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ORIGINAL ARTICLE

Concomitant use of clopidogrel and proton pump inhibitors: A retrospective analysis of prescription behaviour

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Abstract

Aims: Since omeprazole and esomeprazole reduce the effect of clopidogrel on the inhibition of platelet aggregation, concomitant use of these drugs has been discouraged by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) since 2010. Currently, it is unknown how often this undesired drug–drug combination is prescribed. The aim of this article is to determine the proportion of patients using omeprazole or esomeprazole among patients using clopidogrel with gastroprotective drugs and to identify differences between these two groups with regard to patient characteristics and prescriber characteristics.

Methods: This was a retrospective analysis of Dutch outpatient medication prescription records between 2015 and 2022. The database had a coverage of approximately 62% of all outpatient prescriptions dispensed in The Netherlands.

Results: The proportion of patients using omeprazole or esomeprazole as gastroprotective drug in combination with clopidogrel declined from 19.7% to 8.7% between 2015 and 2022. The undesired drug–drug combination was more often prescribed by internists, to women and to patients with polypharmacy (using >10 drugs).

Conclusions: Although the proportion of patients using clopidogrel together with omeprazole or esomeprazole declined between 2015 and 2022, the undesired combination is still frequently prescribed in The Netherlands. Education about this drug–drug interaction for pharmacists and prescribers is needed since pharmacotherapeutic alternatives are available.

KEYWORDS
clopidogrel, drug interactions, outpatients, proton pump inhibitors, retrospective studies

1 | INTRODUCTION

Platelet aggregation inhibitors (PY12 inhibitors), such as clopidogrel, are associated with an increased risk of gastrointestinal (GI) bleeding.[1] Therefore, in patients with additional risks of GI bleeding who are taking platelet aggregation inhibitors, the use of gastroprotective drugs is recommended.[2,3] However, the commonly prescribed proton pump inhibitors omeprazole and esomeprazole can reduce the effect of clopidogrel on the inhibition of platelet aggregation.[4] Due to this drug–drug interaction, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) stated in 2010 that the combination of clopidogrel and omeprazole or esomeprazole should be avoided.[5,6]

In accordance with the international guidelines, Dutch guidelines[7–9] dissuade the combination of clopidogrel and omeprazole or esomeprazole. Since other gastroprotective drugs, such as pantoprazole are not associated with the risk of reducing the effectiveness of clopidogrel, alternative gastroprotective drugs are recommended for patients using clopidogrel.[10] For cardiac indications, clopidogrel can be replaced by prasugrel[11] or ticagrelor.[12]

Although omeprazole and esomeprazole significantly reduce the effect of clopidogrel on platelet aggregation inhibition,[4,13] the scientific proof on primary endpoints, such as cardiovascular events, is inconclusive.[14] Some observational studies show a higher incidence of cardiovascular events in patients using clopidogrel and omeprazole or esomeprazole,[15–19] while other studies found no difference on these endpoints.[20–22]

Since the evidence of the drug–drug interaction is inconclusive, most hospitals and pharmacies have developed their own protocols regarding the combination of clopidogrel and omeprazole or esomeprazole. A previous study in 2008 showed that of the patients using gastroprotective drugs who started with clopidogrel, 20.7% used esomeprazole or omeprazole.[23] This declined to 15.1% in 2011.[23] This indicates that many patients still receive the undesired drug–drug combination while a safer pharmaceutical alternative is available. Currently, it is unknown how often the combination of clopidogrel with omeprazole or esomeprazole is prescribed in clinical practice after 2011.

The aim of the study is to determine the proportion of patients using omeprazole or esomeprazole among patients using clopidogrel in combination with gastroprotective drugs in The Netherlands between 2015 and 2022. We also identify differences between these two groups with regard to patient characteristics and prescriber characteristics.

