The Efficacy of Early versus Delayed P2Y12 Inhibition in Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction: *A Systematic Review and Meta-Analysis*

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for the ACTION Study Group

CENTRE HOSPITALIER ANTIBES JUAN-LES-PINS

DISCLOSURES

- ✓ Personal disclosures: Research grants from Daiichi-Sankyo, Eli Lilly, Fédération Française de Cardiologie and Société Française de Cardiologie, consulting fees from AstraZeneca, Daiichi-Sankyo and Eli Lilly, and speaker honoraria from AstraZeneca, Daiichi-Sankyo, Servier, Biotronik and Novartis

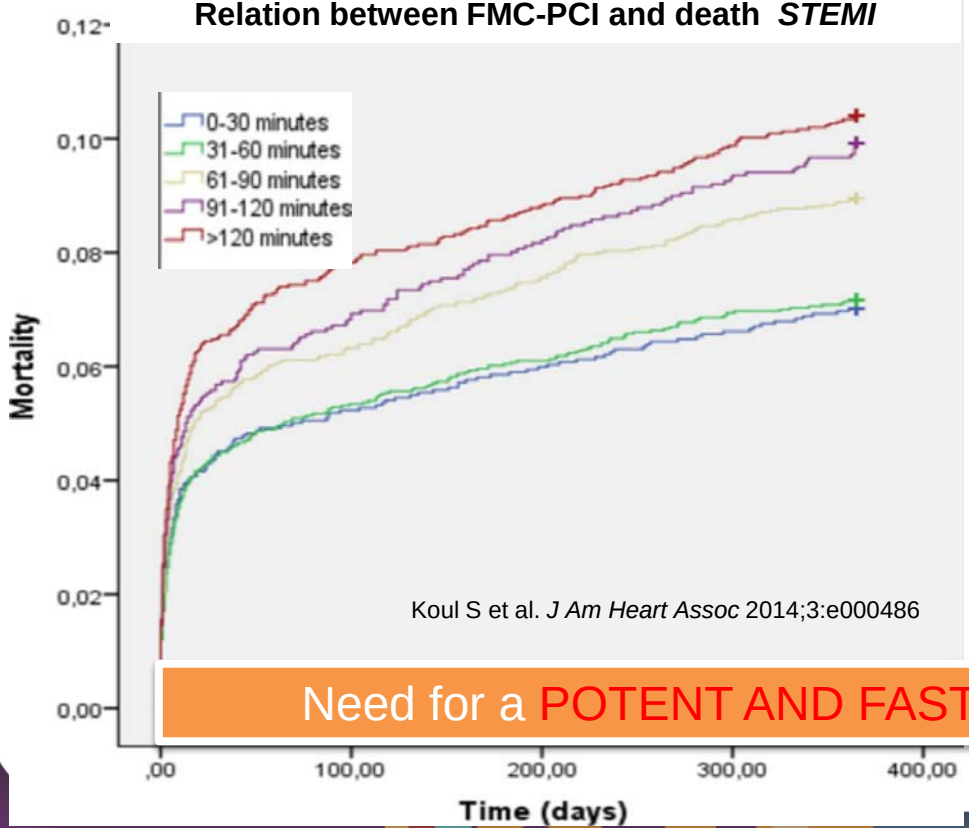
- ✓ There was no external source of funding

- ✓ This meta-analysis was led by the academic ACTION-study-group (www.action-coeur.org).

Background

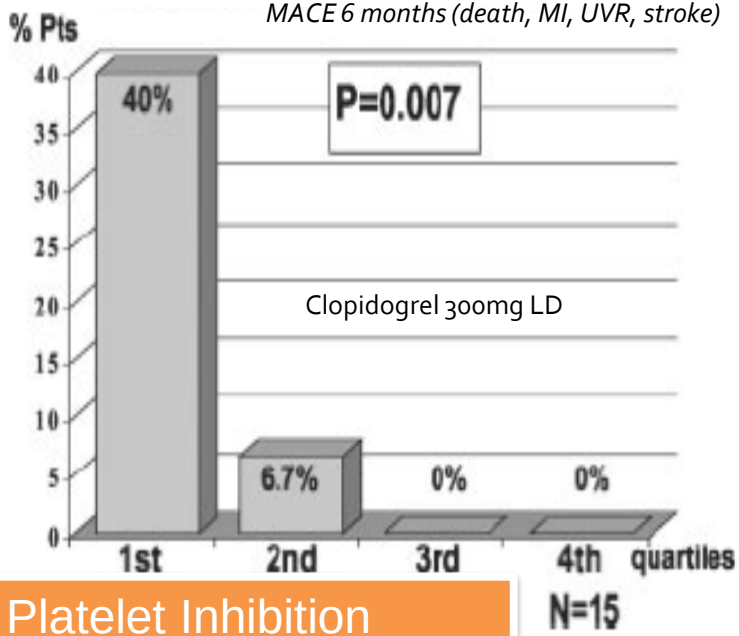
PRIMARY PCI OF STEMI: *Platelet inhibition and MACEs*

Relation between FMC-PCI and death *STEMI*



Koul S et al. *J Am Heart Assoc* 2014;3:e000486

Relation between Platelet reactivity-MACEs *STEMI*



Need for a POTENT AND FAST Platelet Inhibition

Matetzky et al., *Circulation*, 2004;109:3171-3175

CLOPIDOGREL pre-treatment primary PCI of STEMI

META-ANALYSIS Primary PCI STEMI

Vlaar et al. Circulation 2008, 118:1828-1836

	Multivariate-Adjusted Treatment Effect*			Jackknife Estimation*			Propensity Score–Adjusted Treatment Effect		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
TIMI grade 2/3 flow	1.51	1.31–1.74	<0.0001	1.51	1.31–1.74	<0.0001	1.53	1.39–1.68	<0.0001
Mortality	0.57	0.38–0.85	0.0055	0.57	0.40–0.81	0.0019	0.52	0.41–0.67	<0.0001
Death/reinfarction	0.54	0.38–0.75	0.0003	0.54	0.39–0.73	0.0001	0.50	0.40–0.62	<0.0001

