ORIGINAL ARTICLE

Snapshot of the prescribing practice for the clopidogrel and esomeprazole coprescription and cost evaluation of the application guidelines

Nathalie Vernaz[1], Victoria Rollason[2], Liene Adlere[3], Christophe Combescure[4], Antoine Poncet[4], Pascal Bonnabry[1,3] & Jules Desmeules[2,3]

[1]Pharmacy, Geneva University Hospitals, Geneva, Switzerland
[2]Division of Clinical Pharmacology and Toxicology, Geneva University Hospitals, Geneva, Switzerland
[3]School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva University Hospitals, Geneva, Switzerland
[4]Division of Clinical Epidemiology, University of Geneva, Geneva University Hospitals, Geneva, Switzerland

Abstract

The antiplatelet clopidogrel and the proton pump inhibitor esomeprazole demonstrate a pharmacokinetic interaction through CYP2C19 that could translate into clinical inefficacy of clopidogrel. No medical consensus as to their coprescription has been reached, and different guidelines are available. We evaluated the prescribing practices at the Geneva University Hospitals (HUG) by measuring whether the coprescription was staggered as suggested by experts. We estimated the financial impact of different implementation guidelines. We used the HUG electronic patient records to follow the physicians' prescriptions and the administration by nurses from January 2013 to April 2014. We performed a time series analysis to assess 15 years of proton pump inhibitors (PPIs) and antiplatelet drug use. "Extra costs" were calculated assuming that clopidogrel or esomeprazole would replace prasugrel or ticagrelor and pantoprazole or ranitidine, respectively. Only 10.8% of the patient medical orders for the clopidogrel and esomeprazole coprescription specified to stagger the administration, 12.6% specified a concomitant coprescription, and 76.6% had no clear information. A high rate of 49.6% of the nurses staggered the clopidogrel and esomeprazole coprescription when no clear information was given. We found a statistically significant decrease in clopidogrel use after the publication of the OCLA (Omeprazole–CLopidogrel–Aspirin) study and a significant increase in the trend of esomeprazole. Alternative treatments to avoid this interaction are cost ineffective or offer therapeutic options of lesser quality. We observed a high rate of 56.2% of the clopidogrel and esomeprazole coprescription in our hospital and can therefore not ignore the PK/PD interaction. The most common prescription practice was to not specify the time frame of administration, which was translated by nurses in 49.6% of the cases to a scheduled staggered coprescription of clopidogrel and esomeprazole. As long as no consensus has been reached, the medical orders time frame information should be mandatory to allow a clear and harmonious staggering strategy.

Abbreviations
ACCF, American College of Cardiology Foundation; ACG, American College of Gastroenterology; AHA, American Heart Association; CPOE, computerized physician order entry; CYP, cytochrome; LOF, loss of function; PPI, proton pump inhibitor.

Introduction

Coronary heart disease is a major health concern worldwide and is associated with the highest risk of mortality and morbidity (Leading causes of death in Switzerland 2014). Clopidogrel is an antiplatelet drug that is frequently prescribed in patients suffering from myocardial infarction, ischemic stroke, and peripheral arterial disease (Tran and Anand 2004). Administration of clopidogrel is related to increased risk of gastrointestinal bleeding and bleeding from other sites (Tsai et al. 2012). To attenuate the clopidogrel-induced gastrointestinal bleeding events, concomitant therapy with a proton pump inhibitor (PPI) is recommended (Tsai et al. 2012).

