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# PPI Increases the cardiovascular risk in patient on clopidogrel

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Assistant Professor
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#### RISK OF GI BLEEDING

- Current clopidogrel users who are not PPI users had an overall risk of hospitalisation for gastroduodenal bleeding of 12.2 per 1,000 patient-years (py).
- The risk increased according to number of GI bleeding risk factors from 3.2 per 1,000 py for those with no risk factors to 46.7 per 1,000 py for those with 3 or more.

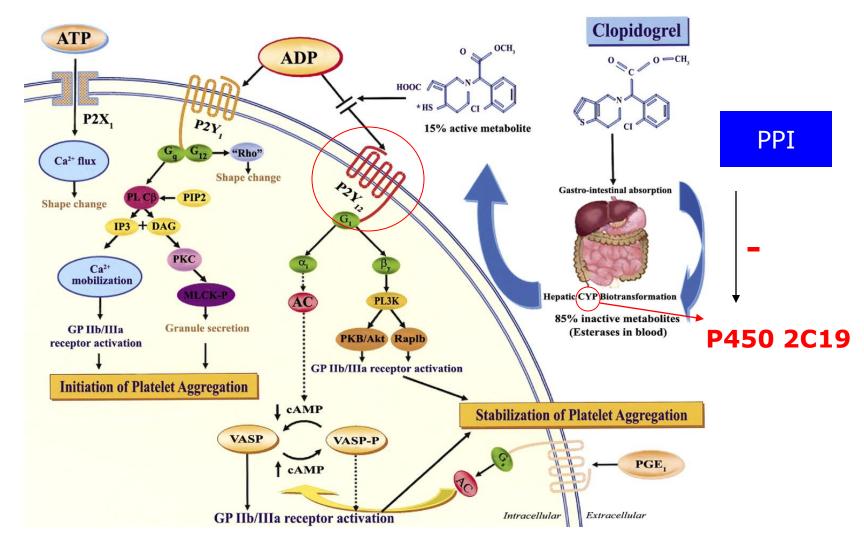
Ann Intern Med 2010; 152: 337-45

#### RISK OF GI BLEEDING contd.

• The overall risk was reduced by 50% in PPI users (hazard ratio [HR], 0.50; 95% CI, 0.39 to 0.65), and in those at highest risk (3 or more risk factors) the absolute rate of hospitalisation was reduced by 28.5 (CI, 11.7 to 36.9) per 1,000 patient.

Ann Intern Med 2010; 152: 337-45

Clopidogrel is a prodrug that is converted in the liver to an active thiol metabolite, which irreversibly inhibits the platelet **P2Y12 ADP receptor**.



Angiolillo, D. J. et al. J Am Coll Cardiol 2007;0:j.jacc.2006.11.044v1-12782

# Proton Pump Inhibitor and clopidogrel interaction fact or fiction ???

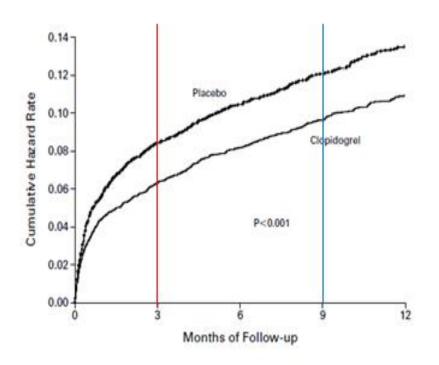
## EBM - What We Say

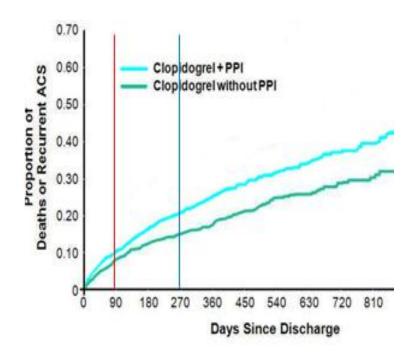
### A SYSTEMATIC REVIEW OF THE POTENTIAL INTERACTION BETWEEN CLOPIDOGREL AND PROTON PUMP INHIBITORS

