Trends in the Co-Prescription of Proton Pump Inhibitors with Clopidogrel: An Ecological Study

David N. Juurlink MD, PhD
Tara Gomes MHSc.
J. Michael Paterson, MSc.
Chelsea Hellings, MSc.
Muhammad M. Mamdani, PharmD, MPH

Affiliations: The Institute for Clinical Evaluative Sciences (DNJ,TG, JMP, CH, MMM); Sunnybrook Research Institute (DNJ); Li Ka-Shing Knowledge Institute of St. Michael's Hospital (TG; MMM); Institute of Health Policy, Management, and Evaluation, and the Leslie Dan Faculty of Pharmacy (TG) at the University of Toronto; and the Department of Family Medicine, McMaster University (JMP)

Word Count: 1621

Correspondence: Dr. David Juurlink
G Wing 106
Sunnybrook Health Sciences Centre
2075 Bayview Avenue, Toronto, Ontario CANADA M4N 3M5
Tel: (416) 480-6100 ext: 3039
Fax: (416) 480-6048
dnj@ices.on.ca

Key Words: clopidogrel; proton pump inhibitors

ABSTRACT

Background: In early 2009, two observational studies and a Food and Drug Administration advisory addressed the drug interaction between proton pump inhibitors (PPIs) and clopidogrel. A study in *The Canadian Medical Association Journal* suggested pantoprazole could be used safely in this setting, while the other study and the advisory did not distinguish among PPIs. We examined the extent to which these events influenced PPI prescribing among clopidogrel recipients.

Methods: Using population-based prescription claims data, we conducted a cross-sectional time series analysis of Ontarians aged 66 or older treated with clopidogrel between April 1, 1999 and September 30, 2013. Each quarter, we determined the proportion of clopidogrel recipients dispensed a PPI, and the proportion of these that were issued for pantoprazole or other PPIs. The primary outcome of interest was the change in pantoprazole utilization.

Results: Pantoprazole use increasing dramatically in 2009, from 23.7% of all PPI prescriptions issued to patients receiving clopidogrel in late 2008 to 52.5% of all such prescriptions by late 2009 ($p<0.0001$). This trend continued into 2013. A transient decline of approximately 10% was noted in overall PPI use was also observed beginning in early 2009.

Interpretation: A major shift occurred in the prescribing of PPIs with clopidogrel beginning in early 2009. Pantoprazole rapidly became the most commonly used agent, while overall PPI use declined slightly. The latter finding may reflect insufficiently detailed regulatory warnings or suboptimal translation of new drug safety information to clinical practice.

INTRODUCTION

Clopidogrel is a widely used drug for patients with ischemic heart disease and stroke. As a prodrug, its antiplatelet activity is partly dependent upon conversion to an active metabolite by cytochrome P450 isoenzyme 2C19.(1,2) Over the past several years, many studies have explored the possibility that some proton pump inhibitors (PPIs) – omeprazole in particular - might inhibit this process, thereby attenuating the effect of clopidogrel. In 2006, Gilard and colleagues published the first report describing a potential pharmacodynamic interaction between omeprazole and clopidogrel, (3) a finding that was subsequently confirmed by others.(4-6) However, in 2009 Cuisset et al. showed that the same phenomenon did not occur with pantoprazole,(6) an observation predicted by the fact that pantoprazole does not inhibit the same cytochrome enzyme.(7) This finding was also reaffirmed by several other groups, (8-11) including a randomized crossover study by Angiolillo et al. (12)

In early 2009, we published the first observational study of the clinical consequences of this newly described drug interaction.(13) We found that among patients taking clopidogrel following acute myocardial infarction, use of PPIs was associated with readmission for myocardial infarction; however, this risk did not extend to pantoprazole, as predicted by the drug's pharmacology. Five weeks after the online publication of our study, another observational study was published using different methodology but reaching a similar conclusion.(14) These findings were controversial; over the ensuing two years they were disputed by other studies,(15,16) including one randomized controlled trial that found that the combination of omeprazole and clopidogrel was associated with a significantly lower risk of gastrointestinal hemorrhage

and no increased risk of adverse cardiovascular events.(17) However, the trial's intervention was a proprietary product (CGT-2168) specifically formulated to avoid a pharmacokinetic interaction between clopidogrel and omeprazole, thereby precluding valid inference about the safety of the drug combination.(18)

