

# Outcome of stroke patients on clopidogrel plus proton-pump inhibitors: a single-center cohort study

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**BACKGROUND:** Recent studies suggest a higher risk of adverse cardiovascular outcome and mortality in patients co-prescribed clopidogrel with proton pump inhibitors (PPI).

**OBJECTIVE:** Investigate the impact of concomitant prescription of clopidogrel and PPI on 30-day unplanned readmission and one-year all-cause mortality.

**DESIGN:** Retrospective longitudinal cohort study.

**SETTING:** Single academic tertiary center.

**PATIENTS AND METHODS:** The study included patients admitted with a diagnosis of ischemic or hemorrhagic stroke between 2010 and 2014. Demographic and outcome data were collected and compared for patients on clopidogrel plus PPI vs those on clopidogrel plus H2-blockers and those not on clopidogrel.

**MAIN OUTCOME MEASURES:** One-year mortality and 30-day unplanned readmissions were compared among different patient groups using multivariable logistic regression modeling.

**SAMPLE SIZE:** 464 patients.

**RESULTS:** Out of 464 patients, 175 (37.7%) were discharged on clopidogrel. The concomitant prescription of clopidogrel and PPI was noted in 107 (24.4%) and clopidogrel and H2 blockers in 36 patients (7.8%). The one-year all-cause mortality in the entire cohort was 22.2%. Patients on clopidogrel plus PPI did not have a higher risk of one-year mortality compared to the non-PPI cohort (6.2% vs. 4.8%,  $p=0.7$ ). There was a non-significant suggestion of lower one-year mortality in patients on clopidogrel plus PPI vs those not on clopidogrel (6.2% vs. 10.1%,  $p=0.23$ ). In multivariable logistic regression, the use of clopidogrel plus PPI did not predict higher one-year mortality (odds ratio 0.6,  $P=0.6$ ). The risk of unplanned 30-day readmission was lower in those with clopidogrel plus PPI (odds ratio 0.6,  $P=0.03$ ).

**CONCLUSION:** The use of clopidogrel plus PPI resulted in lower readmission rates and was not associated with higher mortality compared with the non-PPI cohorts.

**LIMITATIONS:** Single center study, not generalizable. Given the retrospective nature of this study, we did not collect data on duration of treatments or patient compliance.

**CONFLICT OF INTEREST:** None.

Thienopyridines impair platelet activation through inhibition of the P2Y<sub>12</sub> adenosine phosphate receptor.<sup>1</sup> Thienopyridines including clopidogrel, prasugrel and ticlopidine are prodrugs that are converted to active forms through cytochrome P450 isoenzymes including CYP2C19 and CYP3A4.<sup>2</sup> Due to their effective antiplatelet actions, they are commonly used in secondary stroke prevention.<sup>3-6</sup> A common adverse effect of these antiplatelet agents is gastrointestinal bleeding.<sup>7,8</sup> Consequently, these drugs are commonly prescribed concurrently with proton pump inhibitors (PPI) to reduce the occurrence of GI bleeding. Treatment with PPIs is also indicated for other conditions that are common medical comorbidities in stroke patients, including peptic ulcer disease, gastroesophageal reflux disease, eradication of *Helicobacter pylori*.

In addition to their therapeutic effect, PPIs act as competitive inhibitors of the cytochrome P450 pathway resulting in pharmacological interactions between these drugs and thienopyridines. This could decrease the antiplatelet efficacy of clopidogrel and increase the possibility of a cardiovascular event, including stroke. In comparison, histamine-2 (H2) receptor antagonists also inhibit acid secretion through blocking H2 receptors on parietal cell.<sup>9</sup> Some H2 blockers are inhibitors of the P450 enzymes but the more recently-developed H2-receptor antagonists (e.g. ranitidine) are less likely to alter CYP metabolism.

