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Using Famotidine as an alternative for Omeprazole to prevent drug-drug interaction between Clopidogrel and Omeprazole in CVS Patients: A Systematic Literature Review

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Abstract

Background: Omeprazole is a proton pump inhibitor that is the most widely prescribed agent for the treatment of gastrointestinal diseases such as GERD, esophagitis, and peptic ulcer disease. Patients having CVS diseases (MI, stroke, and stent thrombosis) also receive omeprazole for the treatment of gastrointestinal bleeding due to frequent consumption of clopidogrel. In the last few years, there are certain case reports that the use of omeprazole with clopidogrel is associated with severe CVS adverse effects such as increased risks of MI, ischemic stroke, and thrombosis, due to drug-drug interactions between them.

Objective: This study aimed to review the use of famotidine, a Histamine H2 receptor blocker, as a potential alternative to omeprazole to prevent CVS adverse effects in patients on dual antiplatelet therapy (DAPT).

Methodology: A systematic literature review was conducted following the PRISMA guidelines. So, for this purpose, a systematic literature review was performed according to PRISMA guidelines to gain insight about the drug-drug interaction between omeprazole and clopidogrel and about the safety of famotidine in cardiovascular patients. PubMed, NCBI, Medline, and Google Scholar were searched to identify relevant articles with a focus on drug-drug interaction between omeprazole and clopidogrel and the safety of famotidine in CVS patients. Studies published between 2010 and 2024 were included for data collection and analysis.

Results: Randomized controlled trials and observational studies comparing CVS patients treated with clopidogrel and omeprazole to those treated with clopidogrel and famotidine were analyzed, it was found that the use of famotidine prevents mucosal injury without having interaction with clopidogrel and thus can be safer for CVS patients on DAPT.

Conclusion: Although this study provides basic precautions and guidelines for healthcare professionals and clinicians when prescribing this therapy, further experimental studies are recommended to evaluate the safety and drug-drug interactions between omeprazole and clopidogrel as well as for famotidine and clopidogrel in CVS patients on DAPT therapy.

Keywords: Clopidogrel, antiplatelet therapy, famotidine, drug-drug interaction, and omeprazole.

Introduction

Omeprazole, a commonly prescribed proton pump inhibitor (PPI), is widely used for the treatment of gastroesophageal reflux disease (GERD), esophagitis, and peptic ulcers. However, its chronic use has been associated with various adverse effects, including gastrointestinal infections, bone fractures, nephrotoxicity, and cardiovascular complications such as myocardial infarction and stroke [1, 2]. These risks are particularly significant in patients taking omeprazole alongside clopidogrel, a common combination in cardiovascular patients to prevent GI bleeding [1]. Moreover, omeprazole may impair cardiovascular health through mechanisms like endothelial dysfunction and elevated plasma levels of chromogranin A (CgA) [1, 3].

Omeprazole

PPI especially omeprazole is among the most broadly prescribed agent for the treatment of GERD, esophagitis as well as peptic ulcer diseases. Moreover, omeprazole is extensively being given to

patients for the long-term treatment of GIT disorders often without an indication [1]. But, over the last few years, there is a large number of reports indicating that chronic omeprazole use is linked to many adverse effects such as GIT infections, pneumonia, bone fractures, nephron toxicity, antithrombotic drug interactions, and nutritional deficiencies [2]. Furthermore, due to the chronic use of clopidogrel (blood thinner), patients with cardiovascular disorders are the most prevalent patient group getting omeprazole for the treatment of gastrointestinal (GI) bleeding [1].

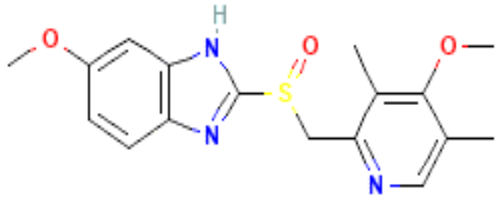

Figure 1: Structure of Omeprazole [3]

Chronic use of omeprazole is linked with an increased risk of cardiovascular disorders (myocardial infarction, stent thrombosis, and stroke), and GERD patients exposed to omeprazole also have an increased chance of MI irrespective of clopidogrel use. It was also linked to an increased risk of mortality due to CVS diseases and upper GIT cancer in patients without a proven need for acid suppression medications [4]. In addition, the use of low-dose omeprazole (10 mg) has decreased the risk of ischemic stroke, cardiac arrhythmias, and MI when compared to the use of high-dose omeprazole (40 mg) [1]. Many studies have shown that omeprazole has deleterious effects when used in conjunction with clopidogrel. It is also mentioned that long-term usage of omeprazole can lead to hypomagnesaemia, which can lead to ventricular arrhythmias and problems in cardiac conduction due to prolongation of QT interval. While H2 receptor blockers such as famotidine are not linked to any cardiovascular disorders and therefore it can be an alternative therapeutic choice for omeprazole in certain patients [5].

