

## ORIGINAL ARTICLE

# Prescription behavior for gastroprotective drugs in new users as a result of communications regarding clopidogrel – proton pump inhibitor interaction

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## Keywords

Antiulcer agents, clopidogrel, drug interactions, drug safety, histamine H2 antagonists, pharmacoepidemiology, pharmacovigilance, proton pump inhibitors, risk assessment, risk factors.

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## Abstract

Safety concerns of the concomitant use of clopidogrel and proton pump inhibitors (PPIs) were published in 2009 and 2010 by the medicines regulatory agencies, including a direct healthcare professional communication. We examined the association between various safety statements and prescription behavior for gastroprotective drugs in naïve patients in the Netherlands during the years 2008–2011. Data from the PHARMO Database Network were analyzed with interrupted time series analyses to estimate the impact of each communication on drug prescriptions. Dispensings were used as a proxy variable for prescription behavior. After the early communication in January 2009, 15.5% (95% CI 7.8, 23.4) more patients started concomitantly with (es)omeprazole and 13.8% (95% CI 6.5, 21.2) less with other PPIs. Directly after the first statement in June 2009, we found a steep increase in histamine 2-receptor antagonists (H2RA) peaking at 25%, placing those patients at risk for gastrointestinal events. This effect for H2RA faded away after a few months. In February 2010, when the official advice via an adjusted statement was to avoid (es)omeprazole, we found a decrease of 11.9% (95% CI 5.7, 18.2) for (es)omeprazole and an increase of +16.0% (95% CI 10.3, 21.7) for other PPIs. Still 22.6% (95% CI 19.5, 25.7) of patients started on (es)omeprazole in February 2010, placing them at risk for cardiovascular events. Advices of regulatory authorities were followed, however, reluctantly and not fully, probably partly because of the existing scientific doubt about the interaction.

## Abbreviations

ANOVA, analysis of variance; ATC, anatomical therapeutic chemical; CV, cardiovascular; DHPC, direct healthcare professional communication; EMA, European Medicines Agency; FDA, Food and Drug Administration; GI, gastrointestinal; GP, gastroprotective; H2RA, histamine 2-receptor antagonists; MEB, Dutch Medicines Evaluation Board; PPI, proton pump inhibitor.

## Introduction

Clopidogrel is mainly used in cardiology – especially during the period 2008–2011 in the Netherlands – for patients with acute coronary syndromes or undergoing

percutaneous coronary intervention. As platelet aggregation inhibitors, clopidogrel alone, aspirin alone, as well as their combination, are all associated with increased risk of gastrointestinal (GI) bleeding. The Expert Consensus Document of the American College of Cardiology

Foundation on the concomitant use of proton pump inhibitors (PPIs) and thienopyridines recommends PPIs to reduce GI bleeding among patients with a history of upper GI bleeding (Abraham *et al.* 2010). The Dutch Harm-Wrestling Task Force published in 2008 recommended to apply the same recommendations to clopidogrel as to aspirin, to err on the safe side of caution (Warle-van Herwaarden *et al.* 2012). PPIs are appropriate in patients with multiple risk factors for GI bleeding, who require antiplatelet therapy. The risk of GI bleeding increases as the number of risk factors increases and is also dependent on ethnic differences. In patients with serious coronary heart disease treated with clopidogrel, concurrent PPI use was associated with reduced incidence of hospitalizations for gastroduodenal bleeding (Ray *et al.* 2010).

In 2009 and 2010, various official statements about the safety of the concomitant use of clopidogrel and PPIs were published:

I *Early communication.* In the United States, the U.S. Food and Drug Administration (FDA) posted an early communication on 26 January 2009 to notify healthcare professionals that studies were going to be conducted to obtain additional information on the effects of genetic factors and certain drugs (especially the PPIs) on the effectiveness of clopidogrel (U.S. Food and Drug Administration [FDA] 2009a).

II *First statement.* On 29 May 2009, the European Medicines Agency (EMA) published a public statement on the possible interactions between clopidogrel and PPIs (European Medicines Agency [EMA] 2009). On 3 June 2009, the Dutch Medicines Evaluation Board (MEB) concluded in an official statement that the combination of clopidogrel and omeprazole was not recommended unless the combination was indispensable according to the prescriber (Dutch Medicines Agency Board [MEB] 2009). In August 2009, a direct healthcare professional communication (DHPC or “Dear Doctor” letter) was sent to the concerned groups of professionals. The FDA on 17 November 2009 discouraged the use of omeprazole for gastroprotection and was not able to give specific information on the use of other PPIs (U.S. Food and Drug Administration [FDA] 2009b).

III *Adjusted statement.* On 16 February 2010, the statement was adjusted by MEB not to combine clopidogrel with (es) omeprazole because of the effect on clopidogrel’s active metabolite levels and anticlotting activity (Dutch Medicines Evaluation Board [MEB] 2010). The EMA followed on 17 March 2010 (European Medicines Agency [EMA] 2010).

The last warning dated from 27 October 2010, and is a reminder by the FDA to avoid concomitant use of

clopidogrel and omeprazole, where pantoprazole could be an alternative (U.S. Food and Drug Administration [FDA] 2010).