What is already known about this subject

- The proton pump inhibitors omeprazole and esomeprazole can reduce the effect of clopidogrel on the inhibition of platelet aggregation.
- Concomitant use of these drugs has been discouraged by the FDA and EMA since 2010.
- Currently, it is unknown how often this unwanted drug–drug combination is prescribed in clinical practice and which patients are at risk of receiving this combination.

What this study adds

- The proportion of patients using omeprazole or esomeprazole as gastroprotective drug in combination with clopidogrel declined from 19.7% to 8.7% between 2015 and 2022.
- The undesired drug–drug combination was more often prescribed by internists, to women and to patients with polypharmacy (using >10 drugs).
- Awareness about this drug–drug interaction for pharmacists and prescribers is needed since pharmacotherapeutic alternatives are available

2 | METHODS

2.1 | Design and setting

A retrospective analysis of medication prescription records in the Netherlands was performed using the IQVIA Xtrend Real-World Data Longitudinal Prescription database (LRx, Amsterdam, The Netherlands). This longitudinal database contains coded patient prescription records including patient characteristics (age, sex), dispenses (pharmacy, prescription date), medication (name, dose, strength, therapy duration) and prescriber information. The pharmacies send prescription data monthly to a trusted third party. This party collects all data and ensures encrypted data. In total, the database provides a coverage of approximately 62% of all outpatient prescriptions dispensed in The Netherlands, represented by retail pharmacies, outpatient hospital pharmacies and dispensing general practitioners (see Supporting Information, SI 1). The data contain no prescriptions from inpatient hospital pharmacies. (See Supporting Information, SI 2 for more detailed information about the prescription database.) The prescriptions in the database are electronic, as electronic prescribing combined with a clinical decision support system has been mandatory within the Dutch healthcare system since 2014.

2.2 | Ethics

The study protocol was reviewed by the Erasmus MC Medical Ethics Committee. This committee provided a waiver for obtaining informed consent (MEC-2019-0651).

2.3 | Primary and secondary outcomes

The primary outcome of this study is the proportion of patients using omeprazole or esomeprazole among patients using clopidogrel with gastroprotective drugs. The secondary outcome is the identification of differences in patient characteristics and prescriber characteristics between these two groups and to describe regional differences.

2.4 | Inclusion criteria

Patients were selected in the database from 1 January 2015 up to 31 December 2022 and descriptive data were displayed. Patients were included if they were prescribed with concomitant drug use according to patient groups of interest as displayed in Table 1. The analysis was performed for each calendar year between 2015 and 2022. In each year, patients could only be included once, based on

TABLE 1 Patient groups of interest.

	Concomitant medication
1	Patients using clopidogrel and omeprazole or esomeprazole
2	Patients using clopidogrel and lansoprazole, pantoprazole, rabeprazole or high dose H2 receptor antagonists[a]
3	Patients using prasugrel or ticagrelor and omeprazole or esomeprazole
4	Patients using prasugrel or ticagrelor and lansoprazole, pantoprazole, rabeprazole or high dose H2 receptor antagonists[a]

[a]Cimetidine (≥400 mg per day), famotidine (≥40 mg per day), nizatidine (≥300 mg per day), ranitidine (≥300 mg per day and retrieved from the market in 2019), calculated daily dosage per patient per year.

the first combination of concomitant medication during that year. For example, a patient who started using prasugrel with omeprazole in 2015, and switched from prasugrel to clopidogrel in May 2017, and in June 2018 stopped using medication, was included in group 3 in 2015, 2016 and 2017, and in group 1 in 2018. For group 4, we only included high-dose H2 receptor antagonists since these drugs are only effective for the prevention of gastrointestinal bleeding at a high dose[24]; cimetidine (≥400 mg/day), famotidine (≥40 mg/day), nizatidine (≥300 mg/day) and ranitidine (≥300 mg/day). The dosage of the high-dose H2 antagonists was based on the average daily dose (total dose divided by dispensing days).

