



HAL
open science

Risk of recurrent myocardial infarction with the concomitant use of clopidogrel and proton pump inhibitors.

Vera E. Valkhoff, Geert W.T Jong, Eva Marianne van Soest, Ernst J Kuipers,
Miriam C Sturkenboom

► **To cite this version:**

Vera E. Valkhoff, Geert W.T Jong, Eva Marianne van Soest, Ernst J Kuipers, Miriam C Sturkenboom. Risk of recurrent myocardial infarction with the concomitant use of clopidogrel and proton pump inhibitors.. *Alimentary Pharmacology and Therapeutics*, 2010, 33 (1), pp.77. 10.1111/j.1365-2036.2010.04485.x . hal-00599494

HAL Id: hal-00599494

<https://hal.science/hal-00599494>

Submitted on 10 Jun 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Risk of recurrent myocardial infarction with the concomitant use of clopidogrel and proton pump inhibitors.

| | |
|-------------------------------|--|
| Journal: | <i>Alimentary Pharmacology & Therapeutics</i> |
| Manuscript ID: | APT-0591-2010.R1 |
| Wiley - Manuscript type: | Original Scientific Paper |
| Date Submitted by the Author: | 23-Sep-2010 |
| Complete List of Authors: | Valkhoff, Vera; Erasmus MC, Gastroenterology and Hepatology; Erasmus MC, Medical Informatics 't Jong, Geert; Erasmus MC, Medical Informatics van Soest, Eva; Erasmus MC, Medical Informatics Kuipers, Ernst J; Erasmus MC, Gastroenterology and Hepatology; Erasmus MC, Internal Medicine Sturkenboom, Miriam; Erasmus MC, Medical Informatics; Erasmus MC, Epidemiology |
| Keywords: | Peptic ulcer disease < Disease-based, Clinical pharmacology < Topics, Epidemiology < Topics, Outcomes research < Topics, Guidelines < Topics, Non-variceal bleeding < Topics |
| | |

1
2 1 Risk of recurrent myocardial infarction with the concomitant use of clopidogrel
3
4 2 and proton pump inhibitors.
5

6
7 3 Vera E. Valkhoff^{1,2}, Geert W. 't Jong², Eva M. van Soest², Ernst J. Kuipers^{1,3}, and Miriam
8
9 4 C.J.M. Sturkenboom^{2,4}
10

11
12 5
13
14 6 ¹Department of Gastroenterology and Hepatology, Erasmus University Medical Centre,
15
16 7 Rotterdam, The Netherlands.
17

18
19 8 ²Department of Medical Informatics, Erasmus University Medical Centre, Rotterdam, The
20
21 9 Netherlands.
22

23
24 10 ³Department of Internal Medicine, Erasmus University Medical Centre, Rotterdam, The
25
26 11 Netherlands.
27

28
29 12 ⁴Department of Epidemiology, Erasmus University Medical Centre, Rotterdam, The
30
31 13 Netherlands.
32

33 14
34 15 Address correspondence and reprint requests to:

35
36 16 V.E. Valkhoff, Department of Gastroenterology and Hepatology,
37
38 17 Erasmus University Medical Centre, Postbus 2040, 3000 CA Rotterdam, The Netherlands
39

40 18 Telephone number: 0031-10-7044116

41
42 19 E-mail: v.valkhoff@erasmusmc.nl

43
44 20 Fax number: 0031-10-7044722
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2 1 Authors' declaration of personal interests:
3

4 2 V.Valkhoff, E.van Soest, and G. 't Jong do not have any conflicts to declare.
5

6 3 As employee of Erasmus MC, M. Sturkenboom has been involved as project leader and in
7

8 4 analyses contracted by various pharmaceutical companies. She received unconditional
9

10 5 research grants from AstraZeneca, Pfizer, Merck, Johnson&Johnson, Amgen, Roche, GSK,
11

12 6 Boehringer, Yamanouchi, and Altana, none of which are related to the subject of this study.
13

14 7 M. Sturkenboom has been consultant to Pfizer, Servier and Lundbeck on issues not related to
15

16 8 this manuscript. E. Kuipers has served as a speaker and advisory board member for
17

18 9 AstraZeneca.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1 Key words:
- 2
- 3
- 4
- 5 2 Proton pump inhibitors
- 6
- 7
- 8 3 Clopidogrel
- 9
- 10
- 11 4 Myocardial infarction
- 12
- 13 5 Case-control study
- 14
- 15
- 16 6
- 17
- 18 7 Type of article: Original investigation
- 19
- 20
- 21 8 Word count abstract: 190
- 22
- 23
- 24 9 Word count body text: 3912 words
- 25
- 26 10 References: 31
- 27
- 28
- 29 11 Number of tables: 5
- 30
- 31
- 32 12 Number of figures: 1
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

Deleted: 200

Deleted: 3572

For Peer Review

1
2 **Abstract**
3

4 *Background:* The association between myocardial infarction (MI) and co-administration of
5
6
7 PPIs and clopidogrel remains controversial.

8
9
10 *Aim:* To quantify the association between concomitant use of PPIs and clopidogrel and
11
12 occurrence of recurrent MI.

13
14 *Methods:* We conducted a case-control study within a cohort of acute MI patients in
15
16 PHARMO Record Linkage System (1999-2008). Cases were patients readmitted for MI. PPI
17
18 exposure was categorized as current (3-1 days before MI), past (30-3 days before MI), or no
19
20 use (>30 days before MI). We used conditional logistic regression analyses.

21
22
23 *Results:* Among 23,655 patients hospitalized following MI, we identified 1,247 patients
24
25 readmitted for MI. Among clopidogrel users, current PPI use was associated with an increased
26
27 risk of recurrent MI (OR:1.62, 95%CI:1.15-2.27) when compared to no PPI use, but not when
28
29 compared to past PPI use (OR:0.95, 95%CI:0.38-2.41). Among clopidogrel-non-users, current
30
31 PPI use was associated with an increased risk of recurrent MI (OR:1.38, 95%CI:1.18-1.61)
32
33 when compared to no PPI use.

Deleted: , but not when compared to past PPI use (OR:1.22, 95%CI:0.79-1.88).

34
35
36 *Conclusions:* The apparent association between recurrent MI and use of PPIs with clopidogrel
37
38 depends on the design and is affected by confounding by indication. The association is not
39
40 present when (un)measured confounding is addressed by design.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Introduction

2 Clopidogrel is an oral antiplatelet agent commonly used in addition to aspirin to
3 reduce cardiovascular (CV) events. Clopidogrel is converted in the liver from an inactive pro-
4 drug to its active metabolite, that binds irreversible to P2Y₁₂ adenosine diphosphate (ADP)
5 receptors on the platelet surface, thereby preventing platelet aggregation ¹.

6 Clopidogrel conversion is catalyzed by several cytochrome P450 (CYP) enzymes, of
7 which CYP2C19 is the most important. Patients with loss-of-function polymorphisms in the
8 gene encoding for CYP2C19 have lower levels of the active metabolite and have reduced
9 platelet inhibition during clopidogrel treatment. This results in higher rates of acute
10 myocardial infarction (MI) ^{2,3}. In contrast, rapid metabolizers of clopidogrel (with CYP2C19
11 variants leading to increased enzyme activity) have a higher rate of clopidogrel activation and
12 more efficient platelet inhibition ⁴.