The scientific proof underpinning the statement on omeprazole or esomeprazole is not without dispute. Gilard *et al.* (2008) first found decreased levels of the active metabolite of clopidogrel and an increased platelet reactivity in patients coadministered a PPI. Focks *et al.* (2013) published a systematic review of all following publications on the impact of the addition of PPIs to clopidogrel on platelet function and cardiovascular (CV) outcome. They state that the emerging evidence from recent prospective studies does not support the statement that the addition of PPIs in patients who use clopidogrel should be considered harmful.

Safety monitoring of drugs is a regulatory responsibility and the effectiveness of DHPCs in achieving the desired clinical behavior has been questioned, especially in light of the new pharmacovigilance legislation from 2012 (European Parliament and the European Council 2010). Several studies looked into this, and there is a clear need for more research to understand the impact of different ways of safety communication (Mol *et al.* 2010; Piening *et al.* 2012a,b; Ruiter *et al.* 2012). While the annual number of DHPCs is rising, studies demonstrate that the intended and unintended impact of the instrument itself is not always self-evident and the safety information does not always reach the healthcare professionals (Gispens-de Wied and Leufkens 2013). In the case of the hypothesized interaction between clopidogrel and PPIs, safety communications, including those by the regulatory authorities, caused a lot of turmoil.

The objective of our study was to investigate the association between the various communications on the safety of the combined use of clopidogrel and PPIs on the prescribing behavior as deduced from dispensing records following DHPCs and EMA press releases in the EU member state the Netherlands in the years 2008–2011 for patients starting on gastroprotective (GP) drugs.

## Materials and Methods

### Design and data

Data were retrieved from the out-patient pharmacy database of the PHARMO Database Network, which comprises general practitioner or specialist prescribed healthcare medication dispensed by out-patient pharmacies (Herings and Pederson 2012). We used dispensing data as a proxy variable for prescribing. The dispensing records include information on the type of the product, date, strength, dosage regimen, quantity, route of administration,

prescriber specialty, and costs. Drug dispensings are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Out-patient pharmacy data cover a catchment area representing 3.6 million (>20%) residents throughout the Netherlands. Healthcare coverage regarding the reimbursement of concerned drugs was similar for all Dutch citizens and they were all equally included. Only patients 18 years and older were included, in accordance with the marketing authorization for clopidogrel (ATC code B01AC04 and B01AC30).

We divided the study into four separate periods. The first period started in January 2008 and ended by the end of January 2009, when the FDA early communication was posted on 26 January 2009 (U.S. Food and Drug Administration [FDA] 2009a). The public statements of the EMA (29 May 2009) and MEB (3 June 2009) made the second period to start in February 2009 and end by the end of May 2009 (European Medicines Agency [EMA] 2009; Dutch Medicines Evaluation Board [MEB] 2009). The third period lasted from June 2009 till the end of February 2010, since the adjusted statement by EMA was published in 16 February 2010 (Dutch Medicines Evaluation Board [MEB] 2010). The data collection ended in December 2011. In June 2009, as a result of the statements of the EMA and MEB, the interaction was integrated into the Dutch national drug–drug interaction database (G-standard), which is used by almost all pharmacies in the Netherlands. As a result, pharmacists started to contact prescribers in case of a combined prescription for PPI and clopidogrel. We therefore chose June 2009 as intervention month instead of August 2009, when the DHPC was sent, dated 6 August 2009.

Dispensings were clustered into episodes of continuous use of the same chemical entity based on the date and amount of dispensing, accepting a 30-day gap between following dispensings as described by Catalan and LeLorier (2000). Dispensing of a GP drug (histamine 2-receptor antagonists [H2RA] ATC code A02BA, PPIs ATC code A02BC) started a new episode of use. Clopidogrel will usually be prescribed for 3 up to 12 months. If a patient was included in the PHARMO Database Network less than 120 days before the first dispensing of clopidogrel, we excluded this patient for the analysis of first use, as the maximum prescribing period for a drug is 90 days. Patients who started using a GP drug at least 2 weeks before the start of clopidogrel, were classified as prior users. These patients were not included in our analysis of choice for GP because their choice of GP drug was made in the absence of clopidogrel. Concomitant users started a GP drug 2 weeks before until 4 weeks after the start of clopidogrel, the first episode of use in this time frame is analyzed. If the GP drug was started four or more weeks after the start of clopidogrel, we used the first episode of

use for the analysis of post users. For these two groups we analyzed the choice of GP drug. PPIs were fully reimbursed in the years 2008 until 2011. H2RA for GP use must be prescribed by a physician in a double dose in order to be reimbursed. We therefore assume all dispensings for H2RA in our study were done for gastroprotection. Theoretically some patients could enter our study cohort twice; by starting clopidogrel twice in our study, we expected this to be minimal.

## Analysis

The observational research file was created using SAS programs organized within SAS Enterprise Guide version 4.3 (SAS Institute Inc., Cary, NC) and conducted under Windows using SAS version 9.2. Statistical analysis was performed using SPSS software version 22 (IBM SPSS Statistics, Armonk, New York, USA).

Descriptive statistics were used to summarize the characteristic of the study cohort. Means for age were compared between the 4 years with analysis of variance (ANOVA) and Tukey's Honestly Significant Difference (HSD) as post hoc test. Gender distribution over the years was tested with a chi-square test for nominal variables. A chi-square test for trend was used to assess a trend over time in use of GP medication.

We used interrupted time series analyses (segmented linear regression analyses) to estimate the impact of each event on the dispensing of GP drugs, as described by the Cochrane Collaboration (2013). Statistical significance was set at  $P \leq 0.05$ .

