A Comparison of Aspirin and Clopidogrel With or Without Proton Pump Inhibitors for the Secondary Prevention of Cardiovascular Events in Patients at High Risk for Gastrointestinal Bleeding

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ABSTRACT

Objective: This study was conducted to compare the risk of recurrent hospitalization for major gastrointestinal (GI) complications (peptic ulcer, bleeding, and perforation) in patients at high GI risk who require ongoing antiplatelet therapy (aspirin [acetylsalicylic acid] or clopidogrel) with or without proton pump inhibitors (PPIs).

Methods: This population-based, retrospective cohort study employed data from the Taiwanese National Health Insurance database (January 2001 through December 2006) for patients who had a history of hospitalization for GI complications before the initiation of antiplatelet therapy with aspirin or clopidogrel. Recurrent hospitalizations for major GI complications were analyzed using a Cox proportional hazards model, with adjustment for age, sex, ulcer-related medical history, ulcer-related risk factors, and use of ulcer-related medications during follow-up. The propensity score method was applied to adjust for selection bias.

Results: The analysis included data from 14,627 patients (12,001 receiving aspirin, 2626 receiving clopidogrel). The incidence of recurrent hospitalization for major GI complications was 0.125 per person-year in aspirin users, 0.103 per person-year in users of aspirin plus a PPI, 0.128 per person-year in clopidogrel users, and 0.152 per person-year in users of clopidogrel plus a PPI. Among aspirin users, those taking PPIs had a significantly lower adjusted risk of hospitalization for major GI complications than did non-PPI users (hazard ratio [HR] = 0.76; 95% CI, 0.64–0.91). Use of a PPI was not associated with a significant risk reduction among clopidogrel users (HR = 1.08; 95% CI, 0.89–1.33). An adjusted survival curve for the risk of recurrent hospitalization for major GI complications indicated that the risk increased numerically faster in clopidogrel users compared with those using aspirin plus a PPI, although the mean drug cost per person-year was 5.08 times higher in clopidogrel users than in users of aspirin plus a PPI.

Conclusions: In this analysis in patients at high GI risk who were receiving antiplatelet therapy for the secondary prevention of cardiovascular events, aspirin plus a PPI was associated with a reduced risk of recurrent hospitalization for major GI complications. This was not the case for clopidogrel plus a PPI. (*Clin Ther.* 2009;31:2038–2047) © 2009 Excerpta Medica Inc.

Key words: clopidogrel, aspirin, proton pump inhibitors, PPIs, peptic ulcer, gastrointestinal bleeding or perforation, hospitalization.

INTRODUCTION

Antiplatelet therapy is universally recommended for the secondary prevention of cardiovascular events in patients with stroke, transient ischemic attack, acute or chronic coronary artery disease, or peripheral arterial disease.[1,2] Low-dose (75–150 mg) aspirin (acetylsalicylic acid), which has been reported to reduce the risk of vascular events by as much as 25%,[3] is the cornerstone of antiplatelet therapy. However, aspirin's association with gastrointestinal (GI) adverse effects is well known. Low-

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dose aspirin has been associated with a 2-fold greater risk of major GI bleeding compared with placebo.[4–6]

Clopidogrel, an antiplatelet agent whose effects occur through a different mechanism than those of aspirin, has been approved and recommended for use in patients who are unable to tolerate or have contraindications to aspirin.[3] The CAPRIE[7] (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial found that long-term clopidogrel monotherapy was more effective and better tolerated than aspirin in the secondary prevention of cardiovascular events. Clopidogrel was associated with fewer GI adverse events (eg, abdominal pain, dyspepsia, upper GI ulceration) compared with aspirin (27.1% vs 29.8%, respectively; $P < 0.001$). Although this result was statistically significant, it is not clear that this difference in the frequency of GI events is clinically significant.

