Use of calcium channel blockers and risk of hospitalized gastrointestinal tract bleeding

Rosendaal, F.R.

ORIGINAL INVESTIGATION

Use of Calcium Channel Blockers and Risk of Hospitalized Gastrointestinal Tract Bleeding

Robert C. Kaplan, PhD; Susan R. Heckbert, MD, PhD; Thomas D. Koepsell, MD, MPH; Frits R. Rosendaal, MD, PhD; Bruce M. Psaty, MD, PhD

Background: We conducted a case-control study of the association between calcium channel blocker use and gastrointestinal (GI) tract bleeding in hypertensive members of a health maintenance organization.

Methods: Case patients (n=174) were treated hypertensive health maintenance organization members hospitalized for GI tract bleeding between January 1992 and December 1994. Case patients were identified using computerized diagnosis codes and were confirmed by medical record review. Control subjects (n=771) were treated hypertensive members selected from ongoing studies at the health maintenance organization. Computerized pharmacy data and medical records were used to assess medication use and other risk factors for GI tract bleeding.

Results: Compared with β-blocker users, calcium channel blocker users had an age-, sex- and calendar year–adjusted relative risk (RR) of GI tract bleeding of 2.60 (95% confidence interval [CI], 1.71-3.96). The RR associated with calcium channel blocker use was 2.05 (95% CI, 1.33-3.17) after further adjustment for number of recent visits, diastolic blood pressure, chronic congestive heart failure, and duration of hypertension. No significant dose-response relationship was observed. Compared with β-blocker users, angiotensin-converting enzyme inhibitor users had an RR of 1.22 (95% CI, 0.75-1.97). Calcium channel blocker use tended to be more strongly associated with risk of lower GI tract bleeding (RR, 2.56; 95% CI, 1.08-6.05) than with risk of upper GI tract bleeding (RR, 1.54; 95% CI, 0.91-2.59) or peptic ulcer–related bleeding (RR, 1.17; 95% CI, 0.62-2.21), although these results were compatible with chance.

Conclusions: Calcium channel blocker use might be associated with an elevated risk of GI tract bleeding. These findings require confirmation in randomized studies.

Arch Intern Med. 2000;160:1849-1855

From the Cardiovascular Health Research Unit (Drs Kaplan, Heckbert, Koepsell, Rosendaal, and Psaty) and the Departments of Epidemiology (Drs Kaplan, Heckbert, Koepsell, Rosendaal, and Psaty), Medicine (Drs Koepsell and Psaty), and Health Services (Drs Koepsell and Psaty), University of Washington, Seattle; and the Department of Clinical Epidemiology, University Hospital Leiden, Leiden, the Netherlands (Dr Rosendaal). Dr Kaplan is now with the Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY.

ALTHOUGH the results of some observational studies[1,2] suggest that use of calcium channel blockers might be associated with an approximately 2-fold increased risk of gastrointestinal (GI) tract bleeding, other studies[3-5] have not confirmed this finding. Each of the 3 major calcium channel blocker subclasses has been shown to inhibit platelet function in experimental studies.[6-10] Calcium channel blocker therapy also has a vasodilatory effect that might interfere with the normal vasoconstrictive response to bleeding.[11] It is therefore biologically plausible that calcium channel blocker therapy might increase the risk of GI tract bleeding, although whether it does so in practice remains an unanswered question.

Various methodological features may explain why the epidemiological studies conducted to date have not been consistent. Some studies[3] have examined GI tract bleeding caused by a particular underlying pathological condition, such as peptic ulcer disease, whereas others[1] have included bleeding from a variety of GI tract lesions. Some studies[1,4] have relied solely on computerized diagnosis codes to identify individuals with GI tract bleeding, although unvalidated diagnosis codes for GI tract bleeding may have poor predictive value.[12] Information on the presence of hypertension and other cardiovascular diseases has often been unavailable, and consequently it was not possible in some previous studies[3,5] to limit the study population to patients who had an indication for calcium channel blocker therapy. In contrast, other studies[1] have included only individuals being treated for hypertension with calcium channel blockers or other medications.

We conducted a case-control study of the association between the use of calcium channel blockers and the risk of hospitalized upper or lower GI tract bleed-

SUBJECTS AND METHODS

STUDY POPULATION AND SETTING

The setting for this study was Group Health Cooperative (GHC) of Puget Sound, a health maintenance organization based in Seattle, Wash, with more than 500 000 members. This was an ancillary study to an ongoing case-control study of cardiovascular disease conducted in pharmacologically treated hypertensive patients at GHC.[13] For the analyses presented herein, we drew control subjects from among treated hypertensive patients who were identified for the main study and we identified case patients with GI tract bleeding who were also treated for hypertension. The time frame for this study was January 1992 through December 1994, which predates the published studies[1] that raised concern about the safety of calcium channel blocker use.

