Bleeding Complications Associated With Combinations of Aspirin, Thienopyridine Derivatives, and Warfarin in Elderly Patients Following Acute Myocardial Infarction

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Background: Combinations of aspirin with thienopyridine derivatives (clopidogrel bisulfate or ticlopidine hydrochloride) and/or warfarin sodium are increasingly being used in various cardiac conditions. However, little is known about the bleeding risks associated with these combinations, particularly in elderly individuals at the population level. This study estimates the bleeding risks associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients.

Methods: We conducted a population-based observational cohort study using linked administrative databases. A total of 21,443 elderly survivors of acute myocardial infarction between 1996 and 2000 were studied. Patients were divided into 5 groups according to drug exposure: aspirin alone, warfarin alone, aspirin plus a thienopyridine derivative (antiplatelet combination), aspirin plus warfarin (anticoagulant combination), and aspirin plus warfarin plus a thienopyridine derivative (3-drug combination). Hospitalizations for bleeding events were examined.

Results: Hospitalizations for bleeding were observed in 1,428 patients (7%). Compared with rates of patients receiving aspirin alone (0.03 per patient-year), rates of bleeding were higher among patients receiving the antiplatelet combination (0.07 per patient-year), the anticoagulant combination (0.08 per patient-year), and the 3-drug combination (0.09 per patient-year). Compared with aspirin alone, the adjusted odds ratios (95% confidence intervals) for bleeding were 1.65 (1.02-2.73) for patients receiving the antiplatelet combination and 1.92 (1.28-2.87) for patients receiving the anticoagulant combination. Only 1 of 141 patients in the 3-drug combination group had a bleeding event.

Conclusion: In practice, antiplatelet and anticoagulant combinations lead to modest increases in bleeding risk in elderly patients, but the overall risk is small.

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A LARGE BODY OF LITERATURE supports the use of aspirin for secondary prevention in patients with acute myocardial infarction (AMI). However, some patients with AMI also require long-term or short-term anticoagulation with warfarin sodium for indications such as atrial fibrillation, thromboembolic disease, and mechanical heart valves or for the prevention of left ventricular mural thrombus formation after anterior AMI. Furthermore, patients with AMI who undergo percutaneous coronary intervention (PCI) with stenting benefit from thienopyridine derivatives (ticlopidine hydrochloride or clopidogrel bisulfate) in addition to aspirin. The combination of aspirin and a thienopyridine derivative should be prescribed for 2 to 4 weeks after PCI to prevent acute in-stent thrombosis and up to 6 to 12 months after brachytherapy or drug-eluting stents. In addition, recent trials have suggested that the long-term addition of clopidogrel or warfarin to an aspirin treatment regimen in patients with acute coronary syndrome leads to further reduction in fatal and nonfatal cardiovascular events and is, therefore, considered to be superior to aspirin alone. Finally, the combination of aspirin, warfarin, and thienopyridine derivatives is used in patients with permanent atrial fibrillation who receive drug-eluting stents following AMI.

Several studies have reported varying degrees of bleeding complications with combination therapies. Most of these studies were clinical trials conducted in selected groups of patients with specific inclusion and exclusion criteria. For example, most of these trials excluded elderly patients, a population that is at higher risk of AMI and cardiac complications than is the population of younger patients selected for inclusion in randomized clinical trials. Little is known about the effec-
tiveness of a treatment regimen of aspirin plus warfarin or a thienopyridine derivative in elderly patients in real-world practice among the general population. The goals of this study were to estimate at the population level the bleeding risks associated with the use of various antiplatelet and anticoagulant combinations in elderly post-AMI patients and to identify clinical factors that may influence risk of bleeding.

METHODS

DATA SOURCES

Two longitudinal administrative databases were merged to construct and follow up the study cohort. The hospital discharge summary database provides information on the principal diagnosis and comorbidities for all patients admitted to the hospital with AMI in Quebec, Canada (population, 7.1 million according to the 1996 census). In addition, the database records demographics, length of stay, and hospital complications and mortality. The ability of this database to identify patients with AMI has previously been validated through medical record audits.15

Using encrypted Quebec Medicare numbers, the AMI cohort was linked to the provincial drug and physician’s claim database. This database records all outpatient prescriptions written for patients 65 years or older. This database has previously been shown to be accurate in recording prescriptions,16 and it was used to identify the prescription medications for every patient in the study cohort.