2.5 | Concomitant use

Since the drug–drug interaction between clopidogrel and omeprazole or esomeprazole is only clinically relevant when this combination is used for at least 7 days, patients were selected when the prescription for omeprazole or esomeprazole was for at least 7 consecutive days. Concomitant drug use was defined as overlapping supply days of clopidogrel and omeprazole or esomeprazole for at least 7 days. Gaps between following dispenses were bridged by filling in the gap between dispenses with the number of supply days, and a 30-day gap for the following dispensings was accepted.

2.6 | Patient characteristics

Patient characteristics were retrieved from the database including: sex, birth year and the number of different Anatomical Therapeutic Chemical (ATC)02 codes used. The number of ATC02 codes was used as a measure of polypharmacy. Contraceptive drugs and vaccines were excluded. Age was measured at inclusion and categorized into four groups: <60 years, 60–70, 70–80 and ≥80 years.

2.7 | Prescriber and pharmacy characteristics

Information about the specialty of the prescriber who started the concomitant drug was selected from the database, namely; general practitioner, cardiologist, internists, neurologist or other medical specialist. If the prescription was not initiated by a medical specialist, the patient was included in the prescriber group of general practitioners. To analyse regional differences in prescription behaviour, the province of the dispensing pharmacy was included in the analysis.

2.8 | Switching between drug groups

To gain insight in switching behaviour between the drug groups, we analysed the medication that patients used before and after the combination of clopidogrel with omeprazole or esomeprazole for the year 2022. To describe switching between drug groups, patients were selected in the database when they used PY12 inhibitors, gastroprotective drugs or a combination of both over a period of 4 months before or after the concomitant use of clopidogrel and omeprazole or esomeprazole.

2.9 | Statistical analysis

For the primary outcome—the proportion of patients using omeprazole or esomeprazole among patients using clopidogrel in combination with gastroprotective drugs—we calculated confidence intervals (CIs) as population proportion. Numbers (%) are presented for the categorical variables. We conducted chi-squared tests to assess differences between patients using clopidogrel with omeprazole or esomeprazole and patients using clopidogrel with other gastroprotective drugs for the categorical variables. *P*-values of <0.05 were considered statistically significant. Standardized residuals (SRs) were reported to identify which subgroups where responsible for the results. If these residuals were >2.0 or <−2.0, we considered the observed count to be significantly larger or smaller, respectively, than would be expected. All analyses were performed using SPSS version 28.0.1.0.

3 | RESULTS

Of the patients using PY12 inhibitors and gastroprotective drugs between 2015 and 2022, the combination of clopidogrel with gastroprotective drugs other than omeprazole and esomeprazole was most often prescribed (see Figure 1). The combination of prasugrel or ticagrelor and omeprazole or esomeprazole was prescribed least frequently. An overview of patients using only clopidogrel, prasugrel or ticagrelor in the database is provided in Table S1 in Supporting Information SI 3.

From 2015 to 2022, the proportion of patients using omeprazole or esomeprazole among patients using clopidogrel with gastroprotective drugs declined gradually from 19.7% (CI: 19.3–20.0%) in 2015 to 8.7% (CI: 8.5–8.8%) in 2022 (see Table 2). Table 3 displays the distribution of the drugs included in the group of gastroprotective drugs by year, showing that pantoprazole was used most often (>67%) throughout the years.

Table 4 displays characteristics of patients using clopidogrel and proton pump inhibitors in 2015 (first year of analysis) and the most recent data, between 2020 and 2022. The analysis of data from 2016 to 2019 is available in Supporting Information SI 3 and shows similar trends. The combination of clopidogrel with omeprazole or esomeprazole was more often prescribed to women. This finding was statistically significant in each analysed year (2015–2022). In three of the eight analysed years (2016, 207 and 2019), patients >80 years received the unwanted combination more often. In 2022, patients aged between 60 and 70 years more often received clopidogrel with omeprazole or esomeprazole compared to clopidogrel with other gastroprotective drugs. However, these findings were not statistically significant in the other analysed years. Adherence to the guidelines differed significantly across different prescribers in every analysed year. Between 2017 and 2021, the combination of clopidogrel with omeprazole or esomeprazole was prescribed more often by internists and medical specialists from an unspecified specialism compared to prescriptions from cardiologists, general practitioners and neurologists (SR between 2.7 and 8.6). In 2015 cardiologists more often prescribed the desired combination of clopidogrel and GI drugs (SR −4.3). In 2016 the unwanted combination was more often prescribed by general practitioners (SR 3.2). Neurologists and cardiologists more often adhered to the guidelines than other medical specialists (SR between: −2.6 and 5.6), shown in the years 2016–2021 for neurologists and between 2015 and 2019 for cardiologists. Patients who used more than 10 drugs more often received the unwanted combination of clopidogrel with omeprazole or esomeprazole. This finding was statistically significant in each analysed year (2015–2022).