Recent studies suggest a higher risk of incident stroke, adverse cardiovascular outcome, and mortality in patients co-prescribed clopidogrel with PPIs.<sup>10,11</sup> However, few studies have explored the risk of recurrent stroke after the concomitant use of these agents. This is reflected by the lack of evidence-based guidelines and a clear consensus which can affect clinical decision-making in prescription of clopidogrel and PPIs. In this study, we investigated the impact of concomitant prescription of clopidogrel and PPI or clopidogrel and a H2-antagonist on the 30-day unplanned readmission and one-year all-cause mortality in a cohort of stroke patients.

## PATIENTS AND METHODS

The details of this longitudinal cohort study were published before.<sup>12</sup> In summary, we included all patients admitted to a single academic center (King Abdulaziz University Hospital, Riyadh) with a diagnosis of ischemic or hemorrhagic stroke between 2010 and 2014 (5-year period). We collected demographic and clinical data from the medical records including discharge medications. Follow-up data included any records of unplanned hospital readmissions within 30 days of dis-

charge as well as all-cause mortality within the first year of the index stroke. Data were summarized and tabulated for patients according to discharge on clopidogrel. Subsequently, groups were subdivided according to concomitant prescription of one of the PPI medications, an H2-blocker, or neither. Baseline and outcome variables were compared among the groups, as appropriate using the t test or chi-square test. A multivariable logistic regression model was used to assess factors associated with one-year all-cause mortality following stroke. All tests were two-tailed at a .05 significance level. Analyses were performed with Stata 15.1.

## RESULTS

The entire cohort comprised 548 patients and records of discharge medications were available for 464 patients as 80 patients (14.6%) died during hospitalization and 2 patients did not have documentation on discharge medications. Of the 464 patients, 175 (37.7%) were discharged on clopidogrel. The concomitant prescription of clopidogrel and PPI was identified in 107 (24.4%) while clopidogrel and H2 blockers were co-prescribed in 36 patients (7.8%). **Table 1** summarizes the clinical characteristics of these patients.

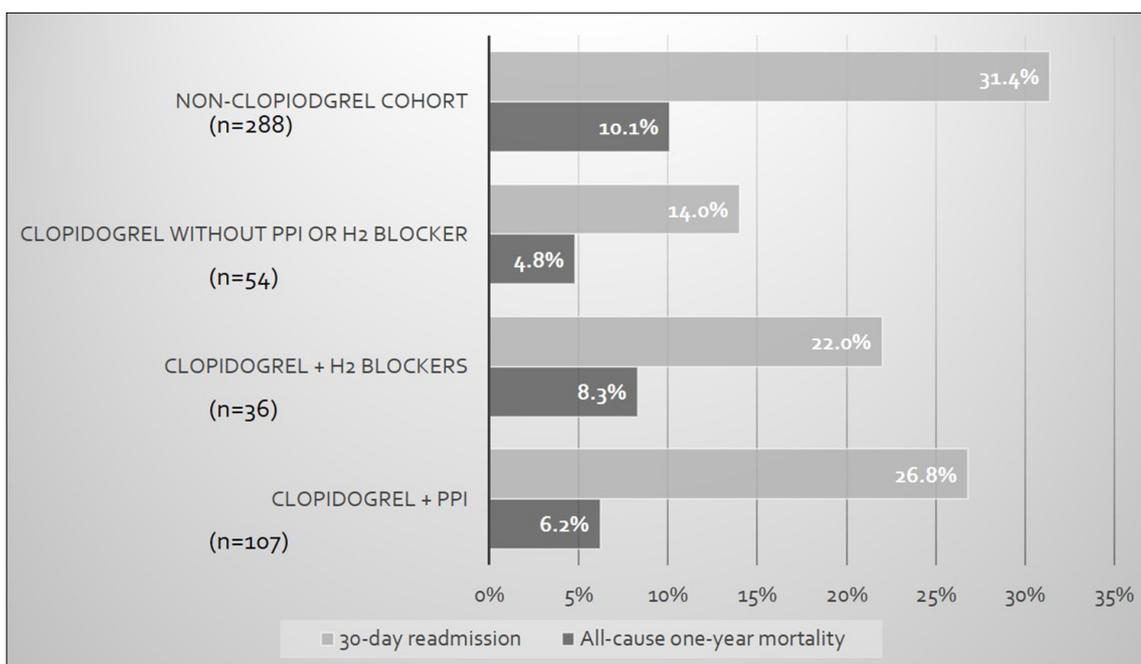
The overall 30-day readmission risk was 24.9% and one-year all-cause mortality was 22.2%. **Figure 1** shows patient outcomes according to the prescribed discharge medications. Patients on clopidogrel had a non-significant lower rate of one-year mortality compared to the non-clopidogrel cohort (5% vs. 10.1%,  $P=.2$ ). There was no difference in the one-year mortality between patients on clopidogrel with PPI vs those without (6.2% vs. 4.8%,  $P=.7$ ). Patients not discharged on clopidogrel had a significantly higher 30-day readmission risk compared to those discharged on clopidogrel alone without concomitant PPI or H2 blockers (31.4% vs 14%,  $P<.01$ ). However, there was no difference in the readmission rate among the subgroups of patients discharged on clopidogrel with PPI vs clopidogrel with H2 blockers vs those not discharged on clopidogrel (27.4% vs 22.2% vs 31.4%). Common reasons for readmission included infections (18.1%), recurrent stroke symptoms (15.8%) and cardiac events (11.3%).