The question remains whether clopidogrel is an acceptable substitute for aspirin in patients with a history of GI bleeding. Such patients were excluded from the CAPRIE[7] trial, which, in addition, compared clopidogrel with an aspirin dose of 325 mg/d, much higher than the dose usually recommended for the prevention of cardiovascular events (75–150 mg). One observational study in patients with a history of GI complications reported recurrence rates of GI complications as high as 14% in those taking clopidogrel,[8] similar to the rate with aspirin (15%) in a study enrolling a comparable population.[9]

Neither the 2007 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of chronic stable angina[10] nor the 2004 American College of Chest Physicians guidelines for antithrombotic therapy in coronary artery disease[11] contain specific recommendations regarding the use of clopidogrel in patients with a history of GI hemorrhage. However, the 2007 ACC/AHA guidelines for unstable angina/non–ST-elevation myocardial infarction[12] state that proton pump inhibitors (PPIs) may be used with aspirin or clopidogrel to minimize the risk of recurrent bleeding in patients with a history of GI hemorrhage. This recommendation may have reflected the findings of 2 studies suggesting a potential benefit of concomitant PPI use with clopidogrel in patients with previous GI bleeding.[8,13]

If clopidogrel, with or without a PPI, were found to be no better tolerated than aspirin in patients at high GI risk, aspirin—which is considerably less costly than clopidogrel—plus a PPI might be preferable for the management of these patients. The present study compared the risk of recurrent hospitalization for major GI complications (peptic ulcer, bleeding, and perforation) in patients at high GI risk who require ongoing antiplatelet therapy (aspirin or clopidogrel), with or without PPIs, for the secondary prevention of cardiovascular events.

MATERIALS AND METHODS

Data Source

The mandatory National Health Insurance (NHI) program covers >99% (~23 million) of the Taiwanese population. Beneficiaries are free to choose among health care providers contracted with the NHI and receive comprehensive benefits that include inpatient care, ambulatory care, dental care, and prescription drugs. Data for the present population-based retrospective cohort study were obtained from the NHI claims database for January 2001 through December 2006. Because all patient identifiers are encrypted, ethical approval for use of the data was not required.

Study Population

Patients were identified who initiated antiplatelet therapy with low-dose aspirin (<325 mg) or clopidogrel 75 mg between January 1, 2001, and December 31, 2006, and had a history of hospitalization for major GI complications of peptic ulcer (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 531–533) or hospitalization with major GI bleeding or perforation detected on surgery. Antiplatelet therapy was identified by a record of the following indications and associated *ICD-9-CM* codes: coronary heart disease (413–414), peripheral vascular disease (444.2), ischemic stroke (433–434), or transient ischemic attack (435–437.1). Because cardiologists frequently prescribe low-dose aspirin for the secondary prevention of cardiovascular events, which is covered by the NHI program, the NHI database captures data on the use and costs of low-dose aspirin for this purpose.

Patients whose records indicated continuous use of antiplatelet therapy with low-dose aspirin or clopidogrel from the cohort entry date (the date of the first prescription for aspirin or clopidogrel) to the end of the study period were eligible for inclusion. Those already taking aspirin or clopidogrel at the beginning of the observation period were eligible if they used this therapy continuously during follow-up. Patients who

used a combination of these agents were excluded. Data on the use of all NHI resources (physician visits, hospital care, and prescribed medications) during the study period were obtained for each patient included in the study. Patients were stratified into those who used antiplatelet therapy alone or in combination with a PPI.

Outcome Measures

Follow-up began at the cohort entry date and continued until the first occurrence of recurrent major GI complications or the end of the study period in the case of those with no recurrence of major GI complications. The outcome of interest was the first recurrence of hospitalization for major GI complications with peptic ulcer (*ICD-9-CM* codes 531–533) or major GI bleeding or perforation detected on surgery occurring after the initiation of antiplatelet therapy.

Exposure to antiplatelet agents was quantified in terms of the defined daily dose (DDD). Based on the World Health Organization definition,[14] a *DDD* is the mean daily maintenance dose of a drug used for its main indication. The DDD does not necessarily reflect the recommended or prescribed daily dose.

The estimated direct cost of drug treatment was based on drug costs listed in the Bureau of NHI pharmaceutical reimbursement schedule for health care providers. Costs were calculated in New Taiwanese dollars (NT$) (1 US$ = 33 NT$).

Statistical Analysis

A Cox proportional hazards model was used to evaluate the potential associations of aspirin and clopidogrel with the risk of recurrent hospitalization for major GI complications. For patients with no recurrence of major GI complications, survival time was marked by the end of the study period. For those who had died during the study period, survival time was the day of death.

