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The efficacy of early versus delayed P2Y$_{12}$ inhibition in percutaneous coronary intervention for ST-elevation myocardial infarction: a systematic review and meta-analysis

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KEYWORDS

- adjunctive pharmacotherapy
- antithrombotic treatment
- bleeding
- death
- myocardial infarction
- STEMI

Abstract

Aims: The aim of this meta-analysis was to compare the benefit of "early" vs. "delayed" P2Y$_{12}$ inhibition in patients undergoing percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI).

Methods and results: We conducted a meta-analysis including seven randomised controlled trials (RCTs) which compared early vs. delayed P2Y$_{12}$ inhibition in STEMI patients scheduled for PCI, providing data on major adverse cardiac events (MACE), all-cause death, and major bleeding. The primary endpoint was MACE. Secondary endpoints included stent thrombosis and the use of GP IIb/IIIa inhibitors (GPI). All endpoints were analysed at the shortest follow-up available. A total of 9,648 patients were included ("early"=4,792, "delayed"=4,856). "Early" P2Y$_{12}$ inhibition was associated with a significant reduction in MACE rate (OR 0.73, 95% CI: 0.61-0.88, p=0.0008), myocardial infarction (OR 0.71, 95% CI: 0.57-0.90, p=0.004), bail-out GPI use (OR 0.87, 95% CI: 0.75-1.00, p=0.04) and improved coronary reperfusion before PCI (OR for Thrombolysis In Myocardial Infarction [TIMI] flow grade 2-3=1.12, 95% CI: 1.00-1.26, p=0.04). Major bleeding was not increased (OR 0.87, 95% CI: 0.62-1.21, p=0.41).

Conclusions: A strategy of early effective P2Y$_{12}$ inhibition in PCI of STEMI appears to improve coronary reperfusion before PCI, and reduce MACE, MI and bail-out GPI use without increase of major bleeding.

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Abbreviations

CV	cardiovascular
GPI	glycoprotein IIb/IIIa inhibitors
MACE	major adverse cardiac events
MI	myocardial infarction
PCI	percutaneous coronary intervention
RCT	randomised controlled trial
STEMI	ST-elevation myocardial infarction
ST	stent thrombosis
TIMI	Thrombolysis In Myocardial Infarction

Introduction

STEMI is a highly thrombotic situation that needs rapid reperfusion and potent platelet inhibition. Previous studies have shown that mortality increases with delays to PCI exceeding 60 minutes after the first medical contact[1], and that poor platelet inhibition increases the risk of recurrent ischaemic events[2]. Clopidogrel was the first $P2Y_{12}$ inhibitor to show an effect on ischaemic events in secondary PCI of STEMI[3]. More recently, more potent and fast-acting $P2Y_{12}$ inhibitors have demonstrated superiority over clopidogrel in PCI of STEMI[4-6]. Current European guidelines state that $P2Y_{12}$ inhibitors are recommended before PCI of STEMI, or at the latest at the time of PCI (class of recommendation I, level of evidence A), reflecting the lack of certainty in the exact timing of $P2Y_{12}$ inhibitor administration[7].

The concept of early antiplatelet therapy during patient transfer to the catheterisation laboratory was first investigated with glycoprotein IIb/IIIa inhibitors (GPI), showing improved reperfusion and reduced ischaemic event rates, in particular for patients presenting early[8].

Pretreatment with clopidogrel, while applicable for many clinical situations, is not appropriate for primary PCI of STEMI; due to its slow onset and low magnitude of effect, platelet inhibition is not obtained in time[9]. Prasugrel and ticagrelor are more potent and more rapidly acting than clopidogrel, but a delay of action of one to two hours is necessary to obtain significant platelet inhibition[10]. A strategy of early administration of these drugs in STEMI patients is compatible with a partially effective $P2Y_{12}$ inhibition at the time of PCI. Finally, cangrelor is more potent than the oral drugs with an immediate onset of action after intravenous administration: it has the potential to provide a fully effective $P2Y_{12}$ inhibition at the time of PCI[11]. For these reasons, we decided to compare in STEMI patients a strategy of early effectiveness of $P2Y_{12}$ inhibitors (that sought to produce effective $P2Y_{12}$ inhibition as rapidly as possible) compared with a strategy of effectiveness delayed to after PCI (that did not rely on the potential benefits of a more rapid effectiveness obtained with an earlier administration, or with the use of more rapidly acting drugs).

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Methods

This meta-analysis was performed and reported according to PRISMA standards[12]. Details of the protocol for this systematic review were submitted for acceptance on PROSPERO (but not yet registered).

DATA SOURCES AND SEARCHES

The search included the following combination of terms: "PCI" AND "ST-elevation myocardial infarction" AND "clopidogrel" OR "prasugrel" OR "ticagrelor" AND "pre-treatment", OR "loading" OR "timing" OR "upstream" OR "pre-hospital", with no language restriction; for IV drugs, the search was enlarged to "PCI" AND "cangrelor" OR "elinogrel". MEDLINE, Cochrane Controlled Trials Register, EMBASE and BioMed Central databases were scrutinised from January 1980 up to July 2017. Additional searches were also performed in Google Scholar, the medical websites tctmd.com, cardiosource.com and clinicaltrials.gov. Full-text articles and meeting abstracts of randomised controlled trials and pre-specified subgroups of randomised studies reporting data on $P2Y_{12}$ inhibitor administration in STEMI were considered for analysis.

STUDY SELECTION

Titles and abstracts were reviewed and two independent reviewers (A. Bellemain-Appaix and G. Montalescot) evaluated full text articles for inclusion. Discrepancies were adjudicated by consensus. We included all studies published or presented at major meetings, with no language restriction, that met all of the following inclusion criteria: 1) randomised controlled trials including STEMI patients scheduled for PCI; 2) controlled comparison between early and delayed administration of a $P2Y_{12}$ inhibitor or between two different $P2Y_{12}$ inhibitors of different onset of action; 3) control arm corresponding to the administration of an oral $P2Y_{12}$ inhibitor in the catheterisation laboratory at the time of PCI (no effective platelet inhibition during PCI); 4) data available on the type of $P2Y_{12}$ inhibitor treatment, dose and timing of administration; and 5) data available on at least major adverse cardiac events (MACE), all-cause death, and major bleeding.

Exclusion criteria were: 1) studies where patients could have received any $P2Y_{12}$ inhibitor before randomisation; and 2) all duplicate reports and ongoing studies.

DATA EXTRACTION AND QUALITY ASSESSMENT

Data extraction from published reports was carried out independently by two authors (A. Bellemain-Appaix and C. Bégué). Outcomes were reported at the shortest follow-up available in each study. The "early strategy" of $P2Y_{12}$ inhibitor administration was defined as follows: i) administration of the drugs before arrival of the STEMI patients in the catheterisation 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 catheterisation laboratory (delayed strategy) or, ii) administration in the catheterisation laboratory before PCI of rapidly acting $P2Y_{12}$ inhibitors (i.e., intravenous $P2Y_{12}$ inhibitors or prasugrel or ticagrelor) in comparison with clopidogrel used in the control arm (delayed strategy). Late effectiveness always corresponded to the late administration of oral drugs in the catheterisation laboratory or after PCI.

The risk of bias was assessed independently by two reviewers (A. Bellemain-Appaix and C. Bégué), using the tool recommended

and developed by the Cochrane Collaboration[13]. Disagreements were resolved through discussion.

DATA SYNTHESIS AND ANALYSIS

The primary efficacy endpoint was MACE according to each study definition at the shortest follow-up available **(Supplementary Table 1)**. The primary safety endpoint was major bleeding according to the definition of each study **(Supplementary Table 2)**. Secondary clinical endpoints included all-cause death, stent thrombosis (definite, according to the Academic Research Consortium definition), cardiovascular (CV) death, myocardial infarction according to each study definition **(Supplementary Table 2)**, stroke, urgent target vessel revascularisation, minor and any bleeding. Additional surrogate endpoints were analysed when available: Thrombolysis In Myocardial Infarction (TIMI) 2-3 flow rate before and after PCI, ST-segment elevation resolution on the ECG before and after PCI, and the use of GPI. The corresponding authors of RCTs were contacted and asked to provide additional information not available in the literature: 1) in the TRITON-STEMI study[4], only patients randomised at the time of PCI and who received $P2Y_{12}$ inhibitors during or after PCI (72% of the population) were considered (for primary and secondary PCI) with a randomised comparison between prasugrel and clopidogrel; secondary PCI patients who may have received both drugs hours or days before reaching the catheterisation laboratory were excluded; 2) in the CHAMPION studies[14,15], subgroup level data for STEMI patients were pooled by the authors; administration of cangrelor defined the "early" group (immediate efficacy), clopidogrel the "delayed" one; 3) the PLATO-STEMI study[6] included 44% of patients treated with clopidogrel before randomisation; unpublished data on the other patients could not be obtained from the authors; the study was thus excluded from the main analysis, but we provide informative analysis integrating PLATO published data on MACE (without patients pre-treated), and the other endpoints (including patients pre-treated).