Clopidogrel is a prodrug that requires a two-step enzymatic activation in the liver by cytochrome P450 (CYP) isoenzymes. CYP2C19 is the main enzyme involved in the conversion of clopidogrel to its pharmacologically active metabolite (Furuta et al. 2010; Ma et al. 2011). Gilard et al. (2008) published the OCLA (Omeprazole–CLopidogrel–Aspirin) study in 2008 in which he demonstrated for the very first time a significant reduction of the clopidogrel antiplatelet effect due to CYP2C19 inhibition consecutive to the addition of omeprazole in vitro. According to Liu and Jackevicius (2010), all PPIs inhibit CYP2C19, but not with the same potency; lansoprazole produces the highest inhibitory effect and pantoprazole produces the smallest. Angiolillo et al. (2011a) found a drug–drug interaction between clopidogrel and omeprazole but not between clopidogrel and pantoprazole, suggesting that the clopidogrel–PPI interaction is not a PPI class effect. Therefore, from a pharmacological point of view, pantoprazole, having the weakest inhibitory effect on CYP2C19, might be a more appropriate PPI option for patients receiving clopidogrel. Despite the robust evidence of a pharmacokinetic–pharmacodynamic (PK/PD) interaction between clopidogrel and PPIs, meta-analyses report a lack of significantly important clinical evidence of this interaction (Lima and Brophy 2010; Chen et al. 2012; Huang et al. 2013; Kwok et al. 2013; Melloni et al. 2015).

This lack of evidence could explain the different guidelines established to address this coprescription. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) published a warning discouraging combined therapy with clopidogrel and PPIs (especially omeprazole and esomeprazole) (Wathion 2009; U.S. Food and Drug Administration 2014a). In March 2010, the FDA added a black box warning to Plavix® (clopidogrel), mentioning a diminished effectiveness of antiplatelet therapy in patients who are poor metabolizers of CYP2C19 and informing about the availability of genetic testing to identify genetic differences in CYP2C19 function (U.S. Food and Drug Administration 2014b).

The FDA noted that physicians should consider alternatives to standard clopidogrel treatment, including the prescription of another antiplatelet drug, such as ticagrelor or prasugrel, or a higher dose of clopidogrel in patients who are carriers of a loss-of-function (LOF) CYP2C19 allele. In contrast, the American College of Cardiology Foundation (ACCF), the American College of Gastroenterology (ACG), and the American Heart Association (AHA) published a consensus on the concomitant use of PPIs and clopidogrel as an appropriate choice in patients with multiple risk factors for gastrointestinal bleeding receiving antiplatelet drugs (Abraham et al. 2010). The Clinical Pharmacogenetics Implementation Consortium (CPIC) published guidelines regarding CYP2C19 genetic testing for patients receiving clopidogrel treatment and recommended an alternative antiplatelet drug treatment, such as prasugrel or ticagrelor (Scott et al. 2011). In France, the Agence Nationale de Sécurité du Médicament (ANSM 2009) also discourages the use of concomitant PPI and clopidogrel and requests consideration of the use of H2-receptor antagonist drugs or other antacid drugs instead of PPIs.

Between strongly discouraging PPI–clopidogrel combinations and recommending their use, some clinicians have suggested staggering the dosing of these two medications to minimize the risk, if any (Juurlink 2009; Fleury and Beney 2010; Furuta et al. 2010; Ferreiro et al. 2011). This assumption is based on the short half-life of both clopidogrel and PPIs. Some authors recommend separating the administration of the two drugs by at least 4 h, ideally 12 h, whereas others clinicians claim that the separation of administration would not benefit the patient (O'Donoghue et al. 2009; Fleury and Beney 2010; Furuta et al. 2010; Momary and Cavallari 2010). Moreover, there is still an uncertainty about whether the CYP2C19 inhibition by omeprazole is reversible or irreversible (Ferreiro et al. 2011).

However, no specific guidelines exist at the Geneva University Hospitals (HUG) on the coprescription of the two drugs. Our study aims to take a snapshot of the prescription practice of the clopidogrel and esomeprazole coprescription based on 16 months from January 2013 to April 2014. Based on the literature suggesting staggering the administration, we considered the optimum medical order when a time frame of more than 10 h (morning, evening, bedtime) was specified (Lettino 2010).

To put our results into long-term perspective, we performed a retrospective analysis of 15 years on a monthly basis to measure clopidogrel, the incoming new antiplatelet drugs prasugrel and ticagrelor, and the PPIs between January 2000 and March 2014. We also analyzed the impact of the OCLA study on clopidogrel prescription in our hospital (Gilard et al. 2008).