All survival analyses were adjusted for potential confounders, including the number of outpatient visits and hospitalizations for peptic ulcer in the year before study entry and ulcer-related risk factors (ie, diabetes, ischemic heart disease, an alcohol-related diagnosis, a tobacco-related diagnosis, cirrhosis of the liver, and renal failure) during follow-up. Further adjustments were made for concomitant ulcer-related drugs, including antiulcer drugs (histamine-2 antagonists [H_2As]), NSAIDs, oral anticoagulants, *Helicobacter pylori* therapy, systemic corticosteroids, and selective serotonin reuptake inhibitors, during the follow-up period. A prescription profile of the cumulative dosage (DDDs) of antiplatelet agents, PPIs, H_2As, and NSAIDs during the follow-up period was created to better adjust for the association between exposure to these drugs and the risk of recurrent major GI complications. The assumption of the Cox proportional hazards model was checked and found reasonable (all P values were >0.05). Residual analysis indicated that the residuals were distributed between –3 and 3 in no particular pattern, indicating that the model was a reasonable fit. The Cox proportional hazards analysis was performed using *coxph* in S-plus version 7.0.3 (SolutionMetrics Pty Ltd., Sydney, Australia).

The propensity score method was applied to balance the distribution of confounders between patients who received aspirin and clopidogrel. The propensity score indicated the probability that an individual would receive a specific regimen (aspirin or clopidogrel) and that this probability could be estimated by a logistic regression given the observed covariates. Variables included in the propensity score model were demographic characteristics (sex and age), previous hospitalization for cardiovascular events (myocardial infarction, stroke, percutaneous transluminal coronary angioplasty [PTCA], and coronary artery bypass grafting), and previous hospitalization for major GI complications.

RESULTS

A total of 14,627 patients were identified who had been hospitalized for major GI complications before initiating regular use of antiplatelet drugs (12,001 aspirin, 2626 clopidogrel) for the secondary prevention of coronary heart disease, peripheral vascular disease, ischemic stroke, or transient ischemic attack (**Table I**). The mean ages of aspirin and clopidogrel users were 70.97 and 71.65 years, respectively. Numerically more women than men in both groups were receiving concomitant PPIs. In general, the mean time between the previous hospitalization for major GI complications and the initiation of antiplatelet therapy was longer in aspirin users than in clopidogrel users (569.61 vs 447.72 days). Smaller proportions of aspirin users had a history of myocardial infarction (12.31% vs 19.31%), stroke (28.69% vs 35.30%), and PTCA (2.32% vs 13.59%). During follow-up, the aspirin group used fewer H_2As (56.38 vs 81.63 DDDs),

Table I. Patients' baseline characteristics, medical history, and use of drug therapy during follow-up.

Characteristic	Aspirin			Clopidogrel		
	Total (N = 12,001)	Without PPI (n = 11,463)	With PPI (n = 538)	Total (N = 2626)	Without PPI (n = 2036)	With PPI (n = 590)
Sex, no. (%)						
Male	7212 (60.09)	6901 (60.20)	311 (57.81)	1566 (59.63)	1227 (60.27)	339 (57.46)
Female	4789 (39.91)	4562 (39.80)	227 (42.19)	1060 (40.37)	809 (39.73)	251 (42.54)
Age, mean (SD), y	70.97 (11.44)	70.98 (11.45)	70.79 (11.20)	71.65 (10.72)	71.50 (10.63)	72.17 (11.00)
Age group, no. (%)						
<64 y	3062 (25.51)	2911 (25.39)	151 (28.07)	612 (23.31)	473 (23.23)	139 (23.56)
65–74 y	3941 (32.84)	3771 (32.90)	170 (31.60)	928 (35.34)	729 (35.81)	199 (33.73)
75–84 y	4076 (33.96)	3902 (34.04)	174 (32.34)	855 (32.56)	664 (32.61)	191 (32.37)
≥85 y	922 (7.68)	879 (7.67)	43 (7.99)	231 (8.80)	170 (8.35)	61 (10.34)
GI history in year before cohort entry						
No. of GI-related outpatient visits, mean (SD)	4.25 (6.33)	4.22 (6.32)	4.84 (6.34)	4.94 (6.34)	5.16 (6.34)	4.17 (5.33)
No. of GI-related hospitalizations, mean (SD)	0.50 (0.62)	0.49 (0.61)	0.87 (0.68)	0.63 (0.63)	0.63 (0.63)	0.91 (0.57)
Time from most recent GI hospitalization to initiation of antiplatelet therapy, mean (SD), d	569.61 (98.32)	583.66 (97.81)	270.43 (406.99)	447.72 (464.38)	512.83 (470.92)	223.05 (360.09)
Patients with GI bleeding/perforation identified on surgery at most recent GI hospitalization, no. (%)	9546 (79.54)	9083 (79.24)	463 (86.06)	1953 (74.37)	1466 (72.00)	487 (82.54)
Medical history, no. (%)						
Diabetes	4954 (41.28)	4703 (41.03)	251 (46.65)	1099 (41.85)	845 (41.50	254 (43.05)
Stroke	3443 (28.69)	3322 (28.98)	121 (22.49)	927 (35.30)	738 (36.25)	189 (32.03)
Myocardial infarction	1477 (12.31)	1403 (12.24)	74 (13.75)	507 (19.31)	362 (17.78)	145 (24.58)
PTCA	278 (2.32)	266 (2.32)	12 (2.23)	357 (13.59)	266 (13.06)	91 (15.42)
CABG	85 (0.71)	80 (0.70)	5 (0.93)	34 (1.29)	25 (1.23)	9 (1.53)