## Results

Demographic characteristics and use of GP drugs are presented in Table 1. The average age in our study was 67 years and 64% was male.

During the study period (2008–2011), 40% of the patients did not use GP drugs at all. Approximately a quarter of the patients (27%) were already using GP drugs prior to the start of clopidogrel. About the same percentage (23%) started GP drugs and clopidogrel concomitantly. During the study period, about 10% of the patients started GP drugs at least 4 weeks after the start of clopidogrel. The percentage of patients without GP at the start of clopidogrel decreased from 55% to 42%. A small number of patients were using H2RA at the moment they started clopidogrel. A considerable part of the patients was using (es)omeprazole, decreasing from around 20% (2008 and 2009) to about 15% (2010 and 2011).

Table 1 also presents the use of GP drugs at the start of clopidogrel use in relation to age. The percentage of patients without GP drug at the start of clopidogrel

**Table 1.** Demographic characteristics and use of gastroprotective (GP) drugs.

	2008	2009	2010	2011	Total study population	Age, year (SD)	Male, %
Number of patients starting clopidogrel	9717	10,261	10,010	9508	39,496		
Age, year (SD) <sup>1</sup>	66.1 (12.4)	66.3 (12.6)	66.9 (12.6)	67.3 (12.5)	66.6 (12.6)		
Male, % <sup>1</sup>	63.7%	64.5%	64.0%	63.4%	63.9%		
Patients without GP drugs 2008–2011 (%)	4229 (44%)	4250 (41%)	3893 (39%)	3465 (36%)	15,837 (40.1%)	64.6 (12.6)	69.5%
GP starting before clopidogrel start (%)	2345 (24%)	2698 (26%)	2669 (27%)	2893 (30%)	10,605 (26.9%)	69.5 (11.5)	55.8%
GP starting together with clopidogrel (%)	1984 (20%)	2101 (20%)	2367 (24%)	2615 (28%)	9067 (23.0%)	67.5 (13.0)	62.8%
GP starting after clopidogrel start (%)	1159 (12%)	1212 (12%)	1081 (11%)	535 (6%)	3987 (10.1%)	65.4 (12.3)	65.6%
Patients without GP at the start of clopidogrel <sup>1</sup>	5388 (55.4%)	5462 (53.2%)	4974 (49.7%)	4000 (42.1%)	19,824 (50.2%)		
Patients on GP the moment they start clopidogrel	4329 (44.6%)	4799 (46.8%)	5036 (50.3%)	5508 (57.9%)	19,672 (49.8%)		
of whom using histamine 2-receptor antagonists	134 (1.4%)	395 (3.8%)	216 (2.2%)	144 (1.5%)	889 (2.3%)		
of whom using (es)omeprazole	2009 (20.7%)	2153 (21.0%)	1449 (14.5%)	1437 (15.1%)	7048 (17.8%)		
Age ≥60 years	6766 (69.6%)	7182 (70.0%)	7130 (71.2%)	6913 (72.7%)	27,991 (70.9%)		
of whom without GP	3572 (52.8%)	3583 (49.9%)	3280 (46.0%)	2617 (37.9%)	13,052 (46.6%)		
Age ≥70 years	4076 (41.9%)	4366 (42.5%)	4422 (44.2%)	4354 (45.8%)	17,218 (43.6%)		
of whom without GP	1990 (48.8%)	2042 (46.8%)	1860 (42.1%)	1455 (33.4%)	7347 (42.7%)		
Age ≥80 years	1470 (15.1%)	1685 (16.4%)	1786 (17.8%)	1743 (18.3%)	6684 (16.9%)		
of whom without GP	663 (45.1%)	735 (43.6%)	676 (37.8%)	505 (29.0%)	2579 (6%)		

