RESEARCH

Reappraisal of thienopyridine pretreatment in patients with non-ST elevation acute coronary syndrome: a systematic review and meta-analysis

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Abstract

Objective To investigate the effect of pretreatment with P2Y₁₂ receptor inhibitors compared with no pretreatment on efficacy and safety of treatment of non-ST elevation acute coronary syndrome (ACS).

Data sources Two reviewers independently searched Medline, Embase, Cochrane Controlled Trials, and BioMed Central databases for randomized placebo controlled trials and observational studies from August 2001 to March 2014.

Study eligibility Studies must have reported both all-cause mortality (primary efficacy endpoint) and major bleeding (safety endpoint) outcomes.

Data extraction Data on sample size, characteristics, drug dose and delay of administration, and outcomes were independently extracted and analyzed.

Data synthesis A random-effect model was applied. The analysis was performed (i) in all patients independently of the management strategy and (ii) only in patients undergoing percutaneous coronary intervention.

Results Of the 393 titles identified, seven (four randomized controlled trials, one observational analysis from a randomized controlled trial, and three observational studies) met the inclusion criteria. No study was identified for ticagrelor or cangrelor, and analyses were thus limited to thienopyridines. A total of 32 383 non-ST elevation ACS patients were included, 18 711 coming from randomized controlled trials. Of these, 55% underwent percutaneous coronary intervention (PCI). Pretreatment was not associated with a significant lower risk of mortality in all patients

(odds ratio 0.90 (95% confidence interval 0.75 to 1.07), P=0.24), in particular when considering only the randomized controlled trials (odds ratio 0.90 (0.71 to 1.14), P=0.39). Similar results were observed in the cohort of patients undergoing PCI. A significant 30-45% excess of major bleeding was consistently observed in all patients (odds ratio 1.32 (1.16 to 1.49), P<0.0001) and in those undergoing PCI, as well as in the subset analyses of randomized controlled trials of these two cohorts of patients. There was a reduction in major adverse cardiovascular events in the analysis of all patients (odds ratio 0.84 (0.72 to 0.98), P=0.02), driven by the old clopidogrel studies (CURE and CREDO), but the difference was not significant for the cohort of patients undergoing PCI. Stent thrombosis, stroke, and urgent revascularization did not differ between groups (pretreatment v no pretreatment). The results were consistent for both thienopyridines and confirmed in sensitivity analyses.

Limitations Analysis was not performed on individual patient's data.

Conclusion In patients presenting with non-ST elevation ACS, pretreatment with thienopyridines is associated with no significant reduction of mortality but with a significant excess of major bleeding no matter the strategy adopted, invasive or not. Our results do not support a strategy of routine pretreatment in patients with non-ST elevation ACS.

Introduction

Non-ST elevation acute coronary syndrome (ACS) holds a significant burden in global healthcare systems with a one year incidence of more than 1.5/1000 people.^{1,2} In real world management, two thirds of patients presenting with a non-ST

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Supplemental tables 1 and 2

elevation ACS have coronary angiography performed, a third have coronary stenting, and 7-10% have coronary bypass surgery.² Despite optimal evidence based treatment, these patients have worse mid-term and long term prognoses than patients with ST elevation ACS, with more frequent recurrent ischemic events and a twofold higher death rate at two years.³⁻⁵

Dual antiplatelet therapy with aspirin and a P2Y₁₂ receptor antagonist has been the cornerstone of the treatment of ACS, managed either medically or invasively. This is based on the single randomized CURE study, in which clopidogrel (300 mg pretreatment loading dose, 75 mg maintenance dose) for a mean duration of nine months reduced ischemic endpoints by 20% in non-ST elevation ACS patients medically managed.⁶ In the CREDO trial, in which two thirds of enrolled patients had non-ST elevation ACS, significant superiority of pretreatment in patients undergoing percutaneous coronary intervention (PCI) was not demonstrated but was suggested only in subgroup analyses.⁷⁻⁸ These trials were conducted 15 years ago when clinical practice was different in many ways.

