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ORIGINAL RESEARCH ARTICLE

The Impact of Direct Healthcare Professional Communication on Prescribing Practice in the UK Hospital Setting: An Interrupted Time Series Analysis

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Abstract

Background Direct Healthcare Professional Communications (DHPCs) aim to quickly disseminate information to key healthcare professionals to inform practice and minimize patient harm. The Medicines and Healthcare products Regulatory Agency (MHRA) issues warnings and alerts to communicate safety information effectively in the UK.

Objective To investigate the impact of MHRA DHPCs on prescribing practice in the secondary-care setting, looking specifically at a drug-drug interaction–the concomitant use of clopidogrel and proton pump inhibitors (PPIs) [as omeprazole]–and a drug-disease contraindication–the use of conventional (typical) antipsychotics in dementia.

Methods The effects of the MHRA DHPCs were analysed using segmented binary logistic regression of interrupted time series. This allowed for the detection of any significant changes in prescribing practice occurring after the MHRA warnings were issued, whilst controlling for the baseline period.

Results Of the patients concomitantly prescribed clopidogrel and omeprazole on admission, the rate at which omeprazole was substituted for either another PPI (with the exception of esomeprazole), or for a histamine H_2-antagonist showed a significant step-change increase after the DHPC was issued. The modelled rate increased from 5.1 % in the month directly before the intervention to 25.1 % in the following month (odds ratio [OR] 6.18; $p < 0.001$). However, the action taken in the switching of therapy was not always consistent with the advice from the current MHRA warning. The rate of typical antipsychotic prescribing in patients with dementia was declining significantly by 3.9 % per quarter prior to the DHPC being issued (OR 0.970; $p = 0.035$). No significant step-change was detected immediately after the DHPC ($p = 0.962$). However, the rate of decline increased significantly in the post-warning period to 12.3 % per quarter (OR 0.938; $p = 0.006$).

Conclusion This study has shown that DHPCs issued by the MHRA as warnings are associated with changes in prescribing practices in secondary care. However, their impact is variable depending on the intervention described by the warning. A national initiative to ensure patient safety information is effectively translated into practice and the effect of the warning continues beyond the period of the issue would be beneficial.

1 Introduction

An estimated 500,000 prescriptions are generated on a daily basis in hospitals across the UK [1]. Many treatments are initiated in this setting and continued in the community, so influencing practice here can impact on patient safety over the longer term.

In Europe, the monitoring of medicines is supervised and regulated by the European Medicines Agency (EMA) [2]. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) works closely with the EMA as a trusted independent source of expertise [3]. In the US, it is the responsibility of the FDA to ensure human (and

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veterinary) drugs, vaccines, and other biological products and medical devices are safe and effective. When a threat is posed to public health, regulatory bodies must respond promptly and appropriately. The MHRA will work in collaboration with manufacturers and wholesalers on the most appropriate and timely action to take. Depending on the nature and scale of the threat, a drug may be withdrawn from the market, or a warning or alert issued to healthcare professionals, and publicized widely in print and online [3]. In the US, 'Black-Box Warnings' are the highest level warnings published by the FDA and relate to medicines that carry a serious risk of death or severe injury [4]. In the UK, the MHRA issue alerts, warnings and 'Drug Safety Updates' [3]. These warnings have been referred to as 'Direct Healthcare Professional Communications' (DHPCs), and aim to quickly disseminate information to key healthcare professionals to inform practice and minimize patient harm.

In both Europe and the US, studies have been carried out to examine prescribing trends in primary and ambulatory care before and after a DHPC [4–9]. These studies showed that DHPCs can have a significant but variable effect on prescribing trends. In some cases, excellent compliance has been seen with warnings that stated a contraindication or named a contraindicated drug [4], but in other studies, impact varied according to the type of adverse drug event, availability of alternative agents and the type of prescriber [5]. This shows that some professionals implement some guidelines, but neglect others, implying a potential limitation in the power of DHPCs to affect patient health, care and safety [7]. This is certainly true in the UK, where many hospitals do not comply with DHPCs, and incidents are still occurring relating to alerts that were over 5 years old [10]. A systematic review of FDA drug risk communications concluded that these DHPCs have a varied and unpredictable impact [11]; for example, advisories recommending increased monitoring for specific drug therapies did not appear to influence a large or sustained change, but information relating to drug therapy was often adopted quickly for new patients, rather than existing ones.