Joao Paulo de Aquino Lima1, James M. Brophy, MD, PhD2

1Federal University of Ceará School of Medicine, Fortaleza, Brazil

2Division of Clinical Epidemiology, McGill University, Montreal, Canada

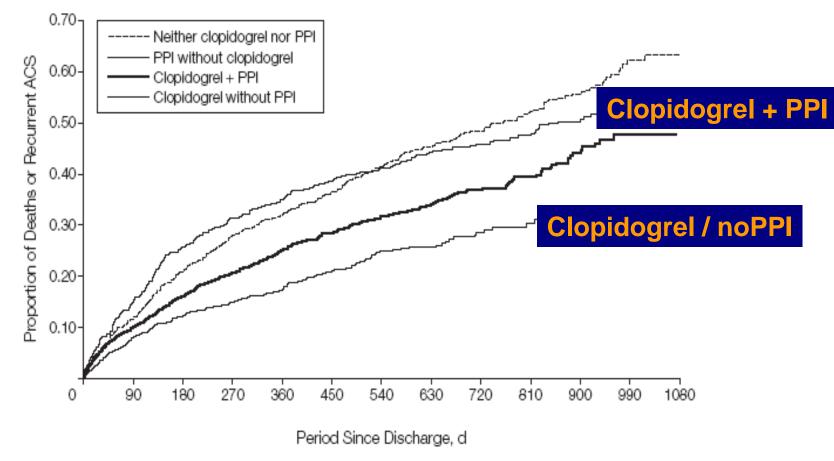




## Risk of All-Cause Mortality and Recurrent ACS in Patients Taking Clopidogrel and PPI

Of 8205 patients with ACS taking clopidogrel after hospital discharge,

63.9% (n=5244) were prescribed PPI at discharge



Ho et al. JAMA. 2009;301(9):937-944.

# Clopidogrel plus PPI After Hospitalization for ACS Increased Risk of Adverse Outcomes

- Eight hundred twenty patients with drug-eluting coronary stents
  - Five hundred two patients who were not prescribed a PPI at discharge
  - Three hundred eighteen patients who were prescribed a PPI.
- All patients were taking clopidogrel.
- One year follow up

# Clopidogrel plus PPI After Hospitalization for ACS Increased Risk of Adverse Outcomes

- Univariate survival analysis of the outcomes showed a greater rate of MACE (13.8% vs 8.0%, p = 0.008) and overall mortality (4.7% vs 1.8%, p = 0.02) in the PPI group.
- After multivariate analysis, the adjusted MACE hazard ratio for PPI at discharge was 1.8 (95% confidence interval 1.1 to 2.7, p = 0.01).

## **EBM - What they say**

- Three randomized databases all suggest that there is no significant adverse interaction between clopidogrel and PPIs.
  - CREDO trial, presented at the AHA 2008
  - TRITON trial
  - PRINCIPLE 44 trial

- Meta-analysis by Kwok CS, 'the effects of proton pump inhibitors on cardiovascular events and mortaliy in patients receiving clopidogrel', Alimnt pharmacol Ther 31, 810-823.
- Analyzing these studies found ----
- Twelve studies showing MI and ACS showed a higher risk with PPI and Clopidogrel group.
- Thirteen studies where all effects including mortality was seen the result was inconclusive.

- So this is only true for mortality rates.
- Regarding adverse cardiac events leading to MI or Stroke there was no universal proof in the three studies.

#### CONCLUSION

From different observational studies and meta-analysis show:

- Concomitant use of clopidogrel and PPI increases MACE
- Even PPI alone increases MACE

- Meta-analysis of 23 studies recommended
  - to be cautious about the use of PPI
  - should find an alternative combination
  - drug interaction can be minimized by increasing the gap between the doses as half life is short for both



Clopidogrol +PPI- Increase chance of CV catastrophy