(continued)

Table I (continued).

Characteristic	Aspirin			Clopidogrel		
	Total (N = 12,001)	Without PPI (n = 11,463)	With PPI (n = 538)	Total (N = 2626)	Without PPI (n = 2036)	With PPI (n = 590)
Ulcer-related risk factors during follow-up, no. (%)						
Ischemic heart disease	7659 (63.82)	7292 (63.61)	367 (68.22)	1545 (58.83)	1192 (58.55)	353 (59.83)
Alcohol-related diagnosis	52 (0.43)	51 (0.44)	1 (0.19)	4 (0.15)	4 (0.20)	0
Tobacco-related diagnosis	113 (0.94)	107 (0.93)	6 (1.12)	9 (0.34)	9 (0.44)	0
Cirrhosis of liver	2115 (17.62)	2002 (17.46)	113 (21.00)	321 (12.22)	252 (12.38)	69 (11.69)
Renal failure	628 (5.23)	592 (5.16)	36 (6.69)	174 (6.63)	134 (6.58)	40 (6.78)
Medication use during follow-up, mean (SD), DDD						
Aspirin or clopidogrel	234.35 (327.61)	230.33 (322.58)	320.00 (411.89)	223.71 (274.76)	223.16 (274.16)	225.59 (277.06)
PPIs	59.71 (87.21)	–	59.71 (87.21)	83.14 (90.27)	–	83.14 (90.27)
H_2As	56.38 (91.62)	54.15 (89.93)	72.23 (101.83)	81.63 (120.68)	75.78 (89.18)	96.33 (176.52)
NSAIDs	46.55 (95.26)	46.10 (95.06)	54.68 (98.70)	62.70 (119.58)	73.11 (36.28)	34.38 (41.69)
Oral anticoagulants	43.03 (80.03)	43.89 (81.74)	24.92 (17.58)	54.04 (106.20)	54.91 (109.37)	50.04 (95.03)
Medication use during follow-up, no. (%)						
Helicobacter pylori therapy	313 (2.61)	277 (2.42)	36 (6.69)	76 (2.89)	56 (2.75)	20 (3.39)
Systemic corticosteroids	937 (7.81)	868 (7.57)	69 (12.83)	156 (5.94)	101 (4.96)	55 (9.32)
SSRIs	220 (1.83)	203 (1.77)	17 (3.16)	75 (2.86)	54 (2.65)	21 (3.56)

Aspirin = acetylsalicylic acid; PPI = proton pump inhibitor; GI = gastrointestinal; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting; DDD = defined daily dose; H_2As = histamine-2 antagonists; SSRIs = selective serotonin reuptake inhibitors.

NSAIDs (46.55 vs 62.70 DDDs), and oral anticoagulants (43.03 vs 54.04 DDDs) than the clopidogrel group.