Mechanisms of omeprazole-related cardiovascular effects

In order to explain the problems of long-term use of omeprazole, many mechanisms have been proposed that disrupt the vascular homeostasis such as endothelial dysfunction, hypomagnesaemia, decreased NO (nitric oxide) in endothelial cells, and high blood levels of chromogranin A (CgA) [1, 4]. According to a study on vascular endothelial cells, it is observed

that omeprazole enhanced the formation of free radicals by affecting the endothelium's lysosomal proton pumps, which are responsible for the majority of vascular alterations. Long-term use of omeprazole impairs the hepatic enzymes, lysosomal acidification along with protein accumulation which results in the production of reactive oxygen species and so, in this way it affects the nitric oxide (NO) synthesis pathway that ultimately leads to decreased production and release of NO by endothelial cells, and it's one of the major pathways linked with dysfunction of the endothelium [1].

In certain studies, it's observed that increased plasma asymmetrical dimethyl arginine (ADMA) level is linked with an increased risk of CVS disorders, most likely due to a reduction in the vascular protective actions of endothelial NO synthase. Omeprazole was discovered to raise plasma ADMA levels, which decreases the vasodilation of endothelium and nitric oxide level when observed in ex-vivo human tissues. PPI's bind to dimethylaminohydrolase (an enzyme that degrades ADMA) and inhibits its activity resulting in increased ADMA levels caused by omeprazole [4]. Omeprazole also affects ADMA levels by interacting with vitamin B12 absorption that converts homocysteine to cysteine. So, the increased levels of homocysteine levels elevate the ADMA, as well as cause different degrees of endothelial dysfunction and greater vulnerability to Coronary artery disease (CAD), depending on the pre-existing state of cardiovascular health. Moreover, as indicated earlier that dimethylaminohydrolase (DDAH2) enzyme has also been found to stimulate the expression of vascular endothelial growth factor (VEGF), so its inhibition by omeprazole further increases the VEGF-related vasculopathies such as atherosclerosis [1].

The release of chromogranin-A (CgA) is significantly increased after taking omeprazole. CgA is a key marker for neuroendocrine tumors and cardiovascular diseases and therefore, its increased levels can interfere with endocrine tumor examination. Chromogranin A and its peptides such as vasostatins and cetastatin have cardiac regulatory and vasodilator actions that can be adaptive in short term. Chromogranin A (CgA) released by omeprazole has become more prominent in cases of severe hypertension and renal insufficiency which results in elevated blood CgA levels. CgA also stimulates the release of endothelin-1 (vasoconstrictor) from the endothelium of blood vessels and more endothelin-1 causes CVD and vascular dysfunction via pro-atherosclerotic and pro-

inflammatory effects. Thus, the high CgA plasma levels are linked with increased mortality after heart failure or myocardial infarction [1, 6].

Omeprazole, as previously indicated, can produce hypomagnesemia which causes vascular arrhythmias. Although the exact mechanism of hypomagnesemia caused by omeprazole is not known, still it is hypothesized that it interferes with the absorption of magnesium across the GIT wall or stimulates the excessive loss of magnesium into the intestine [7]. Thus, all these mechanisms tell that PPI-induced minor changes in the body can have a lethal impact on Cardiovascular patients.

