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► To cite this version:

Ben Disney, Rob Watson, Andrew Blann, Gregory Lip, Mark Anderson. Review article: Proton pump inhibitors with clopidogrel; evidence for and against a clinically important interaction. *Alimentary Pharmacology and Therapeutics*, 2011, 33 (7), pp.758. 10.1111/j.1365-2036.2011.04585.x . hal-00613926

HAL Id: hal-00613926

<https://hal.science/hal-00613926>

Submitted on 8 Aug 2011

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**Review article: Proton pump inhibitors with clopidogrel;
evidence for and against a clinically important interaction**

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0918-2010.R2
Wiley - Manuscript type:	Systematic Review
Date Submitted by the Author:	12-Jan-2011
Complete List of Authors:	Disney, Ben; City Hospital, Dept of Gastroenterology Watson, Rob; City Hospital, Cardiology Blann, Andrew; University of Birmingham, Cardiovascular Medicine Lip, Gregory; University of Birmingham, Cardiovascular Medicine Anderson, Mark; City Hospital, Dept of gastroenterology
Keywords:	Clinical pharmacology < Topics, Stomach and duodenum < Organ-based, Acidity (intra-gastric) < Topics, Non-variceal bleeding < Topics

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3 **Review article: Proton pump inhibitors with clopidogrel; evidence for and against a**
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5 **clinically important interaction**
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47 **Word Count:** 4534 (7216 including references)

48
49 **Tables:** 1

50
51 **Figures:** 1

52
53 **References:** 73

54
55 **Funding:** Nil

56
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58 **Ethical approval:** Not required
59
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Abstract

Background: The treatment of acute coronary syndromes involves a combination of anti-platelet therapies. Proton pump inhibitors are frequently recommended for patients receiving clopidogrel in addition to aspirin, to minimise the risk of bleeding. Several studies have shown that proton pump inhibitors can affect the platelet inhibitory effects of clopidogrel. However, the data on whether this has an effect on clinical outcomes are conflicting and a definitive answer is still awaited.

Aim: To provide an overview of the evidence for the pharmacological interaction between proton pump inhibitors and clopidogrel and to discuss whether this interaction translates into adverse clinical outcomes. Despite recent developments a clear consensus is still lacking.

Methods: A search of the published literature combined with the authors' knowledge of the field.

Results: There is evidence to show that proton pump inhibitors can influence the pharmacodynamics of clopidogrel but the data suggesting clinical effects are weak and conflicting. Supporting a clinically important interaction are four retrospective studies including over 11,000 patients prescribed both clopidogrel and a proton pump inhibitor. Evidence against a clinically important interaction is derived from over 18,000 patients from seven studies, including the only prospective trial to examine the potential interaction. Confounding variables are relevant and prospective clinical evidence is lacking.

Conclusions: Proton pump inhibitors offer clear protection, and the concern over clinically relevant interactions with clopidogrel is biologically plausible but not yet proven.

Key words: clopidogrel, PPI, proton pump inhibitor, drug interaction

Introduction

The treatment of Acute Coronary Syndromes (ACS) with dual anti-platelet therapy (i.e. aspirin plus clopidogrel) reduces recurrent cardiovascular events (1). However, with the advent of dual anti-platelet therapy comes an inevitable increased risk of bleeding as a side effect. With regards to gastrointestinal bleeding, this occurs in 1.3-2.7% of patients treated for ACS with aspirin, clopidogrel and enoxaparin (2,3). Even patients on low dose aspirin have an incidence of gastrointestinal peptic ulcer bleeding of 0.5% per year (4).

In the context of ACS, gastrointestinal bleeding should be regarded as a serious condition that is independently associated with increases in both mortality and ischaemic complications (3). Co-prescription with a proton pump inhibitor (PPI) could significantly reduce the risk of bleeding (2). As a result, the near-universal use of a PPI is recommended in order to reduce the incidence of gastrointestinal bleeding in patients taking clopidogrel, most of whom are taking aspirin in addition (5). In addition to these guidelines, gastroenterologists frequently prescribe PPIs to prevent drug-induced upper gastrointestinal bleeding, supported by a Cochrane meta-analysis of PPI use to prevent NSAID induced peptic ulceration (6).

The aim of this review article is to provide an overview of the evidence for the pharmacological interaction between proton pump inhibitors and clopidogrel and its impact on clinical outcomes.

A clinically relevant interaction between clopidogrel and PPI?

The possibility of a clinically relevant interaction between clopidogrel and PPIs was first noted in 2008 (7). This came on the background of an observational study from 2006 which found clopidogrel activity on platelets to be diminished in patients receiving PPI treatment (8).