STUDY POPULATION

All patients 65 years or older who were admitted to the hospital with a principal diagnosis of AMI (International Classification of Disease, Ninth Revision [ICD-9], code 410) between January 1, 1996, and March 31, 2000, were included in the cohort using the hospitalization database (N=25795). To increase the specificity of AMI diagnosis, we excluded patients whose total hospital length of stay was less than 3 days and patients for whom AMI was coded as a complication. To increase the comparability of AMI diagnoses, we excluded patients who had an AMI in the preceding year. Finally, to have prescription data available on all patients, we excluded patients discharged to nursing homes (because drug data are not available) and patients who died during AMI hospitalization. After exclusions, the study population included 21 443 patients (83% of the original population).

EXPOSURE TO MEDICATIONS

To classify patients according to their exposure to different drug combinations of aspirin, clopidogrel, ticlopidine, and warfarin, their prescriptions were examined starting at discharge. Since the prescriptions for each patient might vary from one period to another during the follow-up, the cohort prescriptions were monitored throughout the follow-up period on a monthly basis and were grouped as follows: (1) aspirin alone, (2) warfarin alone, (3) aspirin plus warfarin (anticoagulation combination), (4) aspirin plus either ticlopidine or clopidogrel (antiplatelet combination), and (5) aspirin plus warfarin plus either ticlopidine or clopidogrel (3-drug combination). An individual patient could belong to different exposure regimens at different intervals, because multiple crossovers between regimens are unavoidable and part of usual care.

DEFINITION OF BLEEDING OUTCOMES

A bleeding outcome was defined as any hospital admission that occurred after the index AMI hospitalization with a principal or new secondary diagnosis of intracranial hemorrhage (ICD-9 codes 430, 431, 432, 432.0, 432.1, and 432.9), gastrointestinal tract hemorrhage (ICD-9 codes 578 and 530.7-530.8), aortic aneurysm dissection or rupture (ICD-9 codes 441.0, 441.1, and 441.3), intraocular hemorrhage (ICD-9 codes 362.8 and 379.2), hematuria (ICD-9 code 599.7), hemoptysis (ICD-9 code 786.3), epistaxis (ICD-9 code 784.7), or hemorrhage not otherwise specified (ICD-9 code 459). A new secondary diagnosis was defined as a diagnosis that was not present in the patient’s medical records at the time of the index AMI hospitalization.

Patients were considered to have bleeding during the index AMI hospitalization if a new secondary diagnosis (not noted as a principal or secondary diagnosis in the preceding year of the index AMI) of 1 or more of the bleeding conditions listed herein were coded on their AMI hospitalization discharge summaries. To reduce the chances of double counting bleeding outcomes, patients who developed a first bleeding outcome were censored from follow-up thereafter. For the adjustment of bleeding risk, patients were considered to have had a bleeding event before AMI hospitalization if they were hospitalized in the preceding 6 months of the index AMI with a principal diagnosis of 1 of the bleeding conditions listed herein.

DRUG EXPOSURE-OUTCOME RELATIONSHIP

In this study, an outcome was related to a drug exposure if it occurred within the time frame starting from the prescription date of the drug plus 1 day and ending 10 days after the duration of the prescription for that drug. In case of overlap (eg, the bleeding event occurred during the 10 days overlapping 2 different prescriptions, one for aspirin and the other for a combination therapy), the bleeding event was related to the combination therapy. However, such overlap occurred in less than 1% of the cases.

STATISTICAL ANALYSIS

Descriptive statistics (means and proportions) were used to evaluate the baseline demographic and clinical characteristics of patients at the index AMI hospitalization, comparing patients who developed bleeding outcomes with those who did not. Patients with a bleeding event were censored further according to their exposure to different medication groups.

To assess the risk of bleeding associated with the use of different drug combinations, the crude incidence rate of bleeding for each regimen was calculated for every month of the follow-up period individually. The average incidence rates for the different drug groups were calculated subsequently and compared in terms of patient-years with the aspirin group as the reference. To calculate the 95% credible intervals, Bayesian posterior incidence rates and ratios were calculated. This was done by simulating the distributions of interest.