There was a suggestion of lower mortality in association with discharge on clopidogrel (with either PPI or H2 blockers) in the univariable logistic regression (odds ratio 0.54, CI95 0.3 to 1.1,  $P=.11$ ). In a multivariable logistic regression, only age (odds ratio 1.1,  $P<.001$ ) and readmission within 30 days (odds ratio 21.5,  $P<.001$ ) predicted higher one-year mortality (**Table 2**). The use of clopidogrel plus PPI did not predict higher one-year mortality (odds ratio 0.6,  $P=.6$ ). However, discharge on

**Table 1.** Baseline characteristics of patients according to the prescribed discharge medications.

	Clopidogrel plus PPI (n=107)	Clopidogrel plus H2 blockers (n=36)	Clopidogrel (without either) (n=54)	Not discharged on clopidogrel (288)
Age (years, median)	64	66.5	64	61
Females	52 (49)	13 (36)	20 (37)	119 (41.3)
Hypertension	98 (92)	36 (97)	48 (90)	256 (88.9)
Diabetes mellitus	88 (82)	32 (89)	35 (65)	178 (61.8)
Hyperlipidemia	35 (32.7)	10 (27.8)	20 (37.1)	74 (25.7)
Coronary artery disease	14 (13.1)	4 (11.1)	6 (11.1)	15 (5.2)
Abnormal renal function on admission	19 (17.8)	5 (13.9)	12 (20.8)	62 (21.5)
Glycosylated Hb on admission (median, %)	8%	9.8%	7.7%	7.3%
Length of stay (days, median)	8	9	6	11

Data are number (%) unless indicated otherwise.



**Figure 1.** Outcomes of patients by prescribed discharge medications.

clopidogrel was associated with a lower odds of readmission at 30 days in a multivariable logistic regression model (OR 0.6,  $P=.03$ ).

## DISCUSSION

In this single-center longitudinal study, we did not identify a higher risk of mortality among patients discharged on clopidogrel plus PPI. The use of clopidogrel suggested lower mortality at one year in our cohort and was

associated with a significantly lower odds of unplanned readmission. Exploring the pharmacological effects of PPIs on thienopyridines is important for several reasons. These agents are frequently co-prescribed for prevention of gastrointestinal side effects. Together, the inhibition of the cytochrome P450 pathway by PPIs result in pharmacological interactions between these drugs resulting in a possible decrease in the antiplatelet efficacy of clopidogrel and increasing the possibility of a