In response to studies suggesting that PPIs could diminish the effects of clopidogrel (9), the European Medicines Agency (EMA) released a statement in May 2009 (10), and the FDA also in 2009 (11), warning of the potential interaction. Since then, clinicians have faced difficult and uncertain decisions regarding patient care. Various suggestions have been made for prescribing, such as evening dosing of a PPI to ensure a 12 hour gap after a morning clopidogrel dose or the preferential use of pantoprazole (12). However, there appears to be little evidence to back these approaches. Any potential interaction between PPIs and clopidogrel needs to be clarified due to the increased risk of poor cardiovascular outcomes in potentially large numbers of patients.

Pharmacological basis of a clopidogrel-PPI interaction

Clopidogrel, a thienopyridine, is a prodrug which is metabolised in the liver via the cytochrome p450 (mainly CYP2C19) pathway to its active metabolite (13,14). This compound targets and irreversibly inhibits the ADP P2Y₁₂ receptor on circulating platelets which prevents platelet aggregation. CYP2C19, which has a major role in the metabolism of clopidogrel, also metabolises the PPIs. Reduced conversion of clopidogrel to its active metabolite by the CYP450 system could be in part responsible for clopidogrel resistance (15) and clopidogrel resistance is associated with adverse cardiovascular events (16). In addition to this, reduced intestinal absorption may play a role (15,17).

As mentioned above, clopidogrel is metabolised to its active metabolite by various cytochrome p450 enzymes, the key enzyme being CYP2C19 (18,19). Approximately 15% of the absorbed dose is converted to an active thiol metabolite, R-130964 (20). The extent of platelet inhibition by clopidogrel varies between patients and reduced platelet inhibition is associated with poor cardiovascular outcomes (21-24).

The activity of CYP2C19 can have a profound effect on the conversion of clopidogrel to its active metabolite. In healthy volunteers, those with CYP2C19 loss-of-function polymorphisms have impaired responsiveness to clopidogrel demonstrated by platelet aggregation and higher vasodilator-stimulated phosphoprotein (VASP) phosphorylation (13). It is thought that approximately 90% cases of poor metabolism is accounted for by the CYP2C19*2 allele (13,25). In patients suffering myocardial infarction who received clopidogrel, those with CYP2C19 loss-of-function alleles have lower levels of the active metabolite of clopidogrel and a higher rate of subsequent cardiovascular events than those

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3 that do not (17,26-28). The common polymorphisms of CYP2C19 are present in
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5 approximately 3-30% of whites, 3-40% of blacks and 12-100% of various Asian populations
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7 (29,30). In the study by Mega et al, 30% of healthy recruits had a loss-of-function allele for
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9 CYP2C19, which resulted in a relative reduction of 32.4% of the active metabolite of
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11 clopidogrel compared to non-carriers, and a 9% reduction in platelet aggregation (26). This
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13 resulted in an increase in death from cardiovascular cause, myocardial infarction and stroke
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15 (26). These effects are most notable in patients undergoing percutaneous coronary
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17 intervention with a HR of 3.58 (CI 1.71-7.51) for recurrent cardiovascular events (17). The
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19 CYP2C19 loss-of-function polymorphism is also associated with stent thrombosis with rates
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21 as high as a factor of 3 as compared with noncarriers (26,31). Thus, any medication that
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23 reduces the conversion of clopidogrel to its active metabolite may reduce the platelet
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25 inhibition caused by clopidogrel.
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32 Indeed, clopidogrel has been at the centre of controversy previously, with a reported possible
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34 interaction with atorvastatin, which competes for CYP3A4 (see figure 1) (32). Atorvastatin
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36 was found to attenuate the antiplatelet activity of clopidogrel in a dose-dependent manner in
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38 vitro (33). However, this observation has since been refuted and was not found to be
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40 associated with worse clinical outcomes (34-37).
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47 The potential mechanism of interaction lies in the fact that both clopidogrel and the PPIs, in
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49 varying degrees, are both metabolised by the same cytochrome p450 enzyme – CYP2C19
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51 (13,38). PPIs have the potential to competitively inhibit the metabolism of clopidogrel to its
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53 active metabolite. This leads to reduced circulating concentrations of the active metabolite.
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56 The earliest evidence of a pharmacological interaction between clopidogrel and PPIs is from
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58 platelet aggregation studies. One study of 105 patients found PPI users (omeprazole, n=24)
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60 had VASP phosphorylation levels than none PPI users and suggested an interaction (8). In the

