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Meta-analysis of clopidogrel pretreatment in acute coronary syndrome patients undergoing invasive strategy

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ABSTRACT

Background: It is unknown whether pretreatment with clopidogrel in acute coronary syndrome (ACS) managed invasively, is superior to a strategy of administering clopidogrel in the cardiac catheterization laboratory at the time of percutaneous coronary intervention (PCI). Current practice guidelines do not endorse one strategy over the other.

Methods: A comprehensive literature search was done to identify all relevant studies comparing pretreatment with clopidogrel to administration in the cardiac catheterization laboratory at the time of PCI (no pretreatment). A meta-analysis using a random effects model was used to calculate outcomes of interest.

Results: Our search identified 16 studies including 61,517 ACS patients undergoing cardiac catheterization. At 30 days, clopidogrel pretreatment was associated with lower MACE 7.67% vs 9.46% (odds ratio (OR) 0.77, 95% confidence interval (CI) [0.68, 0.86]; $P < 0.0001$) and all-cause mortality 2.8% vs 4.1% (OR 0.70, 95% CI [0.58, 0.85]; $P = 0.0003$). Mortality according to the longest follow up available was also significantly lower with pretreatment. No difference in major bleeding events was observed. These results were not significantly different between randomized vs observational studies or STEMI vs NSTEACS patients. Sensitivity analysis showed significantly lower MACE 7.98% vs 9.6% (OR 0.83, 95% CI [0.71, 0.96]; $P = 0.01$) without increased major bleeding in NSTEACS patients undergoing PCI within 48 h from pretreatment.

Conclusion: In ACS patients undergoing PCI, clopidogrel pretreatment was associated with significantly lower 30 day all-cause mortality and major adverse cardiovascular events without increased major bleeding events.

1. Introduction

Antiplatelet therapy plays a pivotal role in the treatment of acute coronary syndrome (ACS) patients. Aspirin was the first antiplatelet agent shown to have pronounced benefits and is universally given on presentation [1]. P2Y12 inhibitors, including clopidogrel consistently improved outcomes when combined with aspirin therapy [2–6], but the timing of their administration in relation to PCI remains controversial [7–8]. Current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines lack clear consensus regarding the timing of administration of P2Y12 inhibitors [9,10]. In contrast, European practice guidelines recommend early administration of P2Y12 inhibitors only in STEMI, but acknowledge that widespread evidence to support this recommendation is lacking [11]. Previous meta-analyses evaluating clopidogrel pretreatment found no mortality benefit with pretreatment [12,13]. However, these analyses did not take into account time to PCI in patients with NSTEMI and since their publication additional clinical studies were published. Therefore, the objective of the current study was to perform a comprehensive meta-analysis of all studies comparing pretreatment with clopidogrel to no pretreatment in ACS patients managed invasively as well as to explore whether time to PCI in NSTEMI patients is a treatment modifier in regards to pretreatment.

2. Methods

We comprehensively searched all possible sources to identify all English language studies comparing clopidogrel pretreatment with no pretreatment prior to percutaneous coronary intervention. We systematically searched the online databases including