An important finding of our 2009 study was that while PPIs as a class were associated with an increased risk of recurrent myocardial infarction, pantoprazole was not. In both the abstract and the media attention that accompanied our study, we emphasized that patients need not avoid the concomitant use of PPIs with clopidogrel when both drugs were necessary. Rather, when a PPI was indicated, we suggested the preferential use of pantoprazole on the basis of our findings, the known pharmacology of these drugs (7) and the previously reported findings of Cuisset and colleagues.(6) In contrast, an advisory issued by the United States Food and Drug Administration two days before our publication (19), as well as a large observational study published in the Journal of the American Medical Association shortly after ours (14) did not distinguish among the PPIs. Indeed, the Food and Drug Administration advisory suggested that "healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI…". (19) Similarly, a Health Canada advisory issued in August 2009 also did not distinguish among PPIs.

Our study(13) the one that followed,(14) and the contemporaneous advisory received considerable media attention nationally and internationally. This is highly unusual in the field of drug interactions, which are generally described in basic pharmacology literature and case reports, with gradual diffusion into clinical practice. In

the present study, we examined the extent to which these publications and the Food and Drug Administration advisory influenced trends in the use of PPIs with clopidogrel.

METHODS

Setting

We conducted a population-based cross-sectional study of Ontario residents aged 66 and older prescribed clopidogrel between April 1, 1999 and March 31, 2010. These individuals have universal access to health services and prescription drug coverage. The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

Data Sources

We identified prescriptions for PPIs and clopidogrel using the computerized prescription records of the Ontario Public Drug Program, which contains comprehensive records of prescription medications dispensed to Ontario residents 65 years of age or older. Patient age was obtained from the Registered Persons Database, which contains demographic information on all Ontarians ever issued a health card. These databases were anonymously linked using encrypted 10-digit health card numbers.

Identification of Patients and Rates

In each quarter of each calendar year, we identified all patients who received at least one prescription for clopidogrel. Patients were excluded if they had invalid

identifiers, if their age was unknown, or if they were younger than 66 on the date of their clopidogrel prescription. Among clopidogrel recipients, we identified those who received any prescription for pantoprazole, omeprazole, rabeprazole, lansoprazole or esomeprazole during the quarter.

Analysis

In each quarter, we calculated the proportion of patients treated with clopidogrel who also received a PPI therapy during that same quarter. Analyses were conducted for all PPIs as a group, and then stratified into pantoprazole versus other PPIs (omeprazole, rabeprazole, lansoprazole or esomeprazole).

We used autoregressive integrated moving average (ARIMA) models to evaluate changes in quarterly PPI prescribing rates beginning in the first quarter of 2009. Stationarity was assessed using the autocorrelation function and the augmented Dickey Fuller test. The autocorrelation, partial autocorrelation, and inverse autocorrelation functions were used to model parameter appropriateness and seasonality. The presence of white noise was assessed by examining the autocorrelation at various lags using the Lung-Box chi-square statistic. Analyses were conducted using SAS 9.1 software (SAS Institute, Cary, North Carolina).

RESULTS

During the nearly 15-year study period, the number of people aged 66 years or older who received clopidogrel increased from 330 in the second quarter of 1999 (the first full quarter of clopidogrel's availability on the Ontario formulary) to 83,921 by the

third quarter of 2013. Similarly, co-prescription of a PPI with clopidogrel increased considerably over this same period, from 12.7% (42 of 330 patients) to 41.6% (34,879 of 83,921 patients) (Figure). In the final quarter of 2008, immediately preceding the publications and Food and Drug Administration advisory, rabeprazole was the PPI most commonly prescribed with clopidogrel, reflecting its lower cost and preferred status on the provincial formulary.

A major shift in PPI prescribing patterns became evident in 2009. The proportion of clopidogrel patients receiving pantoprazole increased from 9.4% (4,446 of 47,344 clopidogrel recipients) in the final quarter of 2008 - prior to the two publications and FDA advisory - to 20.0% (12,433 of 62,129 clopidogrel recipients) by the final quarter of 2009 ($p<0.0001$) (Figure). This was accompanied by a corresponding decrease in the use of all other PPIs with clopidogrel, from roughly 31.5% in late 2008 (14,926 of 47,344 clopidogrel recipients) to 20.0% in late 2009 (12,443 of 62,129 clopidogrel recipients; $p=0.0002$). This change was sustained; by the third quarter of 2013, nearly a third (24,768 of 83,921; 29.5%) of clopidogrel recipients received pantoprazole, while only 10,811 (12.9%) received a different PPI.

