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New $P2Y_{12}$ Inhibitors Versus Clopidogrel in Percutaneous Coronary Intervention

A Meta-Analysis

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Objectives The purpose of this study was to perform a meta-analysis of randomized trials that compare new $P2Y_{12}$ inhibitors with clopidogrel to determine whether they improve clinical outcomes after percutaneous intervention (PCI).

Background Ticlopidine/clopidogrel prevents major adverse cardiac events after PCI, but no trials have shown an effect on mortality. New $P2Y_{12}$ inhibitors are more potent and evaluated in PCI. Whether they decrease mortality after PCI compared with clopidogrel is unknown.

Methods MEDLINE and Cochrane Controlled Trials Register databases were searched from January 1980 through January 2010. Randomized, placebo-controlled trials that compared new $P2Y_{12}$ antagonists with clopidogrel in PCI were selected. Data from 8 studies were evaluated and analyses performed for all randomized patients, PCI patients (any PCI), and PCI for ST-segment elevation myocardial infarction (STEMI) patients. All-cause mortality was the primary efficacy end point. Thrombolysis In Myocardial Infarction major bleeding was the primary safety end point.

Results A total of 48,599 patients were included with 94% of patients with acute coronary syndrome and 84% of patients undergoing PCI. New $P2Y_{12}$ inhibitors significantly decreased death (odds ratio [OR]: 0.83, 95% confidence interval [CI]: 0.75 to 0.92, $p < 0.001$ for the whole cohort; OR: 0.85, 95% CI: 0.75 to 0.96, $p = 0.008$ for any PCI; and OR: 0.78, 95% CI: 0.66 to 0.92, $p = 0.003$ for PCI for STEMI). In PCI patients, new $P2Y_{12}$ inhibitors also significantly decreased major adverse cardiac events by 18% ($p < 0.001$) and stent thrombosis by 40% ($p < 0.001$). Although there was an increase in Thrombolysis In Myocardial Infarction major bleeding for any PCI (OR: 1.23, 95% CI: 1.04 to 1.46, $p = 0.01$), no difference was observed in PCI for STEMI (OR: 0.98, 95% CI: 0.85 to 1.13, $p = 0.76$), with similar outcomes in primary PCI for STEMI. Results were confirmed in sensitivity analyses that removed the largest study.

Conclusions New $P2Y_{12}$ inhibitors decrease mortality after PCI compared with clopidogrel. The risk/benefit ratio is particularly favorable in PCI for STEMI patients. (J Am Coll Cardiol 2010;56:1542–51) © 2010 by the American College of Cardiology Foundation

Thienopyridines have become the cornerstone of treatment before, during, and after percutaneous coronary intervention (PCI), with significant decreases in the rate of 30-day major adverse cardiac events (MACE) in studies that initially compared ticlopidine and aspirin with aspirin alone or with warfarin and aspirin ($p = 0.0001$) (1). Clopidogrel showed

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a better tolerance profile than ticlopidine (2), and the benefit of a loading dose and long-term treatment was suggested in the CREDO (Clopidogrel for Reduction of Events During Observation) study (1–3) and confirmed in a meta-analysis that combined registries and randomized studies (4).

A survival effect of clopidogrel compared with placebo was shown in a large randomized non-PCI study performed in ST-segment elevation myocardial infarction (STEMI) patients, in which a 7% relative risk decrease in death was measured at 30 days with clopidogrel 75-mg daily treatment combined with aspirin (5). A nonsignificant decrease in cardiovascular (CV) mortality was also observed with clopidogrel at 30 days in STEMI patients treated with fibrinolysis and undergoing secondary PCI (6). Thus, no single study has shown a decrease in mortality with clopidogrel when used in the setting of PCI or in STEMI patients treated by PCI. A recent study also showed that doubling the dose of clopidogrel had no impact on mortality in PCI patients (7,8).

Newly developed $P2Y_{12}$ inhibitors are more potent and have a faster onset of action than clopidogrel, characteristics that make them particularly attractive for PCI. Four new $P2Y_{12}$ inhibitors have now been tested in several clinical studies that recruited STEMI, non–ST-segment elevation acute coronary syndromes, and stable coronary artery disease patients, predominantly treated with PCI. Each of these antagonists has individual properties: prasugrel is an oral pro-drug leading to irreversible blockade of the $P2Y_{12}$ receptor (9), ticagrelor is a direct-acting and reversible inhibitor of the $P2Y_{12}$ receptor with potentially more pleiotropic effects (10), cangrelor is an intravenous direct and reversible inhibitor of the $P2Y_{12}$ receptor providing the highest level of inhibition, and elinogrel is an intravenous and oral $P2Y_{12}$ antagonist with a direct and reversible action (11). None of the individual studies was powered to detect a difference in mortality compared with clopidogrel. However, 1 trial demonstrated a significant decrease in mortality in acute coronary syndromes (ACS) patients, 64.3% of whom underwent PCI (12). We hypothesized that the benefit of these new agents should be particularly present when PCI is performed, especially PCI for STEMI, an urgent and high-risk situation in which the benefit of fast and potent platelet inhibition is theoretically of most value. The aim of the present work was to perform a combined analysis of all the trials conducted comparing one of these new $P2Y_{12}$ antagonists with clopidogrel. In this way, we have been able to increase the statistical power in addressing the important question of whether there is a decrease in mortality with these new agents when used in PCI globally and in PCI for STEMI in particular.