**Table 2.** Multivariable logistic regression model of predictors of 30-day readmission and one-year mortality.

Independent variables	Odds ratio	P value	95% Confidence interval
<b>30-day readmission</b>			
Discharged on clopidogrel	0.72	.03	0.39 to 0.95
Age	1.01	.11	0.99 1.02
<b>One-year mortality</b>			
Discharged on clopidogrel	0.68	.39	0.29 to 1.63
Age	1.1	.001	1.02 1.1
Length of stay	1.01	.09	0.99 1.03
Readmission within 30 days	20.9	.0001	7.68 to 57.0

For 30-day readmission: Hosmer-Lemeshow  $\chi^2 = 10.32$ ,  $P > \chi^2 = .2433$ , Log likelihood =  $-269.39939$ , Pseudo  $R^2 = 0.3213$ . For one-year mortality: Hosmer-Lemeshow  $\chi^2 = 11.78$ ,  $P > \chi^2 = .1625$ , Log likelihood =  $-87.363167$ , Pseudo  $R^2 = 0.3213$ .

cardiovascular event, including stroke. Previous studies suggested an association between PPI use and adverse cardiovascular outcomes, all-cause mortality and adverse cerebrovascular outcomes including ischemic stroke. In a systematic review and meta-analysis of patients on thienopyridine treatment with or without PPI, Malhotra et al found that concomitant use of PPI was associated with an increased risk of stroke, myocardial ischemia and cardiovascular disease. However, results vary as some studies have not demonstrated significant outcome differences with concomitant use of PPI and thienopyridines on adverse cerebrovascular events.<sup>13-15</sup>

Our results suggest that the concurrent use of PPIs and a thienopyridine agent (clopidogrel) does not increase the one-year mortality compared to clopidogrel use without a PPI. On the contrary, the use of clopidogrel in general (including patients taking clopidogrel plus a PPI) predicted lower readmissions and may result in lower mortality. These results support the findings of a propensity score-matched analysis that found no increase in stroke risk with concomitant use of clopidogrel and PPI.<sup>16</sup> Furthermore, no relationship was found between stroke recurrence or mortality and concomitant use of clopidogrel and PPI from a large case-control study on stroke patients.<sup>17</sup>

Other studies have found a positive association between the concomitant use of a PPI and thienopyridines and increased risk of cerebrovascular events while others have not.<sup>13-15</sup> One factor that may explain this is the differences between the study variables themselves, including variation in study cohorts, different types of PPIs that were used, as well as limited data on the stroke subtype. In systematic reviews,<sup>13</sup> many of the patients that were included had acute coronary syndromes and in addition, the studies had significant variability in study endpoints. The protective effects

noted in our study could be explained by the high prevalence of undiagnosed large vessel disease in our population.<sup>18,19</sup>

There are several limitations with our study. First, we relied on discharge records of the prescribed medications, but could not assess medication intake or compliance. There are multiple sources of potential bias in this cohort. Our data are from a single tertiary-center which may not be generalizable to other centers. Not all the important baseline predictors of stroke outcome were documented in the medical records, including clinical stroke severity or stroke mechanism. We analyzed mortality rates up to one year post-discharge. Although this data is reassuring in suggesting the safety of co-prescribing PPIs and clopidogrel with regards to at least in the relatively acute period, there may be a significant difference in mortality rates with more extended analysis of outcomes after discharge. Our study looked at unplanned 30-day readmissions and all cause one-year mortality, but did not take into consideration other adverse events, which may have resulted from prescription of a PPI and clopidogrel including minor gastrointestinal bleeding that may not have presented to the hospital or presented after 30 days. Finally, the study specifically looked at clopidogrel but not other thienopyridine agents, which may have different outcomes from clopidogrel.<sup>17</sup>

In conclusion, in this cohort of stroke patients, the use of clopidogrel plus PPI resulted in lower readmission rates and was not associated with higher mortality. Our results support the findings of similar studies on the association between concomitant clopidogrel and PPI use, and cerebrovascular outcomes. Further investigations may be necessary to explore risk of recurrent stroke beyond 30 days or the risk of mortality at one year in high quality randomized, controlled trials.

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