Simultaneous use of omeprazole and clopidogrel

Prophylactic omeprazole therapy is typically given to patients on dual antiplatelet therapy (DAPT) to lower the risk of GI hemorrhages [5]. The clopidogrel-omeprazole interaction has also been linked to an increase in myocardial infarction rates. Omeprazole interacts with cytochrome p450 (CYP2C19) and the metabolism of clopidogrel, so these agents can amplify this effect [1]. Some studies have found that there are no significant interactions between clopidogrel and omeprazole in patients who use aspirin and clopidogrel with either omeprazole or placebo. But, these findings do not rule out the significant CV events as a result of omeprazole use [5, 8]. Omeprazole, as previously indicated, is linked to an elevated risk of cardiovascular disease, whether taken alone or in combination with clopidogrel. Some other studies have found that taking clopidogrel and omeprazole at the same time after a Percutaneous Coronary intervention (PCI) operation is linked to an increased risk of myocardial infarction (MI), major adverse cardiovascular effects (MACE), and stent thrombosis. Patients taking omeprazole do, however, have a decreased risk of GI bleeding [9].

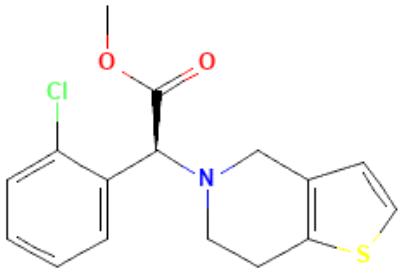

Figure 2: Structure of Clopidogrel [10]

Importantly, in some studies, it is indicated that analysis of randomized controlled trials (RCTs) with CAD patients demonstrate that non-PPI group users have a lower risk of MACE as compared to the PPI user group, despite the fact that mortality and bleeding events are similar. These analyses also have revealed that there are increased risks of myocardial infarction and MACE in patients who use omeprazole plus clopidogrel as compared to those who use clopidogrel alone [1].

Omeprazole and clopidogrel drug-drug interactions

Omeprazole can affect the bioavailability of drugs such as aspirin and clopidogrel by disturbing their absorption through gastrointestinal mucosa. Omeprazole affects CYP2C19 activity via competitive antagonism and therefore, they may interact with clopidogrel and its metabolism. Specifically, omeprazole has a high potency to block the CYP2C19 enzyme as compared to other PPIs such as pantoprazole or rebeprazole. As a result, omeprazole may lower the active metabolites of clopidogrel. Importantly, the patients with loss of CYP2C19 functional allele are at high risk of cardiovascular disease and mortality. Furthermore, there is evidence of enhanced susceptibility to the omeprazole-clopidogrel interaction, resulting in poor clopidogrel response and an increased risk of adverse CV events in certain patient categories, especially in those with higher CV risk. Furthermore, the FDA has advised against taking clopidogrel with either of the two PPIs, omeprazole or esomeprazole, at the same time [11, 12].

Famotidine

Famotidine is a competitive histamine-2 receptor antagonist that works through the inhibition of gastric acid secretion. It is commonly used in gastrointestinal conditions related to acid secretion such as gastric ulcers and GERD in adults and children. Compared to other H2 receptor antagonists, famotidine displays high selectivity toward this receptor [13, 14]. Therefore, it can be an alternative option for omeprazole to prevent GI bleeding in CVS patients who are on DAPT.

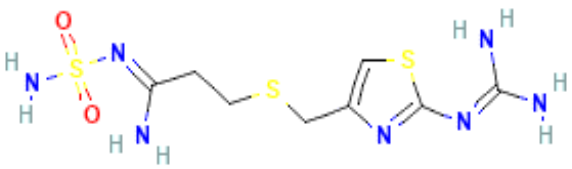

Figure 3: Structure of Famotidine [14]

Despite the fact that proton pump inhibitors are more useful than H2-blockers at relieving symptoms in GERD patients, but still, H2 receptor blockers may have an advantage in some situations. In some studies, it was found that omeprazole is superior to H2 receptor blockers in preventing GI complications, but these inhibitors have increased the risk of platelet reactivity, which can lead to severe cardiovascular disorders [1, 15]

In certain studies, it was noted that patients taking omeprazole died more frequently than those taking H2 receptor blockers, and the increased mortality was attributed to CVD and upper GI malignancy [16]. So, H2-blockers may be a better option for gastric protection, such as in people with a reduced risk of GI bleeding but an increased risk of cardiovascular disease.