Methods

Study objectives, design, and selected trials. The primary aim was to evaluate the effect of new $P2Y_{12}$ inhibitors compared with clopidogrel in PCI patients. We restricted our analysis to trials that met all the following inclusion criteria: 1) study population of coronary patients with PCI performed at least in a majority of this population (>70%); 2) the reference treatment was clopidogrel or, in the case of short half-life intravenous $P2Y_{12}$ inhibitors, placebo before clopidogrel administration; and 3) the report supplied data on both mortality and bleeding.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CI = confidence interval
CV = cardiovascular
MACE = major adverse cardiac event(s)
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
ST = stent thrombosis
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

We searched MEDLINE and Cochrane Controlled Trials Register databases from 1980 to January 2010. Full electronic search strategy was used, and the terms used for research were new $P2Y_{12}$, PCI, clopidogrel, prasugrel, ticagrelor, cangrelor, elinogrel. We used no language restrictions. Furthermore, we searched reference lists of relevant studies and reviews, editorials, and letters on this topic. Full-text articles, substudies, and meeting abstracts were all included.

The quality of the identified studies was assessed to ensure minimization of bias. In detail, we evaluated information regarding control for confounders, measurement of exposure, completeness of follow-up, and blinding. No formal scoring system was used. Reviewers were not blinded to journal, author, or institution of publication. With regard to our specific research questions, we collected the following variables: clopidogrel and comparator loading and maintenance dose and the percentage and type of PCI. For STEMI, all types of PCI, primary PCI (within first 24 h of symptom onset), and secondary PCI (>24 h after symptom onset) were considered. We evaluated definitions and frequencies of clinical ischemic events (all-cause death, CV death, myocardial infarction (MI), stent thrombosis (ST), stroke, MACE, and bleeding outcomes.

Selection, quality assessment, and data extraction of studies to be included in this review were all independently performed by 3 reviewers (A.B.-A., J.-P.C., and G.M.).

End points and definitions. The primary efficacy end point was all-cause death. We also examined CV death, MACE, MI, stroke, and ST. MI definitions were those of the trials concerned and were either the American College of Cardiology/American Heart Association definitions (11,13–15) or the universal definition of MI (12). Stent thrombosis was defined according the Academic Research Consortium definitions (16) and reported as definite or probable ST, although 1 study used clinical target vessel thrombosis (15). The composite end point of MACE used the definitions of the trials concerned (Table 1).

The primary safety end point for this meta-analysis was Thrombolysis In Myocardial Infarction (TIMI) non-coronary artery bypass graft major bleeding, except for 1 small study in which only major and minor bleeding combined were reported (17). For all the other studies, TIMI definitions of bleeding were considered for major or minor bleeding (18).

All end points were considered at the longest follow-up available in each study (Table 1). Only data from intention-to-treat cohorts were used for our meta-analysis.

First, a global meta-analysis of all the studies was done, including all patients regardless of the clinical presentation and the treatment with PCI. Then, the PCI meta-analysis was done, restricting the analyses to the PCI studies and PCI cohorts of studies that had also included medically treated patients; 2 small studies included in the global analysis were excluded in this any PCI analysis data because PCI patients were not individualized (17,19). Finally, a meta-analysis of PCI for STEMI patients was performed, restricting the analyses to STEMI patients undergoing either primary or secondary PCI. The same analysis was repeated in STEMI patients undergoing primary PCI (exclusion of secondary PCI patients).

Statistical analysis. We obtained the raw number of patients experiencing the outcomes of interest among all patients in each randomized treatment group from each of the publications of the selected clinical trials. Results are alternatively presented in text or in graphs.

The common effect calculation was obtained by analyses of all randomized patients (intention to treat). To give a global estimation of the treatment effect, the results of all studies were combined using a random model to minimize heterogeneity between groups and confirmed by a fixed-effects model to avoid small studies being overly weight. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by use of the EasyMa software (20). A 2-tailed α risk of 5% was used for hypothesis testing.

The main objective of the study was to evaluate efficacy and safety of the new $P2Y_{12}$ inhibitors compared with clopidogrel in the setting of PCI; we performed the analyses in all types of patients undergoing PCI (any PCI) and in STEMI patients undergoing PCI (PCI for STEMI). An additional analysis was also run for primary PCI for STEMI patients, restricting the calculation to PCI performed within 24 h of STEMI.

Although the random-effects model accommodated variability among studies, the extent of heterogeneity in the trials was also examined. The Q_Cochran test was used to look for heterogeneity between groups and a 2-tailed p value of 0.1 was considered as a cutoff for statistical heterogeneity (21). The I2 test for heterogeneity is also reported for each end point in the Online Appendix.

A systematic search for publication bias was conducted using funnel-plot graphs to check symmetrical distribution and convergence toward the pooled effect as the weight of the trials increased. As none of these graphs suggested publication bias, the funnel plots are not shown.

Finally, a sensitivity analysis was done by removing the largest study when a significant result was observed. Another sensitivity analysis was performed by removing the cangrelor studies (intravenous agent with a short half-life).