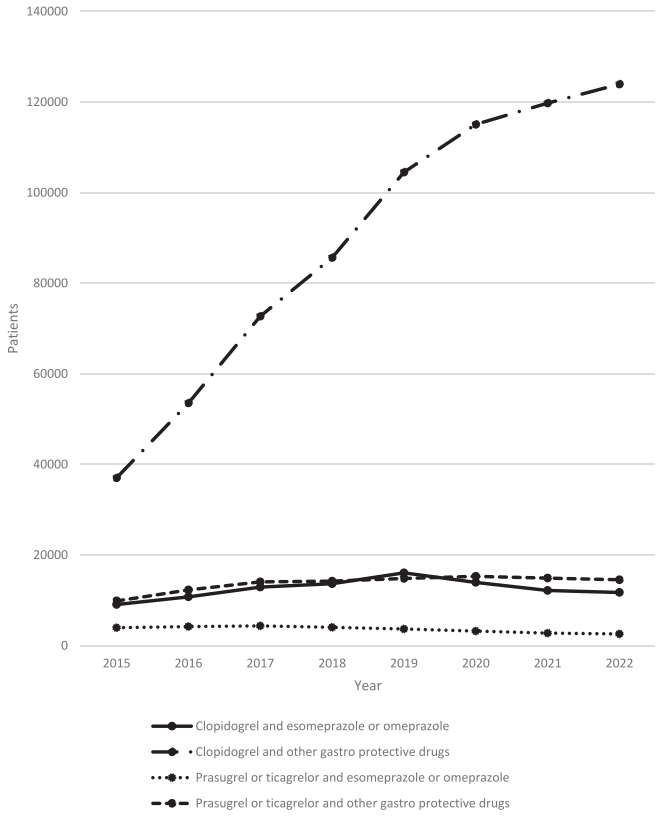

FIGURE 1 Concomitant use of PY12 inhibitors and gastroprotective drugs between 2015 and 2022.

Adherence to the recommendation to avoid concomitant use of clopidogrel with omeprazole or esomeprazole varies by province (see Supporting Information SI 4). In the provinces Noord-Brabant, Overijssel and Zuid-Holland, the highest percentages of patients using clopidogrel with omeprazole or esomeprazole were found among all patients using clopidogrel with gastroprotective drugs.

Figure 2 displays changes in drug use before and after the concomitant use of clopidogrel and omeprazole or esomeprazole in 2022. Most often, omeprazole or esomeprazole was used before a prescription of concomitant clopidogrel and omeprazole or esomeprazole was started. In total, 536 patients switched from clopidogrel with a recommended gastroprotective drug to the undesired drug–drug combination of clopidogrel with omeprazole or esomeprazole. When patients stopped using the undesired drug–drug combination, they switched to monotherapy clopidogrel (1990 switchers) or omeprazole or esomeprazole (1715 switchers). Also, the switch to the recommended drug–drug combination clopidogrel with other gastroprotective drugs was detected for 1168 users. If patients continued a combination of gastroprotective drugs and a PY12-inhibitor, the gastroprotective drug was more frequently replaced than the PY12-inhibitor.

TABLE 2 Concomitant use of PY12 inhibitors and gastroprotective drugs between 2015–2022.