The rationale for pretreatment with oral P2Y₁₂ inhibitors is based on the need for a strong antiplatelet effect in non-ST elevation ACS patients scheduled for PCI,⁹⁻¹⁰ and the delay of action of these drugs, clopidogrel in particular, which provide a low and slow platelet inhibition in many patients.¹¹⁻¹²

Following the CURE and CREDO studies, clopidogrel pretreatment has been generalized for non-ST elevation ACS management with a Class I-B recommendation in the European and US guidelines, with the paradigm that "sooner is better."¹³⁻¹⁴ However, there has been no specific trial randomizing non-ST elevation ACS patients for clopidogrel pretreatment versus no pretreatment before routine catheterization as performed nowadays. Moreover, the time from hospital admission to catheterization has been considerably shortened in the past 10 years.¹⁵ The risk-benefit of pretreatment can now be reevaluated, considering the changes in practice and the accumulation of studies since the seminal publication of the CURE study allowing evaluation of low frequency but hard endpoints such as mortality and major bleeding. Indeed, pretreatment, a treatment administered before the coronary angiogram, may be detrimental in patients finally oriented towards coronary artery bypass graft surgery, which is performed within five days of clopidogrel loading in 87% of cases,¹⁶ with associated higher perioperative transfusion rates of blood products and a twofold increase of reoperation for bleeding complications.¹⁷ Patients medically managed may also not benefit from pretreatment, especially when there is no significant coronary disease or an alternate diagnosis for the clinical presentation. Finally, a few randomized studies have questioned the risk-benefit of pretreatment in patients undergoing PCI,¹⁸⁻¹⁹ and, in a meta-analysis performed in 37 814 patients undergoing PCI (elective, urgent, or primary), we found no benefit of clopidogrel pretreatment on mortality.

The recent randomized ACCOAST trial demonstrated the absence of benefit of pretreatment with prasugrel in non-ST elevation ACS patients invasively managed. Moreover, there was hazard associated with pretreatment, suggesting an unfavorable risk-benefit of systematic pretreatment for patients with non-ST elevation ACS.²⁰

We decided to evaluate the risk-benefit of routine pretreatment with P2Y₁₂ receptor inhibitors administered to patients with non-ST elevation ACS independently of the treatment strategy applied, medical or invasive. We included in the present meta-analysis not only randomized placebo controlled trials but also registries; we evaluated the global effect independently of

revascularization (all patients included in the analysis) and the effect only in patients undergoing PCI, to evaluate potential differences according to the management strategy used.

Methods

We conducted a comparison of pretreatment with P2Y₁₂ inhibitors versus no pretreatment in patients with non-ST elevation ACS independently of the strategy applied (invasive or conservative), using a methodology described previously.²¹⁻²²

We selected studies in which a majority (>50%) of patients had non-ST elevation ACS. The main analysis was performed combining randomized controlled trial and observational studies together. Two separate analyses were performed: (i) for all patients included in the analysis (whatever the final treatment strategy, invasive or not) and (ii) for patients undergoing PCI revascularization after coronary angiography. Additional analyses were also performed for randomized controlled trials and observational studies considered separately.

Searches from Medline, Cochrane Controlled Trials Register, Embase, and BioMed Central databases were done from January 1980 through March 2014. Predefined search terms were: "non-ST-elevation acute coronary syndrome"; "clopidogrel" OR "prasugrel" OR "ticagrelor" OR "cangrelor" OR "elinogrel" AND "pretreatment" OR "loading dose" OR "preload" OR "timing" OR "upstream". No language restriction was used. Published articles, abstracts from selected major cardiology scientific meetings (American Heart Association, American College of Cardiology, European Society of Cardiology, and Transcatheter Cardiovascular Therapeutics) as references from reviews and selected articles were screened. Selection was done by two independent reviewers (ABA and MK).

Eligibility criteria and data extraction

Inclusion criteria were defined as follows: (i) studies including >50% of patients with non-ST elevation ACS either medically treated or scheduled for catheterization; (ii) controlled comparison between pretreatment with P2Y₁₂ inhibitors and no pretreatment (that is, placebo or no treatment) through random or non-random allocation; (iii) data supplied on loading dose of P2Y₁₂ inhibitors; (iv) data available on at least mortality and bleeding. Full text articles and meeting abstracts of randomized controlled trials, registries, and pre-specified subgroups of randomized studies reporting data on pretreatment with P2Y₁₂ inhibitors were considered for analysis. Exclusion criteria were duplicate reports, the lack of control group, and ongoing studies. Extraction of data on study design and on clinical and safety outcomes was performed independently by two reviewers (ABA and MK), and discrepancies were resolved by consensus.