Results

Studies characteristics and global analysis. A flow chart of the meta-analysis is shown in Figure 1. By subsequent screening and assessment of titles, abstracts, and full-text articles, we included 8 studies that incorporated a total of 48,599 patients (Fig. 2). In those, 94% were ACS patients and 84% underwent PCI (Table 1). All trials were randomized, double-blind trials, and among them 3 were phase 2 studies (11,15,19). Five studies compared new oral $P2Y_{12}$ inhibitors with clopidogrel (12,15,17,19,22), 2 compared a new intravenous $P2Y_{12}$ inhibitor with an intravenous placebo with pre-PCI clopidogrel administration (11,14), and 1 compared a new intravenous $P2Y_{12}$ inhibitor to an intravenous placebo with clopidogrel administration after PCI (13). Clopidogrel loading doses varied between 300 mg (15,17,22) and 600 mg (11,13,14,19), and 1 study authorized 300-mg to 600-mg loading doses at the discretion of the treating clinician (12). Three studies tested prasugrel (15,19,22), 2 studies cangrelor (13,14), 2 others ticagrelor (12,17), and 1 elinogrel (11). Characteristics of these new $P2Y_{12}$ inhibitors are presented in Table 2. All PCI substudies included in the meta-analysis were pre-specified subanalyses of the main studies (23,24). The global analysis regardless of PCI use included 8 studies (11–15,17,19,22), with 24,697 patients of 48,599 patients receiving a new $P2Y_{12}$ inhibitor. There was no significant heterogeneity for the analyses of any studied end point. New $P2Y_{12}$ inhibitors decreased death by 17% from 3.35% to 2.75% (OR: 0.83, 95% CI: 0.75 to 0.92, $p < 0.001$), CV death by 18% from 3.61% to 2.95% (OR: 0.82, 95% CI: 0.72 to 0.92, $p < 0.001$), MACE by 14% from 10.33% to 8.81% (OR: 0.86, 95% CI: 0.8 to 0.93, $p < 0.001$). MI, ST, and target vessel revascularization were also all significantly decreased. There was no difference in stroke between groups with 0.83% for the new $P2Y_{12}$ inhibitors group and 0.75% for the clopidogrel group (OR: 1.12, 95% CI: 0.92 to 1.37, $p = 0.27$). There was a significant increase in TIMI major bleeding from 1.43% to 1.78% (OR: 1.21, 95% CI: 1.05 to 1.4, $p = 0.009$) and a modest increase in TIMI major or minor bleeding (from 5.2% to 5.73%, OR: 1.15, 95% CI: 1.01 to 1.31, $p = 0.04$). Results were confirmed when a fixed-effects model was used. In the sensitivity analysis removing studies with cangrelor, similar results were obtained (Online Appendix).

New $P2Y_{12}$ inhibitors versus clopidogrel in PCI-treated patients (any PCI). This analysis included 5 studies (11,13–15,22) and 1 PCI subset of a larger study (24), with

Table 1 Main Studies and Published Substudies Included in This Meta-Analysis

Study (Ref. #)	Year	Design	n	Follow-Up	Reference LD/Long Term	Comparator	Population	% PCI	MACE Definition
JUMBO (15)	2005	Phase II, RCDB; groups ratio 4:4:5:5	904	30 days	Clopidogrel 300 mg/75 mg	Prasugrel 60/15 mg, 40/7.5 mg or 60/10 mg	40% UA/NSTEMI, 60% SCAD	99	Death/MI/ST/stroke/hospital*
PRINCIPLE–TIMI 44 (19)	2007	Phase II RCDB, crossover at 15 days	201	15 days	Clopidogrel 600 mg/75 mg	Prasugrel 60/10 mg	100% SCAD	55	MACE/CV death/MI/stroke <15 days
TRITON (22)	2007	Phase III RCDB	13,608	15 months	Clopidogrel 300 mg/75 mg	Prasugrel 60/10 mg	8.1% STEMI, 91.9% UA/NSTEMI	99	CV death/MI/stroke
TRITON STEMI (25)†	2007	Primary PCI	1,438	15 months	Clopidogrel 300 mg/75 mg	Prasugrel 60/10 mg	STEMI	97	CV death/MI/stroke
		Secondary PCI	1,094	15 months	Clopidogrel 300 mg/75 mg	Prasugrel 60/10 mg	STEMI		
CHAMPION PCI (14)	2009	Phase III RCDB; analysis at 70% (lack of benefit)	8,716	30 days	IV placebo + clopidogrel 600 mg 30 min before PCI + placebo at the end of PCI	PO placebo + cangrelor 30-μg/kg bolus 30 min before PCI, 4 μg/kg/min 2 h, then clopidogrel 600 mg	11% STEMI, 74% NSTE-ACS, 15% SCAD	98	Death/MI/TVR for ischemia
CHAMPION PCI STEMI‡	2009	Subanalysis	996	30 days	IV placebo + clopidogrel 600 mg 30 min before PCI + placebo at the end of PCI	PO placebo + cangrelor 30-μg/kg bolus 30 min before PCI, 4 μg/kg/min 2 h, then clopidogrel 600 mg	STEMI	99	Death/MI/TVR for ischemia
CHAMPION PLATFORM (13)	2009	Phase III RCDB vs. placebo	5,362	30 days	IV placebo + clopidogrel 600 mg at the end of PCI	Cangrelor 30-μg/kg bolus, 4 μg/kg/min 2–4 h, then clopidogrel 600 mg	59% NSTEMI, 35% UA, 5% SCAD	100	Death/MI/TVR for ischemia
DISPERSE2 (17)	2007	Phase II RCDB; 1:1:1; random for ticagrelor 270 mg LD	984	4 months	Clopidogrel 300 mg/75 mg	Ticagrelor 90 or 180 mg twice daily	100% SCAD	42	Death/MI/stroke
PLATO (12)	2009	Phase III RCDB	18,624	12 months	Clopidogrel 300–600 mg/75 mg	Ticagrelor 180 mg LD, then 90 mg twice daily	45% STEMI, 43% NSTEMI, 12% UA	64	Death/MI/stroke
PLATO STEMI (27)§	2009	Phase III RCDB	8,430	12 months	Clopidogrel 300–600 mg/75 mg	Ticagrelor 180 mg LD, then 90 mg twice daily	100% STEMI	80	Death/MI/stroke
PLATO Invasive (24)§	2009	Phase III RCDB	13,408	12 months	Clopidogrel 300–600 mg/75 mg	Ticagrelor 180 mg LD, then 90 mg twice daily	49% STEMI, 51% NSTE-ACS	77	Death/MI/stroke
ERASE MI (11)	2009	Phase IIa RCDB vs. placebo; groups ratio 1:1	70	30 days	IV placebo + clopidogrel 600 mg pre-PCI, 300 mg 4 h post-PCI	Elinogrel IV doses (10 mg/20 mg/40 or 60 mg) + clopidogrel 600 mg before PCI, 300 mg 4 h post-PCI	100% STEMI	91	

*Hospitalization for recurrent ischemia. †Subgroup analysis of Wiviott et al. (22). ‡Subgroup analysis of Harrington et al. (14). §Subgroup analysis of Wallentin et al. (12).