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3 OCLA study (7), which was a double-blind placebo-controlled trial, measurements of VASP
4 expressed as platelet reactivity index (PRI) were measured in 124 patients undergoing
5 coronary stent insertion. Patients receiving aspirin and clopidogrel were treated with
6 omeprazole 20mg or placebo for 7 days. By day 7, 26.7% of placebo-treated patients and
7
8 60.9% of omeprazole-treated patients were classified as poor responders to clopidogrel
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10 (PRI>50%) indicating a significantly decreased effect of clopidogrel in the presence of a PPI.
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20 As all PPIs are metabolised by CYP2C19 to varying degrees, and share the ability to inhibit
21 CYP2C19, do all PPIs have negative effects on clopidogrel? Several studies have tried to
22 answer this question.
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29 One small study showed that lansoprazole 30mg given in addition to clopidogrel 300mg
30 diminished the inhibition of platelet aggregation when compared to clopidogrel alone (39).
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32 However, no effect was seen with regards to PPIs interacting with prasugrel. Another study
33 found that the inhibitory profiles for all PPIs were similar but with some heterogenicity; for
34 example, lansoprazole is the most potent in vitro inhibitor of CYP2C19 with pantoprazole
35 exhibiting more of an effect on CYP2C9 (40).
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46 Although lansoprazole has been shown to be the most potent inhibitor of CYP2C19 (40),
47 other evidence reports that in patients prescribed clopidogrel, concomitant treatment with
48 lansoprazole does not alter the pharmacokinetics or pharmacodynamics of clopidogrel (39).
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51 Data from 1000 patients on clopidogrel undergoing angiography examined the effect the
52 various PPIs had on platelet aggregation (41). Platelet aggregation was significantly greater
53 in patients prescribed omeprazole (n=64) than those without PPI therapy. It was observed that
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3 platelet aggregation was similar in patients taking clopidogrel and pantoprazole (n=162),
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5 esomeprazole (n=42) or no PPI.
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10 Another study found that omeprazole (n=3132) was associated with adverse cardiovascular
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12 outcomes (e.g. death or rehospitalisation for ACS) (42). In the same study similar results
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14 were found with rabeprazole (n=151), however, small numbers weaken this data. Results
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16 from 300 patients looking at clopidogrel responsiveness by VASP phosphorylation and
17
18 platelet aggregometry, in patients with coronary artery disease undergoing PCI found no
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20 difference between esomeprazole (n=74) and pantoprazole (n=152), and indeed no suggestion
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22 that either was associated with impaired response to clopidogrel (43). Unfortunately,
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24 omeprazole was not included in the analysis.
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31 Other evidence suggests pantoprazole has less of a deleterious effect on clopidogrel than
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33 omeprazole (44). PRI VASP was measured in 104 patients undergoing PCI who were
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35 randomised to either omeprazole (n=52) or pantoprazole (n=52) in addition to both aspirin
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37 and clopidogrel. After 1 month patients receiving pantoprazole had significantly better
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39 platelet response to clopidogrel as assessed with the PRI VASP (36% versus 48%).
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46 These observations have led authors to put forward the case that pantoprazole is the preferred
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48 PPI in the context of concomitant clopidogrel use (45-47). Some data suggests that
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50 pantoprazole is less likely to inhibit CYP2C19 than omeprazole and does not attenuate the
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52 pharmacodynamic response to clopidogrel (40,43,44,47). However, recently updated
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54 guidelines suggest that no one PPI should be used preferentially over another. This is due to
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56 the lack of head to head trials and that studies showing a difference between PPIs were in
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58 different populations using different methods (48).
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3 Although drug–drug interactions of omeprazole for CYP2C19 are thought to be one of
4 competitive inhibition, the issue of its short plasma half-life (<1 h) has been brought up to
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6 refute this argument (45). However, omeprazole has a high affinity for CYP2C19 and its
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8 binding is extensive and it is unknown how long this inhibition persists. Omeprazole has a
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10 short half-life, however, separating the dose of omeprazole and clopidogrel is not a way of
11
12 overcoming the interaction as some CYP2C19 may still be bound by omeprazole metabolism
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14 (45). In addition, there has been no obvious dose–response relationship found between PPI
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16 dose and adverse outcomes, which one would expect from competitive inhibition (42,45).
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20 At present there is insufficient evidence to suggest that one particular PPI (e.g. pantoprazole)
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22 should be prescribed in preference to another to avoid an interaction. The ongoing SPICE
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24 (Evaluation of the Influence of Statins and Proton Pump Inhibitors on Clopidogrel
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26 Antiplatelet Effects) trial is directly comparing the effect of all PPIs on platelet aggregation
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28 and VASP and should help answer the question of which PPI is preferable. In addition the
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30 trial will examine clopidogrel resistance, CYP2C19 polymorphism and its effect on PPI on
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32 the antiplatelet activity of clopidogrel, mortality and the need to stop medication due to peptic
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34 ulcer disease or GI bleeding (49).
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Clinical evidence – evidence of an interaction

From the evidence above there is no doubt that PPIs have an effect on the pharmacokinetics and pharmacodynamics of clopidogrel, as evidenced by laboratory assays, but these are surrogate markers of clinical effect. The question has to be asked, does a pharmacokinetic or pharmacodynamic effect have any impact on clinical outcomes?