Endpoints definitions

All cause mortality and major bleeding were the primary efficacy and safety endpoints, respectively. Secondary endpoints included major adverse cardiac events, myocardial infarction, stroke, and urgent revascularization (as defined in each study), and, when available, cardiovascular death, minor bleeding, and stent thrombosis (stent thrombosis recorded as definite or probable according to the criteria of the Academic Research Consortium) (table 1). All bleeding were considered for the analysis of all patients, and non-coronary artery bypass graft surgery bleeding was considered for the analysis of patients undergoing PCI. Pretreatment was defined as the administration of a P2Y₁₂ inhibitor before catheterization or PCI. Each endpoint

was taken at the shortest follow-up available in each study (table 1).

Risk of bias

We assessed the risk of bias within randomized clinical trials by analyzing the sequence generation, allocation concealment, blinding (of patients, investigators, and outcome assessment), incomplete outcome data, and selective outcome reporting. Each dimension was rated as low or high risk of bias, or unclear.²³ The risk of bias within observational studies was assessed by analyzing selection of patients, comparability, and outcome; grading was done by two independent reviewers according to the Newcastle-Ottawa Scale for registries (www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

Statistical analysis

Statistical analysis was conducted as follows: a random model was used and confirmed by the Mantel-Haenszel fixed-effect model; the extent of heterogeneity between trials was assessed with the Q Cochran test (a P cut-off value of 0.1 was considered significant for heterogeneity) and I² test for heterogeneity between subgroups was reported in each figure²⁴; probability values were two-tailed with P=0.05 considered as significant. Odds ratios with 95% confidence intervals were calculated with the RevMan software version 5.0 (Cochrane Collaboration) and language R by using the meta-package. The main analysis was performed on all studies (randomized controlled trial and observational), for two groups: all patients with non-ST elevation ACS and the patients treated by PCI only. After assessment of heterogeneity, several sensitivity analyses were performed:

- (1) Type of drug for randomized controlled trial
- (2) Clopidogrel dose: pretreatment <600 mg. Only one study included patients with clopidogrel 600 mg loading dose only,²⁵ and the analysis was done after exclusion of this study for assessment of the pretreatment effect of clopidogrel 300 mg loading dose
- (3) Analysis that removed data from the CURE study from the analysis of patients who underwent PCI treatment. This was because the CURE study may not reflect contemporary practice (10 days of pretreatment with revascularization using plain balloon angioplasty or stent PCI).

Results for the main endpoints are reported in graphs by groups (all patients with non-ST elevation ACS and only those who underwent PCI), and in tables or text for secondary endpoints and sensitivity analyses.

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Results

Studies and patient characteristics

Of the 393 abstracts identified from our search, seven studies published between 2001 and 2013 met the inclusion criteria with a total of 32 383 patients.

Three were randomized controlled trials with a total of 18 711 patients. The first study randomized non-ST elevation ACS patients for clopidogrel versus placebo,⁶ but the study protocol recommended a conservative strategy with medical management of the patients; subsequently only 43.8% of patients had a coronary angiogram performed and only 21.2% underwent

PCI.²⁶ The second trial was performed with clopidogrel in elective PCI with most (67%) patients being patients with non-ST elevation ACS (n=1407 patients),^{6, 8} and randomization occurred mostly after the coronary angiogram (>90% PCI) not corresponding really to the definition of pretreatment. The third study randomized non-ST elevation ACS patients with a significant rise of troponin to pretreatment with prasugrel or placebo started 2-48 hours before coronary angiography.²⁰

One study was an observational pre-specified subgroup analysis of a randomized controlled trial (n=7523 patients) for the question of clopidogrel pretreatment.^{27, 28}

Three included studies were observational (n=6149 patients) for the question of pretreatment with clopidogrel.^{18, 25, 29}

No randomized study was found for pretreatment with any of the other P2Y₁₂ receptor antagonists (ticagrelor, elinogrel, or cangrelor). Thus the final analysis only included studies with clopidogrel (six studies) and prasugrel (one study). The flow chart of study selection is shown in figure 1. The observational studies, randomized controlled trials, and observational data from randomized controlled trials all had acceptable risks of bias (supplemental tables 1 and 2). Adjustments for the risk of confounding bias in the three observational studies were done by propensity score using a multivariable logistic regression model. Covariates that were tested included most important individual demographic characteristics, preprocedural clinical characteristics, and procedural variables.^{18, 25, 29}

