

Review

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Ischaemic and bleeding complications with new, compared to standard, ADP-antagonist regimens in acute coronary syndromes: a meta-analysis of randomized trials

E.P. NAVARESE^{1,2}, M. VERDOIA¹, A. SCHAFFER¹, P. SURIANO¹, M. KOZINSKI²,
F. CASTRIOTA³, S. DE SERVI⁴, J. KUBICA² and G. DE LUCA¹

From the ¹Division of Cardiology, 'Maggiore della Carità' Hospital, Università del Piemonte Orientale 'A. Avogadro', Novara, Italy, ²Department of Cardiology and Internal Medicine, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, ³GVM Care and Research, Interventional Cardio-Angiology Unit, Cotignola, Italy and ⁴Department of Cardiovascular Disease, Civic Hospital, Legnano, Italy

Address correspondence to G. De Luca, MD, PhD, Aggregate Professor of Cardiology, Chief Interventional Cardiology, 'Maggiore della Carità' Hospital, Università del Piemonte Orientale 'A. Avogadro', Novara, Italy. email: giuseppe.deluca@maggioreosp.novara.it

Summary

Background: Platelets play a pivotal role in the pathogenesis of acute coronary syndromes (ACS) and their inhibition remains a mainstay therapy in this setting. We aimed to perform a meta-analysis of randomized trials to evaluate the benefits of new oral antiplatelet regimens to block platelet ADP-receptors compared to standard-dose clopidogrel (300 mg loading dose followed by 75 mg/daily).

Methods: We obtained results from all randomized trials enrolling patients with ACS. Primary endpoint was mortality. Secondary endpoints were myocardial infarction and definite in-stent thrombosis. Safety endpoint was the risk of major bleeding complications. We prespecified subanalyses according to new antiplatelet drugs (prasugrel/ticagrelor), high-dose clopidogrel (600 mg) and patients undergoing percutaneous coronary intervention.

Results: A total of seven randomized trials were finally included in the meta-analysis ($n=58\,591$).

We observed a significant reduction in mortality (2.9% vs. 3.4%, OR=0.87, 95% CI 0.79–0.95, $P=0.002$), recurrent myocardial infarction (4.2% vs. 5.2%, OR=0.80, 95% CI 0.74–0.87, $P<0.0001$), definite in-stent thrombosis (0.9% vs. 1.7%, OR=0.52, 95% CI 0.43–0.63, $P<0.0001$).

The benefits in mortality and reinfarction were driven by the treatment with prasugrel or ticagrelor, without a significant difference in terms of major bleeding complications as compared to standard-dose clopidogrel (5% vs. 4.7%, OR=1.06 95% CI 0.96–1.17, $P=0.25$).

Conclusions: This meta-analysis showed that new oral antiplatelet regimens are associated with a significant reduction in mortality, reinfarction and in-stent thrombosis in ACS patients without an overall increase of major bleeding when treated with new antiplatelet drugs.

Introduction

Platelets play a pivotal role in the pathogenesis of acute coronary syndromes (ACS). The combination of aspirin and clopidogrel (300 mg loading dose followed by 75 mg/daily) has represented for years the oral antiplatelet therapy of choice.¹ Large interests have been focused on new therapeutic strategies to block ADP receptors in order to overcome several limitations of clopidogrel, such as large interindividual variability, delay in onset of action and irreversibility.²⁻⁴ However, it must be recognized that an improvement in platelet aggregation inhibition may be counterbalanced by a higher risk of bleeding complications.⁵ Thus, the aim of the current study was to perform a meta-analysis of randomized trials to evaluate the benefits in terms of ischemic and bleeding complications of new oral antiplatelet regimens to block platelet ADP receptors as compared to standard dose of clopidogrel.

