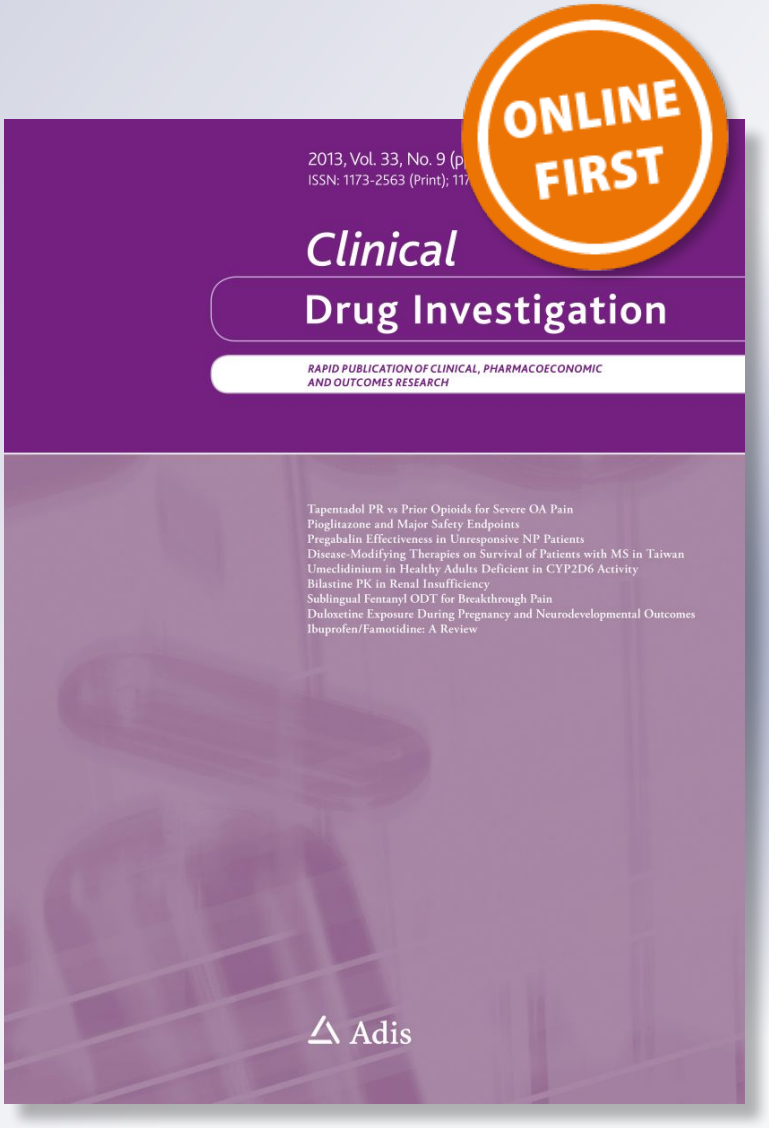
Decrease in Switches to 'Unsafe' Proton Pump Inhibitors After Communications About Interactions with Clopidogrel

Willemien J. Kruik-Kollöffel, Job van der Palen, Myrthe P. P. van Herk-Sukel, H. Joost Kruik & Kris L. L. Movig

Clinical Drug Investigation

ISSN 1173-2563

Clin Drug Investig
DOI 10.1007/s40261-017-0536-x



Springer

Clin Drug Investig
DOI 10.1007/s40261-017-0536-x

ORIGINAL RESEARCH ARTICLE

Decrease in Switches to 'Unsafe' Proton Pump Inhibitors After Communications About Interactions with Clopidogrel

Willemien J. Kruik-Kollöffel[1,2] · Job van der Palen[3,4] · Myrthe P. P. van Herk-Sukel[5] · H. Joost Kruik[6] · Kris L. L. Movig[7]

Abstract

Background In 2009 and 2010 medicines regulatory agencies published official safety statements regarding the concomitant use of proton pump inhibitors and clopidogrel. We wanted to investigate a change in prescription behaviour in prevalent gastroprotective drug users (2008–2011).

Methods Data on drug use were retrieved from the Outpatient Pharmacy Database of the PHARMO Database Network. We used interrupted time series analyses (ITS) to estimate the impact of each safety statement on the number of gastroprotective drug switches around the start of clopidogrel and during clopidogrel use.

