

Is There Any Co-Relation between Ischemic Stroke and Combined Use of Pips and Ant platelet Agents– Aspirin and Clopidogrel? - A Review

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Abstract: Proton pump inhibitors (PPI) are prescribed with the dual antiplatelet therapy, the association of PPI with the reduction of clopidogrel efficacy is controversial. An electronic search in Pub Med, EMBASE, and Scopus was conducted, all the relevant articles published during the period from January 2011 to present were included. The following search terms such as "proton pump inhibitors" "ischemic stroke" "aspirin" "clopidogrel" "omeprazole," "rabeprazole" and "pantoprazole" are used along with appropriate boolean operators AND or OR. The search is limited to the articles in English language and human adults and experimental research evidence. Out of 2453 items, 19 pieces of evidence were selected for analysis. Four trials, three reviews, three case-control studies, four comparative studies, three retrospective, and two prospective studies. The randomized control trials showed no clinically significant association with stroke when PPIs are combined with dual antiplatelet therapy. Other studies found pantoprazole is the safest drug. Further randomized controlled trials are needed to assess if the association of PPI use and stroke is a class effect.

Keywords: Proton pump inhibitors, Dual antiplatelet therapy, Stroke

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I. Background

Proton pump inhibitors are among the most widely used drugs worldwide, and omeprazole is on the World Health Organization Model List of Essential Medications, they act mainly through gastric acid suppression. They follow the Histamine 2 receptors antagonists, and they superseded them due to the prolonged and potent acid suppression (1,2).

Aspirin and clopidogrel (dual antiplatelet therapy) are prescribed to acute coronary syndrome patients for the secondary prevention at the expense of significant gastrointestinal bleeding, low dose aspirin therapy has been associated with a two-fold higher risk of major bleeding and the risk is nearly doubled when clopidogrel is combined with aspirin (3-5). To reduce the risk of gastrointestinal bleeding, proton pump inhibitors (PPIs) are usually prescribed to the patients undergoing dual antiplatelet therapy. There is an increasing concern that PPIs could reduce clopidogrel efficacy (6) with deleterious consequences (increasing cardiovascular and all-cause death, myocardial infarction, and stroke).

All proton pump inhibitors (to different degrees) and clopidogrel use the cytochrome P450 enzyme system, in particular, P450 2C19 (CYP2C19) (7), resulting in competitive inhibition that may affect clopidogrel action as antiplatelet therapy. Several studies have raised concerns about omeprazole (8) might decrease the antiplatelet effects of clopidogrel, others concluded that other proton pump inhibitors are to blame (9). A recent randomized control trial found that pantoprazole does not increase platelets aggregation in patients receiving dual antiplatelet therapy (10).

Several studies concluded the association of the proton pump inhibitors with the adverse cardiovascular events and the risk is independent of antiplatelet agents. However other researchers found that some proton pump inhibitors are safe to combine with clopidogrel suggesting that the clopidogrel interaction with the proton pump inhibitors is not a class effect (11,12).

Previous literature showed that recurrent ischemic stroke among patients taking clopidogrel and proton pump inhibitors could be due to patients factors including diabetes mellitus, clopidogrel resistance, and the loss of function of CYP2C19*2 (AG/AA genotype) or CYP3A5 (GG/AG genotype) (13).

Given the above controversy and the fact that acute coronary syndrome is the leading cause of death worldwide necessitating the frequent use of dual antiplatelet therapy. It is prudent to review the most recent literature regarding the use of PPIs with antiplatelet treatment to help the concerned doctors selecting the most appropriate drug for use in the acute coronary care setting. To our best of knowledge, no researchers have reviewed the literature for the association of specific proton pump inhibitors with ischemic stroke. Thus we conducted this search with objectives to assess the association of the combined use of PPIs and antiplatelet agents (aspirin and clopidogrel) with ischemic stroke and to hypothesize the possible mechanism for the interaction between PPIs and antiplatelet drugs.