Five hundred thirty-eight aspirin users (4.48%) and 590 clopidogrel users (22.47%) were taking concomitant PPIs. During the study period, aspirin users were receiving a numerically lower cumulative dosage of PPIs compared with clopidogrel users (59.71 vs 83.14 DDDs) (**Table I**). Numerically greater proportions of those using aspirin or clopidogrel with a PPI had undergone surgery for GI bleeding or perforated duodenal or peptic ulcer compared with those using either agent alone (aspirin: 86.06% with and 79.24% without PPI; clopidogrel: 82.54% with and 72.00% without PPI). Furthermore, the mean time from the previous hospitalization for major GI complications to cohort entry was shorter among PPI users (aspirin: 270.43 days with and 583.66 days without PPI; clopidogrel: 223.05 days with and 512.83 days without PPI). PPI users were also taking more H_2As than were non-PPI users (aspirin: 72.23 DDDs with and 54.15 DDDs without PPI; clopidogrel: 96.33 DDDs with and 75.78 DDDs without PPI).

The crude incidence of recurrent hospitalization for major GI complications was numerically lower for aspirin users than for clopidogrel users (0.124 vs 0.134 per patient-year, respectively), regardless of PPI use (**Table II**). The overall cost of aspirin therapy was numerically lower than that of clopidogrel therapy, regardless of whether patients were or were not taking a PPI. The mean (SD) annual per-patient costs of aspirin and clopidogrel without a PPI were NT$328.48 (536.39) and NT$12,500.08 (15,134.46), respectively. The corresponding mean annual per-patient costs with a PPI were NT$3712.39 (14,608.05) and NT$18,870.95 (33,552.50). This represents a mean annual medication cost ratio of 5.08.

Table III shows the results of the survival analysis. Before adjustment, patients taking clopidogrel had a nonsignificantly lower risk of hospitalization for recurrent major GI complications compared with those taking aspirin (hazard ratio [HR] = 0.99; 95% CI, 0.91–1.09). After adjustment, the risk of hospitalization for recurrent major GI complications became significantly lower in clopidogrel users compared with aspirin users (HR = 0.83; 95% CI, 0.74–0.92). After application of the propensity score to adjust for potential self-selection, patients taking clopidogrel had a significantly lower risk of recurrent hospitalization for major GI complications compared with those taking aspirin (HR = 0.85; 95% CI, 0.76–0.95).

Before adjustment, patients taking aspirin and a PPI had a nonsignificantly lower risk of recurrent hospitalization for major GI complications compared with those using aspirin without a PPI (HR = 0.88; 95% CI, 0.74–1.05). Their risk became significantly lower, however, after adjustment for other covariates (HR = 0.80; 95% CI, 0.67–0.95) and when the propensity score was applied (HR = 0.76; 95% CI, 0.64–0.91). The difference between patients taking clopidogrel with and without a PPI was nonsignificant (HR = 1.15; 95% CI, 0.95–1.40) and continued to be nonsignificant after adjustment by other covariates (HR = 1.10; 95% CI, 0.90–1.34) and after adjustment and application of the propensity score (HR = 1.08; 95% CI, 0.89–1.33).

An adjusted survival curve for the risk of recurrent hospitalization for major GI complications in patients using clopidogrel or aspirin with/without PPI is shown in the **figure**. The risk of hospitalization increased numerically faster in users of clopidogrel with/without a PPI compared with users of aspirin with/without PPI.

DISCUSSION

This study of Taiwanese NHI claims data found that after adjustment for propensity score, patients with a history of major GI complications who used clopidogrel were less likely than those using aspirin to be hospitalized for recurrent major GI complications, regardless of concomitant PPI use. Concomitant use of PPIs was associated with a significant reduction in risk among aspirin users but not among clopidogrel users. This finding supports the recommendation in the ACC/AHA guideline on the management of non–ST-segment myocardial infarction[10] that aspirin users with a history of GI complications should receive concomitant PPIs to minimize the risk of recurrent bleeding.