We conducted a study-level meta-analysis to give pooled estimates for each outcome. To avoid underweighting of some populations, studies were pooled using the Mantel-Haenszel fixed-effect model; a random-effects model was also tested as assuming the between-trial variance. The extent of heterogeneity between trials was assessed with Cochran's Q test (with a cut-off p-value of 0.1 considered as significant for heterogeneity), and the I^2 test for heterogeneity between subgroups was reported in each figure. Probability values were two-tailed with p=0.05 considered as significant. Odds ratios with 95% confidence intervals (CI) were calculated with the RevMan software version 5.0 (The Cochrane Collaboration) and the R meta-package (R Foundation for Statistical Computing, Vienna, Austria).

The main analysis was performed on all RCTs for the entire group of STEMI patients undergoing PCI. Several sensitivity analyses were performed to help to address the heterogeneity of study drugs and delay of administration according to: (1) the route of administration: IV vs. oral; cangrelor is the only available IV drug and, as opposed to oral drugs, has an immediate and potent effect; (2) the type of drug: clopidogrel vs. ticagrelor/prasugrel vs. cangrelor/elinogrel, that have a potency and onset of action gradually more favourable than clopidogrel; another analysis between clopidogrel and new $P2Y_{12}$ inhibitors (all the others) was also performed; and 3) primary vs. secondary PCI, for which the time factor allows a longer delay to obtain effective $P2Y_{12}$ inhibition. We also performed a stepwise influential analysis to identify trials that could have significantly driven the pooled effect.

Results

Finally, the search resulted in seven RCTs being selected (eight studies with fusion of STEMI data from the two CHAMPION studies) with a total of 9,648 STEMI patients (4,792 with an early and 4,856 with a delayed strategy of $P2Y_{12}$ inhibition) **(Supplementary Figure 1)**[3,4,14-19]. Of the 9,648 patients, 6,694 received an oral drug (clopidogrel, ticagrelor or prasugrel), 6,914 were primary PCI patients, and 7,282 received a new $P2Y_{12}$ antagonist (ticagrelor, prasugrel, cangrelor, or elinogrel). Details of the studies are provided in **Supplementary Table 1**. The overall risk of bias of the included studies never exceeded 25% **(Supplementary Figure 2)**. No publication bias was observed, with a linear regression test of funnel plot asymmetry (p=NS for all explored outcomes).

MAIN ANALYSIS

MACE were reported at 30 days for six studies[3,4,15-18] and at 48 hours for two studies[14,19]. The early inhibition strategy was associated with a significant reduction in the MACE rate with a fixed-effect model (OR 0.73, 95% CI: 0.61-0.88, p=0.0008), and confirmed by the random-effects model **(Figure 1)**.

Stent thrombosis information **(Supplementary Table 2)** was available in four of the seven studies[4,14,15,17,18], accounting for 61 events for 7,359 patients (23/3,647 in the "early" group and 38/3,712 in the "delayed" $P2Y_{12}$ inhibition group). "Early" $P2Y_{12}$ inhibition was associated with a non-significant reduction in stent thrombosis (OR 0.63, 95% CI: 0.38-1·06, p=0.08); there was no significant heterogeneity between studies for this endpoint **(Supplementary Figure 3)**.

There was no difference between the two strategies for major bleeding (OR 0.87, 95% CI: 0.62-1.21, p=0.41) **(Figure 2)**.

Myocardial infarction (MI) data were available for all studies, with no heterogeneity between studies; "early" $P2Y_{12}$ inhibition was associated with a significant reduction of MI with both the fixed and random models **(Figure 2)**.

For all-cause death, there was no association between the timing strategy of $P2Y_{12}$ inhibition and outcomes **(Figure 2)**. This was also the case for CV death, available in four studies[3,4,15,17] (28/3,722 in the "early" group vs. 44/3,733 in the "delayed" group; OR 0.63, 95% CI: 0.39-1.01, p=0.05), stroke available in four studies[3,4,16,18] (9/3,385 vs. 19/3,379; OR 0.51, 95% CI: 0.24-1.08, p=0.08), and urgent revascularisation available in five studies[4,15,16,18,19] (33/3,859 vs. 41/3,926; OR 0.83, 95% CI: 0.52-1.32, p=0.44).

Additional analyses on reperfusion criteria showed a significant impact of early or rapid $P2Y_{12}$ inhibition on coronary

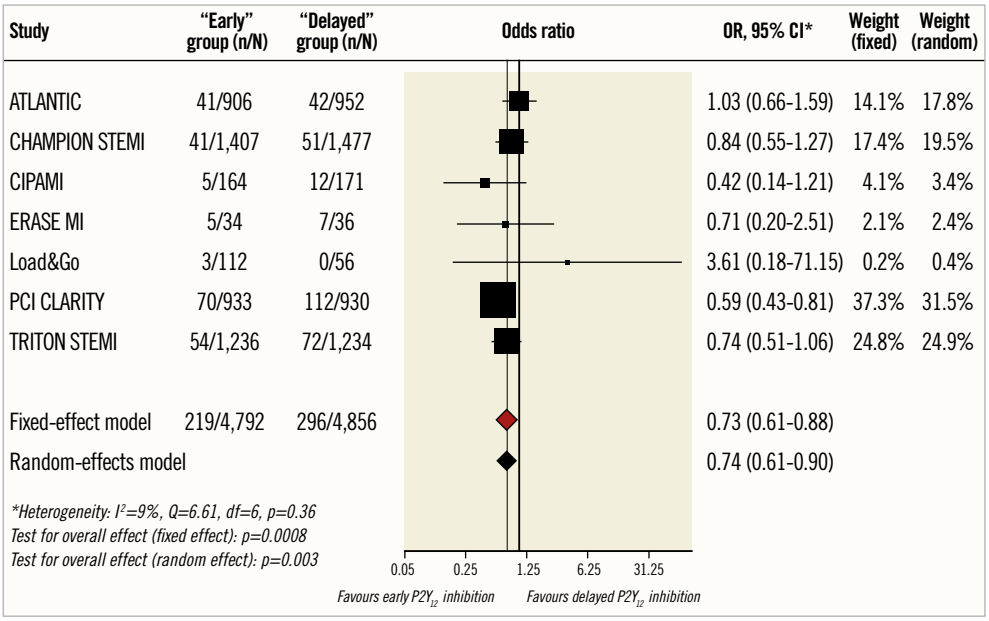

Figure 1. *Forest plot for MACE by study. Fixed- and random-effects global results are shown. CI: confidence interval; MACE: major adverse cardiac events*

TIMI flow rate before PCI and a reduction of bail-out use of GPI **(Supplementary Table 3)**.

SENSITIVITY ANALYSIS

When comparing the groups of drugs, we found no significant interaction between groups, except for death **(Supplementary Table 4)**.

There was no interaction between the route of P2Y$_{12}$ inhibitor administration (oral: five studies[3,4,17-19], 6,694 patients, vs. IV: two studies[14-16], 2,954 patients) and the effect of "early" inhibition on both MACE and stent thrombosis (**Supplementary Figure 4**, **Supplementary Figure 5**), as for other endpoints **(Supplementary Table 5)**.

