The Safety of Proton Pump Inhibitors and Clopidogrel in Patients After Stroke

David N. Juurlink, MD, PhD; Tara Gomes, MHSc; Muhammad M. Mamdani, PharmD, MBA, MPH; David J. Gladstone, MD, PhD; Moira K. Kapral, MD, MSc

Background and Purpose—Evidence suggests that some proton pump inhibitors can attenuate the antiplatelet effect of clopidogrel. The significance of this potential drug interaction in patients with cerebrovascular disease is unknown.

Methods—We conducted a nested case–control study of all Ontario residents aged ≥66 years newly treated with clopidogrel after a stroke between April 1, 2002, and September 30, 2008. In the primary analysis, case patients were those readmitted for stroke, and a secondary analysis examined all-cause mortality. For each case, up to 4 event-free control subjects were matched on age, gender, and outcome type (stroke or transient ischemic attack). Exposure to proton pump inhibitors was categorized as current (within 60 days), previous (61 to 180 days), or remote (181 to 365 days).

Results—Among 2765 patients entering the cohort, we identified 118 cases readmitted for stroke and 472 control subjects. After multivariable adjustment, current use of proton pump inhibitors was not associated with a significantly increased risk of recurrent stroke (adjusted odds ratio, 1.05; 95% CI, 0.60 to 1.82) or death (adjusted odds ratio, 1.84; 95% CI, 0.88 to 3.89).

Conclusions—As a class, proton pump inhibitors are not associated with an increased risk of recurrent stroke or death among older patients treated with clopidogrel after stroke. **(*Stroke*. 2011;42:128-132.)**

Key Words: clopidogrel ■ drug interactions ■ pharmacoepidemiology ■ proton pump inhibitors ■ stroke

Platelet aggregation plays an important role in the pathogenesis of stroke, and drugs that interfere with platelet function are an important element of treatment. Antiplatelet drugs such as aspirin and clopidogrel are widely prescribed for secondary stroke prevention in patients after ischemic stroke or transient ischemic attack (TIA). A prodrug, clopidogrel is metabolized by the liver to an active metabolite that irreversibly inhibits the platelet $P2Y_{12}$ ADP receptor.[1,2] This bioactivation is mediated by various cytochrome P-450 isoenzymes with cytochrome P-4502C19 (CYP2C19) playing a major role.[3] Loss-of-function polymorphisms in the gene encoding for CYP2C19 are associated with lower levels of the active metabolite of clopidogrel, diminished platelet inhibition during clopidogrel treatment, and an increased risk of cardiovascular events.[4,5]

Recently studies have explored the possibility that some proton pump inhibitors (PPIs) may interfere with the effect of clopidogrel by inhibiting CYP2C19, hindering enzymatic conversion to its active metabolite. Several in vitro studies demonstrate that omeprazole and other PPIs can attenuate the antiplatelet effect of clopidogrel,[6–8] but the clinical significance of this drug interaction is disputed. Some research suggests that PPIs may be associated with an increased risk of adverse cardiac events, including recurrent myocardial infarction as well as hospitalization for acute coronary syndrome and death in patients taking clopidogrel,[9–11] whereas other studies find no such association.[12,13]

No published studies have specifically explored the potential drug interaction between PPIs and clopidogrel in patients with cerebrovascular disease. In contrast to coronary artery disease, dual antiplatelet therapy is not generally recommended for long-term secondary stroke prevention.[14,15] Consequently, PPI-mediated attenuation of clopidogrel's effect may assume particular importance in patients receiving clopidogrel as the sole antiplatelet agent after stroke. In this study, we sought to characterize whether the concomitant use of a PPI with clopidogrel was associated with an increased risk of adverse outcomes among older patients discharged from the hospital after stroke.

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From the Sunnybrook Research Institute (D.N.J., D.J.G.) and Regional Stroke Centre (D.J.G.), Toronto, Ontario, Canada; Li Ka-Shing Knowledge Institute of St Michael's Hospital (M.M.M.), Toronto, Ontario, Canada; University Health Network (M.K.K.), Toronto, Ontario, Canada; Departments of Medicine (D.N.J., M.M.M., D.J.G., M.K.K.), Pediatrics (D.N.J.), Health Policy, Management, and Evaluation (D.N.J., M.M.M., M.K.K.), and the Leslie Dan Faculty of Pharmacy (T.G., M.M.M.) at the University of Toronto, Toronto, Ontario, Canada; and The Institute for Clinical Evaluative Sciences (D.N.J., T.G., M.M.M., D.J.G., M.K.K.), Toronto, Ontario, Canada.