Therefore, this systematic review was conducted to review the famotidine as an alternative to omeprazole and to check the safety profile of the famotidine in cardiovascular patients when used along with clopidogrel in patients on DAPT therapy. There is limited data regarding the safety of famotidine in CVS patients when prescribed along with clopidogrel. So, this systematic review will help to understand the safety profile of famotidine in CVS patients when used in DAPT therapy instead of omeprazole. This might be helpful for clinicians in the clinical decision when prescribing the DAPT therapy for cardiovascular patients and will also help researchers in the future if they want to evaluate the safety of famotidine in cardiovascular patients when used along with clopidogrel.

Methodology

A systematic literature review was conducted from recent publications (2010-2024), in accordance with Preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines to increase the comprehensiveness and transparency of reporting. The data was collected from medical and scientific databases like Pubmed, Google Scholar, Medline, NCBI, and Pharmacology (Lippincott Illustrated Reviews Series) 6th Edition. Different keywords were used to access the collected data which include, PPIs, Proton pump inhibitors (omeprazole), Clopidogrel, Omeprazole and Clopidogrel, Percutaneous coronary intervention, antiplatelet therapy, and famotidine, histamine H-2 receptor antagonist. In addition, abbreviations such as PPI, PCI, and DAPT were also used. In order to widen the search process PPIs namely, omeprazole and

esomeprazole were also used in the search strategy. Our inclusion criteria included the articles after 2010. All English-language titles and abstracts and suggested additional citations that met the following eligibility criteria were included and exclusion criteria included all articles published before 2010 and those without full access.

This systematic literature review focused on the drug-drug interaction between clopidogrel and omeprazole, as well as between clopidogrel and famotidine. A total of 105 articles were initially identified in the search. We reviewed the abstracts, conclusions, and results of these articles, and 10 were found to be relevant to our topic. The literature was assessed by reviewers based on inclusion and exclusion criteria. RCTs and observational studies were included if they compared patients treated with clopidogrel and omeprazole to those treated with clopidogrel and famotidine. Adverse cardiovascular outcomes were reported as clinical endpoints. All articles were published after 2010.

Results

A total of 10 relevant articles from 2010 to 2024 were analyzed, selected from an initial search of 105 articles on the drug-drug interaction between clopidogrel and omeprazole, as well as the use of famotidine as an alternative to omeprazole in DAPT for cardiovascular patients. The findings from these 10 studies were identified based on different research methods that met our criteria.