Methods

Eligibility and search strategy

We obtained results from all randomized controlled trials (RCTs) on adjunctive ADP receptor antagonists among patients with ACS. The literature was scanned by formal searches of electronic databases (MEDLINE and CENTRAL) from January 1990 to January 2010, the scientific session abstracts in *Circulation*, *Journal of the American College of Cardiology*, *European Heart Journal* and *American Journal of Cardiology* from January 1990 to January 2011. Furthermore, oral presentations and/or expert slide presentations were included (searched on the TCT (www.tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org), AHA (www.aha.org) and ESC (www.escardio.org) websites from January 2002 to January 2011. The following key words were used: randomized trial, ACS, unstable angina, coronary angiography, coronary angioplasty, antiplatelet therapy, thienopyridine, ADP antagonist, clopidogrel, high-dose clopidogrel, prasugrel, ticagrelor, AZD-6140. Inclusion criteria were: (i) randomized treatment allocation and (ii) availability of complete clinical data. Exclusion criteria consisted of: (i) follow-up data in <90% of the patients; (ii) ongoing studies or irretrievable data and (iii) intravenous therapy with periprocedural but not chronic administration. No language restrictions were enforced.

Data extraction and validity assessment

Data were independently abstracted by two investigators. In case of incomplete or unclear data, authors, where possible, were contacted. Disagreements were resolved by consensus. Data were managed according to the intention-to-treat principle.

Outcome measures and prespecified subanalyses

Clinical endpoints assessed were mortality as primary endpoint (all-cause mortality was preferred when reported, or cardiovascular mortality), myocardial infarction and definite in-stent thrombosis (secondary endpoints) at follow-up, whereas major bleeding complications (according TIMI major bleeding definition when available, or according to study definition) were assessed as safety endpoint.

We performed prespecified subanalyses according to new antiplatelet drugs (prasugrel/ticagrelor), high-dose clopidogrel (600 mg) and patients undergoing percutaneous coronary intervention (PCI).

Data analysis

Statistical analysis was performed using the Review Manager 4.27 freeware package, SPSS 11.5 statistical package. Odds ratio (OR) and 95% confidence intervals (95% CIs) were used as summary statistics. The pooled OR was calculated by using a fixed effect model (the Mantel-Haenszel method) and the random effect model between study heterogeneity was analyzed by means of $I^2 = [(Q-df)/Q] \times 100\%$, where Q is the χ^2 statistic, and df is its degrees of freedom. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value >50% may be considered substantial heterogeneity. The potential publication bias was examined by constructing a 'funnel plot', in which the standard error (SE) of the ln OR was plotted against the OR (mortality). Prespecified subanalyses were conducted according to new antiplatelet drugs (prasugrel/ticagrelor), high-dose clopidogrel and patients undergoing PCI. The study was performed in compliance with the Quality of Reporting of Meta-Analyses (QUOROM) guidelines.⁶

Results

A total of 10 RCTs were initially identified (Figure 1).⁷⁻¹⁹ Two trials^{17,18} were excluded because of a temporary (periprocedural) intravenous

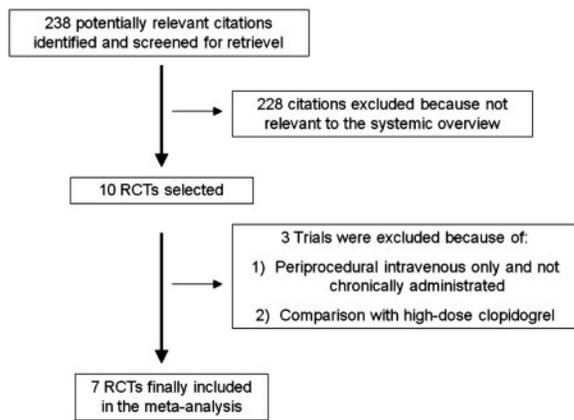


Figure 1. Flow diagram of the systematic overview process.

ADP-blocker administration but not chronic therapy. One trial was excluded because of comparison between prasugrel and high-dose clopidogrel.¹⁹ Therefore, a total of seven randomized trials were finally included in the meta-analysis (Table 1), with 58 591 patients randomized to 300 mg clopidogrel ($n=29\,284$) or new antiplatelet drugs (prasugrel or ticagrelor) or dosages (high-dose clopidogrel) ($n=29\,307$). A total of 43 807 patients underwent PCI.

The TRITON-TIMI 38^{7,8} included only patients undergoing coronary angioplasty, with randomization occurring just before the procedure. In the PLATO trial,^{9,10} the decision to administer a bolus of 300 or 600 mg was left to the discretion of local investigator. Finally, in the clopidogrel arm 59.5% of participants were treated with a loading dose of 300 mg. In this study, 15 170 of 18 624 enrolled patients (81.4%) underwent coronary angiography.