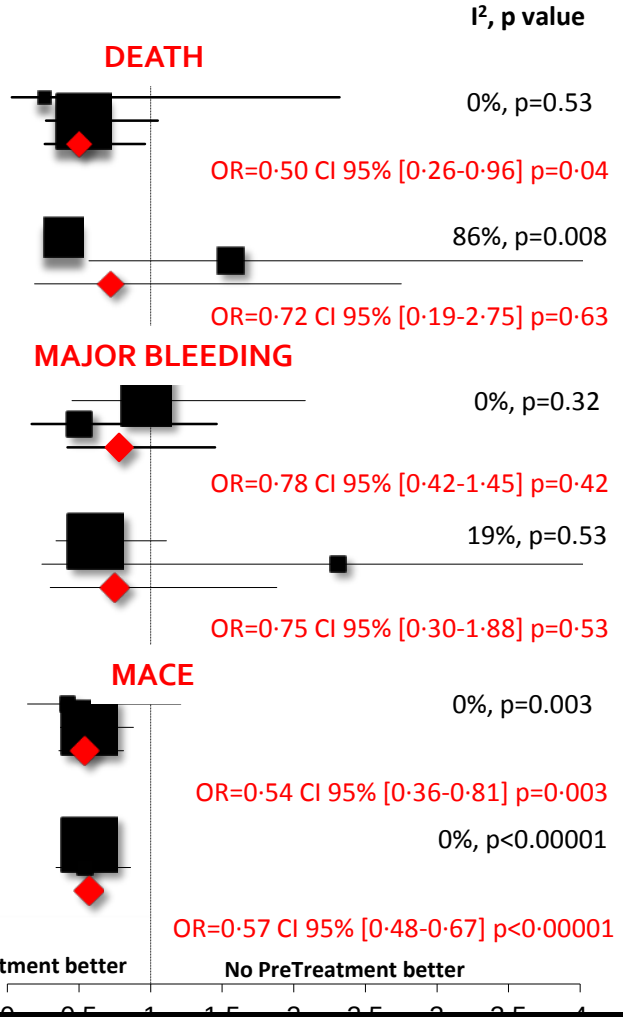
OR is for the occurrence of TIMI grade 2/3 flow, mortality, and death/reinfarction for pretreatment with clopidogrel.

*Adjusted for age, gender, history of diabetes mellitus, history of hypertension, heparin dose (high vs low dose), symptom duration, smoking, and year of publication.

	Events / Size, Clopidogrel *Pretreatment*	*No*	OR [CI 95%]	Relative Weight [%]
RCT* *N=2198*				
CIPAMI	1/164	4/171	0·26 [0·03-2·32]	8·7%
CLARITY PCI	13/933	24/930	0·53 [0·27-1·05]	91·3%
All	14/1097	28/1101	0·50 [0·26-0·96]	100%
Observational studies *N=6338*				
Dorler et al.	209/4879	110/1076	0·39 [0·31-0·50]	56·4 %
Fefer et al.	12/217	6/166	1·56 [0·57-4·25]	43·6 %
All	221/5096	116/1242	0·72 [0·19-2·75]	100%
RCT*				
CIPAMI	14/164	15/171	0·97 [0·45-2·08]	66·7%
CLARITY PCI	5/933	10/930	0·50 [0·17-1·46]	33·3%
All	19/1097	25/1101	0·78 [0·42-1·45]	100%
Observational studies				
Dorler et al.	42/4879	15/1076	0·61 [0·34-1·11]	85·3 %
Fefer et al.	3/217	1/166	2·31 [0·24-22·44]	14·7 %
All	45/5096	16/1242	0·75 [0·30-1·88]	100%
RCT*				
CIPAMI	5/164	12/171	0·42 [0·14-1·21]	14·2%
CLARITY PCI	34/933	58/930	0·57 [0·37-0·88]	85·8%
All	39/1097	70/1101	0·54 [0·36-0·81]	100%
Observational studies				
Dorler et al.	480/4879	173/1076	0·57 [0·47-0·69]	85·5%
Fefer et al.	47/217	56/166	0·54 [0·34-0·86]	14·5%
All	527/5096	229/1242	0·57 [0·48-0·67]	100%