CV = cardiovascular; IV = intravenous; LD = loading dose; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; NSTE-ACS = non–ST-segment elevation acute coronary syndromes; PCI = percutaneous coronary intervention; PO = oral; RCDB = randomized, controlled, double-blind; SCAD = stable coronary artery disease; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; TVR = target vessel revascularization; UA = unstable angina.

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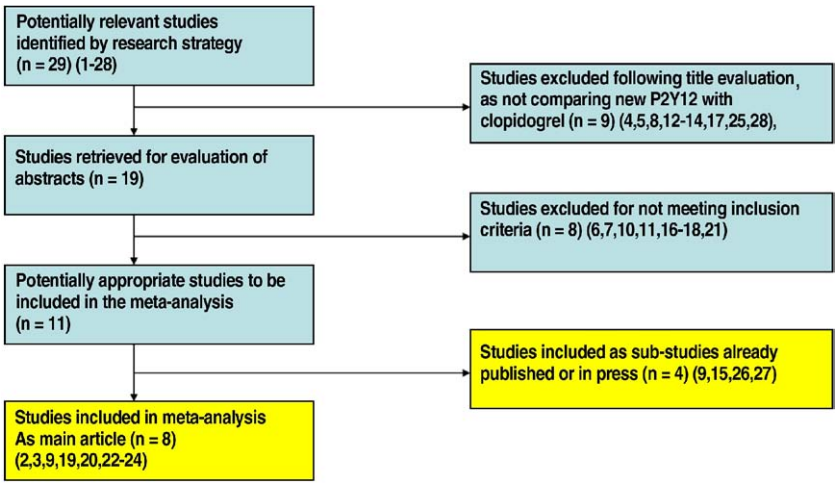

Figure 1 **Flow Chart of Study Selection**

Of 28 potentially relevant studies identified by our search strategy, only 8 main studies and 4 published substudies were kept for analysis; the others were excluded because they did not compare the new $P2Y_{12}$ with clopidogrel or not meet the inclusion criteria. (See the Online Appendix for references.)

a total of 42,198 patients (n = 21,337 in the new $P2Y_{12}$ inhibitors group versus n = 20,861 in the clopidogrel group). Most patients (95%) presented with moderate-to-high risk ACS (11,13,14,22), with 1 small study enrolling a majority of stable coronary patients (15). Results are presented in Figure 3. Death was significantly decreased by 15% from 2.89% with clopidogrel to 2.43% with the new $P2Y_{12}$ inhibitors (p = 0.008). Similarly, a significant 13% decrease in MACE from 9.99% to 8.61% (p = 0.003) and a 40% decrease in ST from 1.68% to 1.02% (p < 0.001) were observed. There was also a significant 16% decrease in CV death from 3.11% to 2.61% (OR: 0.84, 95% CI: 0.72 to 0.96, p = 0.01), and a 14% decrease in MI from 7.39% to 6.32% (OR: 0.86, 95% CI: 0.74 to 1.01, p = 0.07). There was no difference in stroke between groups with 0.72% with new $P2Y_{12}$ inhibitors versus 0.38% with clopidogrel (OR: 1.06, 95% CI: 0.84 to 1.34, p = 0.62). There was a significant increase in TIMI major bleeding from 1.28% in the clopidogrel group to 1.56% in the new $P2Y_{12}$ inhibitors group (OR: 1.23, 95% CI: 1.04 to 1.46, p = 0.01), and in TIMI major or minor bleeding, which increased from 2.56% with clopidogrel to 3.14% with new $P2Y_{12}$ inhibitors (OR: 1.25, 95% CI: 1.11 to 1.4, p < 0.001). These results were confirmed in a fixed-effects model.

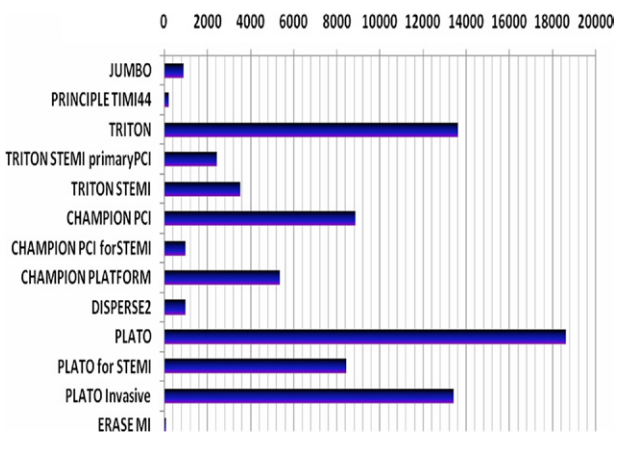

Figure 2 **Size of Studies and Substudies Included in the Meta-Analysis**

The 8 studies, 4 substudies, and the primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) subgroup of TRITON considered for analysis are shown.