Samples from the posterior distributions, given noninformative priors, of the parameters of interest were obtained from the Gibbs sample, a Markov chain Monte Carlo technique to simulate from posterior distributions.17 The results were obtained from 10000 Markov chain Monte Carlo iterations by using the statistical software BUGS (Bayesian inference Using Gibbs Sampling; MRC Biostatistics Unit, Cambridge, England) with 3000 burn-ins.

To obtain an adjusted risk of bleeding among the different drug groups, a nested case-control study was designed. In this design, patients who experienced a bleeding event during the
study period were defined as cases. For each case, a random sample of 3 controls per case was drawn from among the patients without any bleeding event and patients at risk of future bleeding events. Matching was performed for the time of bleeding of the case.

The demographic and clinical characteristics of patients with a bleeding event in each of the different exposure groups were examined to identify potential confounding variables. The simultaneous effect of the identified potentially confounding variables that might influence the risk of bleeding was accounted for using multiple logistic regression modeling. The variables controlled for included age, sex, comorbidities at the time of index AMI (hypertension, diabetes, cerebrovascular disease, chronic renal failure, peptic ulcer disease, cancer, history of bleeding during AMI hospitalization, or history of bleeding in the 6 months preceding the AMI), and the specialty of the treating physician.

### RESULTS

#### BASELINE CHARACTERISTICS

Between January 1, 1996, and March 31, 2000, a total of 21,443 patients met the inclusion and exclusion criteria and constituted the final cohort. We had a mean of 654 days of follow-up data for the study patients (range, 5-1551 days). Among these patients 14,28 (6.7%) developed a bleeding event during the follow-up period (Table 1). Overall, 57.1% of the patients were men, and the median age was 74 years. Patients with a bleeding episode after discharge were older and more likely to have a history of cerebrovascular disease, chronic renal failure, and/or a bleeding complication during AMI hospitalization. Also, patients with bleeding after discharge were more likely to be treated by a physician other than a cardiologist during the AMI hospitalization but were less likely to be treated at a hospital with a cardiac catheterization laboratory.

#### BLEEDING EVENTS IN RELATION TO DRUG EXPOSURE

During the study period, 89% of patients had 1 or more outpatient prescriptions for aspirin, 24% for warfarin, and 16% for ticlopidine or clopidogrel (10% ticlopidine and 6% clopidogrel), either separately or in combinations. Only 4% of patients received low-dose aspirin (80-325 mg/d); most received 300 to 325 mg/d. Among the 20176 patient-years of aspirin alone, 656 patients sustained a bleeding event (crude incidence rate, 0.032 per patient-year; 95% credible interval, 0.030-0.035) (Table 2). Compared with patients who received aspirin alone, the crude incidence of bleeding complication was twice as high among patients receiving warfarin alone (crude incidence rate ratio, 1.81; 95% credible interval, 1.54-2.11), among patients receiving aspirin plus warfarin (crude incidence rate ratio, 2.55; 95% credible interval, 1.77-3.56), and among patients receiving the antiplatelet combination (crude incidence rate ratio, 2.10; 95% credible interval, 1.29-3.18). Only 1 patient taking the 3-drug combination experienced a bleeding event, and so the incidence rate ratio was not calculated for these patients. A total of 522 patients among the study cohort experienced bleeding events during the follow-up period but were not exposed to 1 of the 5 exposure groups during or immediately before the bleeding events.

#### CHARACTERISTICS OF PATIENTS WITH A BLEEDING EVENT IN THE DIFFERENT EXPOSURE GROUPS

Patients in the antiplatelet combination group who had a bleeding complication were younger (69 vs 76 years, \( P<.001 \)) than patients in other exposure groups (Table 3). Patients in the aspirin plus warfarin group were predominantly male and were less likely to have a history of peptic ulcer disease, malignancy, hypertension, and diabetes. However, these patients were also more likely to have a history of cerebrovascular disease, chronic renal failure, and bleeding during the AMI hospitalization.