The DISPERSE-2 study¹⁶ was a second phase clinical trial in which patients were randomly assigned in a 1:1:1 double-blind fashion to receive either twice daily ticagrelor 90 mg, ticagrelor 180 mg or clopidogrel 300 mg loading dose plus 75 mg once daily for up to 12 weeks. In our meta-analysis, we included only patients receiving the dose of ticagrelor used in the PLATO trial.

In the CURRENT OASIS-7 trial,¹⁴ patients referred to invasive management were assigned to high-dose clopidogrel [600 mg bolus and a daily double dose of clopidogrel (150 mg) up to 7 days after enrolment] or to a standard clopidogrel regimen. In this trial, patients were additionally randomized to low (75–100 mg) or high-dose (300–325 mg) aspirin. In the ALBION trial,¹¹ patients were randomized to 300, 600 and 900 mg clopidogrel.

Primary endpoint

Follow-up data were collected at 30 days or up to 12–15 months (PLATO and TRITON-TIMI 38)^{7–10} follow-up. A total of 1886 patients died (3.2%). We observed a significant reduction in mortality with new regimens (2.9% vs. 3.4%, OR=0.87, 95% CI 0.79–0.95, $P=0.002$, $P_{\text{heter}}=0.32$) (Figure 2: total), that was confined to new molecules (3.6% vs. 4.3%, OR=0.83, 95% CI 0.74–0.92, $P=0.0002$, $P_{\text{heter}}=0.21$), especially to ticagrelor, as observed in the PLATO trial (Figure 2A: novel antiplatelet drugs). Similar results were observed in patients undergoing PCI ($n=43\,807$) (2.4% vs. 2.7%, OR=0.88 (95% CI 0.78–0.99, $P=0.03$, $P_{\text{heter}}=0.13$) (Figure 2B: PCI subgroup). As shown in Figure 3, no publication bias was observed.

Secondary endpoints

Myocardial infarction

Follow-up data were collected at 30 days or up to 12–15 months (PLATO and TRITON-TIMI 38)^{7–10} follow-up. Recurrent myocardial infarction was observed in 2740 (4.7%) patients. A significant reduction was observed with new regimens as compared to standard-dose clopidogrel (4.2% vs. 5.2%, OR=0.80, 95% CI 0.74–0.87, $P<0.0001$, $P_{\text{heter}}=0.15$) (Figure 4: total). The benefits were mostly evident with new agents (6.0% vs. 7.5%, OR=0.79, 95% CI 0.72–0.86, $P<0.0001$, $P_{\text{heter}}=0.11$) (Figure 4A: novel antiplatelet drugs) but not with high-dose clopidogrel (2% vs. 2.2%, OR=0.88, 95% CI 0.75–1.05, $P=0.16$, $P_{\text{heter}}=0.3$) (Figure 4B: 600 mg clopidogrel). Similar benefits were observed when restricted to patients undergoing coronary angioplasty (4.5% vs. 6%, OR=0.73, 95% CI 0.67–0.80, $P<0.0001$, $P_{\text{heter}}=0.24$) (Figure 4C: PCI subgroup).

In-stent thrombosis

Follow-up data were collected at 30 days or up to 12–15 months (PLATO and TRITON-TIMI 38)^{7–10} follow-up. Definite in-stent thrombosis was observed in a total of 517 out of 40 276 patients (1.3%). Therapy with ADP-antagonist regimens when compared to standard-dose clopidogrel was associated with a significant reduction in definite in-stent thrombosis (0.9% vs. 1.7%, OR=0.52, 95% CI 0.43–0.63, $P<0.0001$, $P_{\text{heter}}=0.40$) (Figure 5).