In the sensitivity analysis after removal of the largest PCI study (22), the results persisted with significant decreases in death (OR: 0.80, 95% CI: 0.69 to 0.73, p = 0.003), CV death (OR: 0.81, 95% CI: 0.67 to 0.97, p = 0.02), MACE (OR: 0.90, 95% CI: 0.81 to 1.00, p = 0.05), and ST (OR: 0.67, 95% CI: 0.49 to 0.92, p = 0.01). There was no difference between groups for MI and stroke. TIMI major bleeding did not differ between the 2 groups in this sensitivity analysis (OR: 1.11, 95% CI: 0.79 to 1.56, p = 0.54, but TIMI major or minor bleeding was more frequent due to an excess of minor bleeding (OR: 1.19, 95% CI: 1.02 to 1.39, p = 0.03). The results were also confirmed after removal of patients treated with cangrelor in a sensitivity analysis (Online Appendix).

New $P2Y_{12}$ inhibitors versus clopidogrel in STEMI patients treated by PCI (PCI for STEMI). In this analysis, 13,028 STEMI patients were included from 4 studies that enrolled such patients (11,14,23,25). Primary or secondary PCI was performed in 97% of the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) STEMI pa-

Table 2 New and Old $P2Y_{12}$ Inhibitor Characteristics

$P2Y_{12}$ Antagonist	Type	Mode of Administration	Action	Loading Dose/Maintenance
Clopidogrel	Thienopyridine	PO	Hepatic metabolism to the active form; irreversible inhibition	300–600 mg, 75 mg
Prasugrel (CS-747)	Thienopyridine (new generation)	PO	Hepatic metabolism to the active form; irreversible inhibition	60 mg, 10 mg
Ticagrelor (AZD-6140)	Cyclopentyl-triazolo-pyrimidine	PO	Direct reversible inhibition; competitive link	180 mg, 90 mg × 2
Cangrelor (ARC-669931MX)	ATP analogue	IV	Direct reversible inhibition; competitive link	30-μg/kg bolus, 4 μg/kg/min, 2–4 h
Elinogrel	Thienopyridine (PRT060128)	IV, PO	Direct reversible (8 h) inhibition; competitive link	Bolus ranging from 10–60 mg

ATP = adenosine triphosphate; IV = intravenous; PO = oral.

tients (with 69% of primary PCI), 91.4% of the ERASE MI (Early Rapid Reversal of Platelet Thrombosis With Intravenous Elinogrel Before PCI to Optimize Reperfusion in Acute Myocardial Infarction) patients, 72% of the PLATO (Study of Platelet Inhibition and Patient Outcomes) STEMI patients, and 99% of the CHAMPION (Cangrelor versus Standard