Results After the first statement (June 2009), significantly fewer patients switched from another proton pump inhibitor to (es)omeprazole (−14.9%; 95% CI −22.6 to −7.3) at the moment they started clopidogrel compared to the period prior to this statement. After the adjusted statement in February 2010, the switch percentage to (es)omeprazole decreased further (−4.5%; 95% CI −8.1 to −0.9). We observed a temporary increase in switches from proton pump inhibitors to histamine 2-receptor antagonists after the first statement; the decrease in the reverse switch was statistically significant (−23.0%; 95% CI −43.1 to −2.9).

Conclusions With ITS, we were able to demonstrate a decrease in switches from other proton pump inhibitors to (es)omeprazole and an increase of the reverse switch to almost 100%. We observed a partial and temporary switch to histamine 2-receptor antagonists. This effect of safety statements was shown for gastroprotective drug switches around the start of clopidogrel treatment.

Key Points

Since the last communication by regulatory authorities, evidence has emerged with regard to the doubtful scientific evidence of the interaction between clopidogrel and (es)omeprazole. We look back to establish the effect of the safety statements on prescription behaviour in prevalent gastroprotective drug users.

Although changing drugs in general is a risk for therapy adherence, we observed that the advice of regulatory authorities was followed, albeit reluctantly and not fully, and more switches to 'safe' proton pump inhibitors were seen.

Following the communications, a temporary increase in switches to less effective histamine 2-receptor antagonists was observed.

✉ Willemien J. Kruik-Kollöffel
w.kruik@sxb.nl

1 Department of Clinical Pharmacy, Saxenburgh Group, P.O. Box 1, 7770 AA Hardenberg, The Netherlands

2 Department of Clinical Pharmacy, Hospital Group Twente, Almelo, Hengelo, The Netherlands

3 Medical School Twente, Medisch Spectrum Twente, Enschede, The Netherlands

4 Department of Research Methodology, Measurement and Data Analysis, University of Twente, Enschede, The Netherlands

5 Pharmo Institute, Utrecht, The Netherlands

6 Department of Cardiology, Hospital Group Twente, Almelo, Hengelo, The Netherlands

7 Department of Clinical Pharmacy, Medisch Spectrum Twente, Enschede, The Netherlands

Published online: 25 May 2017

1 Introduction

Safety concerns with regard to 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 (DHPC). Concerns originated from a publication by Gilard et al. [1]. In 2008 they reported increased in vitro platelet reactivity and decreased levels of the active metabolite of clopidogrel in patients administered clopidogrel as well as a PPI. These communications caused considerable turmoil among physicians, and the scientific evidence was discussed extensively. Especially in the year following the regulatory agencies' statements, scientists retrospectively explored existing databases and several articles were published in the international literature. In 2013 Focks et al. [2] published a systematic review of all publications on the impact of the addition of PPIs to clopidogrel on platelet function and cardiovascular outcome. They stated that the suggestion that the potential adverse effect should especially be considered if omeprazole is prescribed is based on pharmacological assumptions and laboratory measurements, but is contradicted by the available clinical evidence. The study by Gilard et al. [1] should be considered as hypothesis generating and not confirmation of a clinically relevant interaction. Unfortunately, the regulatory authorities have not given an update after all these reports. Indeed, the statements have altogether been removed from the site of the Dutch regulatory authorities because the usual period of 5 years since publication has passed.

We examined the association between various safety statements and prescription behaviour for gastroprotective (GP) drugs in patients naïve to these drugs who were prescribed clopidogrel in The Netherlands from 2008 to 2011 [3]. We were able to demonstrate statistically significant shifts in the prescription of GP drugs when those statements were launched. In January 2009, after the early communication to re-evaluate the need for a PPI, 15.5% more patients were started concomitantly with (es)omeprazole and 13.8% fewer with other PPIs. In June 2009, directly after the first statement to avoid combinations with a PPI, we measured a steep increase in histamine 2-receptor antagonists (H2RA), peaking at 25%. This effect for H2RA faded away after a few months. An adjusted statement in February 2010 was to avoid (es)omeprazole, and we then found a decrease of 11.9% for (es)omeprazole and an increase of 16.0% for other PPIs. Still, 22.6% of patients started on (es)omeprazole in February 2010. During our study period, a significant proportion of the patients received prescriptions against the advice of regulatory agencies. We philosophised about this discrepancy in an earlier publication [3].