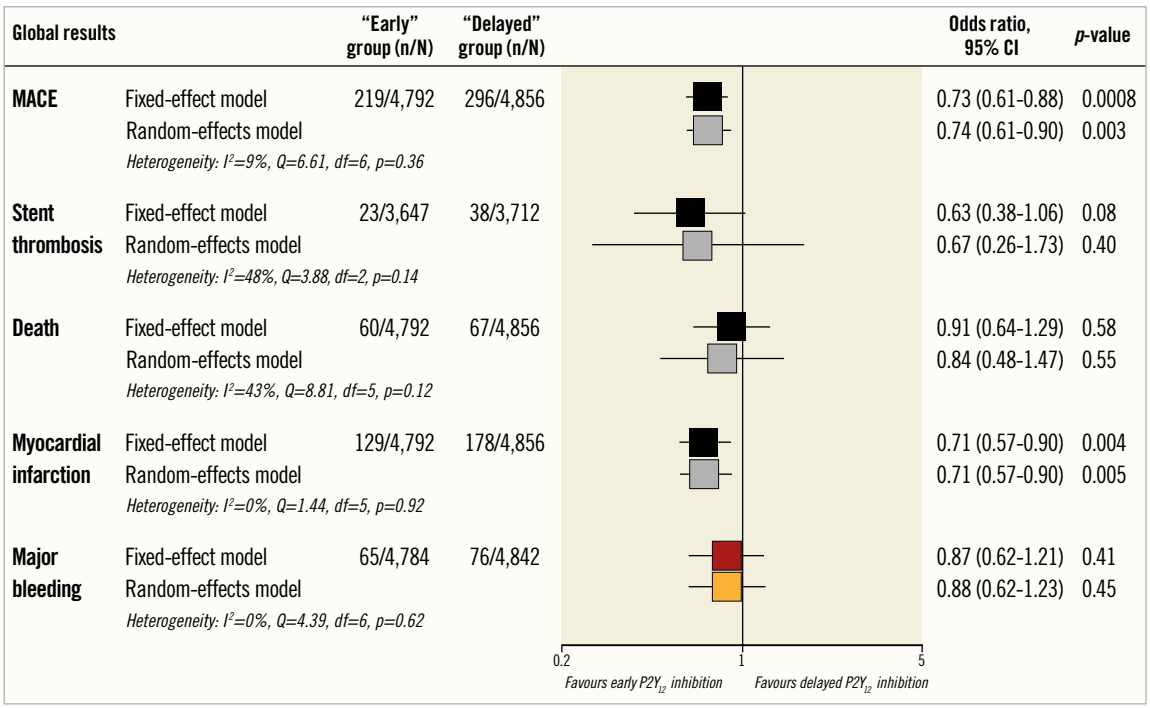

Figure 2. *Forest plot with global view on main reported events. Fixed- and random-effects are shown. CI: confidence interval; MACE: major adverse cardiac events*

Some interactions were reported **(Supplementary Table 6, Supplementary Table 7, Supplementary Figure 4)**, in particular between the type of strategy (early versus delayed) and the type of PCI (primary versus secondary), but only on death and MACE. In both cases, the effect was mainly driven by the old PCI-CLARITY study (that had a three-day delay between the "early" or "delayed" strategy); the interaction disappeared when it was removed.

ADDITIONAL ANALYSIS WITH PLATO-STEMI DATA (Supplementary Appendix)

Results of the main analysis were not changed for MACE (OR 0.81, 95% CI: 0.71-0.92, p=0.002, I^2=22%). The other endpoints are reported in **Supplementary Table 8**.

The influential analysis did not change the global results except for the old PCI-CLARITY study **(Supplementary Table 9)**.

Discussion

This meta-analysis regrouping nearly 10,000 STEMI patients shows that a strategy of early $P2Y_{12}$ inhibition before revascularisation 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 bail-out use of GPI [p=0.04]); and 3) importantly, is associated with a better coronary reperfusion before stenting (TIMI flow grade 2-3).

The early hours of STEMI are key for the management of patients in terms of delays to reperfusion and to effective $P2Y_{12}$ inhibition. Recent data suggest a benefit from earlier inhibition in these patients when the diagnosis (STEMI) and the treatment (stenting) are most likely[4,18,20]. These data are in agreement with older literature concerning the early (pre-hospital) use of GPI in STEMI patients, that showed improved reperfusion and clinical outcomes[8,21]. However, these studies were all associated with an excess of bleeding complications which is not the case here, with earlier $P2Y_{12}$ inhibition.

Several important factors interact in the benefit observed and are difficult to interpret individually. One is the time factor, allowing a longer delay to obtain effective $P2Y_{12}$ inhibition which could explain the apparently more important benefit in secondary PCI. The second factor is the potency and onset of action of the drugs, more favourable with the new oral $P2Y_{12}$ antagonists than with clopidogrel, which may explain their benefit on MI and stent thrombosis compared with clopidogrel in both TRITON-STEMI and ATLANTIC. The third factor is the IV use of cangrelor with an immediate and potent effect leading to a similar trend on MACE and stent thrombosis, despite a later administration than with prasugrel or ticagrelor. Despite the potential heterogeneity and the difficulties in weighing the roles of these different factors, the results consistently favour early $P2Y_{12}$ inhibition to prevent ischaemic events with no excess in bleeding risk. This benefit may even be underestimated here for two reasons: 1) although slow gastric absorption and delayed $P2Y_{12}$ inhibition were likely (STEMI, ± morphine use)[18,22] none of the studies used crushed pills, which favour gastric absorption and accelerate the biological efficacy of oral $P2Y_{12}$ antagonists[23,24]; 2) none of the studies using cangrelor had the drug administered before or during transfer, something which could confer a greater benefit compared with oral $P2Y_{12}$ antagonists administered at the time of the procedure.

Interestingly, the benefit of early $P2Y_{12}$ inhibition in STEMI contrasts with the absence of benefit with early oral $P2Y_{12}$ inhibition in NSTEMI patients when the diagnosis (NSTEMI) is more difficult to ascertain and the treatment (stenting) is less likely to occur than in STEMI[25,26]. A similar disconnection between NSTEMI and STEMI was observed for the early use of GPI[27].

Limitations

Our meta-analysis is subject to several limitations. We worked on new data obtained from previously published studies to limit the publication bias and to be as exhaustive as possible[4,15-17]. However, the PLATO STEMI study could not be included because 44% of patients received clopidogrel before randomisation (exclusion criterion), and because we could not obtain the non-published data for the other patients. We provide a supplementary informative analysis including PLATO that does not change our global conclusions. Otherwise, CHAMPION-PCI and CHAMPION-PHOENIX data on STEMI patients were pooled, but differences exist between trials **(Supplementary Table 1)**.

The comparison was carried out between two strategies (early vs. delayed inhibition) using several drugs that differed by their route of administration, onset and intensity of action, and several standards of care. Heterogeneity among studies was searched, fixed- and random-effects models for all the endpoints were provided, and several sensitivity analyses were conducted across groups that consolidated the global result. However, definite conclusions cannot be drawn on the potential influence of a specific medication used and/or a specific study included.

MACE, MI and major bleeding definitions differed across some studies. 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 $P2Y_{12}$ inhibition. Beyond 24 hours after PCI, both strategies had effective $P2Y_{12}$ inhibition.

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.

Conclusions

A strategy of early effective $P2Y_{12}$ inhibition significantly reduces MACE and MI in PCI for STEMI, improves coronary reperfusion before PCI, with less frequent bail-out use of GPI without any increase in bleeding complications. We believe that the present meta-analysis supports the current myocardial revascularisation guidelines recommending $P2Y_{12}$ inhibition before PCI of STEMI[7].

Impact on daily practice

As oral drug absorption might be decreased by STEMI patient conditions, additional prospective data are needed to define the optimal delay of pre-treatment with $P2Y_{12}$ antagonists in this setting. Our meta-analysis found that, in patients with STEMI scheduled to PCI, the early administration of a $P2Y_{12}$ inhibitor improves coronary reperfusion, reduces MACE, MI and bail-out GPI use without increase in major bleeding, improving the evidence in support of current STEMI guidelines.

