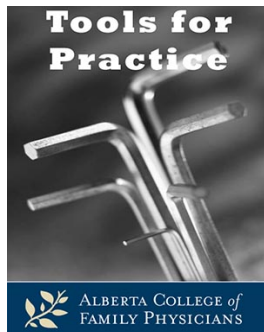


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Evidence Updated: No new evidence
Bottom Line: No change
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PPIs and clopidogrel: Never the twain shall meet?

Clinical Question: Do proton pump inhibitors (PPIs) interact with clopidogrel to reduce its cardiovascular (CV) benefit?

Bottom-line: Studies are inconsistent about the impact of PPIs on clopidogrel effectiveness, though most higher-quality studies show no interaction. The association with CV risk seen with PPI use is likely due to underlying comorbidities rather than a true drug interaction.

Evidence:

- A systematic review¹ of 33 studies encompasses the best-available evidence.
Highlights:
 - ~50% of retrospective observational studies, and ~25% of prospective observational studies found a significant association of increased CV risk with PPI + clopidogrel versus clopidogrel alone.
 - Retrospective studies generally had higher risk of bias.
 - One randomized controlled trial (RCT)² of 3,761 patients receiving clopidogrel and ASA followed for a median of 3.5 months:
 - No difference in CV events, omeprazole 4.9% versus placebo 5.7%.
 - Limitations: Unplanned early termination, underpowered for CV comparisons.
 - Non-randomized subgroup analyses of landmark antiplatelet trials.^{3,4}
 - PPI did not increase CV risk with either clopidogrel or prasugrel.
 - PPI increased CV risk with both clopidogrel (HR 1.20) and ticagrelor (HR 1.24).
 - Note: Ticagrelor does not require enzymatic activation and should therefore not be affected by the postulated PPI drug interaction mechanism.
- Studies that included patients not receiving clopidogrel found that PPI use was associated with increased CV risk (regardless of clopidogrel use).⁵⁻⁹

Context:

- PPIs have inconsistent effects on surrogate markers of clopidogrel efficacy.¹
- American guidelines¹² (though based on outdated evidence) reasonably recommend careful assessment of the indication for PPIs, as they are frequently prescribed without a clear indication.¹³

- There is no consistent difference in CV risk association between PPIs, including pantoprazole.¹⁴

Original Authors:

G Michael Allan MD CCFP, Michael Kolber MD CCFP

Updated:

Ricky D Turgeon BSc(Pharm) ACPR PharmD

Reviewed:

G. Michael Allan MD CCFP

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