Research into changes in prescribing behaviour as a result of safety communications by regulatory authorities is usually performed in new use, because new use is a more sensitive measure than overall use [4]. In patients already on a GP drug, an extra hurdle has to be taken to follow the official advice. A physician has to change the patient's GP drug when starting clopidogrel or summon a patient to come to the office to change it. A change in treatment is a therapy-related factor that can negatively affect adherence according to the WHO report 'Adherence to long-term therapies, evidence for action' [5]. According to this report, adherence averages 50% and is therefore a serious threat to effective and efficient treatment, resulting in the WHO calling for action in 2003. It is therefore to be understood that physicians feel reluctant to change medication therapy on the basis of doubtful scientific evidence. We were anxious to know whether we could nonetheless demonstrate a change in prescription behaviour when the statements were published on patients who were already using GP drugs at the time they started clopidogrel treatment.

2 Methods

2.1 Design

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

I. Early communication by the US Food and Drug Administration (FDA, 26 January 2009) to re-evaluate the need for a PPI [6].
II. First statement by the European Medicines Agency (EMA, 29 May 2009) [7] and the Dutch Medicines Evaluation Board (MEB, 3 June 2009) [8] to avoid the combination of clopidogrel and a PPI. As a result of those statements, the interaction was integrated into the Dutch national drug-drug interaction database (G-standard), and pharmacists started to contact prescribers in case of a combined prescription for PPI and clopidogrel.
III. Adjusted statement by the Dutch MEB (16 February 2010) [9] and EMA (17 March 2010) [10] to avoid the combination of clopidogrel and (es)omeprazole.

We included patients in our study who started clopidogrel in 2008 until 2011. Those three statements divided the study into four separate periods.

2.2 Data Collection and Analysis

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 [11]. We used dispensing data as a proxy variable for prescribing. The Out-patient Pharmacy Database of the PHARMO Database Network covers a catchment area representing 3.6 million (>20% of the population) residents throughout The Netherlands. Healthcare coverage regarding the reimbursement of concerned drugs was similar for all Dutch citizens and they were all included on an equal basis.

In patients who already used a GP drug for at least 2 weeks before the start of clopidogrel, we determined whether a switch in GP drug was made from 2 weeks before the start of clopidogrel (anticipating the start of clopidogrel) until 4 weeks after the start of clopidogrel, i.e. a concomitant switch. A switch in GP drug was defined as a change from one group of GP drugs to another: (es)omeprazole (ATC code A02BC01 and A02BC05), another PPI (ATC code A02BC, not A02BC01 or A02BC05) or H2RA (ATC code A02BA). The first switch from one group of GP drugs to another was analysed. Specialities and generics are combined.

We used interrupted time series analyses (ITS, segmented linear regression analyses) to estimate the impact of each event on the dispensing of GP drugs, as described by the Cochrane Collaboration [12]. Statistical significance was set at $p \leq 0.05$.

More details on the design, data collection and analysis are described in our earlier publication [3].

3 Results

The numbers of patients using and switching GP drugs at the start of the period are shown in Table 1.

Figure 1 shows the switches from (es)omeprazole to another PPI and vice versa. There was a statistically significant decline in the number of switches from another PPI to (es)omeprazole after the first statement (−14.9%; 95% CI −7.3 to −22.6) and after the adjusted statement (−4.5%; 95% CI −8.3 to −0.9). The decrease in the slope for switches from (es)omeprazole to another PPI was statistically significant after the adjusted statement (−2.3; 95% CI −3.8 to −0.7). In January 2008, the percentage of patients switching from another PPI to (es)omeprazole was 11.7% (starting point of the regression line). At the end of our study in December 2011, still 2.6% of patients switched from another PPI to (es)omeprazole (end point of the regression line). This was in contrast to the percentage of patients switching from (es)omeprazole to another PPI, which increased in the same period from 63.1 to 94.0%.

Figure 2a describes the group of patients who switched from a PPI to an H2RA or vice versa in each month. Only the decline in the number of switches from an H2RA to a PPI after the first statement was statistically significant (−23.1%; 95% CI −43.1 to −2.9). In general, no more than 30% of patients who started clopidogrel switched from an H2RA to a PPI or vice versa, except for a distinct increase in the switch from a PPI to an H2RA after the first statement, reaching a peak of about 41% of patients switching their GP drug when starting clopidogrel. This increase faded away in subsequent months to percentages below 5%. Figure 2b shows an enlargement of this part.