Finally, from a hospital perspective, we then aimed to estimate the financial impact of switching either clopidogrel or the esomeprazole to another antiplatelet drug or PPI, respectively, to follow the different and contradictory available guidelines. Our hospital implemented a restrictive drug formulary (RDF) to minimize acquisition costs and to limit the number of medications available (Reynolds et al. 2012; Vernaz et al. 2013). In our hospital, clopidogrel and esomeprazole are both listed in our formulary and are reference drugs in their respective therapeutic classes. Prasugrel and ticagrelor are unrestricted, and all PPI prescriptions have been strictly switched to brand esomeprazole at admission since January 2002.

Materials and Methods

Setting

The Swiss canton of Geneva has a single public hospital system (HUG) that provides primary and tertiary care with 1804 beds (2012); it has approximately 50,000 admissions and 800,000 outpatient visits each year. The Swiss healthcare system provides mandatory health insurance with universal access to healthcare for the entire population. The HUG implemented an RDF, and medications are selected by the Drug and Therapeutic Committee based on their efficacy, safety, and costs with a hospital perspective (Vernaz et al. 2013). Until September 2002, all PPI prescriptions were switched to omeprazole at admission. Since 1 October 2002, all PPI prescriptions have been switched to brand esomeprazole at admission. Clopidogrel is included in the RDF, but prasugrel and ticagrelor are unrestricted. The RDF strictly switched from brand to generic clopidogrel at admission in November 2011. Generic esomeprazole and clopidogrel were available in the community during the coprescription study period, whereas there was no generic available for ticagrelor and prasugrel. Brand and generic H2-receptor antagonists are not restricted. Prices are strongly negotiated at HUG, particularly if drugs are listed in the RDF and are fixed in the community (Vernaz et al. 2013).

Data sources and institutional review board approval

We combined two administrative registries for our analysis: first, the HUG electronic patient record to follow the computerized physician order entry (CPOE) and administration by nurses, and second, the HUG hospital pharmacy database to assess retrospectively 15 years of PPIs and antiplatelet drugs dispensed to the wards (Carli-Ghabarou et al. 2013). We obtained anonymous data from the HUG electronic patient record, including the patient number, gender, date of birth, dose, frequency, route of administration, date of administration of clopidogrel and esomeprazole, the unit where the patient was hospitalized, the frequency of administration, the time schedule if any, and the nurse schedule.

The HUG Ethics Committee considered this study to be exempt from formal institutional review because it was based on retrospective administrative data with anonymous patient involvement. All confidential health information was removed to create anonymous analytic datasets in conformity with Swiss data protection regulations.

Sixteen months of prescription practices: medical orders and nurse schedule coprescription classification

We conducted an observational study on patients prescribed clopidogrel alone and combination therapy with esomeprazole during their stay at HUG between January 2013 and April 2014. We examined the HUG computerized prescription records, which contain comprehensive records of prescription medications dispensed to all hospitalized patients, except those hospitalized in intensive care wards where another computerized system is used.

When the physician prescribes a medication, he selects the drug, the administration route, that is, esomeprazole oral, the dosage (10, 20, 40, or 80 mg), the frequency (once or twice daily), and optionally can specify whether the medication has to be taken in the morning, in the afternoon, in the evening, or at bedtime. Nurses create medication administration schedules (0–24 h) for each physician order, that is, esomeprazole oral 40 mg in the morning scheduled at 8.00 AM.

