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Evaluating the Efficacy and Safety of Concurrent Proton Pump Inhibitors and Clopidogrel Therapy in post-PCI Patients: A Comprehensive Systematic Review and Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - Nil.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202420009

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 February 2024 and was last updated on 02 February 2024.

INTRODUCTION

Review question / Objective To investigate the MACEs risk of clopidogrel combined with PPIs.

Rationale Clopidogrel, a critical medication for managing patients post-percutaneous coronary intervention (PCI), acts as an antiplatelet agent. A notable side effect of clopidogrel includes gastrointestinal (GI) bleeding. To mitigate this, the use of proton pump inhibitors (PPIs) like esomeprazole, lansoprazole, pantoprazole, omeprazole, and rabeprazole is common. Nevertheless, concerns regarding possible interactions between clopidogrel and PPIs have emerged. The objective of our research is to identify which PPIs, when used in combination with clopidogrel, present the least risk of major adverse cardiovascular events (MACEs) and GI bleeding.

Condition being studied The PICO (population, intervention, comparison, outcome) setting of the current meta-analysis included: (1) P: human participants with post-PCI using clopidogrel; (2) I: co-administrated PPI; (3) C: placebo group without intervention; and (4) O: MACEsrisk.

METHODS

Participant or population Human participants.

Intervention PPIs combination.

Comparator Placebo.

Study designs to be included Randomized controlled trials and cohort studies.

Eligibility criteria The criteria for selecting studies to be included in our research are as follows: (1) Randomized controlled trials and retrospective cohort studies involving patients who underwent

PCI and were prescribed clopidogrel, with or without specific PPIs. (2) Randomized controlled trials and retrospective studies including patients post-PCI treated with clopidogrel, with or without specific PPIs, for a duration exceeding one month. (3) A control group in these studies that did not receive any PPIs. (4) Studies that have accessible data regarding major adverse cardiovascular events (MACEs).

Information sources Two authors (MY, Ai and WL, Chang) independently conducted electronic searches across following databases, including PubMed, Cochrane Reviews, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov. The search utilized the following keywords: ('Clopidogrel') AND ('Percutaneous coronary intervention') AND ('Lansoprazole' OR 'Omeprazole' OR 'Esomeprazole' OR 'Pantoprazole' OR 'Rabeprazole' OR 'Dexlansoprazole' OR 'Proton pump inhibitors') through the earliest record to Jan 24, 2024.

Main outcome(s) The primary outcome was the MACEs happened between different PPIs combined with clopidogrel.

Additional outcome(s) The secondary outcome was the GI bleeding happened between different PPIs combined with clopidogrel.

Data management Data extraction from the selected studies was conducted by two independent researchers (M.-Y.A. and W.-L.C.), covering demographic information, study methodology, specifics of the various PPI and clopidogrel combinations compared with placebo treatments, along with the primary and secondary outcome metrics.

Quality assessment / Risk of bias analysis For assessing the methodological integrity of the studies included, the Cochrane Collaboration's Risk of Bias tool for randomized trials, version 2 (RoB 2), was employed. This tool evaluates six critical areas: the process of randomization, adherence to the intervention, handling of missing outcome data, accuracy of outcome measurement, instances of selective outcome reporting, and the general risk of bias. The Newcastle-Ottawa Scale (NOS) assessment for Non-randomized controlstudies.

Strategy of data synthesis Due to the diversity in the populations studied, we opted for a random-effects model for this network meta-analysis, utilizing the Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ), and MetaInsight software (version 4.0.2, Complex Reviews Support Unit, National Institute for Health Research, London, UK). Statistical significance was determined by a two-tailed p-value of less than 0.05. For the measurement of study outcomes, we used Hedges' g along with 95% confidence intervals (CIs), where values of 0.2, 0.5, and 0.8 represent small, moderate, and large effect sizes, respectively. To assess heterogeneity across the studies, the I2 and Cochran's Q statistics were employed, with I2 values of 25%, 50%, and 75% indicating low, moderate, and high levels of heterogeneity, respectively.

Subgroup analysis Nil.

Sensitivity analysis To ensure the reliability of the network meta-analysis findings, sensitivity analyses were conducted by employing a one-study removal approach. This method assessed whether excluding a specific trial from the analysis led to a significant alteration in the overall effect size.

Language restriction No language limit.

Country(ies) involved Taiwan.

Keywords MACEs, GI bleeding, clopidogrel, proton pump inhibitors (PPIs), post-PCI.

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