4 Discussion

In our study, we were able to demonstrate an increase in switches from (es)omeprazole to other PPIs and a decrease of the reverse switch to almost none, following statements by the medicines regulatory agencies. Switches to other PPIs were almost exclusively to pantoprazole, as this is also theoretically the least likely PPI to interact with clopidogrel [13]. Lansoprazole and rabeprazole were seldom used in our study as well as in The Netherlands in general [14]. The percentage of patients switching to another PPI was close to 100% by the end of 2011. We observed a temporary large increase in switches from PPIs to an H2RA, although this change did not reach statistical significance (25.2%; 95% CI −13.1 to 63.5). Although this increase seems radical, the absence of statistical significance can be explained by the high variability following the first statement, as shown in Fig. 2a, b. The number of reverse switches at that moment, i.e. from an H2RA to a PPI, did reach statistical significance (−23.0%; 95% CI −43.1 to −2.9). The distribution among the various PPIs in our study before the start of clopidogrel is in accordance with the use of PPIs in The Netherlands [14]. In our study 71% of the patients used (es)omeprazole in 2008–2011; in The Netherlands these two drugs were used by 72% of patients.

The effect of safety statements on prescription behaviour was shown for GP drug switches around the start of clopidogrel treatment. Although a minority of the changes were statistically significant, the evidence according to the graphic reflection is evident. The percentage of patients being switched from an H2RA to a PPI or vice versa was less than 5%, which reflects an overall decrease in H2RA use in The Netherlands in the period from 2002 (402,512 patients) to 2012 (90,870 patients) [14]. This trend was confirmed by the revised guidelines of the Dutch College of General Practitioners of January 2013, in which H2RA double dosing was no longer considered adequate gastroprotection [15].

We observed an increasing percentage of patients being switched from 2008 through 2011 (Table 1), showing that the advice of regulatory authorities was at least partly

Table 1 Numbers of patients using and switching gastroprotective (GP) drugs

	2008	2009	2010	2011	Total study population
Patients already using GP drug and starting clopidogrel	2345	2698	2669	2893	10,605
Patients switching GP drug when starting clopidogrel, *n* (%)	222 (9%)	566 (21%)	884 (33%)	1049 (36%)	2721 (26%)
Histamine 2-receptor antagonist (ATC-code), *n* (%)[a]					
Cimetidine (A02BA01)	15 (1%)	13 (0%)	7 (0%)	10 (0%)	45 (0%)
Ranitidine (A02BA02)	136 (6%)	143 (5%)	135 (5%)	113 (4%)	527 (5%)
Famotidine (A02BA03)	4 (0%)	6 (0%)	7 (0%)	2 (0%)	19 (0%)
Nizatidine (A02BA04)	4 (0%)	1 (0%)	0 (0%)	0 (0%)	5 (0%)
Proton pump inhibitor (ATC code), *n* (%)[a]					
Omeprazole (A02BC01)	960 (40%)	1231 (46%)	1249 (47%)	1463 (51%)	4903 (46%)
Pantoprazole (A02BC02)	767 (33%)	763 (28%)	769 (29%)	773 (27%)	3072 (29%)
Lansoprazole (A02BC03)	37 (2%)	28 (1%)	26 (1%)	39 (1%)	130 (1%)
Rabeprazole (A02BC04)	78 (3%)	70 (3%)	71 (3%)	59 (2%)	278 (3%)
Esomeprazole (A02BC05)	344 (15%)	443 (16%)	405 (15%)	434 (15%)	1626 (15%)