To define the 16 months of prescribing practice for the clopidogrel and esomeprazole coprescription, the medical orders and drug administration time schedules were classified by patient. Based on the concept of rapid metabolization of both clopidogrel and esomeprazole, and the literature suggesting to stagger the administration, we considered an optimum medical order when a time frame of more than 10 h (morning, evening, bedtime) was specified (Fleury and Beney 2010; Ferreiro et al. 2011). Based on the same assumption, the optimal nurses schedule classification implied a schedule of more than 10 h, that is, 8.00 AM clopidogrel and 18.00 PM esomeprazole. Impossible staggering orders were coprescriptions including esomeprazole, 40 mg twice daily, or clopidogrel twice daily, therefore hindering the possibility of staggering the administration of clopidogrel with esomeprazole. We

excluded these orders from our analysis. We considered the clopidogrel and esomeprazole coprescription as same day administration.

Fifteen years of retrospective PPIs and antiplatelet use

We first collected observed data to capture the long-term use of clopidogrel, ticagrelor, and prasugrel on a monthly basis from January 2000 to March 2014 and then performed an interrupted time series analysis to measure the impact of the OCLA study on these antiplatelet drugs. We measured the PPI trend on a yearly basis from January 2007 to December 2014.

Cost calculation of different guideline applications

To measure the impact of application guidelines on hospital healthcare spending, costs were analyzed under two scenarios, assuming clopidogrel replacement with the corresponding antiplatelet drugs prasugrel or ticagrelor, and esomeprazole replacement with pantoprazole or ranitidine. Lansoprazole, rabeprazole, and omeprazole were not included in the extra costs calculation because they are more or equally potent inhibitors of CYP2C19 than esomeprazole (Liu and Jackevicius 2010; Angiolillo et al. 2011a). The H2-receptor antagonist cimetidine was not included in the "extra costs" calculation because this drug also competitively inhibits CYP2C19.

The "extra cost" was assessed as the difference between the total hospital cost based on the observed data and the expected total hospital cost estimated for both scenarios. Costs were converted from Swiss francs to USD at the established 2014 exchange rate of 1 Swiss franc = 1 USD. Inflation was not taken into account. The study period was between January 2013 and April 2014.

Statistical analysis

Demographic variables were expressed as percentages or means with standard deviations. The OCLA study impact was analyzed under a robust time series analysis, which used autoregressive integrated moving average models according to the Box–Jenkins methodology, which allows the stochastic dependence of consecutive data to be modeled (Helfenstein 1996). We used dummy variables (0 before intervention, 1 after) to assess changes in the level and slope after the OCLA study publication. Significance tests for parameter estimates at $P < 0.05$ were used to eliminate the unnecessary terms. Among different models, we chose the most parsimonious one, that is, the model

with the fewest parameters. All final model residuals passed a "white noise" test (based on Ljung-Box statistics). R^2 represents the overall fitting of a model. Statistical analysis was performed with Eviews 7 software (QMS).

Results

To identify the snapshot of prescription practice, we analyzed a total of 1649 patients who were prescribed clopidogrel alone or combined with esomeprazole from January 2013 to April 2014. Of these patients, 926 (56.2%) had concomitant esomeprazole and clopidogrel therapy, but three were excluded for having a clopidogrel prescription twice daily and nine were excluded for having an esomeprazole prescription twice daily. A total of 914 patients were included.

Table 1 presents the patient characteristics, age (mean, median), number of coprescription days (mean, median), medical specialties where the patient was hospitalized, and patients who changed units. The mean age in years was 74.82 (SD = 12.72), and 391 (43%) patients were female. The mean number of coprescription days was

Table 1. Patient characteristics of the clopidogrel and esomeprazole coprescription, age (mean, median), number of coprescriptions days (mean, median), medical specialties where the patient was hospitalized, and patients who changed units. Geneva University Hospitals, January 2013 to April 2014.

