



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, 0.68-0.144 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)

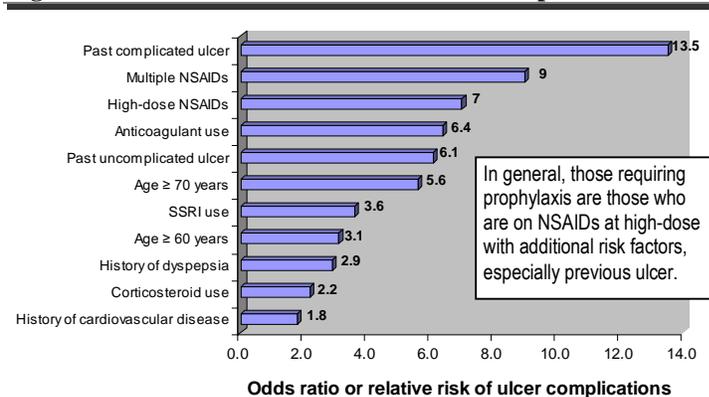
	Variable	Cases %	Controls %	p value
Comorbidity	Acute renal insufficiency	6.1	3.3	<0.001
	CHF	27.7	18.0	<0.001
	Diabetes mellitus with complications	28.3	19.9	<0.001
Other Medications	ACEI	57.1	65.6	<0.001
	ARB	7.5	7.9	0.71
	Beta Blocker	70.2	74.4	0.027
	CCB	19.9	16.1	
	Statin	71.8	77.4	0.002
	Other 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 20, 40mg long football shaped tab Delayed Release; 10mg x sachet	40mg po OD ac 20mg po OD ac	82 82
Lansoprazole PREVACID 15,30mg Delay Release cap(15, 30mg FasTab & IV x)	30mg po OD ac 15mg po OD ac	79 79
Omeprazole LOSEC, Apo, Ratio interchangeable in SK 10,20mg Delayed Release tab; OTC in USA; USA approved 1989	20mg po OD ac 40mg po OD ac 10mg po OD ac	46 ^{APO} , 86 86 ^{APO} , 165 54 ^g , 70
Pantoprazole PANTOLOC, g 40mg Enteric tab, 20mg tab; 40mg Vial g	40mg po OD ac 20mg po OD ac	56 ^g , 75 50
Rabeprazole PARIET, g 10, 20mg Enteric coated tab (USA name=Aciphex)	20mg po OD ac ≥10mg po OD ac	41 ^g , 54 ^g 24 ^g , 30

Ⓜ=Max. allowable cost in SK ☎=Exception Drug Status SK. ✕=non-formulary SK. Ⓞ=prior approval for NIHB ac=before meals; ⊗=not covered by NIHB g=generic

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References

- Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin. J Am Coll Cardiol 2008;51:256-60.
- Pezella E, Day D, Pulliadhath I. Initial assessment of clinical impact of a drug interaction between clopidogrel and proton pump inhibitors. J Am Coll Cardiol 2008;52:1038-9.
- Juurlink DN, Gomes T, Ko D, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180(7). DOI:10.1503/cmaj.082001
- Aubert RE, Epstein RS, Teagarden JR et al. Abstract 3998: Proton pump inhibitors effect on clopidogrel effectiveness: the clopidogrel medco outcomes study. Circulation. 2008;118:S815
- Dunn SP, Macaulay TE, Brennan DM et al. Abstract 3999: Baseline proton pump inhibitors use is associated with increased cardiovascular events with and without the use of clopidogrel in the CREDO trial. Circulation 2008;118:S_815.
- Pharmacist's Letter. Do proton pump inhibitors decrease clopidogrel (Plavix) activity. Nov 2008;24, number 24114.
- Horn JR, Hansten PD. Clopidogrel: Some drugs may reduce its effectiveness. Pharmacy Times April 2008:58. {6b; Collet JP, Hulot JS, Pena A, Villard E, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet. 2008 Dec 22. 6c; Simon T, Verstuyft C, Mary-Krause M, Queteineh L et al. The French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic Determinants of Response to Clopidogrel and Cardiovascular Events. N Engl J Med. 2008 Dec 22. 6d; Mega JL, Close SL, Wiviott SD, Shen L, et al. Cytochrome P-450 Polymorphisms and Response to Clopidogrel. N Engl J Med. 2008 Dec 22.}
- Small DS, Farid NA, Payne CD, et al. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. J Clin Pharmacol 2008;48:475-84.
