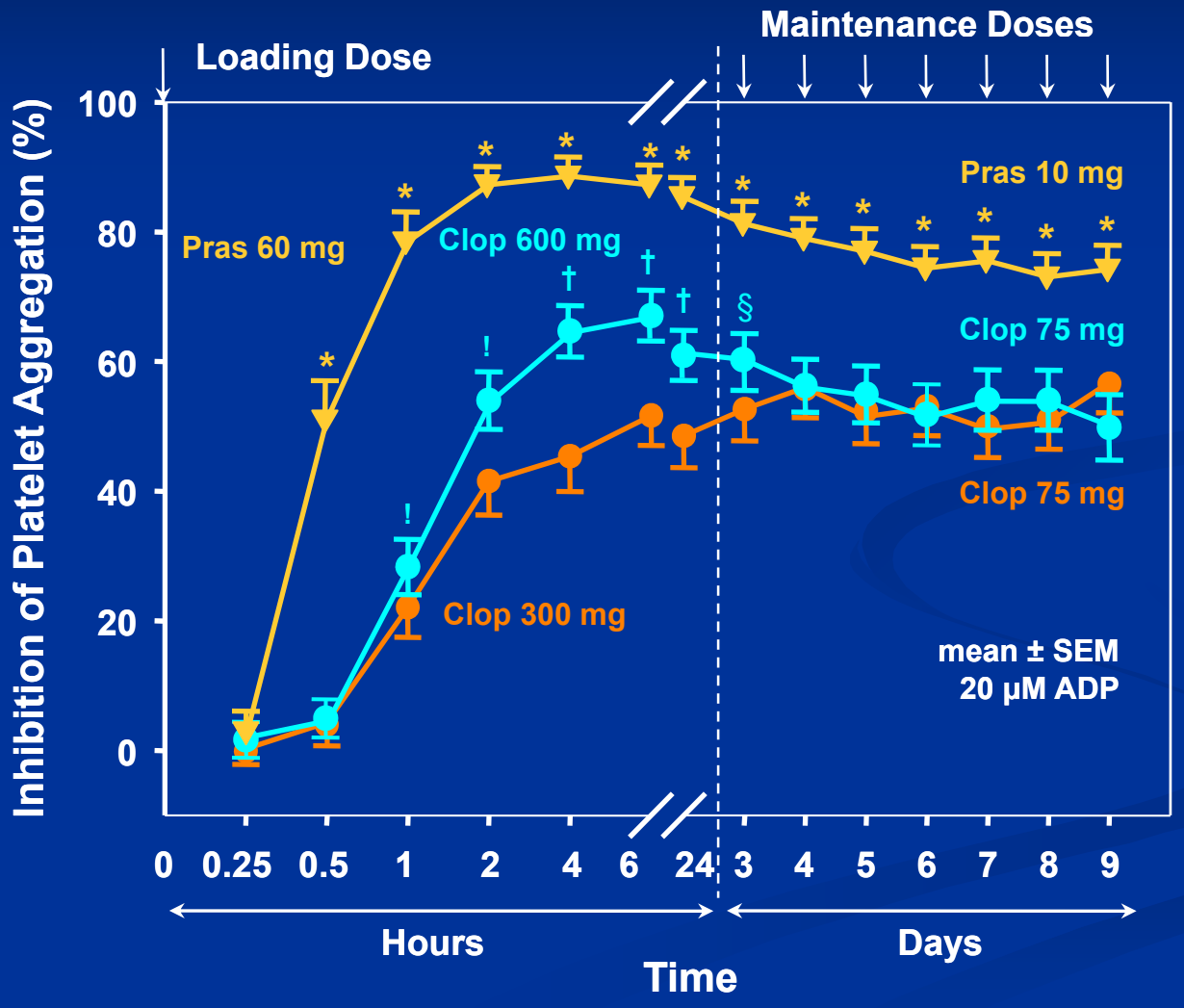
1. GP IIb/IIIa inhibitors following clopidogel 600 mg loading
2. GP IIb/IIIa inhibitors in patients treated with prasugrel
3. GP IIb/IIIa inhibitors in patients treated with ticagrelor

OUTLINE

- Pharmacodynamic considerations
- Clinical data regarding the current role of GP IIb/IIIa inhibitors in patients with STEMI:

1. GP IIb/IIIa inhibitors following clopidogel 600 mg loading
2. GP IIb/IIIa inhibitors in patients treated with prasugrel
3. GP IIb/IIIa inhibitors in patients treated with ticagrelor

Prasugrel 60/10 mg vs Clopidogrel 300-600/75 mg in healthy volunteers



* *P*<0.001 vs. Clop 300 mg or 600 mg LD

† *P*<0.001 vs. Clop 300

! *P*<0.05 vs. Clop 300

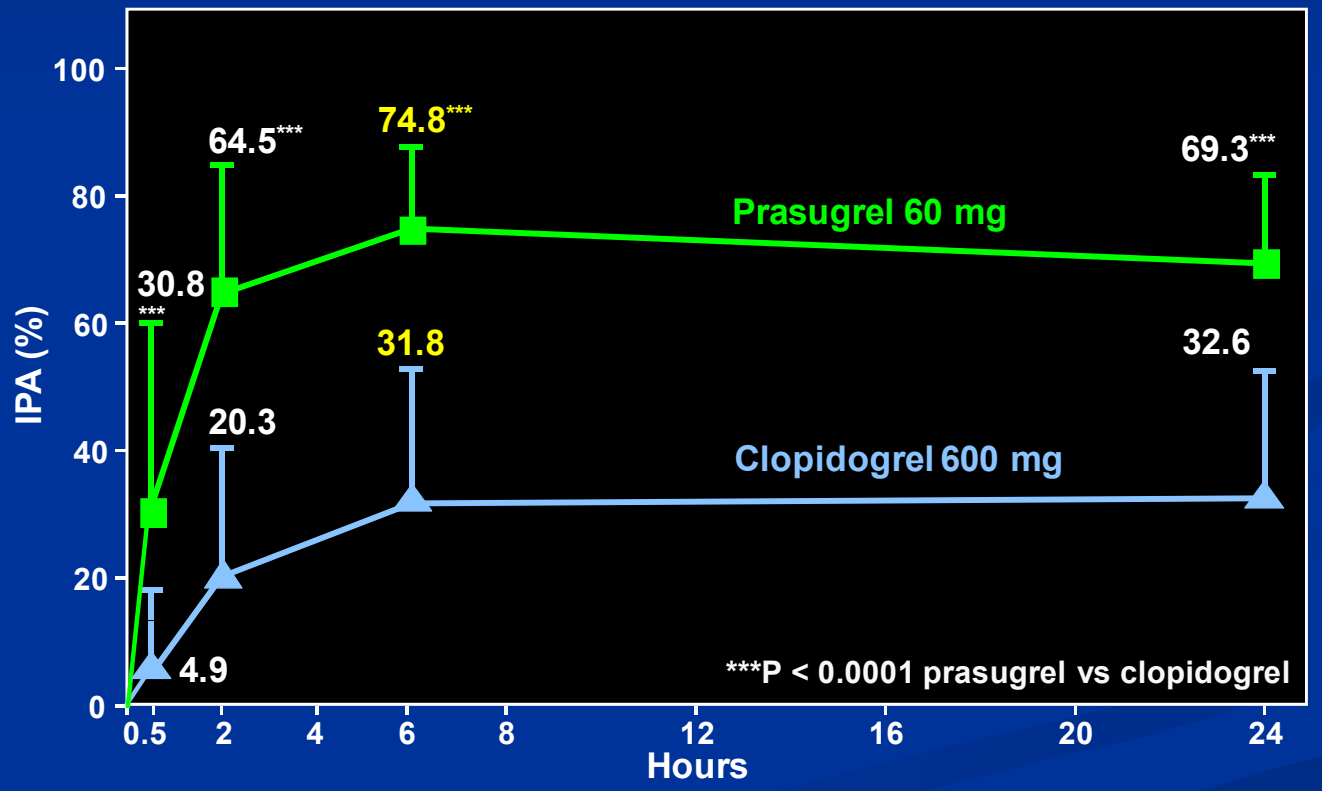
§ *P*<0.05 vs Clop 300/75

Jakubowski, J Payne CD et al. J Cardiovasc Pharmacol 2006

PRINCIPLE-TIMI 44 – loading phase

Primary End Point: LD Phase
IPA (20 µM ADP)