	$N = 914$
Age (year) (mean ± SD)	74.82 ± 12.72
Age (year) (median [min–max])	77.2 [22.9–99.7]
Female	391 (43%)
Nb coprescriptions days (mean ± SD)	16.1 ± 26.0
Nb coprescriptions days (median [min–max])	6 [1–270]
Nb coprescriptions days	
1	135 (14.8%)
2–4	216 (23.6%)
5–14	307 (33.6%)
15–24	88 (9.6%)
25–49	96 (10.5%)
>50	72 (7.9%)
Medical specialties (according to clopidogrel)	
Internal medicine	310 (33.9%)
Rehabilitation	189 (20.7)
Surgery	164 (17.9%)
Private practice	137 (15.0%)
Cardiology	104 (11.4%)
Other	20 (2.2%)
Psychiatry	15 (1.6%)
Patient changing hospital units	212 (23.2%)
Only one change	143 (67.5%)
Two and more	69 (32.5%)

16.1 (SD = 26), 310 (33.9%) patients were hospitalized in the internal medicine department and for 212 patients (23.2%), a change in unit occurred during their hospitalization.

Table 2 presents the medical orders given by physicians and the established drug administration regimens of the nurses. Only 214 (23.4%) had clear and complete medical information, whereas 700 (76.6%) patients did not. Physicians' medical orders for 99 (10.8%) patients indicated to stagger the administration by more than 10 h, whereas 115 (12.6%) indicated concomitant administration of clopidogrel and esomeprazole. The physicians' medical orders with clear information were translated by nurses into a staggered administration as ordered for 82 (82.8%) patients, and a concomitant administration of both clopidogrel and esomeprazole were translated as ordered for 104 (90.4%) patients. We found a high rate of 49.6% (283 patients) of patients that had a staggered nurse's schedule in the group of patients with no established medical information regimen.

The long-term use of clopidogrel, ticagrelor, and prasugrel, as well as the impact of the OCLA study on clopidogrel use is described in Table 3 and Figure 1. From January 2000 until December 2007, the clopidogrel use baseline level was 1503 tablets ($P < 0.0001$), and a statistically significant increase in trend of 32 tablets every month ($P < 0.0001$) was observed until December 2008. From January 2008, when the OCLA study was published, a statistically significant monthly decrease of 56 tablets ($P < 0.0001$) was observed. We found a significant first-order correlation ($P = 0.002$), a third-order correlation ($P = 0.0031$), and an R^2 of 80%.

Conversely, Figure 2 shows a significant increase in esomeprazole prescription of 10,564 (95% CI: 7987–13,142 $P < 0.0001$) on a yearly basis from January 2007 to December 2014 ($R^2 = 94\%$).

Based on the "extra costs" calculated from scenario 1 (clopidogrel replacement by prasugrel or ticagrelor), the HUG, with the actual purchase prices, would have had an extra cost of USD 45,852 and 41,761, respectively, over

Table 3. Intervention model analyzing the impact of the OCLA study on the clopidogrel use. Geneva University Hospitals, January 2000 to March 2014.

Variable	Coefficient (SD)[1]	t-Statistic	P-value
Baseline level	1503 (166)	9.08	<0.0001
Trend before OCLA study	32 (2.87)	11.30	<0.0001
Change in the level after OCLA study	4952 (530)	9.35	<0.0001
Change in the trend after OCLA study	−56 (4.84)	−11.61	<0.0001
AR (order 1)[2]	0.24 (0.08)	3.14	0.002
AR (order 3)[2]	0.23 (0.08)	3.002	0.0031

[1]Size and direction of the effect.
[2]The autoregressive term represents the past value of clopidogrel use at months 1 and 3.

the study period. Scenario 2 (esomeprazole replacement by pantoprazole) demonstrated an extra cost of USD 11,509 for the HUG. We found an extra cost of esomeprazole replacement with the corresponding ranitidine of USD 6246 for the HUG.

Discussion

Our study aimed to investigate the HUG prescribing practices for the clopidogrel and esomeprazole coprescription and in particular the administration schedule within the conflicting literature on whether the PPIs may inhibit the antiplatelet metabolism that could result into decreased efficacy of clopidogrel (Gilard et al. 2008).