13 Proton pump inhibitors (PPIs) are routinely co-administered with clopidogrel to
14 prevent upper gastrointestinal (UGI) bleeding ⁵⁻⁷, which is in line with expert consensus
15 guidelines ⁸. PPIs are also metabolized by CYP2C19, and can competitively bind to its
16 catalytic site. Therefore, PPIs are potentially hindering the conversion of clopidogrel to its
17 active metabolite. Both the European Medicines Agency (EMA) and the US Food and Drug
18 Administration (FDA) recently advised against the concurrent use of PPIs and clopidogrel in
19 the absence of a strong indication ^{9,10}, because several pharmacodynamic ¹¹⁻¹⁴ and clinical
20 outcome studies ¹⁵⁻²⁰ suggest a detrimental interaction between clopidogrel and PPIs.

21 Evidence on the association between cardiovascular events and co-administration of
22 PPIs with clopidogrel remains inconclusive. Observational studies show a small increased risk
23 of recurrent MI in patients using PPI – clopidogrel combination therapy compared to those

1 | using clopidogrel alone. Estimated relative risks vary from 0.92 to 1.93^{2, 7, 13, 15-20}. These
2 | results are likely influenced by confounding by indication. Confounding by indication is
3 | introduced when more severely ill patients with a worse prognosis are more likely to receive
4 | PPIs than healthier patients. Furthermore, some published observational studies may have
5 | suffered from immortal time bias^{15,21}. Both biases could distort the studied association in
6 | either directions.

Deleted: with

Deleted: different

7 | Other studies failed to show an interaction between the use of PPIs and clopidogrel^{2, 6,}
8 | ^{7, 13, 19, 22, 23}. Recently, results of a post hoc analysis of a randomized trial revealed no
9 | association between PPI use and the risk of the primary CV endpoint for patients treated with
10 | clopidogrel or the novel thienopyridine prasugrel (a prodrug also requiring metabolism
11 | through CYP enzymes)¹³. The main limitation of this randomized trial was that use of a PPI
12 | was not randomized. Preliminary analysis (pre-specified sample size and follow-up time not
13 | reached) of the unpublished Clopidogrel and the Optimization of Gastrointestinal Events
14 | (COGENT) trial, a randomized double-blind trial of omeprazole 20 milligram (mg) vs.
15 | placebo in patients taking dual therapy (clopidogrel and aspirin) demonstrated no significant
16 | difference in CV events between both study arms (hazard ratio = 1.02, 95% CI: 0.70-1.51)⁶.

17 | Because of the potential clinical consequences for a large patient group at risk for both
18 | recurrent CV as well as UGI events, residual uncertainty about this potential drug-drug
19 | interaction should be minimized. Therefore, we conducted a nested case-control study using
20 | data from the PHARMO Record Linkage System (RLS) (1999-2008) to quantify the
21 | association between use of PPIs and recurrent MI in the absence or presence of clopidogrel,
22 | while addressing the issues of both study design (avoidance of immortal time bias) and
23 | residual confounding (using past exposure to PPIs as the reference category and propensity
24 | score-based adjustments).

1
2 1 **Patients and Methods**
3

4
5 2

6
7 3 *Study design*
8
9

10 4 A population-based nested case-control study (1999-2008) was conducted within a
11 cohort of patients admitted for acute MI during the study period.
12
13

14 6

15
16
17 7 *Setting*
18
19

20 8 The study was conducted using data from the PHARMO RLS. This system comprises
21 drug-dispensing records mostly from community pharmacies and hospital discharge records
22 of more than three million inhabitants of 50 demographically defined areas in the
23 Netherlands. For all participants, the computerized drug-dispensing histories contain data
24 concerning the name of the dispensed drug, dispensing date, dispensed amount, prescribed
25 dosing regimens, and the legend duration of use (prescription length). All drugs are coded
26 according to the Anatomical Therapeutic Chemical (ATC) classification²⁴. The hospital
27 records include detailed information concerning discharge diagnosis, procedures, dates of
28 hospital admission and discharge, discharge destination (or death in the hospital before
29 discharge). Diagnoses are **consistently** classified according to the International Classification
30 of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) **during the entire study**
31 **period**. For a detailed description of the database we refer to a previous publication²⁵.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

20
21 21 *Study cohort*

1
2 1 The study cohort included all patients in the PHARMO RLS who were hospitalized
3
4 2 between January 1st, 1999 and December 31st, 2008 for a primary diagnosis of acute MI.
5
6 3 Cohort entry was date of discharge from hospital of an acute MI, registered as a primary
7
8 4 discharge diagnosis code 410 according to ICD-9-CM. **Secondary diagnoses were not queried,**
9
10 5 **because it is likely that prevalent MI events (co-morbidity) are recoded as secondary**
11
12 6 **diagnosis. Because of the dynamic study population,** patients were required to have had one
13
14 7 prescription filled at least one year preceding the date of cohort entry (i.e. one year of valid
15
16 8 database history) in order to allow uniform assessment of **the presence of co-morbidity and**
17
18 9 **confounding factors.** Patients were followed from cohort entry until diagnosis of recurrent MI,
19
20 10 last filled prescription, or the end of the study period (December 31st, 2008), whichever came
21
22 11 first.

Deleted: baseline characteristics

23 24 25 12 26 27 13 *Case selection*

28
29
30 14 The study outcome was hospitalization for a subsequent acute MI, registered as
31
32 15 primary diagnosis ICD-9-CM code 410. Only the first encountered recurrent acute MI during
33
34 16 follow-up was included in the analysis. The date of rehospitalization for the MI was used as
35
36 17 index date. To avoid misclassification of the exposure, we required a 30-day period between
37
38 18 discharge from baseline MI and recurrent MI, since outpatient time was needed to observe
39
40 19 filling of outpatient prescriptions. In a sensitivity analysis, we used the requirement of a 90-
41
42 20 day period between discharge from baseline MI and recurrent MI.

43 44 45 21 46 47 22 *Control selection*

1 For each case readmitted for acute MI, controls were randomly selected from the
 2 cohort, matched on gender, age (same year of birth), being at risk of a recurrent MI, and
 3 calendar time by means of incidence density sampling²⁶. **Only those controls were considered**
 4 **to be at risk of developing a recurrent MI when they had a baseline acute MI \geq 30 days prior**
 5 **to the index date.**

Deleted: (i.e. having had a baseline acute MI \geq 30 days prior to the index date)

6 *Definition of exposure*

7 Drug exposure data were obtained from outpatient drug dispensing files of community
 8 pharmacies, as recorded in the PHARMO RLS. The exposures of interest were clopidogrel
 9 and PPIs. PPIs included in the analyses were omeprazole, pantoprazole, lansoprazole,
 10 rabeprazole, and esomeprazole. Duration of use was obtained by dividing the total amount of
 11 dispensed units by the prescribed amount per day. **We calculated the end of each prescription**
 12 **by adding the duration to the dispensing date.**

13 Clopidogrel use was classified at the index date as either “no” use (no use or use at
 14 least 30 days before index date), “past” use (end of prescription between seven and 30 days
 15 before the index date), or “current” use (use at index date, or end of prescription less than
 16 seven days before index date). Because half-time values of PPIs are short (a few hours), the
 17 current, past, and no use of PPIs was defined differently: “no” use (no use or use at least 30
 18 days before index date), “past” use (end of prescription between three and 30 days before
 19 index date), and “current” use (use at index date, or end of prescription less than three days
 20 before index date). To avoid protopathic bias, only prescriptions dispensed at least one day
 21 before index date were considered “current” use. In sensitivity analyses, the definition of past
 22 PPI use (which was the reference) was adjusted to use between three to 90 days or between 14
 23