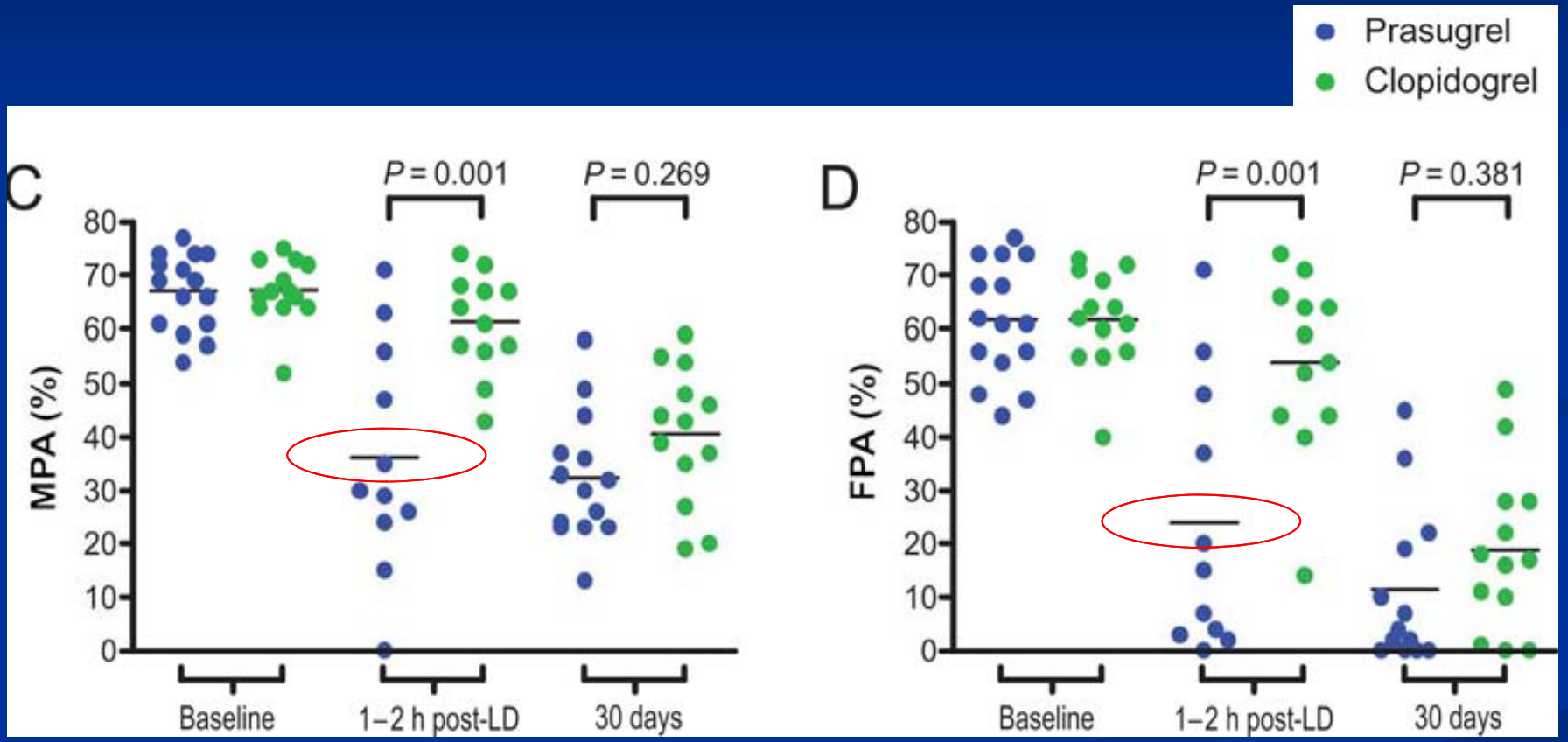
PRINCIPLE
TIMI 44



Primary efficacy end point was IPA at 6 hours.
ADP=Adenosine Diphosphate; IPA=Inhibition of Platelet Aggregation; LD=Loading Dose
Wiviott SD et al. *Circulation* 2007;116:2923-2932

201 pts undergoing planned elective PCI, 28 day crossover design. *Wiviott et al, Circulation 2007*

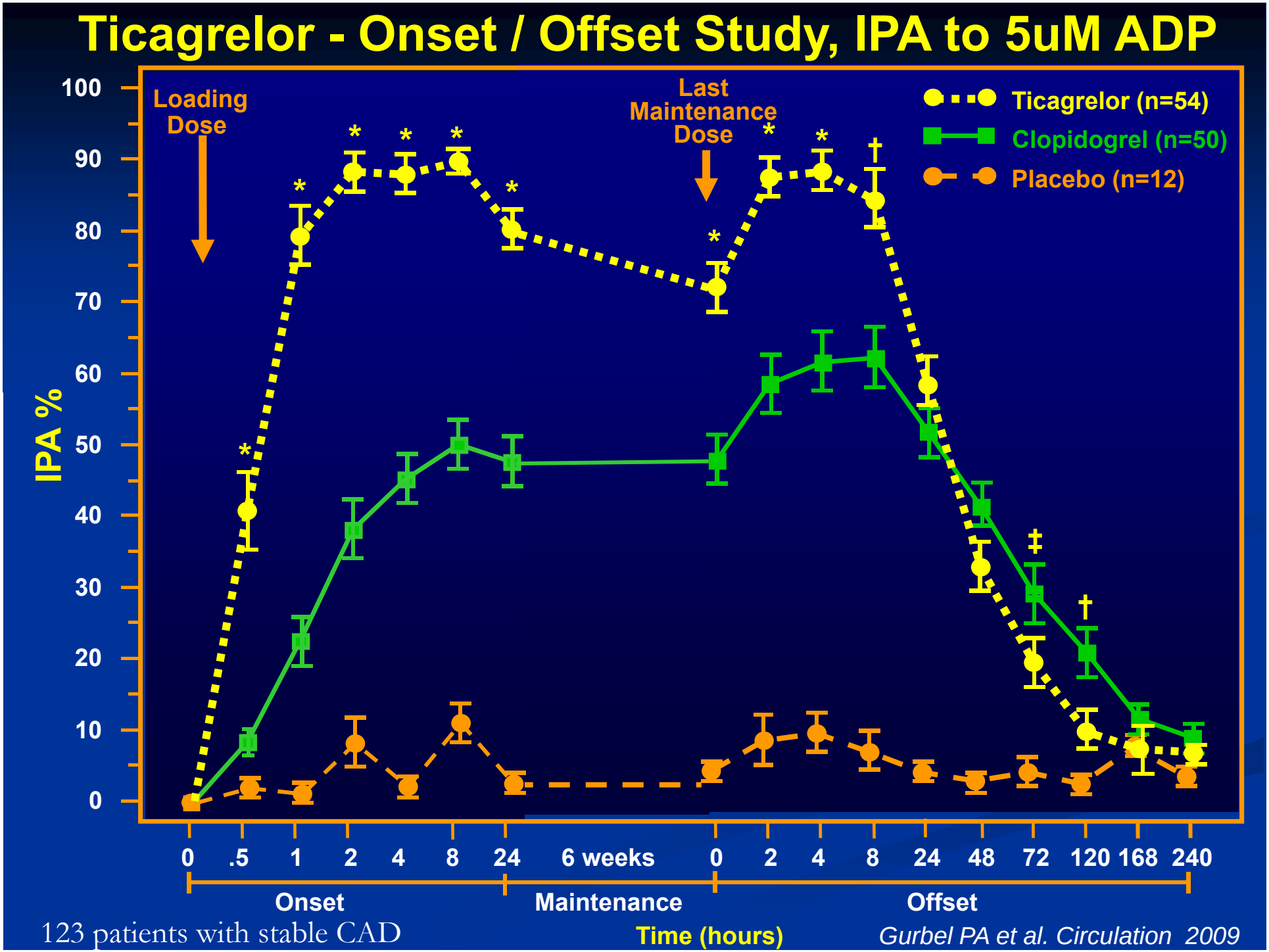
Pharmacodynamic substudy of TRITON - ACS patients



Aggregation in response to 5 microM ADP

Michelson AD, EHJ 2009

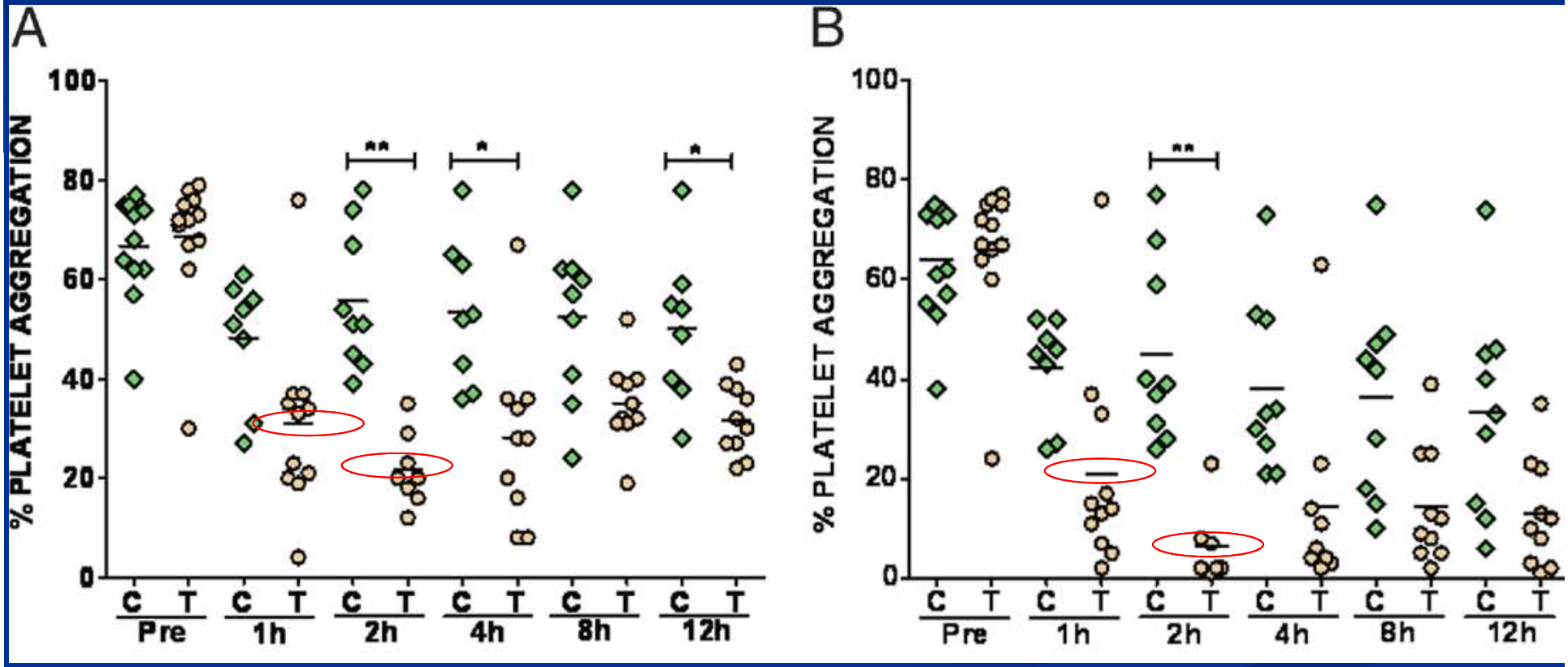
Ticagrelor - Onset / Offset Study, IPA to 5uM ADP