Several studies analyzed the prevalence of PPI and clopidogrel coprescription, demonstrating that there is a wide range of coprescription rates (Juurlink et al. 2009; Momary and Cavallari 2010; Bhurke et al. 2012; Urtane et al. 2013). Juurlink et al. (2009) found 20% of coprescriptions for 13,636 patients in Ontario, and Ho et al. (2009) found a higher rate of 64% for all patients discharged from any Veteran Affairs hospitals with acute myocardial infarction or unstable angina. Our study found a high rate of 56.2% of patients had a clopidogrel

Table 2. Medical orders given by physicians and the established drug administration regimens of the nurses. Geneva University Hospitals, January 2013 to April 2014.

|	Clear medical information N = 214 (23.4%)		No clear medical information N = 700 (76.6%)		
	Staggered administration N = 99 (10.8%)	Concomitant administration N = 115 (12.6%)	Partly staggered administration N = 3 (<1%)	No information given N = 571	Mixed N = 126
Nurses staggered administration	82 (82.8%)	4 (3.5%)	1 (33.3%)	171 (29.9%)	23 (18.3%)
Nurses did not staggered administration	6 (6.1%)	104 (90.4%)	0 (0%)	288 (50.4%)	32 (25.4%)
Sometimes nurses staggered administration	11 (11.1%)	7 (6.1%)	2 (66.7%)	112 (19.6%)	71 (56.3%)
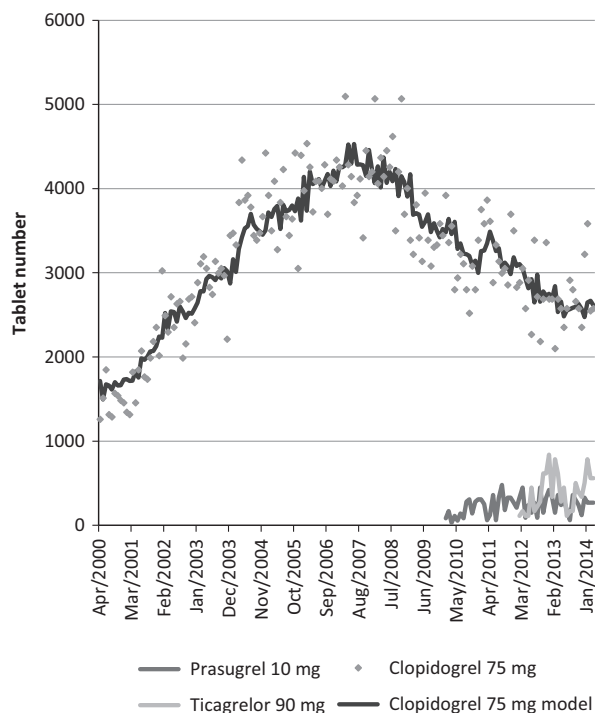
Figure 1. Intervention model analyzing the effect of the OCLA study on clopidogrel, prasugrel, and ticagrelor use. Geneva University Hospitals, January 2000 to March 2014.

Figure 2. Model analyzing PPI prescriptions over time. Geneva University Hospitals, January 2007 to December.

and esomeprazole coprescription. If the clopidogrel–PPI interaction is clinically relevant, then this finding suggests that there is a higher risk for our patients of inefficacy of treatment if PPIs inhibit the antiplatelet activity of clopidogrel. This high rate of coprescription might also be linked to the high use of esomeprazole at HUG in the Geneva community, and in many hospitals in general (Naunton et al. 2000; Ramirez et al. 2010; Roulet et al. 2012; Vernaz et al. 2013). We found that 5% of the patients have a medical prescription of esomeprazole at 80 mg, a dosage 2–4 times higher than usually prescribed by physicians (20 mg or 40 mg). Angiolillo et al. (2011b) reported that the clopidogrel–PPI interaction cannot be overcome by administrating 150 mg of clopidogrel with a 600 mg loading dose in patients receiving 80 mg of omeprazole. For these patients, the risk–benefit of this particular coprescription should therefore be considered.

