Supplement to the ACP Journal Club structured abstract for: *Juurlink DN, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ. 2009;180:713-8.*

Major Limitations:

Methods

- **Confounding** – No access to smoking status, BMI, diet and activity level, GRACE score at discharge, renal function (beyond ICD-10 coding), history of GI bleed, GERD, etc.
  - *Consequence: Confounding may completely account for the apparent association between PPIs and recurrent MI with patients taking clopidogrel*
- **Allocation bias** – Patients on PPIs may be more likely to have prior hospitalizations and more severe angina
  - *Consequence: Patients taking PPIs may have more serious – and prognostically worse – CAD*

Results

- **Size of OR** does not suggest a large effect (generally desire OR > 5)
- **Related outcomes do not share a direction of effect –** Association between PPI and recurrent MI is suggested (1.27; 1.03-1.57), but not all-cause mortality (0.82; 0.57-1.18)
  - *Consequence: Presumably, an increase in cardiac events should lead to an increased risk of death. Disagreement between these two outcomes reduces our confidence in the results*

Generalizability

- Good; Ontario

Context from other studies:

- COGENT: Truncated double-blind RCT comparing omeprazole to placebo in clopidogrel users
  - Reduced composite GI events based on 55 events
  - No increase in CV events based on 109 events (PPI 4.9%, placebo 5.7%; HR 0.99 (0.68-1.44)
    - Limited by truncation and likely underpowered (cannot rule out 44% RRI)
- Post-hoc analyses of RCTs:
  - CREDO, PLATO: Use of PPI associated with increased CV events independent of group
    - Yep, even in the placebo group
    - Ticagrelor does not require CYP2C19 activation, so no PK interaction with PPIs
  - PRINCIPLE-TIMI 44, TRITON-TIMI 38: No association between PPI use and CV events in either (clopidogrel or prasugrel) group
- Numerous retrospective cohort studies have shown an independent association between PPIs (or the underlying confounding comorbidities more common in PPI users) and CV events *(Ann Intern Med. 2010;153:378-86, Aliment Pharmacol Ther. 2012;35:165-74)*
- Further going against the CYP2C19 theory: Pantoprazole (*Arch Intern Med. 2010;170:704-10*) and H2-blockers (*Gastroenterology. 2010;139:1165-71, BMJ. 2012;345:e4388*) also associated with increased CV events.
- Wait, I didn't think citalopram was much of a CYP2C19 inhibitor…? *(BMJ. 2012;345:e4388)*
- Is ASA metabolized by CYP2C19 too? (*BMJ. 2011;342:d2690*)

Methodology

Study design	Nested Case-Control
Biases	**Efforts to Minimize Them**
Confounding	Design • Restricted to ≥66 yo patients who filled a prescription for clopidogrel within 3 days after hospitalization for MI • Excluded patients in LTC • Excluded patients on clopidogrel, ticlopidine or dipyridamole within 1 y Analysis • Multivariable regression adjustment of ORs including: Age, sex, income quintile (estimated from the zip code), Charlson comorbidity index, LOS in hospital during the 1st admission for MI, 9 medical conditions previously shown to correlate with short-term mortality following MI and identified at the index hospital admission (diabetes with complications, dysrhythmias, pulmonary edema, cardiogenic shock, acute renal insufficiency, chronic renal insufficiency, CHF & CVA; use of CYP2C19 or 3A4 inhibitors or inducers
Allocation	• Matching ○ Age (born within 3 years), receipt of PCI in hospital, date of hospital discharge (within 4 days), predicted probability of short-term mortality (within 0.05 of that of the corresponding case) determined using the Ontario Acute Myocardial Infarction Mortality Prediction Rules
Misclassification	• Events identified by ICD-10 without adjudication
Performance, detection, interviewer/observer	**N/A**
Attrition	Case-control design obviates this
Intervention	• Current, previous, or remote use of PPI • No PPI
Outcomes	• **Recurrent MI** ○ Defined by ICD-10 code • **Death**
Duration	90 days (sensitivity analysis: 1 y)
Sensitivity analysis	• Analysis of pantoprazole alone • Association of PPI use and recurrent MI in patients *not taking* clopidogrel • Association between recurrent MI and H2-blockers • Analysis of recurrent MI at 1 y