Several studies suggest a link between co-prescription of a PPI and clopidogrel, and an increased risk of adverse clinical outcomes (see Table 1).

Data from 14383 patients in the Medco Integrated database was presented in abstract format at the AHA Scientific Sessions 2008 Symposium. The study population were patients who had undergone PCI and were prescribed clopidogrel alone or clopidogrel plus a PPI. Patients with no preceding cardiovascular disease taking PPIs had a 32.5% incidence of a major cardiovascular event within 1 year versus 21.2% of patients not taking a PPI (adjusted OR 1.79, 95% CI 1.62-1.97). Effects were more pronounced in patients with a preceding cardiovascular event (adjusted OR 1.86, 95% CI 1.63-2.12). However, confounding may be an issue and the study did not have information on valuable cardiovascular risk factors, such as smoking, blood pressure and serum cholesterol levels (50).

Data retrospectively analysed from 4800 patients admitted with acute myocardial infarction and subsequently receiving clopidogrel classified patients as no PPI exposure, low PPI exposure and high PPI exposure based upon adherence rates to PPIs (51). One year event rates for acute myocardial infarction were 1.38% for no PPI, 3.08% in the low exposure and 5.03% in the high exposure group. However, patients prescribed PPIs may be older with greater co-morbidity, and indeed this is the case in this study which limits the applicability of

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3 the results; after adjustment, the high exposure group still had a relative risk of 337%
4 compared to the no exposure group.
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8 Further evidence suggesting a clinically relevant interaction comes from the retrospective
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10 analysis of 8205 patients from Veteran Affairs hospitals between 2003-2006 who had been
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12 admitted with ACS (42). Of these patients 63.9% were prescribed PPI at discharge, during
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14 follow up or both: omeprazole n=3132, rabeprazole n=151, lansoprazole n=22, pantoprazole
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16 n=15, more than one PPI n=1924. Death or rehospitalisation for ACS occurred in 20.8% of
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18 patients prescribed clopidogrel without PPI and 29.8% of patients prescribed clopidogrel plus
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20 a PPI. The use of a PPI during any point was associated with an increased risk of death or
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22 rehospitalisation with ACS – Odds Ratio (OR) 1.25 (95% CI 1.11-1.41). Adjusted OR for all
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24 cause mortality revealed no difference between the two groups. The authors, however,
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26 conclude that concomitant use of clopidogrel and a PPI may be associated with an attenuation
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28 of the benefits of clopidogrel but stop short of confirming a causal relationship. Again, one
29
30 limitation of this study is the difference in baseline characteristics – those prescribed a PPI
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32 tended to be older with more comorbidity (e.g. diabetes, prior MI, heart failure, CVA, COPD,
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34 renal and liver disease) and may therefore represent a population with a higher risk of adverse
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36 outcomes, rather than PPIs being the problem.
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46 One Canadian population based study examined patients admitted with acute myocardial
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48 infarction between 2002-2007 (9). PPI prescribing was common – 31% of patients receiving
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50 a PPI within 90 days of discharge. The authors report a significant association between
51
52 readmission due to MI and current use of a PPI (adjusted OR 1.27, 95%CI 1.03-1.57) and a
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54 40% increase in recurrent MI within 90 days (OR 1.4, 95% CI 1.10-1.77). Pantoprazole and
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56 histamine receptor antagonists were not associated with adverse outcomes. Unfortunately the
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58 number of prescriptions and breakdown of which PPI was prescribed is not given. As with
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3 the previous study (42), the baseline characteristics varied considerably. Those on a PPI had
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5 greater comorbidity with higher rates of renal failure, diabetes and congestive cardiac failure.
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8 The study also lacked data on smoking status and blood pressure. Again, because of these
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10 differences it is unclear if the adverse outcomes observed are related to PPI use or to
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12 confounding factors such as comorbidity (52).
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15 Thus, the results seen from these observational studies may simply reflect a greater tendency
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17 to prescribe prophylactic PPIs to patients at higher risk of cardiovascular events (12,53).
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For Peer Review

Clinical evidence - evidence against a clinically relevant interaction

The first data against an interaction was presented in abstract format at the AHA Scientific Sessions 2008 Symposium was in direct conflict with Medco data presented at the same meeting (50,54). In this retrospective analysis of the Clopidogrel for the Reduction of Events During Observation (CREDO) Trial, no increase in cardiovascular or cerebrovascular events was seen in the clopidogrel-PPI group at 1 year.