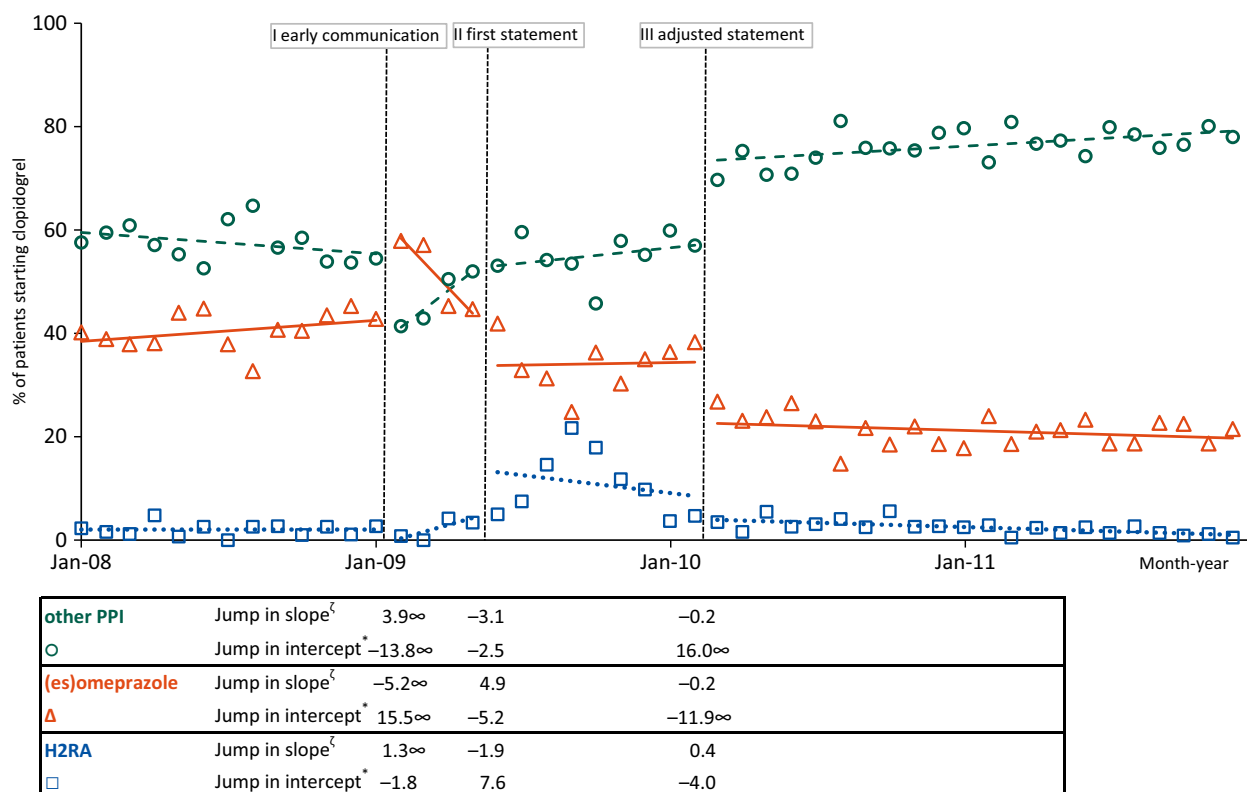
<sup>1</sup>Age and percentage of patients without GP at the start of clopidogrel were statistically significantly different ( $P \leq 0.001$ ) and gender was not ( $P > 0.05$ ).

decreased from 55% in the total study population in 2008 to 29% in 2011 if the age group was 80 years or older.

In Figure 1 the group of patients is described who started a GP drug and clopidogrel concomitantly. Before the early communication of the FDA an average of 40% of the patients started on (es)omeprazole. This percentage decreased significantly after the safety statements, reaching a new steady level around 20%. The percentage of patients starting on other PPIs rose from 60% to about 80%. A small percentage of the patients started on H2RA, with the exception of the period immediately after the first statements of the FDA and MEB and the introduction in the Dutch interaction database, where a short but significant increase is shown for a few months. After the early communication, a statistically significant ( $P \leq 0.05$ ) jump in slope and intercept is seen for all groups, except the jump in intercept for H2RA. The jump in intercept for (es)omeprazole was +15.5% (95% CI 7.8, 23.4), and for other PPIs it was -13.8% (95% CI -21.2, -6.5). After the adjusted statement, the jump in intercept is statistically significant ( $P \leq 0.05$ ) for (es)omeprazole (-11.9%, 95% CI -18.2, -5.7) and the other PPIs (+16.0%, 95% CI 10.3, 21.7).

In Figure 2, data on patients who started with a GP drug at least 4 weeks after the start of clopidogrel are presented. In this figure we removed the first 6 months, because the number of patients was too small. Roughly the patterns were similar to those in Figure 1: a decrease in starting on (es)omeprazole to about 20%, an increase in other PPIs to 80%, and a temporarily but obvious shift to more dispensing of H2RA. After the early communication, the jump in intercept was statistically significant ( $P \leq 0.05$ ) for other PPIs (-5.9%, 95% CI -11.7, -0.2). After the adjusted statement, the jumps in intercept for all three groups were statistically significant ( $P \leq 0.05$ ), for (es)omeprazole it was -12.8% (95% CI -21.3, -4.4), for other PPIs +22.4% (95% CI 14.7, 30.2), and for H2RA -9.7% (95% CI -16.5, -2.9).

If a patient without previous GP use started clopidogrel, the physician had to decide whether to prescribe a GP drug, or not. A patient was on average 67.5 years if a GP drug was started on that moment, and 64.7 years if started later or did not start at all in our study ( $P \leq 0.001$ ). Each year the probability of being prescribed a GP drug increased by a factor 1.016, corrected for gender. The probability of being prescribed a GP drug,



**Figure 1.** Choice of gastric protection in patients starting concomitantly with clopidogrel and (es)omeprazole ( $\Delta$ ), other proton pump inhibitor (PPI) ( $\circ$ ), or histamine 2-receptor antagonist (H2RA) ( $\square$ ). Monthly, on average, 183 patients start clopidogrel without prior use of medication for gastric protection. I, Early communication to re-evaluate need for PPI; II, first statement to avoid combination with PPI; III, adjusted statement to avoid combination with (es)omeprazole.  $\zeta$  indicates jump in slope from the previous to the following period. \* indicates jump from the predicted % just infinitely close to that month to the predicted % for becoming the first month of the next period.  $\infty$  Statistically significant ( $P \leq 0.05$ ).

however, was 1.2 (95% CI 1.14, 1.27) larger for a female patient to start a GP drug at the same age.