To investigate the impact of DHPCs as a risk minimization strategy in the secondary-care setting, prescribing trends relating to two MHRA warnings in the UK will be examined: (i) drug-drug interaction: clopidogrel and proton pump inhibitors (PPI) [July 2009] [12]; and (ii) drug-disease contraindication: conventional (typical) antipsychotics in dementia (December 2008) [13].

1.1 Clopidogrel and Proton Pump Inhibitors (PPIs)

In July 2009, the EU Committee for Medicinal Products for Human Use (CHMP) considered the available evidence for the interaction between clopidogrel and PPIs, and concluded that a clinically significant interaction exists that makes clopidogrel less effective [12]. The UK MHRA issued a Drug Safety Update recommending that concomitant use of a PPI with clopidogrel should be avoided unless considered essential. The existence of the interaction was debated by many; published studies showed no observed interaction and therefore no support for the need to avoid concomitant use [14–18], but evidence was also available for the interaction [19–26]. In April 2010, this advice was updated to recommend that only omeprazole and esomeprazole need be avoided in patients concomitantly prescribed clopidogrel [27].

1.2 Conventional (Typical) Antipsychotic Prescribing in Dementia

In 2008, a European assessment concluded that conventional antipsychotics were associated with increased mortality when used in older adults with dementia. The MHRA subsequently issued a Drug Safety Update, stating "it is reasonable to assume that the increased risk now noted for conventional antipsychotics applies to all drugs in this class" [13]. Although risperidone may be used in this patient group for the short-term management of persistent aggression, the advice from the MHRA regarding typical antipsychotics remained consistent [13].

2 Methods

2.1 Data Collection

The study population was drawn from patients admitted to the Queen Elizabeth Hospital Birmingham (QEHB), a large acute teaching hospital in Birmingham, UK. The data were collected from a locally developed electronic prescribing system (Prescribing, Information and Communication System, or *PICS*). Developed in 1996 by the Wolfson Computer Laboratory Unit (Birmingham), PICS is a rules based e-prescribing system that provides decision support to doctors, based on clinical protocols and best practice guidelines [28] for all prescribing across approximately 1200 inpatient beds (with the exception of some chemotherapy regimens).

For analysis of the drug-drug interaction between clopidogrel and PPIs, data were collected for every inpatient spell during the study period in which both clopidogrel and omeprazole were prescribed. Omeprazole prescribing was only examined since the advice from the MHRA about its concomitant use with clopidogrel remained consistent throughout the time period. For each in-patient spell, the final antisecretory agent prescribed prior to discharge was

identified. Where this prescribed regimen was an antisecretory agent other than omeprazole, it was considered a switch in therapy. If an antisecretory agent was not prescribed at this stage, we assumed this was not required by the patient (i.e. not considered essential), therefore the spell was excluded.

For the analysis of the use of conventional antipsychotics in dementia, data were collected for all inpatient spells where a diagnosis of dementia was indicated on LORENZO, an administrative database for patient episodes used at the QEHB. Dementia patients were defined as those with any recorded International Classification of Diseases, 10th revision, code in the range F00–F03, incorporating Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere and unspecified dementia. Additional dementia patients were identified as those prescribed an anti-dementia drug (or cognitive enhancer), namely donepezil, galantamine, memantine or rivastigmine, even in the absence of an explicit dementia diagnosis.