Perhaps the most definitive data on whether mechanistic changes translate into clinical data come from over 13000 patients participating in the Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in Myocardial Infarction (PRINCIPLE-TIMI) 44 and Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition with Prasugrel-TIMI (TRITON-TIMI) 38 studies. Both studies were subanalysed to look at individual PPI use and showed no association between PPI and adverse cardiovascular outcomes. The authors found no independent association between any of the PPIs and the risk of MI or cardiovascular death (55). These two randomised trials studied over 13000 patients. There was no difference among the PPIs used: omeprazole (n=1675), lansoprazole (n=441), esomeprazole (n=613), pantoprazole (n=1844). As with previous studies patients taking PPIs were older and sicker, with more frequent history of peptic ulcer disease and lower baseline haemoglobin. After adjustment for confounders, no significant association between use of a PPI and risk of primary endpoint (composite of cardiovascular death, non-fatal-MI, or non-fatal stroke) with HR 0.94 (95% CI 0.80-1.11, p=0.46). Consistent PPI use (i.e. use of PPI for the whole duration of follow up) was not associated with an increased risk of cardiovascular death, MI or stroke in patients treated with clopidogrel (HR 1.05, 95% CI 0.85-1.30). An accompanying editorial commended the work

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3 but highlighted that the patients included in the TRITON-TIMI trial were much younger, with
4 less diabetes or renal failure than those in the previously highlighted observational studies
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8 (56).
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12 Rassen *et al* analysed data of 64561 patients who underwent PCI or hospitalisation for ACS
13 between 2001 and 2005 (53). Crude rates of MI hospitalisation or death were higher in the
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18 PPI group with a relative risk of 1.74 (CI 1.44-2.10). However, after multivariable adjustment
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21 the RR fell to 1.32 (CI 1.08-1.61). With high-dimensional propensity score (hd-PS)
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24 adjustment a RR of 1.22 (CI 0.99-1.51) for MI hospitalisation or death was seen. Thus, no
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27 statistically significant clopidogrel-PPI interaction is seen.
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30 Zairis *et al*'s study of 588 patients undergoing PCI showed no difference in cardiovascular
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33 outcomes in the PPI (omeprazole only n=340) group at 1 year (57). The primary endpoint
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36 was defined as cardiac death or rehospitalisation with for a non-fatal MI. This endpoint was
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39 reached by 10% in PPI group and 9.7% in the no PPI group – hazard ratio 1.1 (95% CI 0.6-
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42 1.8). The study groups were well matched in terms of baseline characteristics which is in
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45 contrast to other studies where patients on a PPI were older and with more comorbidity
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48 (9,42).
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51 The genetic determinants of response to clopidogrel have been evaluated and the use of
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54 omeprazole, or any other PPI, had no effect on the clinical response to clopidogrel (17). A
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57 large retrospective analysis of 20596 Medicare patients again drew negative results with
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60 regards to the effect any drug interaction had on clinical events. Those patients receiving both
clopidogrel and a PPI (pantoprazole n=4707, omeprazole n=683) had a HR 0.99 (CI 0.82-
1.19) for serious cardiovascular disease (ACS or revascularisation). The study also raises the

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3 importance of PPIs in this group of patients with regards to reducing the incidence of
4 gastrointestinal bleeding. In those patients receiving concurrent PPI the incidence of
5 hospitalisation with gastrointestinal bleeding was 50% lower than those not prescribed a PPI
6 (58).
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15 The recently published Clopidogrel and the Optimisation of Gastrointestinal Events
16 (COGENT) trial is the first, and only, prospective study of the potential interaction (59). The
17 study was well designed specifically to address the issue of a clinically relevant interaction.
18 Unfortunately the trial was halted early due to bankruptcy of its sponsor with 3873 of 5000
19 patients enrolled. The study groups were well matched. With respect to cardiovascular
20 outcomes 109 patients had an event (MI, stroke, coronary artery bypass graft, PCI, CV
21 death), 4.9% and 5.7% with omeprazole and placebo respectively (HR 0.99, 95% CI 0.68-
22 1.44). In addition, overt upper gastrointestinal bleeding was reduced in those patients
23 prescribed a PPI (HR 0.13, 95% CI 0.03-0.56). The authors err on the side of caution,
24 however, stating “that the results do not rule out a clinically meaningful difference in
25 cardiovascular events due to use of a PPI.” This is due to a low number of clinical events
26 during follow up and, as a result, wide confidence intervals.
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46 It should be highlighted that confounding can have a significant effect on results and their
47 subsequent interpretation. Work by Valkhoff et al has highlighted the problems with
48 confounding by indication when analysing data retrospectively collected regarding the use of
49 PPIs with clopidogrel (60). This analysis examined 23655 patients admitted with MI, with
50 1247 readmitted with recurrent MI. All PPIs were included in the analysis. PPI users were
51 noted to be older, with more co-morbidity and co-medication. With current users of
52 clopidogrel, current PPI use was associated with recurrent MI (OR 1.62, 95% CI 1.15-2.27).
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3 However, when applying past PPI use as the reference category, rather than PPI non-use, no
4 association between recurrent MI and current PPI use was noted (OR 0.95, 95% CI 0.38-
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8 2.41). The authors suggest that the observed association between current PPI use and
9
10 recurrent MI when PPI non-use was the reference may be the result of residual confounding.
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For Peer Review