#### BLEEDING LOCATION AMONG DIFFERENT EXPOSURE GROUPS

Most bleeding complications were gastrointestinal tract hemorrhages in all exposure groups. However, these hemorrhages were more common in the antiplatelet combination group and in the aspirin-plus-warfarin group than in the warfarin-alone or aspirin-alone groups (Table 3). Intracranial hemorrhages tended to be more common in the aspirin-plus-warfarin group than the aspirin-alone group, and such bleeding did not occur in the antiplate-
let combination group. Similarly, intraocular or aortic aneurysm bleeding was not observed in the antiplatelet combination group or in the aspirin-plus-warfarin group. Other less serious types of bleeding tended to occur more frequently in the antiplatelet group than in the aspirin-alone group, such as hematuria (20.0% vs 11.1%, \( P = .12 \)) and hemoptysis (10.0% vs 4.9%, \( P = .15 \)).

### NESTED CASE-CONTROL ANALYSIS

To explore the independent effect of the various drug exposures after adjusting for demographic and clinical characteristics, a nested case-control study was conducted. Warfarin use was associated with an 85% increased risk compared with aspirin-alone use (odds ratio [OR], 1.85; 95% confidence interval [CI], 1.54-2.22), and the combination of aspirin-plus-warfarin was associated with a similar risk (OR, 1.84; 95% CI, 1.23-2.76). Although the use of an antiplatelet combination was associated with a higher bleeding risk than aspirin alone (OR, 1.68; 95% CI, 1.02-2.77), this combination carried less of a risk than the aspirin-plus-warfarin combination. Only 1 patient in the 3-drug group required hospitalization (hematuria). Thus, ORs and 95% CIs could not be calculated for this group. The independent predictors of a bleeding event were age, cerebrovascular disease, diabetes, chronic renal failure, peptic ulcer disease, and bleeding during index AMI hospitalization. We also found that patients who were treated by cardiologists had a lower risk of bleeding compared with those treated by general practitioners and internists (Table 4). Sex and hypertension were not found to be independent risk factors for bleeding.

### COMMENT

In this population-based study, we evaluated the bleeding risk associated with aspirin, thienopyridine derivatives, and warfarin combinations in elderly patients fol-
owing AMI. The study results demonstrate that, at the population level in real-world practice, the combination of aspirin plus warfarin or a thienopyridine derivative is associated with at least a 2-fold increase in bleeding complications in elderly patients. However, the incidence of bleeding complications overall is relatively low and on the order of 0.06 to 0.08 events per patient-year.

PREVIOUS STUDIES

The bleeding rates associated with antiplatelet combinations and anticoagulant combinations in this study population are comparable to the rates of major bleeding reported in clinical trials. However, there is a wide range of bleeding rates reported in trials for antiplatelet combinations (0.005-0.7 per patient-year) and for the anticoagulant combination (0.005-0.8 per patient-year). The heterogeneity of these rates is first attributable to the inconsistency in the definition of bleeding complications in different trials. In the PCI trials, bleeding rates tend to be higher than in non-PCI trials owing to the inclusion of procedure-related bleeding complications. Finally, differences in the intensity of anticoagulation, clinical characteristics of the study populations, and aspirin dosages may explain the differences in bleeding rates. Our study estimated the bleeding rates associated with different regimens in the general elderly population outside the context of a trial setting. Thus, our results likely reflect the bleeding risk associated with such regimens among elderly patients in daily practice. For example, we found a doubling of the bleeding rate for patients taking aspirin plus thienopyridine compared with aspirin alone, whereas in the Clopidogrel in Unstable Angina to Prevent Recurrence (CURE) trial, there was an approximately 25% relative increase in bleeding for this combination in comparison with aspirin. The difference in the age distribution between the 2 study populations could explain this difference.