Main analysis: randomized controlled trials and observational studies

For the analysis of all patients with non-ST elevation ACS, a total of 32 383 patients were included. Of those, 17 545 (54.5%) underwent PCI and had been the subject of a separate analysis. Characteristics and definitions differed from one study to another and are summarized in the table 1. Four studies and one sub-study of PCI intervention had a 300 mg loading dose of clopidogrel as pretreatment,^{6, 18, 26, 29, 30} one study had a 600 mg loading dose,²⁵ and in one substudy the clopidogrel loading dose was left to the discretion of the investigators but was ≥300 mg in all cases.^{27, 28} In the ACCOAST study, the prasugrel pretreatment dose was 30 mg, completed at the time of PCI with another 30 mg dose, compared with 60 mg in the control group given only to PCI patients at the time of the revascularization procedure.²⁰

All patients with non-ST elevation ACS

Mortality

Pretreatment with P2Y₁₂ inhibitors was not associated with a significant reduction in death (any cause) (odds ratio 0.90 (95% confidence interval 0.75 to 1.07), P=0.24) (fig 2) nor in cardiovascular death (reported in only two randomized controlled trials and one PCI sub-study of a randomized controlled trial,^{6, 20, 26} and one observational study,¹⁸ n=16 894 patients) (odds ratio 0.72 (0.39 to 1.35), P=0.31, I²=44%, P=0.17).

Safety

Pretreatment with P2Y₁₂ inhibitors was associated with a significant increase of major bleeding (odds ratio 1.32 (1.16 to 1.49), P<0.0001) (fig 3).

Minor and any bleeding were exploratory endpoints, reported in 5 studies only^{6, 8, 20, 25, 29} and were both increased by pretreatment (N=24 561 patients: minor bleeding: OR=1.58,

95%CI (1.09 to 2.29), $p=0.02$, $I^2=27\%$, $p=0.25$; any bleeding: OR=1.49, 95%CI (1.16 to 1.91), $p=0.002$, $I^2=38\%$, $p=0.20$).

Secondary endpoints

Major adverse cardiovascular events and myocardial infarction—Pretreatment with P2Y₁₂ inhibitors was associated with a significant reduction of major adverse cardiovascular events (odds ratio 0.84 (0.72 to 0.98), $P=0.02$) but a non-significant reduction of myocardial infarction (odds ratio 0.81 (0.64 to 1.03), $P=0.09$, $I^2=58\%$, $P=0.09$).

Stroke—Pretreatment with P2Y₁₂ inhibitors was not associated with a reduction of stroke in the analysis of the four studies available for this endpoint ($n=19\ 752$ patients) (odds ratio 0.86 (0.65 to 1.13), $P=0.27$, $I^2=0\%$, $P=0.94$).^{6 8 20 25}

Urgent revascularization—Pretreatment with P2Y₁₂ inhibitors was not associated with a reduction of urgent revascularization in the analysis of the five studies available for this endpoint ($n=11\ 397$) (odds ratio 0.79 (0.53 to 1.18), $P=0.25$, $I^2=0\%$, $P=0.87$).^{8 18 20 25 29}

Patients with non-ST elevation ACS undergoing PCI

Mortality

Pretreatment with P2Y₁₂ inhibitors was not associated with a significant reduction in death (any cause) (odds ratio 0.83 (0.59 to 1.17), $P=0.29$) (fig 2) nor in cardiovascular death ($n=5730$ patients) (odds ratio 0.78 (0.28 to 2.14), $P=0.63$, $I^2=46\%$, $P=0.63$).

Safety

Pretreatment with P2Y₁₂ inhibitors was associated with an increase of major bleeding (odds ratio 1.23 (1.00 to 1.50), $P=0.048$) (fig 3), minor bleeding (1.37 (0.98 to 1.90), $P=0.06$, $I^2=39\%$, $P=0.19$), and any bleeding ($n=13\ 385$ patients, 1.37 (1.00 to 1.88), $P=0.048$, $I^2=68\%$, $P=0.04$)).

