



PPIs May Reduce Effectiveness Of Clopidogrel (PLAVIX®)

What is the concern regarding co administration of clopidogrel with a proton pump inhibitors (PPIs) ?^{1,2,3,4}

- Limited trial data notes that some PPIs are associated with a ↓ in the antiplatelet effect of clopidogrel and an ↑ risk of cardiac events.

What is the proposed mechanism of this potential drug interaction?^{3,5,6}

- The Cytochrome P450-2C19 (2C19) enzyme plays a role in the metabolism of the prodrug, clopidogrel to its active form. (3A4 may also be involved).
- Certain PPIs (especially omeprazole LOSEC and esomeprazole NEXIUM) inhibit 2C19 and may interfere with clopidogrel activation.
- Polymorphism: it has been noted that 2C19 metabolic activity is genetically determined with 10-30% of patients (especially some Asians) having reduced 2C19 activity; these patients may not have an adequate response to clopidogrel treatment. ^{6; 6b,6c,6d.}
- Other potential explanations for the results: impaired absorption of clopidogrel could also be related to stomach pH or PPI dose.

How well documented is this potential drug interaction ?^{1,2,3,4}

- Observational data suggests an *association* of PPIs use with increased risk of clopidogrel failure. Most studies are small and have typical limitations associated with observational data such as the ability to adjust for confounders (eg. 2C19 deficiency).
- A recent CMAJ publication³ described a small population-based nested **case-control study** of Ontario patients aged 66 years or older who received **clopidogrel** ^{n=13,636} **within 3 days following hospital discharge after acute MI** ⁿ⁼⁷³⁴. Readmission rates for myocardial infarction were tracked in those receiving a PPI and those not. **After extensive multivariable adjustments, current use of proton pump inhibitors was associated with an increased risk of recurrent MI within 90days (adjusted odds ratio (OR) 1.27, 95% confidence interval (CI) 1.03-1.57). Pantoprazole, evaluated separately, was not associated with increased risk based on only 46 events; however confidence intervals for pantoprazole effect versus other PPIs effect overlap (OR CI: Pant 0.70-1.47; Other PPI 1.1-1.77)!**
 - ⇒ Limitations of this trial include lack of data on cardiac risk factors, type of MI, LV function, use of non-prescription ASA and multiple significant differences between the case and control groups (see Table 1). [See also Letter: <http://www.cmaj.ca/cgi/eletters/cmaj.082001v1#53931>]
 - ⇒ Only pantoprazole data was reported separately from other PPIs so comparison with other individual PPIs is not available. {Omeprazole was the other most used PPI in Canada (2002-2005); Rx's for rabeprazole & esomeprazole rose in 2006-2007. ^{Top 200 RxDrugs list}}
- Other Studies: In one study, stent patients taking PPIs with clopidogrel showed a 32.5% incidence of a major CV event within one year vs. 21.2% of patients not taking PPIs (adjusted OR 1.79, CI 1.62-1.97).⁴ Abstract only
- In another study, among angioplasty patients on ASA and clopidogrel, omeprazole significantly reduced the clopidogrel effect.¹
- In TRITON-TIMI 38: ^{26, n=13,608} ACS pts ^{33% of pts on a PPI with clopidogrel or prasugrel}, no association between PPI use & the primary endpoint ^{CV death, MI, or stroke} was seen.
- In Cogent ^{n=3,761; 180day; 41} clopidogrel+ASA with omeprazole or placebo: less GI bleed HR=0.13; 95% CI, 0.03-0.56 with omeprazole, not ↑CV events HR=0.99; 95% CI, 0.68-0.1.44 with omeprazole.