- Li XQ, Andersson TB, Ahlstrom M, et al. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos 2004;32:821-7.
- Siller-Matula JM, Spiel AO, Lang IM et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. Am Heart J 2009;157: 148.e1-148.e5.
- Bhatt DL, Scheiman J, Abraham NSACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use. Circulation online Oct 3, 2008 DOI: 10.1161/CIRCULATIONAHA.108.191087 American College of Cardiology Foundation Task Force on Expert Consensus Documents, Abraham, Neena S., Hlatky, Mark A., Antman, Elliott M., Bhatt, Deepak L., et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use J Am Coll Cardiol 2010 0: j.jacc.2010.09.010 http://content.onlinejacc.org/cgi/reprint/j.jacc.2010.09.010v1.pdf
- Horn JR, Hansten PD. Get to know the enzyme CYP2C19. Pharmacy Times May 2008.
- Delaney JA, Opatryny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ. 2007 Aug 14;177(4):347-51.
- Hunt RH, Barkun AN, Baron D, Bombardier C, et al. Recommendations for the appropriate use of anti-inflammatory drugs in the era of the coxibs: defining the role of gastroprotective agents. Can J Gastroenterol. 2002 Apr;16(4):231-40.
- Medical Letter Consultants. PPI Interactions with Clopidogrel. Medical Letter, Jan 12, 2009. Other: 15. FDA Jan 2009 Plavix warning: http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm
- Chan FKL, et al Clopidogrel versus Aspirin and Esomeprazole to Prevent Recurrent Ulcer Bleeding. N Engl J Med 2005;352:238-44. n=320 1yr.
- Lai KC, et al. Esomeprazole 20mg/d + ASA (100mg/d) vs clopidogrel 75mg od for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol. 2006 Jul;4(7):860-5.

18. Brandt JT, Close SL, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost*. 2007 Dec;5(12):2429-36. Epub 2007 Sep 26.
19. Sibbing D, Stegheer J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. *Eur Heart J* 2009; DOI:10.1093/eurheartj/ehp041. <http://eurheartj.oxfordjournals.org>.
20. Ho PM et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009 Mar 4; 301:937.
21. Sibbing D, Morath T, Stegheer J, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. *Thromb Haemost* 2009; 101:714-719.
22. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 Genetic Polymorphisms and the Response to **Prasugrel**. Relationship to Pharmacokinetic, Pharmacodynamic, and Clinical Outcomes. *Circulation*. 2009 May 4. [Epub ahead of print]
23. FDA label changes May 2009 "The CYP2C19*1 allele corresponds to fully functional metabolism, while the CYP2C19*2 and CYP2C19*3 alleles correspond to reduced metabolism. The CYP2C19*2 and CYP2C19*3 alleles account for 85% of reduced-function alleles in whites and 99% in Asians. Other alleles associated with reduced metabolism include CYP2C19*4, *5, *6, *7, and *8, but these are less frequent in the general population."
24. Health Canada Aug/09 Plavix & PPI Interaction http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advvisories-avis/prof/2009/plavix_hpc-cps-eng.pdf
25. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy (**PAPI**). *JAMA* 2009; 302: 849-858.
26. O'Donoghue ML, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: An analysis of two randomised trials. (**TRITON-TIMI 38 & PRINCIPLE-TIMI 44**) *Lancet* 2009; DOI:10.1016/S0140-6736(09)61525-7.
27. Rassen JA, Choudhry NK, Avorn J, et al. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. *Circulation* 2009; 120:2322-2329.
28. Sibbing D, Koch W, Gebhard D, et al. Cytochrome **2C19*17** Allelic Variant, Platelet Aggregation, Bleeding Events, and Stent Thrombosis in Clopidogrel-Treated Patients With Coronary Stent Placement. *Circulation*. 2010 Jan 18.