Concomitant medication	2015 $n = 46\,130$	2016 $n = 64\,335$	2017 $n = 85\,650$	2018 $n = 99\,326$	2019 $n = 120\,594$	2020 $n = 129\,037$	2021 $n = 131\,953$	2022 $n = 135\,701$
Clopidogrel and omeprazole or esomeprazole	9076	10 771	12 925	13 669	16 064	13 962	12 174	11 741
Clopidogrel and other gastro protective drugs	37 054	53 564	72 725	85 657	104 530	115 075	119 779	123 960
Proportion of patients using omeprazole or esomeprazole among patients using clopidogrel with gastro protective drugs	19.7% CI: 19.3–20.0%	16.7% CI: 16.5–17.0%	15.1% CI: 14.9–15.3%	13.8% CI: 13.6–14.0%	13.3% CI:13.1–13.5%	10.8% CI: 10.7–11.0%	9.2% CI: 9.1–9.4%	8.7% CI: 8.5–8.8%

Abbreviation: CI, confidence interval.

TABLE 3 Distribution of the drugs included in the group of gastroprotective drugs per year.

	2022		2021		2020		2019	
	Total 29 954	Percentage	Total 30 715	Percentage	Total 33 828	Percentage	Total 34 865	Percentage
Cimetedine	88	0.29	61	0.20	222	0.66	134	0.38
Esomeprazole	1827	6.10	1875	6.10	2072	6.13	2245	6.44
Famotidine	589	1.97	411	1.34	204	0.60	94	0.27
Lansoprazole	569	1.90	595	1.94	555	1.64	494	1.42
Nizatidine	0	0.00	0	0.00	1	0.00	5	0.01
Omeprazole	4104	13.70	4506	14.67	5366	15.86	6128	17.58
Pantoprazole	21 666	72.33	22 190	72.24	24 341	71.96	24 516	70.32
Rabeprazole	1111	3.71	1077	3.51	1067	3.15	1007	2.89
Ranitidine	0	0.00	0	0.00	0	0.00	242	0.69
	2018		**2017**		**2016**		**2015**	
	Total 33 529	Percentage	Total 32 379	Percentage	Total 28 071	Percentage	Total 22 746	Percentage
Cimetedine	23	0.07	37	0.11	47	0.17	46	0.20
Esomeprazole	2285	6.81	2289	7.07	2081	7.41	1837	8.08
Famotidine	26	0.08	30	0.09	27	0.10	26	0.11
Lansoprazole	436	1.30	413	1.28	345	1.23	281	1.24
Omeprazole	5980	17.84	5914	18.26	5282	18.82	4542	19.97
Nizatidine	2	0.01	2	0.01	2	0.01	1	0.00
Pantoprazole	23 640	70.51	22 571	69.71	19 367	68.99	15 249	67.04
Rabeprazole	908	2.71	904	2.79	765	2.73	608	2.67
Ranitidine	229	0.68	219	0.68	155	0.55	156	0.69

4 | DISCUSSION

In this retrospective analysis of medication prescription records in The Netherlands, we demonstrated that the proportion of patients using omeprazole or esomeprazole among patients using clopidogrel with gastroprotective drugs declined gradually from 19.7% in 2015 to 8.7% in 2022. The number of patients using concomitant clopidogrel and omeprazole or esomeprazole varies widely in the literature: from 6% for patients with acute coronary syndrome in an outpatient setting in Finland,[25] 12.5% for inpatients in Qatar,[26] to 56% in a hospital in Switzerland.[27] These variations can be explained by differences in local governance with regard to this drug–drug interaction and different patient settings. The decline in concomitant use of clopidogrel with omeprazole or esomeprazole is also in line with previous studies.[28–31] In The Netherlands, Kruik-Kolloffel et al.[23,32] studied prescriptions in an outpatient database covering 20% of Dutch residents. They demonstrated that 20.7% of the patients using clopidogrel with gastroprotective drugs received prescriptions for omeprazole or esomeprazole in 2008, while this declined to 15.1% in 2011.[23,32]