We also observed a decline in the overall use of PPIs among patients receiving clopidogrel. In the first quarter of 2010, 38.3% (13,170 of 62,843) older Ontarians taking clopidogrel also received a PPI, roughly 10% lower than the projected estimate of 42.9%. As with the primary analysis, the observed trend was significantly different from expected trends generated by ARIMA models ($P<0.001$). In absolute terms, the difference between observed and expected PPI utilization represents approximately

2885 fewer older individuals co-prescribed a PPI than expected in the first quarter of 2010.

INTERPRETATION

Main findings

We observed major changes in the prescribing of PPIs to clopidogrel recipients in 2009, with a substantial increase in the use of pantoprazole and a modest decrease in overall PPI use. We speculate that the shift towards preferential use of pantoprazole among patients taking clopidogrel resulted from media coverage associated with our initial publication (13), since neither the contemporaneous regulatory warning (19) nor the subsequent observational study (14) distinguished among the available PPIs.

The clinical impact of these prescribing changes is unclear. The mass shift toward preferential use of pantoprazole may have favourably influenced cardiac outcomes among some clopidogrel recipients. Conversely, because overall PPI prescribing among clopidogrel recipients declined slightly following our publication, this may have been associated with harm – specifically, an increase in gastrointestinal hemorrhage. Neither of these hypotheses is easily tested given the intricacies of the drug interaction,(20) which remain the subject of some controversy.{Wedemeyer, 2014 27 /id}

It is important to reiterate that recent data clearly indicate that the use of a PPI with clopidogrel reduces the risk of gastrointestinal hemorrhage. (17) While the observed decline in overall PPI use in 2009 may reflect appropriate discontinuation of PPI therapy in some patients, it may also reflect misinterpretation of our study (in which

the safety of concomitant pantoprazole therapy was clearly documented) or the wholesale avoidance of PPI therapy on the assumption, either by patients or physicians, of a “class effect”, as might have been inferred from a subsequent publication (14) or the widely publicized Food and Drug Administration advisory.(19) This highlights the importance of clearly communicating within-class differences in drug effects when they exist.

Limitations

The principal limitation of this study is that we focused solely on drug utilization trends. Because this was an ecological rather than a patient-level analysis, and because it is generally accepted that the interaction between PPIs and clopidogrel is not likely to present a hazard for most patients (20), we did not examine whether the shift in PPI prescribing was associated with differences in clinical outcomes at the population level. We also have no information regarding the extent to which these results can be generalized to other jurisdictions.

Conclusions

In early 2009, the prescribing of PPIs to patients taking clopidogrel changed dramatically. We believe this reflects the response to a widely publicized study of a newly described drug interaction of potential relevance to large numbers of patients. Our study highlights the substantial impact that observational research can have on prescribing behavior, and indicates that this response can be both rapid and drug-specific when a clear message is communicated to clinicians and patients.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Drug Innovation Fund and the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario MOHLTC. We thank Jen Levi for assistance with manuscript preparation and Brogan Inc., Ottawa for use of their Drug Product and Therapeutic Class Database.

The opinions, results, and conclusions are those of the authors, and no endorsement by Ontario's Ministry of Health and Long-term Care or by the Institute for Clinical Evaluative Sciences is intended or should be inferred. Dr. Muhammad Mamdani has received honoraria from Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Bayer. *All other authors report no conflicts of interest.*

Author Contributions:

DMJ conceived of the study and drafted the manuscript. All authors participated in the design, interpretation and critical revision of the manuscript for intellectual content, and all approved the final version. TG performed the data extraction and the time series analysis. DNJ is the study guarantor. We thank Mariam Mukati for assistance with manuscript preparation.

Reference List

1 Giusti B, Gori AM, Marcucci R, Saracini C, Sestini I, Paniccia R, et al. Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients. *Pharmacogenet Genomics* 2007;17:1057-64.