The results of the present study are consistent with those of 2 other studies, in which clopidogrel was no more effective or better tolerated in terms of GI adverse events than aspirin with a PPI. In a randomized, double-blind, controlled trial in 320 patients with previous GI bleeding, Chan et al[15] reported that the cumulative incidence rate of recurrent hospitalization for peptic ulcer was higher in users of clopidogrel alone compared with users of aspirin ≤325 mg along with the PPI esomeprazole (8.6% vs 0.7%, respec-

Table II. Incidence and cost of recurrent major gastrointestinal (GI) complications (peptic ulcer, bleeding, and perforation) among users of antiplatelet therapy with a history of GI complications.

Variable	Aspirin			Clopidogrel		
	Total (N = 12,001)	Without PPI (n = 11,463)	With PPI (n = 538)	Total (N = 2626)	Without PPI (n = 2036)	With PPI (n = 590)
Duration of follow-up						
No. of days, mean (SD)	720.5 (769.0)	713.07 (565.00)	879.13 (609.62)	602.5 (483.8)	611.09 (485.51)	572.81 (477.26)
No. of patient-days, mean	8,646,894	8,173,920	472,974	1,582,137	1,244,177	337,960
Recurrent major GI complications						
No. of events	2931	2797	134	579	438	141
Incidence, per patient-year	0.124	0.125	0.103	0.134	0.128	0.152
Medication cost for antiplatelet therapy, mean (SD), NT$						
Aspirin/clopidogrel						
Per patient	419.18 (602.03)	411.90 (593.09)	574.47 (752.27)	12,694.58 (15,639.68)	12,661.98 (15,605.68)	12,807.08 (15,769.24)
Per patient-year	328.60 (537.53)	328.48 (536.39)	331.10 (561.78)	12,556.95 (15,498.54)	12,500.08 (15,134.46)	12,753.19 (16,706.18)
PPI						
Per patient	2382.68 (3061.97)	–	2382.68 (3061.97)	2937.56 (2932.67)	–	2937.56 (2932.67)
Per patient-year	3381.29 (14,135.20)	–	3381.29 (14,135.20)	6117.75 (19,126.20)	–	6117.75 (19,126.20)
PPI and aspirin/clopidogrel						
Per patient	526.00 (1055.74)	411.90 (593.09)	2957.15 (3346.57)	13,354.58 (15,957.02)	12,661.98 (15,605.68)	15,744.64 (16,911.30)
Per patient-year	480.18 (3211.64)	328.48 (536.39)	3712.39 (14,608.05)	13,931.46 (20,910.38)	12,500.08 (15,134.46)	18,870.95 (33,552.50)

Aspirin = acetylsalicylic acid; PPI = proton pump inhibitor; NT$ = New Taiwanese dollars (1 US$ = 33 NT$).

Table III. Survival analysis of hospitalization for major gastrointestinal (GI) complications (peptic ulcer, bleeding, and perforation) among patients receiving antiplatelet therapy alone or in combination with a proton pump inhibitor (PPI). Data are hazard ratios (95% CIs).

		Adjustment*	
All Patients	No Adjustment	Without Propensity Score	With Propensity Score†
Clopidogrel vs aspirin (1 vs 0)	0.99 (0.91–1.09)	0.83 (0.74–0.92)	0.85 (0.76–0.95)
Patients Using Aspirin	Adjustment for Aspirin Use, DDD/d	Adjustment* Without Propensity Score	Adjustment* With Propensity Score†
With vs without PPI (1 vs 0)	0.88 (0.74–1.05)	0.80 (0.67–0.95)	0.76 (0.64–0.91)
Patients Using Clopidogrel	Adjustment for Clopidogrel Use, DDD/d	Adjustment* Without Propensity Score	Adjustment* With Propensity Score†
With vs without PPI (1 vs 0)	1.15 (0.95–1.40)	1.10 (0.90–1.34)	1.08 (0.89–1.33)

Aspirin = acetylsalicylic acid; DDD = defined daily dose.

*Adjusted by sex; age group; GI history; DDDs of clopidogrel, aspirin, PPIs, histamine-2 antagonists, and NSAIDs during follow-up; and ulcer-related risk factors (diabetes, ischemic heart disease, an alcohol-related diagnosis, a tobacco-related diagnosis, cirrhosis of the liver, and renal failure) during follow-up.