Deleted: final

Deleted: date

Deleted: final

Deleted: date

Deleted: final

Deleted: date

Deleted: final

Deleted: date

1
2 1 and 90 days preceding the index date. In the latter case the definition of “current” PPI
3
4 2 switched to use at index date, or final prescription date less than 14 days before index date.
5
6 3 The study is not subject to immortal time bias as the outcome under study could be assessed
7
8 4 equally for cases and controls after the 30- or 90-day period.
9

10 5

11
12
13 6 *Covariates*
14

15
16 7 At baseline, we considered the following factors as potential covariates: percutaneous
17
18 8 transluminal coronary artery angiography (PTCA) within 30 days of baseline MI, prior
19
20 9 hospitalization for cardiogenic shock, congestive heart failure, cancer, cerebrovascular
21
22 10 disease, acute renal failure, chronic renal failure, cardiac dysrhythmia (including atrial
23
24 11 fibrillation), or upper gastrointestinal (UGI) ulcer. The covariate diabetes mellitus was a
25
26 12 combination of prior hospitalization for diabetes mellitus and anti-diabetic drug use. As a
27
28 13 proxy for (the degree of) comorbidity, we aggregated all prescriptions per ATC-code in the
29
30 14 one year preceding cohort entry and we refer to this ‘score’ as the number of different
31
32 15 prescriptions. Additionally, we considered use of commonly prescribed cardiovascular
33
34 16 medications (anti-hypertensive drugs, low-dose acetylsalicylic acid, β -adrenergic antagonists,
35
36 17 digoxin, and lipid lowering drugs) or NSAIDs at baseline. We defined comorbidity and
37
38 18 medication at baseline rather than at recurrent MI to avoid adjustment on intermediates in the
39
40 19 pathway from exposure to outcome. Medications inducing or inhibiting cytochrome P450
41
42 20 2C19 or cytochrome P450 3A4 (directly affecting levels of clopidogrel and PPIs)²⁷, as well
43
44 21 as standard secondary prevention medications such as lipid lowering drugs and anti-
45
46 22 hypertensive agents were assessed at the index date. Furthermore, days of follow-up (number
47
48 23 of days between date of discharge of baseline MI and index date) and length of hospital stay
49
50 24 for the baseline MI were also considered as covariates.

1
2 1 Because the use of PPIs was not randomly assigned, we developed a propensity score
3
4 2 (summary exposure risk score). The propensity score represents the likelihood of exposure to
5
6 3 a PPI for each individual patient²⁸. The propensity score for use of PPI was developed using
7
8 4 logistic regression modeling. The log odds of the probability that a patient received a PPI at
9
10 5 any point of time during follow-up was modeled as a function of all previously described
11
12 6 baseline covariates and was included in our dataset as a separate confounder. The PPI
13
14 7 propensity score was only included in the adjusted analysis when it changed the odds ratio
15
16 8 with more than 10 percent, unless we adjusted for individual covariates, to avoid double
17
18 9 adjustment for the same covariate.

19
20 10 Statistical significance was assumed for two-sided p-values <0.05. All statistical
21
22 11 analyses were performed using SPSS software version 15.0 (SPSS inc, Chicago, Ill).
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Results

2 The initial study population comprised 27,513 patients who were admitted to the
3 hospital with an acute MI during follow-up. After exclusion of patients of whom not one year
4 of valid data before baseline MI was available, the final cohort comprised 23,655 patients.
5 The mean age was 64.7 (\pm standard deviation (SD) 13.2) years and 15,897 (67.2%) were
6 male. The median follow-up time after discharge was 42.6 months (interquartile range (IQR)
7 16.8 to 71.7 months). Co-morbidity at baseline was substantial: 4.4% of patients had been
8 hospitalized for cancer, 3.3% for cardiac dysrhythmia, and 2.8% for cerebrovascular disease.
9 Prevalence of diabetes mellitus was 21.6%. The median number of distinct prescribed drugs
10 in the one year before cohort entry was 5 (IQR 2 to 9 prescriptions) (Table 1; column 2). At
11 baseline, 10.5% of the patients used proton pump inhibitors (PPIs) and 315 patients (1.3%)
12 used clopidogrel.

13 Figure 1 shows that prescription rates of both PPIs and clopidogrel changed over time
14 between January 1st, 1999 and December 31st, 2008, illustrating the increased use of the
15 study drugs over a decade.

16 Within the study cohort, 1,247 patients were readmitted to the hospital with an acute
17 MI. The risk of a recurrent MI at least 30 days after discharge was 2.8% (95% CI: 2.6% -
18 3.0%) in the first year, and 10.3% (95% CI: 9.1% - 11.5%) in 10 years.

19 Of the cases **with a recurrent MI**, 1,224 (98.2%) could be matched to at least one
20 control **without a recurrent MI**. Characteristics of cases and controls (in the unexposed group
21 **to PPIs**) are depicted in Table 1 (Columns 3 and 4). As expected, cases were more likely to
22 have been hospitalized for co-morbidities associated with an increased risk of recurrent MI,
23 such as congestive heart failure and diabetes mellitus. At baseline, cases used several types of

1 cardiovascular drugs more frequently, for instance angiotensin-converting-enzyme (ACE)
2 inhibitors and lipid lowering drugs. To understand whether selective prescribing (channeling)
3 of PPIs to persons at increased risk of recurrent MI occurred, we assessed the presence of risk
4 factors in PPI users and PPI non-users (in patients who did not develop a recurrent MI) (Table
5 1; columns 5 and 6). Patients using PPIs were older, were more frequently male, had been
6 hospitalized more frequently prior to cohort entry for several co-morbid conditions, and more
7 frequently used cardiovascular medications at baseline.

Deleted: control group

8 Among current clopidogrel users, a significant association was observed between
9 current PPI use and recurrent MI when compared to PPI non-use (OR: 1.62, 95% CI: 1.15-
10 2.27). When applying past PPI use as the reference category rather than PPI non-use, we
11 found no association between recurrent MI and current use of PPI (OR: 0.95, 95% CI: 0.38-
12 2.41) (Table 2). Repeated analyses with variations in the definition of past PPI use (3 to 90
13 days or 14 to 90 days) did not affect the study findings appreciably; OR: 1.15, 95% CI: 0.51-
14 2.61, and OR: 1.34, 95% CI: 0.50-3.62, respectively.

15 Among clopidogrel non-users, current use of PPI was associated with recurrent MI
16 when compared to PPI non-use (OR:1.38, 95% CI: 1.18-1.61). When applying past PPI users
17 as the reference category, a weak association between recurrent MI and current use of PPI
18 was found (OR: 1.22, 95% CI: 0.79-1.88), although the latter's confidence interval cross the
19 null, which was likely due to insufficient power (Table 3).