As suggested by the literature, we aimed to measure whether staggering the coprescription by more than 10 h was a common practice at HUG (Fleury and Beney 2010; Liu and Jackevicius 2010). This staggering is one of the recommendations offered by the experts in the field, in addition to increasing the clopidogrel dose or screening patients to identify CYP2C19 variants to reduce the risk of reduced antiplatelet activity (Fleury and Beney 2010;
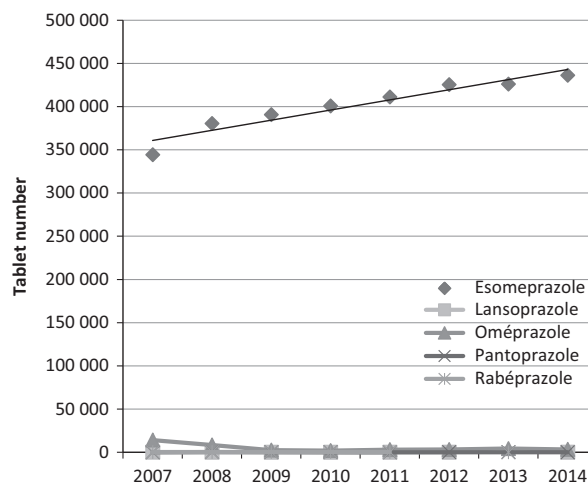
McLachlan 2010). Despite the fact that our HUG CPOE system allows to specify the medical order to be staggered, this action is not mandatory. Our study reveals that only 10.8% of patient medical orders for coprescription specified a difference of 10 h, and another 12.6% specified a concomitant coprescription of esomeprazole with clopidogrel; the remaining 76.6% medical orders had no clear information. Most importantly, we found that when the medical order includes the time frame information, the nurses followed the order in 82.8% of cases for the staggered administration and 90.4% of cases for the concomitant prescriptions, respectively. We found that a high rate of 49.6% of nurses' schedules staggered the clopidogrel and esomeprazole coprescription when no information was given on the time of administration. We also found that the same patient might have different episodes of care or was transferred to a different unit having a different medical order, different nurses schedules, or both, which might affect the patient adherence when leaving the hospital and could therefore lead to decreased clopidogrel efficacy (McLachlan 2010).

We also analyzed the antiplatelet and PPIs drug use over 15 years and measured a statistically significant and continuous decrease after the OCLA study publication (from 2008 onward) without a total replacement by other antiplatelet drugs (Gilard et al. 2008). We confirm a high, robust, and exclusive increase in esomeprazole prescription at HUG over time, thus highlighting the difficulty of implementing prudent strategies, such as evaluating the necessity of PPI therapy or considering the use of another PPI (Naunton et al. 2000; Juurlink 2009; Ramirez et al. 2010).

Considering the HUG prescribing practices and the different guidelines, we measured the extra costs of clopido-

grel replacement with the corresponding antiplatelet drugs, such as prasugrel or ticagrelor, as advised by the ACCF/ACG/AHA and CPIC guidelines (Abraham et al. 2010; Scott et al. 2011). Both drugs offer faster and stronger platelet inhibition regardless of genotype, which has to be balanced with the increased bleeding risk observed with prasugrel (Wiviott et al. 2007; Braun et al. 2013). Ticagrelor might be a better strategy because it provides a significantly higher platelet inhibition than prasugrel and a significantly greater decrease in mortality, myocardial infarction, and stroke compared to clopidogrel (Kowalczyk et al. 2009; Alexopoulos et al. 2012). Moreover, unlike clopidogrel and prasugrel, ticagrelor does not require metabolic activation; therefore, the interindividual variability in response to ticagrelor is lower. This advantage has to be balanced with the increased risk of dyspnea (Sinha 2012; Serebruany et al. 2014). However, these switches would cause a significant extra cost for the hospital because generic clopidogrel has been listed in the HUG drug formulary since November 2011 at a negotiated price, and prasugrel and ticagrelor are not.