Patients with a prescription for clopidogrel and omeprazole or esomeprazole were compared to patients with a prescription for clopidogrel and other gastroprotective drugs to identify potential differences in patient or prescriber characteristics associated with the undesired drug–drug combination. The undesired combination was consistently more frequently prescribed to women. Manteuffel et al.[33] studied the influence of patients' sex and gender on prescribing alignment with the guidelines for diabetes and cardiovascular treatment. They found that women were less likely to receive the treatment recommended by the guidelines. The reasons for this disparity were unclear. Manteuffel et al.[33] suggest there may be differences in the clinical circumstances of individual patients that would support differences in treatment, there may be differences in how physicians apply clinical guidelines to women and men, or there may be differences in the likelihood of women and men filling prescriptions they have received.

The undesired drug–drug combination was also more often prescribed to patients with polypharmacy (>10 drugs). For patients receiving polypharmacy, adherence to the guideline might be more challenging for prescribers since other relevant drug–drug interactions could occur as well. In half of the analysed years, patients >80 years more often received a prescription for clopidogrel with omeprazole or esomeprazole. Cardiologists and neurologist adhered to the guidelines most often. Between 2017 and 2021 the unwanted combination was more often prescribed by internists and unspecified medical specialists. We found regional differences in prescription behaviour. These regional differences in prescription behaviour can be explained by

TABLE 4 Characteristics of patients using clopidogrel and proton pump inhibitors in 2015, 2020, 2021 and 2022 in Panels A, B, C and D, respectively. The standardized residual (SR) is provided when the value is >1.96 or <−1.96.

Panel A: 2015					
	Patients with clopidogrel and omeprazole or esomeprazole (*n*, %)		**Patients with clopidogrel and other gastroprotective drugs (*n*, %)**		
Total	9076		37 054		***P*-value**
Sex					
Female	4298	47.4	15 780	42.6	**<0.001**
Male	4778	52.6	21 274	57.4	
Age					
<60	1629	17.9	6709	18.1	0.387
60 to 70	2361	26.0	9932	26.8	
70 to 80	2935	32.3	11 808	31.9	
≥80	2151	23.7	8605	23.2	
Prescriber					
Cardiologist	1386	15.3 (SR: −4.3)	6522	17.6 (SR: 2.1)	**<0.001**
General practitioner	5447	60.0	21 636	58.4	
Internist	389	4.3	1591	4.3	
Neurologist	936	10.3	3696	10.0	
Other	918	10.1	3609	9.7	
Number of concomitant medications					
0	27	0.3	146	0.4	**<0.001**
1–5	598	6.6 (SR: −3.7)	2931	7.9	
6–10	3940	43.4 (SR: −4.6)	17 622	47.6 (SR: 2.3)	
11–15	3297	36.3 (SR: 4.1)	12 319	33.2 (SR: −2.0)	
>15	1214	13.4 (SR: 5.6)	4036	10.9 (SR: −2.8)	
Panel B: 2020					
	Patients with clopidogrel and omeprazole or esomeprazole (*n*, %)		**Patients with clopidogrel and other gastro protective drugs (*n*, %)**		
Total	13 962		115 075		***P*-value**
Sex					
Female	6987	50.0	52 957	46.0	**<0.001**
Male	6975	50.0	62 118	54.0	
Age					
<60	1864	13.4	15 888	13.8	0.174
60 to 70	3231	23.1	26 365	22.9	
70 to 80	4897	35.1	40 884	35.5	
≥80	3970	28.4	31 938	27.8	
Prescriber					
Cardiologist	865	6.2	7647	6.7	**<0.001**
General practitioner	10 449	74.8 (SR: −2.0)	88 037	76.5	
Internist	316	2.3 (SR: 4.1)	2008	1.7	
Neurologist	629	4.5 (SR: −3.8)	6142	5.3	
Other	1703	12.2 (SR: 8.1)	11 241	9.8 (SR: −2.8)	
Number of concomitant medications					
0	53	0.4	532	0.5	**<0.001**
1–5	1355	9.7 (SR: −10.8)	15 442	13.4 (SR: 3.8)	
6–10	6539	46.8 (SR: −6.1)	58 609	50.9 (SR: 2.1)	