123 patients with stable CAD

Gurbel PA et al. Circulation 2009

PLATO – PLATELET substudy



Aggregation in response to 20 microM ADP

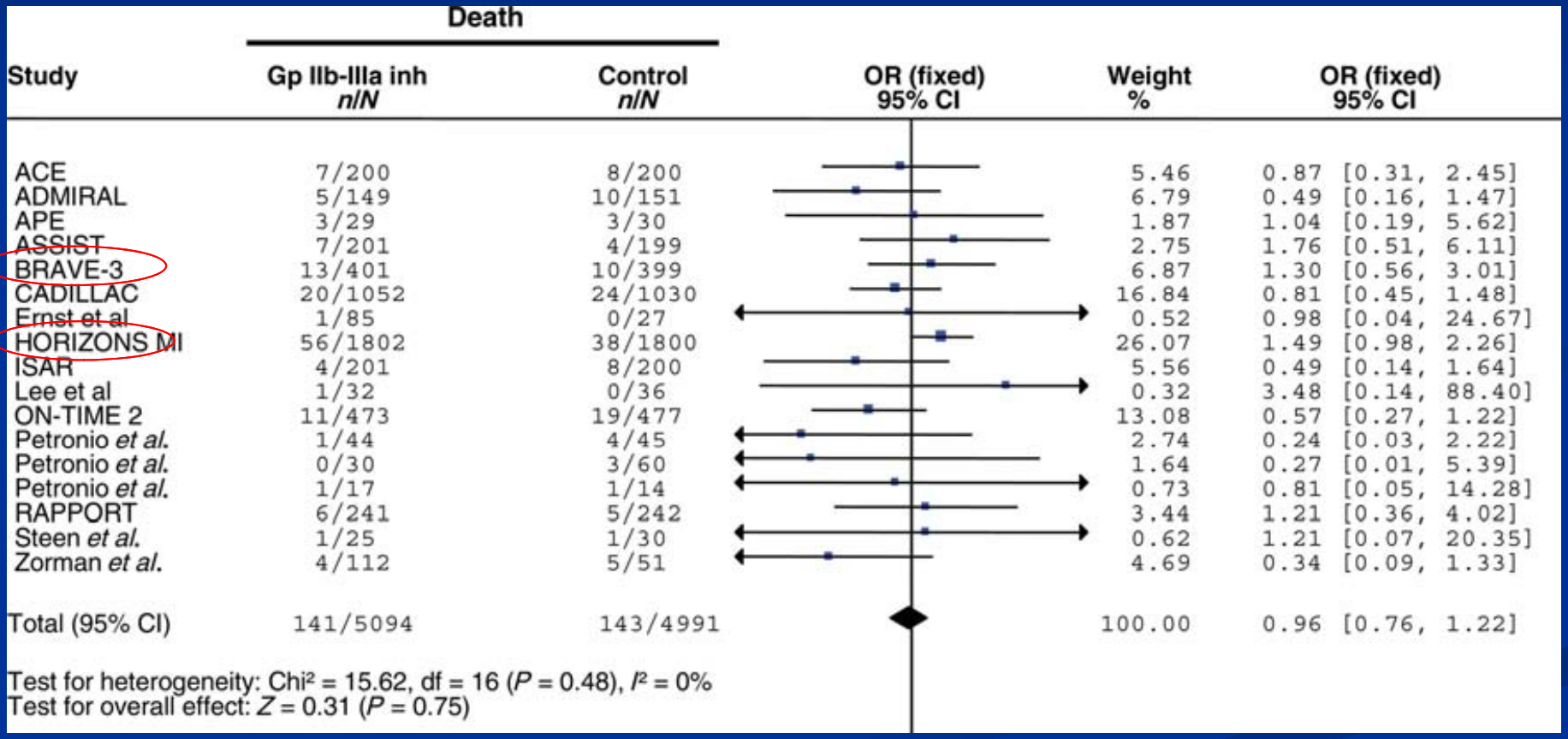
Storey et al, JACC 2010

OUTLINE

- Pharmacodynamic considerations
- **Clinical data regarding the current role of GP IIb/IIIa inhibitors in patients with STEMI:**

1. GP IIb/IIIa inhibitors following clopidogel 600 mg loading
2. GP IIb/IIIa inhibitors in patients treated with prasugrel
3. GP IIb/IIIa inhibitors in patients treated with ticagrelor

Updated meta-analysis of effect of GPIs on 30 day mortality in pts with STEMI



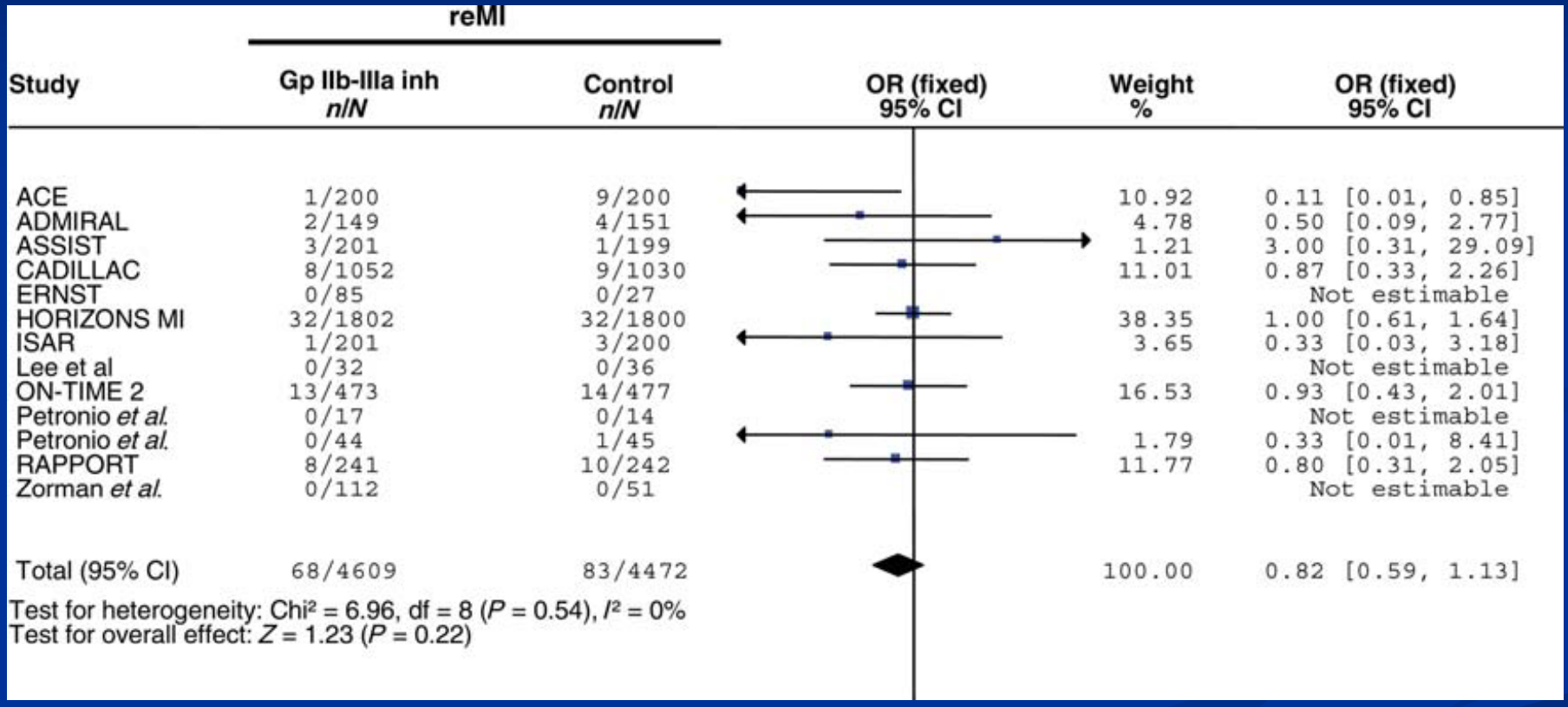
Study	Death: Gp IIb-IIIa inh *n/N*	Death: Control *n/N*	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
ACE	7/200	8/200		5.46	0.87 [0.31, 2.45]
ADMIRAL	5/149	10/151		6.79	0.49 [0.16, 1.47]
APE	3/29	3/30		1.87	1.04 [0.19, 5.62]
ASSIST	7/201	4/199		2.75	1.76 [0.51, 6.11]
BRAVE-3	13/401	10/399		6.87	1.30 [0.56, 3.01]
CADILLAC	20/1052	24/1030		16.84	0.81 [0.45, 1.48]
Ernst et al	1/85	0/27		0.52	0.98 [0.04, 24.67]
HORIZONS MI	56/1802	38/1800		26.07	1.49 [0.98, 2.26]
ISAR	4/201	8/200		5.56	0.49 [0.14, 1.64]
Lee et al	1/32	0/36		0.32	3.48 [0.14, 88.40]
ON-TIME 2	11/473	19/477		13.08	0.57 [0.27, 1.22]
Petronio *et al.*	1/44	4/45		2.74	0.24 [0.03, 2.22]
Petronio *et al.*	0/30	3/60		1.64	0.27 [0.01, 5.39]
Petronio *et al.*	1/17	1/14		0.73	0.81 [0.05, 14.28]
RAPPORT	6/241	5/242		3.44	1.21 [0.36, 4.02]
Steen *et al.*	1/25	1/30		0.62	1.21 [0.07, 20.35]
Zorman *et al.*	4/112	5/51		4.69	0.34 [0.09, 1.33]
Total (95% CI)	141/5094	143/4991		100.00	0.96 [0.76, 1.22]