** RCT=Randomized Controlled Trials*

2 RCTs; N=2 198 pts
2 Registries; N=6 338 pts

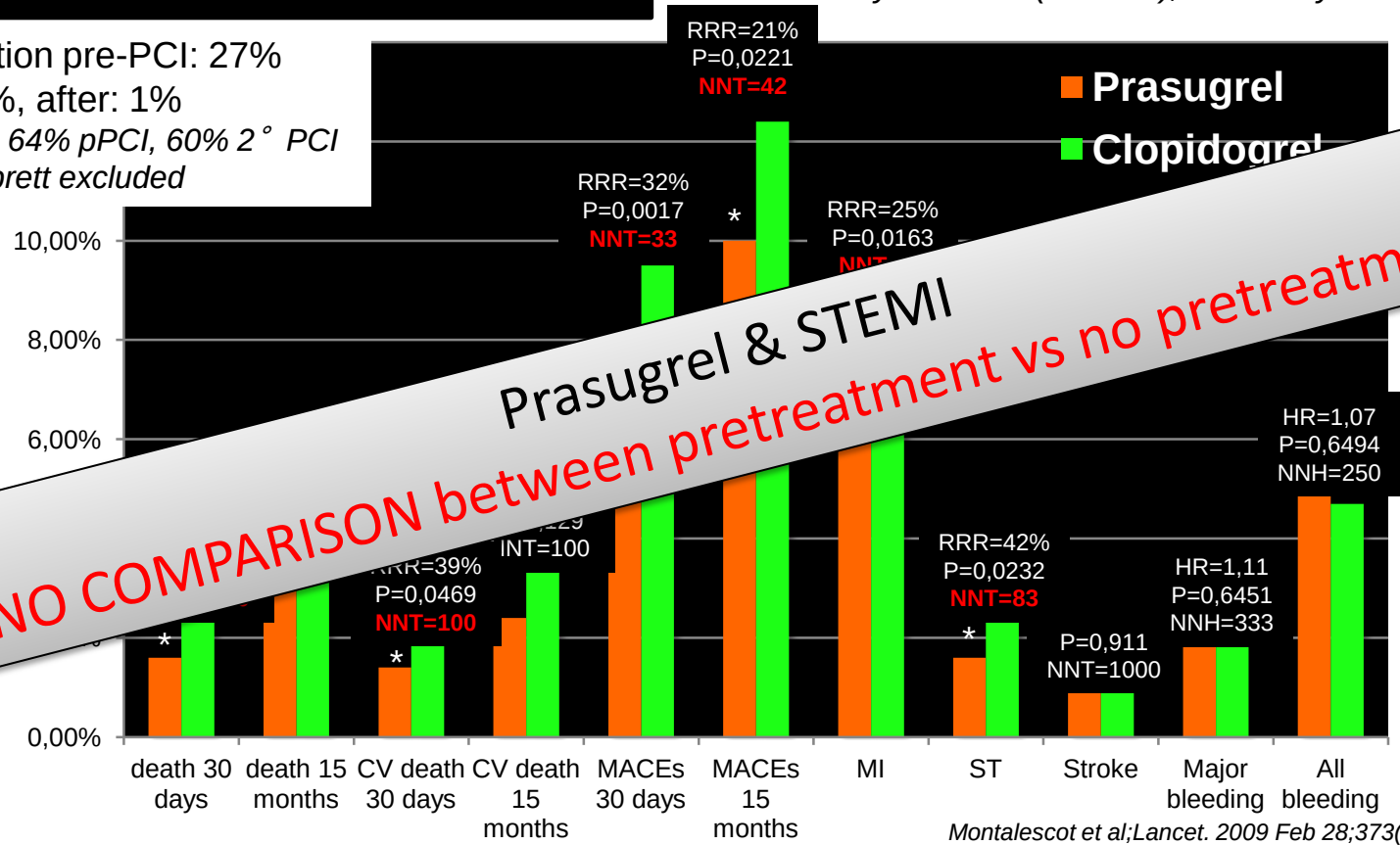


MA clopidogrel pre-tt; sub-analysis PCI STEMI *Bellemain-Appaix et al. JAMA2012;308(23):2507-2517*

PRASUGREL - *TRITON STEMI - PCI*

RCT 3 534 STEMI*; Prasugrel 60/10 vs Clopidogrel 300/75mg
** Primary PCI<H12 (n=2 438), secondary H12-D14 (N=1 094)***

Administration pre-PCI: 27%
during: 72%, after: 1%
NFH 72% GI 64% pPCI, 60% 2˚ PCI
Clopidogrel prett excluded



Prasugrel & STEMI
NO COMPARISON between pretreatment vs no pretreatment

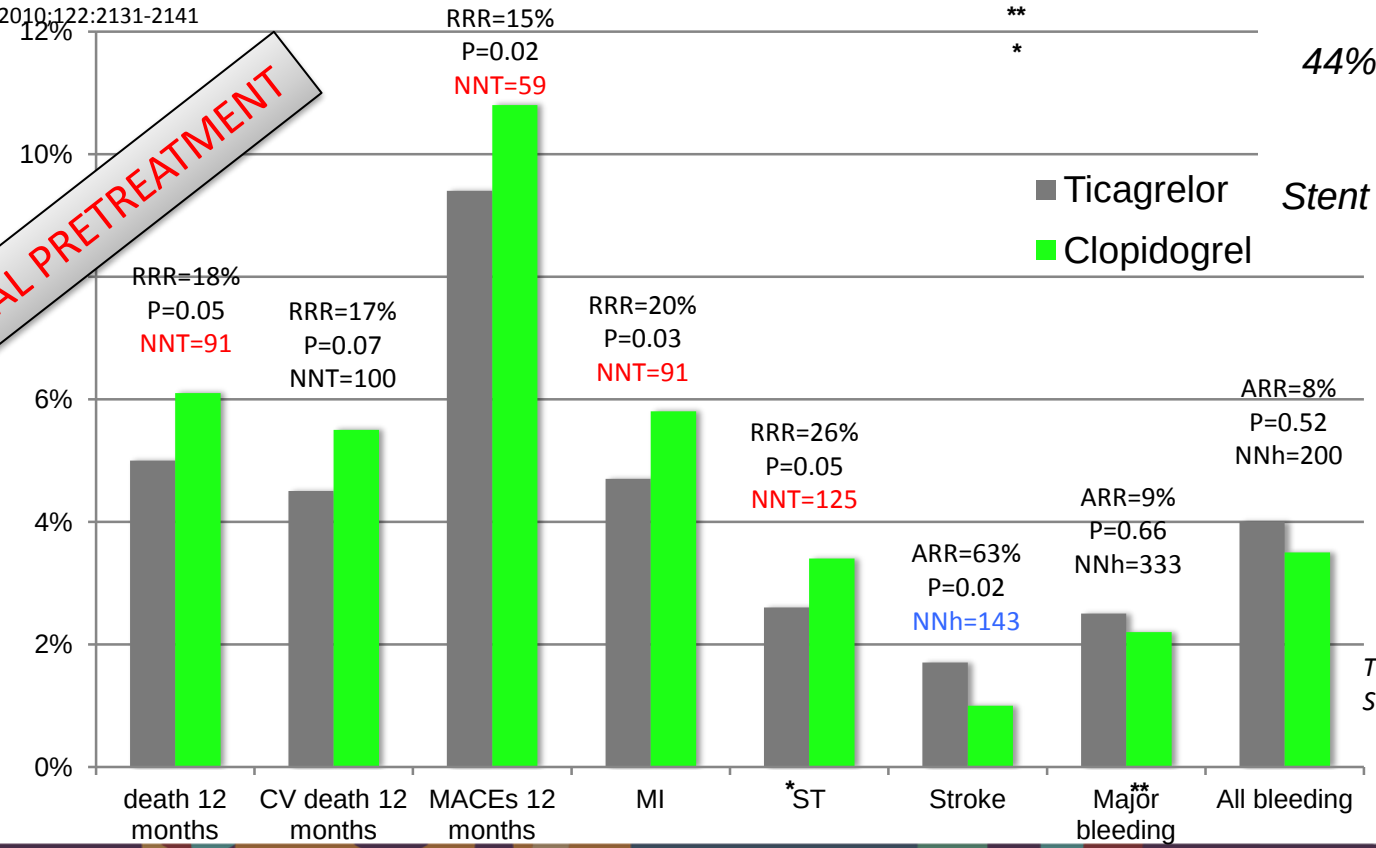
Montalescot et al;Lancet. 2009 Feb 28;373(9665):723-31

TICAGRELOR- *PLATO STEMI - PCI*

RCT 7 544 STEMI/LBB (9.5%) primaryPCI<H24
Ticagrelor 180/90bd vs Clopidogrel 300(+300PCI)/75mg

Steg et al; *Circulation.* 2010;122:2131-2141

IN HOSPITAL PRETREATMENT



44% clopi pré-rando
PCI 82%
CABG 2.5%
Stent 75%, DES 21%

TIMI non CABG bleeding
ST: definite & probable

ATLANTIC

A 30 Day Study to Evaluate Efficacy and Safety of Pre-hospital vs. In-hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for Percutaneous Coronary Intervention (PCI)

N ~ 1770

STE –ACS planned for PCI

RANDOMIZE
DOUBLE BLIND

- Written informed consent in mobile care unit
- Symptoms of acute MI of more than 30 min but less than 6 hours
- New persistent ST-segment elevation ≥ 1 mm in two or more contiguous ECG leads

Ticagrelor 180mg loading dose	Pre-Hospital	Loading dose placebo
Loading dose placebo	In-Hospital	Ticagrelor 180mg loading dose