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Conflict of interest statement

The following authors report receiving research grants or consulting/lecture fees. G. Montalescot: ADIR, Amgen, AstraZeneca, Bayer, Berlin Chimie AG, Boehringer Ingelheim, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Brigham Women's Hospital, Cardiovascular Research Foundation, Celladon, CME Resources, Daiichi Sankyo, Eli Lilly, Europa, Elsevier, Fédération Française de Cardiologie, Fondazione Anna Maria Sechi per il Cuore, Gilead, ICAN, Janssen, Lead-Up, Menarini, Medtronic, MSD, Pfizer, Sanofi-Aventis, The Medicines Company, TIMI Study Group, WebMD. J-P. Collet: Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Guerbet Medical, Medtronic, Boston Scientific, Cordis, Stago, Centocor, Fondation de France, INSERM, Federation Française de Cardiologie, Société Française de Cardiologie. A. Bellemain-Appaix: Daiichi Sankyo, Eli Lilly, Fédération Française de Cardiologie, Société Française de Cardiologie, AstraZeneca, Servier, Biotronik and Novartis. J. Silvain: Sanofi-Aventis, Daiichi Sankyo, Eli Lilly, Brahms, INSERM, Fédération Française de Cardiologie, Société Française de Cardiologie, AstraZeneca, Iroko Cardio and Servier. M. Cucherat: Bristol-Myers Squibb, AstraZeneca, Bayer, Haute Autorité de Santé. D. Bhatt: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences, Boston VA Research Institute, Society of Cardiovascular Patient Care, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi-Aventis, The Medicines Company, Elsevier, Biotronik, Boston Scientific, St. Jude Medical, FlowCo, PLx Pharma, Takeda. R. Harrington: Amgen, Gilead Sciences, Merck, MyoKardia, TMC, WebMD, AZ, CSL Behring, GSK, Merck, Portola, Regado, Sanofi-Aventis, TMC, Janssen, SignalPath, Scanadu, Element Science. K. Ducci: AstraZeneca. M. Roe: Eli Lilly, Sanofi-Aventis, Daiichi Sankyo, Janssen Pharmaceuticals, Ferring Pharmaceuticals, MyoKardia, AstraZeneca, American College of Cardiology, American Heart Association, Familial Hypercholesterolemia Foundation, PriMed, Boehringer Ingelheim, Merck, Actelion, Amgen, Novartis, Quest Diagnostics, Elsevier Publishers. S. Wiviott: Amgen, Arena, AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, Janssen, Merck, Sanofi-Aventis, Aegerion, Allergan, Angelmed, Boehringer Ingelheim, Boston Clinical Research Institute, Icon Clinical, Lexicon, St. Jude Medical, Xoma. All conflicts of interest are listed at https://www.dcri.org/about-us/conflict-of-interest. The other authors have no conflicts of interest to declare.

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Supplementary Figure 5. Forest plot for stent thrombosis according to STEMI subgroups.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/134th_issue/12

Supplementary data

Supplementary Appendix 1.

Contributors

ABA and GM prepared the first draft of the report after discussion by the writing committee of results from an agreed analysis plan. ABA and MC designed and performed the statistical analyses. CB, ABA, KD, SW, DLB, RAH and GM participated in data collection, study design, data analysis and interpretation. All authors critically reviewed the report and approved the final version. ABA and GM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary Table 1. Included studies.

Study	Year	Design	N	Follow-up	Reference LD/chronic	Comparator	GPI	MACE
ATLANTIC [18]	2014	RCDB	1,862	30 days bleeding H48-30d	Ticagrelor in the cathlab	Ticagrelor Pre-hosp (in ambulance)	*Discouraged* Pre-hosp 30.1% In hosp 27.2%	Death, MI, ST, stroke, UVR
Load&Go [17]	2013	RCT not blinded	168	30 days	Clopidogrel 300 mg in cathlab before PCI	Clopidogrel 600-900 mg in ambulance at FMC	*At physician discretion* 84.8% pre-treatment 92.9% no pre-treatment	CV death, MI, stroke, definite ST
PCI CLARITY [3]	2005	RCT Post-random. subgroup	1,863	30 days	Placebo LD and MD Open-label 300 mg LD after CA then 75 mg MD if PCI	300 mg LD pre-PCI (<45 min /start fibrinolysis) (median 3 days) then 75 mg MD	*Left to physician discretion* 33.5%	CV, death, MI, stroke
CIPAMI [19]	2011	PROBE	337	Until 7 days or hospital discharge	600 LD in cath lab post CA	600 mg at FMC	*Left to physician discretion* 47.2% pre-treatment 48.8% no pre-treatment	Death, MI, UTVR
CHAMPION PCI STEMI [15]	2009	Sub-analysis of CHAMPION PCI RCDB	8,877 STEMI 996	30 days	IV placebo + clopidogrel 600 mg 30 min before PCI+placebo at the end of PCI	Placebo po + cangrelor 30 µg/kg bolus 30 min before PCI, 4 µg/kg/min 2 hrs, then clopidogrel 600 mg	*Left to physician discretion* Not allowed <12 hrs before PCI cangrelor 52.3% clopidogrel 50.4%	Death/MI/TVR for ischaemia
CHAMPION PHOENIX [14]	2013	RCDB	11,145 STEMI 1992	48 hrs	IV placebo+clopidogrel 300-600 mg (74%) before or at the end of PCI, +placebo at the end of PCI	Placebo po+cangrelor 30 µg/kg bolus 30 min before PCI, 4 µg/kg/min 2 hrs, then clopidogrel 300-600 mg	*Only in bail-out** cangrelor: 2.3% clopidogrel: 3.5% Not available for STEMI patients	Death/MI/UVR/ stent thrombosis

ERASE MI [16]	2009	Phase IIa RCDB vs. placebo	70	30 days	IV placebo+10 min before CA, clopidogrel 600 mg before PCI (after CA), +300 mg H4 post-PCI	IV elinogrel before CA, clopidogrel 600 mg before PCI, +300 mg H4 post PCI	Strongly recommended post CA placebo 75% elinogrel 94%	Death/MI/CF/ UVR/stroke
TRITON STEMI [4]	2009	RCDB Pre-specified sub-analysis of STEMI patients of the "delayed" cohort (prasugrel vs. clopidogrel at the time of PCI)	2,470 (primary PCI: 1,599)	48 hours	Clopidogrel 300 mg at the time of PCI	Prasugrel 60 mg at the time of PCI	*Left to physician discretion* prasugrel: 68% clopidogrel 69% *Bail-out only* prasugrel 4.3% clopidogrel 5.4%	CV death/MI/ stroke

Bail-out: rescue therapy during PCI to treat new or persistent thrombus formation, slow or no reflow, side branch compromise, dissection, or distal embolisation; CA: coronary angiography; CF: cardiac failure; *GPI: GP IIb/IIIa inhibitors; LD: loading dose; MD: maintenance dose; MI: myocardial infarction; PROBE: Prospective, Randomised, Open-label, Blinded endpoint Evaluation; RCDB: randomised controlled double blinded; RCT: randomised controlled trial; ST: stent thrombosis; TVR: target vessel revascularisation; UTVR: urgent target vessel revascularisation; UVR: urgent vessel revascularisation

Supplementary Table 2. Stent thrombosis, major bleeding, MI definitions.

	Stent thrombosis			Major bleeding		MI
Study	**Definition**	**Delay**	**Criteria status**	**Definition**	**Delay**	**Definition**
ATLANTIC	ARC definite	≤24 hours	Pre-specified secondary endpoint	PLATO non-CABG	48 hours	Non-UDMI[$a]
Load&Go	ARC definite	30 days	Secondary endpoint	TIMI	30 days	Non-UDMI[$b]
CHAMPION PCI	ARC definite	48 hours	Pre-specified secondary endpoint	GUSTO severe/moderate	48 hours	Non UDMI[$c] ECG or cardiac marker changes
CHAMPION PHOENIX	ARC definite+intraprocedural*	48 hours	Pre-specified secondary endpoint	GUSTO severe/moderate	48 hours	UDMI intended[dc] *PCI-related MI not assessed in STEMI*
TRITON STEMI	ARC definite	48 hours	Pre-specified secondary endpoint	TIMI non-CABG	30 days	Non UDMI ischaemic, ECG and/or biomarker changes[$e]
PCI CLARITY	NA	NA	NA	TIMI	30 days	Non UDMI

						defined as recurrent MI[$f]
CIPAMI	NA	NA	NA	TIMI	48 hours	Non UDMI recurrent MI[$g]
ERASE MI	NA	NA	NA	TIMI	30 days	Non UDMI recurrent MI

*Defined as any new or worsened thrombus related to the stent procedure that was confirmed angiographically.
ARC: Academic Research Consortium; CABG: coronary artery bypass graft; GUSTO: Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI: myocardial infarction; NA: not available; PLATO: Study of Platelet Inhibition and Patient Outcomes; TIMI: Thrombolysis In Myocardial Infarction; UDMI: universal definition of myocardial infarction

[$a] ATLANTIC definition of MI

1) Recurrent MI within 18 hours of onset of the index MI: new ST elevation of ≥1 mm (0.1 mV) in at least two contiguous leads and recurrent cardiac ischaemic symptoms ≥20 minutes at rest.