†Variables in the propensity score model were demographic characteristics (sex and age), previous hospitalization for cardiovascular events (myocardial infarction, stroke, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting), and previous hospitalization for major GI complications.

tively; $P = 0.001$). In a similarly designed study (N = 170), Lai et al[16] found that the cumulative incidence rate of recurrent hospitalization for peptic ulcer was higher in clopidogrel users than in those who used aspirin plus omeprazole (13.6% vs 0%, respectively; $P = 0.002$). The present observational, retrospective cohort study extended the findings of previous studies by examining a nationwide population and including exposure (DDDs) to aspirin and clopidogrel in the analysis. Each patient was followed for ~2 years. According to the adjusted survival curve, the risk of hospitalization for recurrent GI complications increased numerically faster among clopidogrel users than among those who used aspirin plus a PPI. Given the lower cost of aspirin, the study findings suggest that concomitant use of aspirin and a PPI may be clinically superior to clopidogrel monotherapy for the secondary prevention of coronary heart disease, peripheral vascular disease, ischemic stroke, and transient ischemic attack in patients at high GI risk.

This study fills a need for more comprehensive information on the GI tolerability of clopidogrel, particularly in patients with previous GI complications. Evidence for the GI tolerability of clopidogrel monotherapy is scarce and mostly indirect. Although the CAPRIE[7] trial found that clopidogrel monotherapy was better tolerated than aspirin monotherapy, that study excluded patients with previous GI bleeding. A mechanistic study by Fork et al[17] suggested that clopidogrel may cause less gastric mucosal inflammation than does aspirin. The results of the present study suggest that clopidogrel monotherapy may be associated with less risk of recurrent major GI complications compared with aspirin among patients at high GI risk.

In this study, the adjusted risk of hospitalization for recurrent major GI complications in patients at high GI risk was significantly reduced when a PPI was added to aspirin therapy. This was not the case when a PPI was added to clopidogrel in any of the models. Although the mechanism for ulcer recurrence with clopidogrel is not known, Ng et al[8] suggested that clopidogrel may not induce new ulcers, but may cause rebleeding due to impaired hemostasis in patients with underlying mucosal defects or scarring. Further