Secondary endpoints

Major adverse cardiovascular events and myocardial infarction—Pretreatment with P2Y₁₂ inhibitors was associated with a non-significant reduction of major adverse cardiovascular events (odds ratio 0.83 (0.69 to 1.01), $P=0.06$) and myocardial infarction (0.77 (0.57 to 1.02), $P=0.07$, $I^2=68\%$, $P=0.04$).

Stent thrombosis was available in only two studies ($n=3814$ patients).^{20 25} The reduction of stent thrombosis after pretreatment with P2Y₁₂ inhibitors was not statistically significant (odds ratio 0.26 (0.04 to 1.57), $P=0.14$, $I^2=0\%$, $P=0.74$).

Stroke—Pretreatment with P2Y₁₂ inhibitors was not associated with a reduction of stroke in the analysis of the three studies available for this endpoint ($n=5918$) (odds ratio 0.77 (0.37 to 1.59), $P=0.48$, $I^2=0\%$, $P=0.77$).^{8 20 25}

Urgent revascularization—Pretreatment with P2Y₁₂ inhibitors was associated with a reduction of urgent revascularization in the six studies available for the analysis only of patients undergoing PCI ($n=13\ 395$) (odds ratio 0.72 (0.52 to 1.00), $P=0.0488$, $I^2=0\%$, $P=0.93$).^{18 20 25 26 28-30} driven by the PCI subgroup of the CURE study, where the delay of pretreatment was 10 days on average.

Randomized controlled trial analysis

Results of the analysis restricted to the randomized controlled trials, including the two oldest studies with clopidogrel for all patients with non-ST elevation ACS,^{8 26} and for those who

underwent PCI,^{6 8} and the recent ACCOAST study with prasugrel,²⁰ are shown in figures 2-5. Globally, pretreatment with a P2Y₁₂ inhibitor was not associated with a reduction of all cause death in the analysis of all patients with non-ST elevation ACS ($n=18\ 410$) (odds ratio 0.90 (0.71 to 1.14), $P=0.39$) nor in the analysis restricted to those who underwent PCI ($n=4774$) (0.92 (0.43 to 1.98), $P=0.83$). There was no reduction in major adverse cardiovascular events in both analyses. In contrast, major bleeding was significantly increased in the analysis of all patients, but not significantly in the analysis restricted to those who underwent PCI. One additional large randomized study with a subgroup analysis for the issue of clopidogrel pretreatment confirmed the absence of effect of pretreatment on mortality and major adverse cardiovascular events; major bleeding trended in the wrong direction in this study.²⁷ There was no significant heterogeneity between trials for these endpoints. A modest effect on major adverse cardiovascular events was observed only in the old randomized clopidogrel studies but not in the more recent studies with clopidogrel^{27 28} or prasugrel.²⁰ The deleterious safety impact of pretreatment was observed in all randomized studies with both drugs in the analysis of all patients with non-ST elevation, but was limited only to the more potent prasugrel in the analysis restricted to those who underwent PCI.

Sensitivity analysis

The sensitivity analyses (i) for clopidogrel 300 mg loading dose only that excluded one study ($n=31\ 342$ patients)²⁵ and (ii) for the patients who underwent PCI that excluded the CURE study ($n=16\ 064$ patients)²⁶ confirmed the main results of the previous analyses.

Discussion

Principal findings

Pretreatment with P2Y₁₂ receptor antagonists (here thienopyridines, in the absence of data for the other drugs of the same class) is not associated globally with a favorable risk-benefit ratio in patients with non-ST elevation ACS. We were unable to show a benefit on mortality, but there was significant harm with a consistent excess of major bleeding across all the analyses. The modest reduction of major adverse cardiovascular events was driven by the old randomized studies of clopidogrel and the observational studies with clopidogrel, but not confirmed in the more recent randomized studies using clopidogrel.^{20 27 28} Surprisingly, this effect on major adverse cardiovascular events was not driven by the cohort of patients who underwent percutaneous coronary intervention (PCI), in which we may have expected a particular benefit of pretreatment.