Deleted: Among clopidogrel non-users, current use of PPI was associated with recurrent MI when compared to PPI non-use (OR:1.38, 95% CI: 1.18-1.61). When applying past PPI users as the reference category, no

20
21 The analysis by type of PPI among current clopidogrel users showed that pantoprazole
22 was most frequently used, followed by omeprazole and esomeprazole. Lansoprazole and
23 rabeprazole were rarely used. Using current pantoprazole as the reference category, current

Deleted: association between recurrent MI and current use of PPI was found (OR: 1.22, 95% CI: 0.79-1.88) (Table 3)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 use of omeprazole and of esomeprazole were not associated with an increased risk of
2 recurrent MI (respectively, OR: 1.07, 95 % CI: 0.58-1.99 and OR: 0.83, 95 % CI: 0.40-1.69,
3 respectively) (Table 4).

For Peer Review

1 Discussion

2 This population-based cohort study showed that the association between clopidogrel –
3 PPI co-therapy and risk of recurrent MI is highly affected by confounding by indication²⁹,
4 which **may** explain the contrasting results in the literature. To illustrate the problem of
5 confounding we compared current PPI users to none or past PPI users in the absence of
6 clopidogrel. To deal with the problem of confounding by indication, we compared current use
7 of clopidogrel plus current use of PPI not only to current clopidogrel without PPIs, but also to
8 current clopidogrel use plus past use of PPIs, which reduces confounding by indication. When
9 current PPI use was compared to past PPI use the association disappeared, suggesting that the
10 observed association between current PPI use and recurrent MI when PPI non-use was the
11 reference, may have been the result of residual confounding.

12 Our findings are in line both with other observational studies showing an increased
13 risk among PPI users when compared to PPI non-users¹⁵⁻²⁰, and those that did not find such
14 an association if better control of confounding was applied^{6, 13, 19, 30}. In observational studies
15 or post-hoc analyses in randomized controlled trials, the use of PPI is by definition not
16 randomly assigned, most likely leading to confounding by indication. It is arguable whether
17 adequate adjustment for this harmful type of confounding is possible since much of the
18 confounding will be subtle and unmeasurable. Design choices and progressive adjustment
19 techniques can be used to avoid residual confounding, as we have shown. By careful selection
20 of the study design one can match cases and controls on important covariates, including
21 calendar time. We illustrated the increased use of the study drugs over a decade (Figure 1),
22 and thereby the importance of matching on index date (thus calendar time) as potential
23 confounder. Additionally, one can use a so-called ‘active comparator’ as reference, such as
24 past users of PPIs instead of none users. For adjustment high-dimensional propensity scores

Deleted: s

19, summary disease risk scores (probability of short term mortality) ¹⁶, or conventional propensity scores ^{13,20} can be applied. Table 5 provides an overview of techniques used in other observational studies on this topic to deal with confounding by indication.

Our study further confirms the relevance of confounding, illustrated by the fact that PPI users had more co-morbidity and used more co-medication than PPI non-users at baseline and also by the results of the analysis in clopidogrel non-users. The increased risk for recurrent MI with current PPI use (OR 1.38, 95% CI: 1.18-1.61) compared to no PPI use in the absence of clopidogrel therapy provides further support for this. ~~Another explanation would be that PPIs have a harmful effect irrespective of clopidogrel status. We are aware of two studies that conducted similar analysis in clopidogrel non-users which also showed significantly elevated risks with PPI use (adjusted OR 1.29 and 1.55) compared to PPI non-use ^{23,31}. In two other observational studies however, no significant increase in CV events was shown in patients prescribed PPIs without clopidogrel ^{15,32}.~~

Deleted: alternative

Deleted: c

Deleted: one

Deleted: y

Deleted: performed

Deleted: a

We addressed the confounding issue by all possible design and adjustments measures, but still the comparison against none-use of PPI seemed confounded. Applying past PPI use as active comparator changed the association from increased to no effect and was the most powerful approach to deal with channeling of PPIs, more than adjustment for the propensity score. The propensity score did not have large explanatory power in this study due to the fact that relatively little clinical information was available to construct the score.

Our study is internally valid since we used a population-based design, so selection bias was unlikely as all cases and controls came from the same source population. The same pertains to information bias, because data were gathered prospectively without knowledge of the hypothesis studied. The method to control for confounding was discussed previously. The database is proven valid for research as the diagnoses are labeled with ICD-9-CM codes in

1
2 1 each hospital by official coding personnel from the national registry of hospitalization
3
4 2 discharge records and linked to pharmacies with complete information on outpatient
5
6 3 dispensing. In the Netherlands patients usually go to one pharmacy because of billing
7
8 4 purposes (invoices being directly sent to insurance without the need to pre-pay by patient) and
9
10 5 medication surveillance. The exposure drugs, clopidogrel and PPIs, are dispensed through
11
12 6 regular pharmacies. With regard to external validity, the individuals captured in the database
13
14 7 are representative for the entire population of the Netherlands in terms of age, gender, socio-
15
16 8 economic background, morbidity and mortality, drug use, and geographic distribution.

17
18
19 9 This study adds to the existing literature because we revealed the difficulties to deal
20
21 10 with confounding by indication in observational studies and we adjusted for confounding in
22
23 11 the most optimal way by applying past PPI use as the reference category. Furthermore, few
24
25 12 other studies could account for the use of low-dose aspirin as important risk factor for
26
27 13 recurrent MI^{19,20}. We avoided immortal time bias by assigning exposure to the category it
28
29 14 belongs to and not using follow-up time to define exposure. Immortal time bias alludes to the
30
31 15 fact that the outcome under study cannot be assessed when follow-up time is used to define
32
33 16 the exposure status. We used a time varying exposure assessment whereas some other cohort
34
35 17 studies applied a fixed exposure status^{13,20}, which leads to misclassification of exposure at
36
37 18 the index date (e.g. patients were defined at baseline as PPI non-users irrespective of changes
38
39 19 in PPI use during follow-up). In addition, we used an European database whereas many
40
41 20 published studies so far were conducted in North-America. None of the PPIs were available
42
43 21 over the counter during the study period and we have illustrated that there was no difference
44
45 22 in the risk of recurrent MI between esomeprazole, omeprazole, and pantoprazole.

46
47 23 There are several important limitations to this analysis. First, we were unable to study
48
49 24 actual drug utilization and adherence to dispensed drugs, because only dispensing data were

1 available in the database instead of more reliable proxies for drug use. Second, using the past
2 PPI group as reference, we may compare current PPI users to past PPI users who had not
3 been fully adherent to the prescribed PPI and therefore still had medication available and were
4 actually also current PPI users at the time of the recurrent MI. To address this point, we
5 conducted several sensitivity analyses varying the time window to define past PPI use and this
6 did not affect the estimates. Additionally, although the internal validity may be jeopardized by
7 non-compliance of the patient, this is unlikely to have affected the comparison between active
8 compounds (e.g. omeprazole/esomeprazole compared to pantoprazole). Third, since most
9 persons continue PPIs once started, applying past PPI use as reference reduces study power
10 substantially (resulting in wide confidence intervals). Finally, residual confounding remained
11 due to lack of data on important cardiac risk factors, such as smoking status, lipoproteins, or
12 type of coronary stents, which was likely providing an overestimation of the effect measure
13 and this was illustrated when applying PPI non-use as the reference.