Primary Objective:

- TIMI flow grade 3 of MI culprit vessel at initial angiography or
- ≥70% ST-segment elevation resolution pre-PCI

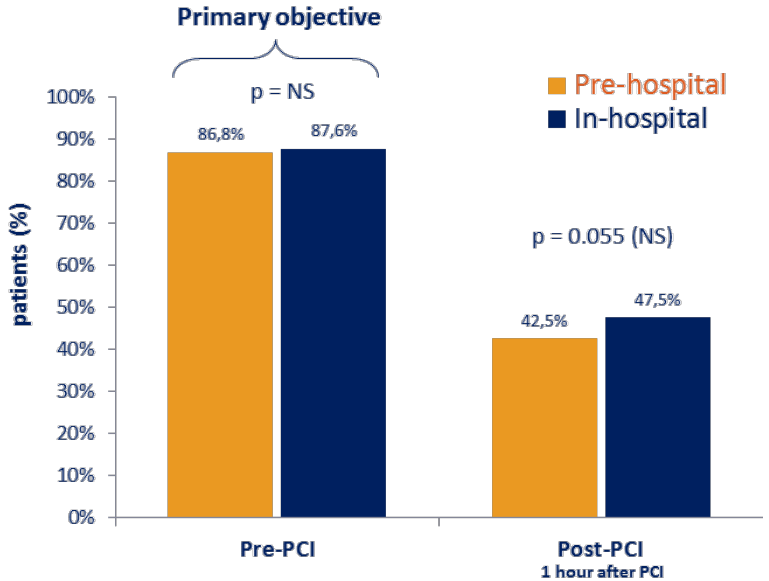
Ticagrelor 90mg/bid — 30d

1862 patients, STEMI <6 hours

Median time

-random-angio=48 min

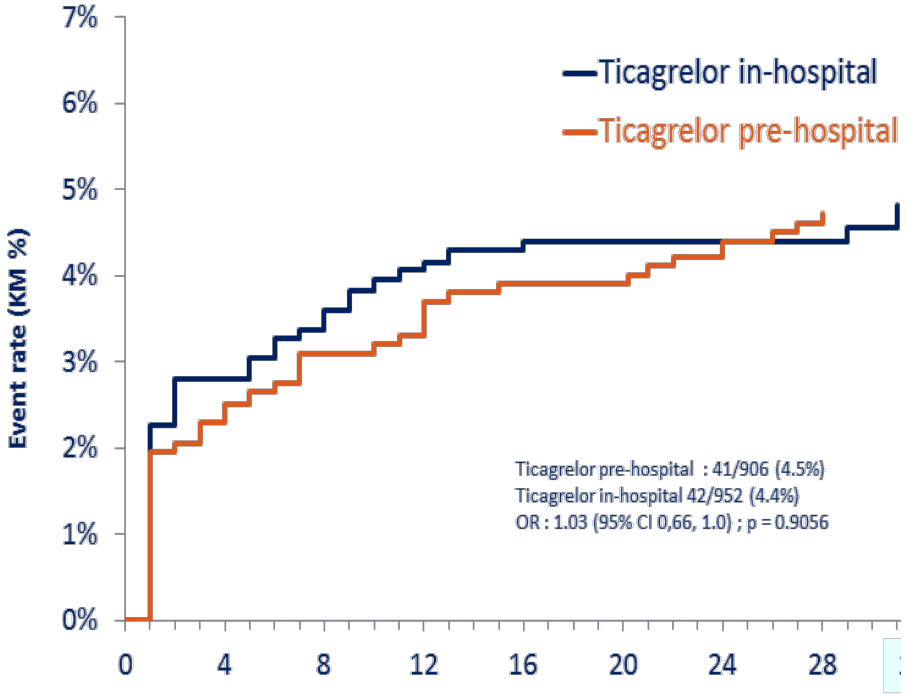
-between the two treatment=31 min



No ST-segment resolution (≥70%)

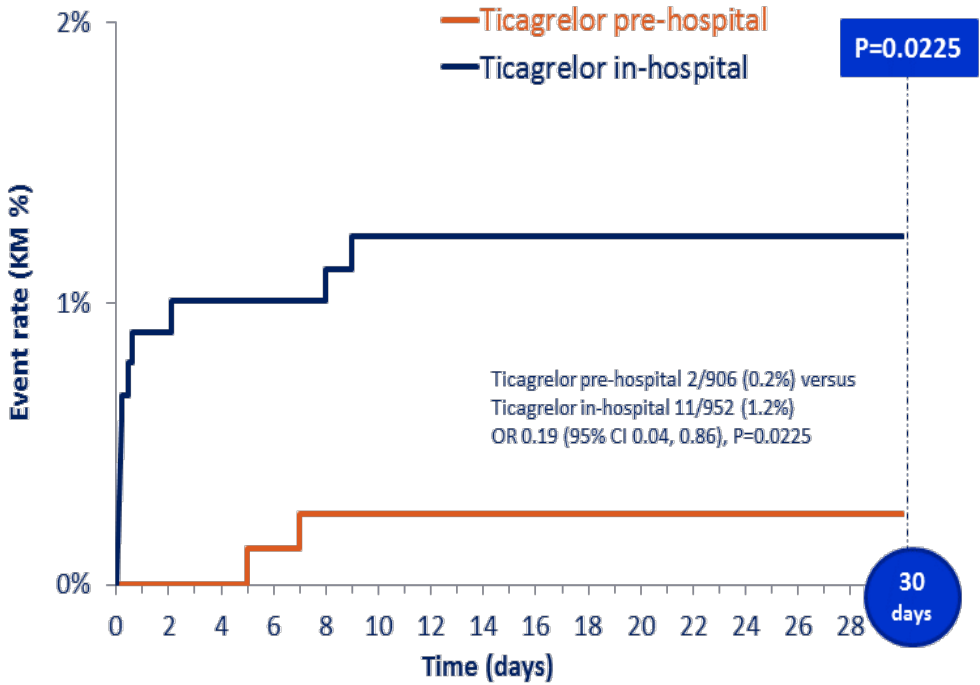
Montalescot G, et al. *N Engl J Med* 2014; 11;371(11):1016-27.