Does bleeding have an impact?

An alternative hypothesis is that bleeding *per se* in the ACS setting is bad. Indeed, bleeding in the context of ACS is an independent risk for poor short and long term clinical outcomes (61-64). Therefore, it may not be that PPIs are associated with adverse clinical outcomes but that patients taking them may have had a history of bleeding resulting in PPI prescription or may be deemed at high risk of bleeding. A bleeding episode could lead to a prolonged prothrombotic state which in turn leads to increased adverse clinical events. This is an area which requires further studies to clarify.

Other possibilities include that PPIs do have a direct effect on cardiovascular risk, or that PPIs interact with clopidogrel but it is individuals with genetic polymorphism of the gene encoding CYP2C19 leading to loss-of-function that may be more susceptible to this interaction. The TRITON-TIMI 38 study examined those patients with a loss-of function CYP2C19 polymorphism and current PPI use in patients prescribed clopidogrel. The study was underpowered to address this specific point, however, no association of increased adverse events was observed (HR 0.76, CI 0.39-1.48) (55).

Ultimately though, the association between clopidogrel and PPIs is likely to suffer from channelling bias – that is that physicians tend to prescribe PPIs to patients with more severe underlying illness (65).

Further controversy for PPIs?

In addition to the concerns regarding clopidogrel there are also conflicting reports on the use of PPIs with aspirin. Studies have shown that omeprazole has the ability to reduce the absorption and bioavailability of aspirin in animals (66) and by doing so has the ability to reduce the analgesic and antipyretic effects (67).

However, with respect to aspirin the interaction is thought to lie in the PPIs ability to increase intragastric pH and thereby reduce the absorption and thus bioavailability of aspirin, rather than inhibit the enzymes that metabolise it, as is the mechanism with clopidogrel. Aspirin is normally absorbed in a lipid-soluble state by diffusion. By increasing intragastric pH above the pKa of aspirin absorption is reduced (66,68)

Unfortunately, as with the clopidogrel interaction, there is ongoing debate as to the importance and accuracy of the aspirin-PPI interaction in humans. Two studies on small numbers of patients report that PPIs do not interfere with the antiplatelet effects of aspirin; one studied omeprazole (69) and the other lansoprazole (70) in 14 and 24 patients respectively. One study, however, reported enhanced antiplatelet activity of aspirin when co-administered with pantoprazole (71). The largest study examining this interaction which enrolled 418 patients with stable coronary disease found that the antiplatelet effect of aspirin was reduced by PPIs (72).

Conclusion

Although, the current data are conflicting, much concern has been raised in the medical press regarding the potential negative effects of PPIs on the efficacy of clopidogrel. There is extensive evidence demonstrating that PPIs do have an effect on the pharmacokinetics and pharmacodynamics of clopidogrel, but it is important to highlight that abnormal laboratory indices do not always translate into clinically relevant interactions.

Patients who have a GI bleed have increased mortality, and the protection PPIs offer against such events is not to be underestimated (73). Based on the available evidence, the decision to prescribe a PPI to a patient on clopidogrel should be made after an individual risk assessment balancing gastrointestinal bleeding risk against thrombotic risk. Further prospective randomised clinical trials are needed, but in the meantime, we must be careful not to jump to the wrong conclusions, and deny our patients the protection that PPIs clearly offer, compared with a concern about cardiovascular outcomes that has not yet been proven. However, a clinically important interaction cannot be excluded in certain groups such as those patients with loss-of-function polymorphisms and further work should be aimed at this area.