2.2 Statistical Methods

The effects of the MHRA warnings were analysed using segmented binary logistic regression of interrupted time series. In the analysis of the drug-drug interaction between clopidogrel and omeprazole, data were collated for each inpatient spell in which the drugs were concomitantly prescribed. A dichotomous variable was then generated to indicate whether the omeprazole had been substituted for an alternative antisecretory agent, as per the MHRA guidance. Similarly, for the consideration of conventional antipsychotic prescribing in dementia, data were collected for all inpatient spells in which dementia was indicated, with a dichotomous variable indicating whether a conventional antipsychotic was prescribed during the spell. In each case, the dichotomous variables produced were used as the outcomes in the analysis.

For each of the datasets, three additional variables were then generated for each inpatient spell, in order to define the time that the spell commenced, relative to the MHRA intervention. The first stated the month number since the start of the period in which each inpatient spell began. The coefficient for this factor reflected the gradient in the pre-intervention period, testing whether the rate at which an outcome occurred was changing over the months of the study. A similar variable which took the value of zero for pre-intervention inpatient spells, and the number of months since the intervention for post-intervention inpatient spells, was also created. This was used to test whether the gradient observed in the pre-intervention period differed after the MHRA warnings were released. A final dichotomous variable was produced that stated whether an inpatient spell occurred before or after the MHRA warnings. This was used to consider 'step-changes' in outcome rates brought about by the intervention. The three variables were then entered simultaneously into binary logistic regression models for each of the outcomes considered.

Since there was the potential for patients to be included in the data multiple times if they had more than one inpatient spell during the period, the analysis was repeated using generalized estimating equations. These allowed for within-patient correlation to be considered, the presence of which would contravene the assumptions of binary logistic regression.

All analyses were performed using SPSS 19 (IBM SPSS Inc., Chicago, IL, USA), with $p < 0.05$ considered significant.

3 Results

3.1 Clopidogrel and Omeprazole

During the period January 2007–December 2011, there were a total of 1,759 inpatient spells that commenced with clopidogrel and omeprazole being concomitantly prescribed. Figure 1 displays the proportions of these co-prescriptions in which omeprazole was substituted for an alternative antisecretory agent. A line representing the segmented binary logistic regression model is also included to show the changes in trends over time, the coefficients of which are reproduced in Table 1.

The analysis found no evidence to suggest that the proportion of substitutions of omeprazole to more appropriate drugs was changing significantly over the months prior to the intervention ($p = 0.244$). There was also no evidence that the intervention resulted in a significant change in this gradient ($p = 0.324$). However, a significant ($p < 0.001$) step-change increase was observed after the MHRA warning was released, with an odds ratio (OR) of 6.18 (95 % CI 3.33–11.47). This implies that the MHRA warning coincided with a significant increase in the proportion of patients who had their omeprazole substituted for either another PPI or for a histamine H_2-antagonist. The model found that the rate of substitutions increased from 5.1 % in June 2009 to 25.1 % in the following month, a near fivefold increase.

Figure 2 shows the proportion of omeprazole switches made to an alternative PPI or to a histamine H_2-antagonist. From July/August 2009, switching to an alternative PPI was the most frequent outcome, with the exception of the period between September and December 2009 when switching to a histamine H_2 antagonist occurred more frequently.