SUBJECTS

Case patients were treated hypertensive GHC patients aged 30 to 79 years who were hospitalized for upper or lower GI tract bleeding between January 1992 and December 1994. We identified potential case patients from computerized GHC hospital discharge records and Washington state death files using the following *International Classification of Diseases, Ninth Revision*,[14] diagnosis codes: gastric, duodenal, peptic, or gastrojejunal ulcer with bleeding (531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, and 534.6); bleeding of rectum or anus (569.0); hematemesis (578.0); melena (578.1); or GI tract bleeding not otherwise specified (578.9). We specified in advance that the antihypertensive medications of interest for this study would be angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and calcium channel blockers, and we included as potential case patients only those who had filled a prescription for one of these medications during the 4 months preceding hospitalization for GI tract bleeding, according to GHC's computerized pharmacy database.

We reviewed discharge summaries and other information in the outpatient medical records maintained by GHC to confirm that all case patients had evidence of GI tract bleeding noted at or within a few days of hospital admission. We did not include bleeding that was a complication of surgery or a procedure, and we included only the first episode of bleeding if more than one occurred during the study. Using information in the medical records, we confirmed that case patients were being treated with medications for hypertension, that they were aged 30 to 79 years, and that they had made at least 4 previous visits to a GHC provider.

Control subjects were treated hypertensive patients aged 30 to 79 years who were enrolled at GHC between January 1992 and December 1994. We required that the controls had filled a recent prescription for an ACE inhibitor, β-blocker, or calcium channel blocker and that according to the medical records they were being treated for hypertension, were within the proper age range, and had made 4 previous visits to a GHC provider. In the main study that served as the source of our control population, controls were a stratified random sample of GHC patients with hypertension who were frequency matched by sex, age, and year to incident cases of myocardial infarction and stroke.[13] Control subjects with previous myocardial infarction or stroke were included in this analysis.

INDEX DATES

Each subject was assigned an index date. The index date for case patients was the date of hospital admission for GI tract bleeding and for control subjects was a randomly selected date during the year for which they were selected as a control.

COLLECTION OF DATA ON MEDICATION USE AND OTHER RISK FACTORS

The computerized GHC pharmacy database served as the primary source of information for assessing the use of antihypertensive and other prescription medications. The pharmacy database contains a record of every drug prescription

ing in health maintenance organization patients being treated for hypertension.

RESULTS

We reviewed 381 potential case patients with GI tract bleeding and determined that 174 met eligibility criteria and were current users of one of the antihypertensive medications of interest on the index date. We identified 771 control subjects who were similarly eligible for this study. Cases were slightly older and had a lower proportion of men than controls, and these differences in age and sex reflect the use of controls from a parent study (**Table 1**). Compared with controls, case patients had more recent visits; lower mean diastolic blood pressure and body mass index; and more preexisting diseases, including diabetes mellitus, chronic congestive heart failure, previous myocardial infarction, pulmonary disease, chronic liver disease, and alcoholism. Cases were more likely than controls to be current smokers or to be physically inactive. Use of salicylate and ibuprofen did not differ between cases and controls, and use of other NSAIDs, oral corticosteroids, and anticoagulants and recent thrombolytic therapy were more common in cases than controls.

Among control subjects, current users of calcium channel blockers were older than users of β-blockers or ACE inhibitors (**Table 2**). Use of aspirin and other salicylates was more common among calcium channel blocker users (46.0%) than among β-blocker users (43.3%) or ACE inhibitor users (33.9%). Other characteristics of the drug user groups in Table 2 reflect relative contraindications or indications other than hypertension for use of β-blockers, ACE inhibitors, and calcium channel blockers, including angina, diabetes mellitus, claudication, congestive heart failure, chronic obstructive pulmonary disease, and asthma.

Compared with current users of β-blockers, current users of calcium channel blockers had an age-, sex- and year-adjusted RR of GI tract bleeding of 2.60 (95% confidence interval [CI], 1.71-3.96) (**Figure 1**). After fur-

dispensed at a GHC pharmacy and includes information on the type of drug, pill strength, quantity, dosing instructions, and dispensing date. According to a telephone survey conducted as part of a previous study, 94.5% of GHC enrollees filled "all or almost all" prescriptions at a GHC pharmacy.[15] For the antihypertensive medications of interest, we defined current users as those who filled a prescription that would be expected to last until the index date, assuming that patients were 80% compliant with the dosing instructions. We also identified subjects who had started using calcium channel blockers or other agents within 6 months before the index date.

We defined subjects as users of oral corticosteroids or oral anticoagulant agents if they filled a prescription for these medications within 45 days before the index date. We used the medical records to determine whether subjects had received thrombolytic therapy within the 2 weeks before the index date or whether heparin was administered during the index hospitalization. We defined subjects as users of salicylates or other nonsteroidal anti-inflammatory drugs (NSAIDs) if the medical records noted that they were using these medications regularly at the index date or if they filled 2 or more prescriptions for these medications during the year before the index date.

Other risk factors for GI tract bleeding were recorded by trained abstractors using the medical records from the period before, but not including, the index date. Records abstractors were not masked to case-control status or medication use, although they were unaware of the study hypothesis.