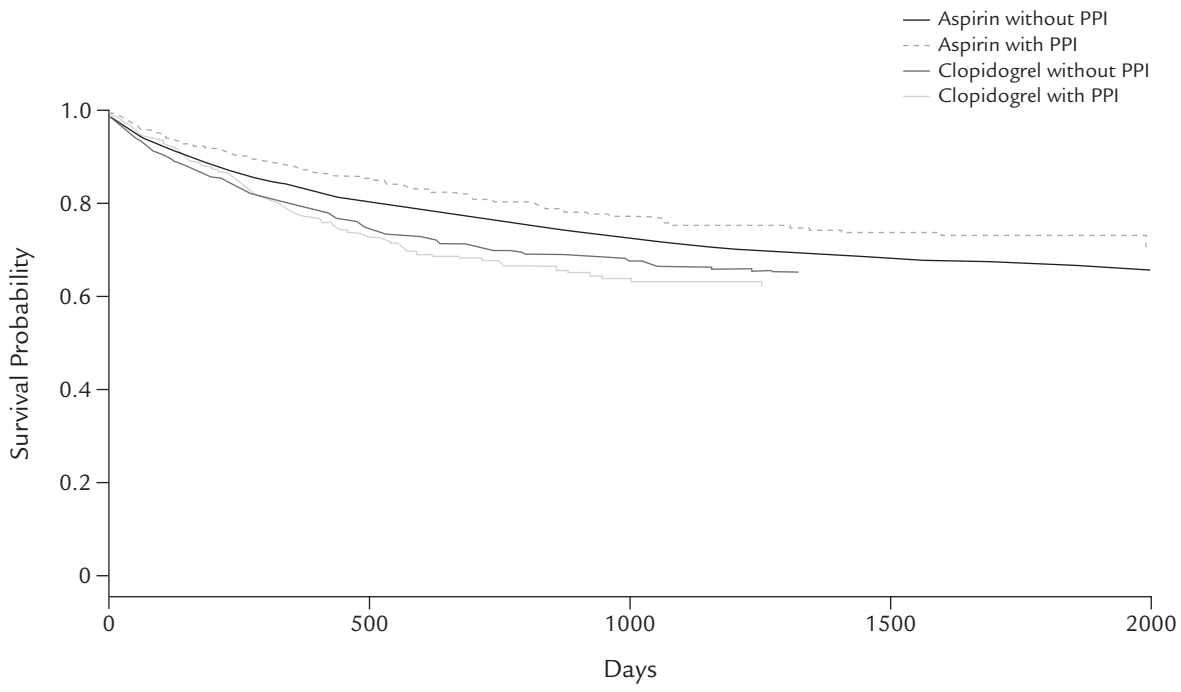

Figure. Adjusted survival curve for hospitalization for recurrent major gastrointestinal (GI) complications (peptic ulcer, bleeding, and perforation) in patients at high GI risk who were using clopidogrel or aspirin (acetylsalicylic acid) with/without a proton pump inhibitor (PPI).

studies of this hypothesis are needed. Because there is ongoing controversy regarding the effect of PPIs on the efficacy of clopidogrel,[18] aspirin plus a PPI may be considered a more cost-effective option for patients at high GI risk who require ongoing antiplatelet therapy for the secondary prevention of cardiovascular events.

This study had some limitations. First, there is the measurement error associated with using the prescribed amount of a medication in the claims data to represent the amount of exposure to that medication, which assumes that patients are completely adherent. Second, despite adjustment for a wide range of potential GI risk factors, it was not possible to include variables not routinely captured in the claims database, including use of over-the-counter NSAIDs.

CONCLUSIONS

In this analysis in patients at high GI risk who were receiving antiplatelet therapy for the secondary prevention of cardiovascular events, aspirin plus a PPI was associated with a reduced risk of recurrent hospitalization for major GI complications. This was not the case for clopidogrel plus a PPI.

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REFERENCES

1. Tran H, Anand SS. Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease. *JAMA*. 2004;292:1867–1874.
2. Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med.* 2005;353:2373–2383.

3. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [published correction appears in *BMJ*. 2002;324:141]. *BMJ*. 2002;324:71–86.
4. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: Meta-analysis. *BMJ*. 2000;321:1183–1187.
5. Laine L. Review article: Gastrointestinal bleeding with low-dose aspirin—what's the risk? *Aliment Pharmacol Ther*. 2006;24:897–908.
6. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med*. 2006;119:624–638.
7. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.
8. Ng FH, Wong SY, Chang CM, et al. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. *Aliment Pharmacol Ther*. 2003;18:443–449.
9. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med*. 2002;346:2033–2038.
10. Fraker TD Jr, Fihn SD, Gibbons RJ, et al, for the 2002 Chronic Stable Angina Writing Committee; American College of Cardiology; American Heart Association. 2007 Chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina [published correction appears in *J Am Coll Cardiol*. 2007;50:e1]. *J Am Coll Cardiol*. 2007;50:2264–2274.
11. Harrington RA, Becker RC, Ezekowitz M, et al. Antithrombotic therapy for coronary artery disease: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(Suppl 3):513S–548S.
12. Anderson JL, Adams CD, Antman EM, et al, for the American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction); American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association of Cardiovascular and Pulmonary Rehabilitation; Society for Academic Emergency Medicine. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): Developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine [published correction appears in *Circulation*. 2008;117:e180]. *Circulation*. 2007;116:e148–e304.
13. Ng FH, Wong BC, Wong SY, et al. Clopidogrel plus omeprazole compared with aspirin plus omeprazole for aspirin-induced symptomatic peptic ulcers/erosions with low to moderate bleeding/re-bleeding risk—a single-blind, randomized controlled study. *Aliment Pharmacol Ther*. 2004;19:359–365.
14. WHO Collaborating Centre for Drug Statistics Methodology. The ATC and DDD system. http://www.whocc.no/atcddd/. Accessed September 29, 2008.
15. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med*. 2005;352:238–244.
16. Lai KC, Chu KM, Hui WM, et al. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. *Clin Gastroenterol Hepatol*. 2006;4:860–865.
17. Fork FT, Lafolie P, Tóth E, Lindgärde F. Gastroduodenal tolerance of 75 mg clopidogrel versus 325 mg aspirin in healthy volunteers. A gastroscopic study. *Scand J Gastroenterol*. 2000;35:464–469.
18. Gilard M, Arnaud B, Cornily JC, 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;51:256–260.

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