Do all PPIs interact with clopidogrel?^{3,6,9}

- It is not entirely clear if the mechanism of this drug interaction/potential association relates solely to 2C19 inhibition.
- Apart from omeprazole, it is not totally clear which other PPIs inhibit 2C19 to a significant extent:
 - Esomeprazole has been demonstrated to inhibit 2C19, however, the significance of the effect on clopidogrel is unknown.
 - There is consensus that pantoprazole does NOT inhibit 2C19 to any great extent.
 - Rabeprazole is also less likely to inhibit 2C19 to a significant extent. {Rabeprazole is actually thought to have minimal effect on 2C19 as it undergoes primarily non-enzymatic metabolism (although thioether metabolite may have some effect).⁸. The literature is not clear on lansoprazole's effect.}⁶

How should I manage patients currently receiving clopidogrel with a PPI?

- Determine if the acid suppression / gastroprotection is really required, if not stop the PPI. See Figure 1.
- Patients taking PPIs for acid suppression (i.e. GERD) with well-controlled symptoms may be candidates for an H₂ antagonist. Currently there is no evidence, including this data, that ranitidine (an H₂RA), antacids or misoprostol interfere with clopidogrel.
- Patients should receive gastroprotection with a PPI if they are taking an NSAID (including low dose ASA) and are at high risk for a GI bleed {according to recent guidelines¹⁰ this includes anyone taking ASA + clopidogrel (especially if ulcer history, age >70 etc.)}.
- If PPI required consider agents that do not significantly effect 2C19; preference for pantoprazole (& possibly rabeprazole).

What about other drugs that inhibit the CYP2C19 enzyme?¹¹

- Drug interaction experts suggest that until data are available showing a lack of interaction, patients taking clopidogrel should avoid drugs that inhibit CYP2C19 (cimetidine, delavirdine, efavirenz, fluvoxamine, fluoxetine, fluconazole, isoniazid, moclobemide, modafinil, oxcabazepine, voriconazole). The makers of Plavix, Sanofi-Aventis and Bristol-Myers Squibb have agreed to work with the FDA to conduct studies to better understand the effects of genetic factors and other drugs on clopidogrel.

Bottom Line for patients on the combination of clopidogrel (Plavix) and a PPI:

- Determine if patient on clopidogrel needs a PPI?** Some patients will be candidates for discontinuation of the PPI or a switch to an H₂RA such as ranitidine or misoprostol. {One reviewer suggested indication for, and duration of clopidogrel therapy should also be assessed.}
- Remember that PPIs may decrease the effectiveness of clopidogrel! However, if a PPI is indicated:**
 - Avoid omeprazole (and possibly esomeprazole)** due to high likelihood of 2C19 interaction & potentially increased MI risk. {Update Nov09: FDA restates this: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm>}
 - Pantoprazole may be the PPI of choice due to a low likelihood of 2C19 interaction and limited outcome evidence from new observational data that MI/reinfarction rates are potentially reduced relative to other PPIs.
 - Rabeprazole is also unlikely to have a significant 2C19 interaction however outcome data is not available to confirm or suggest any effect on MI/reinfarction risk.
- Remember that the data from the Juurlink trial is observational** with several significant limitations and potential for confounding. Being a case-control study, the interpretation of the results requires caution given the small number of events, CIs and lack of specifics as to what "other PPIs" means. Further RCT data from a well designed trial is required.
- Update Sep09:** TRITON-TIMI 38 trial in ACS patients showed no association in clinical event risk with the use of a PPI & clopidogrel.²⁶
- Update Oct10:** Cogent showed less GI bleeding, without increased cardiovascular events when omeprazole ^{vs placebo} was used with clopidogrel.⁴¹

Were the groups equal?
Were the groups treated equally?

Table 1: Major Differences Between Case And Control Groups (Juurlink study)