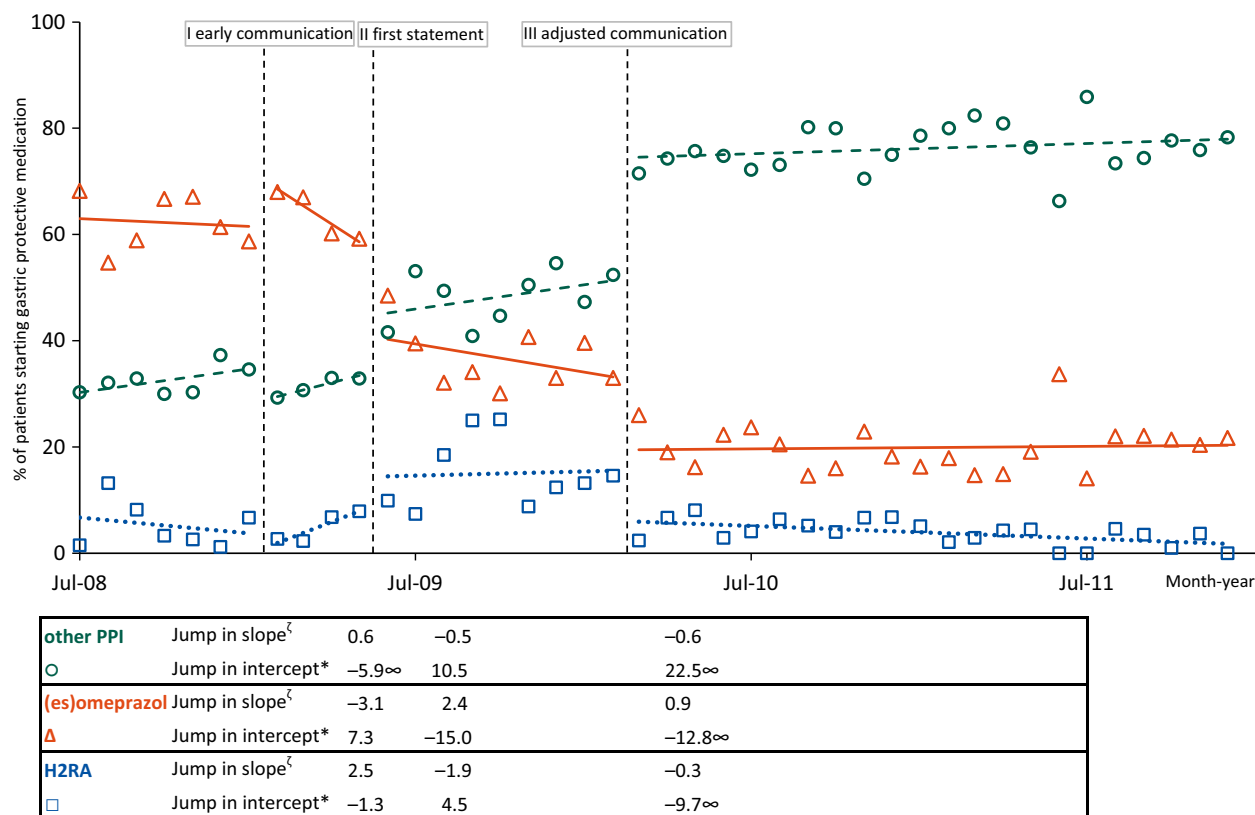
Notable is the difference in the first period between patients who start a GP drug and clopidogrel concomitantly (Fig. 1) and patients who start a GP drug later (Fig. 2). In patients who start clopidogrel and GP drug concomitantly, other PPIs than (es)omeprazole were favored, whereas in patients who start later with a GP drug, (es)omeprazole was preferred. In Figure 3, we investigated this topic by splitting both groups into omeprazole and esomeprazole. For patients who started later with GP drugs, more omeprazole was prescribed in comparison with those who started at the same time.

## Discussion

We were able to demonstrate a significant effect on prescription and subsequent dispensing behavior in the EU member state the Netherlands due to the various statements and DHPCs by the regulatory agencies. Directly after the first statement in June 2009, we found a shift in prescribing of H2RA peaking at 25%. In February 2010,

when the adjusted statement became to prescribe non(es) omeprazole, still 22.6% of patients started on (es)omeprazole. The effect was hesitant, not fully complying to the official advices. In the case of clopidogrel there was not one single abrupt change, because there were multiple statements over time. The early communication of the FDA in January 2009 was a precursor to the later statements. The DHPC in August 2009 came 2 months after the statement of the EMA and the introduction in the Dutch interaction database. The solitary effect of the DHPC can therefore not be examined, and we designed the study with three breaking points.

Not being prescribed a GP drug if needed could be considered to be an unintended effect of the safety warnings. Patients are unnecessarily at risk for GI side effects of clopidogrel. Although the Harm-Wrestling report published in the Netherlands in 2008 was quite clear in their recommendations for adequate gastric protection with a PPI, a considerable percentage of the patients did not receive a GP drug at all or a less effective one, namely a H2RA (Warle-van Herwaarden et al. 2012). According to the guideline of the Dutch College of General