STATISTICAL ANALYSES

We estimated the relative risk (RR) of GI tract bleeding in current users of calcium channel blockers and in current users of ACE inhibitors compared with current users of β-blockers. Subjects using more than 1 of these antihypertensive medications were excluded from this study. We also estimated the RRs associated with use of specific calcium channel blocker agents with doses that were less than, equal to, or greater than the modal daily doses used by the study population (240 mg for verapamil, 180 mg for diltiazem, 30 mg for nifedipine, 60 mg for nicardipine, and 5 mg for amlodipine) and with recently starting use of calcium channel blockers.

We conducted separate analyses for upper and lower GI tract bleeding, peptic ulcer–associated bleeding, and bleeding that was "life threatening" (complicated by circulatory shock, surgical intervention, transfusion of 3 U or more of blood, death, or "severe blood loss" as noted in the medical record). We did not have a particular a priori hypothesis regarding which etiologic subtypes of bleeding would be most strongly associated with calcium channel blocker use. We also estimated RRs in subgroups defined by age (above or below the median of 68 years), sex, diabetes status, smoking status, and use of other medications associated with GI tract bleeding (NSAIDs, oral corticosteroids, or anticoagulants).

We estimated RRs by odds ratios derived from multivariate logistic regression models computed using Stata 5.0.[16] We included age, sex, and year of index date as adjustment variables, in addition to other potential risk factors for hospitalized GI tract bleeding that modified the RRs of interest when added to the multivariate models. We examined the following risk factors as potential confounders: use of oral corticosteroids, NSAIDs, and anticoagulants; race (white vs nonwhite); number of visits in the year before the index date; duration of enrollment at GHC; recent systolic and diastolic blood pressures (mean of up to 3 readings); current angina; duration of treated hypertension, pharmacologically treated diabetes mellitus; claudication; chronic congestive heart failure; previous myocardial infarction; chronic obstructive pulmonary disease; asthma; current smoking; alcohol consumption (none, occasional, or heavy); current or history of alcoholism; chronic liver disease; physical activity (active vs not active); current marital status; weight; height; and body mass index. Risk factor measurements were missing for fewer than 5% of subjects for all variables except alcohol consumption (12% missing). We used multiple imputation for handling missing data and a "hot deck" approach for selecting imputed values.[17] Similar results were obtained when we repeated the analyses after excluding subjects with missing values of covariates.

ther adjustment for number of visits in the previous year, diastolic blood pressure, chronic congestive heart failure, and duration of treated hypertension, the RR associated with calcium channel blocker use was 2.05 (95% CI, 1.33-3.17). Compared with current users of β-blockers, current users of ACE inhibitors did not have a significantly increased risk of GI tract bleeding after adjustment for risk factors (RR, 1.22; 95% CI, 0.75-1.97). Further adjustment for other risk factors had little effect on the RRs after we adjusted for number of visits, diastolic blood pressure, chronic congestive heart failure, and duration of hypertension (**Table 3**).

The adjusted RR of GI tract bleeding was 1.48 for subjects using calcium channel blockers at doses lower than the modal doses, 2.29 for those using the modal doses of calcium channel blockers, and 2.16 for those using calcium channel blockers at doses greater than the modal doses compared with β-blocker users ($P=.22$ for trend) (**Figure 2**). The RR was similar in subjects using verapamil (RR, 2.06 compared with β-blocker users), diltiazem (RR, 1.73), and nifedipine (RR, 2.38) (Figure 2). Subjects using immediate-release calcium channel blockers had a similar RR as those using sustained-release calcium channel blockers (RR, 2.01 for immediate-release agents; and RR, 2.47 for sustained-release agents) (Figure 2).

Twenty-five subjects (12 cases and 13 controls) had started using calcium channel blockers within 6 months before the index date and, compared with β-blocker users, these recent starters of calcium channel blocker therapy had an adjusted RR of 5.12 (95% CI, 2.06-12.70) (data not shown). After removing recent starters of calcium channel blocker therapy from the analysis, calcium channel blocker users remained at elevated risk of GI tract bleeding compared with β-blocker users (RR, 1.81; 95% CI, 1.17-6.87). We examined whether there was an association between recently starting use of other antihypertensive agents and higher risk of GI tract bleeding. Thirty subjects (6 cases and 24 controls) had started using ACE inhibitors within 6 months before the index date, and these subjects had a similar risk of GI tract bleed-

Table 1. Characteristics of Case Patients With Hospitalized Gastrointestinal Tract Bleeding and Control Subjects Among Hypertensive Patients Enrolled at GHC, January 1992 to December 1994*