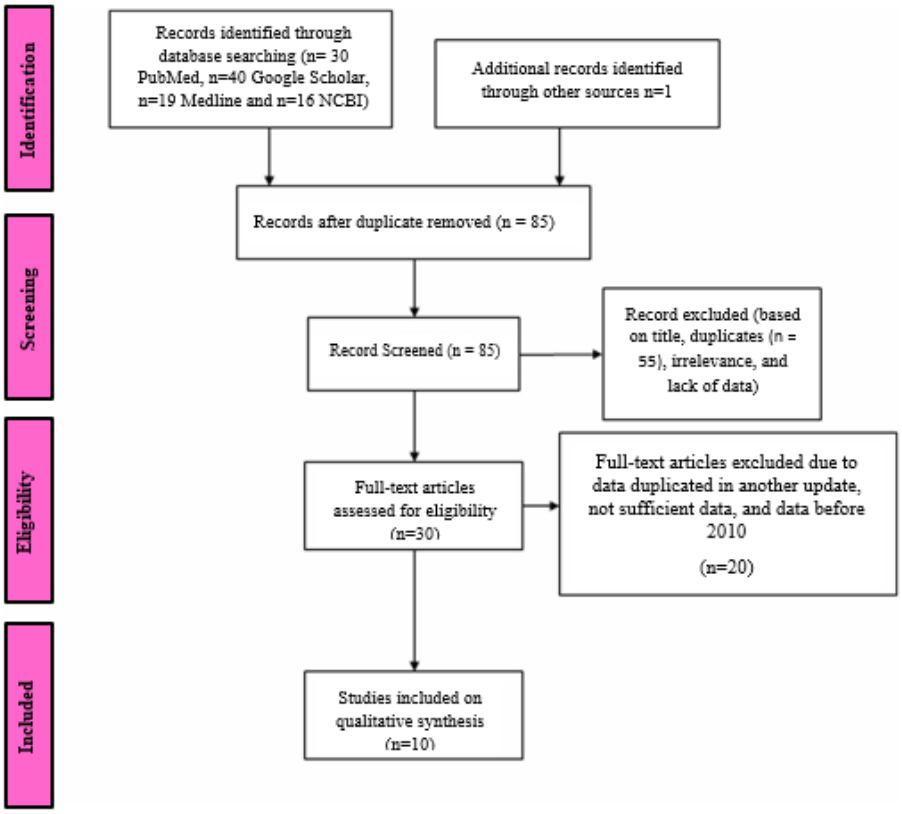

Figure 4: Drug-Drug interaction search strategy using PRISMA flowchart

Minimum number of patients across all studies was 20 and maximum number of patients was 84,729. The studies were conducted in various countries, including Japan, China, and the United States, and focused on the drug-drug interaction between clopidogrel and proton pump inhibitors (PPIs), particularly omeprazole, as well as the use of famotidine as an alternative [9, 17-19]. Several studies, such as those by Ohbuchi et al. (2012) and Yamane et al. (2012), highlighted that PPIs inhibit the metabolic activation of clopidogrel via CYP2C19, leading to reduced antiplatelet effects, while famotidine did not show any significant drug-drug interaction with clopidogrel. Other studies, including those by Azab et al. (2021) and Huang et al. (2017), revealed that the concomitant use of clopidogrel and PPIs resulted in increased adverse cardiovascular outcomes, such as major adverse cardiovascular events (MACE). Contrarily, famotidine was consistently found to be a safer alternative, showing no such interactions or adverse effects

Masato Ohbuchi et al. in 2012 checked the effect of PPI's and famotidine on the metabolic activation of clopidogrel by the recombinant isoenzyme CYP2B6, CYP2C19, and CYP3A4. Drugs stereoisomers and their active metabolites were detected with the help of liquid chromatography-mass spectrometry They found the evidence that the PPI's inhibits the metabolic activation of clopidogrel by inhibiting the CYP2C19 and they found this is the main cause of drug-drug interaction between PPI's and clopidogrel while they found famotidine as a safe ant-acid drug as no drug-drug interaction found between clopidogrel and famotidine [20].

Keiichiro Yamane et al. in 2012 in cross-over study, checked the effect of proton pump inhibitors and H2 antagonist famotidine on the Japanese patients who are taken antiplatelet therapy with clopidogrel due to prior PCI and they found that the use of PPI's with clopidogrel reduces the antiplatelet effect of clopidogrel while the using the famotidine with clopidogrel does not affect the antiplatelet effect of clopidogrel [18].

A retrospective cross-sectional study published in 2021 by Azab et al., found a link between clopidogrel and PPIs when they're taken together and the clinical outcomes of cardiovascular events. They did a study on 4078 patients after a percutaneous coronary intervention and stent implantation. They found that when patients are administered omeprazole and clopidogrel there is an increase in the negative outcomes of cardiac events and there is an increased risk of MACE and including death [21].

Wei-Qiang Huang et al. in 2017 did a systemic review and meta-analysis of observational studies and RCTs issued between 2012-2016 in which they consider 11 studies and a total of 84,729 patients of which 29,235 patients were from the PPI's group and 55,494 patients from the non-PPI's group. They found that the combined use of clopidogrel and PPI's is associated with highly adverse cardiovascular outcomes like MACE, MI, and SI [19].

Yaron Arbel et al. 2013 worked on CVS patients to see the platelet inhibitory consequence of omeprazole and famotidine on clopidogrel in a prospective, randomized cross-over study. They gave medicine to patients for a period of at least 1 month and each medicine is given twice daily. They found that the omeprazole therapy was associated with higher platelet reactivity (HPR)

(Associated with increased risk of myocardial infarction and even death) than the therapy with famotidine means famotidine therapy is safer than omeprazole [22].

In 2014 Takahiro Uotani et al. conducted a randomnized study on 20 healthy Japanese volunteers to see the effect of famotidine in order to prevent gastric mucosal damage induced by anti-platelet drugs such as clopidogrel. They found famotidine is effective in order to avoid gastric mucosal injury caused by anti-platelet drugs such as clopidogrel without attenuation and disturbing antiplatelet functions [17].

In another study in 2016, Michael A. Serbin et al. conducted a meta-analysis to see the adverse cardiovascular events that occur after co-administration of clopidogrel and PPI's. They found that the concomitant clopidogrel and PPI's therapy following PCI found to be associated with an increased risk of adverse cardiovascular events. So they suggest caution be taken while using these two drugs together [23].