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.

Correspondence to David N. Juurlink, MD, PhD, G Wing 106, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5. E-mail dnj@ices.on.ca

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Methods

Setting

We conducted a population-based nested case–control study among residents of the province of Ontario, Canada, aged ≥66 years, who were discharged from the hospital after ischemic stroke between April 1, 2002, and September 31, 2008. These individuals have universal access to hospital care, physicians' services, and prescription drug coverage. The study was approved by the research ethics board of Sunnybrook Health Sciences Centre.

Data Sources

We identified hospital visits using the Canadian Institute for Health Information Discharge Abstract Database, which contains detailed diagnostic and procedural information regarding hospital admissions. All hospitalizations in Ontario are identified in this database, which is population-based and comprehensive. We examined the computerized prescription records of the Ontario Public Drug Program Benefit Program, which contains comprehensive records of prescription medications dispensed to Ontario residents ≥65 years of age. We used the Ontario Health Insurance Plan database to identify claims for inpatient and outpatient physician services. Basic demographic information, including date of death, was identified using the Registered Persons Database, which contains a unique entry for all Ontario residents ever issued a health card. These databases are routinely used to study drug safety,[16–18] including the clinical consequences of drug–drug interactions,[19–21] and were linked in an anonymous fashion using encrypted 10-digit health card numbers.

Identification of Patients and Outcomes

We established a cohort of patients aged ≥66 years who filled a prescription for clopidogrel within 30 days of hospital discharge after ischemic stroke or TIA. The date of discharge from the hospital served as the date of cohort entry. We excluded patients who received clopidogrel in the year before hospitalization, or ticlopidine or dipyridamole in the 90 days before hospitalization, as well as patients in long-term care facilities and those who received PPI combination products used to eradicate *Helicobacter pylori* in the year preceding the index date or 90 days thereafter. Finally, we excluded patients who underwent carotid endarterectomy within 90 days after hospitalization, as well as those readmitted for stroke between the cohort entry date and the first prescription for clopidogrel.

Patients were followed during clopidogrel therapy for a maximum of 180 days from hospital discharge or until readmission for ischemic stroke or TIA. Ongoing use of clopidogrel was assured using an adherence algorithm that required prescription refills of the drug at intervals not exceeding 50% of the days supplied with the preceding prescription. Hospitalizations were identified using the International Classification of Disease and Related Health Problems, 10th Revision for ischemic stroke (I63, I64) and TIA (G45). The date of hospital readmission for stroke or TIA (in the primary analysis) or death (in the secondary analysis) served as the index date. Only the first readmission was considered for patients with multiple readmissions during the study period.

We defined cases as patients who experienced an outcome of interest within 180 days of discharge after stroke. For each case, up to 4 control subjects were sampled randomly with replacement[22] from the same cohort of patients and were required to be event-free but at risk on the index date. Control subjects were matched to cases on age (born within 1 year), gender, and outcome type (stroke or TIA). When <4 control subjects could be matched to a case patient, we used only those control subjects and did not alter the matching algorithm.

Exposure to PPIs

We used prescription records to determine exposure to PPIs during clopidogrel therapy, including omeprazole, rabeprazole, pantoprazole, and lansoprazole. We did not study esomeprazole because it was not an insured benefit of the provincial formulary during the