Safety endpoint

A total of 1973 patients (3.4%) had a major bleeding complication. High-dose (600 mg) clopidogrel as compared with 300 mg clopidogrel was associated

Table 1 Study characteristics

References	Study name	Journal	Year	ACS type	Overall pts ^a	PCI group pts	Study drug design		Survival endpoint	Follow-up time (months)	Definition of major bleeding
							Loading dose	Maintenance dose			
Cuisset <i>et al.</i> ¹²	–	JACC	2006	NSTE-ACS	387	387	300 vs. 600 mg clopidogrel	75 mg/daily	CV mortality	1	TIMI classification
Montalescot <i>et al.</i> ¹¹	ALBION	JACC	2006	NSTE-ACS	69	–	300 vs. 600 vs. 900 mg clopidogrel	75 mg/daily	All-cause mortality	1	GUSTO classification
Cannon <i>et al.</i> ¹⁶	DISPERSE-2	JACC	2007	NSTE-ACS	650	–	300 mg clopidogrel vs. 90 mg ticagrelor vs. 180 mg ticagrelor	75 mg/daily clopidogrel vs. twice daily 90 mg ticagrelor vs. twice daily 180 mg ticagrelor	All-cause mortality	0.9	Modified TIMI classification
Wiviott <i>et al.</i> ^{7,8}	TRITON TIMI-38	NEJM, Lancet	2007	STEMI and NSTE-ACS	13 608	12 844	300 vs. 60 mg prasugrel	75 mg/daily clopidogrel vs. 10 mg/daily prasugrel	All-cause mortality	15	TIMI classification
Wallentin <i>et al.</i> ^{9/ Cannon <i>et al.</i>¹⁰}	PLATO	NEJM, Lancet	2009	STEMI and NSTE-ACS	18 624	13 408	300/600 mg clopidogrel vs. 180 mg ticagrelor	75 mg/daily clopidogrel vs. twice daily 90 mg ticagrelor	All-cause mortality	12	TIMI classification
Yong <i>et al.</i> ¹³	PRACTICAL	Am. Heart J.	2009	NSTE-ACS	256	140	300 vs. 600 mg clopidogrel	at the discretion of the treating physician	All-cause mortality death	6	TIMI classification
Mehta <i>et al.</i> ^{14,15}	CURRENT OASIS-7	NEJM	2010	STEMI and NSTE-ACS	25 086	17 263	300 vs. 600 mg clopidogrel	75 mg/daily clopidogrel vs. 150 mg/daily clopidogrel up to 7 days, and later 75 mg/daily clopidogrel	All-cause mortality	1	TIMI classification

^aThe total of patients allocated in the included studies to novel drugs or 600 vs. 300 mg clopidogrel. CV = cardiovascular, GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries, NSTE-ACS = non-ST-segment elevation acute coronary syndrome, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction; pts = patients.