In 2020 Antonis et al. worked on the use of PPI's and clopidogrel to check the cardiovascular effects associated with them. According to them, PPI's should only be taken when medically necessary and for a minimum duration not for a long time as they were associated with increased CVS risks and they suggest in certain circumstances famotidine has advantages over the PPI's and can be used as alternative medicine in place of PPI's for long term use in antiplatelet therapy [1].

A single-center retrospective study was conducted in 2021 by Wanbing He et al. on 683 patients with chronic heart disease who were continuously administered clopidogrel therapy for at least 1 year. Their findings suggest that the irregular use of proton pump inhibitors and clopidogrel is not linked with an increased adverse clinical cardiac outcomes. It is associated with a lower risk of MACE and NACE (Net adverse clinical events) [24].

Michael D Drepper et al. in 2012 found in their study that there is a drug-drug interaction present between the PPI's and clopidogrel but they think that the bleeding reduction benefit of PPI's overweighs the possible risk of adverse cardiovascular events taking PPI's during dual antiplatelet therapy [25].

Discussion

The aim of this systematic review was to review the famotidine as an alternative to omeprazole and to check the safety profile of the famotidine in cardiovascular patients when used along with clopidogrel in patients on DAPT. In this study, we discuss and compare the adverse clinical outcomes which will be resulted from their concomitant use in DAPT. We compare the different adverse clinical outcomes by using the data which is obtained from the literature and recently published articles. There are a lot of controversies still exist regarding the concomitant use of omeprazole and clopidogrel in CVS patients. In this study, we have shown that omeprazole can interfere with the antiplatelet effect of clopidogrel in patients who are taking dual antiplatelet therapy.

Different studies have shown that the omeprazole reduces the antiplatelet effect of clopidogrel and as a result, the risk of adverse CVS clinical outcomes increases, and the use of famotidine is safe as compared to omeprazole in CVS patients taking dual antiplatelet therapy [18-20].

Masato Ohbuchi et al. also checked the effect of PPI's and histamine H2 receptor antagonists (Famotidine) on the antiplatelet effect of clopidogrel. They used the recombinant isoenzyme CYP2B6, CYP2C19, and CYP3A4. During their study, they found that the omeprazole with the value IC50 of μmol/L inhibits the clopidogrel activation by CYP2C19 and more faintly inhibited that by CYP2B6 and CYP3A4. When they checked the famotidine, the famotidine showed no more than (NMT) 20% inhibition of clopidogrel activation by CYP2B6, CYP2C19, and CYP3A4 up to 100 μmol/L and there is no time-dependent CYP2C19 and CYP3A4 inhibition. And thus they declared that the PPI's inhibits the metabolic activation of clopidogrel by inhibiting the CYP2C19 and they found this is the main cause of drug-drug interaction between PPI's and clopidogrel and the use of famotidine with clopidogrel is safe [20]. We agree with their results as the drug-drug interaction between the PPI's and clopidogrel is also reported in different research articles and there is no drug-drug interaction is reported between the famotidine and clopidogrel [1, 18, 19, 22].

Keiichiro Yamane et al. checked the effect of proton pump inhibitors and H2 antagonist famotidine on the Japanese patient. They enrolled the patients who are taking DAPT due to prior PCI who took either omeprazole or rabeprazole. In their study, they add the famotidine in place of the

omeprazole and saw the results. They have done the P2Y12 assay of the patients and saw that the platelet agreeability is higher in patients who are taking omeprazole while the concomitant use of famotidine does not affect antiplatelet therapy (Yamane et al., 2012). We agree with their results as the drug-drug interaction between the PPI's and clopidogrel occurred due to PPI's inhibits the metabolic activation of clopidogrel by inhibiting the CYP2C19 which is also reported in different research articles and there is no drug-drug interaction is reported between the famotidine and clopidogrel [18-20, 22].

Azab et al. (2021) found an association between the administration of clopidogrel and PPI's and the clinical outcomes of cardiovascular events. They did a cross-sectional study on 4078 patients after a percutaneous coronary intervention (PCI) and stent implantation. They found the interaction between the drugs and relate it with the adverse clinical outcomes such as all-cause mortality, MACE, MI, and cardiac hospitalizations during the time period of one year. They found that when patients are administered omeprazole and clopidogrel there is an increase in the negative outcomes of cardiac events and there is an increased risk of MACE and including death [21]. Their findings are consistent with various studies in which it is reported that when the patient is co-administered PPI's and clopidogrel drug-drug interaction results and the efficacy of clopidogrel is reduced which results in adverse clinical outcomes [18-20, 22].