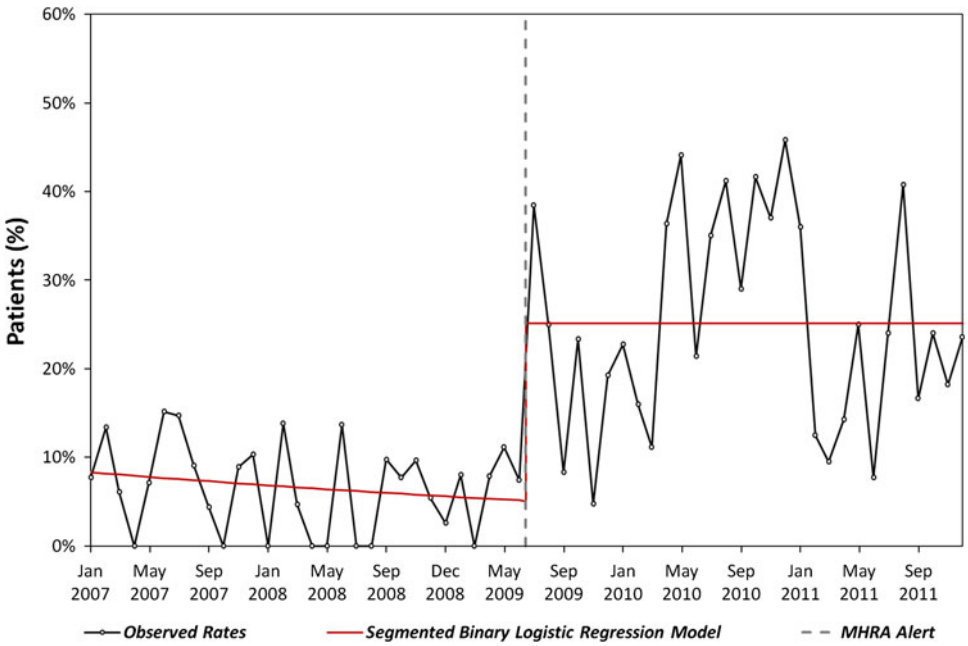

Fig. 1 Percentage of patients switched from omeprazole to an alternative proton pump inhibitor or histamine H_2-receptor antagonist when concomitantly prescribed clopidogrel. The logistic regression model is represented as linearly interpolated predicted probabilities, rather than odds ratios, for ease of interpretation. *MHRA* Medicines and Healthcare products Regulatory Agency

3.2 Conventional Antipsychotic Prescribing in Dementia

During the period January 2006–December 2011, there were a total of 6,734 inpatient spells in which dementia was indicated. Figure 3 displays the observed monthly rates during the period, as well as the segmented binary logistic regression model, the coefficients of which are reproduced in Table 2.

The analysis demonstrated that the rate of conventional antipsychotic prescribing in dementia was already in significant decline before the MHRA warning was released ($p = 0.035$; OR 0.97; 95 % CI 0.94–1.00). In January 2006, 17.6 % of dementia patients were estimated to have prescriptions for conventional antipsychotics, declining to 13.0 % in December 2008, a reduction of 3.9 % per quarter. No significant step-change was detected after the MHRA warning was released ($p = 0.962$); however, a significant change in the gradient was identified ($p = 0.006$; OR 0.94; 95 % CI 0.90–0.98). During this post-warning period, the rate of conventional antipsychotic prescribing in dementia fell from 12.9 % in January 2009 to 4.7 % in December 2011, equivalent to a 12.3 % per quarter reduction, almost three times that observed in the pre-intervention period.

The analyses of both concomitant prescriptions of clopidogrel and omeprazole, and of conventional antipsychotics in dementia were also repeated using generalized estimating equations in order to consider the within-patient correlation for those patients who had multiple in-patient spells during the study period. However, this correlation was found to be minimal, with coefficients in the region of 0.1. This meant that the results were consistent with the binary logistic regression analysis and, hence, it is the results of this method that are reported.

Table 1 Binary logistic regression results for clopidogrel and omeprazole prescribing

Factor	Odds ratio (95 % CI)	p value
Constant	0.092	<0.001*
Gradient (per quarter) pre-intervention	0.948 (0.867–1.037)	0.244
Step change after MHRA alert	6.184 (3.333–11.474)	<0.001*
Change in the gradient (per quarter) post-intervention	1.054 (0.949–1.172)	0.324

MHRA Medicines and Healthcare products Regulatory Agency

* Significant at $p < 0.05$

4 Discussion

In this study, both of the warnings issued by the MHRA were associated with a significant change in prescribing habits, although this was not always consistent with the advice from the regulatory agency. For the drug-drug interaction between clopidogrel and omeprazole, a significant step-change occurred following the release of the MHRA warning, with the new rate being sustained for the remainder of the study. However, in the majority of cases the actions taken by the prescribers between July 2009 and April 2010 were not made in line with MHRA advice. In