14 In conclusion, this study provides an unique angle on the association between
15 clopidogrel –PPI co-therapy and risk of recurrent MI by using several techniques to deal with
16 confounding by indication and other methodological issues. Among clopidogrel users, current
17 use of PPIs was associated with an increased risk of recurrent MI when compared to PPI non-
18 use, but not when compared to past PPI use, which shows the magnitude of the confounding
19 by indication that is present. In clopidogrel-non-users, current PPI use was also associated
20 with an increased risk of recurrent MI when compared to PPI non-use. This study thus
21 demonstrates that previously reported associations between PPI-clopidogrel co-therapy and
22 risks of recurrent MI are influenced by confounding. It further demonstrates that such
23 confounding can be (at least partly) circumvented by careful selection of study design and
24 conventional adjustments techniques. Further work should concentrate on well-conducted

Deleted: omeprazole and pantoprazole were available over the counter since respectively February 2004 and November 2007. We could not control for over the counter use of medication. However, since PPIs are only being reimbursed when on prescription, it is unlikely that we missed much (long-term) PPI use

Deleted: a drawback of

Deleted: is that

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
- 1 prospective randomized trials to dissolve the confusion around this controversial drug-drug
2 interaction.

For Peer Review

1
2 **1 Tables**

3
4
5 **2 Table 1:** Characteristics of cohort patients (column 1), of those readmitted to the hospital with
6
7 **3 MI** (cases) versus their controls (column 2 and 3), and of PPI users versus non-PPI users in
8
9 **4** the case-control setting (column 4 and 5).

| | Total n(%) | Cases with recurrent MI n (%) | Controls without recurrent MI n (%) | PPI users n(%) | No PPI users n(%) |
|---|-----------------------------|--|--|---|--|
| | | <i>In unexposed to PPIs</i> | | <i>In controls without recurrent MI</i> | |
| Number | 23,655 (100) | 616 (100) | 126,817 (100) | 69,313 (100) | 126,817 (100) |
| Mean age (SD) | 64.7 (13.2) | 66.1 (13.2) | 66.3 (10.4) | 68.1 (10.3) | 66.3 (10.4) |
| Median follow-up time in months (IQR) | 42.6 (16.8- 71.7) | 11.4 (4.1- 29.4) | 29.5 (13.1- 51.6) | 34.5 (16.0- 58.4) | 29.5 (13.1- 51.6) |
| Median number of different prescriptions (IQR)* | 5 (2 - 9) | 5 (2 - 8) | 3 (1 - 6) | 6 (3 - 10) | 3 (1 - 6) |
| Median length of stay baseline MI in days (IQR) | 7 (4 - 10) | 7 (5 - 9) | 7 (5 - 10) | 7 (5 - 10) | 7 (5 - 10) |

| | | | | | | |
|----|---|-----------|-------------------|---------------------|---------------------|---------------------|
| 1 | | | | | | |
| 2 | Male sex | 15,897 | 436 (70.8) | 72,020 | 55,377 | 72,020 |
| 3 | | | | | | |
| 4 | | (67.2) | | (85.1) | (79.9) | (85.1) |
| 5 | | | | | | |
| 6 | PTCA during or within 30 days of | 7,889 | 126 (20.5) | 23,808 | 21,851 | 23,808 |
| 7 | | | | | | |
| 8 | baseline MI | (33.4) | | (28.1) | (31.5) | (28.1) |
| 9 | | | | | | |
| 10 | Presence of diabetes mellitus | 5,100 | 125 (20.3) | 13,774 | 14,022 | 13,774 |
| 11 | | | | | | |
| 12 | | (21.6) | | (16.3) | (20.2) | (16.3) |
| 13 | | | | | | |
| 14 | Hospitalizations before baseline MI: | | | | | |
| 15 | | | | | | |
| 16 | Cardiogenic shock | 12 (0.1) | 1 (0.2) | 31 (0.0) | 37 (0.1) | 31 (0.0) |
| 17 | | | | | | |
| 18 | Congestive heart failure | 551 (2.3) | 14 (2.3) | 858 (1.0) | 961 (1.4) | 858 (1.0) |
| 19 | | | | | | |
| 20 | Cancer | 1,045 | 13 (2.1) | 2,380 (2.8) | 2,710 (3.9) | 2,380 (2.8) |
| 21 | | | | | | |
| 22 | | (4.4) | | | | |
| 23 | | | | | | |
| 24 | Cerebrovascular disease | 651 (2.8) | 11 (1.8) | 1,378 (1.6) | 1,836 (2.6) | 1,378 (1.6) |
| 25 | | | | | | |
| 26 | Acute renal failure | 32 (0.1) | 0 (0.0) | 49 (0.1) | 84 (0.1) | 49 (0.1) |
| 27 | | | | | | |
| 28 | Chronic renal failure | 210 (0.9) | 4 (0.6) | 449 (0.5) | 667 (1.0) | 449 (0.5) |
| 29 | | | | | | |
| 30 | Cardiac dysrhythmia | 775 (3.3) | 18 (2.9) | 1,898 (2.2) | 1,960 (2.8) | 1,898 (2.2) |
| 31 | | | | | | |
| 32 | UGI ulcer and gastritis | 153 (0.6) | 1 (0.2) | 101 (0.1) | 630 (0.9) | 101 (0.1) |
| 33 | | | | | | |
| 34 | Medication use at the time of baseline | | | | | |
| 35 | | | | | | |
| 36 | MI: | | | | | |
| 37 | Angiotensin-converting-enzyme | 3,141 | 84 (13.6) | 9,122 (10.8) | 8,601 (12.4) | 9,122 (10.8) |
| 38 | | | | | | |
| 39 | inhibitor | (13.3) | | | | |
| 40 | | | | | | |
| 41 | Angiotensin-receptor antagonist | 1,787 | 38 (6.2) | 4,200 (5.0) | 5,034 (7.3) | 4,200 (5.0) |
| 42 | | | | | | |
| 43 | | (7.6) | | | | |
| 44 | | | | | | |
| 45 | Acetylsalicylic acid | 5,364 | 153 (24.8) | 16,181 | 17,120 | 16,181 |
| 46 | | | | | | |
| 47 | | (22.7) | | (19.1) | (24.7) | (19.1) |
| 48 | | | | | | |
| 49 | | | | | | |