Table 1. Characteristics of Case and Control Subjects

Variable	Cases (N=118)	Control Subjects (N=472)	Standardized Difference
Age at cohort entry			
Median (IQR)	77 (73–83)	77 (73–83)	0.00
Age categories, years			
66 to 75	45 (38.1%)	180 (38.1%)	0.00
76 to 85	55 (46.6%)	220 (46.6%)	0.00
85+	18 (15.3%)	72 (15.3%)	0.00
Male	50 (42.4%)	200 (42.4%)	0.00
Medication use			
ACE Inhibitor	58 (49.2%)	209 (44.3%)	0.10
ARB	18 (15.3%)	64 (13.6%)	0.05
Aspirin	10 (8.5%)	34 (7.2%)	0.05
β-blocker	39 (33.1%)	128 (27.1%)	0.13
Calcium channel blocker	30 (25.4%)	105 (22.2%)	0.08
Statin	59 (50.0%)	255 (54.0%)	0.08
Nonstatin antilipemic	≤5*	13 (2.8%)	0.07
Thiazide diuretic	19 (16.1%)	80 (16.9%)	0.02
Other diuretics (including loop agents)	17 (14.4%)	58 (12.3%)	0.06
Other miscellaneous hypertensives	≤5*	≤5*	0.06
Warfarin	≤5*	18 (3.8%)	0.02
Other 2C19 inducers	6 (5.1%)	7 (1.5%)	0.25
Other 2C19 inhibitors	≤5*	6 (1.3%)	0.04
Other 3A4 inducers	7 (5.9%)	21 (4.4%)	0.07
Other 3A4 inhibitors	13 (11.0%)	56 (11.9%)	0.03
Hospital type			
District stroke center	25 (21.6%)	95 (20.8%)	0.02
Regional stroke center	11 (9.5%)	63 (13.8%)	0.13
Other hospital	80 (69.0%)	299 (65.4%)	0.07
Length of stay			
Median (IQR)	5 (3–8)	4 (3–8)	0.02
Charlson category			
0	0 (0.0%)	≤5*	0.09
1	41 (34.7%)	234 (49.6%)	0.30
2+	77 (65.3%)	235 (49.8%)	0.31
Comorbidity in past 5 years			
Diabetes	7 (5.9%)	59 (12.5%)	0.21
Coronary revascularization	23 (19.5%)	78 (16.5%)	0.08
Stroke	25 (21.2%)	51 (10.8%)	0.31
Income quintile			
1 (lowest)	34 (28.8%)	106 (22.5%)	0.15
2	26 (22.0%)	90 (19.1%)	0.07
3	19 (16.1%)	104 (22.0%)	0.15
4	24 (20.3%)	102 (21.6%)	0.03
5 (highest)	15 (12.7%)	69 (14.6%)	0.05
Missing	0 (0.0%)	≤5*	0.05
No. of drug names in previous year			
Median (IQR)	12 (9–18)	10 (7–15)	0.34

*Cells with <6 observations are suppressed in accordance with institutional privacy policy.

IQR indicates interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 2. Association Between PPI Exposure and Readmission for Stroke Among Patients Receiving Clopidogrel After Stroke

PPI Exposure	Cases (N=118)	Control Subjects (N=472)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
No PPI	75 (63.6%)	332 (70.3%)	1.0 (reference)	1.0
Current PPI	32 (27.1%)	95 (20.1%)	1.50 (0.93 to 2.42)	1.05 (0.60 to 1.82)
Recent PPI	10 (8.5%)	33 (7.0%)	1.35 (0.64 to 2.84)	1.22 (0.55 to 2.68)
Remote PPI	≤5†	12 (2.5%)	0.37 (0.05 to 2.91)	0.24 (0.03 to 2.12)

*Adjusted for age, gender, income quintile (estimated from the residential postal code), Charlson comorbidity index,[23] length of stay in the hospital during the first admission for stroke, hospital type (regional stroke center, district stroke center, or other), and history of diabetes, stroke, or coronary revascularization in the preceding 5 years, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, β-adrenergic receptor antagonists, calcium channel blockers, statins, other lipid-lowering agents, thiazide diuretics, other diuretics and warfarin, other cytochrome P-450 2C19 inhibitors or inducers, and other cytochrome P-450 3A4 inhibitors or inducers.

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study period. We categorized PPI use according to the most proximate prescription as either current (within 60 days before the index date), previous (61 to 180 days before the index date), or remote (181 to 365 days before the index date).

Statistical Analysis

We used conditional logistic regression to estimate the odds ratio (OR) for the association between stroke readmission and PPI exposure using as the reference a group of patients with no prescription for a PPI. We adjusted for the Charlson comorbidity index,[23] the number of drugs dispensed in the previous year, and history of diabetes, stroke, or coronary revascularization in the preceding 5 years. We also adjusted for use of medications that might influence the risk of stroke recurrence, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, β-adrenergic receptor antagonists, calcium channel blockers, statins, other lipid-lowering agents, thiazide diuretics, other diuretics and warfarin. We also adjusted for use of other common cardiovascular medications, other cytochrome P-450 2C19 inhibitors or inducers, and other cytochrome P-450 3A4 inhibitors or inducers[24] (Appendix) between hospital discharge and the reference date. All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC).