This work focused on patients with non-ST elevation ACS, independently of the management strategy and study drug used for pretreatment. Pretreatment with thienopyridines evaluated in more than 30 000 patients presenting with non-ST elevation ACS was not associated with a reduction in all cause death. The 16% reduction in major adverse cardiovascular events was driven by a (non-significant) reduction of myocardial infarction—a diagnosis based on an elevation of cardiac markers which may be related to the initial event, the procedure of revascularization, or, more rarely, to a recurrent event. This reduction in major adverse cardiovascular events was balanced by a 27-43% excess of major bleeding depending on the analysis performed. Unfortunately, we were unable to define a subgroup that may benefit more from pretreatment, like the PCI cohort, which did not perform better in this analysis, alike in the recent

ACCOAST study.²⁰ Pretreatment in patients who finally underwent PCI was associated with little effect on major adverse cardiovascular events (17% odds reduction, $P=0.06$) and an excess of major bleeding of a larger magnitude (23% odds excess, $P=0.048$). This may explain the absence of effect observed on survival.

Strengths and limitations of the meta-analysis and relations with other studies

The concept of pretreatment was introduced for patients with non-ST elevation ACS after the CURE study. This study already showed a similar pattern (reduction in myocardial infarction and excess of major bleeding) but with a conservative management strategy and only 21% of patients undergoing PCI (82% of stents), for which only the control group had four weeks of clopidogrel 75 mg after PCI. Consequently, CURE and its sub-study PCI-CURE did not really evaluate pretreatment, a treatment given before scheduled catheterization or PCI, but evaluated dual antiplatelet therapy in patients managed medically with a minority undergoing delayed catheterization, often several days after admission. The addition of more recent studies in this meta-analysis, including observational studies, allows better representation of contemporary practice with more frequent intervention and faster access to the catheterization laboratory, but also with more heterogeneity.

Examining the randomized studies only or all the studies did not modify the results, with a questionable risk-benefit balance and no impact on mortality despite an analysis performed on more than 32 000 patients. The benefit observed on major adverse cardiovascular events in all patients with non-ST elevation ACS was driven by the observational studies and the two oldest randomized trials with clopidogrel. The results were at odds with the two recent randomized trials with clopidogrel^{27 28} and the one with prasugrel.²⁰ It is difficult to sort out the benefit of pretreatment on major adverse cardiovascular events in the current era, with rapid access of patients to the catheterization laboratory and use of modern techniques of revascularization. Similar results were also found in patients with stable coronary artery disease who underwent elective PCI, where pretreatment with clopidogrel did not confer any ischemic benefit but significantly increased bleedings complications.³¹

Routine pretreatment is even more questionable nowadays, when patients reach the catheterization laboratory within 3–4 hours of admission,^{32–34} a delay that does not allow adequate platelet inhibition with clopidogrel in case of PCI but still exposes all patients, sometimes unnecessarily, to the risk of bleeding for several days after loading. The advantage of pretreatment is also less obvious with the availability of the new P2Y₁₂ antagonists that have a rapid onset of action, are indicated in non-ST elevation ACS,^{35 36} and can be used after coronary artery disease has been diagnosed and the indication of PCI confirmed, as tested now in three large trials.^{36 37 20} Indeed, cangrelor, an intravenous P2Y₁₂ antagonist of immediate action, showed superiority over clopidogrel in patients undergoing PCI with an excellent safety profile.³⁷ Prasugrel, which has a faster and stronger antiplatelet effect than clopidogrel, also showed the validity of a strategy of later administration once the coronary anatomy has been defined.^{20 36}

We acknowledge several limitations to our study. As with any meta-analysis, several biases may have interfered with the final results, for which precautions and limitations have been described elsewhere.²¹ Confidence intervals are wide, and definite conclusion cannot be made solely on point estimates without taking the variability about them into consideration. In

addition, confounding by indication, although controlled, cannot be excluded in registries, and we found significant heterogeneity between observational studies on clopidogrel, which may limit conclusions. This heterogeneity might be due to differences in clinical presentation (non-ST elevation ACS at low or higher risk), in bleeding risk, and in the dose and timing of clopidogrel pretreatment (table 4). However, the global results using all studies available were confirmed in the more robust subgroup of randomized controlled trials and the pre-specified sensitivity analyses.