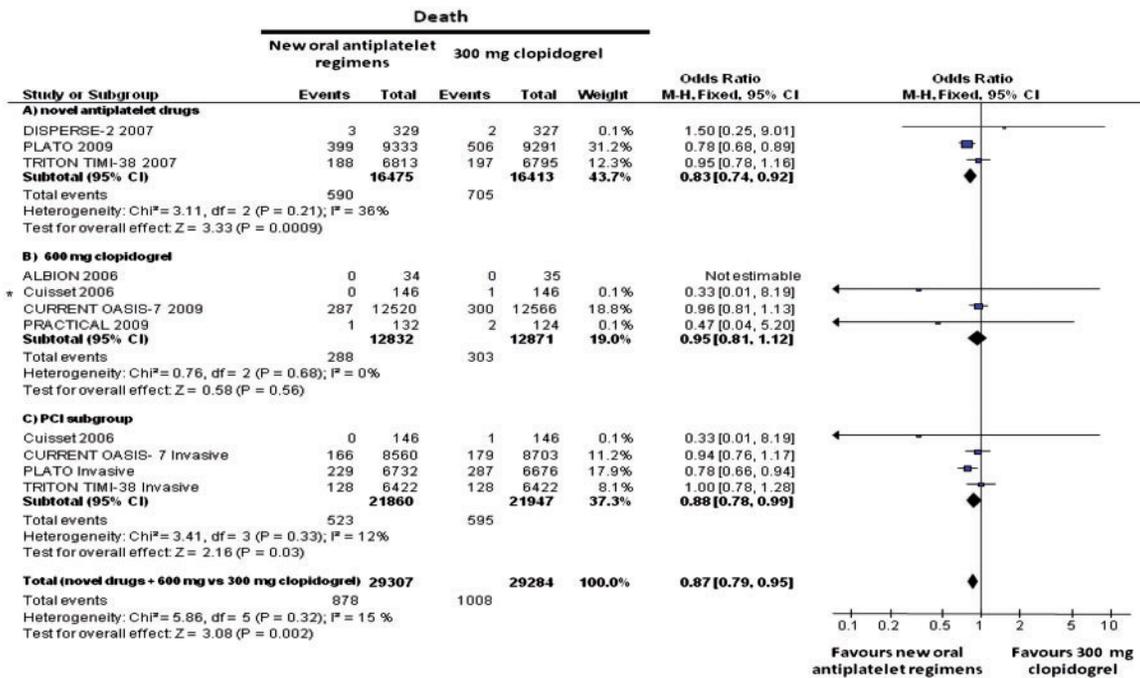


Figure 2. All-cause mortality in the overall population with ORs and 95% CI. (A–C) Prespecified subanalysis for mortality in the group of novel antiplatelet drugs (A), 600 mg of clopidogrel (B) and PCI subgroup (C); ORs and 95% CI are reported. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial; * = cardiovascular mortality.

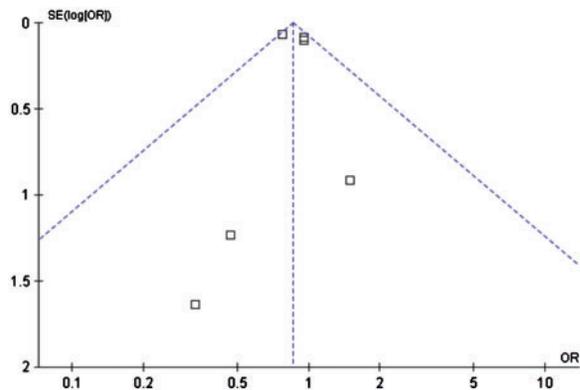


Figure 3. Funnel plot for mortality of the studies included in the meta-analysis. The SE of the ln OR was plotted against the OR for mortality. No skewed distribution was observed, suggesting no publication bias. ALBION study was not included in the graph because there was no computed effect size due to absence of events in the two arms (novel antiplatelet regimens vs. standard-dose clopidogrel).

with a higher rate of major bleedings (1.6% vs. 1.3%, OR=1.25, 95% CI 1.02–1.53, $P=0.03$, $P_{heter}=0.45$) (Figure 6B: 600 mg clopidogrel).

Conversely, as compared with standard dose of clopidogrel, the new drugs did not significantly increase the rate of major bleeding complications (5% vs. 4.7%, OR=1.06, 95% CI 0.96–1.17, $P=0.25$, $P_{heter}=0.10$) with the lower rates of bleedings

confined to ticagrelor (Figure 6A: novel antiplatelet drugs). These results did not differ when the analysis was restricted to patients undergoing coronary intervention (Figure 6C: PCI subgroup).

Discussion

New antiplatelet regimens are regarded as major advance in cardiovascular therapy. The results of our meta-analysis of seven RCTs,^{7–16} including 58 591 patients with ACS, showed that, when compared with standard-dose clopidogrel (300 mg loading dose), new antiplatelet regimens are associated with a significant reduction in mortality, reinfarction and in-stent thrombosis.

High-dose clopidogrel significantly increased the risk of major bleeding complications; an increased number of major bleedings was also observed with prasugrel, even though the overall subgroup of new antiplatelet drugs (prasugrel and ticagrelor) was not associated with an increased rate of major bleedings.

In terms of clinical efficacy and safety, the overall benefits were more pronounced with the new antiplatelet compound ticagrelor. The same clinical benefits observed in the overall analysis were consistent in the prespecified subgroup of patients