2) Recurrent MI after 18 hours of onset of the index MI but before myocardial necrosis biomarkers have returned to normal: myocardial necrosis biomarker re-elevation (troponin) defined as an increase of at least 50% over a previous value that was decreasing **and at least one of the following**: recurrent cardiac ischaemic symptoms ≥20 minutes at rest or one of the following ECG changes: new ST elevation of ≥1 mm (0.1 mV) in at least two contiguous leads OR development of new pathological Q-waves on the ECG OR new LBBB.

3) Patients with recurrent MI after myocardial necrosis biomarkers have returned to normal (excluding MI in patients undergoing PCI or CABG in the previous 24 hours): elevation of myocardial necrosis biomarkers typical of acute MI with **at least one of the following:** recurrent cardiac ischaemic symptoms ≥20 minutes at rest or development of new pathological Q-waves on the ECG or ECG changes indicative of ischaemia or pathological findings of an acute MI.

4) MI within 24 hours after PCI: troponin ≥3x local laboratory upper normal limit, and, if the pre-PCI troponin was >ULN, both an increase by at least 50% over the previous value and documentation that troponin was decreasing prior to the suspected recurrent MI (no symptoms are required) OR development of new pathological Q-waves on the ECG (no symptoms are required).

5) MI within 24 hours after CABG:

- Troponin ≥5x local laboratory upper normal limit, and, if the pre-CABG troponin was >ULN, both an increase by at least 50% over the previous value and documentation that troponin was decreasing prior to the suspected recurrent MI and development of new pathological Q-waves on the ECG (no symptoms are required) OR
- Troponin ≥10x local laboratory upper normal limit and, if the pre-CABG troponin was >ULN, both an increase by at least 50% over the previous value and documentation that troponin was decreasing prior to the suspected recurrent MI (no Q-waves and no symptoms are required).

6) For patients who die of suspected MI and for whom no myocardial necrosis biomarkers were obtained:

- The presence of new ST-segment elevation and new cardiac ischaemic symptoms OR
- Pathological evidence of an acute MI.

Definition of terms

- Cardiac ischaemic symptoms: chest pain or discomfort or equivalent (e.g., neck or jaw symptoms, dyspnoea believed to represent an angina pectoris equivalent) believed due to impaired coronary flow secondary to atherosclerotic disease.

- At rest: started with exercise or spontaneously and did not resolve with rest.

- Development of pathological Q-waves: development of any new or presumed new Q-waves that are ≥0.03 sec in width and ≥1 mm (0.1 mV) in depth in at least two contiguous leads.

- Myocardial necrosis biomarker evidence of acute MI - any of the following: maximal concentration of troponin exceeding the 99th percentile of the values for a reference control group. Elevations should be seen on at least one occasion but preferably with a rising or falling pattern during the first 24 hours following the index clinical event. The coefficient of variation (CV; imprecision) at the 99th percentile should be lower or equal to 10%. Otherwise, the concentration at the 10% CV should be regarded as the diagnostic cut-off. For cardiac troponin T the diagnostic cut-off is equal to or greater than 0.03 μg/L. Cut-offs for cardiac troponin I assays vary among different manufacturers and should be read off from approved tabulations.

- ECG changes indicative of ischaemia - any of the following: ST-segment elevation: new or presumed new ST-segment elevation ≥1.0 mm (0.1 mV) in two or more contiguous leads. New or presumed new ST-segment depression of ≥0.5 mm (≥0.05 mV) in two or more contiguous leads. New or presumed new T-wave abnormalities - inversion of ≥1 mm (0.1 mV) in two or more contiguous leads.

- Laboratory upper normal limit: this is the value that is considered abnormal. For institutions that report an intermediate or indeterminate range for troponin I or T, these values are considered abnormal for this study.

- Procedure in case of recurrent cardiac ischaemic symptoms: if the patient experiences cardiac ischaemic symptoms ≥20 minutes at rest, he/she will be treated in accordance with local practice and the following procedures will be performed: cardiac biomarkers of necrosis (troponin) should be measured locally approximately every eight hours for at least 24 hours. A standard 12-lead electrocardiogram should be obtained during or as soon after the episode of ischaemia as possible and 24 hours after resolution of symptoms.

$b Load&Go definition of MI

New ST elevation at the J point in two contiguous leads with the cut-points ≥0.1 mV in all leads or new presence of left bundle branch block (LBBB) with ongoing symptoms of ischaemia or development of new pathological Q-waves on ECG.

$c CHAMPION PCI definition of MI

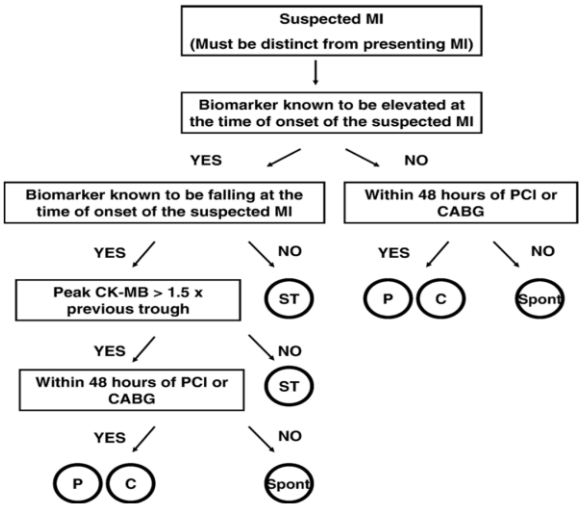
One baseline sample:
1) Biomarker normal at baseline: MI defined as CK-MB ≥3×ULN post PCI.
2) Biomarker elevated at baseline: elevation in CK-MB ≥3×ULN and 50% increase from baseline sample.

$d CHAMPION PHOENIX definition of MI

Two baseline samples ≥6 hrs apart required in NSTE-ACS patients to confirm resolving MI at baseline.
Baseline normal patients: MI defined as CK-MB ≥3×ULN post PCI.
Baseline abnormal patients were classified into MI increasing or decreasing at baseline:

Increasing: re-elevation in CK-MB post PCI (≥3×ULN and 50% increase from baseline)+additional evidence of ischaemia (2 of 2): ECG changes AND angiographic evidence.
Decreasing: re-elevation in CK-MB post PCI (≥3×ULN and 50% increase from baseline)+additional evidence of ischaemia (at least one of three): ischaemic symptoms, ECG changes, or angiographic evidence.

[$e] TRITON definition of MI



Schema from TRITON-TIMI 38 study protocol: definition of non-fatal MI [28].

ST: elevation or re-elevation of ST segment and one of the following: 1) ischaemic chest pain or equivalent longer than 20 minutes, 2) haemodynamic decompensation.
Spont: spontaneous: CK-MB or troponin greater than the ULN and one of the following: 1) ischaemic chest pain (or anginal equivalent) greater than 20 minutes; 2) ST-segment deviation 1 mm or more in one or more leads.
P: PCI: CK-MB greater than three times ULN on two samples post PCI, or greater than five times ULN on one sample, provided it is the final sample and is greater than 12 hours after PCI.
C: CABG: CK-MB greater than 10 times ULN on one sample after CABG.

New Q-waves 0.04 seconds or longer, or pathology distinct from prior MI.

[$f] CLARITY PCI definition of MI: defined as recurrent MI

Within 24 hours after a PCI: prospectively defined as needing to meet one of the following three criteria: (1) CK-MB value (or total CK value if CK-MB not available) of at least 3x upper limit of normal and, if the pre-PCI CK-MB (or total CK) value was greater than the upper limit of normal, both an increase by at least 50% over the previous value and documentation that the CK-MB (or total CK) value was decreasing prior to the suspected recurrent MI; or
(2) development of new, abnormal Q-waves in two or more contiguous leads; or
(3) pathological findings of an acute MI thought to be distinct from the qualifying MI.

[$g] **CIPAMI definition of MI: defined as recurrent MI**

Within the first 48 hrs after primary event: defined as recurrent angina and recurrent increase of CK-MB over 50% of the last level or the upper limit of normal (if CK-MB has already normalised) or angiographic documentation of reocclusion.

Supplementary Table 3. Additional analyses on the impact of early $P2Y_{12}$ inhibition on coronary reperfusion criteria.