Major adverse CV events up to 30 days



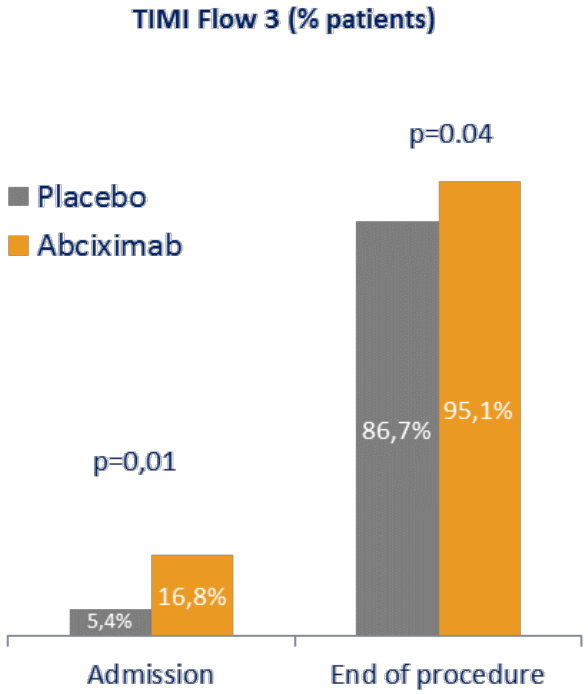
MACE: death, MI, stent thrombosis, stroke or urgent revascularization

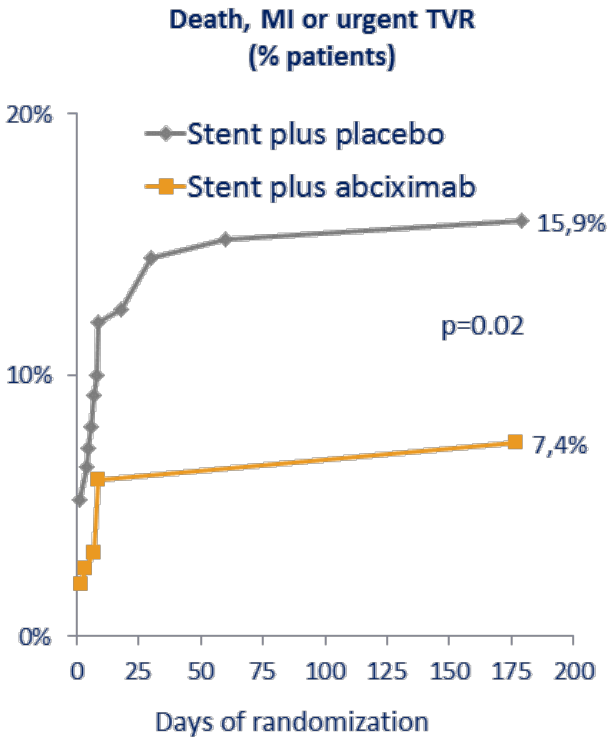
Definite stent thrombosis up to 10 days



Major bleeding no differents at 48 h and 30 days

Pre-hospital GPIIbIIIa inhibitors - *Primary PCI of STEMI*





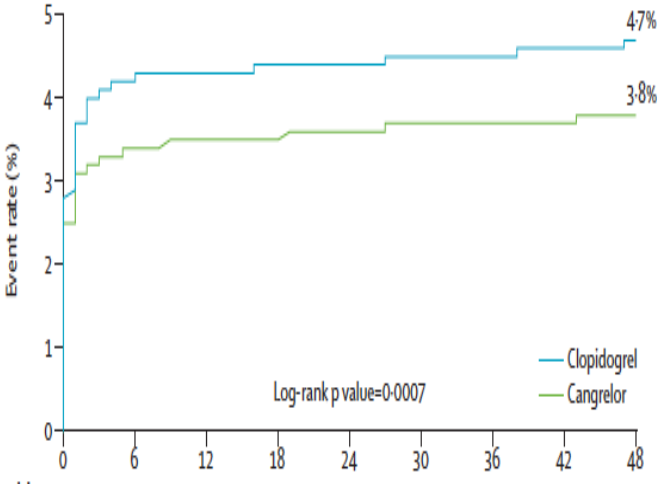
Montalescot G for the ADMIRAL investigators. NEJM 2001

CANGRELOR: CHAMPION meta-analysis– *STEMI subgroup*

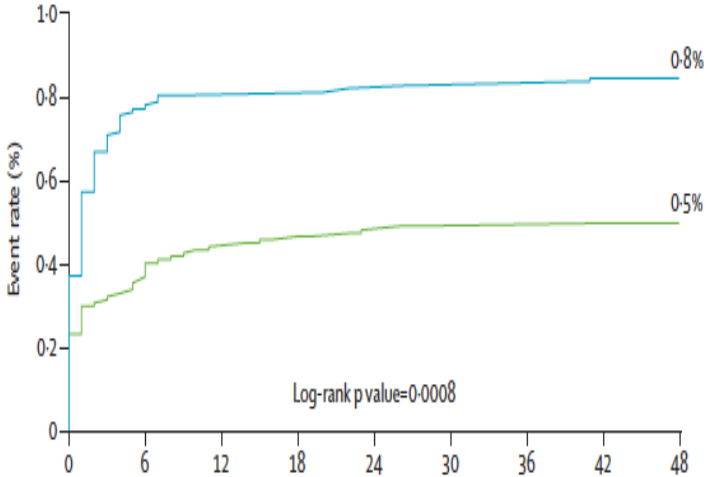
N=2 891 patients (11,6% of CHAMPION studies): Cangrelor (N=1 412) vs Clopidogrel (N=1 479)

GI 12.7%. Bivalirudin 25%; DES 53%; clopidogrel 600mg 89%; pretreatment 56%

MACEs *(death, MI, IDR, ST)* **H48**



Stent thrombosis H48



MACE H48 PCI for
STEMI (OR 0·84, 95% CI 0·55–1·27, p=0·4104)
NSTEACS (0·82, 0·68–0·99, p=0·0421)
stable angina (0·77, 0·64–0·93, p=0·0053)

no interaction between treatment effect and clinical presentation (interaction p=0·8663).

2014 ESC Myocardial Revascularisation Guidelines: Primary PCI

Patients undergoing primary PCI should receive a combination of DAPT with ASA and a $P2Y_{12}$ receptor blocker, as early as possible before angiography, and a parenteral anticoagulant.

Recommendations	Class[a]	Level[b]
Antiplatelet therapy		
ASA is recommended for all patients without contraindications at an i… dose of 150–300mg (or 80-150mg i.v.) and at a maintenance dose of 75–100mg daily l… ess of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to AS… ed over 12 months unless there are contraindications such as excessive risk of b… are:	I	A
• Prasugrel (60-mg loading do… dose) if no contraindication	I	B
• Ticagrelor 180-m… 90 mg twice daily if no contraindication	I	B
• Clopid… ading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are…	I	B
P2Y… tors should be given at time of first medical contact.	I	B

Not Based On Randomized Controlled Trial (RCT) Results

European Heart Journal DOI 10.1093/eurheartj/ehu278

Meta-Analysis: Design

Objectives & Methods

OBJECTIVES

To conduct a meta-analysis of randomized controlled trials (RCTs) comparing a strategy of P2Y12 inhibition before versus after (or during) PCI for STEMI.