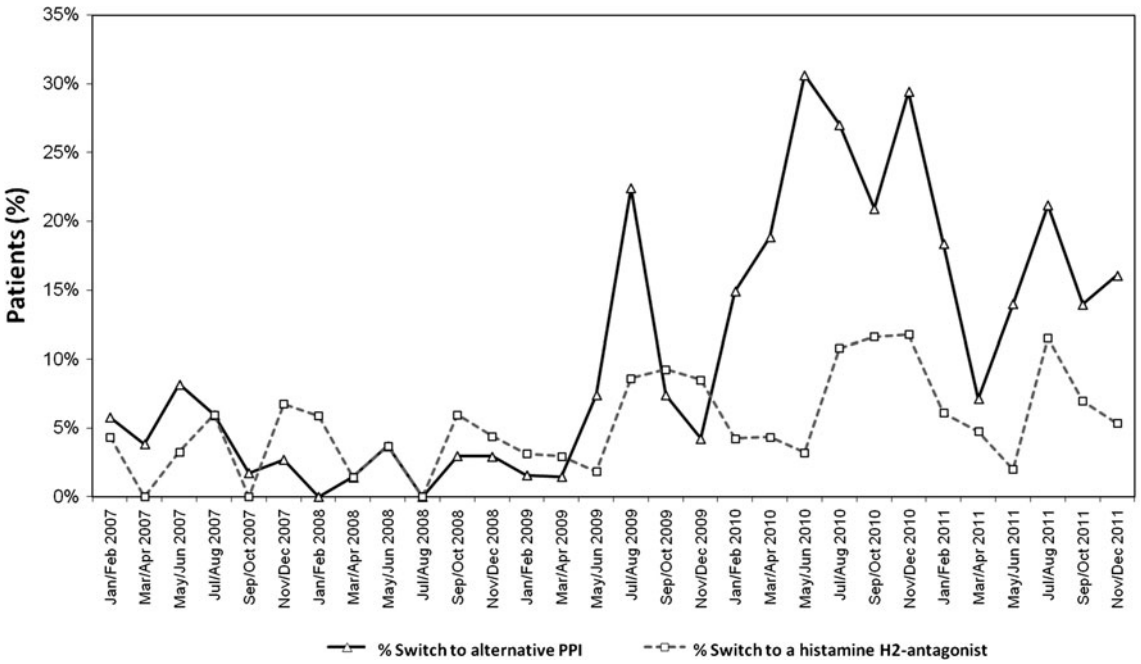

Fig. 2 The percentage of admitted patients receiving omeprazole who have a final prescription of either an alternative proton pump inhibitor (PPI) or a histamine H_2-receptor antagonist