Test for heterogeneity: $Chi^2 = 15.62$, df = 16 ($P = 0.48$), $I^2 = 0\%$
Test for overall effect: $Z = 0.31$ ($P = 0.75$)

Favors GPIs Favors Control

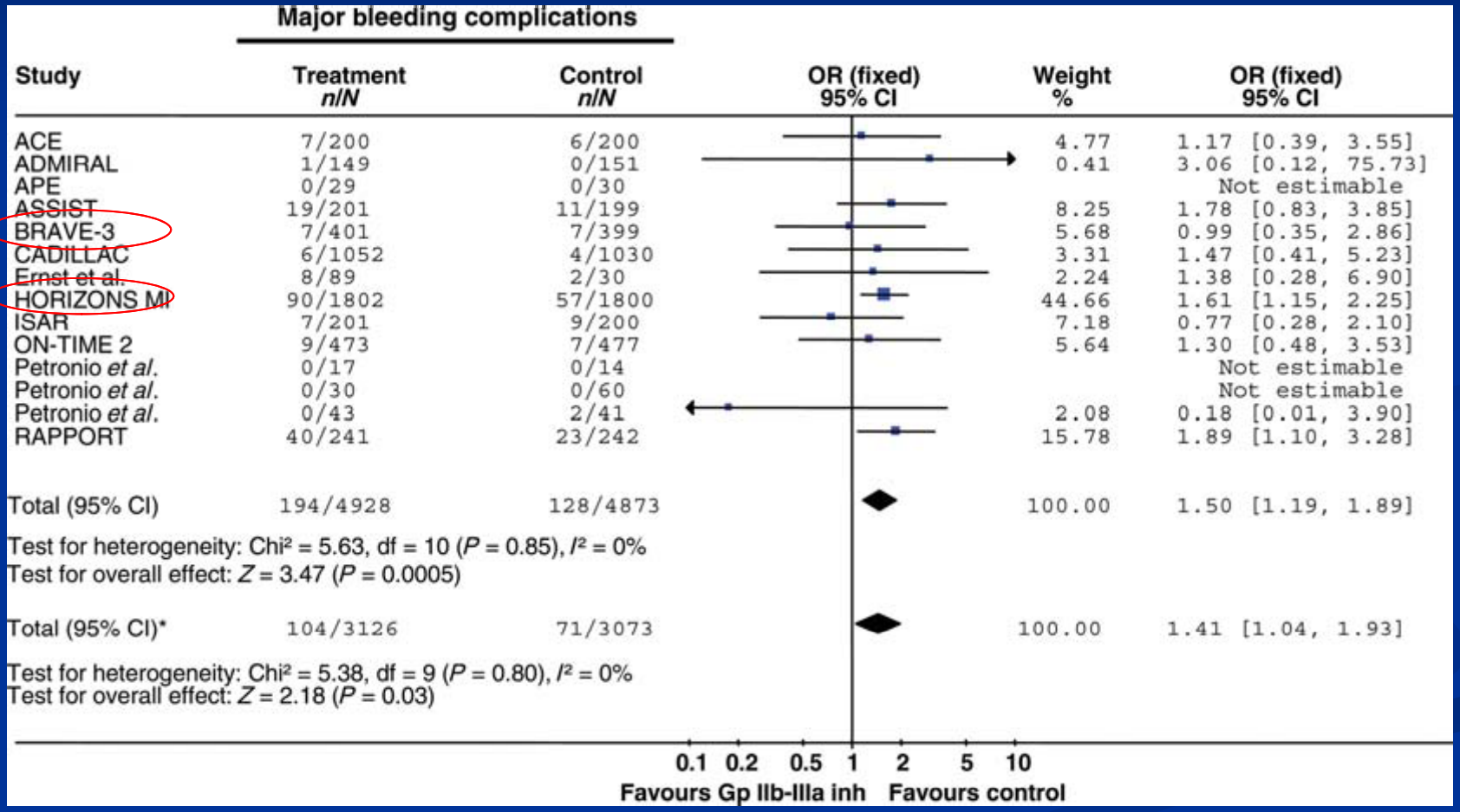
De Luca rt al, EHJ 2009

Updated meta-analysis of effect of GP IIb/IIIa inhibitors on 30 day re-MI



De Luca rt al, EHJ 2009

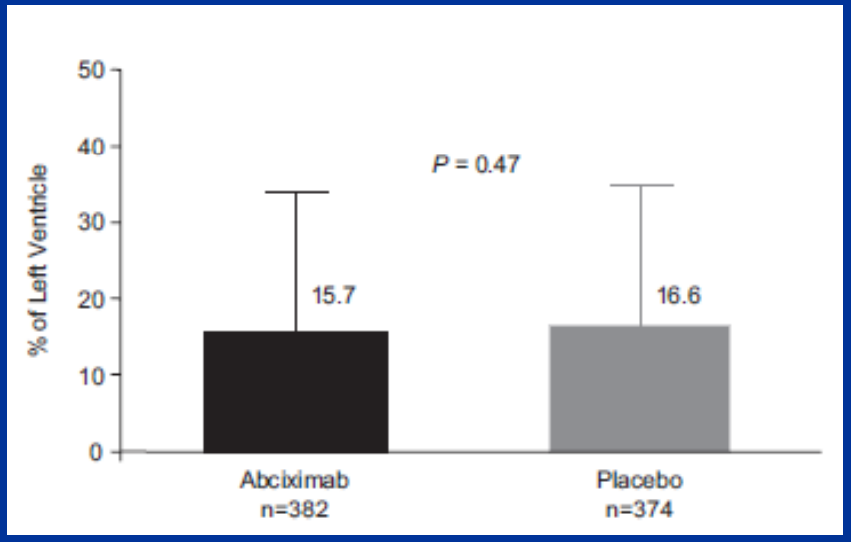
Updated meta-analysis of effect of GP IIb/IIIa inhibitors on major bleeding



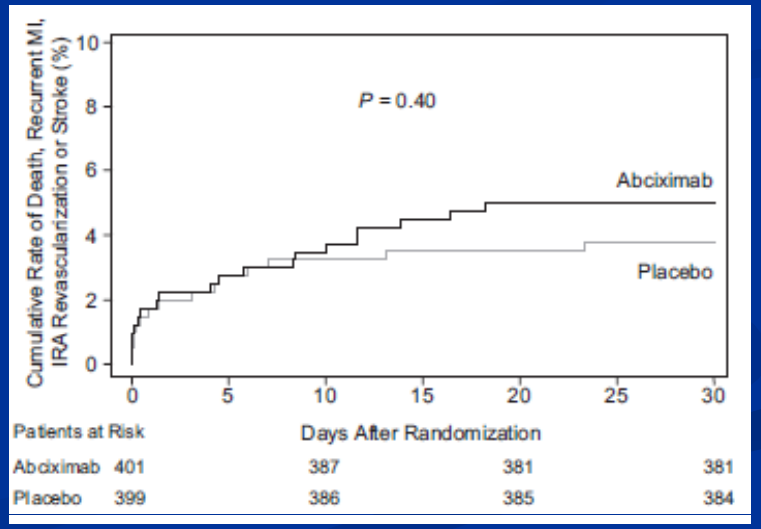
De Luca rt al, EHJ 2009

BRAVE-3 Trial

- 800 patients with acute STEMI, all treated with 600 mg clopidogrel, were randomly assigned receive either abciximab (for 12 hrs) or placebo in the ICU before being sent to the cath lab for 1º PCI
- The primary end point, infarct size measured by SPECT before hospital discharge