[a] First use of GP drug

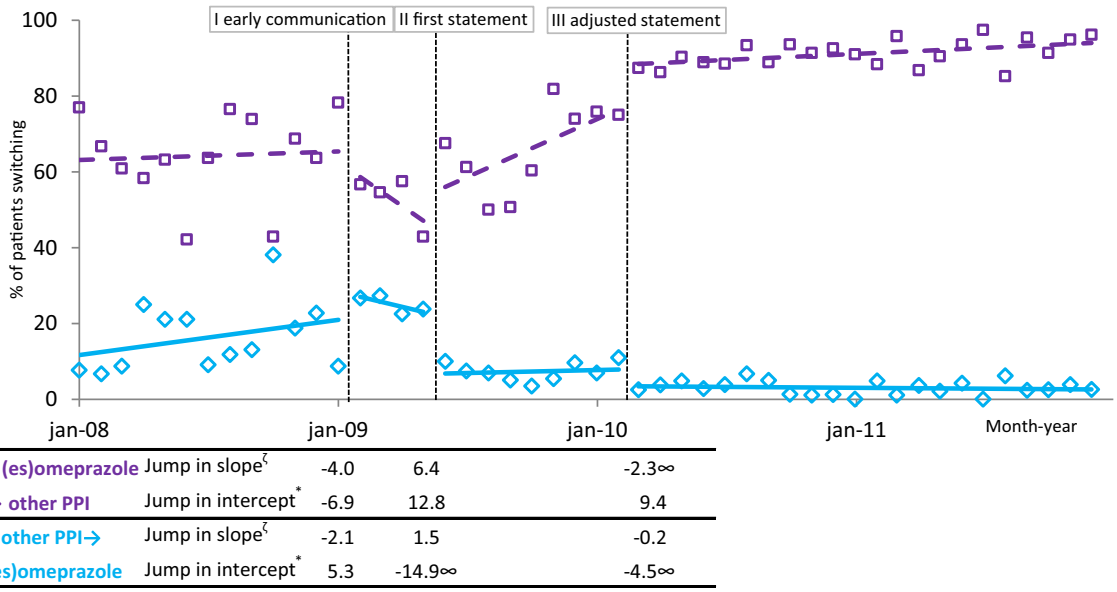
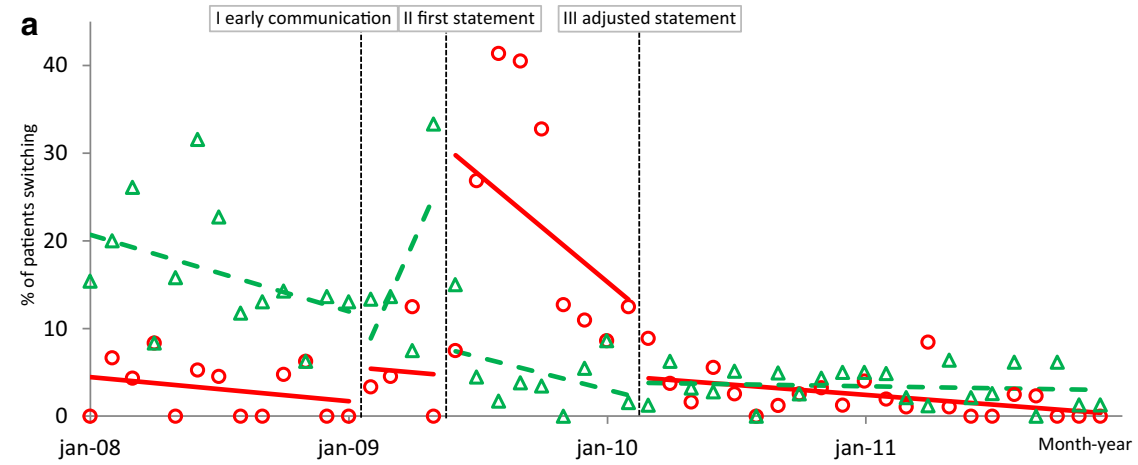


Fig. 1 Patients with prior gastroprotection switching at the start of clopidogrel to *open square* other proton pump inhibitor (PPI) (*purple*) or *open diamond* (es)omeprazole (*blue*). *I* Early communication to re-evaluate need for PPI; *II* first statement to avoid combination with PPI; *III* adjusted statement to avoid combination with (es)omeprazole. $^{\zeta}$Jump in slope from the previous to the following period. *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 ($p \leq 0.05$)

accepted. As already discussed in our previous study [3], official advice on this supposed interaction was followed reluctantly and not fully. As a rule, physicians, including cardiologists, are sensitive to up-to-the-minute reported evidence. Safety statements are usually delayed from the latest information. Doubtful scientific evidence has probably been the cause of the delay in the case of clopidogrel-(es)omeprazole. As can be seen from the figures, the deflection of the curves starts when the statements are published. Cabana [16] described that, to achieve a change in behaviour, various hurdles have to be overcome: knowledge, attitudes and behaviour. With regard to knowledge, Piening et al. [17] investigated by means of a questionnaire in December 2009 and January 2010 the level of knowledge on safety information on four specific drugs (rimonabant, moxifloxacin, clopidogrel and etoricoxib) among general practitioners, internists, community pharmacists and hospital pharmacists; 88% indicated that



○ PPI → H2RA	Jump in slope$^{\zeta}$	0.02	-1.9	1.9
	Jump in intercept*	3.9	25.2	-6.9
Δ H2RA → PPI	Jump in slope$^{\zeta}$	6.1	-6.0	0.6
	Jump in intercept*	-2.3	-23.0$^{\infty}$	2.0