29. Yun KH, Rhee SJ, Park HY, Yoo NJ, Kim NH, Oh SK, Jeong JW. Effects of **omeprazole** on the antiplatelet activity of clopidogrel. *Int Heart J*. 2010 Jan;51(1):13-6.
30. Breet NJ, van Werkum JW, Bouman HJ et al. Comparison of **platelet function tests** in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA* 2010; 303:754-762.
31. Depta JP, Bhatt DL. Omeprazole and clopidogrel: Should clinicians be worried? *Cleve Clin J Med*. 2010 Feb;77(2):113-6.
32. Ray Wayne A., Murray Katherine T., Griffin Marie R., Et al. Outcomes With Concurrent Use of Clopidogrel and Proton-Pump Inhibitors: A Cohort Study. *Ann Intern Med* March 16, 2010.
33. Stockl Karen M., Le Lisa; Zakharayan Armen; et al. Risk of Rehospitalization for Patients Using Clopidogrel With a Proton Pump Inhibitor. *Arch Intern Med*. 2010;170(8):704-710.
34. Ho PM, Tsai TT, Maddox TM, et al. Delays in filling clopidogrel prescription after hospital discharge and adverse outcomes after drug-eluting stent implantation. Implications for transitions of care. *Circ Cardiovasc Qual Outcomes* 2010
35. Hulot JS, Collet JP, et al. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor co-administration. A systematic meta-analysis. *J Am Coll Cardiol*2010;56:134-143.
36. Wu CY, Chan FK, Wu MS, Kuo KN, Wang CB, Tsao GR, Lin JT. Histamine-2-receptor antagonist as an alternative to proton pump inhibitor in patients receiving clopidogrel. *Gastroenterology*. 2010 Jul 2.
37. Paré G, Mehta SR, Yusuf S, et al. Effects of CYP2C19 genotype on clopidogrel treatment in **CURE** and **ACTIVE**. *N Eng J Med* 2010; DOI: 10.1056/NEJMoa008410.
38. van Boxel OS, van Oijen MG, Hagenars MP, Smout AJ, Siersema PD. Cardiovascular and Gastrointestinal Outcomes in Clopidogrel Users on Proton Pump Inhibitors: Results of a Large Dutch Cohort Study. *Am J Gastroenterol*. 2010 Aug 24.
39. Angiolillo DJ, Gibson CM, Cheng S, et al. Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: Randomized, placebo-controlled, crossover comparison studies. *Clin Pharmacol Ther* 2010; DOI:10.1038/clpt.2010.219.
40. Charlot M, Ahlehoff O, Norgaard ML, et al. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. *Ann Intern Med*. 2010 Sep 21;153(6):378-86.
41. Bhatt DL et al. for the **COGENT** Investigators. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010 Oct 6; [e-pub ahead of print].
42. Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with **clopidogrel** and **prasugrel** in the TRITON-TIMI 38 trial: A pharmacogenetic analysis. *Lancet* 2010; DOI:10.1016/S0140-6736(10)61273-1.
43. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI. (Meta-analysis) *JAMA* 2010; 304:1821-1830.
44. Kreuz RP, Stanek EJ, Aubert R, et al. Impact of proton pump inhibitors on the effectiveness of clopidogrel after coronary stent placement: the clopidogrel **medco outcomes study**. *Pharmacotherapy*. 2010 Aug;30(8):787-96.
45. Blackburn DF, Lamb DA, McLeod MM, Eurich DT. **Increased use of acid-suppressing drugs before** the occurrence of ischemic events: a potential source of confounding in recent observational studies. *Pharmacotherapy*. 2010 Oct;30(10):985-93.
46. Sánchez Muñoz-Torero JF, Escudero D, Suárez C, et al.; the FRENA Investigators. Concomitant use of proton-pump inhibitors and clopidogrel in patients with coronary, cerebrovascular or peripheral artery disease in the FRENA Registry. *J Cardiovasc Pharmacol*. 2010 Dec 15.
47. Juurlink DN, Gomes T, Mamdani MM, et al. The Safety of Proton Pump Inhibitors and Clopidogrel in Patients After Stroke. *Stroke*. 2010 Dec 16. As a class, proton pump inhibitors are not associated with an increased risk of recurrent stroke or death among older patients treated with clopidogrel after stroke.