TABLE 4 (Continued)

Panel B: 2020					
	Patients with clopidogrel and omeprazole or esomeprazole (*n*, %)		**Patients with clopidogrel and other gastro protective drugs (*n*, %)**		
11–15	4496	32.2 (SR: 9.3)	31 667	27.5 (SR: −3.2)	
>15	1519	10.9 (SR: 11.9)	8825	7.7 (SR: −4.2)	
Panel C: 2021					
	Patients with clopidogrel and omeprazole or esomeprazole (*n*, %)		**Patients with clopidogrel and other gastroprotective drugs (*n*, %)**		
Total	12 174		119 779		***P*-value**
Sex					
Female	6196	50.9	55 411	46.3	**<0.001**
Male	5978	49.1	64 368	53.7	
Age					
<60	1566	12.9	15 943	13.3	0.266
60 to 70	2851	23.4	27 341	22.8	
70 to 80	4294	35.3	42 684	35.6	
≥80	3463	28.5	33 811	28.2	
Prescriber					
Cardiologist	704	5.8	7033	5.9	**<0.001**
General practitioner	9331	76.7	92 821	77.5	
Internist	250	2.1 (SR: 4.4)	1804	1.5	
Neurologist	464	3.8 (SR: −5.0)	5870	4.9	
Other	1425	11.7 (SR: 4.6)	12 251	10.2	
Number of concomitant medications					
0	61	0.5	613	0.5	**<0.001**
1–5	1165	9.6 (SR: −11.4)	16 445	13.7 (SR: 3.6)	
6–10	5674	46.6 (SR: −6.7)	61 568	51.4 (SR: 2.1)	
11–15	3895	32.0 (SR: 8.9)	32 693	27.3 (SR: −2.8)	
>15	1379	11.3 (SR: 15.6)	8460	7.1 (SR: −5.0)	
Panel D: 2022					
	Patients with clopidogrel and omeprazole or esomeprazole (*n*, %)		**Patients with clopidogrel and other gastroprotective drugs (*n*, %)**		
Total	11 741		123 960		***P*-value**
Sex					
Female	5978	50.9	57 500	46.4	**<0.001**
Male	5763	49.1	66 460	53.6	
Age					
<60	1437	12.2	15 940	12.9	**<0.012**
60 to 70	2776	23.6 (SR: 2.0)	28 094	22.7	
70 to 80	4105	35.0	44 414	35.8	
≥80	3423	29.2	35 512	28.7	
Prescriber					
Cardiologist	594	5.1	6619	5.3	**<0.001**
General practitioner	9277	79.0	97 192	78.4	
Internist	212	1.8 (SR: 3.7)	1688	1.4	
Neurologist	405	3.5 (SR: −5.3)	5682	4.6	
Other	1253	10.7	12 779	10.3	

(Continues)

TABLE 4 (Continued)

Panel D: 2022					
	Patients with clopidogrel and omeprazole or esomeprazole (*n*, %)		**Patients with clopidogrel and other gastroprotective drugs (*n*, %)**		
Number of concomitant medications					
0	56	0.5	698	0.6	**<0.001**
1–5	1076	9.2 (SR: −11.1)	16 328	13.2 (SR: 3.4)	
6–10	5505	46.9 (SR: −6.4)	63 816	51.5 (SR: 2.0)	
11–15	3896	33.2 (SR: 10.1)	34 429	27.8 (SR: −3.1)	
>15	1208	10.3 (SR: 12.0)	8689	7.0 (SR: −3.7)	