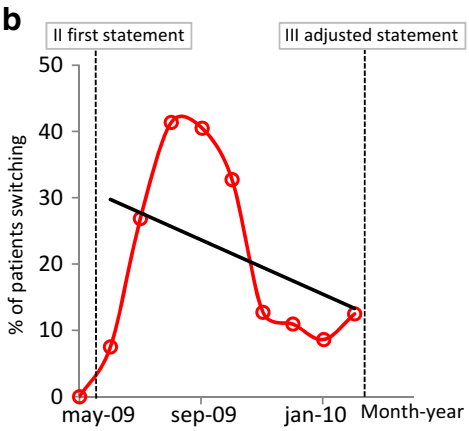


Fig. 2 **a** Patients with prior gastroprotection switching at the start of clopidogrel to *open circle* histamine 2-receptor antagonist (H2RA) (*red*) or *open triangle* proton pump inhibitor (PPI) (*green*). *I* Early communication to re-evaluate need for PPI; *II* first statement to avoid combination with PPI; *III* adjusted statement to avoid combination with (es)omeprazole. $^{\zeta}$Jump in slope from the previous to the following period. *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 ($p \leq 0.05$). **b** Augmentation of Fig. 1, patients switching from proton pump inhibitor to histamine 2-receptor antagonist. *Black* regression line and *red* connecting line

they were aware of the safety issues for clopidogrel. The trustworthiness of the source of the safety information is an aspect that determines the factor attitude. In the case of clopidogrel, the source, i.e. the Dutch Medicines Evaluation Board, is considered to be very trustworthy. The power of the message could have been augmented, in our opinion, by adding another trustworthy source, i.e. the professional associations. No attention was given to this issue in general medicine or cardiology journals in The Netherlands (e.g. Medisch Contact, Nederlands Tijdschrift voor Geneeskunde, Netherlands Heart Journal). With regard to behaviour, the healthcare professionals reported to have taken action (e.g. adjusting therapy, informing colleagues, discussion with patients) in response to 29% of the DHPCs, ranged from 23% of internists to 37% of community pharmacists [17]. In the case of the interaction of clopidogrel with GP drugs, this was probably partly because of the existing scientific doubt about the interaction [2].

The clinical implication of not complying with the official advice is unknown, because the scientific evidence of the interaction is in doubt. The Cogent study group [18] concluded that there was no apparent cardiovascular interaction between clopidogrel and omeprazole, but could not rule out a clinically meaningful difference in cardiovascular events in a group of patients prescribed clopidogrel with or without omeprazole. However, the prophylactic use of omeprazole reduced the rate of upper gastrointestinal (GI) bleeding. In 2011 Fernando et al. [19]

recommended in a review that only patients with previous GI bleeding or multiple risk factors for GI bleeding should be prescribed a GP drug. With regard to the pharmacological basis of the interaction, (es)omeprazole is the most potent inhibitor of the liver enzyme CYP2C19 out of all the PPIs. It could interfere with clopidogrel metabolism and reduce exposure to the active metabolite of clopidogrel [19]. Not complying with the official advice could have legal complications in a case where a patient has adverse effects from inadequate clopidogrel dosing. On the other hand, following the advice could result in gastrointestinal events in patients prescribed no GP drug at all or, as we now know, a less effective H2RA. If a PPI is indicated, a consideration could be to switch to pantoprazole when starting clopidogrel.

In our study, about 40% of patients did not use a GP drug at all. Not being prescribed a GP drug if needed could be considered an unintended effect of safety warnings. We discussed this point in our earlier publication [3]. It would have been interesting to add the clinical outcomes of these patients. Unfortunately, our database-based study does not have this information. The uncertainty among physicians and pharmacists about the supposed interaction could have led to the instruction to patients to interrupt the use of GP drugs. This effect is hard to deduce from our data based on dispensing information. However, a more pronounced effect would have been seen in patients not starting a GP drug at all. The percentage of patients without gastroprotection in our cohort decreased from 44 to 36% [3]. We suppose that a greater proportion of these patients would have qualified for GP drugs according to the guidelines implemented in those years, such as the Expert Consensus Document of the American College of Cardiology Foundation on the concomitant use of PPIs and thienopyridines [20] and the report of the Dutch Harm-Wrestling Task Force [21].