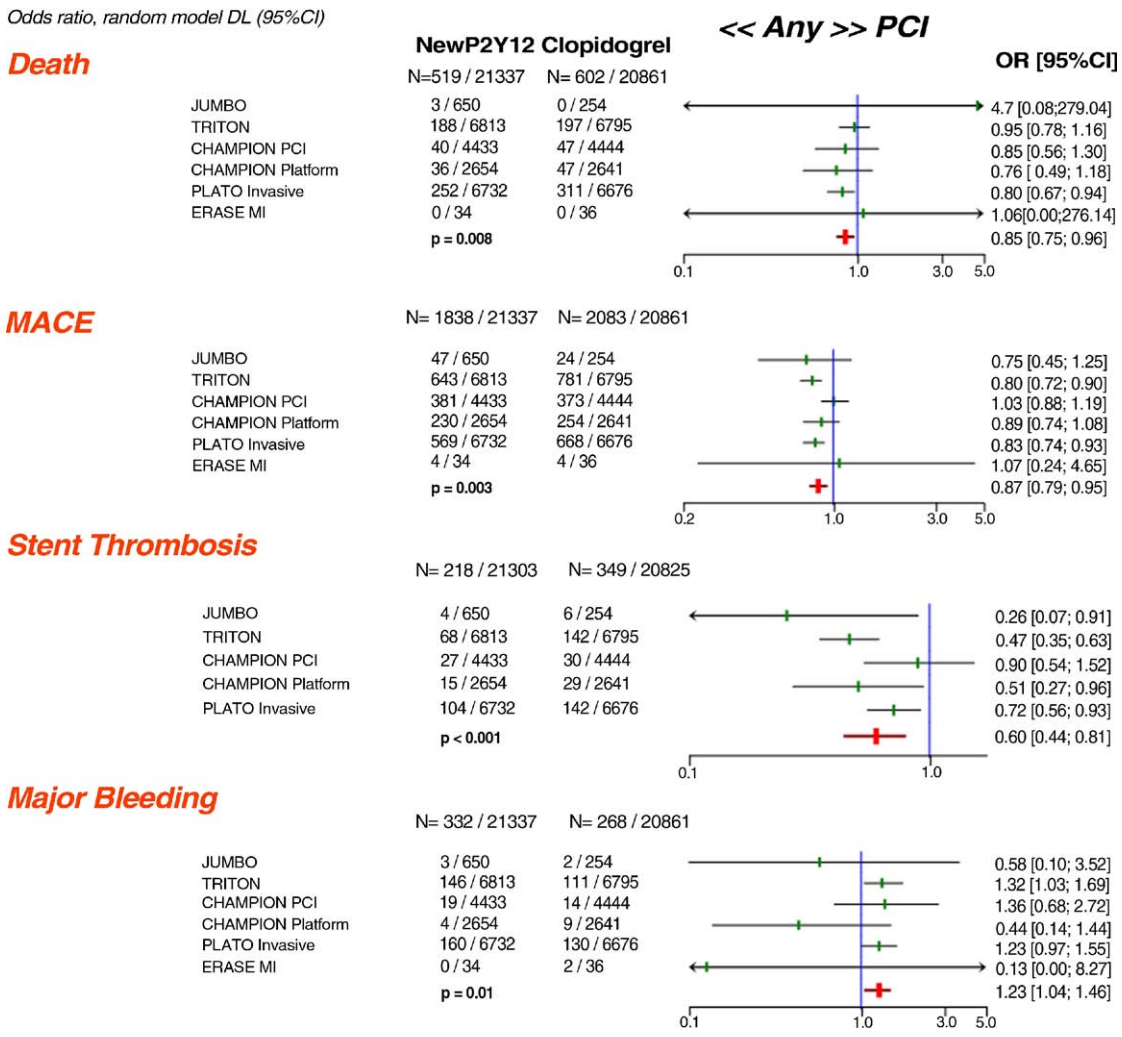

Figure 3 Effect of New $P2Y_{12}$ Antagonists on Any PCI

Ninety-five percent of patients presented with moderate-to-high risk acute coronary syndromes. Compared with clopidogrel, new $P2Y_{12}$ inhibitors significantly decreased death by 15% (from 2.89% to 2.43%, p = 0.008), major adverse cardiac events (MACE) by 13% (from 9.99% to 8.61%, p = 0.003), and stent thrombosis by 40% (from 1.68% to 1.02%, p < 0.001). They produce a significant increase in Thrombolysis In Myocardial Infarction major bleeding from 1.28% to 1.56% (OR: 1.23, 95% CI: 1.04 to 1.46, p = 0.01). CI = confidence interval; OR = odds ratio; other abbreviation as in Figure 2.

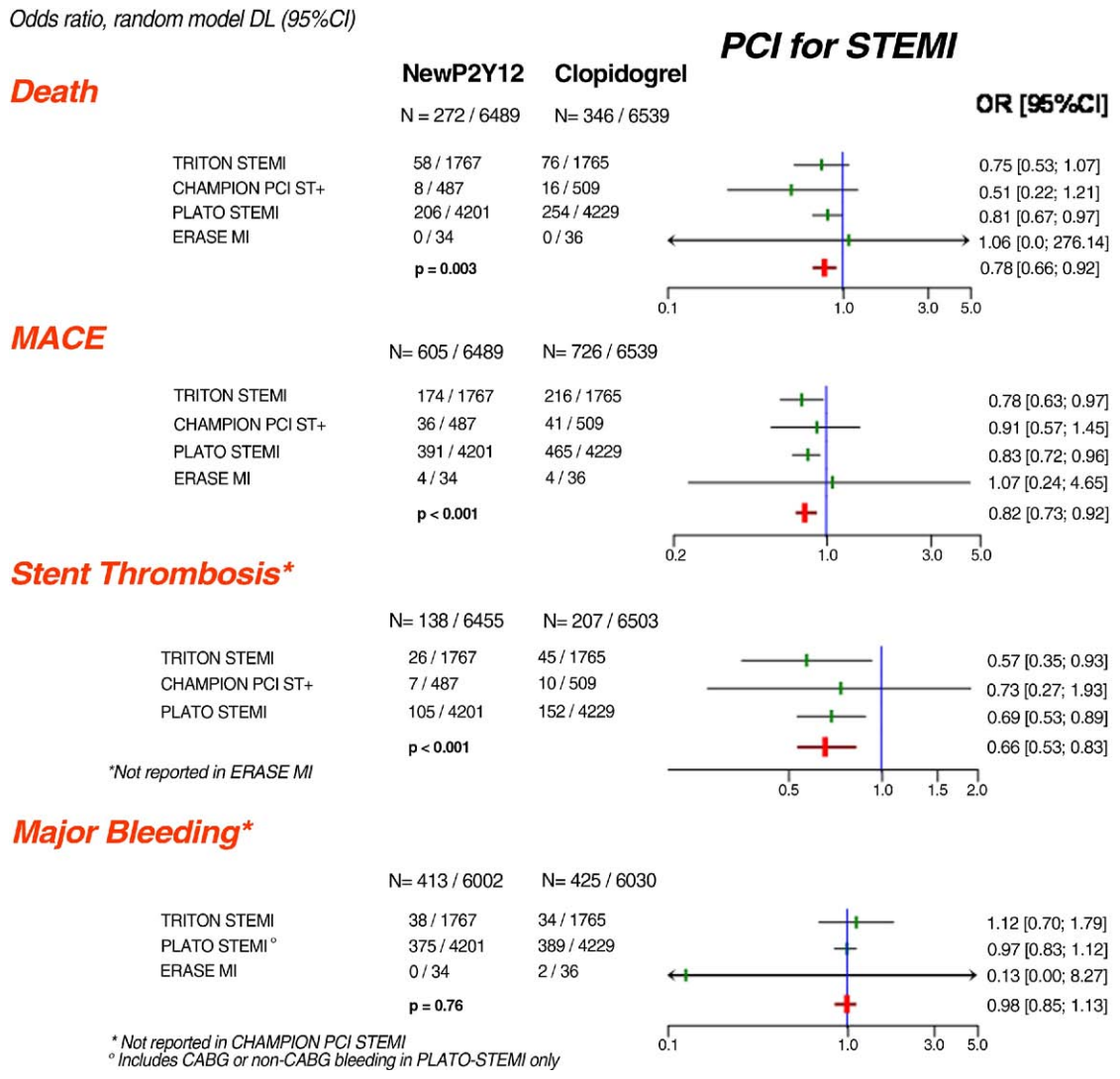

Figure 4 **Effect of New P2Y$_{12}$ in PCI for STEMI (Primary and Secondary PCI)**

There was a stronger anti-ischemic effect of new P2Y$_{12}$ antagonists in PCI for STEMI than in the any PCI analysis, with a significant decrease in death by 22% (from 2.56% to 2.09%), in MACE by 16% (from 5.29% to 4.19%), and in stent thrombosis by 33% (from 3.18% to 2.14%). Thrombolysis In Myocardial Infarction major bleeding was not different between the 2 groups. Abbreviations as in Figures 2 and 3.