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0167-5273/

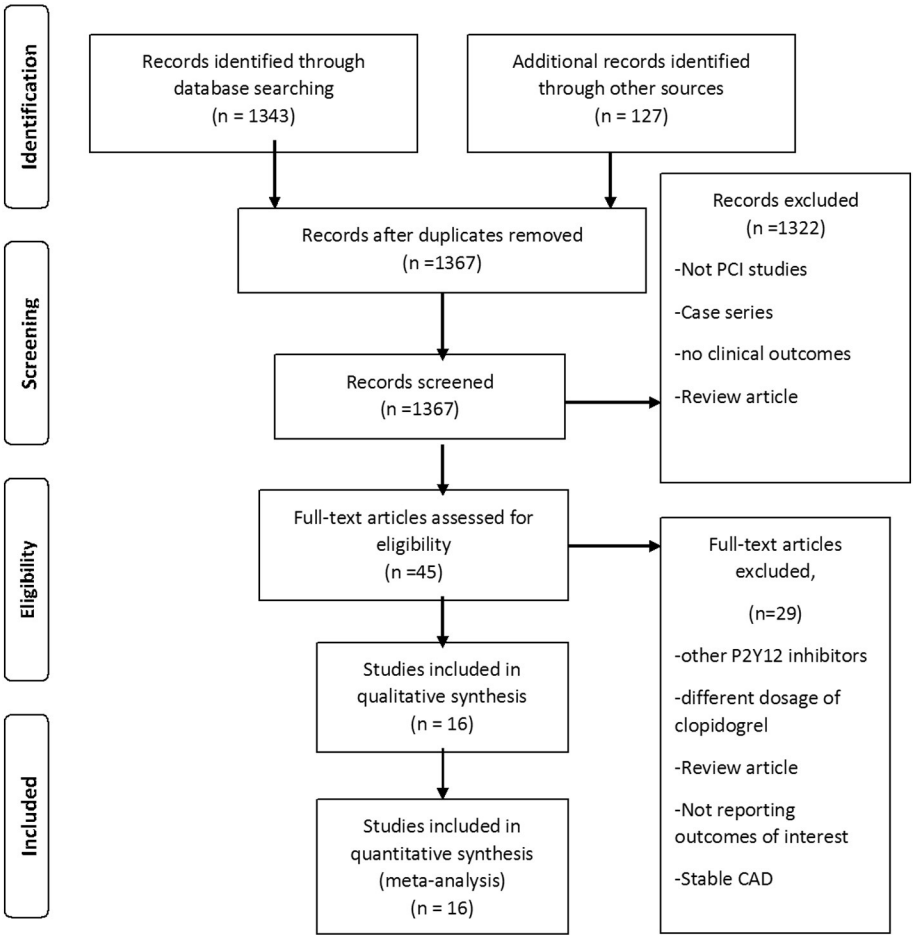

Fig. 1. Search strategy and study selection as per PRISMA checklist.

PubMed, Cochrane CENTRAL, EMBASE, EBSCO, Web of Science and CINAHL databases up until March 2016 for full length articles published in the English language in peer-reviewed journals. The search strategy was broad and used the following keywords separately and in combination: "pretreatment", "clopidogrel", "PCI", "STEMI", "NSTEMI", "Upstream" and "before PCI". Abstracts were screened for established inclusion/exclusion criteria and studies that were relevant to our search were fully reviewed. In an attempt to identify all possible studies, references from relevant manuscripts were hand searched for additional studies not identified from the initial database search.

To select the studies for this review the strengthening Meta-analysis Of Observational Studies in Epidemiology checklist was used [14]. We also used the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for reporting systematic reviews and meta-analyses [15]. Pretreatment with clopidogrel entailed its administration on presentation, as soon as possible, and prior to arrival to the catheterization lab, while no pretreatment was identified as clopidogrel administration in the catheterization lab at the time of PCI or afterwards. Our inclusion criteria were: 1) studies comparing pretreatment with clopidogrel to no pretreatment in acute coronary syndrome patients undergoing invasive strategy, 2) observational or randomized, 3) follow up of at least 48 h, and 4) reporting any of the outcomes of interest: major adverse cardiovascular events (MACE), all-cause mortality, and major bleeding. Exclusion criteria were 1) non-English language studies, 2) abstracts only, 3) medically managed patients, 4) use of 900 mg loading dose of clopidogrel, 5) studies comparing unequal loading doses of clopidogrel in the comparator treatment arms, and 6) studies not reporting outcomes of interest or not meeting the inclusion criteria. Definitions of outcomes in each of the included studies are detailed in Table 1 supplementary material.

Data were independently extracted from the relevant published articles by two physician reviewers (RN and YR) after determining their eligibility for inclusion. Discrepancies and disagreements in data incorporation were resolved through consensus among all authors. The baseline characteristics of patients (e.g. sample size, age, sex, and intervention in the study/control group) were collected from eligible studies as available. We abstracted the following primary outcomes of interest: MACE, all-cause mortality, and major bleeding at 30 days as well as mortality according to the longest follow up for both comparator arms. Sensitivity analysis examined outcomes of interest as follows: 1) STEMI vs NSTEACS patients, 2) NSTEACS patients who underwent cardiac catheterization within 48 h from presentation and 3) excluding the largest study. Studies which included >60% NSTEACS patients were included. The trial quality and risk of bias in reporting data for individual studies were objectively assessed using the methods specified in the Cochrane Handbook of Systematic Reviews and the New Castle-Ottawa scale for case control studies [16,17] and reported in Tables 2 and 3 supplementary materials.

Measurement of the effect size of outcomes reported was done using odds ratios (ORs), with the corresponding 95% confidence intervals (CIs). We used random effects models (DerSimonian and Laird) to calculate a summary estimate across all included studies. Heterogeneity testing was performed by using the Cochran Q test and Higgins I^2 test. Cochran's Q $P < 0.10$ and $I^2 > 50\%$ were considered to be indicative of significant heterogeneity. P value for interaction was considered significant if <0.10. All analyses were done using RevMan 5.2.4 software (Nordic Cochrane Centre, Cochrane Collaboration, 2013) [18].

3. Results

Our initial search screened 1367 potential articles, of which 45 full text articles were retrieved and reviewed for possible inclusion (Fig. 1). Among those, we excluded 5 studies for including mostly stable coronary artery disease patients [19–23], one article for examining 900 mg loading dose of clopidogrel [24], and another study by Ducci et al. for comparing 600 mg loading dose to a 300 mg loading dose [25]. After further revisions and exclusions, 16 studies met all our inclusion criteria and were included in this analysis [2,4,26–39].

A total of 61,517 acute coronary syndrome patients undergoing invasive strategy with cardiac catheterization and PCI when indicated were included in this analysis. The characteristics of the included studies, loading doses of clopidogrel and treatment times are detailed in Table 1. Patient characteristics and procedural characteristics in both treatment arms are summarized in Table 2.

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