2 Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost* 2007;5:2429-36.

3 Gilard M, Arnaud B, Le Gal G, Abgrall JF, Boschat J. Influence of omeprazol on the antiplatelet action of clopidogrel associated to aspirin. *J Thromb Haemost* 2006;4:2508-9.

4 Siriswangvat S, Sansanayudh N, Nathisuwan S, Panomvana D. Comparison between the effect of omeprazole and rabeprazole on the antiplatelet action of clopidogrel. *Circ J* 2010;74:2187-92.

5 Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, 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.

6 Cuisset T, Frere C, Quilici J, Poyet R, Gaborit B, Bali L, 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;54:1149-53.

7 Li XQ, Andersson TB, Ahlstrom M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metab Dispos* 2004;32:821-7.

8 Siller-Matula JM, Spiel AO, Lang IM, Kreiner G, Christ G, Jilma B. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart J* 2009;157:148-5.

9 Fontes-Carvalho R, Albuquerque A, Araujo C, Pimentel-Nunes P, Ribeiro VG. Omeprazole, but not pantoprazole, reduces the antiplatelet effect of clopidogrel: a randomized clinical crossover trial in patients after myocardial infarction evaluating the clopidogrel-PPIs drug interaction. *Eur J Gastroenterol Hepatol* 2011;23:396-404.

10 Neubauer H, Engelhardt A, Kruger JC, Lask S, Borgel J, Mugge A, et al. Pantoprazole does not influence the antiplatelet effect of clopidogrel-a whole blood

aggregometry study after coronary stenting. *J Cardiovasc Pharmacol* 2010;56:91-7.

11 Zuern CS, Geisler T, Lutilsky N, Winter S, Schwab M, Gawaz M. Effect of comedication with proton pump inhibitors (PPIs) on post-interventional residual platelet aggregation in patients undergoing coronary stenting treated by dual antiplatelet therapy. *Thromb Res* 2010;125:e51-e54.

12 Angiolillo DJ, Gibson CM, Cheng S, Ollier C, Nicolas O, Bergougnan L, et al. Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. *Clin Pharmacol Ther* 2011;89:65-74.

13 Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009;180:713-8.

14 Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009;301:937-44.

15 Ray WA, Murray KT, Griffin MR, Chung CP, Smalley WE, Hall K, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Ann Intern Med* 2010;152:337-45.

16 O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009;374:989-97.

17 Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, et al. Clopidogrel with or without Omeprazole in Coronary Artery Disease. *N Engl J Med* 2010;363:1909-17.

18 Juurlink DN. Clopidogrel with or without omeprazole in coronary disease. *N Engl J Med* 2011;364:681-2.

19 U.S.Food and Drug Administration. Early Communication about an Ongoing Safety Review of clopidogrel bisulfate (marketed as Plavix). http://www fda gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079520 htm 2009 January 26 [cited 2011 Jul 12];Available from: URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079520.htm