Therapy to Achieve Optimal Management of Platelet Inhibition) PCI STEMI patients. Results are reported in Figure 4. This pooled analysis revealed a stronger anti-ischemic effect than in the previous analysis (any PCI), with a significant 22% decrease in death (from 2.56% to 2.09%), a significant 16% decrease in MACE (from 5.29% to 4.19%), and a significant 33% decrease in ST (from 3.18% to 2.14%). Similarly, significant decreases were observed for CV death (from 4.77% to 3.89%; OR: 0.81, 95% CI: 0.67 to 0.97, p = 0.02) and MI (from 6.45% to 5.04%; OR: 0.81, 95% CI: 0.69 to 0.95, p = 0.008). There was an increase in stroke (from 1.13% to 1.54%, OR: 1.48, 95% CI: 1.07 to 2.07, p = 0.02). Major bleeding was not different between the 2 groups, nor was TIMI major or minor bleeding (4.89% vs. 4.78% for clopidogrel, OR: 1.0, 95% CI: 0.42 to 2.36, p = 1.0). All results were confirmed with a fixed-effects model.

In a sensitivity analysis excluding the largest dataset (12), these differences persisted with the same magnitude for death (OR: 0.72, 95% CI: 0.52 to 0.99, p = 0.04), MACE (OR: 0.81, 95% CI: 0.67 to 0.98, p = 0.03, and ST (OR: 0.60, 95% CI: 0.39 to 0.93, p = 0.02). Similar trends were observed for CV death (OR: 0.74, 95% CI: 0.49 to 1.1, p = 0.13), and MI (OR: 0.8, 95% CI: 0.62 to 1.04, p = 0.09), and there was no difference in stroke, TIMI major bleeding, and TIMI major or minor bleeding (Fig. 5).

In the additional sensitivity analysis restricted to primary PCI (after exclusion of the secondary PCI of the TRITON

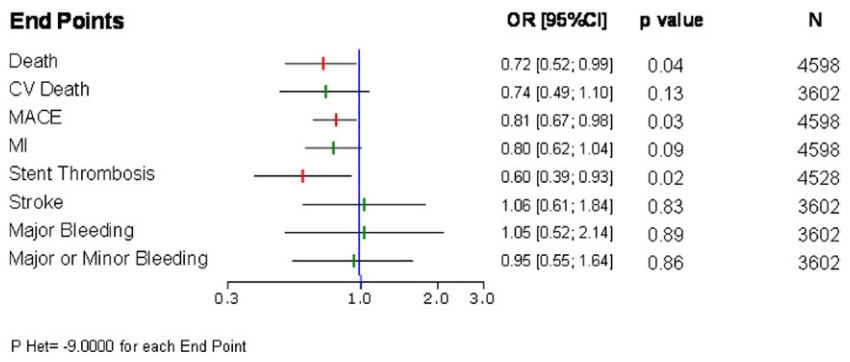

Figure 5 **Effect of New P2Y$_{12}$ in PCI for STEMI: Sensitivity Analysis After Removing the PLATO STEMI (Largest Dataset)**

The differences observed in Figure 4 persisted with the same magnitude for death, MACE, and stent thrombosis, with no difference in Thrombolysis In Myocardial Infarction major bleeding. CV = cardiovascular; MI = myocardial infarction; other abbreviations as in Figures 2, 3, and 4.

STEMI study), all the previous results were confirmed (i.e., a significant decrease in death and all ischemic events, without an increase in major bleeding or TIMI major or minor bleeding, as shown in Fig. 6).

All results were confirmed in the sensitivity analyses restricted to PCI for STEMI or primary PCI after removal of patients treated with cangrelor (Online Appendix).

Discussion

Increasing loading doses of clopidogrel has been used to decrease the time to reach maximal platelet inhibition, decrease interindividual variability, and subsequently decrease major ischemic events after PCI, without any detectable effect on survival (8,26–29). Greater and more rapid inhibition of platelet aggregation has become the goal for new antiplatelet agents with the expectation of further improving outcomes after PCI. A large majority of patients recruited in the phase 3 studies that evaluated P2Y$_{12}$ inhibitors were PCI patients. The main finding of the present meta-analysis is the decrease in mortality observed with these new P2Y$_{12}$ inhibitors compared with clopidogrel when used in patients treated with PCI. This finding is further supported by the significant decreases in death also observed in STEMI patients treated by PCI or by primary PCI, 2 smaller groups of patients, but at higher risk and therefore theoretically obtaining greater benefit from rapid platelet inhibition for PCI. Additional findings on MACE and ST are also in line with the survival benefit.