Primary endpoint

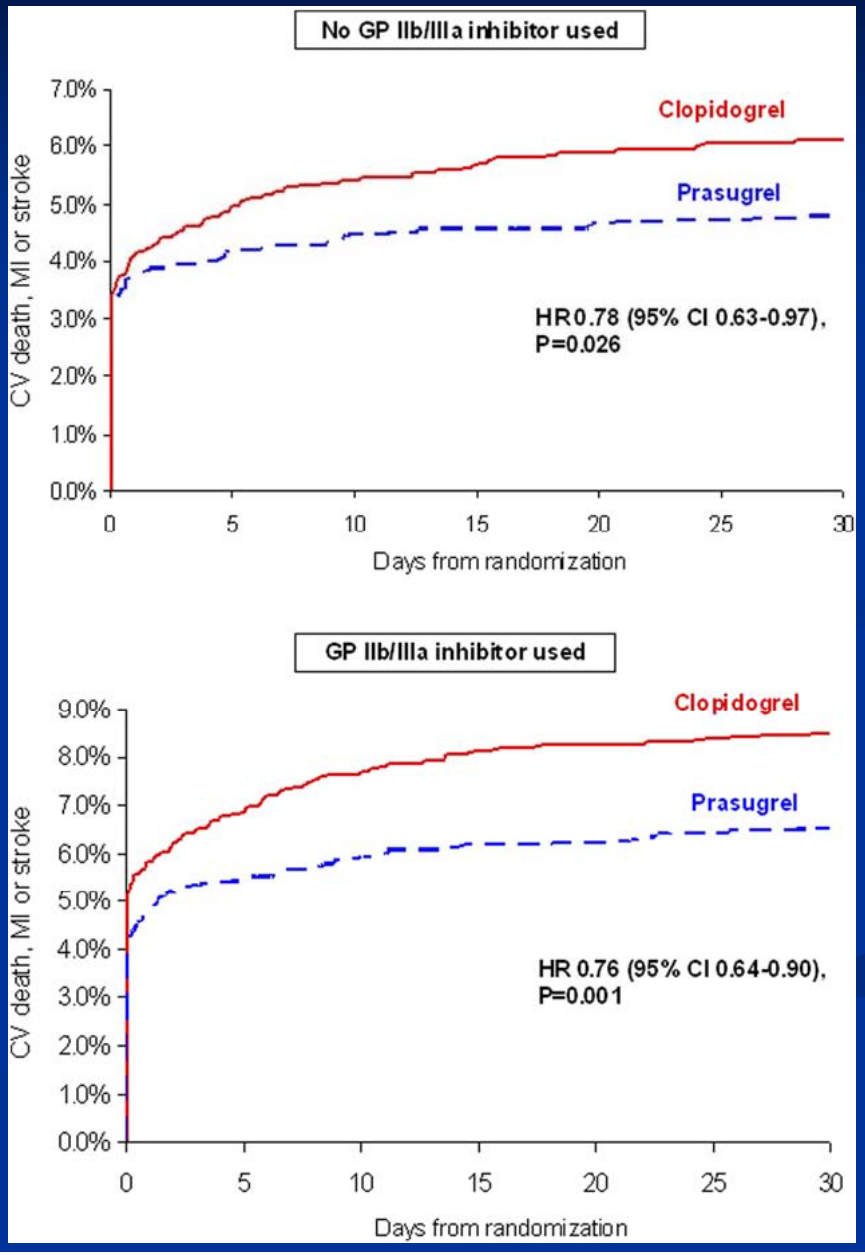


MACE

Mehilli et al, Circulation 2009

GPIIb/IIIa's and prasugrel in the TRITON

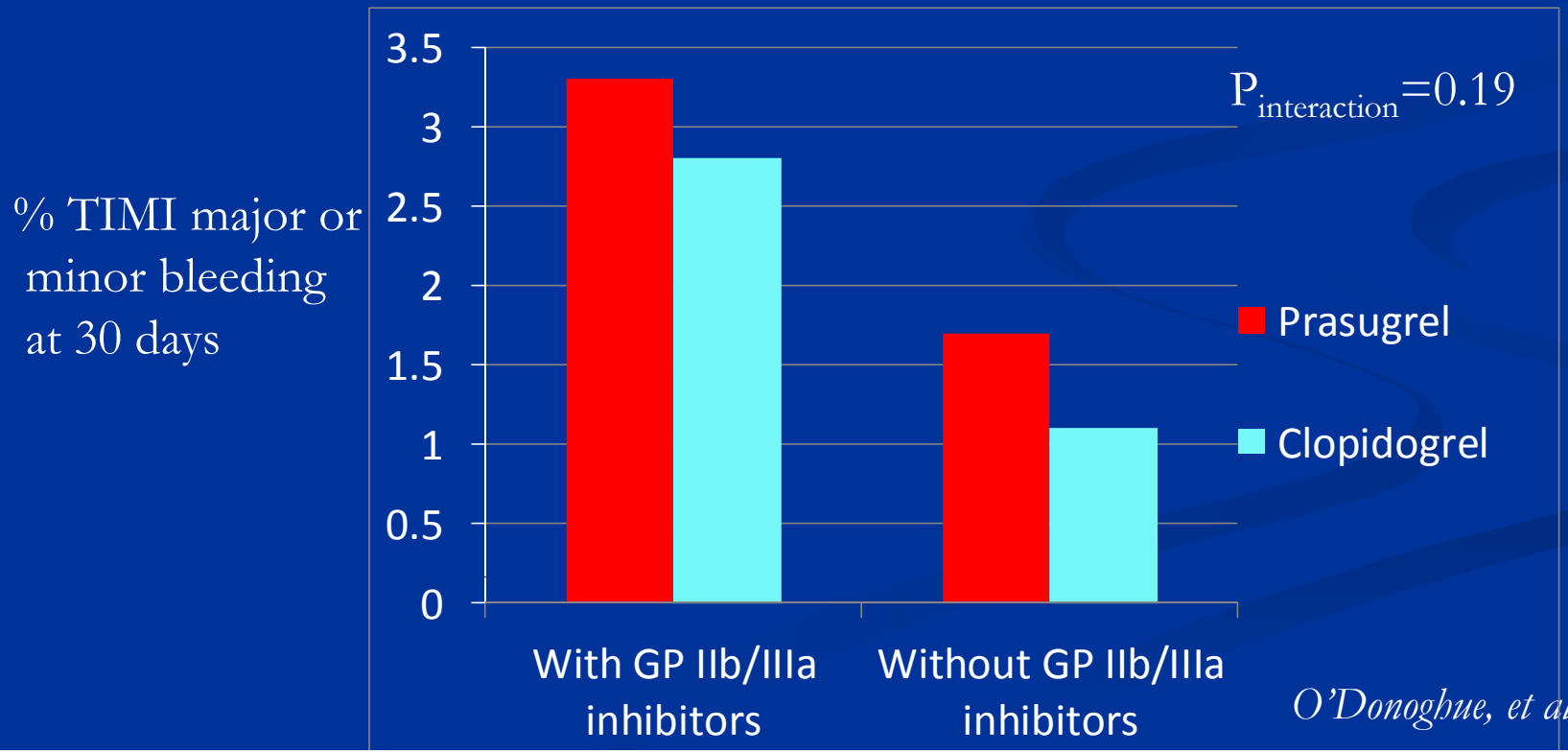
- In pts with STEMI 27% received the study drug as pre-treatment
- 54% of the pts received GP IIB/IIIa inhibitors (STEMI pts – 63%)
- Prasugrel significantly reduced the risk of MACE regardless of whether or not a GP IIb/IIIa inhibitor was used ($P_{interaction}$=0.8)



O'Donoghue, et al, JACC 2009

GPIIb/IIIa's and prasugrel in the TRITON
Effect on bleeding

- Although the relative risk of TIMI major or minor bleeding with prasugrel vs. clopidogrel was not sig. affected by the use of GP IIb/IIIa inhibitors, **"subjects treated with a GP IIb/IIIa inhibitor had greater rates of bleeding"**