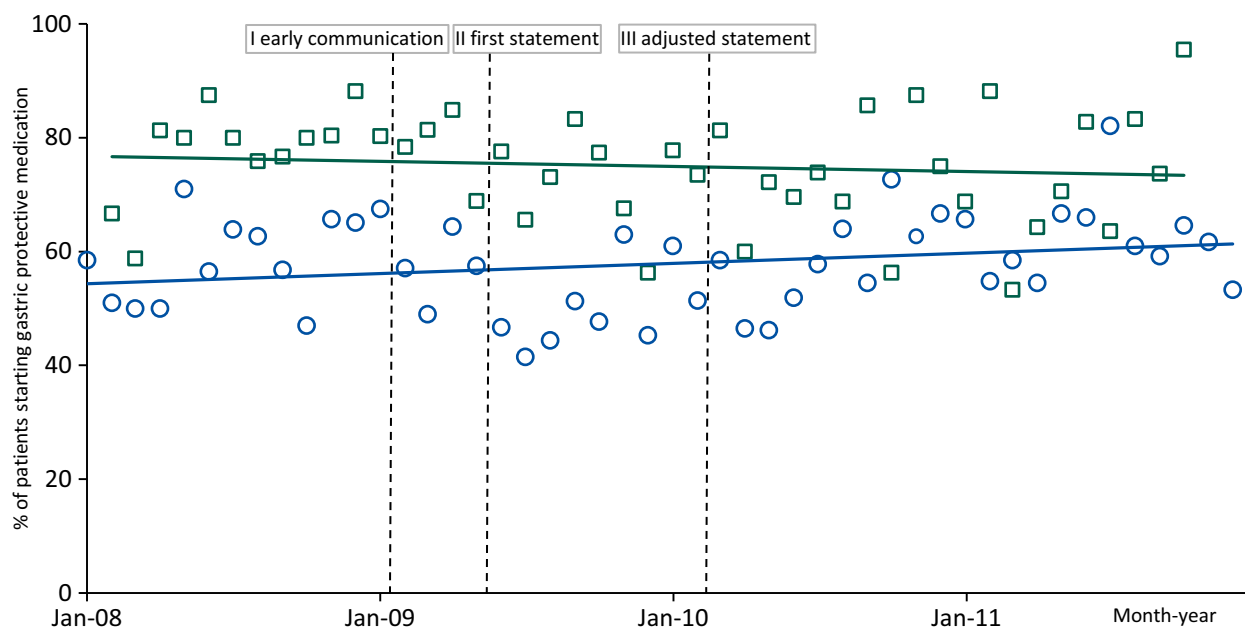
**Figure 2.** Choice of gastric protection in patients starting at least 4 weeks after clopidogrel with (△) (es)omeprazole, (○) other proton pump inhibitor (PPI), or (□) histamine 2-receptor antagonist. After June 2008, monthly, on average, 92 patients start clopidogrel without prior use medication for gastric protection. I, Early communication to re-evaluate need for PPI; II, first statement to avoid combination with PPI; III, adjusted statement to avoid combination with (es)omeprazole. <sup>ζ</sup> indicates jump in slope from the previous to the following period. \* indicates jump from the predicted % just infinitely close to that month to the predicted % for becoming the first month of the next period. ∞ Statistically significant ( $P \leq 0.05$ ).

Practitioners of January 2013, H2RA double dosing is no longer considered adequate GP (Numans et al. 2013). We suppose a greater proportion of the patients qualify for GP than is observed in our study. Partially this might be caused by the uncertainty among physicians and pharmacists caused by the supposed interaction between clopidogrel and PPIs, and partly by the time needed to integrate the recommendations into daily practice. This is demonstrated by the increase of PPI users in the Netherlands in the years 2002 till 2012 with a factor 2.6 (Drug Information Institute of National Health Care System 2015).

In the age group of 80 years or older, we found that on average in 39% clopidogrel was not combined with a PPI or H2RA. Most of the patients in our population – at least those 70 years or older – should probably be prescribed GP drugs. According to the Dutch Harm-Wrestling Task Force published in 2008, adequate gastro-protection was recommended above the age of 80, for patients older than 70 if they were treated simultaneously with one other medication that increased the risk of GI

complications, and for patients older than 60 if they were treated simultaneously with two or more other medications that increased the risk of GI complications (Warle-van Herwaarden et al. 2012). In the years 2008–2011, clopidogrel was almost exclusively prescribed by cardiologists in combination with aspirin. A considerable part of the patients in our study therefore was at risk for GI events.

The present study shows that a significant part of the patients is prescribed (es)omeprazole when they start clopidogrel (Figs. 1, 2). Those patients are at risk for not being protected effectively for CV events, if the scientific proof of the combination clopidogrel with (es)omeprazole is valid. We believe that only a minority of the cardiologists was informed of the supposed interaction by the beginning of June 2009, because there was no attention at all in general medicine or cardiology journals in the Netherlands (e.g., *Medisch Contact*, *Nederlands Tijdschrift voor Geneeskunde*, *Netherlands Heart Journal*). The integration in the Dutch drug database is supposed to be



**Figure 3.** Choice for omeprazole or esomeprazole in (○) concomitant starters and (□) post starters. Percentage of omeprazole as part of total (es)omeprazole for patients who started concomitantly or at least 4 weeks after the start of clopidogrel. I, Early communication to re-evaluate need for proton pump inhibitor (PPI); II, first statement to avoid combination with PPI; III, adjusted statement to avoid combination with (es)omeprazole.

the starting point for the change in prescription and dispensing behavior. This lack of change in behavior can have three different sources: the prescriber, the patient, or the factors outside those two. Because we studied dispensing data, a lack of change can be caused by the prescriber–pharmacist combination or the type of prescriber (general practitioner or specialist). The prescriber might not have received the information about the interaction, not “believe” in it, or did not think it is the cardiologists’ duty to think about gastroprotection. It does not feel right to withhold an otherwise advisable drug because it might harm the patient. On the other hand, could an individual professional be liable if he has not stuck to this kind of official statement by EMA, FDA, and MEB in case a patient experiences side effects in view of those statements. A change in medication is a risk factor for reduced medication adherence, which might be one of the reasons why not all hospitals changed the GP medication when a patient with (es)omeprazole was admitted to a hospital. Besides communicated safety issues, other factors such as the introduction of new drugs, type of prescriber and patient’s characteristics can influence prescribing and dispensing patterns. Unfortunately, these data are not adequately available in the PHARMO database.