Endpoint	No. of events/patients		OR (95% CI)	*p*-value
	Early	Delayed		
ST resolution before PCI [18,19]	125/865	130/935	1.06 (0.81-1.39)	0.66
ST resolution after PCI [18,19]	467/838	476/883	1.08 (0.89-1.30)	0.45
TIMI 2-3 flow before PCI [3,4,16-19]	1,553/3,258	1,467/3,232	1.12 (1-1.26)	0.04
TIMI 2-3 flow after PCI [3,4,16-19]	2,858/3,027	2,828/3,018	1.11 (0.89-1.40)	0.35
Bail-out GP IIb/IIIa inhibitors [3,4,15-19]	622/3,385	638/3,379	0.87 (0.75-1.00)	0.04

Supplementary Table 4. Interaction between "early" vs. "delayed" $P2Y_{12}$ inhibition and clopidogrel vs. ticagrelor/prasugrel vs. cangrelor/elinogrel.

	OR (95% CI)			***p*-value**
Endpoint	**Clopidogrel**	**Ticagrelor/ prasugrel**	**Cangrelor/ elinogrel**	***p* for interaction**
MACE	OR=0.59 95% CI (0.44-0.80)	OR=0.84 95% CI (0.64-1.11)	OR=0.83 95% CI (0.56-1.23)	3.29 *p*=0.19
All death	OR=0.54 95% CI (0.29-1.01)	OR=1.49 95% CI (0.88-2.52)	OR=0.70 95% CI (0.31-1.56)	6.46 *p*=0.04
CV death	OR=0.59 95% CI (0.31-1.13)	OR=0.60 95% CI (0.14-2.51)	OR=0.70 95% CI (0.31-1.56)	0.11 *p*=0.95
Myocardial infarction	OR=0.64 95% CI (0.45-0.90)	OR=0.77 95% CI (0.54-1.09)	OR=0.86 95% CI (0.42-1.76)	0.87 *p*=0.65
Stent thrombosis	NA	OR=0.53 95% CI (0.22-1.27)	OR=0.70 95% CI (0.37-1.32)	0.26 *p*=0.61
Stroke	OR=0.33 95% CI (0.11-1.03)	OR=0.62 95% CI (0.19-1.98)	OR=3.27 95% CI (0.13-83.03)	1.94 *p*=0.38
UVR	OR=0.64 95% CI (0.21-2.00)	OR=0.89	OR=0.87	0.25 *p*=0.88

		95% CI (0.42-1.87)	95% CI (0.43-1.75)	
Major bleeding	OR=0.90 95% CI (0.49-1.62)	OR=1.11 95% CI (0.65-1.89)	OR=0.61 95% CI (0.32-1.15)	1.99 *p*=0.37
Minor bleeding	OR=1.48 95% CI (0.63-3.48)	OR=0.88 95% CI (0.52-1.49)	OR=0.71 95% CI (0.20-2.51)	1.32 *p*=0.52
Any bleeding	OR=1.05 95% CI (0.55-2.00)	OR=0.98 95% CI (0.67-1.44)	OR=0.52 95% CI (0.15-1.74)	1.09 *p*=0.58

UVR: urgent vessel revascularisation

Supplementary Table 5. Interaction between "early" and "delayed" $P2Y_{12}$ inhibition and route of administration.

	OR (95% CI)		***p*-value**
Endpoint	**Oral**	**IV**	***p* for interaction**
All death	OR=0.87 95% CI (0.42-1.81)	OR=0.70 95% CI (0.31-1.56)	0.17 *p*=0.68
CV death	OR=0.59 95% CI (0.33-1.07)	OR =0.70 95% CI (0.31-1.56)	0.11 *p*=0.74
Myocardial infarction	OR=0.70 95% CI (0.55-0.89)	OR=0.86 95% CI (0.42-1.76)	0.31 *p*=0.58
Stroke	OR=0.44 95% CI (0.20-0.98)	OR=3,27 95% CI (0.13-83.03)	1.39 *p*=0.24
UVR	OR=0.67 95% CI (0.35-1.29)	OR=0.87 95% CI (0.43-1.75)	1.37 *p*=0.93
Major bleeding	OR=1.01 95% CI (0.68-1.50)	OR=0.61 95% CI (0.32-1.15)	1.72 *p*=0.19
Minor bleeding	OR=1.02	OR=0.71	0.27

	95% CI (0.65-1.59)	95% CI (0.20-2.51)	*p*=0.60
Any bleeding	OR=1.00 95% CI (0.72-1.39)	OR=0.52 95% CI (0.15-1.74)	1.06 *p*=0.30

UVR: urgent vessel revascularisation

Supplementary Table 6. Interaction between "early" vs. "delayed" $P2Y_{12}$ inhibition and clopidogrel vs. new $P2Y_{12}$ antagonists.

	OR (95% CI)		***p*-value**
Endpoint	**Clopidogrel**	**New $P2Y_{12}$ antagonists**	***p* for interaction**
All death	OR=0.54 95% CI (0.29-1.01)	OR=1.18 95% CI (0.77-1.83)	4.08 *p*=0.04
CV death	OR=0.59 95% CI (0.31-1.13)	OR=0.67 95% CI (0.33-1.35)	0.08 *p*=0.78
Myocardial infarction	OR=0.64 95% CI (0.45-0.90)	OR=0.79 95% CI (0.57-1.08)	0.79 *p*=0.37
Stroke	OR=0.33 95% CI (0.11-1.03)	OR=0.77 95% CI (0.27-2.22)	1.16 *p*=0.28
UVR	OR=0.64 95% CI (0.21-2.00)	OR=0.88 95% CI (0.53-1.46)	0.25 *p*=0.62
Major bleeding	OR=0.90 95% CI (0.49-1.62)	OR=0.86 95% CI (0.57-1.28)	0.01 *p*=0.91
Minor bleeding	OR=1.48	OR=0.85	1.23

	95% CI (0.63-3.48)	95% CI (0.52-1.38)	*p*=0.27
Any bleeding	OR=1.05 95% CI (0.55-2.00)	OR=0.92 95% CI (0.64-1.33)	0.11 *p*=0.74

UVR: urgent vessel revascularisation

Supplementary Table 7. Interaction between "early" vs. "delayed" $P2Y_{12}$ inhibition and primary vs. secondary PCI.

	OR (95% CI)		***p*-value**
Endpoint	**Primary PCI**	**Secondary PCI**	***p* for interaction**
All death	OR=1.12 95% CI (0.74-1.70)	OR=0.53 95% CI (0.27-1.05)	3.30 *p*=0.07
CV death	OR=0.73 95% CI (0.38-1.44)	OR=0.53 95% CI (0.27-1.05)	0.43 *p*=0.51
Myocardial infarction	OR=0.96 95% CI (0.66-1.39)	OR=0.59 95% CI (0.44-0.80)	3.98 *p*=0.05
Stroke	OR =0.89 95% CI (0.30-2.64)	OR=0.33 95% CI (0.11-0.96)	1.62 *p*=0.20
UVR	OR=0.83 95% CI (0.52-1.33)	OR=0.98 95% CI (0.06-15.78)	0.01 *p*=0.91
Major bleeding	OR=0.91 95% CI (0.63-1.31)	OR=0.66 95% CI (0.27-1.62)	0.43 *p*=0.51
Minor bleeding	OR=0.84 95% CI (0.50-1.42)	OR=1.30 95% CI (0.63-2.68)	0.90 *p*=0.34

Any bleeding	OR=0.94 95% CI (0.64-1.38)	OR=0.99 95% CI (0.57-1.73)	0.03 *p*=0.87

UVR: urgent vessel revascularisation

Supplementary Table 8. Additional PLATO STEMI data for the main analysis

Event	**Without PLATO**		**With PLATO**	
	OR* (95% CI)	*p*-value, I^2	OR* (95% CI)	*p*-value
MACE	0.73 (0.61-0.88)	0.0008; 9%	0.80 (0.71-0.90)	0.0003; 15%
MACE with PLATO not pre-treated with clopidogrel	**PLATO STEMI not pre-treated with clopidogrel** Ticagrelor group: MACE rate =9.9%=210/2,124 Clopidogrel group: MACE rate=10.8%=227/2,104		0.81 (0.71-0.92)	0.002; 22%
Death	0.91 (0.64-1.29)	0.58; 43%	0.83 (0.70-0.99)	0.04; 34%
Definite stent thrombosis	0.63 (0.38-1.06)	0.08; 48%	0.64 (0.47-0.87)	0.004; 22%
Cardiovascular death	0.63 (0.39-1.01)	0.05; 0%	0.78 (0.64-0.95)	0.01; 0%
MI	0.71 (0.57-0.9)	0.004; 0%	0.75 (0.64-0.88)	0.0004; 0%
Stroke	0.51 (0.24-1.08)	0.08; 49%	1.22 (0.85-1.74)	0.29; 63%
TIMI major bleeding	0.87 (0.62-1.21)	0.41; 0%	0.93 (0.79-1.1)	0.42; 0%

TIMI minor bleeding	0.98 (0.64-1.49)	0.91; 0%	1.02 (0.81-1.29)	0.86; 0%
TIMI any bleeding	0.95 (0.69-1.31)	0.77; 0%	0.97 (0.83-1.12)	0.77; 0%

*Fixed-effect model.

