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-control subject matches were subject on age, gender, and outcome type (stroke or transient ischemic attack). Exposure to proton pump inhibitors was categorized as current (within 60 days), previous (181 to 365 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 P2Y12 ADP receptor. This bioactivation is mediated by various cytochrome P-450 isoenzymes with cytochrome P-450C19 (CYP2C19) playing a major role. 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.

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, 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, whereas other studies find no such association.

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.

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.
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 (163, 164) 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 replacement22 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>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Control</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at cohort entry</td>
<td>Median (IQR)</td>
<td>77 (73–83)</td>
<td>77 (73–83)</td>
</tr>
<tr>
<td>Age categories, years</td>
<td>66 to 75</td>
<td>45 (38.1%)</td>
<td>180 (38.1%)</td>
</tr>
<tr>
<td></td>
<td>76 to 85</td>
<td>55 (46.6%)</td>
<td>220 (46.6%)</td>
</tr>
<tr>
<td></td>
<td>85+</td>
<td>18 (15.3%)</td>
<td>72 (15.3%)</td>
</tr>
<tr>
<td>Male</td>
<td>50 (42.4%)</td>
<td>200 (42.4%)</td>
<td>0.00</td>
</tr>
<tr>
<td>Medication use</td>
<td>ACE Inhibitor</td>
<td>58 (49.2%)</td>
<td>209 (44.3%)</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>18 (15.3%)</td>
<td>64 (13.6%)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>10 (8.5%)</td>
<td>34 (7.2%)</td>
</tr>
<tr>
<td></td>
<td>β-blocker</td>
<td>39 (33.1%)</td>
<td>128 (27.1%)</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blocker</td>
<td>30 (25.4%)</td>
<td>105 (22.2%)</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>59 (50.0%)</td>
<td>255 (54.0%)</td>
</tr>
<tr>
<td></td>
<td>Nonstatin antilipemic</td>
<td>13*</td>
<td>28 (2.8%)</td>
</tr>
<tr>
<td></td>
<td>Thiazide diuretic</td>
<td>19 (16.1%)</td>
<td>80 (16.9%)</td>
</tr>
<tr>
<td></td>
<td>Other diuretics (including loop agents)</td>
<td>17 (14.4%)</td>
<td>58 (12.3%)</td>
</tr>
<tr>
<td></td>
<td>Other miscellaneous hypertensives</td>
<td>5*</td>
<td>5*</td>
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<tr>
<td></td>
<td>Warfarin</td>
<td>18 (3.8%)</td>
<td>39 (8.5%)</td>
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<tr>
<td></td>
<td>Other 2C19 inducers</td>
<td>6 (5.1%)</td>
<td>7 (1.5%)</td>
</tr>
<tr>
<td></td>
<td>Other 2C19 inhibitors</td>
<td>6 (5.1%)</td>
<td>10 (2.1%)</td>
</tr>
<tr>
<td></td>
<td>Other 3A4 inducers</td>
<td>7 (5.9%)</td>
<td>21 (4.4%)</td>
</tr>
<tr>
<td></td>
<td>Other 3A4 inhibitors</td>
<td>13 (11.0%)</td>
<td>56 (11.9%)</td>
</tr>
<tr>
<td>Hospital type</td>
<td>District stroke center</td>
<td>25 (21.6%)</td>
<td>95 (20.8%)</td>
</tr>
<tr>
<td></td>
<td>Regional stroke center</td>
<td>11 (9.5%)</td>
<td>63 (13.8%)</td>
</tr>
<tr>
<td></td>
<td>Other hospital</td>
<td>80 (69.0%)</td>
<td>299 (65.4%)</td>
</tr>
<tr>
<td>Length of stay</td>
<td>Median (IQR)</td>
<td>5 (3–8)</td>
<td>4 (3–8)</td>
</tr>
<tr>
<td>Charlson category</td>
<td>0</td>
<td>0 (0.0%)</td>
<td>5*</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>41 (34.7%)</td>
<td>234 (49.6%)</td>
</tr>
<tr>
<td></td>
<td>2+</td>
<td>77 (65.3%)</td>
<td>235 (49.8%)</td>
</tr>
<tr>
<td>Comorbidity in past 5 years</td>
<td>Diabetes</td>
<td>7 (5.9%)</td>
<td>59 (12.5%)</td>
</tr>
<tr>
<td></td>
<td>Coronary revascularization</td>
<td>23 (19.5%)</td>
<td>78 (16.5%)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>25 (21.2%)</td>
<td>51 (10.8%)</td>
</tr>
<tr>
<td>Income quintile</td>
<td>1 (lowest)</td>
<td>34 (28.8%)</td>
<td>106 (22.5%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>26 (22.0%)</td>
<td>90 (19.1%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>19 (16.1%)</td>
<td>104 (22.0%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>24 (20.3%)</td>
<td>102 (21.6%)</td>
</tr>
<tr>
<td></td>
<td>5 (highest)</td>
<td>15 (12.7%)</td>
<td>69 (14.6%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0 (0.0%)</td>
<td>5*</td>
</tr>
</tbody>
</table>