Objectives & Methods

METHODS

We pooled datas from RCTs which
-compared early vs delayed P2Y12 inhibition in STEMI patients scheduled for PCI
-provided data on Major Adverse Cardiac Events (MACE), all cause death, and major bleeding

- ✓ *Primary endpoint* was MACE
- ✓ *Secondary endpoints* included definite ST, death, CV death, MI, Stroke, Urgent Target Vessel Revascularisation, minor and any bleeding.
- ✓ *Additional surrogate endpoints* : TIMI 2-3 flow rate before and after PCI, ST segment elevation resolution on the ECG before and after PCI, and use of GpIIbIIIa inhibitors.

All endpoints were analysed at shortest follow-up available.

Objectives & Methods

DEFINITIONS: EARLY vs DELAYED strategy of P2Y12 inhibition

The “early strategy” was defined as follows

i) administration of the drugs before arrival of the STEMI patients in the catheterization laboratory (i.e., in the ambulance or in the emergency department or at a referring hospital), in comparison with the same drugs administered after arrival in the catheterization laboratory (delayed strategy) or

ii) administration in the catheterization laboratory before PCI of P2Y12 inhibitors rapidly active (i.e. intravenous P2Y12 inhibitors or prasugrel or ticagrelor) in comparison with clopidogrel used in the control arm (delayed strategy).

METHODS

The risk of bias : Cochrane Collaboration Tool (7 parameters).

DATA SYNTHESIS AND ANALYSIS

Mantel Hanszel fixed-effect model, confirmed with a random-effect model
Heterogeneity between trials : Q Cochran test (p cut-off value of 0·1 considered as significant). Probability values: two tailed with p=0.05 considered as significant

The main analysis was performed on all RCTs (entire group of STEMI)
After assessment of heterogeneity, several sensitivity analyses were performed according to:

(1) The route of administration: IV vs. oral
(2) The type of drug: clopidogrel vs. new P2Y12 inhibitors
(3) Primary vs. secondary PCI.

RESULTS

FLOW CHART

Identification

Records identified through database searching (n=262)

Screening

Records screened after duplicates exclusion (n=176)

Records excluded at the title / abstract level (n=164)

Post hoc analyses of randomized trials (n=8)
Biological studies on platelet reactivity (n=14)
Comparison of drug dosage effects (n=13)
Reviews, editorials and study-design papers (n=71)
Non pertinent studies (n=39)
Meta-Analysis (n=8)
Registries (n=10)
Case reports (n=1)

Eligibility

Full-length articles assessed for eligibility (n=12)

Records excluded at the full-length article level (n=4)

Included

Studies included in quantitative synthesis (meta-analysis) (n=8)*

ATLANTIC [1]
LOAD and GO [2]
PCI CLARITY [3]
CIPAMI [4]
CHAMPION PCI STEMI [5]
CHAMPION PHOENIX [6]
TRITON STEMI [7]
ERASE MI [8]

9648 patients
"Early" = 4792
"Delayed" = 4856

6,694 oral drug
6,914 primary PCI
7,282 new P2Y12 inhib.

PRISMA Standards

Data on STEMI patients from the 2 CHAMPION studies where pooled by the corresponding author and they were considered as one simple study for analysis

[1] Montalescot G et al; *N Engl J Med* 2014; 11;371(11):1016-27.
[2] Ducci K et al; *Int J Cardiol* 2013; 168(5): 4814-6.
[3] Sabatine MS et al; *Jama* 2005; 294(10): 1224-32.
[4] Zeymer U et al; *Clin Res Cardiol* 2012; 101(4):305-12.
[5] Harrington RA et al; *N Engl J Med* 2009; 361(24): 2318-29.
[6] Bhatt DL et al; *N Engl J Med* 2013; 368(14):1303-13.
[7] Montalescot G et al; *Lancet* 2009; 373(9665): 723-31.
[8] Berger JS et al; *Am Heart J* 2009; 158(6): 998-1004 e1.

RISK OF BIAS

The overall risk of bias never exceeded 25%
No publication bias was observed, with linear regression test of funnel plot asymmetry (p=NS for all explored outcomes).