Wei-Qiang Huang et al. do a systemic review and meta-analysis of RCTs and obervational studies issued between 2012-2016 in which they consider 11 studies and a total of 84,729 patients in which 29,235 patients were from the PPI's group and 55,494 patients from the non-PPI's group. Their analysis showed that the major adverse cardiac outcome, myocardial infarction favor the patient who did not use the PPI's. Their results showed that the concomitant use of omeprazole and clopidogrel can cause adverse cardiovascular clinical outcomes such as MACE, MI, and SI [19]. We agree with their findings as there is drug-drug interaction between the concomitant use of PPI's with clopidogrel and result in the decreased antiplatelet effect of clopidogrel and as this is also reported in various studies [18, 20-22].

Yaron Arbel et al. worked on CVS patients to see the platelet inhibitory effect of omeprazole and famotidine on clopidogrel. They gave medicine to patients for a period of at least 1 month during

the treatment period and each medicine is given twice daily. They tested 3 study medicines. At the end of each treatment phase, they evaluate the platelet function of the patient with the help of verify now system and calculate P2Y12 units for the proper definition of HRP units. They found that the omeprazole therapy was associated with higher platelet reactivity (HPR) (Associated with increased risk of myocardial infarction and even death) than the therapy with famotidine or pantoprazole (48%, 33%, and 31% respectively) which means famotidine therapy is safer than omeprazole [22]. Their results are consistent with other studies in which drug-drug interaction between clopidogrel and proton pump inhibitors and there is no drug-drug interaction between famotidine and clopidogrel is reported [18, 19].

Takahiro Uotani et al. in their study see the effect of famotidine on 20 healthy Japanese volunteers in order to prevent the gastric mucosal damage induced by anti-platelet drugs such as clopidogrel. They studied the effects of histamine H2 receptors antagonist (Famotidine) on DAPT induced gastric mucosal injury with respect to intragastric pH level, isoenzyme CYP2C19 genotypes, and *H. pylori* infection in a prospective manner, and their results indicated that the protective effect of famotidine in gastric injury is due to gastric acidity and not due to the presence or absence of *H. pylori* infection, and isoenzyme CYP2C19 genotype thus the use of famotidine is safe in CVS patients taking dual antiplatelet therapy. They found famotidine is effective in order to avoid gastric mucosal injury caused by anti-platelet drugs such as clopidogrel without attenuation and disturbing antiplatelet functions [17]. We agree with their findings as there is no drug-drug interaction between the famotidine and clopidogrel reported thus it can’t affect its action [20, 22].

Michael A. Serbin et al. conducted a study to see the adverse cardiovascular events that occur after co-administration of clopidogrel and PPI’s. They found that the concomitant clopidogrel and PPI’s therapy following PCI found to be associated with an increased risk of adverse cardiovascular events. So they suggest caution be taken while using these two drugs together [23]. As there are a lot of studies in which the drug-drug interaction between the clopidogrel and omeprazole is also reported because of the CYP2C19 inhibition by the omeprazole which increases adverse clinical cardiac outcomes [17, 21]

Antonis et al. worked on the use of PPI's and clopidogrel to check the cardiovascular effects associated with them. They found that the long-term use of PPI's needs to be reevaluated and they suggest that PPIs should only be taken when medically necessary and for a short period of time not for a long time as they were associated with increased CVS risks. The chronic use of PPI's may have off-targets and they also have pleiotropic effects which are mounting and we need to be worried [1]. We should use cautionary approaches in prescribing PPIs importantly in the case of the elderly with high doses of PPI's and long-term use. The long term use of omeprazole with clopidogrel is not good because it will results in adverse clinical outcomes so in the cases where long time dual antiplatelet therapy is required use famotidine irrespective of omeprazole as it is not associated with any kind of interaction with clopidogrel [24, 26].