Characteristic	Cases (n = 174)	Controls (n = 771)
Age, mean (SD), y	66.6 (10.9)	65.3 (10.2)
Male sex, %†	50.6	68.5
White race, %	86.1	91.0
Currently married, %†	69.0	80.3
Visits in previous year, mean (SD), No.†	8.8 (7.2)	6.2 (5.2)
Duration of enrollment at GHC, mean (SD), y	17.4 (11.5)	17.8 (11.1)
Duration of treated hypertension, mean (SD), y	10.7 (8.1)	11.3 (8.6)
Systolic blood pressure, mean (SD), mm Hg	145.5 (17.3)	144.7 (15.6)
Diastolic blood pressure, mean (SD), mm Hg†	81.7 (10.0)	84.2 (7.9)
Body mass index, mean (SD), kg/m²†	27.4 (5.9)	28.5 (5.4)
Current angina, %	17.8	13.5
Diabetes mellitus, %†	19.5	12.1
Claudication, %	8.1	5.2
Chronic congestive heart failure, %†	16.7	5.5
Previous myocardial infarction, %†	13.2	8.2
COPD or asthma, %†	15.5	9.5
Chronic liver disease, %†	6.9	1.6
Cancer within the previous 2 y, %	8.6	6.5
Current or history of alcoholism, %†	20.7	9.9
Current alcohol consumption, %		
None	49.0	43.7
Occasional	29.4	33.7
Heavy/alcoholic	21.6	22.6
Current smoker, %†	22.0	12.8
Physically active, %†	64.9	79.3
Salicylate use, %	40.2	41.4
Ibuprofen use, %	24.1	19.7
Other NSAID use, %†	22.4	13.6
Oral corticosteroid use, %†	8.6	1.6
Recent thrombolytic therapy or anticoagulant drug use, %†	6.9	3.1

*GHC indicates Group Health Cooperative; COPD, chronic obstructive pulmonary disease; and NSAID, nonsteroidal anti-inflammatory drug.
†$P<.05$ by t test for continuous variables and χ^2 test for categorical variables.

ing as other users of ACE inhibitors (adjusted RR, 0.90; 95% CI, 0.33-2.47). Eighteen subjects (4 cases and 14 controls) had recently started using β-blockers, and these subjects had an adjusted RR of 1.75 (95% CI, 0.53-5.80) compared with other users of β-blockers.

We repeated the analysis for subtypes of GI tract bleeding defined by anatomical location, cause, and severity (**Figure 3**). Use of calcium channel blockers tended to be more strongly associated with risk of lower GI tract bleeding (RR, 2.56; 95% CI, 1.08-6.05 [35 case patients]) than the risk of upper GI tract bleeding (RR, 1.54; 95% CI, 0.91-2.59 [98 case patients]). Calcium channel blocker users had an RR of 1.17 (95% CI, 0.62-2.21) for bleeding caused by peptic ulcer (58 case patients, all but 1 confirmed by endoscopy). The RR associated with calcium channel blocker use was 2.28 for life-threatening bleeding (52 case patients) and 1.98 for non–life-threatening bleeding (122 case patients). Although these analyses suggested differences in the RRs for subtypes of bleeding, the differences were compatible with chance.

Relative risks were of similar magnitude and did not differ significantly among subgroups defined by age, sex, diabetes, smoking, or use of other medications known to be associated with GI tract bleeding (NSAIDs, oral corticosteroids, or anticoagulants). After we excluded 93 cases and 282 controls with a relative contraindication or an indication other than hypertension for use of one of the antihypertensive medications of interest, the adjusted RRs were 2.58 (95% CI, 1.50-4.45) for calcium channel blocker use and 1.13 (95% CI, 0.69-1.84) for ACE inhibitor use compared with β-blocker use. The RRs were similar after we excluded 65 subjects with a diagnosis of cancer within the 2 years before the index date (RR, 2.09; 95% CI, 1.32-3.31 for calcium channel blocker use and RR, 1.28; 95% CI, 0.77-2.12 for ACE inhibitor use) and after we excluded 36 subjects who were users of anticoagulants or who received thrombolytic therapy in the 2 weeks before the reference date (RR, 1.87; 95% CI, 1.20-2.92 for calcium channel blocker use and RR, 1.26; 95% CI, 0.77-2.05 for ACE inhibitor use).

COMMENT

In this observational study, hypertensive patients who were current users of calcium channel blockers had approximately a 2-fold higher risk of hospitalized upper or lower GI tract bleeding than hypertensive patients who used β-blockers. Users of ACE inhibitors did not have a significantly higher risk of GI tract bleeding than patients who used β-blockers. The association between use of calcium channel blockers and higher risk of GI tract bleeding persisted after adjustment for risk factors recorded from medical records and also after adjustment for use of other medications that might cause GI tract bleeding.

Despite our efforts to adjust for known risk factors for GI tract bleeding, residual confounding might have been present. We relied on information from medical records and computerized pharmacy data to measure use of aspirin and other NSAIDs. Because patients can take these medications without the knowledge of their physician and can purchase them without a prescription, it is likely that we did not identify all users. The antihypertensive medications examined in this study might sometimes be used to treat conditions that might be related to GI tract bleeding (eg, calcium channel blockers for esophageal motility disorders[18] and β-blockers for esophageal varices[19]). However, all subjects in this study were being treated for hypertension, and these additional indications would be expected to be relatively uncommon.