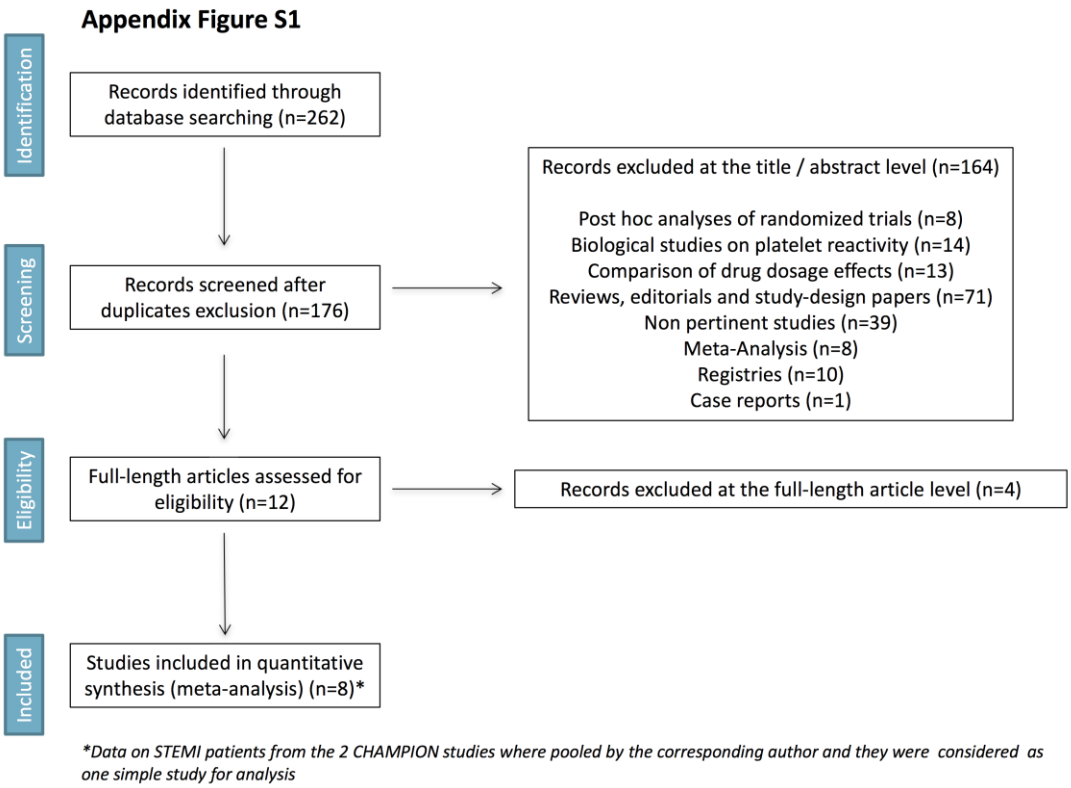
Event rates with OR and 95% CI (fixed-effect model) are reported when integrating the data of the PLATO STEMI study; published data only were available; MACE rate is shown with or without patients pre-treated with clopidogrel; for the other endpoints, all PLATO STEMI patients were included (44% were pre-treated).

Supplementary Table 9. Sensitivity analysis excluding the PCI-CLARITY data.

	OR (95% CI), *p*-value	
Endpoint	**With PCI-CLARITY**	**Without PCI-CLARITY**
MACE	OR 0.73, 95% CI (0.61-0.88), *p*=0.0008	OR 0.82, 95% CI (0.66-1.02), *p*=0.08
All death	OR 0.91, 95% CI (0.64-1.29), *p*=0.58	OR 1.12, 95% CI (0.74-1.69), *p*=0·6
CV death	OR 0.63 95% CI (0.39-1.01), *p*=0.05	OR 0.73, 95% CI (0.37-1.43), *p*=0.36
Myocardial infarction	OR 0.71, 95% CI (0.57-0.90), *p*=0.004	OR 0.78, 95% CI (0.57-1.06), *p*=0.11
Stroke	OR 0.51, 95% CI (0.24-1.08), *p*=0.08	OR 0.77, 95% CI (0.27-2.22), *p*=0.63
UVR	OR 0.83, 95% CI (0.52-1.32), *p*=0.44	OR 0.83, 95% CI (0.52-1.32), *p*=0.44
Major bleeding	OR 0.87, 95% CI (0.62-1.21), *p*=0.41	OR 0.93, 95% CI (0.65-1.32), *p*=0.67

Minor bleeding	OR 0.98, 95% CI (0.64-1.49), *p*=0.91	OR 0.81, 95% CI (0.50-1.31), *p*=0.40
Any bleeding	OR 0.95, 95% CI (0.69-1.31), *p*=0.77	OR 0.93, 95% CI (0.65-1.33), *p*=0.68

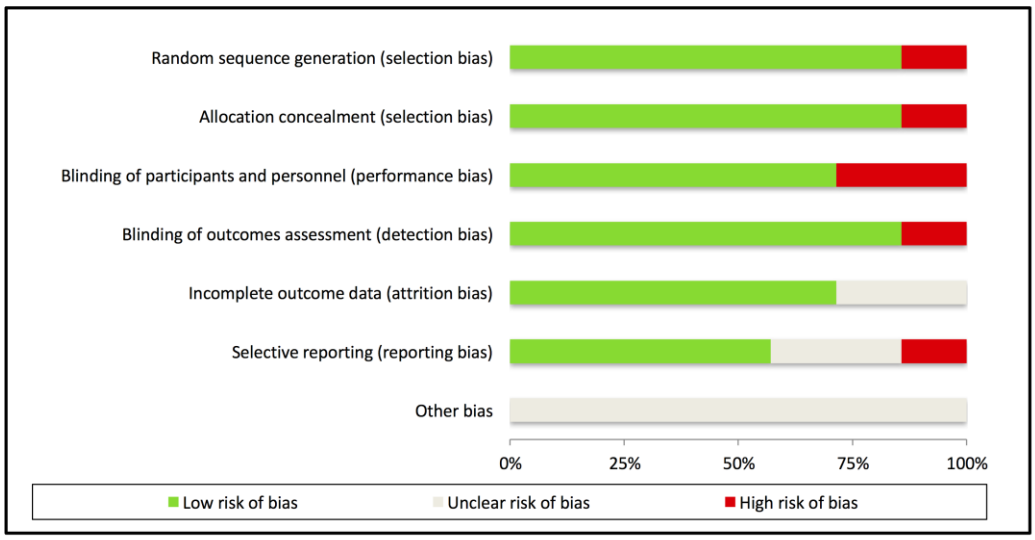
UVR: urgent vessel revascularisation



Supplementary Figure 1. Study flow diagram.

Selection process for the inclusion of studies in the meta-analysis (PRISMA standards).

Appendix Figure S2



Supplementary Figure 2. Risk of bias**.**

Each risk of bias was assessed by review authors' appreciation and items are presented as percentages across all included studies.