O'Donoghue, et al, JACC 2009

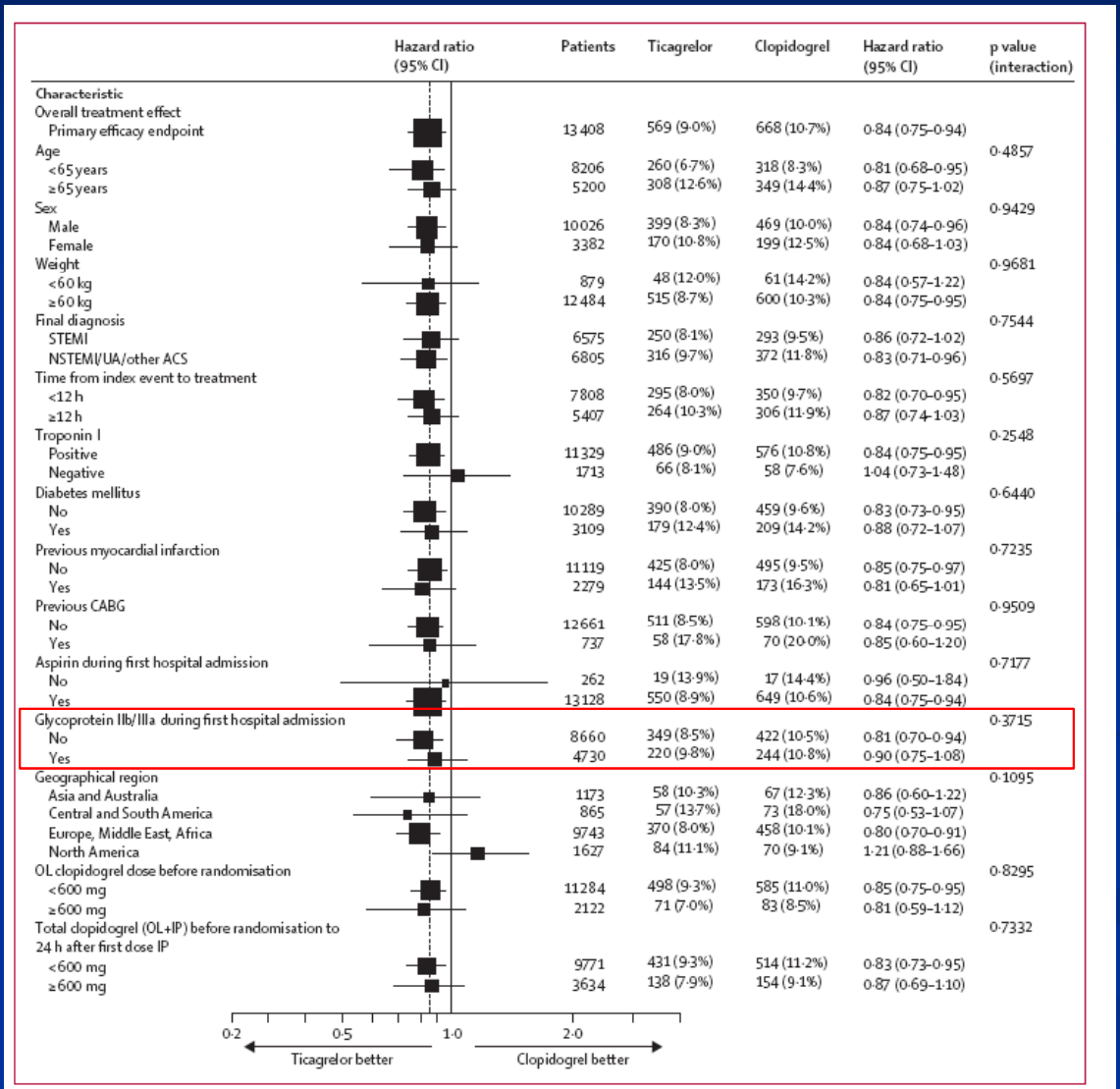
GPIIb/IIIa's in the TRITON
Effect on bleeding

Predictors of serious bleeding

	HR (95% CI)	*P*	Strength of Association With Bleeding*
Predictors of any serious bleeding			
Female sex	1.77 (1.44–2.18)	<0.001	28.79
GPIIb/IIIa inhibitor used	1.59 (1.29–1.95)	<0.001	19.33
Duration of intervention, per 10-min intervals	1.07 (1.04–1.10)	<0.001	17.98
Age, by decade	1.22 (1.09–1.38)	<0.001	11.07
Assignment to prasugrel, vs clopidogrel	1.34 (1.12–1.60)	0.001	10.19
ST-segment elevation myocardial infarction	1.35 (1.10–1.66)	0.005	7.98
Femoral access	1.60 (1.07–2.39)	0.02	5.23
Creatinine clearance, per 10 mL/min decrease	1.05 (1.01–1.09)	0.03	4.84

Hocholzer et al, Circulation 2011

GPIIb/IIIa's and ticagrelor in the PLATO



Characteristic	Patients	Ticagrelor	Clopidogrel	Hazard ratio (95% CI)	p value (interaction)
Overall treatment effect					
Primary efficacy endpoint	13 408	569 (9·0%)	668 (10·7%)	0·84 (0·75–0·94)	
Age					0·4857
<65 years	8206	260 (6·7%)	318 (8·3%)	0·81 (0·68–0·95)	
≥65 years	5200	308 (12·6%)	349 (14·4%)	0·87 (0·75–1·02)	
Sex					0·9429
Male	10 026	399 (8·3%)	469 (10·0%)	0·84 (0·74–0·96)	
Female	3382	170 (10·8%)	199 (12·5%)	0·84 (0·68–1·03)	
Weight					0·9681
<60 kg	879	48 (12·0%)	61 (14·2%)	0·84 (0·57–1·22)	
≥60 kg	12 484	515 (8·7%)	600 (10·3%)	0·84 (0·75–0·95)	
Final diagnosis					0·7544
STEMI	6575	250 (8·1%)	293 (9·5%)	0·86 (0·72–1·02)	
NSTEMI/UA/other ACS	6805	316 (9·7%)	372 (11·8%)	0·83 (0·71–0·96)	
Time from index event to treatment					0·5697
<12 h	7808	295 (8·0%)	350 (9·7%)	0·82 (0·70–0·95)	
≥12 h	5407	264 (10·3%)	306 (11·9%)	0·87 (0·74–1·03)	
Troponin I					0·2548
Positive	11 329	486 (9·0%)	576 (10·8%)	0·84 (0·75–0·95)	
Negative	1713	66 (8·1%)	58 (7·6%)	1·04 (0·73–1·48)	
Diabetes mellitus					0·6440
No	10 289	390 (8·0%)	459 (9·6%)	0·83 (0·73–0·95)	
Yes	3109	179 (12·4%)	209 (14·2%)	0·88 (0·72–1·07)	
Previous myocardial infarction					0·7235
No	11 119	425 (8·0%)	495 (9·5%)	0·85 (0·75–0·97)	
Yes	2279	144 (13·5%)	173 (16·3%)	0·81 (0·65–1·01)	
Previous CABG					0·9509
No	12 661	511 (8·5%)	598 (10·1%)	0·84 (0·75–0·95)	
Yes	737	58 (17·8%)	70 (20·0%)	0·85 (0·60–1·20)	
Aspirin during first hospital admission					0·7177
No	262	19 (13·9%)	17 (14·4%)	0·96 (0·50–1·84)	
Yes	13 128	550 (8·9%)	649 (10·6%)	0·84 (0·75–0·94)	
Glycoprotein IIb/IIIa during first hospital admission					0·3715
No	8660	349 (8·5%)	422 (10·5%)	0·81 (0·70–0·94)	
Yes	4730	220 (9·8%)	244 (10·8%)	0·90 (0·75–1·08)	
Geographical region					0·1095
Asia and Australia	1173	58 (10·3%)	67 (12·3%)	0·86 (0·60–1·22)	
Central and South America	865	57 (13·7%)	73 (18·0%)	0·75 (0·53–1·07)	
Europe, Middle East, Africa	9743	370 (8·0%)	458 (10·1%)	0·80 (0·70–0·91)	
North America	1627	84 (11·1%)	70 (9·1%)	1·21 (0·88–1·66)	
OL clopidogrel dose before randomisation					0·8295
<600 mg	11 284	498 (9·3%)	585 (11·0%)	0·85 (0·75–0·95)	
≥600 mg	2122	71 (7·0%)	83 (8·5%)	0·81 (0·59–1·12)	
Total clopidogrel (OL+IP) before randomisation to 24 h after first dose IP					0·7332
<600 mg	9771	431 (9·3%)	514 (11·2%)	0·83 (0·73–0·95)	
≥600 mg	3634	138 (7·9%)	154 (9·1%)	0·87 (0·69–1·10)	

Efficacy endpoint - MACE

PLATO INVASIVE SUBGROUP ANALYSIS

27% of pts in total cohort received GPIs, 35% of STEMI pts

Cannon C, Lancet 2010;375:283-93

GPIIb/IIIa's and ticagrelor in the PLATO

- **GPIIb/IIIa inhibitor use independently associated with higher risk of non-CABG related major bleeding.**
- Sig. interaction between GPIIb/IIIa inhibitor use and differential bleeding effects of ticagrelor vs. clopidogrel ($P_{interaction}$=0.017)
- Clopidogrel group: pts receiving GP IIb/IIIa inhib. were at sig. higher risk of non-CABG major bleeding (HR 2.02; 95% CI 1.53–2.67)
- Ticagrelor group: a numerical increase in the risk of non_CABG major bleeding in pts receiving GP IIb/IIIa inhib. (HR 1.26; 95% CI 0.96–1.66).