Another limitation relates to the 300 mg clopidogrel loading dose, where we cannot exclude the possibility that a higher dose, which is known to confer faster and stronger platelet inhibition,³⁸ would have given a different result. However, the only study in this meta-analysis that used a 600 mg loading dose did not favor pretreatment,²⁵ and the CURRENT study did not confirm the superiority of 600 mg over 300 mg of clopidogrel in the global management of non-ST elevation ACS.³² Because no data are available for ticagrelor, conclusions cannot be drawn for this drug. Postponing treatment to after the coronary angiogram is certainly acceptable in patients reaching the catheterization laboratory within 48 hours after admission, as in the studies that tested this hypothesis,^{27 28} but not in patients with longer waiting periods or for emergent cases (ST-elevation-like patients) who were not enrolled in these studies.

Conclusions and policy implications

In conclusion, our meta-analysis shows that in patients with non-ST elevation ACS, pretreatment with thienopyridines is not associated with a lower risk of mortality globally or more specifically in patients undergoing PCI. The reduction of ischemic endpoints is modest and counterbalanced by an increase in major bleeding, no matter the final management strategy with or without PCI. The concept of systematic and immediate pretreatment with P2Y₁₂ antagonists in patients admitted with non-ST elevation ACS needs to be reconsidered.

Contributors: GM had the idea, then planned and conducted the study with ABA. ABA and MK performed the literature search and selected studies, ABA and MK extracted study data, ABA and MC assessed risk of bias, performed the statistical analysis, and wrote the manuscript. All authors assisted in formulation of the research question, assessed quality of evidence, contributed to and developed the final manuscript. ABA, GM, MC, and MK had full access to all of the data.

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What is already known on this topic

Pretreatment with P2Y₁₂ inhibitors for non-ST elevation acute coronary syndrome (ACS) patients has a class I-B recommendation, based on old studies done before the contemporary routine and early access to coronarography

Recent randomized and observational studies have questioned the risk-benefit of pretreatment in patients undergoing percutaneous coronary intervention (PCI)

What this study adds

This systematic review and meta-analysis shows that in patients with non-ST elevation ACS, pretreatment with thienopyridines is not associated with a lower risk of mortality globally or more specifically in patients undergoing PCI. The reduction of ischemic endpoints is modest and counterbalanced by an increase in major bleeding, no matter the final management strategy, with or without PCI

The concept of systematic and immediate pretreatment with P2Y₁₂ antagonists in patients admitted with non-ST elevation ACS needs to be reconsidered in daily practice and in guidelines

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Ethical approval: Not required

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

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Table

Table 1 | Overview of studies included in meta-analysis of thienopyridine pretreatment in patients with non-ST elevation acute coronary syndrome