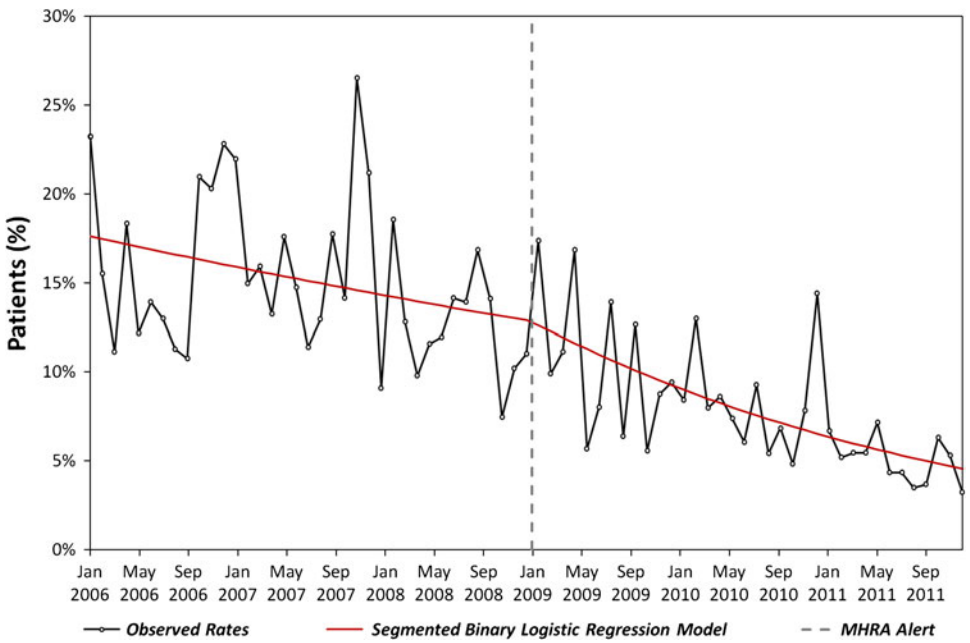

Fig. 3 Percentage of dementia patients prescribed a conventional (typical) antipsychotic. The logistic regression model is represented as linearly interpolated predicted probabilities, rather than odds ratios, for ease of interpretation. *MHRA* Medicines and Healthcare products Regulatory Agency

contrast, our analysis of the drug-disease contraindication demonstrated that the rate of conventional antipsychotic prescribing in dementia was already in significant decline before the MHRA warning was released, and although a significant step-change in prescribing practice was not observed following the release of the warning, it did coincide with a significant further decline in the proportion of dementia patients being prescribed conventional antipsychotics.

There are a number of factors that may have influenced the prescribing patterns observed in both cases. Firstly, a challenge in the design, implementation and dissemination

Table 2 Binary logistic regression results for conventional (typical) antipsychotic prescribing in patients with dementia

Factor	Odds ratio (95 % CI)	*p* value
Constant	0.216	<0.001*
Gradient (per quarter) pre-intervention	0.970 (0.943–0.998)	0.035*
Step change after MHRA alert	1.007 (0.746–1.361)	0.962
Change in the gradient (per quarter) post-intervention	0.938 (0.896–0.982)	0.006*

MHRA Medicines and Healthcare products Regulatory Agency

* Significant at $p < 0.05$

of DHPCs is the finite and ever-evolving evidence base [11]. Following the publication of the clopidogrel-PPI warning, research into the existence of this interaction was well published, potentially impacting on the physician's perception of risk relating to the warning. This may explain why a continued improvement in the prescribing practice was not observed for the interacting drugs and why 100 % compliance was never achieved, and possibly why the actions taken by the prescribers were not always consistent with the MHRA advice.

Secondly, the content of warnings is important. Concise and focused wording should be used as this has been found to be more effective than a less direct message [4, 11]. For the drug-drug interaction warning, the proportion of patients switched from omeprazole to an alternative regimen never exceeded 50 % throughout the study period. This may, in-part, be due to the information provided by the warning; for example, in April 2010 the MHRA advice stated that "concomitant use of clopidogrel and omeprazole or esomeprazole is to be discouraged *unless considered essential*". How physicians rationalize what is '*essential*' will vary, and in this case compliance with the warning may have increased if this was made clear in the information communicated. However, this warning did provide actionable advice for the healthcare professional, suggesting an alternative treatment regimen. In contrast, the 2008 MHRA warning relating to antipsychotics and dementia did not suggest an alternative pharmacological treatment for the management of the behavioural and psychological symptoms. A step-change in the prescribing practice may have been observed had alternative management been recommended. A review of FDA drug communications concluded that messages that recommend an acceptable alternative are found to be more effective [11]. If the physician knows how to respond to a warning, then compliance may be more likely.

Finally, a review of FDA drug communications also found that warnings will be most effective when the message is reinforced over time [11]. It is not standard practice for the MHRA to release reminder warnings to healthcare professionals, only updates when recommendations change, or where more evidence may need presenting. In both cases, a greater impact may have been observed if regular reminder warnings were released.