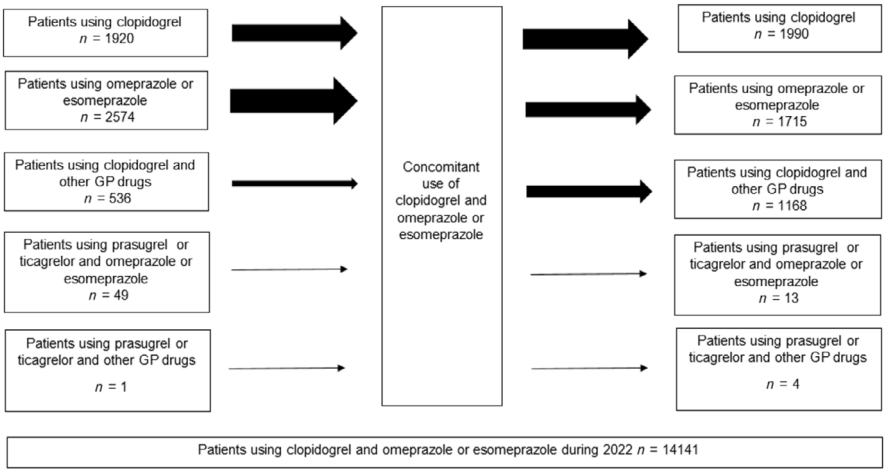

FIGURE 2 The use of PY12 inhibitors and gastroprotective drugs before and after the concomitant use of clopidogrel and omeprazole or esomeprazole in 2022.

different regional protocols between hospitals, general practitioners and pharmacists.

We also studied switching behaviour. Most often, omeprazole or esomeprazole was used before a prescription of concomitant clopidogrel and omeprazole or esomeprazole was started. When patients stopped using the undesired drug–drug combination, they most often switched to monotherapy clopidogrel or monotherapy omeprazole or esomeprazole. If patients continued a combination of gastroprotective drugs and a PY12-inhibitor, more often the gastroprotective drug was replaced than the PY12-inhibitor.

One of the strengths of the study is the use of a prescription database that covers about 62% of Dutch pharmacies. Therefore, these findings are representative for the Dutch outpatient setting. Also, we analysed a substantial period of time, between 2015 and 2022. This study also has several limitations. Firstly, our study makes use of dispensing data and we do not have information on actual drug use, or over-the-counter purchased proton pump inhibitors. Secondly, as our data focused only on a Dutch database, the results should be interpreted with caution when generalizing the results to other countries with different treatment protocols. Furthermore, our database only covered outpatient prescriptions; data on prescribing behaviour of inpatients are lacking. Also, we did not have information on the indications for the prescriptions and we lack data on clinical outcome, for example cardiovascular events or GI bleeding. Finally, the prescription considerations of the prescriber are unknown.

There are many possible factors contributing to adherence to guidelines, for instance awareness of the guideline, familiarity with the guideline, agreement with the guideline and patient-specific factors.[34–36] Further research should be conducted to investigate why the combination of clopidogrel with omeprazole or esomeprazole is still prescribed and which actions pharmacists perform when the combination is prescribed. Although guidelines discourage concomitant use of clopidogrel with omeprazole or esomeprazole, the combination is still prescribed to many patients. The findings of our study may help to avoid the combination of clopidogrel with undesired gastroprotective drugs in the future. Educational material to avoid this drug–drug indication can now be focused on specific prescribers, such as internists and healthcare providers in specific provinces.

Although the proportion of patients using clopidogrel with omeprazole or esomeprazole declined, the combination is still prescribed to many patients. The undesired drug–drug combination was more often prescribed by internists, to women and to patients with polypharmacy (using >10 drugs). Education about this drug–drug interaction for pharmacists and prescribers is needed since suitable pharmacotherapeutic alternatives are available.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation and data collection were performed by Kayleigh van de Wiel, Kelly Mulder and Sarah Wilkes. The analyses were performed by

Sarah Wilkes. The first draft of the manuscript was written by Sarah Wilkes and all authors commented on all versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare that are relevant to the content of this article.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are not openly available but are available from the corresponding author upon reasonable request.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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