48. Ryan D, Madanick. Proton pump inhibitor side effects and drug interactions: **Much ado about nothing?** *Cleveland Clinic Journal of Medicine* 2011; 78(1):39-49; doi:10.3949/ccjm.77a.10087.
49. Hsu PI, Lai KH, Liu CP. **Esomeprazole with Clopidogrel** Reduces Peptic Ulcer Recurrence. Compared to Clopidogrel Alone, in Patients with Atherosclerosis. *Gastroenterology*. 2010 Dec 6.(n=165, 6mon).
50. Mehta SR, Taubert JF, Eikelboom JW, et al. CURRENT-OASIS 7 trial investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (**CURRENT-OASIS 7**): a randomised factorial trial. *Lancet*. 2010 Oct 9;376(9748):1233-43.
51. Simon T, Steg PG, Gilard M, et al. Clinical Events as a function of proton pump inhibitor use, clopidogrel use, and cytochrome P450 2C19 genotype in a large nationwide cohort of acute myocardial infarction: Results from the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (**FAST-MI**) Registry. *Circulation* 2011; DOI: 10.1161/CIRCULATIONAHA.110.965640.
52. Banerjee S, Weideman RA, Weideman MW, et al. Effect of concomitant use of **clopidogrel** and **proton pump inhibitors after percutaneous coronary intervention**. *Am J Cardiol* 2011; 107:871-878. (misindication bias)
53. Harmsze Ankie M, van Werkum Jochem W, Taubert Dirk, et al. **Esomeprazole but Not Pantoprazole** Is Associated with Lower Plasma Concentrations of Clopidogrel's Active Metabolite. Articles Ahead of Print published on 1 April 2011, DOI 10.1345/aph.1P425. *Ann Pharmacother* 45:542-543.
54. Health Canada Sep/11 is informing health professionals and patients of updated recommendations involving the use of Plavix (clopidogrel) in combination with a class of drugs known as proton pump inhibitors (PPIs). New evidence has shown that while PPIs do interact with Plavix, not all reduce the effectiveness of Plavix to the same degree. (Omeprazole interacts, but pantoprazole not interact as strongly)
55. Bauer T, Bouman HJ, van Werkum JW, Ford NF, ten Berg JM, Taubert D. Impact of **CYP2C19 variant genotypes** on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. *BMJ*. 2011 Aug 4;343:d4588.
56. Holmes MV, Parel P, Shah T, et al. **CYP2C19 genotype, clopidogrel** metabolism, platelet function and cardiovascular events. A systematic review and meta-analysis. *JAMA* 2011; 306:2704-2714.
57. Goodman SG, Clare R, Pieper KS, et al. Association of proton pump inhibitor use on cardiovascular outcomes with **clopidogrel** and **ticagrelor**. Insights from PLATO. *Circulation* 2012.
58. Freilinger AL 3rd, Lee RD, Mulford DJ, et al. A randomized, 2-period, crossover design study to assess the effects of **dexiansoprazole, lansoprazole, esomeprazole, and omeprazole** on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. *J Am Coll Cardiol*. 2012 Apr 3;59(14):1304-11.
59. Douglas IJ, Evans SJW, Hingorani A, et al. **Clopidogrel and interaction with proton pump inhibitors**: comparison between cohort and within person study designs. *BMJ* 2012;345:e4388.
60. Jaspers Focks J, Brouwer MA, van Oijen MG, et al. Concomitant use of **clopidogrel and proton pump inhibitors**: impact on platelet function and clinical outcome- a systematic review. *Heart*. 2012 Jul 31.
61. Focks JJ, Brouwer MA, van Oijen MG, et al. Concomitant use of **clopidogrel and proton pump inhibitors**: impact on platelet function and clinical outcome- a systematic review. *Heart*. 2013 Apr;99(8):520-7.
62. Melloni C, Washam JB, Jones WS, et al. Conflicting results between randomized trials and observational studies on the impact of **proton pump inhibitors on cardiovascular events when coadministered with dual antiplatelet therapy**. *Circ Cardiovasc Qual Outcomes* 2015; 8: 47-55.