This study did not investigate the grade of the physician prescribing in each of the cases. To achieve its aims and optimize compliance, a drug-related DHPC should convey information effectively to all relevant healthcare professionals–paying particular attention to those who are most active in the medication process. In the UK hospital setting, this is most likely to be junior doctors, ward nurses and pharmacists. Worryingly, a study commissioned by the National Patient Safety Agency to investigate the quality and impact of warnings and alerts found an inability of around half of National Health Service (NHS) hospitals to communicate effectively and reliably with their junior doctors–those who generate the majority of prescriptions in this healthcare setting [29]. If the junior doctors are not made aware of DHPCs, then their practice cannot be informed.

The Central Alerting System [formerly the Safety Alert Broadcast System] in the UK ensures all urgent communications are received and implemented [30], however subsequent adherence to recommended practice needs to be promoted in the secondary-care setting, such as with a feedback loop to confirm that implementation is complete [30]. Although there are interventions that may be implemented at a local level to monitor and improve adherence to warnings, such as clinical decision support systems and restrictive prescribing rights, to date there remains no system in place to monitor the implementation of these alerts or warnings, nor is there a robust system for checking that NHS hospitals who declare themselves as being compliant actually are [10].

4.1 Limitations

The interrupted time series methodology is one of the strongest quasi-experimental designs for analysis of the longitudinal effects of interventions [31]. A major strength of this approach is the ability to control for baseline levels and trends in the period before the intervention; however, there are also a number of limitations to this type of analysis. Chief amongst these is the assumption that, other than the intervention being considered, all other confounding factors remain unchanged over the period of the investigation. The drug-drug interaction between clopidogrel and PPIs was debated amongst healthcare professionals, and conflicting evidence continued to be published throughout the period of analysis. This may have had an impact on physician prescribing, affecting the rate of switching to an alternative regimen. We are not aware of any other significant events other than the MHRA warnings that occurred during the study period for both interventions. In addition to

this, no decision support existed in PICS for these warnings, and no changes were made to the hospital formulary or PICS during the time period examined. However, any minor changes to prescribing guidelines or procedures that we were not aware of could have had the potential to influence the perceived effect of the intervention. A corollary of this assumption is that the observed effect of the intervention can only be attributed to the date on which it occurred. Hence, the changes in prescribing behaviour cannot be directly attributed to the MHRA warnings; rather, the causal inferences can only be implied.

When the impact of the MHRA warning was analysed for the drug-drug interaction between clopidogrel and PPIs, only omeprazole was selected for analysis. Over time, the advice from the MHRA changed and esomeprazole was also suggested to be avoided. Esomeprazole is a non-formulary PPI at the study site owing to its cost in comparison to other PPIs, and therefore any switches to an alternative PPI made by the physician may be attributed to this restriction rather than by the warning itself. As a result, esomeprazole switches ($n = 28$) were not considered. Finally, we did not investigate the rate at which omeprazole was stopped on admission, and the patient discharged with no alternative antisecretory agent. It would be difficult to ascertain whether the reason for treatment cessation was as a result of the MHRA advice, without medical note review; however, we acknowledge that examining unintended effects of DHPCs, such as stopping necessary treatment, would be worthy of further analysis.

5 Conclusion

This study has shown that DHPCs issued by the MHRA as warnings are associated with changes in prescribing practices in the UK hospital setting. However, their impact is variable depending on the intervention described by the warning.

As with other similar studies, methods to optimize the impact of DHPCs should be explored [5], such as reminder alerts that can continue to inform prescribing and the provision of actionable advice. A national initiative to ensure patient safety information is effectively translated into practice and the effect of the warning continues beyond the period of the issue would be beneficial.

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Competing interests Jamie Coleman is a member of the Pharmacovigilance Expert Advisory Group of the MHRA. The views expressed in this study are, however, his own.

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Conflict of interest Sarah Thomas, James Hodson, Graham McIlroy, Annjeet Dhami and Jamie Coleman have no conflicts of interest to declare that are directly relevant to the content of this study.

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