The first population-based study[1] to suggest that use of calcium channel blockers might have an adverse effect on the risk of GI tract bleeding was conducted among hypertensive patients in the Established Populations for Epidemiologic Studies of the Elderly cohort. In that study, users of calcium channel blockers had an RR of hospitalized or fatal upper or lower GI tract bleeding of 1.86 (95% CI, 1.22-2.82) compared with users of β-blockers. More recently, 3 well-conducted observational studies did not demonstrate a strong association between calcium channel blocker use and confirmed bleeding caused

Table 2. Characteristics of Control Subjects According to Current Use of Antihypertensive Medications*

Characteristic	β-Blocker Users (n = 291)	ACE Inhibitor Users (n = 230)	Calcium Channel Blocker Users (n = 250)
Age, mean (SD), y†	65.2 (10.7)	63.6 (10.3)	67.1 (9.2)
Male sex, %	64.3	72.6	69.6
White race, %†	93.6	91.9	87.1
Currently married, %	79.1	78.7	83.0
Visits in previous year, mean (SD), No.†	5.7 (5.0)	6.8 (5.1)	6.4 (5.6)
Duration of enrollment at GHC, mean (SD), y†	17.9 (10.5)	16.3 (11.1)	19.0 (11.7)
Duration of treated hypertension, mean (SD), y†	12.0 (7.9)	9.7 (8.0)	12.0 (9.6)
Systolic blood pressure, mean (SD), mm Hg†	142.7 (15.2)	144.1 (15.8)	147.7 (15.4)
Diastolic blood pressure, mean (SD), mm Hg†	84.0 (7.6)	85.2 (8.0)	83.5 (8.2)
Body mass index, mean (SD), kg/m^2	28.1 (5.4)	28.9 (5.5)	28.4 (5.3)
Current angina, %†	11.7	6.5	22.0
Diabetes mellitus, %†	8.3	13.9	14.8
Claudication, %†	2.8	5.7	7.6
Chronic congestive heart failure, %†	1.4	7.4	8.4
Previous myocardial infarction, %	8.3	6.7	9.2
COPD or asthma, %†	5.2	9.6	14.4
Chronic liver disease, %	1.0	1.7	2.0
Cancer within the previous 2 y, %	7.6	5.2	6.4
Current or history of alcoholism, %	8.3	10.4	11.2
Current alcohol consumption, %			
None	42.8	44.9	43.8
Occasional	32.6	34.6	34.1
Heavy/alcoholic	24.7	20.5	22.1
Current smoker, %	11.0	14.5	13.3
Physically active, %	81.4	81.8	74.5
Salicylate use, %†	43.3	33.9	46.0
Ibuprofen use, %	20.3	23.9	15.2
Other NSAID use, %	12.0	13.9	15.2
Oral corticosteroid use, %	1.7	1.3	1.6
Recent thrombolytic therapy or anticoagulant drug use, %	2.8	4.4	2.4

*ACE indicates angiotensin-converting enzyme inhibitor; GHC, Group Health Cooperative; COPD, chronic obstructive pulmonary disease; and NSAID, nonsteroidal anti-inflammatory drug.

†P<.05 for overall difference between drug use groups, by analysis of variance for continuous variables and χ^2 test for categorical variables.

by peptic ulcer and other diseases of the upper GI tract. Smalley and colleagues[3] reported an RR of hospitalized bleeding peptic ulcer of 1.1 (95% CI, 0.7-1.7) for users of calcium channel blockers compared with nonusers. Kelly and colleagues[5] reported an RR of major upper GI tract bleeding of 1.2 (95% CI, 0.9-1.6) for calcium channel blocker use compared with nonuse. In a third study[20] conducted in Italy, current use of calcium channel blockers compared with nonuse was associated with an RR of hospitalized upper GI tract bleeding of 1.4 (95% CI, 1.1-1.8), although the authors interpreted this result with caution because past use and current use of calcium channel blockers were associated with an elevated RR.

These studies reporting negative findings included only upper GI tract bleeding outcomes, whereas our study examined lower and upper GI tract bleeding. This difference is perhaps important. We found that calcium channel blocker use tended to be more strongly associated with risk of lower GI tract bleeding (RR, 2.56; 95% CI, 1.08-6.05) than risk of upper GI tract bleeding (RR, 1.54; 95% CI, 0.91-2.59) or peptic ulcer–related bleeding (RR, 1.17; 95% CI, 0.62-2.21). The differences between these RRs were compatible with chance. However, these analyses suggest that our results might be consistent with those of previous studies that have shown only a weak association between calcium channel blocker use and upper GI tract bleeding. The smaller RR for upper GI tract bleeding might be because upper GI tract bleeding is relatively more common than lower GI tract bleeding among middle-aged persons.[21] Experimental studies[22,23] have shown that calcium channel blockers might affect intes-