The Cochrane Collaboration Tool

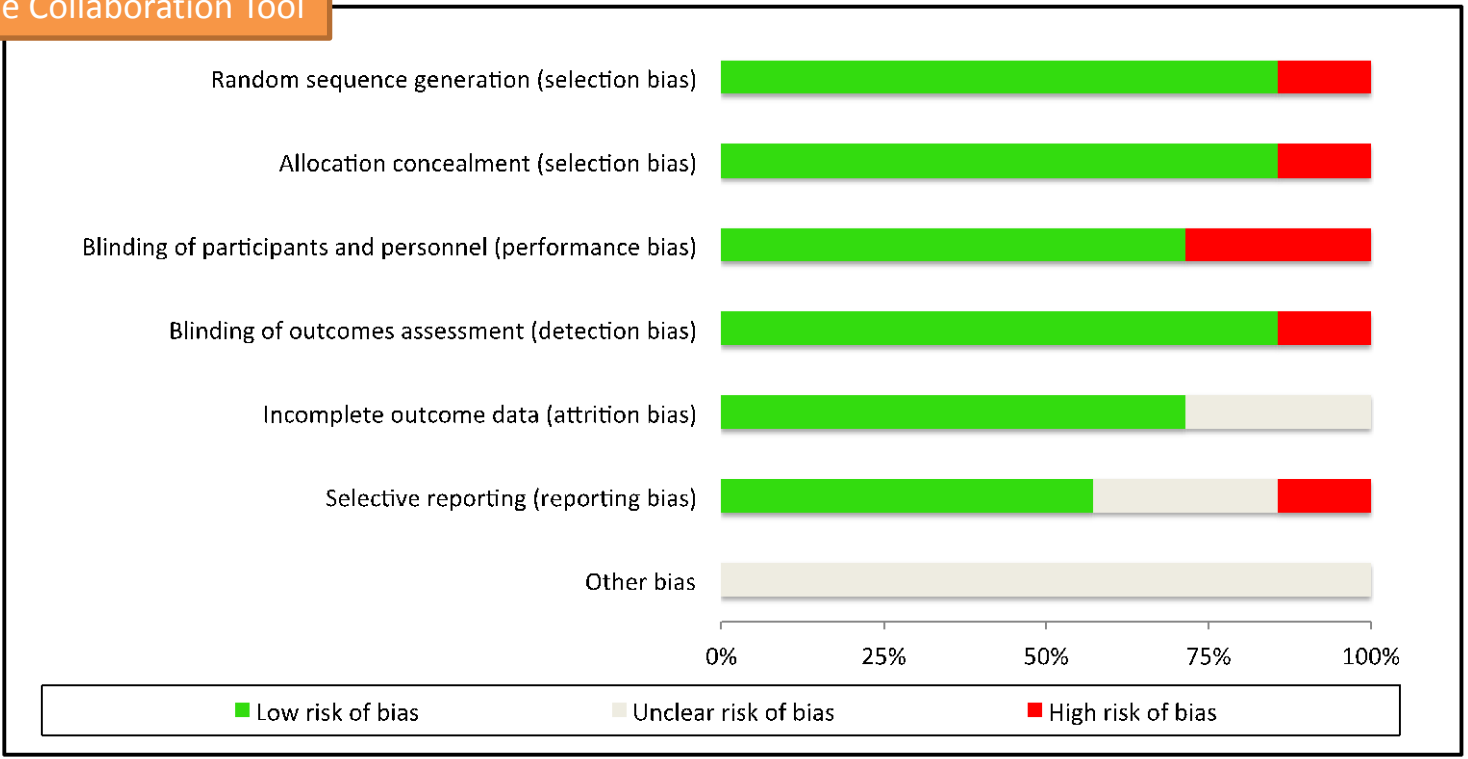
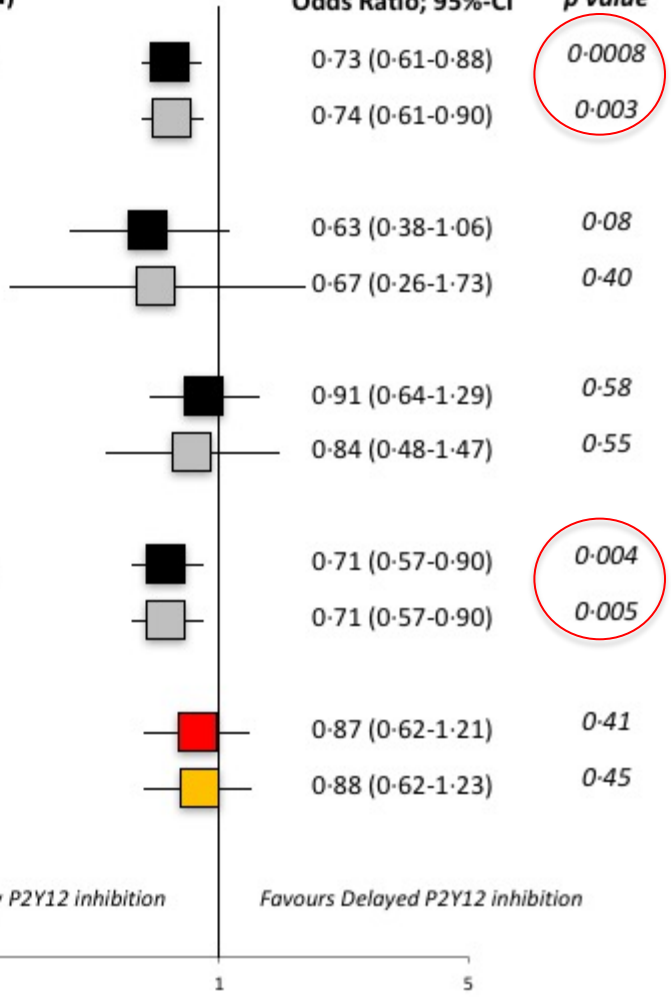
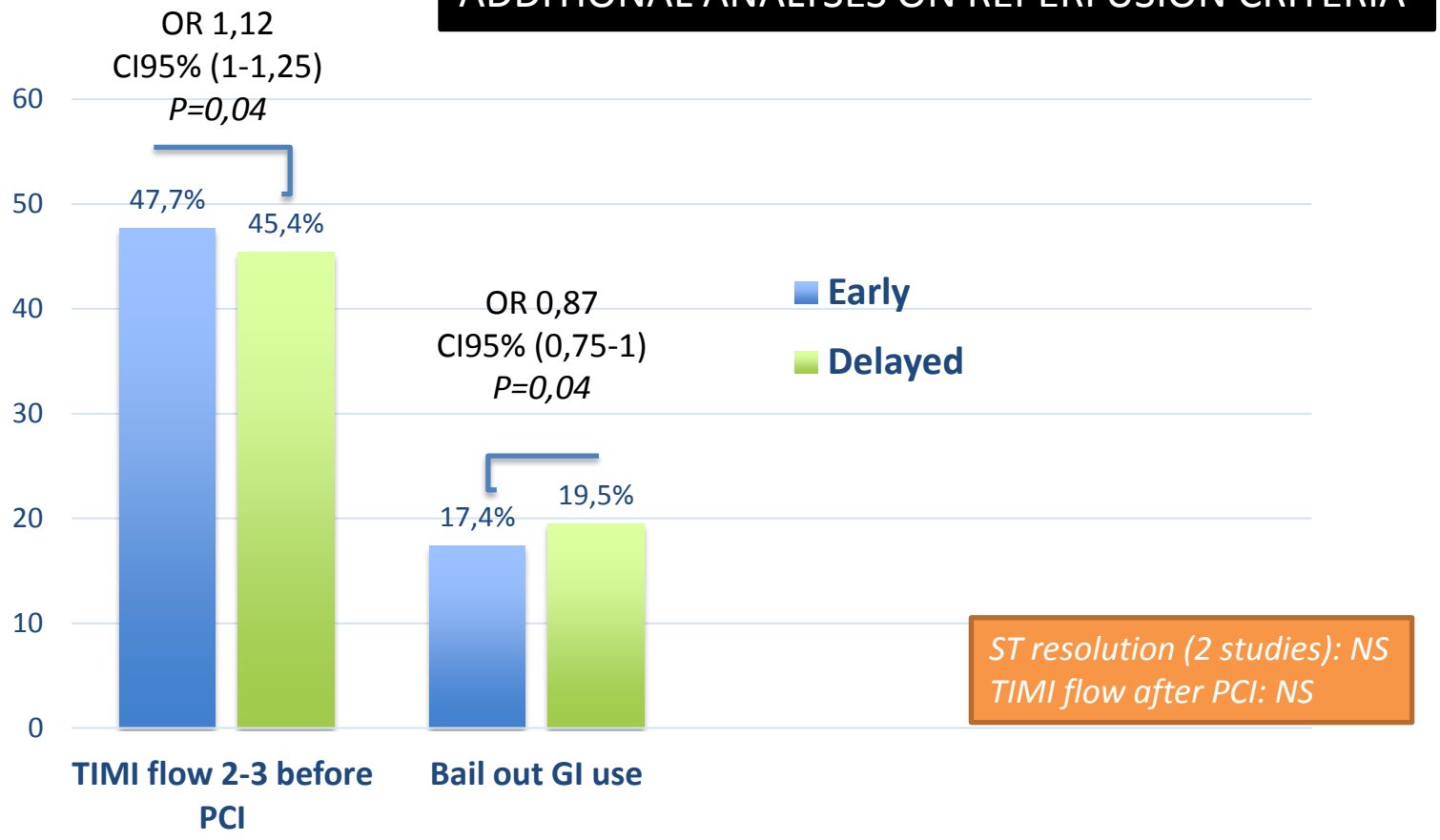