Table 1. Summary of studies examining the interaction between clopidogrel and PPIs

Author	Ref.	PPI	No. of patients on PPI & clopidogrel	Study design	Results & Conclusion
Ho	42	NA	5244	Retrospective	OR 1.25 for death or rehospitalisation for PPI group. Positive link.
Juurlink	9	POLR	734	Retrospective	OR 1.4 (CI 1.1-1.77) for OLR for reinfarction. OR 1.02 (CI 0.7-1.47) for P for reinfarction. Positive link.
Aubert	50	NA	4521	Retrospective	OR 1.86 (CI 1.63-2.12) for PPI group. Positive link.
Pezalla	51	NA	712	Retrospective	5% rate of MI at 1 year in high PPI exposure group (1.38% in controls) Positive link.
Dunn	54	NA	176	Retrospective	OR 1.63 (CI 1.01-2.63) for PPI group. No link.
O'Donoghue	55	POEL	4529	Retrospective	AHR 0.94 for primary endpoint. ^a No link.
Rassen	53	POELR	3996	Retrospective	ARR for MI/death 1.22 (CI 0.99-1.51). No link.
Zairis	57	O	340	Retrospective	HR for MI/death 1.1 (CI 0.6-1.8). No link.
Simon	17	POELR	NA	Retrospective	PPI had no effect on clinical response to clopidogrel. No link.
Ray	58	POELR	7593	Retrospective	HR for CVS events 0.99 (CI 0.82-1.19)
Bhatt	59	O	1876	Prospective	HR 0.99 (CI 0.68-1.44) No link.

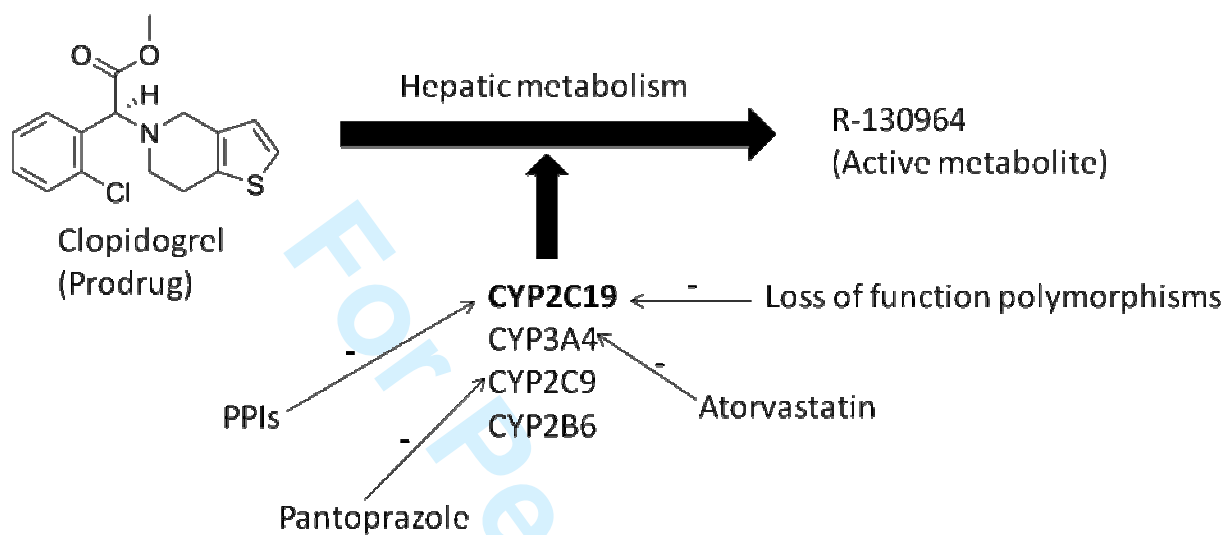
P = pantoprazole, O = omeprazole, E = esomeprazole, L = lansoprazole, R = rabeprazole, OR = odds ratio, HR = hazard ratio, AHR = adjusted hazard ratio, MACE = major adverse cardiac event, ARR = adjusted rate ratio, NA = not available, MI = myocardial infarction
^a = composite of cardiovascular death, non-fatal MI or non-fatal stroke.

Key points

- Clopidogrel is a pro-drug requiring metabolism into an active metabolite by CYP450 enzymes to exhibit its antiplatelet effect
- The key enzyme in the metabolism of clopidogrel is CYP2C19
- The metabolism of clopidogrel can be influenced by genetic polymorphisms and drug interactions
- Several studies demonstrate a pharmacological interaction between clopidogrel and PPIs
- One prospective study found no clinically relevant interaction between clopidogrel and PPIs, although numbers of events were small
- Controversy remains as to the significance of the clopidogrel-PPI interaction

Figure 1. Metabolism of clopidogrel.

Following intestinal absorption, clopidogrel undergoes a two step process to form its active metabolite. These processes are dependent on various cytochrome P450 (CYP450) enzymes.