BLEEDING EPISODES

Our study demonstrated that most bleeding events were gastrointestinal tract hemorrhages across the various drug groups. However, as in previous studies, gastrointestinal tract bleeding was more frequent with the antiplatelet and anticoagulation combinations than with the aspirin alone. Similarly, our results are in concordance with the findings of the CURE trial in that the antiplatelet combination was not associated with an increased risk of intracranial hemorrhage. In fact, none of our patients sustained intracranial hemorrhage during exposure to the antiplatelet combination. On the other hand, we found a tendency toward an increased risk in intracranial bleeding in the aspirin plus warfarin combination compared with aspirin alone (11.1% vs 6.4%, P = .14). This finding is in contrast with the results of Combination Therapy and Mortality Prevention (CHAMP) trial and the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis 2 (APRICOT-2) trial, which both reported no significant increase in intracranial bleeding in the aspirin-plus-warfarin group compared with aspirin alone. Although low-dose aspirin (80-325 mg/d) was used in each of these trials in the combination therapy group, most of our patients were using 300 to 325 mg/d of aspirin, which may explain the higher rate in our study. Although aspirin in higher dosages probably leads to a higher bleeding risk, especially when combined with warfarin or clopidogrel, most patients in our study received 325 mg/d of aspirin and only 4% were receiving low-dose aspirin in all regimens. Therefore, a proper comparison of the bleeding risk between high and low doses of aspirin could not be performed in our study.

PREDICTORS OF BLEEDING

Age, the presence of peptic ulcer disease, cerebrovascular disease, chronic renal failure, diabetes, and bleeding during AMI hospitalization were independent clinical predictors of future bleeding in elderly patients irrespective of the medications prescribed. The presence of these factors may help treating physicians identify those patients with a higher risk of future bleeding. These factors may indicate the need for more frequent monitoring and closer follow-up after discharge, especially if such patients are prescribed antiplatelet and/or anticoagulation combinations.

THREE-DRUG COMBINATION

Because of insufficient statistical power (1 bleeding event per 11.8 patient-years), we were not able to calculate an OR and 95% CI for the 3-drug combination group. The 3-drug combination is often required for patients who need to receive warfarin for indications such as atrial fibrillation or a mechanical heart valve but at the same time need to receive the antiplatelet combination for several weeks after stent deployment. In these situations, the use of the aspirin and warfarin combination but without concomitant thienopyridine treatment was found to be inferior to the antiplatelet combinations in preventing subacute thrombosis and cardiac events after PCI with stenting. Similarly, the antiplatelet combination has been shown to be an ineffective alternative to warfarin for conditions such as mechanical heart valves or atrial fibrillation. However, we
cannot make a definitive conclusion in our study because of the small sample size.

Several potential limitations of our study should be noted. We did not have information on patients who might have sustained bleeding events but were not admitted to the hospital. Such patients include those requiring transfusion, endoscopy, or other interventions. However, unless fatal bleeding occurred outside the hospital, such patients were not likely to have had major bleeding. Also, we did not have information on clinical factors, which potentially could have an influence on the risk of bleeding such as the use of over-the-counter nonsteroidal anti-inflammatory drugs, and laboratory results such as the international normalized ratio. In addition, our study has an inherent selection bias because the treating physician may exclude patients with a high risk for bleeding from receiving combination therapy. Such exclusions could bias the results toward finding higher bleeding rates among patients taking aspirin alone. In this case, the true increase in bleeding risk from combination therapy would likely be greater than the differences observed in this study. However, such exclusions are part of the conventional risk assessment before initiating antithrombotic therapy and reflect actual clinical practice. We also did not assess the length of therapy, which might be associated with a higher rate of bleeding than short-term use. Finally, although we made use of the latest available data, rates of use of ticlopidine or clopidogrel are likely higher in contemporary practice than those observed in our study period of 1996 to 2000. We might also expect that a higher percentage of patients receive low-dose aspirin when given in combination with clopidogrel or ticlopidine plus warfarin in contemporary practice than was observed in our study. Nonetheless, it is unlikely that the associations between the exposure groups and risk of bleeding would be affected by these increases in prevalence.

In conclusion, in this population-based study, we found that the addition of warfarin or a thienopyridine derivative to aspirin is associated with at least a 2-fold increase in bleeding risk among elderly patients with AMI. Age, cerebrovascular disease, chronic renal failure, pectic ulcer disease, diabetes, and bleeding during the index AMI are independent predictors of future bleeding in elderly patients. These results suggest that the overall bleeding risk in practice among the general elderly population is low but not insignificant. Close follow-up of patients at particularly high risk of bleeding is recommended.

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