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

IQR indicates interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
tients aged 66 years who commenced treatment with 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 group9 and others10,11 in patients with acute coronary syndromes.

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

<table>
<thead>
<tr>
<th>PPI Exposure</th>
<th>Cases (N=116)</th>
<th>Control Subjects (N=472)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PPI</td>
<td>75 (63.6%)</td>
<td>332 (70.3%)</td>
<td>1.0 (reference)</td>
<td>1.0</td>
</tr>
<tr>
<td>Current PPI</td>
<td>32 (27.1%)</td>
<td>95 (20.1%)</td>
<td>1.50 (0.93 to 2.42)</td>
<td>1.05 (0.60 to 1.82)</td>
</tr>
<tr>
<td>Recent PPI</td>
<td>10 (8.5%)</td>
<td>33 (7.0%)</td>
<td>1.35 (0.64 to 2.84)</td>
<td>1.22 (0.55 to 2.68)</td>
</tr>
<tr>
<td>Remote PPI</td>
<td>≤5†</td>
<td>12 (2.5%)</td>
<td>0.37 (0.05 to 2.91)</td>
<td>0.24 (0.03 to 2.12)</td>
</tr>
</tbody>
</table>

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

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).
Appendix

Drug Covariates Used in the Multivariable Model

**Cytochrome P-450 2C19 Inhibitors**

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

**Cytochrome P-450 2C19 Inducers**

Norethindrone, prednisone, rifampin.

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. Misclassifying 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 implicates 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, miscoding 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 heterogeneous 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 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 CYP2C1931 and may not attenuate the antiplatelet effect of clopidogrel to the same extent as other PPIs, particularly omeprazole.8,31,32

**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.

**Acknowledgments**

We thank Ashif Kachra and Jill Tomac for assistance with manuscript preparation and Brogan Inc, Ottawa for use of their Drug Product and Therapeutic Class Database.

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**Disclosures**

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뢰졸중 환자에서 양성자 펌프 억제제와 클로피도그레놀의 안전성

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

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(Stroke. 2011;42:128-132.)

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

배경과 목적
몇몇 양성자 펌프 억제제(proton pump inhibitors)는 클로피도그레놀(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 발생하여 클로피도그레놀을 처방받은 66세 이상의 온타리오(Ontario) 주민들 대상으로 코호트 내 환자 대조군 연구(nested case-control study)를 실시하였다. 일차 분석에서 환자군은 뇌졸중으로 재입원한 환자들이고, 이차 분석은 모든 종류의 사망을 분석하였다. 사건이 발생하지 않은 4명 이하의 대조군 대상자를 연령, 성별, 결과 종류(뇌졸중 또는 일차성 흐혈뇌마비(transient ischemic attack))에 따라 한 명의 환자에 적합기(match)하였다. 양성자 펌프 억제제에 대한 노출은 우발(60일 이내), 최근(61~180일), 과거(181~365일)로 분류하였다.

결과
코호트에 참여한 환자 2,765명 중에서 뇌졸중으로 재입원한 118명의 환자군과 472명의 대조군을 찾아냈다. 다변량 분석을 하였을 때 양성자 펌프 억제제를 현재 사용하고 있는 환자는 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 클로피도그레놀을 처방받은 노령의 환자에서 뇌졸중 재발 또는 사망과 관련이 없었다.