Our study is the only one, as far as we know, to study changes in PPI prescription at the individual patient level, using data from over 10,000 patients, aggregated by monthly level before and after the three safety statements. Some other groups studied the effect of the communications on the prescription of PPI. In 398 Spanish patients discharged in 2012 after acute coronary syndrome who were prescribed clopidogrel as well as a GP drug, 36% were prescribed (es)omeprazole and 45% pantoprazole [22]. A minority of 11% were prescribed H2RA (ranitidine). At admission 71% were using (es)omeprazole. A large US cohort identified patients using clopidogrel and a PPI [23]. After 17 November 2009 58% of the PPIs prescribed in combination with clopidogrel were (es)omeprazole. No information on H2RA use is given. A Canadian group focussed on the changes in the prescription of pantoprazole, which rapidly became the most commonly prescribed PPI in 52% of the patients by the end of 2009 (24% in the final quarter of 2008) and 71% by the end of 2013 [24]. The use of omeprazole was decreased further and 4.4% of the patients received an H2RA. In a Qatar hospital in 2012, in 300 patients rabeprazole and lansoprazole were prescribed after acute coronary syndrome in 81 and 13%, respectively [25]. Omeprazole and esomeprazole were the least prescribed PPIs with 4 and 2.6%, respectively, of the total utilization.

We had to deal with three very distinct breaking points of variable length, and we were not able to gather sufficient data points in all periods for a solid ITS, especially for the period after the early communication. For example, of our total study population of 39,496 patients, in August 2008, 177 patients started clopidogrel and were already using a GP drug. Of those 177 patients, only 17 switched: 13 from (es)omeprazole to another PPI, two from another PPI to (es)omeprazole and two from an H2RA to a PPI. The statistical results depend upon the slopes of the lines (as the regression line is steeper, the probability of statistical significance increases), the number of points used in each regression line (after the early communication, we had only 4 months to use in our analysis) and the spread around the regression line (which is among other factors determined by a small amount of patients switching in a certain month to a certain group of drugs). In Fig. 2b, an enlargement of a part of Fig. 2a is shown, which demonstrates the limitations of ITS in some situations: the trend is very clear, but calculating a regression line obscures the true effect. Nevertheless, the trends are clear, mainly due to the large number of patients included in the study. As already shown by Piening et al. [26], ITS is the best available study design to evaluate the impact of policy changes on prescription behaviour. However, to prove an effect in prevalent users is complicated, because, as stated by Reber et al. [4], new use is a more sensitive measure than overall use. In a publication in 2013, this group systematically evaluated the determinants of the impact of 59 DHPCs for 46 drugs issued in The Netherlands, all in new drug users. We also examined the changes in prescribing behaviour at first in new users [3]. Additionally, in the present analysis, we were able to show an effect in prevalent users. In such a group of patients, regulatory authorities would logically have to use more convincing strategies to achieve a change in prescription behaviour, such as collaboration with professional associations and assessing all the existing evidence.

4.1 Conclusion

With ITS, we were able to demonstrate an effect of safety statements on the prescription of GP drugs in patients already on GP drugs. Although the place in therapy of clopidogrel is repositioning to specific, smaller groups of

patients, the lessons learned in this study should be applied to managing drug safety information in general.

Compliance with ethical standards

For this type of study formal consent is not required.

Funding No sources of funding were used to assist in the preparation of this article.