Becker et al, EHJ 2011

Study Design

HORIZONS-AMI

3602 pts with STEMI with symptom onset ≤12 hours

Aspirin, clopidogrel

R
1:1

UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)

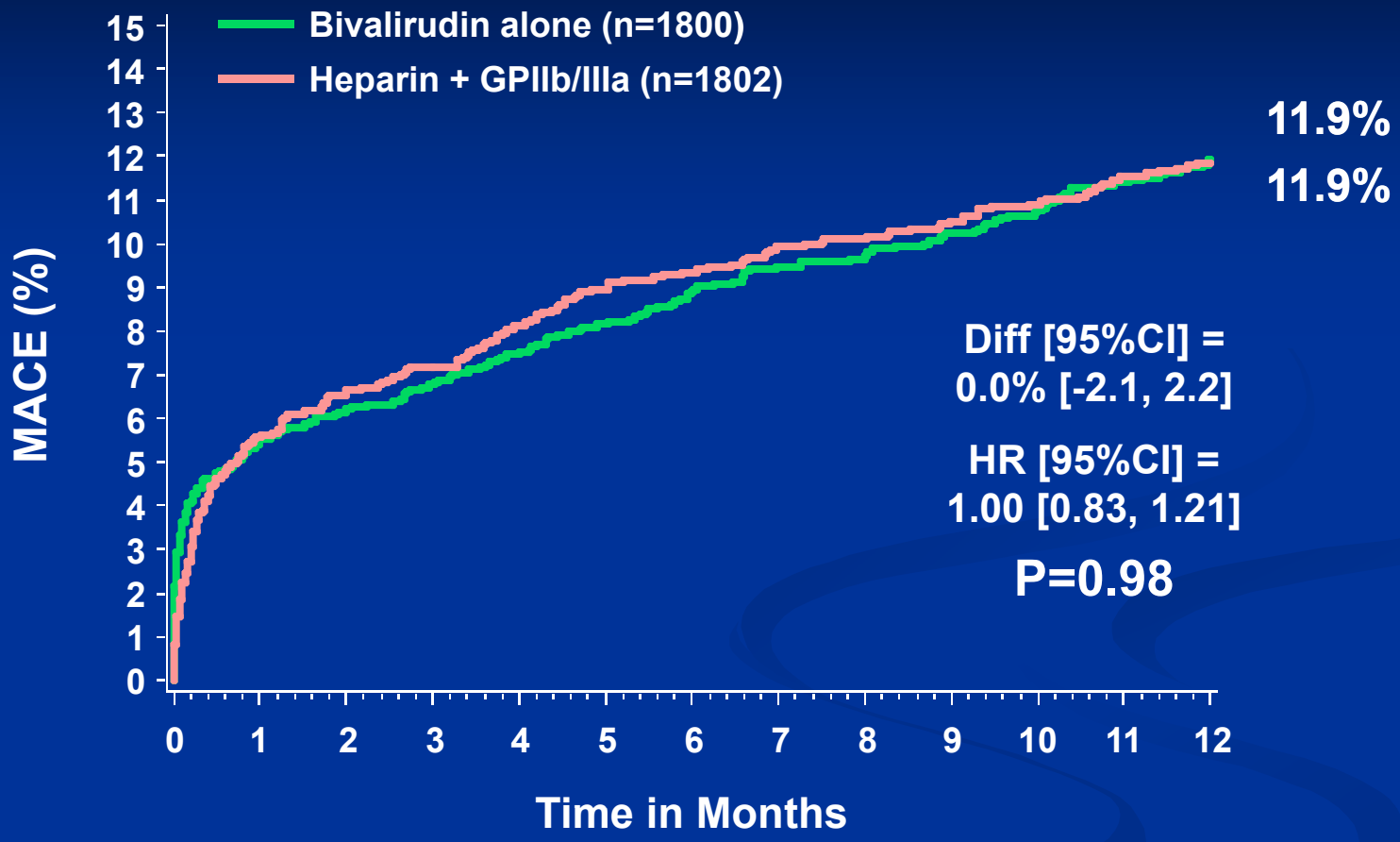
Bivalirudin monotherapy (± provisional GP IIb/IIIa)

Primary PCI

Clinical FU at 30 days, 6 months,
1 year, and then yearly through 5 years

Stone G et al, NEJM 2008, Lancet 2009

HORIZONS AMI - 1-Year Major Adverse CV Events
3602 patients with STEMI

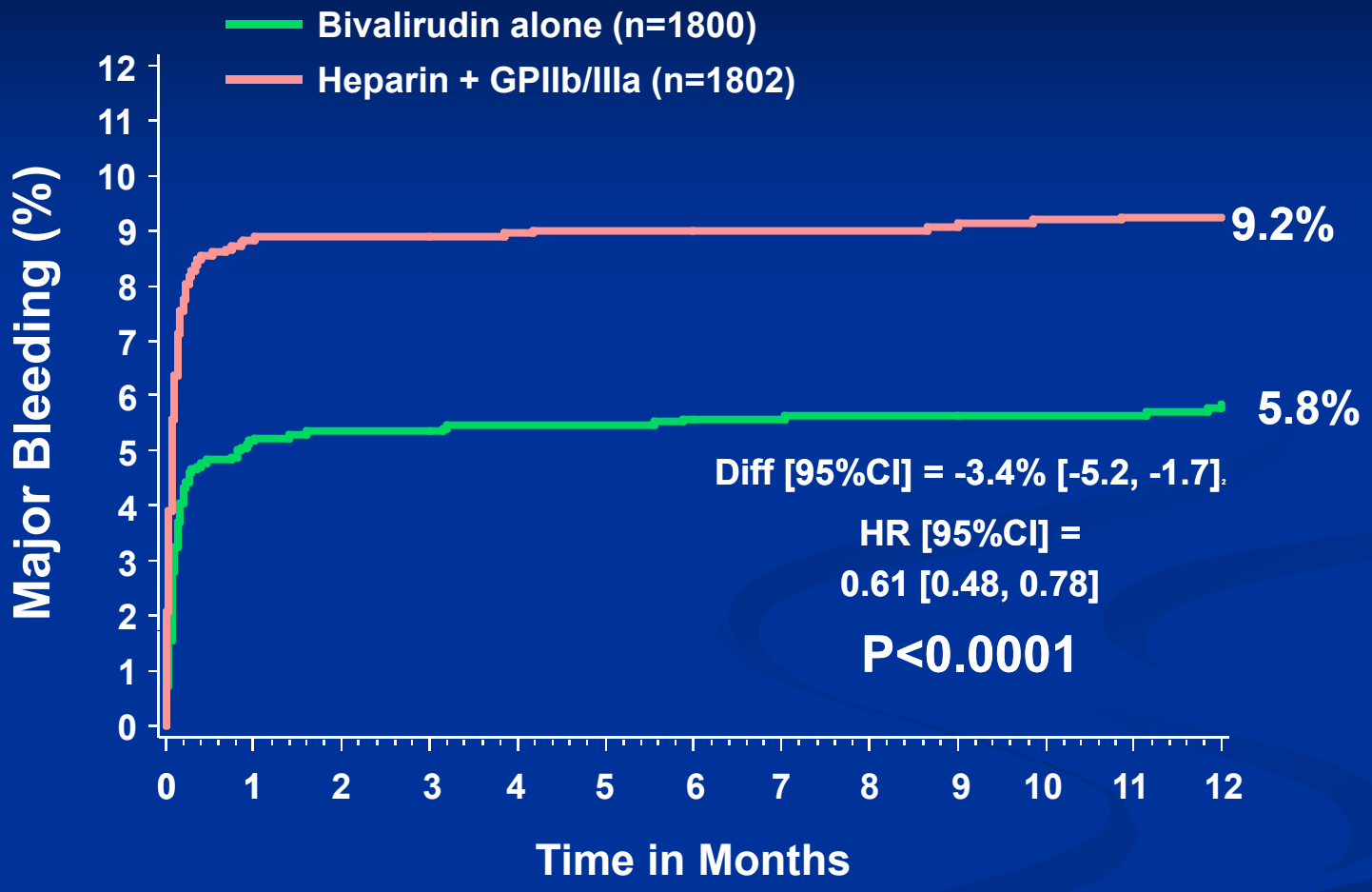


Number at risk					
Bivalirudin alone	1800	1627	1579	1544	1394
Heparin+GPIIb/IIIa	1802	1619	1573	1540	1380