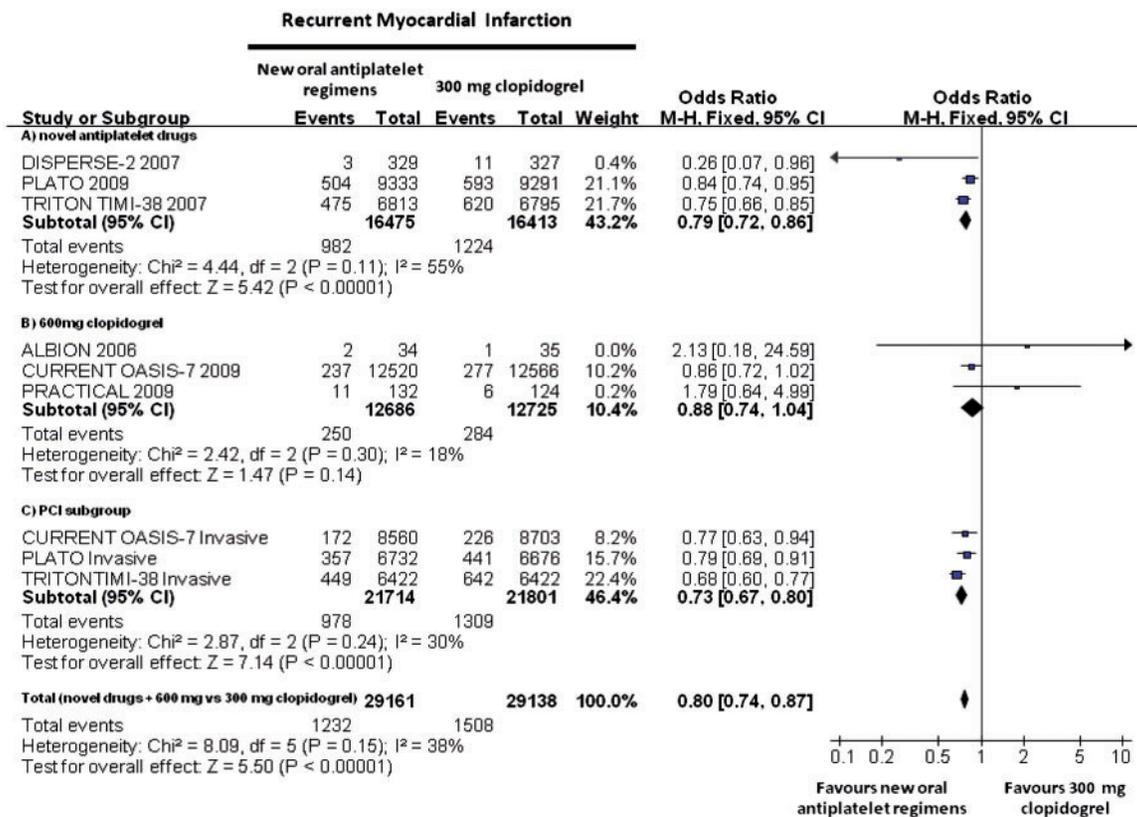


Figure 4. Recurrent myocardial infarction in the overall population, with ORs and 95% CI. (A–C) Prespecified subanalysis for myocardial infarction in the group of novel antiplatelet drugs (A), 600 mg of clopidogrel (B) and PCI subgroup (C); ORs and 95% CI are reported. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

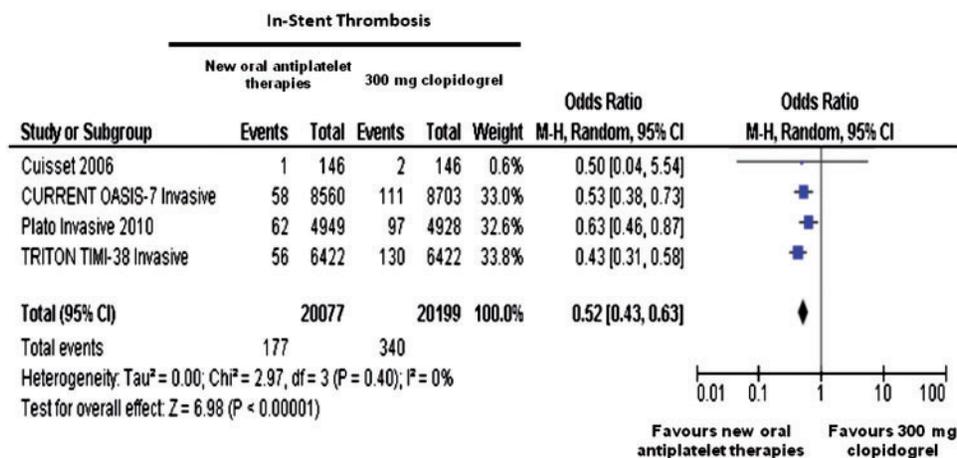


Figure 5. In-stent thrombosis in the overall population with ORs and 95% CI. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

undergoing PCI, where all the treatments did not increase the risk of major bleeding complications.