Results

Over the 78-month accrual period, we identified 2765 patients aged ≥66 years who commenced treatment with clopidogrel within 30 days of hospital discharge after acute ischemic stroke. The median age of these patients was 78 (interquartile range, 73 to 83 years), and 1295 (46.8%) were men. The median length of stay during this admission was 4 days (interquartile range, 3 to 8 days). Postdischarge use of PPIs was common, with 752 (27.2%) patients receiving a PPI within 90 days of discharge.

From this cohort, we identified 118 patients who were readmitted for ischemic stroke or TIA within 180 days of discharge, along with 472 control subjects. The characteristics of cases and control subjects are shown in Table 1. As expected, cases were more likely than control subjects to have had several comorbidities during their index admission. In the primary analysis, after multivariable adjustment, we found no significant association between readmission for stroke and current use of a PPI in patients receiving clopidogrel (adjusted OR, 1.05; 95% CI, 0.60 to 1.82; Table 2). Similarly, in the secondary analysis, we found no statistically significant association between PPI use and death from any cause among older patients taking clopidogrel after stroke (adjusted OR, 1.84; 95% CI, 0.88 to 3.89; Table 3).

Discussion

We found that among older patients treated with clopidogrel after acute ischemic stroke or TIA, concomitant use of a PPI was not associated with a significantly increased short-term risk of readmission for stroke. To our knowledge, this is the first study to examine the potential effect of PPI therapy on recurrent stroke risk in patients treated with clopidogrel for secondary stroke prevention.

Although in vitro studies suggest that some PPIs, in particular omeprazole, can attenuate the antiplatelet activity of clopidogrel,[6,25] our findings suggest that this potential drug interaction is of little clinical consequence in patients with cerebrovascular disease. This observation differs from previously published research by our group[9] and others[10,11] in patients with acute coronary syndromes.

Table 3. Association Between PPI Exposure and Death From Any Cause Among Patients Receiving Clopidogrel After Stroke

PPI Exposure	Cases (N=62)	Control Subjects (N=248)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
No PPI	35 (29.7%)	170 (36.0%)	1.0 (reference)	1.0
Current PPI	22 (18.6%)	56 (11.9%)	2.01 (1.06 to 3.82)	1.84 (0.88 to 3.89)
Recent PPI	≤5†	18 (3.8%)	1.35 (0.46 to 3.92)	0.80 (0.24 to 2.68)
Remote PPI	0	≤5†	N/A	N/A

*Adjusted for age, gender, income quintile (estimated from the residential postal code), Charlson comorbidity index,[23] length of stay in the hospital during the first admission for stroke, hospital type (regional stroke center, district stroke center, or other), and history of diabetes, stroke, or coronary revascularization in the preceding 5 years, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, β-adrenergic receptor antagonists, calcium channel blockers, statins, other lipid-lowering agents, thiazide diuretics, other diuretics and warfarin, other cytochrome P-450 2C19 inhibitors or inducers, and other cytochrome P-450 3A4 inhibitors or inducers.

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Some limitations of our research merit emphasis. We had no data on some important risk factors for stroke such as atrial fibrillation, hypertension, and smoking. Although cases and control subjects were matched on important predictors of outcome, some imbalance is evident in their measured characteristics (Table 1). However, this observation is neither unexpected nor a threat to our primary conclusion, because any bias introduced by this imbalance would tend to favor a spurious association. Miscoding is a potential threat to the validity of all observational studies, but previous validation studies indicate that coding for stroke in Ontario's administrative databases is very good and comparable to that of other administrative databases.[26–29] We did not have a sufficient sample size to explore the possibility that some PPIs may be associated with greater risk than others. This is particularly important because the largest body of in vitro data on this drug interaction implicate omeprazole, whereas pantoprazole appears to be relatively devoid of an effect on clopidogrel's metabolism and does not interfere with its antiplatelet effect.[8,25,30] Importantly, because some patients take PPIs intermittently, misclassification of exposure status is possible in our analysis. However, there is no reason to believe that case and control subjects would differ in this regard.

Stroke is heterogenous and the effectiveness of clopidogrel is expected to be greatest in the subgroup of patients with stroke with large artery atherosclerotic disease rather than those with lacunar disease, cardioembolism, or stroke from other causes. Because administrative databases do not provide reliable information on the etiologic classification of stroke events, we were unable to investigate this interaction in specific subtypes of stroke. Finally, our relatively modest sample size may have limited our ability to detect an association. However, this limitation tends to jeopardize statistical precision, and the point estimate associated with our primary analysis (1.05) suggests that a meaningful Type II error is unlikely.