| | | | | | | |
|----|--|-----------|-------------------|---------------------|---------------------|---------------------|
| 1 | | | | | | |
| 2 | β -Adrenergic antagonist | 5,531 | 148 (24.0) | 16,915 | 16,891 | 16,915 |
| 3 | | | | | | |
| 4 | | (23.4) | | (20.0) | (24.4) | (20.0) |
| 5 | | | | | | |
| 6 | Calcium-channel antagonist | 3,150 | 92 (14.9) | 9,257 (10.9) | 10,031 | 9,257 (10.9) |
| 7 | | | | | | |
| 8 | | (13.3) | | | (14.5) | |
| 9 | | | | | | |
| 10 | Digoxin | 592 (2.5) | 14 (2.3) | 1,204 (1.4) | 1,311 (1.9) | 1,204 (1.4) |
| 11 | Spirolactone | 336 (1.4) | 5 (0.8) | 455 (0.5) | 559 (0.8) | 455 (0.5) |
| 12 | | | | | | |
| 13 | | | | | | |
| 14 | Lipid lowering drugs | 4,144 | 113 (18.3) | 13,034 | 13,307 | 13,034 |
| 15 | | | | | | |
| 16 | | (17.5) | | (15.4) | (19.2) | (15.4) |
| 17 | | | | | | |
| 18 | Thiazide diuretic | 806 (3.4) | 16 (2.6) | 2,080 (2.5) | 1,958 (2.8) | 2,080 (2.5) |
| 19 | | | | | | |
| 20 | Other diuretic, excluding thiazide | 2,713 | 63 (10.2) | 5,299 (6.3) | 6,094 (8.8) | 5,299 (6.3) |
| 21 | | | | | | |
| 22 | | (11.5) | | | | |
| 23 | | | | | | |
| 24 | Nonsteroidal anti-inflammatory drug | 1,720 | 30 (4.9) | 3,910 (4.6) | 6,384 (9.2) | 3,910 (4.6) |
| 25 | | | | | | |
| 26 | | (7.3) | | | | |
| 27 | | | | | | |
| 28 | Medication use at index date**: | | | | | |
| 29 | | | | | | |
| 30 | Angiotensin-converting-enzyme | | 213 (34.6) | 29,328 | 2,4817 | 29,328 |
| 31 | | | | | | |
| 32 | inhibitor | | | (34.6) | (35.8) | (34.6) |
| 33 | | | | | | |
| 34 | Angiotensin-receptor antagonist | | 50 (8.1) | 9,301 (11.0) | 9,535 (13.8) | 9,301 (11.0) |
| 35 | | | | | | |
| 36 | Acetylsalicylic acid | | 408 (66.2) | 56,621 | 45,511 | 56,621 |
| 37 | | | | | | |
| 38 | | | | (66.9) | (65.7) | (66.9) |
| 39 | | | | | | |
| 40 | β -Adrenergic antagonist | | 377 (61.2) | 52,200 | 43,575 | 52,200 |
| 41 | | | | | | |
| 42 | | | | (61.7) | (62.9) | (61.7) |
| 43 | | | | | | |
| 44 | Calcium-channel antagonist | | 116 (18.8) | 14,252 | 13,727 | 14,252 |
| 45 | | | | | | |
| 46 | | | | (16.8) | (19.8) | (16.8) |
| 47 | | | | | | |
| 48 | Lipid lowering drugs | | 356 (57.8) | 54,475 | 45,776 | 54,475 |
| 49 | | | | | | |

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

| | | | | | |
|--|--|-------------------|---------------|--------------------|--------------------|
| | | | (64.4) | (66.0) | (64.4) |
| Thiazide diuretic | | 24 (3.9) | 2,690 (3.2) | 2,672 (3.9) | 2,690 (3.2) |
| Other diuretic, excluding thiazide | | 130 (21.1) | 12,606 | 14,510 | 12,606 |
| | | | (14.9) | (20.9) | (14.9) |
| Medication use at recurrent MI: | | | | | |
| Cytochrome P450 2C19 inhibitor(s) | | 7 (1.1) | 679 (0.8) | 676 (1.0) | 679 (0.8) |
| Cytochrome P450 2C19 inducer(s) | | 13 (2.1) | 1,043 (1.2) | 2,973 (4.3) | 1,043 (1.2) |
| Cytochrome P450 3A4 inhibitor(s) | | 56 (9.1) | 5,725 (6.8) | 5,854 (8.4) | 5,725 (6.8) |
| Cytochrome P450 3A4 inducer(s) | | 8 (1.3) | 823 (1.0) | 724 (1.0) | 823 (1.0) |

- 1 When cases differ statistically significant from controls or when PPI users differ statistically
- 2 significant from non-PPI users, the figures are depicted in bold. **The numbers in columns**
- 3 **three to six (reflecting the case-control setting) can be larger than the total number in column**
- 4 **two (reflecting the cohort setting) due to the control sampling method.**
- 5 * Median number of different prescriptions on full ATC-level one year prior to cohort entry
- 6 ** Index date=date of recurrent MI. Only available for the case-control set.

1
2 *Table 2:* Association between current clopidogrel plus current PPI and recurrent MI compared
3
4 to clopidogrel without PPI and to clopidogrel with past PPI.
5

| | Cases <i>n</i> =1,224 | Controls <i>n</i> =153,967 | OR _{matched} (95% CI) | OR _{adjusted} (95% CI) |
|-----------------------------------|--------------------------|-------------------------------|-----------------------------------|------------------------------------|
| Current clopidogrel / No PPI | 90 | 11,147 | 1 (ref) | 1 (ref) |
| Current clopidogrel / Current PPI | 78 | 4,715 | 1.89 (1.37-2.63) | 1.62 (1.15-2.27)# |
| Other* | 1,056 | 138,105 | | |
| Current clopidogrel / Past PPI | 6 | 436 | 1 (ref) | 1 (ref) |
| Current clopidogrel / Current PPI | 78 | 4,715 | 1.15 (0.46-2.86) | 0.95 (0.38-2.41)± |
| Other** | 1,140 | 148,816 | | |

31 *No or past clopidogrel, or past PPI use.

34 **No or past clopidogrel, or no PPI use.

35 # Adjusted for follow-up time in days and total number of prescriptions one year prior to
36
37 baseline MI.

40 ± Adjusted for follow-up time in days.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Table 3: Association between current PPI use and recurrent MI compared to no PPI and to
2 past PPI use in the absence of clopidogrel.

| | Cases <i>n</i> =1,224 | Controls <i>n</i> =153,967 | OR _{matched} (95% CI) | OR _{adjusted} (95% CI) |
|------------------------------|--------------------------|-------------------------------|-----------------------------------|------------------------------------|
| No clopidogrel / No PPI | 766 | 110,002 | 1 (ref) | 1 (ref) |
| No clopidogrel / Current PPI | 237 | 23,335 | 1.56 (1.34-1.81) | 1.38 (1.18-1.61)# |
| Other* | 221 | 20,630 | | |
| No clopidogrel / Past PPI | 25 | 2,941 | 1 (ref) | 1 (ref) |
| No clopidogrel / Current PPI | 237 | 23,335 | 1.22 (0.79-1.88) | 1.22 (0.79-1.88) χ |
| Other** | 962 | 127,691 | | |

3 *Current or past clopidogrel, or past PPI use.

4 **Current or past clopidogrel, or no PPI use.

5 # Adjusted for total number of prescriptions one year prior to baseline MI.

6 χ No adjustments.

- 1
2 1 *Table 4:* Association between current clopidogrel plus specific current PPI use and recurrent
3
4 2 MI compared to clopidogrel with current pantoprazole.
5

| | Cases | Controls | OR _{matched} | OR _{adjusted} ** |
|---|----------------|------------------|-----------------------|---------------------------|
| | <i>n=1,224</i> | <i>n=153,967</i> | (95% CI) | (95% CI) |
| 6 Current clopidogrel + pantoprazole | 36 | 2,271 | 1 (ref) | 1 (ref) |
| 14 Current clopidogrel + omeprazole | 26 | 1,339 | 1.03 (0.57-1.84) | 1.07 (0.58-1.99) |
| 17 Current clopidogrel+ esomeprazole | 13 | 827 | 0.96 (0.48-1.92) | 0.83 (0.40-1.69) |
| 20 Current clopidogrel + lanso- or 21 abeprazole | 2 | 186 | - | - |
| 24 Other* | 1,147 | 149,344 | | |

- 27 3 Combinations of PPIs were excluded.
28
29
30 4 *No or past clopidogrel, or no or past PPI use.
31
32
33 5 **Adjusted for follow-up time in days and propensity score.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

1
2 1 *Table 5: Summary of used methods to deal with confounding in observational studies*
3 2 assessing the effect of PPI on CV events in clopidogrel users, **excluding restrictions in study**
4 3 **design.**
5
6 4