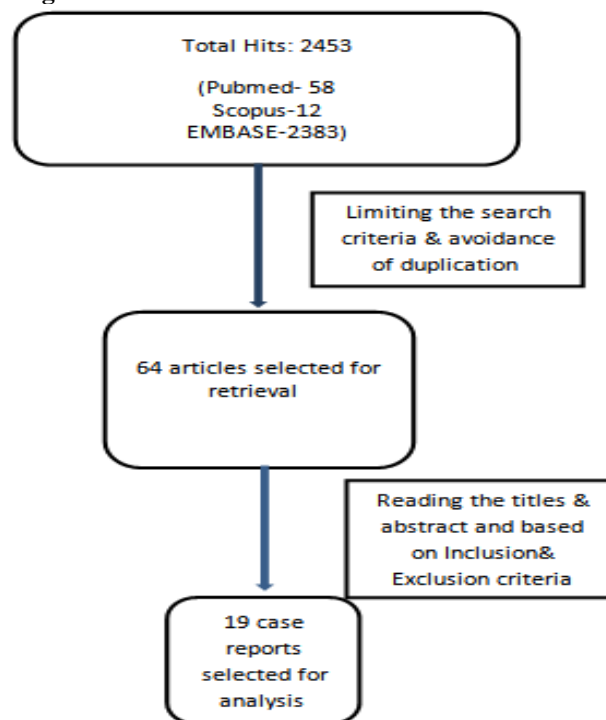
II. Search strategy

An electronic search is carried out for the relevant literature published during 2011 to present in the databases of, MEDLINE, Scopus, and EMBASE. The following search terms such as "proton pump inhibitors" "ischemic stroke" "aspirin" "clopidogrel" "omeprazole," "rabeprazole" and "pantoprazole" are used along with appropriate boolean operators AND or OR. The search is limited to the articles in English language and human adults and experimental research evidence. We also used forward as well as backward chaining for the relevant articles cited in retrieved publications. The selected items are undergoing eligibility assessment according to SIGN checklist criteria and hierarchy of evidence-based on Harbour-Miller system 2001. The first author collected the articles using the search engines and included review articles, systematic-meta-analysis, controlled trials, observational studies which use both groups of drugs concomitantly, excluding the research articles, which included the patients with risk factors for ischemic stroke and those without a description of relevant data. All search results were analyzed by reading titles, and authors name and duplicates were eliminated. Two authors independently appraised the full text of retrieved articles for their potential eligibility for inclusion. The first and second author collected and entered data with following descriptions author' (s) name, year of publication, population studied and type of study, a number of patients, mean age and range, the gender of patients, type of ischemic heart disease, mode of therapy and duration of treatment and dose. Team consensus resolved any discrepancies raised between authors on data.

III. Results

The total number of search hits was 2453 articles and after reading titles and removing duplication of selected 64 articles to retrieval of full articles. Based on fulfillment of criteria for selection, 19 pieces of evidence were selected for analysis (Fig 1). Four trials, three reviews, three case-control studies, four comparative studies, three retrospective, and two prospective studies.

Figure 1: Flowchart of events in the literature search



IV. Discussion

In 2010, Charlot M et al. conducted a year followed up nationwide cohort study including 56406 patients with acute coronary syndrome on the use of clopidogrel with proton pump inhibitors(PPI) or without PPI and found an association of PPIs with an increased incidence of stroke regardless of clopidogrel. Dunn SP et al. in 2013, also confirmed with CAPRIE trial, a negative interaction of PPI with clopidogrel in coronary ischemic disease.

In another review article on two randomized control trial of PRINCIPLE-TIMI 44 and TRITON-TIMI 38, which published by O'Donoghue et al. in 2009, in 13608 patients with the acute coronary syndrome, found no association of PPI use along clopidogrel on primary endpoints such as cardiovascular death, myocardial infarction, and stroke. They interpreted with these RCT findings that no need to avoid concomitant use of PPIs, when clinically indicated, in patients receiving clopidogrel or prasugrel.

In another comparative trial, conducted in 2010, with the participation of 3873 patients with coronary artery disease, Bhatt et al. observed no significant cardiovascular interaction of omeprazole with clopidogrel. But, Goodman et al, 2012, in a randomized trial with participation of total 18599 patients grouped into clopidogrel or ticagrelor with PPI and without PPI, showed the association of proton pump inhibitors with a cardiovascular event such as stroke, myocardial infarction and other cardiovascular events and concluded that it may be due to confounding factors. However, in 2015, Nicolau JC et al. conducted a trial in acute coronary syndrome patients which found no effect of proton pump inhibitors on platelet activity. The same year, Leonard et al., compared the combined use of pantoprazole and clopidogrel with a combination of clopidogrel and other PPIs such as omeprazole, esomeprazole, lansoprazole, and rabeprazole in 325559 patients to find out the risk for ischemic stroke and concluded that no difference between the group. This finding is re-affirmed by Lu, in 2017 in his report on the prognosis of 478 patients with a transient ischemic attack.

Fonte-Carvalho R et al. conducted a randomized cross-over trial, in 2011 with pantoprazole and omeprazole in myocardial infarction patients to find out any drug-drug interaction between clopidogrel and PPIs. They concluded with a significant pharmacodynamic interaction of omeprazole with clopidogrel, but not with pantoprazole. The effect of omeprazole with increased platelet aggregation is reported again in a comparative trial by Yamane K et al. in 2012. They compared the PPIs(omeprazole and rabeprazole) with famotidine and found significantly increased platelet aggregation with both PPIs in 55 coronary arterial patients. Parri MS et al., 2013, carried out a randomized study in 105 patients and found the significant interaction of pantoprazole with platelet aggregation in insufficient coronary patients. In 2017, Choi YJ et al. carried out a randomized control trial in 40 patients on antiplatelet therapy with clopidogrel, to compare the effect of pantoprazole on platelet aggregation with that of ranitidine and showed no significant effect on platelet aggregation with pantoprazole.

Offman E et al. in 2013 found no significant pharmacokinetic or pharmacodynamic interaction between aspirin and omeprazole in their randomized control in sixty coronary arterial disease patients. This finding is confirmed by Goldstein JL et in 2016 in 32540 patients on secondary prevention of cardiovascular disease.

In conclusion, most of the recent randomized controlled trials show a clinically significant interaction of PPIs, especially omeprazole with clopidogrel on platelet aggregation in a patient with the coronary arterial disease, whereas the combined use of aspirin in antiplatelet dose along with PPIs found no clinically significant interaction with platelet aggregation. Some studies favor the use of pantoprazole along with clopidogrel, but some not. In addition to this, the number of patients involved in these studies is less, and it is required to carry out trials with the involvement of large cohort of patients. In 2012 study(Goodman et al.) the number of the patients was high. However, they declared the influence of co-founding factors their finding on the significant interaction of PPI on platelet aggregation with clopidogrel. So it demands well designed randomized control trial with more patient participation for the definite conclusion on the interaction between clopidogrel and proton pump inhibitors.

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