Impact of concomitant use of proton pump inhibitors and clopidogrel on cardiovascular adverse outcomes - *A multicenter study using common data model*

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INTRO

- Proton pump inhibitors (PPIs) inhibiting cytochrome P450 2C19 (CYP2C19) may reduce antiplatelet effects of clopidogrel by affecting its metabolic activation.
- The US FDA and EMA issued an updated statement cautioning against concomitant clopidogrel and PPI use. However, PPIs competitively inhibit CYP2C19 to varying degrees.
- We aimed to compare the cardiovascular adverse outcomes of strong competitive inhibitor for CYP2C19 (inhibiting PPIs) with weak competitive inhibitor for CYP2C19 (other PPIs) in patients who receiving clopidogrel in real world.

METHODS

1. 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 South Korea**
2. 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**
3. The outcome was **major adverse cardiovascular event (MACE)** which includes cardiovascular mortality, and hospitalization or emergency department visit for myocardial infarction or stroke.
4. We compared the **incidence rates (IRs), hazard ratios (HRs) with 95% confidence intervals (CIs)** by Cox proportional hazards model after 1:max propensity score matching.

Identifying the association **concomitant clopidogrel and PPI use and MACE** by affinity for CYP2C19 using 8 hospital databases

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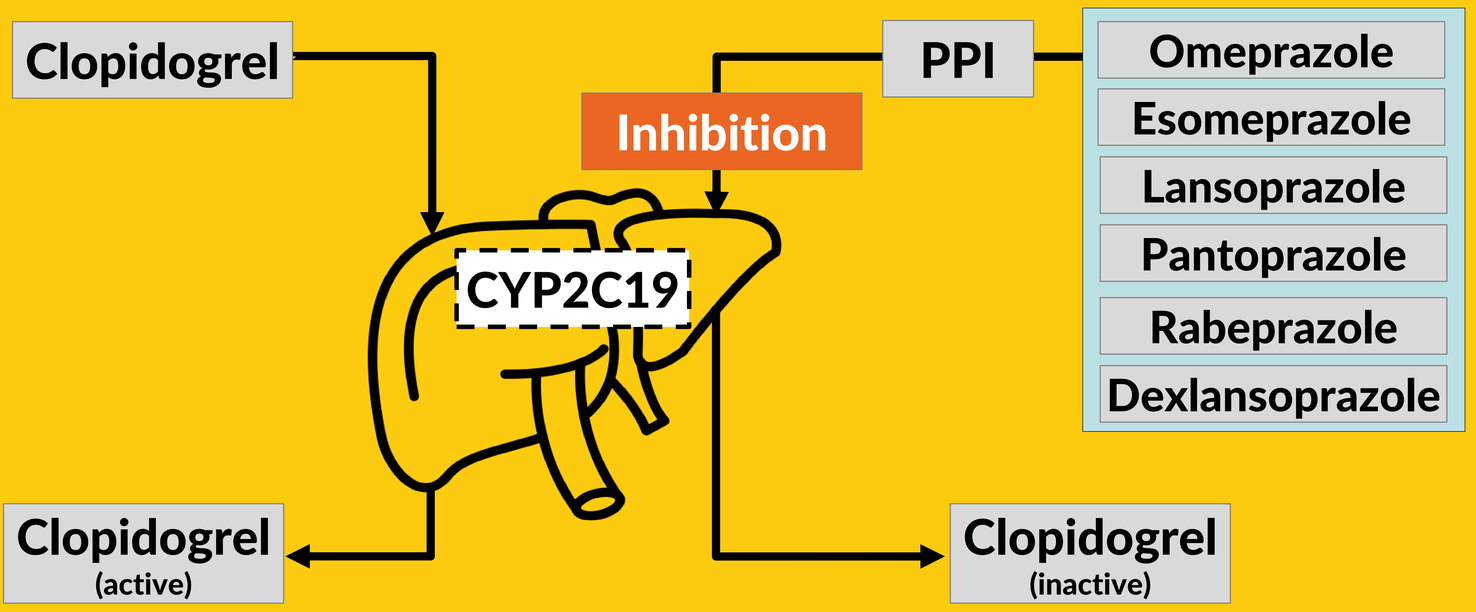
Table 1. Classification of proton pump inhibitors

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)	Lansoprazole, pantoprazole, rabeprazole, dexlansoprazole

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	I2
Primary endpoint				
MACE	3,601	8,002	0.95 (0.46-1.99)	0.09
Secondary endpoint				
Cardiovascular mortality	3,698	8,499	1.07 (0.43-2.69)	0.00
Myocardial infarction	2,610	6,353	1.03 (0.20-5.39)	0.00
Stroke	1,966	4,174	0.95 (0.14-6.30)	0.00
All-cause mortality	3,840	8,846	0.68 (0.37-1.24)	0.00



RESULTS

- The study included 3,604 users of clopidogrel and inhibiting PPIs, and 8,002 users of clopidogrel and other PPIs.
- Concurrent use of inhibiting PPIs and clopidogrel was not associated with increased MACE risks (calibrated HR 0.95, 95% CI 0.46-1.99) (Table 2).
- In case of secondary endpoints, PPIs with high CYP2C19-inhibitory potential were also not associated with cardiovascular mortality (calibrated HR 1.07, 95% CI 0.43-2.69), myocardial infarction (calibrated HR 1.03, 95% CI 0.20-5.39), stroke (calibrated HR 0.95, 95% CI 0.14-6.30) and all-cause mortality (calibrated HR 0.68, 95% CI 0.37-1.24).

CONCLUSION

- In this multicenter observational study, **use of inhibiting PPIs with clopidogrel was 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.

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