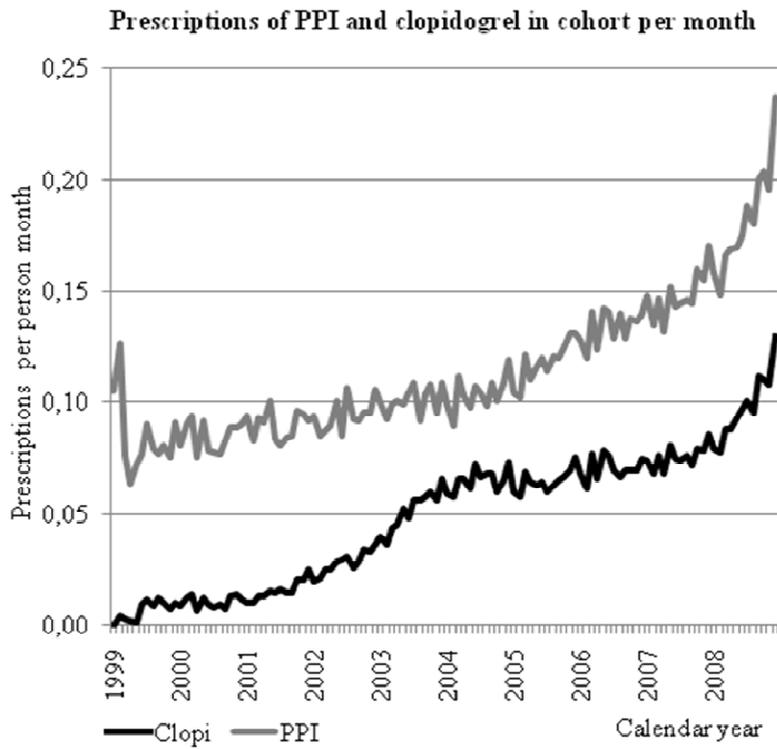
| Authors | Study type | Study population | Outcome | Methods to deal with confounding |
|-------------------------------------|----------------------------------|--|---|---|
| Simon <i>et al.</i> ² | Prospective cohort | Patients with acute MI | Death, MI, stroke | - Multivariable adjustments - Propensity analysis for CYP2C19 loss-of-function-alleles which was used to match 5 controls for each patient with 2 variant alleles |
| Bhatt <i>et al.</i> ⁶ | Double-blind randomized trial | Patients with ACS undergoing coronary stent placement | MI, stroke, CABG, PCI, CV death | - Randomization |
| Ray <i>et al.</i> ⁷ | Retrospective cohort study | Patients hospitalized for MI, coronary artery revascularization, or unstable AP on clopidogrel | serious CV disease ((non)fatal MI, stroke, other CV death). | - Multivariable adjustments - Propensity score for the use of PPI was converted in deciles and included as variable in model |
| O'Donoghue <i>et al.</i> | Retrospective cohort within | Patients with ACS undergoing | CV death, MI, stroke | - Multivariable adjustments - Propensity score for the use of PPI and |

| | | | | | |
|----|-----------------------------|----------------|-------------------|-------------------|---|
| 1 | | | | | |
| 2 | <i>al.</i> ¹³ | RCT | PCI | | strata matched on this score |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |
| 7 | Ho <i>et</i> | Retrospective | Patients with | All-cause | - Multivariable adjustments |
| 8 | | cohort study + | ACS on | mortality, | - Matched on duration of follow-up |
| 9 | <i>al.</i> ¹⁵ | case-control | clopidogrel | rehospitalization | |
| 10 | | study | | for ACS | |
| 11 | | | | | |
| 12 | Juurink | Nested case- | Patients with | Recurrent MI, | - Multivariable adjustments |
| 13 | | control | acute MI on | death | - Matched on age, PCI, date of hospital |
| 14 | <i>et al.</i> ¹⁶ | | clopidogrel | | discharge, predicted probability of |
| 15 | | | | | short-term mortality |
| 16 | | | | | |
| 17 | Pezalla | Retrospective | Patients adherent | Acute MI | - Subgroup analysis; restriction to |
| 18 | | cohort study | to clopidogrel | | patients who all had diagnosis of |
| 19 | <i>et al.</i> ¹⁷ | | | | ischaemic heart disease, congestive |
| 20 | | | | | heart failure, hypertension, |
| 21 | | | | | hyperlipidemia, and diabetes before the |
| 22 | | | | | start of clopidogrel therapy. |
| 23 | | | | | |
| 24 | | | | | |
| 25 | Stanek | Retrospective | Patients adherent | CV events (MI, | - Multivariable adjustments |
| 26 | | cohort study | to clopidogrel | unstable AP, | |
| 27 | <i>et al.</i> ¹⁸ | | following | TIA/stroke, | |
| 28 | | | coronary stenting | coronary | |
| 29 | | | | vascularization, | |
| 30 | | | | CV death) | |
| 31 | | | | | |
| 32 | | | | | |
| 33 | | | | | |
| 34 | | | | | |
| 35 | | | | | |
| 36 | | | | | |
| 37 | | | | | |
| 38 | | | | | |
| 39 | | | | | |
| 40 | | | | | |
| 41 | | | | | |
| 42 | | | | | |
| 43 | | | | | |
| 44 | | | | | |
| 45 | | | | | |
| 46 | | | | | |
| 47 | | | | | |
| 48 | | | | | |
| 49 | | | | | |
| 50 | | | | | |

| | | | | | |
|----|-----------------------------|---------------|-------------------|--------------------|--|
| 1 | | | | | |
| 2 | Rassen | Retrospective | Patients | MI, | - Multivariable adjustments |
| 3 | | | | | |
| 4 | <i>et al.</i> ¹⁹ | cohort study | undergoing PCI | revascularization, | - High-dimensional propensity score |
| 5 | | | or hospitalized | all-cause | and strata matched on this score (1:1) |
| 6 | | | for ACS on | mortality | |
| 7 | | | | | |
| 8 | | | clopidogrel | | |
| 9 | | | | | |
| 10 | | | | | |
| 11 | | | | | |
| 12 | Stockl | Retrospective | Patients with MI | Acute MI | - Propensity score and strata matched on |
| 13 | | | or coronary stent | | this score (1:1) |
| 14 | <i>et al.</i> ²⁰ | cohort study | on clopidogrel | | |
| 15 | | | | | |
| 16 | | | | | |
| 17 | | | | | |
| 18 | | | | | |
| 19 | Collet | Prospective | Survivors of MI | CV death, non- | - Multivariable adjustments |
| 20 | | | (< 45 yrs) | fatal MI, urgent | |
| 21 | <i>et al.</i> ²² | cohort | | revascularisation | |
| 22 | | | | | |
| 23 | | | | | |
| 24 | | | | | |
| 25 | | | | | |
| 26 | Dunn <i>et</i> | Retrospective | Patients | Death, MI, | - No information on adjustment to |
| 27 | | | undergoing PCI | Stroke (1 year) | covariates |
| 28 | <i>al.</i> ²³ | cohort within | | | |
| 29 | | RCT | | | |
| 30 | | | | | |
| 31 | | | | | |
| 32 | | | | | |

-
- 1 MI: Myocardial infarction, ACS: Acute Coronary Syndrome, CABG: Coronary artery bypass
 - 2 graft, PCI: Percutaneous coronary intervention, CV: Cardiovascular, AP: Angina pectoris,
 - 3 PPI: Proton pump inhibitor, RCT: Randomized controlled trial, TIA: Transient ischemic
 - 4 attack

1
2 *Figure 1: Prescriptions of PPI and clopidogrel in MI cohort per month.*



2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Number of prescriptions per person month for PPIs and clopidogrel calculated per calendar month during study period in cohort of acute MI patients (n= 23,655).