Standard-dose clopidogrel (300 mg bolus followed by 75 mg/daily) has been regarded for years as the gold standard of adjunctive antiplatelet

therapy in patients with ACS treated with or without an interventional strategy.¹ Several limitations of clopidogrel^{2–4} have raised the need for new therapies. First of all, many patients still have events despite dual antiplatelet therapy. Several factors may

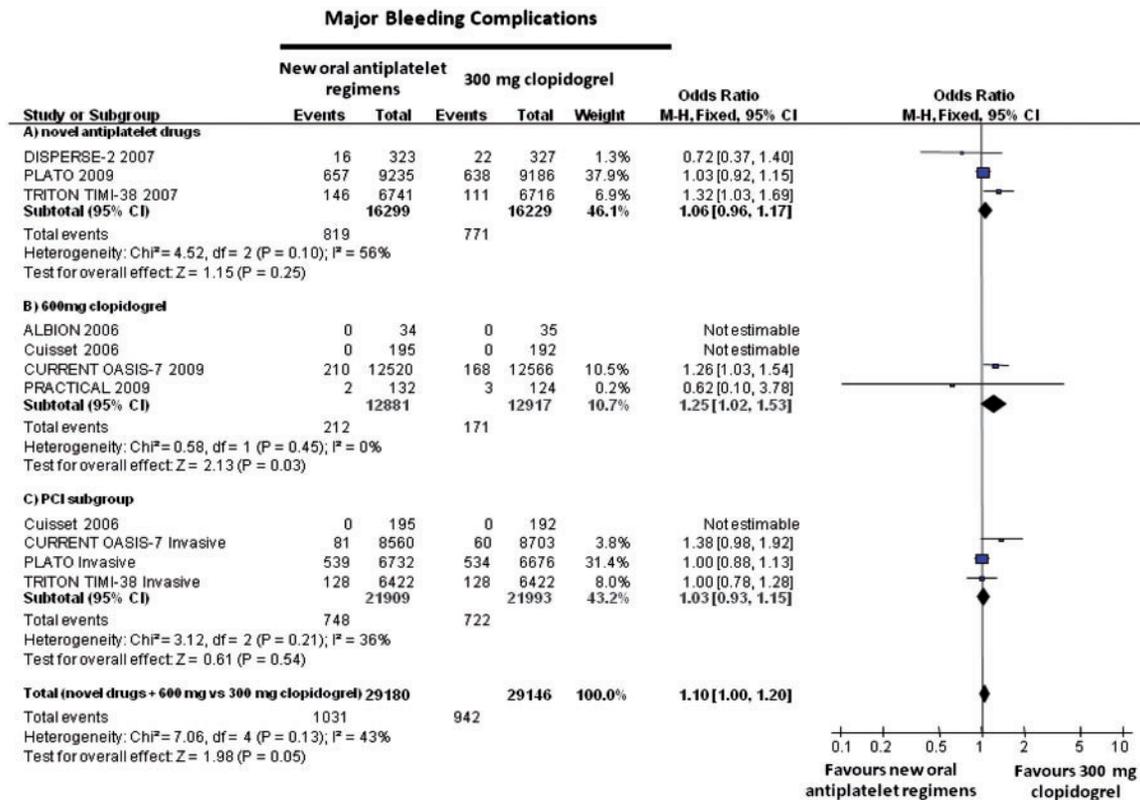


Figure 6. Major bleeding complications in the overall population with ORs and 95% CI. (A–C) Prespecified subanalysis for major bleedings in the group of novel antiplatelet drugs (A), 600 mg of clopidogrel (B) and PCI subgroup (C); the size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

contribute to clinical resistance to clopidogrel.²⁰ Due to its complex metabolic pathway, clopidogrel takes 4 h to reach peak platelet aggregation inhibition. Since many patients take clopidogrel loading dose just before PCI, they are at risk of ischemic periprocedural events. Furthermore, due to polymorphisms of several enzymes involved in the multistep metabolic pathway of clopidogrel, a large interindividual variability in platelet aggregation inhibition has been observed, with prevalence of resistance to clopidogrel ranging from 15% to 30%. Moreover, clopidogrel has irreversible effects that in some cases prevent from early administration before the procedure, especially in the setting of ACS where a relatively large proportion of patients (10–30%) has severe multivessel disease requiring bypass surgery, whereas a drug with reversible effects may overcome this limitation and increase the administration of early antiplatelet therapy.