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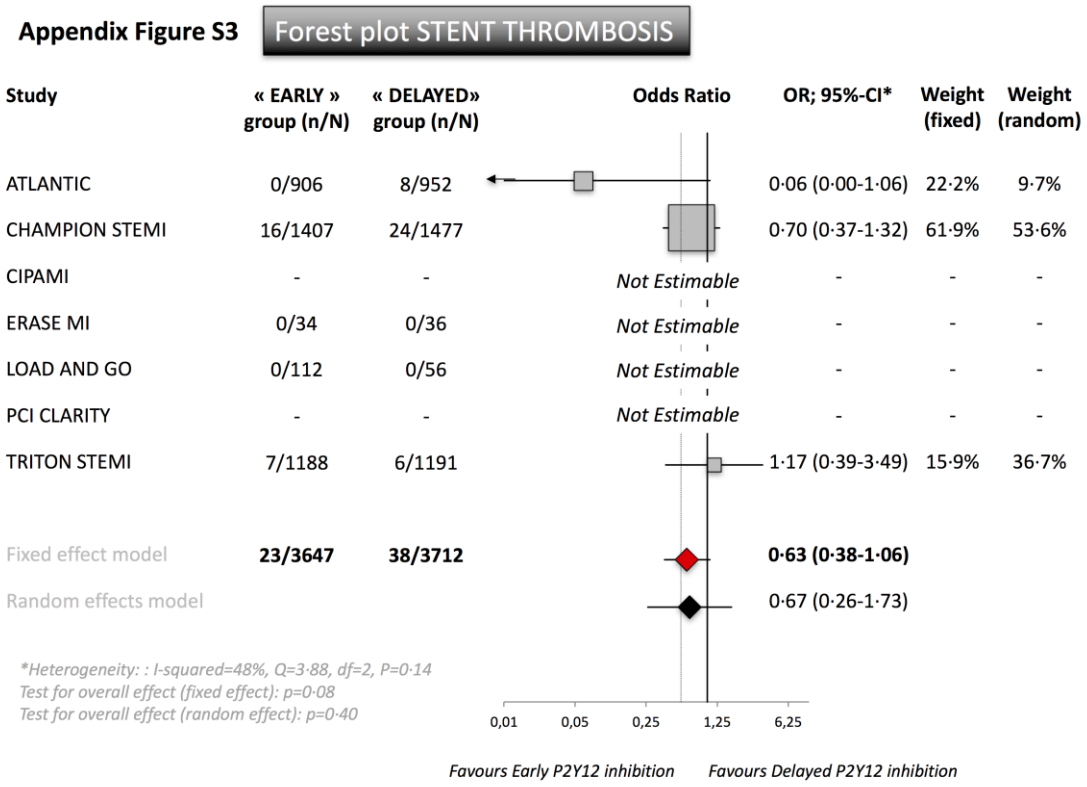
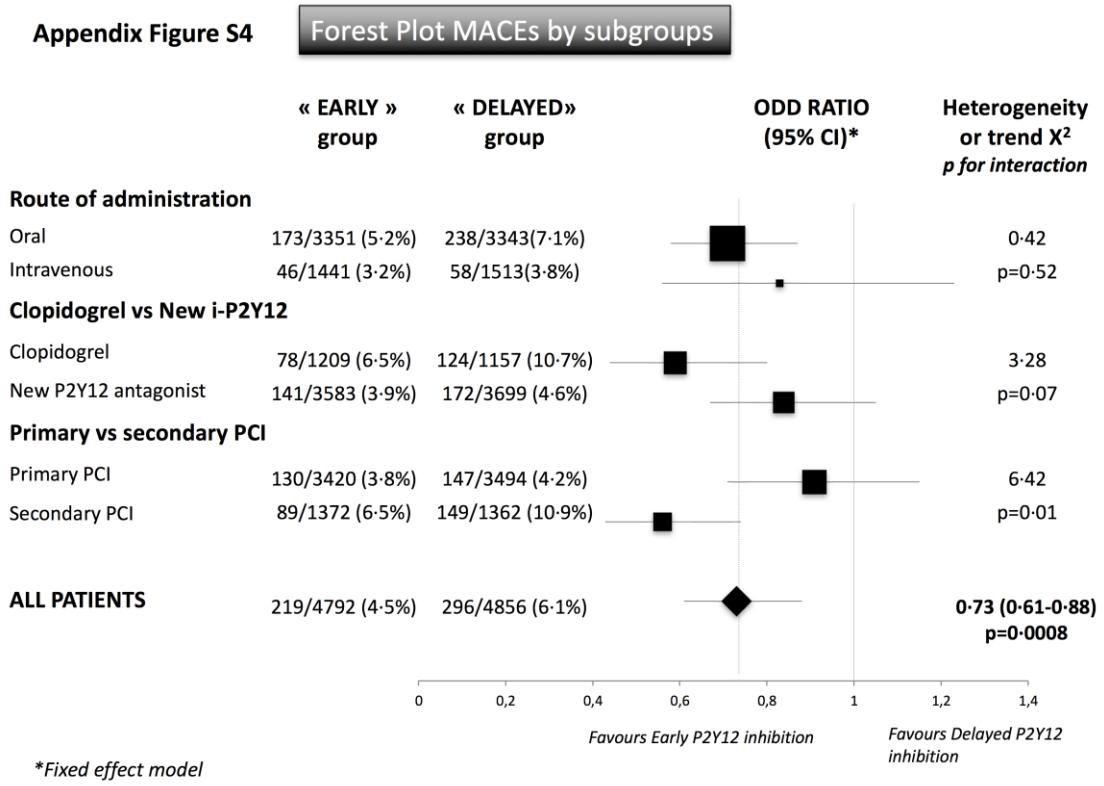


Supplementary Figure 3. Forest plot for stent thrombosis.

Fixed- and random-effect global results are shown; stent thrombosis definition is given in Table 2.

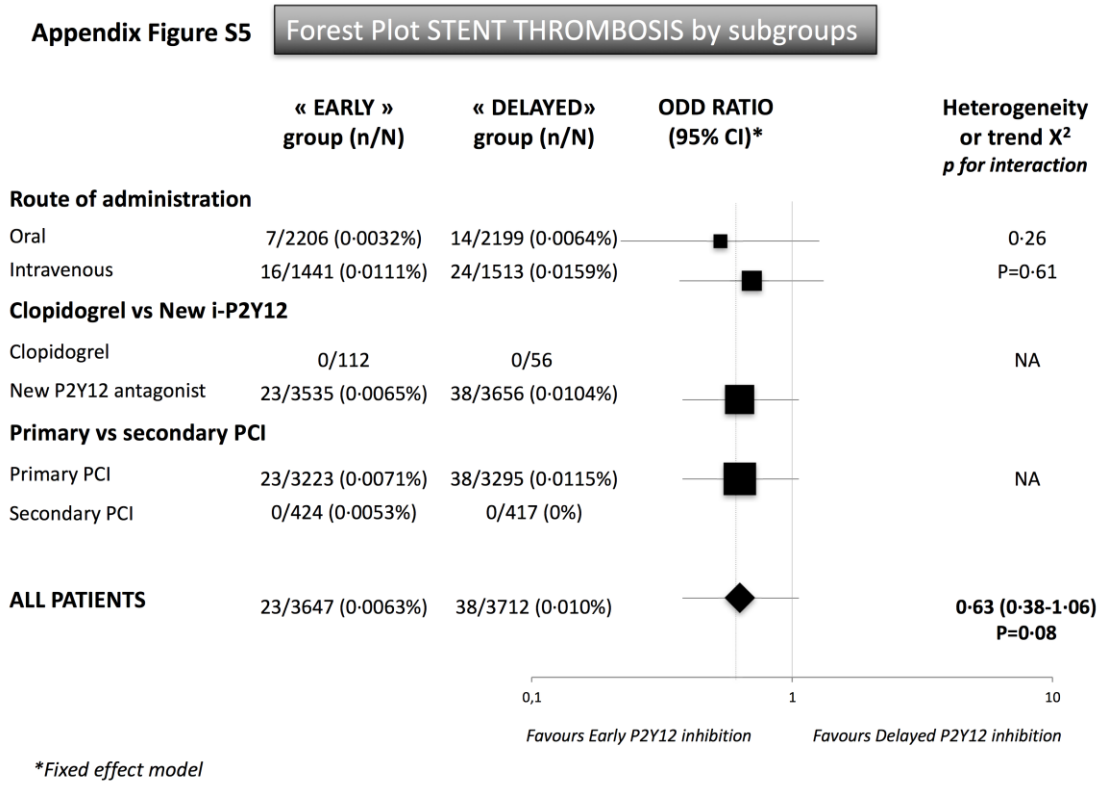
CI: confidence interval; W: weight



Supplementary Figure 4. Forest plot for MACE according to STEMI subgroups.

Fixed-effect model is reported.

CI: confidence interval; MACE: major adverse cardiac events



Supplementary Figure 5. Forest plot for stent thrombosis according to STEMI subgroups.

Fixed-effect model is reported.

CI: confidence interval; MACE: major adverse cardiac events