As shown in Figure 3, in patients who started later with GP drugs, more omeprazole was prescribed in comparison with those who started at the same time. We

hypothesize later that starters to be prescribed a PPI by a general practitioner, who are more cost conscious, with omeprazole being the cheaper drug.

Characteristics for age and gender correspond to those found in the CURE study, the major study for the market authorization of clopidogrel (Yusuf *et al.* 2001). In that study mean age was 64 years and 61% of the clopidogrel users were male.

We observed a striking difference with regard to gender. The risk of starting a GP drug together with clopidogrel was 1.2 (95% CI 1.14, 1.27) greater for a female patient. Patients with a history of upper GI events should be a prescribed GP drug. Women present more frequent with nausea and vomiting when presenting with acute coronary events (Dey *et al.* 2009). Those symptoms could be mistaken for upper GI events while in fact being the preceding symptoms of the following acute coronary syndromes for which they will be prescribed clopidogrel. Another possible explanation for the observed difference in prescribing GP drugs to women could be the incidence of risk factors being unequally distributed among male and female. For example, for female patients the prescription of serotonin reuptake inhibitors in 2014 increased twofold, a risk factor in gastroprotection as well as use of corticosteroids (factor 1.35) (Drug Information System of National Health Care Institute 2015). We concluded gender to be a confounder in our study.

## Strengths and limitations

Our results are limited to the Dutch situation, although we believe our conclusions will hold true for other countries because of the international nature of the discussion. Changes in use of GP drugs are caused by the various communications and not by – for example – the reimbursement rules in the Netherlands, because those were equal for PPIs and H2RA. Zeitoun *et al.* (2014) demonstrated substantial inconsistencies in making safety communications in four European member countries, being a source for possible confusion among patients and physicians.

Because we had to design the study with three breaking points, the solitary effect of the DHPC cannot be examined. We were not able to gather sufficient data points in all periods for a solid interrupted time series analyses, especially for the period after the early communication. However, trends are clear, due to the large number of patients included in the study. We limited our study to patients not using GP drugs the moment they start clopidogrel. New use is known to be a more sensitive measure than overall use, because changes in prescribing behavior are more likely with new users (Reber *et al.* 2013). We limited our statistical analysis of demographic characteristics and use of GP drugs (Table 1) to clinically relevant parameters: age, gender, and percentage of patients without GP drugs at the start of clopidogrel. However, proceeding statistical significance is not very meaningful given the extremely large numbers of patients involved.

The interaction of antiplatelet drugs with (es)omeprazole is limited to clopidogrel. Ticagrelor and prasugrel – both not yet available in the Netherlands in 2008–2011 – do not interact with (es)omeprazole. Among persons treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse CV events, including stent thrombosis, than did noncarriers (Holmes *et al.* 2011). Incidence of this reduced-function allele varies between 1% and 6% in the Caucasian population, and between 12% and 23% in the Asian population. Due to this high percentage, current European and American guidelines (European Society of Cardiology, American College of Cardiology Foundation/American Heart Association) prefer other antiplatelet drugs beside aspirin.

## Conclusions

Lessons learned in this study should be applied to managing drug safety information in general. Although the place in therapy of clopidogrel will be repositioned to specific – smaller – groups of patients, prescribing the drug still needs to be done in a safe way, taking into account all

available safety information and weighing pros and cons of the message.

We suggest that an official statement from regulatory authorities followed by a DHPC could have had more impact on prescribing behavior if the scientific doubt was absent or negligible, the specialist associations had supported it, an alternative treatment had been available and actively promoted, and those statements were regularly updated to conform to new evidence. The MEB is working on a new directive for DHPCs, which provides an opportunity to close the gap between regulatory authorities and healthcare professionals and make a DHPC have an impact.

## Author Contributions

W. J. K. K., H. J. K., M. v. H. S., and K. L. L. M. conceived and designed the study. W. J. K. K. and J. v. d. P. analyzed and interpreted the data. W. J. K. K., J. v. d. P., H. J. K., M. v. H. S., and K. L. L. M. drafted the manuscript and approved the final version.