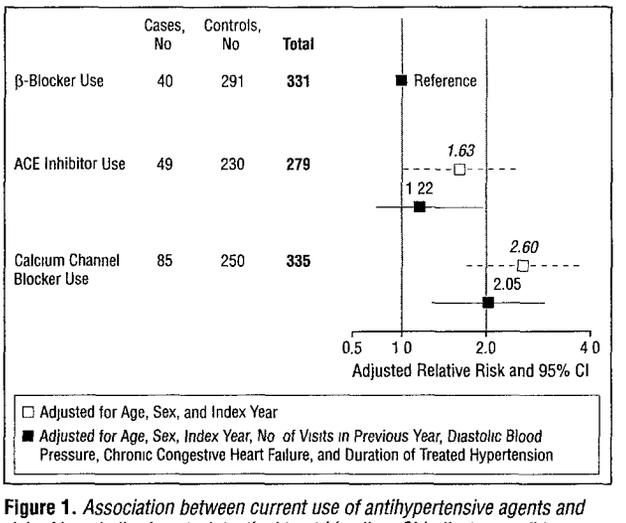

Figure 1. *Association between current use of antihypertensive agents and risk of hospitalized gastrointestinal tract bleeding. CI indicates confidence interval; ACE, angiotensin-converting enzyme.*

Table 3. Association Between Current Use of Antihypertensive Agents and Risk of Hospitalized Gastrointestinal Tract Bleeding After Adjustment for Selected Potential Confounders*

Model No.	Adjustment Variables	Relative Risk (95% CI)		
		β-Blocker Use (Referent)	ACE Inhibitor Use	Calcium Channel Blocker Use
1	Sex, age, and index year	1.00	1.63 (1.03-2.59)	2.60 (1.71-3.96)
2	All of the above, plus visits in the previous year	1.00	1.46 (0.92-2.33)	2.39 (1.56-3.66)
3	All of the above, plus diastolic blood pressure	1.00	1.40 (0.88-2.24)	2.25 (1.47-3.46)
4	All of the above, plus chronic congestive heart failure	1.00	1.28 (0.79-2.06)	2.10 (1.37-3.24)
5†	All of the above, plus duration of treated hypertension	1.00	1.22 (0.75-1.97)	2.05 (1.33-3.17)
6	All of the above, plus salicylate use	1.00	1.20 (0.74-1.94)	2.05 (1.33-3.16)
7	All of the above, plus ibuprofen use	1.00	1.20 (0.74-1.94)	2.06 (1.33-3.18)
8	All of the above, plus other NSAID use	1.00	1.20 (0.74-1.95)	2.04 (1.32-3.16)
9	All of the above, plus recent thrombolytic therapy or anticoagulant drug use	1.00	1.21 (0.75-1.96)	2.03 (1.31-3.14)

*CI indicates confidence interval; ACE, angiotensin-converting enzyme; and NSAID, nonsteroidal anti-inflammatory drug.
†Model 5 corresponds to the multivariate-adjusted model presented in Figure 1.

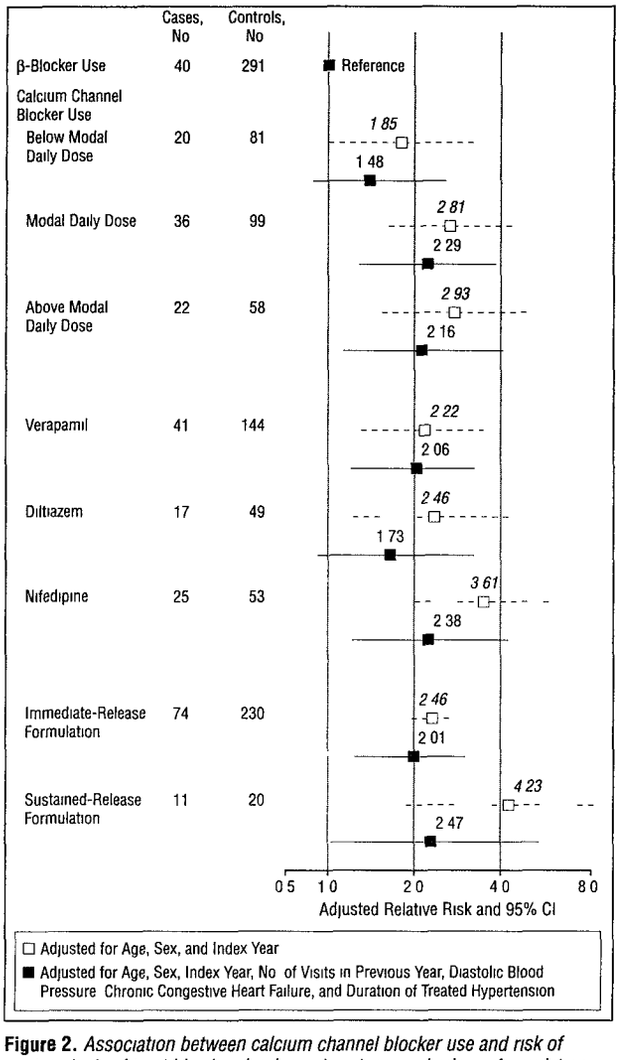

Figure 2. *Association between calcium channel blocker use and risk of gastrointestinal tract bleeding by dose, drug type, and release formulation For dose analyses, 7 cases and 12 controls with unknown dose were excluded For drug type analyses, 2 cases and 4 controls using calcium channel blockers other than verapamil, diltiazem, or nifedipine or more than 1 of these agents were excluded CI indicates confidence interval.*