However, a faster and stronger antiplatelet therapy may be associated with higher risk of bleeding complications that may counterbalance the benefits in terms of thrombotic complications.⁵

Several new therapeutic strategies have been proposed to overcome some limitations of

standard-dose clopidogrel. High-dose clopidogrel has been shown to provide a faster and stronger inhibition of platelet aggregation with a lower percentage of resistance.

The CURRENT OASIS-7 trial showed that high-dose clopidogrel was associated with a slightly higher risk of bleeding complications [TIMI major bleedings: 210 (1.7%) vs. 168 (1.3%), $P=0.03$] but benefits in reinfarction [237 (1.9%) vs. 277 (2.2%), $P=0.09$], mainly due to a significant reduction of in-stent thrombosis [definite in-stent thrombosis 58 (0.7%) vs. 111 (1.3%); $P=0.0001$].^{14,15}

Prasugrel is a third-generation thienopyridine with a rapid and effective metabolic activation that is associated with a faster onset of action and an increased inhibition of platelet aggregation when compared to clopidogrel. Data from the TRITON-TIMI 38 showed significant benefits in terms of myocardial infarction and significant reduction in in-stent thrombosis.^{7,8} Even though it was counterbalanced by a higher risk of major bleeding complications, the benefits in terms of thrombotic complications largely outweighed bleeding complications. Low body weight (≤ 60 kg), advanced age (>75 years) and previous stroke were predictors of

higher risk of bleeding complications, and in such patients the drug should not be administered. However, a new ongoing trial, the TRILOGY trial, is investigating the benefits from a lower (half) dosage (30 mg bolus and 5 mg daily) in patients with ACS undergoing conservative therapy. In fact, one of the limitations of the TRITON-TIMI 38 trial was the enrolment of patients after initial angiography, but not at the very beginning of presentation of ACS (hospital admission).

Ticagrelor is a non-thienopyridine with a faster onset and offset of action and significantly higher inhibition of platelet aggregation as compared to 600 mg clopidogrel. One of the great advantages that make the molecule very appealing is the reversibility of its antiplatelet effect, with the drug administered twice a day. This is extremely important, when the overall ACS population is taken into account. In fact, a considerable proportion of patients, ranging from 20% to 30%, undergo coronary artery bypass grafting (CABG) during hospitalization, where the risk of bleeding may become very high. Data from the large PLATO trial^{9,10} showed a significant reduction in mortality, in addition to benefits in myocardial infarction and in-stent thrombosis. No difference was observed in terms of major bleeding complications. However, paradoxically, while a lower incidence of bleeding was observed in patients undergoing CABG, in non-CABG patients ticagrelor was associated with a significantly higher rate of major bleeding complications.

Our meta-analysis showed in 58 591 ACS patients that new oral antiplatelet therapies are associated with a significant reduction in mortality, recurrent myocardial infarction, especially with new drugs (prasugrel/ticagrelor). The benefits in mortality were mostly observed with ticagrelor, whereas the benefits regarding in-stent thrombosis were consistent with all the strategies. A higher risk of major bleeding complications was observed with both high-dose clopidogrel and prasugrel that disappeared in the analysis restricted to patients undergoing coronary angioplasty.

Limitations

This meta-analysis was not performed on individual patient's data that would have certainly improved the results, particularly by performing subgroup analyses. Furthermore, the trials included in our meta-analysis tested three different regimens (prasugrel, ticagrelor and high-dose clopidogrel) against standard-dose clopidogrel.

Conclusions

This meta-analysis of randomized trials conducted in ACS patients showed that new oral antiplatelet regimens to block platelet ADP-receptor are associated with a significant reduction in mortality, reinfarction, especially with ticagrelor and prasugrel. A higher risk of major bleeding complications was observed with both prasugrel and high-dose clopidogrel, that disappeared in the analysis restricted to patients undergoing coronary angioplasty, where clear and consistent benefits in terms of in-stent thrombosis were observed with all the new therapies as compared to standard-dose clopidogrel.

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Conflict of interest: None declared.

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