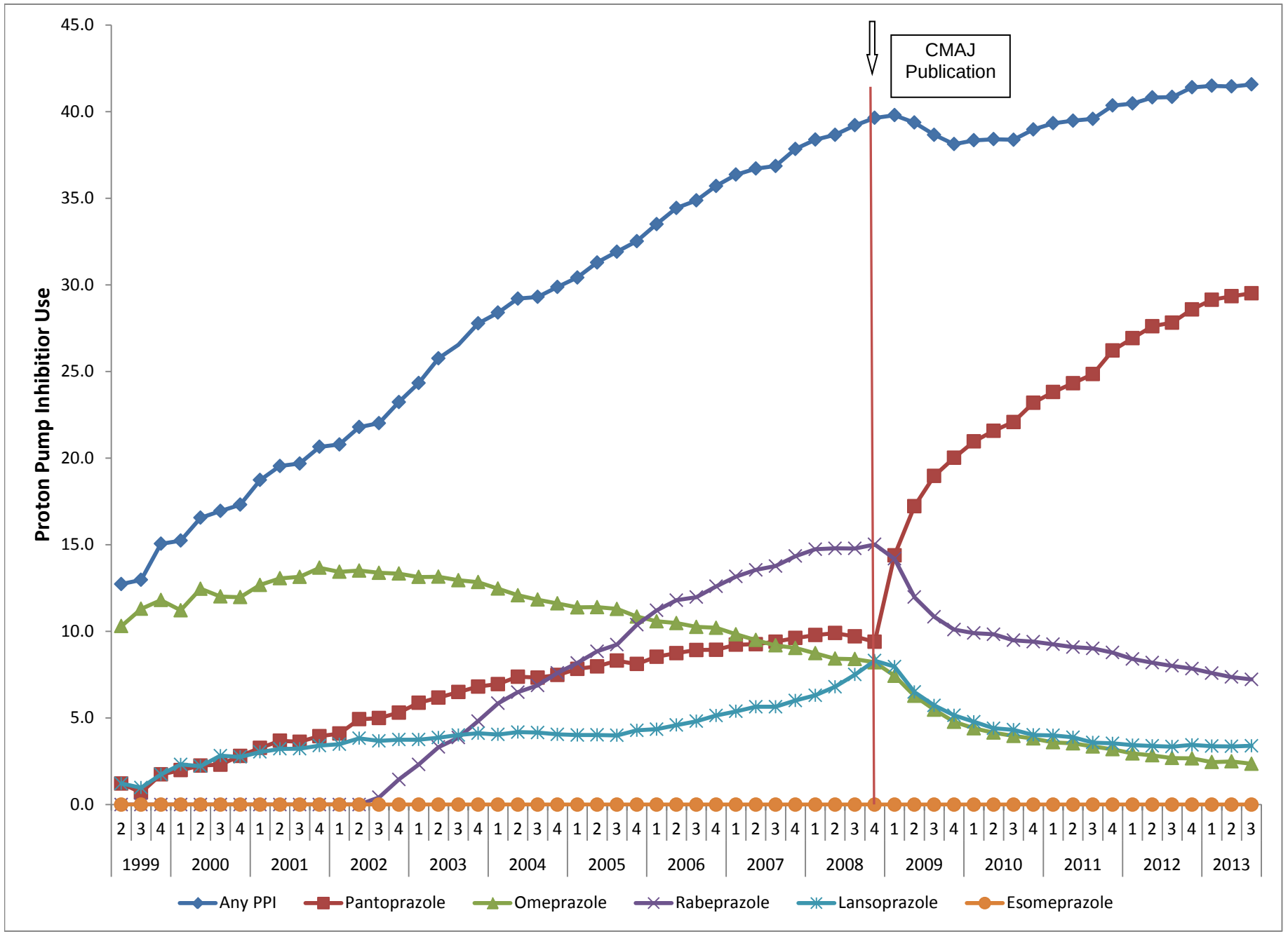
20 Juurlink DN. Proton pump inhibitors and clopidogrel: putting the interaction in perspective. *Circulation* 2009;120:2310-2.

21 Wedemeyer RS, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: An update. Drug Safety 2014;39(4):201-11.

Figure: Co-prescription of proton pump inhibitors with clopidogrel, 1999 to 2013

Legend:

Figure demonstrates the co-prescription of PPIs with clopidogrel during each quarter from 1999 through 2013. The solid line indicates total PPI use, stratified into pantoprazole (short dash) and all other PPIs (long dash). For each PPI category, the solid and dashed grey lines represent projected co-prescription rates and 95% confidence intervals, respectively. The shaded vertical bar represents the first quarter of 2009. The change in pantoprazole prescribing at Q1 is described by an ARIMA model (1,1,0) with a step function (r^2 0.997, P <0.0001), while the change in overall PPI use is described by an ARIMA model (2,1,0) with a ramp function (r^2 0.998, p <0.0001).



STROBE Statement—checklist of items that should be included in reports of observational studies

	PAGE(s)	Recommendation
Title and abstract	1-3	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4-6	Explain the scientific background and rationale for the investigation being reported
Objectives	5-6	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6-7	Present key elements of study design early in the paper
Setting	6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	6-7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	6	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	N/A	Describe any efforts to address potential sources of bias
Study size	N/A	Explain how the study size was arrived at
Quantitative variables	7	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	7	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	7-8	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	7-8	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	7-8 & figure	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	7-8 & figure	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	8-9	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	9	Summarise key results with reference to study objectives
Limitations	10	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	9-10	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	10	Discuss the generalisability (external validity) of the study results
Other information		
Funding	11	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

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