Wanbing He et al. conducted a study on 683 patients with chronic heart disease and continuously administered clopidogrel therapy for at least 1 year. They found that the intermittent use of PPI's was associated with less risk of stroke, MACE, and NACE. And the intermittent PPI's were good in male CHD patients whose age is more than 60 years old, with hypertension or chronic kidney disease, and undergoing PCI during the hospitalization. Their findings suggest that the intermittent use of proton pump inhibitors and clopidogrel is not associated with an increased adverse clinical cardiac outcomes. It is associated with a lower risk of MACE and NACE [24]. The intermittent use of PPIs is good as in other studies their low dose is recommended for use and for a short period of time [26, 27].

Michael D Drepper et al. found in their study that there is a drug-drug interaction present between the PPI's and clopidogrel but they consider that the bleeding reduction benefit of PPI's overweighs the possible risk of adverse cardiovascular events taking PPI's during dual antiplatelet therapy. PPI's treated the gastric injury more efficiently than the famotidine in dual antiplatelet therapy but gastrointestinal risk evaluation should be done [25]. On the basis of this literature review, we agree with their findings and that intermittent use of PPI's as good as in other studies their low dose is recommended for use and for a short period of time [26, 27]

In March 2010 a "black box warning" was issued by the Food and Drug Administration (FDA) in order to announce the drug-drug interaction between the clopidogrel and omeprazole. According

to the FDA that if the patients are identified as CYP2C19 enzyme poor metabolizers then the clopidogrel and omeprazole must not be recommended to use in the patient taking dual antiplatelet therapy. As Omeprazole inhibits the CYP2C19 because it is an irreversible metabolism dependent inhibitor (MDI) of enzyme CYP2C19 but the famotidine and pantoprazole are not thus, famotidine, and pantoprazole have less drug interaction with clopidogrel and can be used for the gastrointestinal bleeding in patients who are taking dual antiplatelet therapy. Food and Drug Administration (FDA) recommends that the use of clopidogrel and omeprazole should be avoided (Heart et al., 2019; *Plavix | FDA Drug Safety Communication | PDR.Net*, n.d.).

The study's strengths are its comprehensive literature evaluation, which followed PRISMA recommendations and covered a wide range of study types from 2010 to 2024, including observational studies and RCTs. The results are very broadly applicable because of the large sample size and regional diversity (research from China, the United States, and Japan). It provides practical insights for cardiovascular treatment by focusing on clinically important outcomes, such as MI and MACE, and identifying famotidine as a safer alternative for omeprazole. Recent research is included to ensure that the information is up to date and useful for modern therapeutic practice. However, our study has some limitations, such as that in this study we only did a systematic literature review, studies before 2010 were not included in our analysis, and the bias risk of the studies included in this analysis was not assessed, so more experimental studies are needed to assess the safety and drug-drug interaction of famotidine and clopidogrel in CVS patients on DAPT therapy.

Conclusion

In conclusion, our systematic literature review of studies from 2010 to 2024 about the drug-drug interaction between clopidogrel and omeprazole and the use of famotidine as an alternative of omeprazole in DAPT suggests that the adjuvant therapy of clopidogrel and omeprazole is associated with an increased risk of MACE such as MI, SI, and NACE and precautions should be used while using the adjuvant therapy with clopidogrel and omeprazole following PCI. In patients where gastrointestinal benefits overweigh the CVS risks omeprazole can be prescribed with a minimum therapeutic dose for a minimum period of time but famotidine is considered the safest option with clopidogrel as no drug-drug interaction is found between them and it can’t effect the

antiplatelet effect of clopidogrel. So, it should be used with clopidogrel in DAPT in CVS patients in place of omeprazole and clopidogrel combination. However, our study is only based on a literature review rather than on RCTs. Further studies must be carried out on experimental bases in order to evaluate the safety and drug-drug interaction between famotidine and clopidogrel in CVS patients on DAPT.

Abbreviations

PPI: Proton pump inhibitor, **GI:** Gastrointestinal, **CV:** Cardiovascular, **CVD:** Cardiovascular disease, **CAD:** Coronary artery disease, **MI:** Myocardial infarction, **MACE:** Major adverse cardiovascular events, **RCTs:** Randomized controlled trials, **PCI:** Percutaneous coronary intervention, **ADMA:** plasma asymmetrical dimethyl arginine, **DDAH2:** dimethylaminohydrolase 2, **DAPT:** Dual antiplatelet therapy, **GERD:** Gastroesophageal reflux disease.

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Declaration of Competing Interest

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