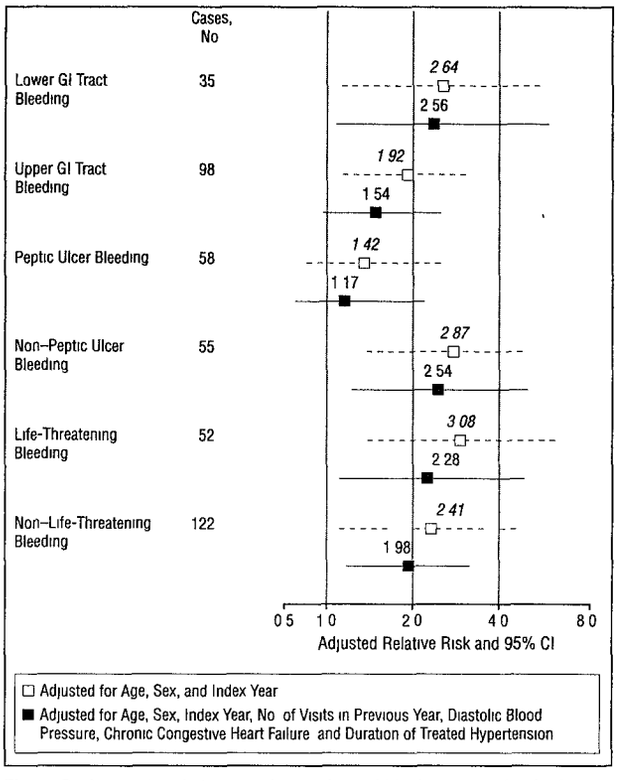

Figure 3. *Association between calcium channel blocker use and risk of gastrointestinal (GI) tract bleeding by characteristics of the bleeding event The location of the bleeding was unknown for 41 cases For non–peptic ulcer bleeding, 61 cases with unknown bleeding location or with upper gastrointestinal tract bleeding with unknown etiology were excluded. The data are for calcium channel blocker use compared with β-adrenergic blocking agent use CI indicates confidence interval*

tinal function, and this suggests that there might be a pathophysiological explanation for the strong association with lower GI tract bleeding.

Like previous investigators,[24,25] we did not find that use of higher daily doses of calcium channel blockers was associated with greater bleeding risk. Given the strong overall relationship between calcium channel blocker use and bleeding, the lack of a dose-response pattern is unexpected. The RR was similar for sustained-release and immediate-release formulations of calcium channel blockers and for each of the major subclasses. Subjects who started using calcium channel blockers within the previous 6 months had a risk of GI tract bleeding that was approximately 5 times higher than that of the comparison

group of β-blocker users Patients who switched antihypertensive medications or who did not regularly fill their prescriptions were likely to be classified as recent starters according to the definition we used and these patients might tend to be in poorer health There was not strong evidence in our data, however, that recent starters of other antihypertensive medications had a markedly elevated risk of GI tract bleeding although the number of subjects available for these analyses was small The finding of a higher RR for recent starters of calcium channel blocker use than among long-term users might reflect a drug effect that becomes attenuated after continuous use

Because of the possibility of bias, the results of observational studies such as this one should be interpreted cautiously Randomized clinical trials are less susceptible to bias, but at this time the available data from clinical studies do not provide an adequate evaluation of the risk of bleeding associated with calcium channel blockers The Syst-Eur trial did not suggest an excess of reported bleeding events among patients treated with nitrendipine compared with placebo (19 vs 20 events $P = 74$) [26] Because of the small number of events, the results of the Syst-Eur trial were compatible at the 95% confidence level, with a 52% lower and a 69% higher rate of bleeding among patients randomized to nitrendipine Furthermore, because Syst-Eur and other clinical studies[27] were mounted before the first reports of a prohemorrhagic effect of calcium channel blocker therapy these studies were not designed to collect information on bleeding in a prospective manner

Results of this observational study suggest an association between calcium channel blocker use and higher risk of GI tract bleeding Studies conducted to date have not been consistent, and this might be because of differences in how cases of bleeding were defined or other methodological differences Ongoing clinical trials[28] provide the opportunity to collect prospectively defined bleeding end points, and when completed, these studies might help clarify the risks and benefits associated with calcium channel blocker therapy for hypertension

Accepted for publication December 8, 1999

This research was supported by grants HL43201 and HL40628 from the National Heart, Lung, and Blood Institute, Bethesda, Md, and grant AG09556 from the National Institute on Aging, Bethesda, Md Dr Kaplan was a Howard Hughes Medical Institute Predoctoral Fellow when this work was conducted Dr Psaty is a Merck/SER Clinical Epidemiology Fellow (sponsored by the Merck Co Foundation, Rahway, NJ, and the Society for Epidemiologic Research, Baltimore, Md)