In summary, we found that among patients treated with clopidogrel after stroke, the concomitant use of PPIs is not associated with an increased risk of readmission for recurrent stroke. This finding should reassure clinicians and patients that treatment with a PPI, when indicated, appears generally safe with respect to stroke recurrence risk in patients receiving clopidogrel. However, this is a rapidly evolving area, and when a PPI is indicated, we believe it is advisable to preferentially use pantoprazole, which exhibits relatively little inhibition of CYP2C19[31] and may not attenuate the antiplatelet effect of clopidogrel to the same extent as other PPIs, particularly omeprazole.[8,31,32]

Appendix

Drug Covariates Used in the Multivariable Model

Cytochrome P-450 2C19 Inhibitors

Chloramphenicol, cimetidine, felbamate, fluoxetine, fluvoxamine, indomethacin, ketoconazole, modafinil, oxcarbazepine, probenecid, topiramate.

Cytochrome P-450 2C19 Inducers

Norethindrone, prednisone, rifampin.

Cytochrome P-450 3A4 Inhibitors

Amiodarone, aprepitant, clarithromycin, delavirdine, diltiazem, erythromycin, imatinib, indinavir, itraconazole, nefazodone, nelfinavir, norfloxacin, ritonavir, saquinavir, telithromycin, verapamil, voriconazole.

Cytochrome P-450 3A4 Inducers

Carbamazepine, efavirenz, nevirapine, phenobarbital, phenytoin, pioglitazone.

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Disclosures

D.J.G. has received speaker fees for continuing medical education events/advisory board honoraria from Sanofi Aventis, Bristol Myers Squibb, and Boehringer Ingelheim. M.M.M. has received an honorarium for an advisory board membership from Pfizer.

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Abstract 5

뇌졸중 환자에서 양성자 펌프 억제제와 클로피도그렐의 안전성

The Safety of Proton Pump Inhibitors and Clopidogrel in Patients After Stroke

David N. Juurlink, MD, PhD; Tara Gomes, MHSc; Muhammad M. Mamdani, PharmD, MBA, MPH; David J. Gladstone, MD, PhD; Moira K. Kapral, MD, MSc

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Key Words: clopidogrel ■ drug interactions ■ pharmacoepidemiology ■ proton pump inhibitors ■ stroke

배경과 목적

몇몇 양성자 펌프 억제제(proton pump inhibitor)는 클로피도그렐(clopidogrel)의 항혈소판 효과를 감소시킨다. 뇌혈관질환(cerebrovascular disease)이 있는 환자에서 이러한 잠재적인 약물 상호작용의 중요도는 잘 알려져 있지 않다.

방법

저자들은 2002년 4월 1일~2008년 9월 30일에 뇌졸중이 발병하여 클로피도그렐을 처음으로 처방받은 66세 이상의 온타리오(Ontario) 주민들을 대상으로 코호트 내 환자 대조군 연구(nested case-control study)를 실시하였다. 일차 분석에서 환자군은 뇌졸중으로 재입원한 환자들이었고, 이차 분석은 모든 종류의 사망을 분석하였다. 사건이 발생하지 않은 4명 이하의 대조군 대상자를 연령, 성별, 결과 종류(뇌졸중 또는 일과성 허혈발작[transient ischemic attack])에 따라 한 명의 환자에 짝짓기(match)하였다. 양성자 펌프 억제제에 대한 노출은 현재(60일 이내), 최근(61~180일), 과거(181~365일)로 분류하였다.

결과

코호트에 참가한 환자 2,765명 중에서 뇌졸중으로 재입원한 118명의 환자군과 472명의 대조군을 찾아냈다. 다변량 분석을 하였을 때 양성자 펌프 억제제를 현재 사용하고 있는 것은 뇌졸중 재발(보정 교차비[adjusted odds ratio], 1.05; 95% CI, 0.60~1.82) 또는 사망(보정 교차비, 1.84; 95% CI, 0.88~3.89)과 유의한 관련이 없었다.

결론

양성자 펌프 억제제들은 뇌졸중으로 클로피도그렐을 처방받은 노령의 환자에서 뇌졸중 재발 또는 사망과 관련이 없었다.

The Safety of Proton Pump Inhibitors and Clopidogrel in Patients After Stroke

David N. Juurlink, Tara Gomes, Muhammad M. Mamdani, David J. Gladstone and Moira K. Kapral

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