The new P2Y$_{12}$ inhibitor agents have in common a greater potency and a faster onset of action than clopidogrel. Because these agents in the same class have individual properties and differ from one another, we cannot confirm here that the survival effect that we observed in our meta-analysis is a real class effect. The largest study, PLATO, which assessed ticagrelor therapy, weigh for 31.8% of the patients of the PCI meta-analysis and 64.7% of the patients of the analysis in STEMI patients, is the one with the greatest effect on mortality in PCI (9). However, when this study is removed, the same trend is observed with still a significant 22% decrease in mortality in STEMI

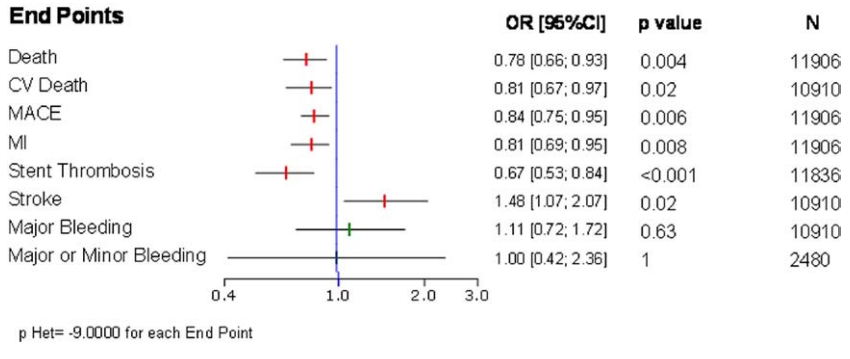

Figure 6 **Effect of New P2Y$_{12}$ in Primary PCI for STEMI**

All the results observed in STEMI analysis were confirmed with a significant decrease in death, MACE, and stent thrombosis, without an increase in major bleeding. Abbreviations as in Figures 2, 3, 4, and 5.

patients treated with PCI. This preponderant benefit observed in PCI for STEMI and in primary PCI is to be highlighted and might be explained by the greatest thrombotic situation encountered and the need for urgent strong platelet inhibition. The benefit for mortality of the new generation of $P2Y_{12}$ inhibitors in STEMI patients treated with PCI is consistent across the 3 large studies (7,14,23) included in this global analysis and is also confirmatory of the observation made in the TRITON STEMI analysis of a significant decrease in mortality with prasugrel at 30 days (1.6% vs. 2.6%; OR: 0.62, 95% CI: 0.39 to 0.99, p = 0.04).

Two confounding variables concerning clopidogrel may have skewed results in favor of the newer agents. The first one is the varying loading doses of clopidogrel (300 mg vs. 600 mg) in the cohorts studied; therefore, it is possible that mortality in the clopidogrel group was negatively influenced by inclusion of the 300-mg loading dose, but a subanalysis with clopidogrel loading dose ≥600 mg studies shows similar results (significant decrease in death, CV death, and ST in all groups and MACE in global and PCI for STEMI groups under new $P2Y_{12}$ antagonists compared with clopidogrel ≥600 mg). The second is that randomization to the clopidogrel arm of the trials did not include genotyping for hepatic cytochrome (Cyp2C19) gene variants (present in 25% to 30% of the population) that confer genetic resistance to clopidogrel and a striking 3-fold increase in risk of ST and death (30–34). It is possible that the enhanced efficacy of newer agents is mostly or only confined to those individuals with clopidogrel-resistant alleles. Finally, the high number needed to treat for benefit from the newer agents and their financial cost compared with clopidogrel's generic copies might temper enthusiasm for these agents in the greater population with the exception of individuals with STEMI.

Although an excess of major bleeding was noted in the analysis done in PCI patients, it disappears in STEMI patients undergoing PCI. This good safety profile in STEMI patients undergoing PCI has been reported before (25). Whether this is related to more intense platelet activation in these patients is possible but cannot be shown here. It is, however, important to acknowledge that most STEMI patients have an intracoronary thrombus, whereas most non–ST-segment elevation ACS patients do not and have less intense platelet activation. Thus, for a similar decrease in platelet aggregation, STEMI patients probably have still higher levels of platelet aggregation than non–ST-segment elevation ACS patients, a possible explanation to the better safety observed in STEMI patients. The excess of stroke restricted to primary PCI of STEMI exposed to the newer agents may challenge the net clinical benefit of these agents. However, the heterogeneity in stroke definitions across studies and the absence of such an effect in other subgroups also suggest a play of chance for this finding.

Study limitations. The present work has potential limitations inherent in meta-analyses such as inevitable differences between trials (study designs, inclusion criteria, lengths of follow-up, and end points). The major limitation may be due to the disparity of the agent characteristics, as already noted. Results are not based on individual data, and thus data on life-threatening and fatal bleeding are not available. Despite these limitations, a significant improvement in survival and other hard clinical outcomes was observed that are particularly interesting for the STEMI subgroup. Indeed, there was an apparent gradient for the risk/benefit ratio with a 15% decrease in death in the any PCI analysis, increasing to a 22% decrease in the PCI for STEMI analysis. At the same time, major bleeding increased significantly in the any PCI analysis by 23%, whereas there was no excess of major bleeding in the PCI for STEMI analysis. However, the excessive bleeding seen with the newer agents represents a major complication of scheduled PCI and has been previously linked to poor clinical outcomes including death. Finally, we used the longest follow-up available for each study, but there were differences between short-term and long-term studies that may induce bias in results. Furthermore, the limited 1-year follow-up of the cohorts from the individual trials may fail to provide an adequate assessment of the substantial safety concerns. However, the results show that most of the effects seem to be concentrated in the first month of follow-up, so we may have decreased rather than increased the differences by taking the longest follow-up reported in each study.

Conclusions

In PCI patients, new $P2Y_{12}$ inhibitors decrease all-cause mortality and major ischemic events. The net benefit is particularly marked in PCI for STEMI patients, in which there is no significant increase in major bleeding when compared with clopidogrel.

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Key Words: acute coronary syndrome ■ cangrelor ■ clopidogrel ■ elinogrel ■ $P2Y_{12}$ antagonists ■ percutaneous coronary intervention ■ prasugrel.

APPENDIX

For additional figures, table, and references, please see the online version of this article.

New P2Y12 Inhibitors Versus Clopidogrel in Percutaneous Coronary Intervention: A Meta-Analysis

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