References:

- [1] Beitelshes AL, McLeod HL. Clopidogrel pharmacogenetics: promising steps towards patient care? *Arteriosclerosis, thrombosis, and vascular biology*. 2006 Aug;26(8):1681-3.
- [2] Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009 Jan 22;360(4):363-75.
- [3] Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009 Jan 22;360(4):354-62.
- [4] 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*. Feb 2;121(4):512-8.
- [5] Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. *The American journal of gastroenterology*. 2007 Mar;102(3):507-15.
- [6] Bhatt DL CB, Contant CF. COGENT: a Prospective, Randomized, Placebo-Controlled Trial of omeprazole in patients receiving aspirin and clopidogrel. . *Transvascular Cardiovascular Therapeutics Annual Meeting*. September 2009.
- [7] Ray WA, Murray KT, Griffin MR, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Annals of internal medicine*. Mar 16;152(6):337-45.
- [8] Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation*. 2008 Oct 28;118(18):1894-909.
- [9] Food and Drug Administration. Public Health Advisory: Updated Safety Information about a drug interaction between Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC).

- 1
2 1 <http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm190825.htm> (accessed Febr 6,
3
4 2 2010). 2009.
5
6 3 [10] European Medicines Agency. Public statement on possible interaction between clopidogrel
7
8 4 and proton-pump inhibitors.
9
10 5 <http://www.ema.europa.eu/humandocs/PDFs/EPAR/Plavix/32895609en.pdf> (accessed Febr 6,
11
12 6 2010). 2009.
13
14 7 [11] Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of
15
16 8 clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLOpidogrel
17
18 9 Aspirin) study. *J Am Coll Cardiol*. 2008 Jan 22;51(3):256-60.
19
20 10 [12] Gilard M, Arnaud B, Le Gal G, Abgrall JF, Bosch J. Influence of omeprazol on the antiplatelet
21
22 11 action of clopidogrel associated to aspirin. *J Thromb Haemost*. 2006 Nov;4(11):2508-9.
23
24 12 [13] O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical
25
26 13 efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two
27
28 14 randomised trials. *Lancet*. 2009 Sep 19;374(9694):989-97.
29
30 15 [14] Sibbing D, Morath T, Stegherr J, et al. Impact of proton pump inhibitors on the antiplatelet
31
32 16 effects of clopidogrel. *Thrombosis and haemostasis*. 2009 Apr;101(4):714-9.
33
34 17 [15] Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant
35
36 18 use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *Jama*. 2009 Mar
37
38 19 4;301(9):937-44.
39
40 20 [16] Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between
41
42 21 proton pump inhibitors and clopidogrel. *Cmaj*. 2009 Jan 28.
43
44 22 [17] Pezalla E, Day D, Pulliadath I. Initial assessment of clinical impact of a drug interaction
45
46 23 between clopidogrel and proton pump inhibitors (Letter). *J Am Coll Cardiol*. 2008 Sep
47
48 24 16;52(12):1038-9; author reply 9.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2 1 [18] Stanek EJ, Aubert RE, Flockhart DA, et al. A National Study of the Effect of Individual Proton
3
4 2 Pump Inhibitors on Cardiovascular
5
6 3 Outcomes in Patients Treated with Clopidogrel Following Coronary Stenting: The
7
8 4 Clopidogrel Medco Outcomes Study. <http://www.scaior.org/pdf/20090506Medcoabstractpdf> (Abstract).
9
10 5 2009.
11
12 6 [19] Rassen JA, Choudhry NK, Avorn J, Schneeweiss S. Cardiovascular outcomes and mortality in
13
14 7 patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or
15
16 8 acute coronary syndrome. *Circulation*. 2009 Dec 8;120(23):2322-9.
17
18 9 [20] Stockl KM, Le L, Zakharyan A, et al. Risk of rehospitalization for patients using clopidogrel
19
20 10 with a proton pump inhibitor. *Archives of internal medicine*. Apr 26;170(8):704-10.
21
22 11 [21] Suissa S. Immortal time bias in pharmaco-epidemiology. *American journal of epidemiology*.
23
24 12 2008 Feb 15;167(4):492-9.
25
26 13 [22] Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients
27
28 14 treated with clopidogrel after myocardial infarction: a cohort study. *Lancet*. 2009 Jan
29
30 15 24;373(9660):309-17.
31
32 16 [23] Dunn S, Macaulay T, Brennan D, et al. Baseline proton pump inhibitor use is associated with
33
34 17 increased cardiovascular events with and without the use of clopidogrel in the CREDO trial (Abstract).
35
36 18 *Circulation*. 2008;118:S815.
37
38 19 [24] WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification
39
40 20 and DDD assignment.
41
42 21 <http://www.whocc.no/atcddd/>. (accessed Sept 4, 2009). 2009.
43
44 22 [25] Herings RM, Bakker A, Stricker BH, Nap G. Pharmaco-morbidity linkage: a feasibility study
45
46 23 comparing morbidity in two pharmacy based exposure cohorts. *Journal of epidemiology and*
47
48 24 *community health*. 1992 Apr;46(2):136-40.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2 1 [26] Richardson DB. An incidence density sampling program for nested case-control analyses.
3
4 2 Occupational and environmental medicine. 2004 Dec;61(12):e59.
5
6 3 [27] Indiana University SoM, Department of Medicine, Division of Clinical Pharmacology, . P450
7
8 4 Drug Interaction Table. <http://medicine.iupui.edu/clinpharm/ddis/table.asp> (accessed July 12, 2010;
9
10 5 last updated on: March 3, 2010). 2010.
11
12 6 [28] Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. American journal of
13
14 7 epidemiology. 1999 Aug 15;150(4):327-33.
15
16 8 [29] Walker AM. Confounding by indication. Epidemiology (Cambridge, Mass. 1996 Jul;7(4):335-6.
17
18 9 [30] Kwok CS, Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular
19
20 10 events and mortality in patients receiving clopidogrel. Alimentary pharmacology & therapeutics.
21
22 11 Apr;31(8):810-23.
23
24 12 [31] Charlot M, Ahlehoff O, Lykke Norgaard M, et al. Proton-pump inhibitors are associated with
25
26 13 increased cardiovascular risk independent of clopidogrel use. Ann Intern Med. 2010 21 September
27
28 14 2010;153(6):378-86.
29
30 15 [32] Stanek EJ, Aubert RE, Flockhart DA, et al. Proton Pump Inhibitors in the Absence of
31
32 16 Clopidogrel Therapy Do Not Affect Cardiovascular Outcomes in Coronary Stent Patients. Presented at
33
34 17 American Heart Association's Ninth Scientific Forum on Quality of Care and Outcomes Research in
35
36 18 Cardiovascular and Stroke. [http://www.medcoresearch.com/servlet/JiveServlet/download/1169-6-](http://www.medcoresearch.com/servlet/JiveServlet/download/1169-6-1082/QCOR_PPI_and_Plavix_FNLpdf)
37
38 19 1082/QCOR_PPI_and_Plavix_FNLpdf (Abstract). 2009 April.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60