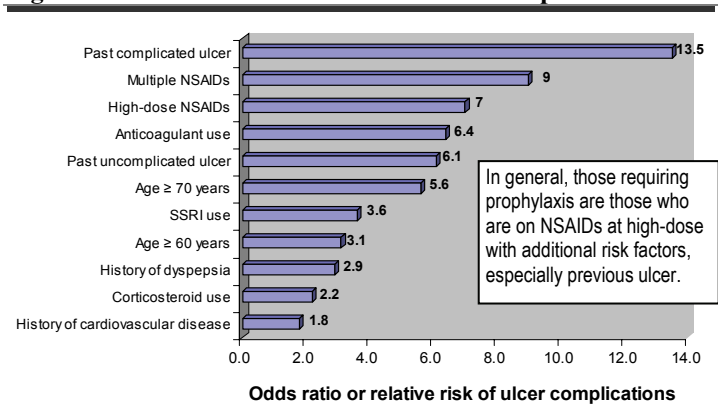
	Variable	Cases %	Controls %	p value
Comorbidity	Acute renal insufficiency	6.1	3.3	<0.001
	CHF	27.7	18.0	<0.001
	Diabetes mellitus with complications	28.3	19.9	<0.001
Other Medications	ACEI	57.1	65.6	<0.001
	ARB	7.5	7.9	0.71
	Beta Blocker	70.2	74.4	0.027
	CCB	19.9	16.1	
	Statin	71.8	77.4	0.002
	Other diuretic (non-thiazide)	7.9	7.0	<0.001
Unknowns (observational trial)	?	?	?	?

Note: Comorbidity risks (e.g. diabetes, HF) of Case group was higher than Control group; however, use of drugs (e.g. ACEIs) with strong outcome evidence for benefit was significantly less. This raises the question of potential confounding, how equal baseline groups were, and how equal the treatment of the groups was (apart from association studied). Methods to adjust for differences may be compromised if the number and degree of differences is high. If the groups are too different, then any analysis, even with adjustments, may be misleading.

Figure 1: Risk Factors for GI Bleed

Those NSAID patients at especially high risk include those with a history of complicated ulcer, on anticoagulants, those who are ≥70 years old & those with multiple risk factors. Combinations of antithrombotic agents also greatly ↑ bleeding risk (e.g. ASA/NSAID, with either warfarin or clopidogrel).¹²

Figure 1: Who's at Risk for NSAID Ulcer Complications¹³



Evidence for NSAID induced ulcer prevention:

What works?

- **PPIs:** Standard dose e.g. pantoprazole 40mg daily ac
- **Misoprostol:** 200mcg po TID-QID \$38-49 / month
- **H2RAs:** not effective at standard doses; may be effective at double dose (but more costly).

Also consider:

- Use lowest effective dose of NSAID or ASA (e.g. 81mg/day).
- Eradicate H. pylori if positive

Patients with an ASA related GI bleed^{10,16,17;}

In H. pylori-negative patients who have a history of ulcer bleeding on low-dose ASA, the combination of low-dose ASA and a PPI is associated with a lower risk of recurrence of ulcer complications as compared to clopidogrel alone. (0.7% vs 8.6%; ARR=7.9; CI: 3.4-12.4; NNT=13)

Table 2: PPI Comparison (Adapted from Acid Suppression Chart - www.RxFiles.ca)

Drug	Dose	Cost \$/month (SK)
Esomeprazole NEXIUM	40mg po OD ac	82
20, 40mg long football shaped tab Delayed Release, 10mg ^x sachet	20mg po OD ac	82
Lansoprazole PREVACID	30mg po OD ac	79
15, 30mg Delay Release cap (15 ^a , 30 ^a mg FasTab & IV ^x)	15mg po OD ac	79
Omeprazole LOSEC , Apo, Ratio interchangeable in Sk	20mg po OD ac	46 ^{APO} , 86
10, 20mg Delayed Release tab; OTC in USA; USA approved 1989	40mg po OD ac	86 ^{APO} , 165
	10mg po OD ac	54 ^g , 70
Pantoprazole PANTOLOC ,g	40mg po OD ac	56 ^g , 75
40mg Enteric tab, 20mg ^g tab; 40mg Vial,g	20mg po OD ac	50
Rabeprazole PARIET ,g	20mg po OD ac	41 ^g , 54 ^g
10, 20mg Enteric coated tab (USA name=Aciphex)	≥10mg po OD ac	24 ^g , 30

=Max. allowable cost in SK =Exception Drug Status SK ^x =non-formulary SK =prior approval for NIHB ac=before meals; =not covered by NIHB =generic

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