Reprints Robert C Kaplan, PhD, Department of Epidemiology and Social Medicine, Belfer Building, Room 1308C, Albert Einstein College of Medicine, 1300 Morris Park Ave, Bronx, NY 10461 (e-mail rkaplan@aecom yu edu)

REFERENCES

1 Pahor M Guralnik JM Furberg CD et al Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old *Lancet* 1996 347 1061 1065

2 Pilotto A Leandro G Franceschi M et al Antagonism to calcium antagonists [letter] *Lancet* 1996 347 1761 1762

3 Smalley WE Ray WA Daugherty JR Griffin MR No association between calcium channel blocker use and confirmed bleeding peptic ulcer disease *Am J Epidemiol* 1998 148 350 354

4 Suissa S Bourgault C Barkun A Sheehy O Ernst P Antihypertensive drugs and the risk of gastrointestinal bleeding *Am J Med* 1998 105 230 235

5 Kelly JP Laszlo A Kaufman DW Sundstrom A Shapiro S Major upper gastrointestinal bleeding and the use of calcium channel blockers [letter] *Lancet* 1999 353 559

6 Ring ME Corrigan JJ Jr Fenster PE Antiplatelet effects of oral dilatizem propranolol and their combination *Br J Clin Pharmacol* 1987 24 615 620

7 Wallen NH Held C Rehnqvist N et al Platelet aggregability in vivo is attenuated by verapamil but not by metoprolol in patients with stable angina pectoris *Am J Cardiol* 1995 75 1 6

8 Blache D Ojeda C Comparative inhibitory effects of dihydropyridines on platelet aggregation calcium uptake and cyclic AMP concentration *Pharmacology 1992 45 250 259*

9 Odawara A Katoh M Karasawa T et al Inhibitory effect of clentiazem (TA 3090) on platelet aggregation alone and in combination with aspirin or ticlopidine *Thromb Res* 1994 75 109 119

10 Ondriasova E Ondrias K Stasko A et al Comparison of the potency of five potential beta adrenoreceptor blocking drugs and eight calcium channel blockers to inhibit platelet aggregation and to perturb liposomal membranes prepared from platelet lipids *Physiol Res* 1992 41 267 272

11 Dollery CT Clinical pharmacology of calcium antagonists *Am J Hypertens* 1991 4 88S 95S

12 Raiford DS Perez Gutthann S Garcia Rodriguez LA Positive predictive value of *ICD 9* codes in the identification of cases of complicated peptic ulcer disease in the Saskatchewan hospital automated database *Epidemiology* 1996 7 101 104

13 Psaty BM Heckbert SR Koepsell TD et al The risk of myocardial infarction associated with antihypertensive drug therapies *JAMA* 1995 274 620 625

14 World Health Organization *International Classification of Diseases Ninth Revision (ICD 9)* Geneva Switzerland World Health Organization 1977

15 Psaty BM Heckbert SR Atkins D et al The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women *Arch Intern Med* 1994 154 1333 1339

16 *Stata Statistical Software* [computer program] Release 5 0 College Station Tex Stata Corp 1997

17 Rubin DB Schenker N Multiple imputation in health care databases an overview and some applications *Stat Med* 1991 10 585 598

18 Allescher HD Ravich WJ Medical treatment of esophageal motility disorders *Dysphagia* 1993 8 125 134

19 Poynard T Cales P Pasta L et al Beta adrenergic antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices an analysis of data and prognostic factors in 589 patients from four randomized clinical trials Franco Italian Multicenter Study Group *N Engl J Med* 1991 324 1532 1538

20 Garcia Rodriguez LA Cattaruzzi C Grazia Troncon M Agostinis L Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac other nonsteroidal anti inflammatory drugs calcium antagonists and other antihypertensive drugs *Arch Intern Med* 1998 158 33 39

21 Rothman KJ Poole C A strengthening programme for weak associations *Int J Epidemiol* 1988 17(suppl) 955 959

22 Krevsky B Maurer AH Niewiarowski T Cohen S Effect of verapamil on human intestinal transit *Dig Dis Sci* 1992 37 919 924

23 Bassotti G Calcara C Annese V Fiorella S Roselli P Morelli A Nifedipine and verapamil inhibit the sigmoid colon myoelectric response to eating in healthy volunteers *Dis Colon Rectum* 1998 41 377 380

24 Zuccala G Pahor M Landi F et al Use of calcium antagonists and need for perioperative transfusion in older patients with hip fracture observational study *BMJ* 1997 314 643 644

25 Pahor M Guralnik JM Furberg CD et al Calcium channel blockers and gastrointestinal hemorrhage more bad press [letter]? *Gastroenterology* 1996 111 1391 1393

26 Staessen JA Fagard R Thijs L et al Randomised double blind comparison of placebo and active treatment for older patients with isolated systolic hypertension *Lancet* 1997 350 757 764

27 Kloner RA Vetrovec GW Materson BJ Levenstein M Safety of long acting dihydropyridine calcium channel blockers in hypertensive patients *Am J Cardiol* 1998 81 163 169

28 Davis BR Cutler JA Gordon DJ et al Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) *Am J Hypertens* 1996 9 342 360