Figure 2 GLOBAL RESULTS

		« EARLY » group (n/N)	« DELAYED» group (n/N)	Odds Ratio; 95%-CI	p value
MACE	Fixed effect model	219/4792	296/4856	0·73 (0·61-0·88)	0·0008
	Random effects model	4,6%	6,1%	0·74 (0·61-0·90)	0·003
	Heterogeneity: I-squared=9%, Q=6·61, df=6, P=0·36				
STENT Thrombosis	Fixed effect model	23/3647	38/3712	0·63 (0·38-1·06)	0·08
	Random effects model	0,6%	1,0%	0·67 (0·26-1·73)	0·40
	Heterogeneity: I-squared=48%, Q=3·88, df=2, P=0·14				
DEATH	Fixed effect model	60/4792	67/4856	0·91 (0·64-1·29)	0·58
	Random effects model	1,3%	1,4%	0·84 (0·48-1·47)	0·55
	Heterogeneity: I-squared=43%, Q=8·81, df=5, P=0·12				
Myocardial Infarction	Fixed effect model	129/4792	178/4856	0·71 (0·57-0·90)	0·004
	Random effects model	2,7%	3,7%	0·71 (0·57-0·90)	0·005
	Heterogeneity: I-squared=0%, Q=1·44, df=5, P=0·92				
MAJOR BLEEDING	Fixed effect model	65/4784	76/4842	0·87 (0·62-1·21)	0·41
	Random effects model	1,4%	1,6%	0·88 (0·62-1·23)	0·45
	Heterogeneity: I-squared=0%, Q=4·39, df=6, P=0·62				



ADDITIONAL ANALYSES ON REPERFUSION CRITERIA

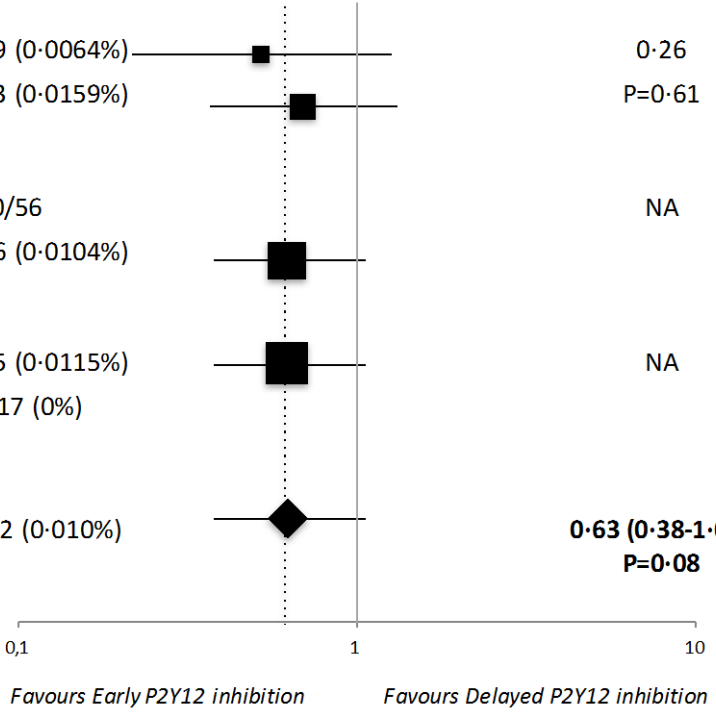


ST resolution (2 studies): NS
TIMI flow after PCI: NS

Forest Plot STENT THROMBOSIS by subgroups

SENSITIVITY ANALYSIS

	« EARLY » group (n/N)	« DELAYED» group (n/N)	ODD RATIO (95% CI)*	Heterogeneity or trend X^2 *p for interaction*
Route of administration				
Oral	7/2206 (0·0032%)	14/2199 (0·0064%)		0·26
Intravenous	16/1441 (0·0111%)	24/1513 (0·0159%)		P=0·61
Clopidogrel vs New i-P2Y12				
Clopidogrel	0/112	0/56		NA
New P2Y12 antagonist	23/3535 (0·0065%)	38/3656 (0·0104%)		
Primary vs secondary PCI				
Primary PCI	23/3223 (0·0071%)	38/3295 (0·0115%)		NA
Secondary PCI	0/424 (0·0053%)	0/417 (0%)		
ALL PATIENTS	23/3647 (0·0063%)	38/3712 (0·010%)		**0·63 (0·38-1·06) P=0·08**



*Fixed effect model

*Route of adm
#no interactio

ESC2017

CONCLUSION

This meta-analysis done on RCTs, regrouping nearly 10,000 STEMI patients shows that a strategy of early P2Y12 inhibition before revascularization:

1/ is associated with a significant **27% relative risk reduction of MACE** (p=0·0008), mainly driven by the **29% relative risk reduction of MI** (p=0,004) and to a lesser degree a reduction of stent thrombosis (NS)

2/ is safe, as it was **not associated with an increase of bleeding**
It was even associated with a **less frequent bailout use of GPI** (p=0·04)

3/ is associated with a **better coronary reperfusion before stenting** (TIMI flow grade 2-3)

LIMITATIONS

1. Those of the included studies, and those of the meta-analysis technique itself. *However, we included only RCTs, or sub-analysis of RCTs, and we used formal analytic methods to decrease the risk of bias*

2. **MACE definitions** differed although several studies used common definitions

3. **The duration of follow-up** also varied *but we were mostly interested in short-term follow-up*, when we expect a benefit from a strategy which shortens the time to effective P2Y12 inhibition. (Beyond 24 hours after PCI, both strategies had effective P2Y12 inhibition)

4. **Heterogeneity between studies** may exist *and was searched*; we also provided results from both fixed and random effect models for all the endpoints

5. Finally, although it is important to reduce MACE with no increase in bleeding rate, our meta-analysis **did not show improved survival with this strategy**