*MACE = All cause death, reinfarction, ischemic TVR or stroke

Stone G et al, NEJM 2008, Lancet 2009

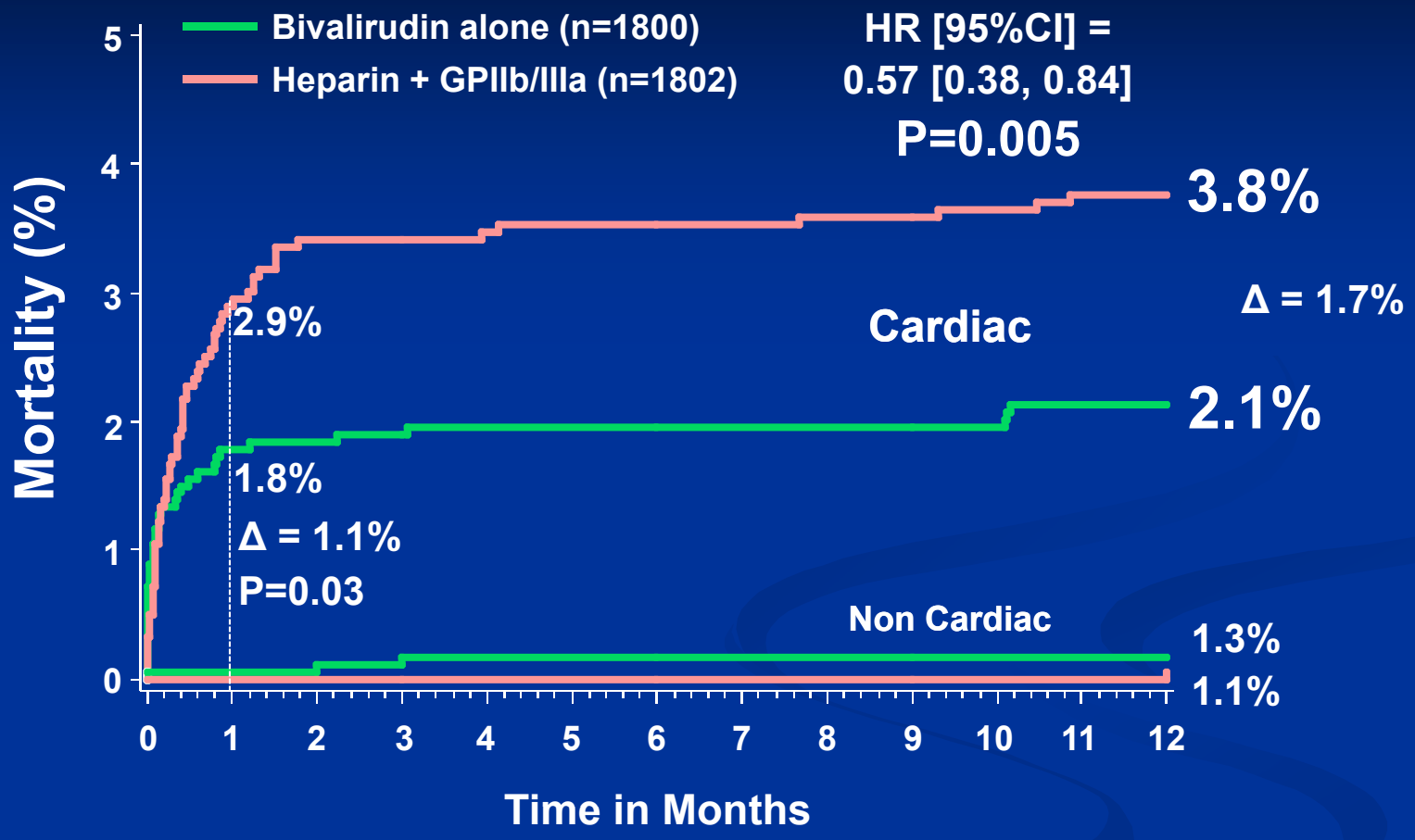
HORIZONS - 1-Year Major Bleeding (non-CABG)



Number at risk					
Bivalirudin alone	1800	1621	1601	1586	1448
Heparin+GPIIb/IIIa	1802	1544	1532	1515	1368

Stone G et al, NEJM 2008, Lancet 2009

HORIZONS AMI 1-Year Mortality



Number at risk

Bivalirudin alone	1800	1705	1684	1669	1520
Heparin+GPIIb/IIIa	1802	1678	1663	1646	1486

Stone G et al, NEJM 2008, Lancet 2009

CONCLUSIONS

1. Pharmaco. - both prasugrel and ticagrelor achieve rapid and potent platelet inhibition – within 2 hrs, close to max. effect (which is similar in magnitude to that of GP IIb/IIIa inhib.)
2. Both prasugrel and ticagrelor are more effective in reducing ischemic events than clopidogrel, regardless of GPIIb/IIIa inhibitor treatment (no sig. interaction)
3. GP IIb/IIIa inhibitor use consistently and independently associated with increased major bleeding rates
4. Bivalirudin compared with heparin + GPIs - safer + ↓mortality
5. I believe GP IIb/IIIa inhibitor use in pts with STEMI treated with new P2Y12 inhib. + primary PCI should be reserved for "bailout" situations - large thrombus load, slow flow etc.

"Clinging" to history and GP IIb/IIIa inhibitors

THANK YOU

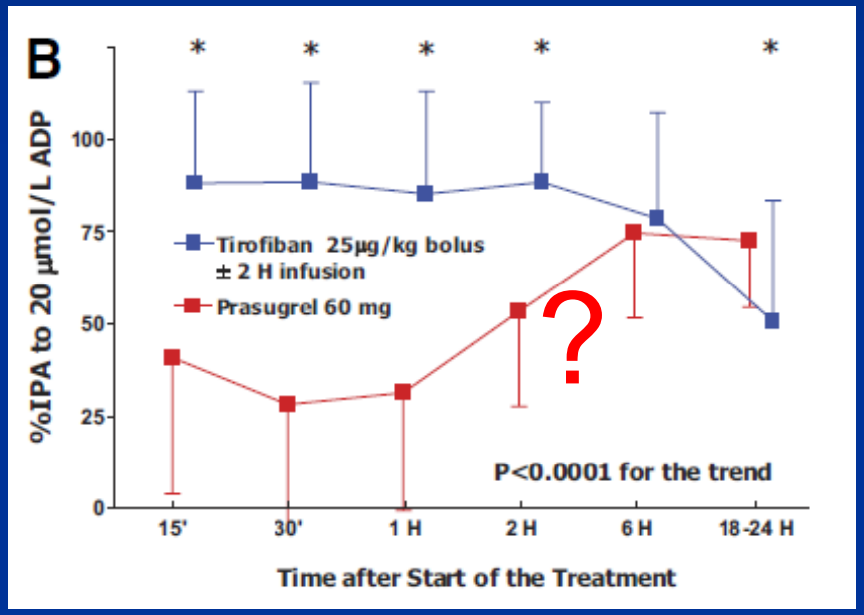
Medical Research

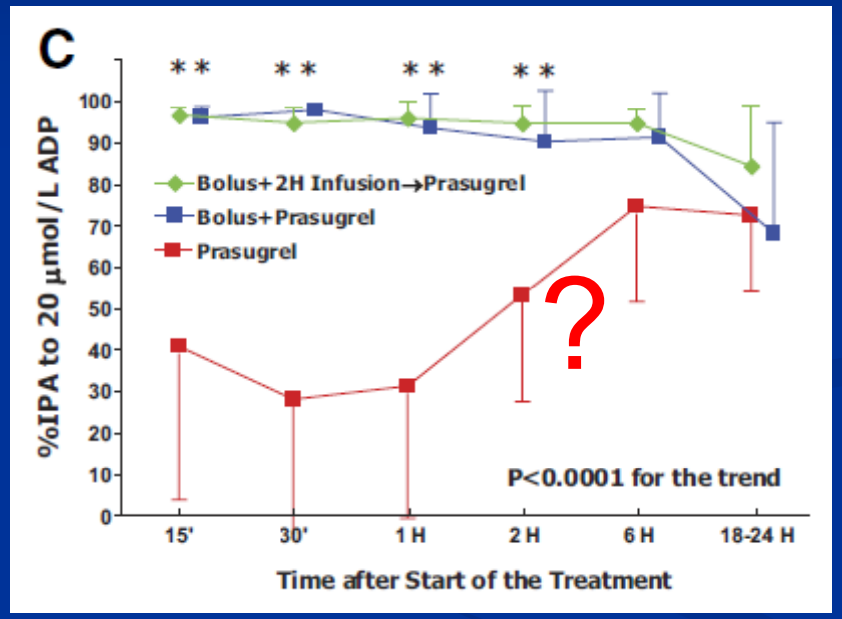
Updated meta-analysis of effect of GP IIb/IIIa inhibitors on 30 day mortality

- Gp IIb-IIIa inhibitors did not reduce 30 day mortality (2.8 vs. 2.9%, P = 0.75)
- Gp IIb-IIIa inhibitors did not reduce re-infarction (1.5 vs. 1.9%, P = 0.22),
- Gp IIb-IIIa inhibitors were associated with higher risk of major bleeding complications (4.1 vs. 2.7%, P = 0.0004).

De Luca rt al, EHJ 2009

FABOLUS-PRO study





100 pts with STEMI randomized to prasugrel or tirofiban bolus ± maint. or ± prasugrel

Valgimigli et al, JACC Interv 2012

GPIIb/IIIa's and prasugrel in the TRITON

Timing of the study drug in the STEMI cohort

	Clopidogrel (n=1765)	Prasugrel (n=1769)
Timing of study drug loading dose		
Pre-PCI (before 1st wire)	27%	27%
During PCI (1st wire to 1 hr after leaving lab)	72%	72%
Post-PCI (>1 h after leaving lab)	1%	1%
GP IIb/IIIa use	64%	62%

Montalescot et al, Lancet 2009