Conflict of interest Willemien J. Kruik-Kollöffel, Job van der Palen, H. Joost Kruik and Kris L. L. Movig declare no support from any organization for the submitted work. Myrthe P. P. van Herk-Sukel is an employee of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. This study, however, was not supported by a pharmaceutical company. None of the other authors have any conflicts of interest to disclose and there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Gilard M, Arnaud B, Cornily JC, et al. 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. 2008;51:256–60.
2. Focks JJ, Brouwer MA, Van Oijen MG, et al. Concomitant use of clopidogrel and proton pump inhibitors: impact on platelet function and clinical outcome—a systematic review. Heart. 2013;99:520–7. doi:10.1136/heartjnl-2012-302371.
3. Kruik-Kollöffel WJ, Van der Palen J, Kruik HJ, et al. Prescription behavior for gastroprotective drugs in new users as a result of communications regarding clopidogrel—proton pump inhibitor interaction. Pharm Res Perspect. 2016;4(4):e00242. doi:10.1002/prp2.242.
4. Reber KC, Piening S, Wieringa JE, et al. When direct health-care professional communications have an impact on inappropriate and unsafe use of medicines. Clin Pharmacol Ther. 2013;93:360–5. doi:10.1038/clpt.2012.262.
5. World Health Organization (WHO). Adherence to long-term therapies: evidence for action. Geneva; January 2003. http://apps.who.int/iris/bitstream/10665/42682/1/9241545992.pdf. Accessed 4 Feb 2017.
6. U.S. Food and Drug Administration (FDA). Drug safety information for healthcare professionals. "Early communication about an ongoing safety review of clopidogrel bisulfate (marketed as Plavix)". 2009. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079520.htm. Accessed 4 Feb 2017.
7. European Medicines Agency (EMA). News and press release archive. "Public statement on possible interaction between clopidogrel and proton pump inhibitors". 2009. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000194.jsp&mid=WC0b01ac058004d5c1. Accessed 4 Feb 2017.
8. Dutch Medicines Evaluation Board (MEB). Direct healthcare professional communications. 2009. Original link has been removed from the internet, but mentioned in Pharm Weekbl 2009;144:7. Accessed 7 Nov 2015.
9. Dutch Medicines Evaluation Board (MEB). 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 Nov 2015.
10. European Medicines Agency (EMA). News and press release archive. "Public statement on interaction between clopidogrel and proton-pump inhibitors". 2010. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/03/news_detail_001008.jsp&mid=WC0b01ac058004d5c1. Accessed 4 Feb 2017.
11. Herings R, Pederson L. Pharmacy-based medical record linkage systems. In: Strom B, Kimmel S, Hennessy S, editors. Pharmacoepidemiology. 5th ed. Oxford: Wiley-Blackwell; 2012. p. 270–86.
12. Cochrane Collaboration. Effective practice and organisation of care (EPOC). Interrupted time series (ITS) analyses. Oslo; 2013. http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/21%20Interrupted%20time%20series%20analyses%202013%2008%2012_2.pdf. Accessed 4 Feb 2017.
13. Cuisset T, Frere C, Quilici J, et al. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study. J Am Coll Cardiol. 2009;54(13):1149–53. doi:10.1016/j.jacc.2009.05.050.
14. Drug Information System of National Health Care Institute. 2016. https://www.gipdatabank.nl/. Accessed 3 Jul 2016.
15. Numans M, De Wit N, Dirven JAM, et al. NHG-standaard maagklachten. The Dutch College of General Practitioners. 2013. https://www.nhg.org/standaarden/volledig/nhg-standaard-maagklachten-derde-herziening Accessed 4 Feb 2017.
16. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? JAMA. 1999;282:1458–65.
17. Piening S, Haaijer-Ruskamp FM, De Graeff PA, et al. Healthcare professionals' self-reported experiences and preferences related to direct healthcare professional communications. Drug Saf. 2012;35:1061–72. doi:10.2165/11635750-000000000-00000.
18. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med. 2010;363(20):1909–17. doi:10.1056/NEJMoa1007964.
19. Fernando H, Dart AM, Peter K, et al. Proton pump inhibitors, genetic polymorphisms and response to clopidogrel therapy. Thromb Haemost. 2011;105(6):933–44. doi:10.1160/TH10-11-0715.
20. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol. 2010;56:2051–66. doi:10.1016/j.jacc.2010.09.010.
21. Warle-van Herwaarden MF, Kramers C, Sturkenboom MC, et al. Targeting outpatient drug safety: recommendations of the Dutch HARM-Wrestling Task Force. Drug Saf. 2012;35:245–59. doi:10.2165/11596000-000000000-00000.
22. Lozano I, Sanchez-Insa E, De Leiras SR, et al. Acute coronary syndromes, gastrointestinal protection, and recommendations regarding concomitant administration of proton-pump inhibitors (omeprazole/esomeprazole) and clopidogrel. Am J Cardiol. 2016;117:366–8. doi:10.1016/j.amjcard.2015.11.007.
23. Guérin A, Mody R, Carter V, et al. Changes in practice patterns of clopidogrel in combination with proton pump inhibitors after an FDA safety communication. PloS One. 2016;11:e0145504. doi:10.1371/journal.pone,0145504.
24. Juurlink DN, Gomes T, Paterson JM, et al. Trends in the coprescription of proton pump inhibitors with clopidogrel: an

ecological analysis. CMAJ Open. 2015;3:E428–31. doi:10.9778/cmajo.20140078.

25. Awaisu A, Hamou F, Mekideche L, et al. Proton pump inhibitor co-prescription with dual antiplatelet therapy among patients with acute coronary syndrome in Qatar. Int J Clin Pharm. 2016;38:353–61. doi:10.1007/s11096-016-0250-4.

26. Piening S, Haaijer-Ruskamp FM, De Vries JT, et al. Impact of safety-related regulatory action on clinical practice: a systematic review. Drug Saf. 2012;35:373–85. doi:10.1002/pds.3509.