		No (%) of study patients						
Study	Type of trial	Non-ST elevation ACS	Undergoing PCI	Pretreatment	No pretreatment	Endpoints MACEs	Bleeding definitions	Follow-up
Registries (for clopidogrel only)								
Feldman et al 2010 ²⁵	Retrospective registry of cohort	1041/1041 (100)	1041/1041 (100)	75 mg MD for ≥5 days <i>or</i> 300 mg LD for ≥12 hours <i>or</i> 600 mg LD for ≥2 hours	600 mg LD for <2 hours <i>or</i> 600 mg LD on table	Death, MI, UTVR, stroke	Major ≥4 g/dL Hb Minor 2—<4 g/dL	In hospital, 1 year
Chan et al 2003 ²⁹	Retrospective registry of cohort	2763/4809 (57.4)	4809/4809 (100)	300 mg pre-PCI: 56.6% <2 hours 27.2% 2-6 hours 16.2% >6 hours (mean 2.1 hours)	300 mg LD immediately after PCI	Death, MI, UTVR	TIMI major or minor bleeding	30 days, 6 months, 1 year (death only)
Assali et al 2008 ¹⁸	Retrospective registry of cohort	205/299 (68.6)	299/299 (100)	75mg MD within 5 days <i>or</i> 300 mg LD in morning <i>plus</i> glycoprotein IIb/IIIa inhibitor	300 mg LD immediately after PCI	CV death, MI, UTVR	IC, transfusion, hemodynamic compromise	In hospital
Randomized controlled trials (RCT)								
Clopidogrel:								
CREDO 2002 ⁸	RCT	1407/2116 (66.5)	1820/2116 (86.0)	300 mg LD 3-24 hours pre-PCI (mean 9.8 hours) then long term MD	No pretreatment 28 days clopidogrel	Death, MI, UTVR per protocol analysis	*	28 days, 1 year
CURE 2001 ⁶	RCT	12 562/12 562 (100)	2663/12 562 (21.2)	300 mg LD (median 10 days pre-PCI) then 75 mg MD for 3-12 months	No LD; no MD If PCI: 75 mg for 4 weeks	CV death, MI, stroke	*	30 days, 1 year
PCI-CURE 2001 ²⁶	RCT Subgroup†	2658/2658 (100)	2658/2658 (100)	300 mg LD (median 10 days pre-PCI) then 75 mg MD for 3-12 months	No LD then 75mg for 4 weeks	CV death, MI, UTVR	*	30 days, 1 year
ACUITY 2004 ²⁷	RCT Subgroup analysis‡	7523/7523 (100)	4243/7523 (56.4)	Subgroup ≥300 mg LD pre-PCI or in cathlab 75 mg MD for 12 months	Subgroup ≥300 mg LD Post-PCI <2 hours 75 mg MD for 12 months	Death, MI, UTVR	*	30 days, 1 year
ACUITY PCI 2007 ²⁸	RCT Subgroup analysis‡	5039/5039 (100)	5039/5039 (100)	Subgroup ≥300 mg LD pre-PCI or in cathlab 75 mg MD for 12 months	Subgroup ≥300 mg LD Post-PCI <2 hours 75 mg MD for 12 months	Death, MI, UTVR	*	30 days, 1 year
Prasugrel:								
ACCOAST 2013 ²⁰	RCT	4033/4033 (100)	2770/4033 (68.7)	Prasugrel 30 mg 2-48 hours pre-PCI (median 4.4 hours) then 30 mg after angiogram or before PCI	No pretreatment Prasugrel 60 mg just before PCI (after angiogram)	CV death, MI, UTVR, stroke, glycoprotein IIb/IIIa inhibitor bailout	*	7 days, 30 days

ACS=acute coronary syndrome. PCI=percutaneous coronary intervention. MACE=major adverse cardiovascular events. MD=maintenance dose. LD=loading dose. MI=myocardial infarction. UTVR=urgent target vessel revascularization. TIMI=thrombolysis in myocardial infarction. CV=cardiovascular. cathlab=catheterization laboratory. IC=intracranial.

*Bleeding definition are TIMI major and minor definition except for CURE and PCI-CURE (major bleeding=substantially disabling bleeding, intraocular bleeding leading to loss of vision, or bleeding necessitating transfusion of ≥2 units of blood) and for ACUITY and ACUITY PCI (defined as "clinically significant bleeds").

†Post-randomization subgroup defined as randomized comparison.

‡Observational studies from RCT database (pre-specified non-randomized subgroup analysis of RCT).

Figures

Fig 1 Flow chart of study selection

Fig 2 All cause death for all patients with non-ST elevation acute coronary syndrome (ACS) (top) and those who underwent percutaneous coronary intervention (PCI) (bottom) comparing pretreatment with P2Y₁₂ inhibitors versus no pretreatment. Death was considered at shortest follow-up available in each study which was 7 or 30 days unless indicated otherwise.

Fig 3 Major bleeding for all patients with non-ST elevation acute coronary syndrome (ACS) (top) and those who underwent percutaneous coronary intervention (PCI) (bottom) comparing pretreatment with P2Y₁₂ inhibitors versus no pretreatment. Major bleeding was considered at shortest follow-up available in each study which was 7 or 30 days unless indicated otherwise

Fig 4 Main composite ischemic endpoint for all patients with non-ST elevation acute coronary syndrome (ACS) (top) and those who underwent percutaneous coronary intervention (PCI) (bottom) comparing pretreatment with P2Y₁₂ inhibitors versus no pretreatment. The composite ischemic endpoint was considered at shortest follow-up available in each study which was 7 or 30 days unless indicated otherwise

Fig 5 Main ischemic and hemorrhagic endpoints in randomized controlled trials only for all patients with non-ST elevation acute coronary syndrome (ACS) (top) and those who underwent percutaneous coronary intervention (PCI) (bottom) comparing pretreatment with P2Y₁₂ inhibitors versus no pretreatment. All endpoints were considered at shortest follow-up available in each study which was 7 or 30 days unless indicated otherwise