Comparative effectiveness and safety of proton pump inhibitors on cardiovascular events in patients receiving clopidogrel

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Background

Proton pump inhibitors (PPIs) inhibiting cytochrome P450 2C19 (CYP2C19) may reduce antiplatelet effects of clopidogrel by affecting its metabolic activation.[1] Especially in patients with loss-of-function CYP2C19, concomitant use of PPIs with clopidogrel may inactivate anti-ischemic effect of clopidogrel and increase the risk of cardiovascular event. The US Food and Drug Administration issued an updated statement cautioning against concomitant clopidogrel and PPI use, and the European Medicines Agency also have published warnings against the coadministration of clopidogrel and PPIs.[3,4] However, PPIs competitively inhibit CYP2C19 to varying degrees. Thus, this study aimed to compare the effectiveness and safety strong competitive inhibitor for CYP2C19 (inhibiting PPIs) with weak competitive inhibitor for CYP2C19 (other PPIs) in patients who receiving clopidogrel.

Methods

We conducted a observational study using electronic medical records converted to the Observational Medical Outcomes Partnership–Common Data Model (OMOP-CDM) in 8 databases from 1986 to 2023 in South Korea: Ajou University Medical Center (AUMC; 1994-2023); Daegu Catholic University Medical Center (DCMC; 2005-2022); Gyeongsang National University Changwon Hospital (GNUCH; 2016-2022); Kangdong Sacred Heart Hospital (KDH; 1986-2022); Kangwon National University Hospital (KWMC; 2003-2022); Kyung Hee University Medical Center (KHMC; 2008-2022); Kyung Hee University Hospital at Gangdong (KHNMC; 2006-2021); and Pusan National University Hospital (PNUH; 2011-2020). We included the patients aged 18 years or older who received PPIs and clopidogrel. The PPIs was classified based on their binding affinity for CYP2C19: inhibiting PPIs and other PPIs (Table 1).[5] The primary outcome was major adverse cardiovascular event (MACE) which includes cardiovascular mortality, and hospitalization or emergency department visit for myocardial infarction or stroke.[6] Secondary outcomes were defined individual events of the primary outcome and all-cause mortality. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) between inhibiting PPIs and other PPIs by Cox proportional hazards model after propensity score stratification. We select 269 negative control outcomes to improve the validity of CIs of a treatment effect estimate. For the meta-analysis, random-effect model and I^2 were performed to calculate HR for pooling effect estimates and heterogeneity across databases.

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Table 1. Classification of proton pump inhibitors and histamine receptor type 2 blocker

Classification	Generic name
Proton pump inhibitors with high CYP2C19-inhibitory potential (inhibiting PPIs)	Esomeprazole, omeprazole
Proton pump inhibitors with low CYP2C19-inhibitory potential (other PPIs)	Dexlansoprazole, lansoprazole, pantoprazole, rabeprazole

Results

The study included 8,317 users of clopidogrel and inhibiting PPIs, and 12,260 users of clopidogrel and other PPIs. Concurrent use of inhibiting PPIs and clopidogrel was not associated with increased MACE risks (calibrated HR, 95% CI; 1.06, 0.63-1.77) (Table 2). In case of secondary endpoints, PPIs with high CYP2C19-inhibitory potential were also not associated with cardiovascular mortality (calibrated HR 1.15, 95% CI 0.62-2.15), myocardial infarction (calibrated HR 0.85, 95% CI 0.33-2.20), stroke (calibrated HR 1.18, 95% CI 0.53-2.62) and all-cause mortality (calibrated HR 0.96, 95% CI 0.58-1.58). The risk of MACE showed similar patterns for sensitivity analyses using various time-at-risk (Table 3).

Table 2. Risk of major adverse cardiovascular event during inhibiting proton pump inhibitor exposure in patients receiving clopidogrel

	Number of inhibiting PPI + clopidogrel	Number of other PPI + clopidogrel	Calibrated hazard ratio	I^2 (%)
Primary endpoint				
Major adverse cardiovascular event	8,317	12,260	1.06 (0.63-1.77)	0.0
Secondary endpoint				
Cardiovascular mortality	8,557	12,640	1.15 (0.62-2.15)	0.0
Myocardial infarction	7,115	9,915	0.85 (0.33-2.20)	0.0
Stroke	7,292	10,357	1.18 (0.53-2.62)	0.0
All-cause mortality	8,557	12,640	0.96 (0.58-1.58)	7.8

Table 3. Sensitivity analyses for risk of major adverse cardiovascular event between inhibiting proton pump inhibitor and other proton pump inhibitor

	Number of inhibiting PPI + clopidogrel	Number of other PPI + clopidogrel	Calibrated hazard ratio	I^2 (%)
time-at-risk windows (30-day)	7,598	10,741	1.27 (0.67-2.38)	25.2
time-at-risk windows (1-year)	9,514	14,063	0.79 (0.59-1.06)	3.2
On-treatment setting	8,317	12,260	1.06 (0.63-1.77)	0.0
Intention-to-treat setting	9,514	14,063	1.02 (0.86-1.21)	3.3

Conclusion

In this observational study reflecting routine clinical practice, use of inhibiting PPIs with clopidogrel was

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not associated with the risk of MACE compared to use of other PPIs in patients using clopidogrel. Further comprehensive large-scale studies including various ethnicity are required.

References

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