## Disclosures

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## References

- Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, *et al.* (2010). ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol* 56: 2051–2066.
- Catalan VS, LeLorier J (2000). Predictors of long-term persistence on statins in a subsidized clinical population. *Value Health* 3: 417–426.
- Cochrane Collaboration (2013). Effective Practice and Organisation of Care (EPOC). Interrupted time series (ITS) analyses. Available at: <http://epoc.cochrane.org/sites/>



- epoc.cochrane.org/files/uploads/21%20Interrupted%20time%20series%20analyses%202013%2008%2012\_2.pdf (accessed 16 May 2016).
- Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, et al. (2009). Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart* 95: 20–26.
- Drug Information System of National Health Care Institute (2015). Available at: <https://www.gipdatabank.nl/> (accessed 7 November 2015).
- Dutch Medicines Evaluation Board (MEB) (2009). Direct Healthcare Professional Communications, June 6, 2009. Original link has been removed from the internet, but mentioned in *Pharm Weekbl* 2009;144: 7 (accessed 7 November 2015).
- Dutch Medicines Evaluation Board (MEB) (2010). Direct Healthcare Professional Communications, February 16, 2010. Original link has been removed from the internet, but mentioned in *Pharm Weekbl* 2010;145: 8-9 (accessed 7 November 2015).
- European Medicines Agency (EMA) (2009). News and press release archive. “Public statement on possible interaction between clopidogrel and proton pump inhibitors”, May 29, 2009. Available at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2009/11/news\\_detail\\_000194.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000194.jsp&mid=WC0b01ac058004d5c1) (accessed 7 November 2015).
- European Medicines Agency (EMA) (2010). News and press release archive. “Public statement on interaction between clopidogrel and proton-pump inhibitors”, March 17, 2010. Available at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2010/03/news\\_detail\\_001008.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/03/news_detail_001008.jsp&mid=WC0b01ac058004d5c1) (accessed 7 November 2015).
- European Parliament and the European Council (2010). Directive 2010/84/EU. Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF> (accessed 8 November 2015).
- Focks JJ, Brouwer MA, Van Oijen MG, Lanan A, Bhatt DL, Verheugt FW (2013). Concomitant use of clopidogrel and proton pump inhibitors: impact on platelet function and clinical outcome- a systematic review. *Heart* 99: 520–527.
- Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, et al. (2008). Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 51: 256–260.
- Gispén-de Wied CC, Leufkens HG (2013). From molecule to market access: drug regulatory science as an upcoming discipline. *Eur J Pharmacol* 719: 9–15.
- Herings R, Pederson L (2012). Pharmacy-based medical record linkage systems. Pp. 270–286 in B. Strom, S. Kimmel and S. Hennessy, eds. *Pharmacoepidemiology*. 5th ed. Wiley - Blackwell, Oxford, UK.
- Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP (2011). CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA* 306: 2704–2714.
- Mol PG, Straus SM, Piening S, De Vries JT, De Graeff PA, Haaijer-Ruskamp FM (2010). A decade of safety-related regulatory action in the Netherlands: a retrospective analysis of direct healthcare professional communications from 1999 to 2009. *Drug Saf* 33: 463–474.
- Numans M, De Wit N, Dirven JAM, Heemstra-Borst CG, Hurenkamp G, Scheele ME, et al. (2013). NHG-Standaard Maagklachten. The Dutch College of General Practitioners [2013] Available at: <https://www.nhg.org/standaarden/volledig/nhg-standaard-maagklachten-derde-herziening> (accessed 7 November 2015).
- Piening S, Haaijer-Ruskamp FM, De Vries JT, Van der Elst ME, De Graeff PA, Straus SM, et al. (2012a). Impact of safety-related regulatory action on clinical practice: a systematic review. *Drug Saf* 35: 373–385.
- Piening S, Reber KC, Wieringa JE, Straus SM, De Graeff PA, Haaijer-Ruskamp FM, et al. (2012b). Impact of safety-related regulatory action on drug use in ambulatory care in the Netherlands. *Clin Pharmacol Ther* 91: 838–845.
- Ray WA, Murray KT, Griffin MR, Chung CP, Smalley WE, Hall K, et al. (2010). Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Ann Intern Med* 152: 337–345.
- Reber KC, Piening S, Wieringa JE, Straus SM, Raine JM, De Graeff PA, et al. (2013). When direct health-care professional communications have an impact on inappropriate and unsafe use of medicines. *Clin Pharmacol Ther* 93: 360–365.
- Ruiter R, Visser LE, Van Herk-Sukel MP, Geelhoed-Duijvestijn PH, De Bie S, Straus SM, et al. (2012). Prescribing of rosiglitazone and pioglitazone following safety signals: analysis of trends in dispensing patterns in the Netherlands from 1998 to 2008. *Drug Saf* 35: 471–480.
- U.S. Food and Drug Administration (FDA) (2009a). Drug Safety Information for Healthcare Professionals. “Early Communication about an Ongoing Safety Review of clopidogrel bisulfate (marketed as Plavix)”, January 26, 2009. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm079520.htm> (accessed 7 November 2015).
- U.S. Food and Drug Administration (FDA) (2009b). Drug Safety Information for Healthcare Professionals. “Update to the labeling of Clopidogrel Bisulfate (marketed as Plavix) to

alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC)", November 17, 2009. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190787.htm> (accessed 7 November 2015).

U.S. Food and Drug Administration (FDA) (2010). Drug Safety Information for Healthcare Professionals. 10. "Information on Clopidogrel Bisulfate (marketed as Plavix)", October 27, 2010. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm190836.htm> (accessed 7 November 2015).

Warle-van Herwaarden MF, Kramers C, Sturkenboom MC, Van den Bemt PM, De Smet PA (2012). Targeting outpatient drug safety: recommendations of the Dutch HARM-Wrestling Task Force. *Drug Saf* 35: 245–259.

Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK (2001). Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 345: 494–502.

Zeitoun JD, Lefevre JH, Downing N, Bergeron H, Ross JS (2014). Inconsistencies among European Union pharmaceutical regulator safety communications: a cross-country comparison. *PLoS One* 9: e109100.