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Table 1. Summary of studies examining the interaction between clopidogrel and PPIs

Author	Ref.	PPI	No. of patients on PPI & clopidogrel	Study design	Results & Conclusion
Ho	42	NA	5244	Retrospective	OR 1.25 for death or rehospitalisation for PPI group. Positive link.
Juurlink	9	POLR	734	Retrospective	OR 1.4 (CI 1.1-1.77) for OLR for reinfarction. OR 1.02 (CI 0.7-1.47) for P for reinfarction. Positive link.
Aubert	50	NA	4521	Retrospective	OR 1.86 (CI 1.63-2.12) for PPI group. Positive link.
Pezalla	51	NA	712	Retrospective	5% rate of MI at 1 year in high PPI exposure group (1.38% in controls) Positive link.
Dunn	54	NA	176	Retrospective	OR 1.63 (CI 1.01-2.63) for PPI group. No link.
O'Donoghue	55	POEL	4529	Retrospective	AHR 0.94 for primary endpoint. ^a No link.
Rassen	53	POELR	3996	Retrospective	ARR for MI/death 1.22 (CI 0.99-1.51). No link.
Zairis	57	O	340	Retrospective	HR for MI/death 1.1 (CI 0.6-1.8). No link.
Simon	17	POELR	NA	Retrospective	PPI had no effect on clinical response to clopidogrel. No link.
Ray	58	POELR	7593	Retrospective	HR for CVS events 0.99 (CI 0.82-1.19)
Bhatt	59	O	1876	Prospective	HR 0.99 (CI 0.68-1.44) No link.

P = pantoprazole, O = omeprazole, E = esomeprazole, L = lansoprazole, R = rabeprazole, OR = odds ratio, HR = hazard ratio, AHR = adjusted hazard ratio, MACE = major adverse cardiac event, ARR = adjusted rate ratio, NA = not available, MI = myocardial infarction
^a = composite of cardiovascular death, non-fatal MI or non-fatal stroke.

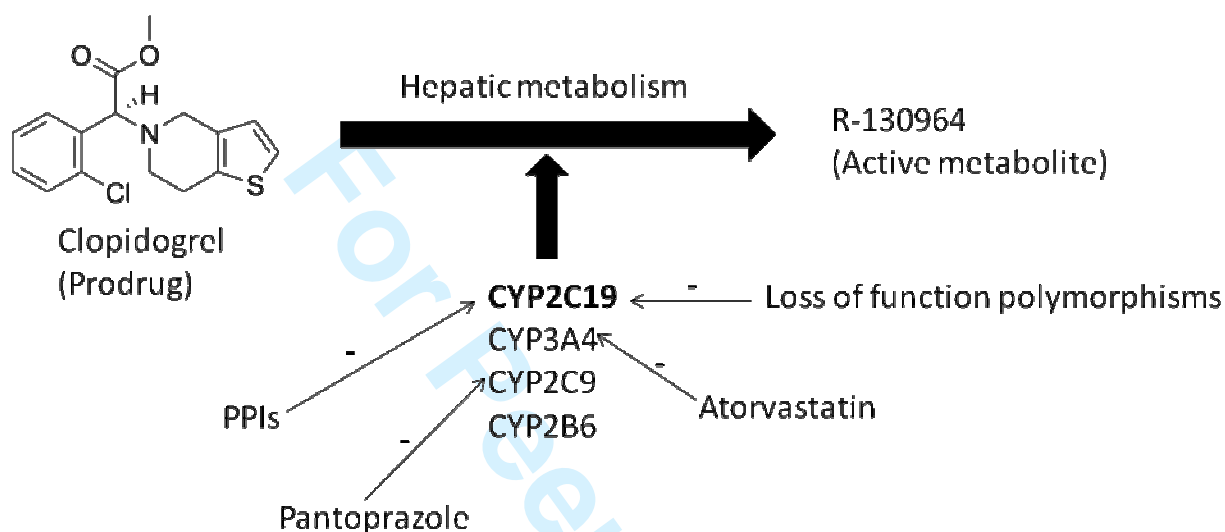
Key points

- Clopidogrel is a pro-drug requiring metabolism into an active metabolite by CYP450 enzymes to exhibit its antiplatelet effect
- The key enzyme in the metabolism of clopidogrel is CYP2C19
- The metabolism of clopidogrel can be influenced by genetic polymorphisms and drug interactions
- Several studies demonstrate a pharmacological interaction between clopidogrel and PPIs
- One prospective study found no clinically relevant interaction between clopidogrel and PPIs, although numbers of events were small
- Controversy remains as to the significance of the clopidogrel-PPI interaction

For Peer Review

Figure 1. Metabolism of clopidogrel.

Following intestinal absorption, clopidogrel undergoes a two step process to form its active metabolite. These processes are dependent on various cytochrome P450 (CYP450) enzymes.



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