We measured the extra costs of the esomeprazole replacement with pantoprazole and ranitidine for patients at lower risk of gastrointestinal bleeding, as suggested by the ACCF/ACG/AHA and ANSM guidelines (ANSM, 2009; Abraham et al. 2010). PPIs are generally of higher efficacy in comparison to histamine-2 receptor antagonists, and they have relatively good safety profiles (Alhazzani et al. 2013).

We demonstrated that switching esomeprazole to pantoprazole or ranitidine would lead to a lower increase in cost than switching the antiplatelet drug. Nevertheless, the financial risk for HUG when switching to pantoprazole is much higher than we calculated because esomeprazole coprescription is a small part (5%) of the total esomeprazole consumption at HUG. Vernaz et al. demonstrated that esomeprazole is particularly strongly negotiated at HUG and is the exclusive PPI listed in the RDF. This leads to a maximizing of the pharmaceutical industry profit by increasing the prescription in the community; the cost of rebates offered to hospitals is thus exceeded and leads to the so-called spillover effect (Vernaz et al. 2013). Including pantoprazole in the RDF or replacing esomeprazole would therefore lead to the highest increase in cost by losing this high rebate on a high-volume prescription drug.

Strengths and Limitations

This study has several strengths. First, we used a single data source to analyze the exposure of clopidogrel with esomeprazole over a 16-month period, which guaranteed a uniform and large data collection system. Second, we analyzed the medical orders and the nurses' schedule and found that there are differences between the two information sources. To our knowledge, this was not demonstrated previously. Third, we measured long-term clopidogrel use using a time series analysis and demonstrated that since the OCLA study was published in 2008, clopidogrel use has been continuously decreasing. Finally, we demonstrated that switching drugs costs more if the drugs are negotiated.

Our study also has several limitations. Patients hospitalized in the intensive care unit were not included in this study because the electronic system is different and was not available for such an analysis. The cost scenarios were based on the assumption that all prescriptions would be switched either to brand or the corresponding generic. In reality, some patients may prefer the Galenic formulation or the color, even if they have to pay an additional 20% copayment (Duerden and Hughes 2010; Greene and Kesselheim 2011). Because prices are negotiated at HUG and the medications listed in the formulary might be different at other institutions, the generalization of our findings is limited. We were unable to measure the interaction between the hospital and the community and the therapeutic or generic switch, if any, at admission or at discharge. We also took a hospital perspective instead a social one to evaluate the "extra costs" of these therapeutic switches and could not measure the impact of strategies implemented at HUG by the pharmaceutical industry to promote their drug.

Conclusion

Because of the high rate of 56.2% of the clopidogrel and esomeprazole coprescription in our hospital, one cannot ignore the PK/PD interaction. Although the clopidogrel–PPI interaction has been extensively described, there is still inconsistent evidence of the increased risk of myocardial infarction due to clopidogrel PPI coadministration, and there is no consensus on whether this drug interaction is dose dependent or if there is a benefit of staggering the administration (Fleury and Beney 2010; Momary and Cavallari 2010). However, in the absence of clear evidence, either staggering or switching the PPI or the antiplatelet drug to another drug is a reasonable alternative. The genetic variability of the clopidogrel efficacy might have been a major confounder in many studies (Furuta et al. 2010; Ma et al. 2011). To lower the risk of our high clopidogrel and esomeprazole coprescription at HUG, further research should be conducted to identify CYP2C19 variants to objectively evaluate the clinical impact of PPI on the antiplatelet effect of clopidogrel. As far as the medical prescription is concerned, the HUG CPOE information on time scheduling should be mandatory.

Author Contributions

Nathalie Vernaz wrote the manuscript, designed the research, performed the research, and analyzed the data. Victoria Rollason wrote the manuscript, designed the research, performed the research, and analyzed the data. Liene Adlere wrote the manuscript, performed the research, and analyzed the data. Christophe Combescure analyzed the data. Antoine Poncet analyzed the data. Pascal Bonnabry wrote the manuscript and designed the research. Jules Desmeules wrote the manuscript and designed the research.

Disclosure

None declared.

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