Twenty-Year Trends in the Incidence of Stroke Complicating Acute Myocardial Infarction

Worcester Heart Attack Study

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Background: Given the improved survival of patients after acute myocardial infarction (AMI), more patients are at risk for cerebrovascular complications of AMI. Trends in the magnitude of stroke in the setting of AMI are not well characterized, however, and neither have contemporary trends in the hospital death rates of patients developing acute stroke been examined.

Results: Of 9220 patients without a history of stroke hospitalized with confirmed AMI between 1986 and 2005 in all greater Worcester medical centers, 132 (1.4%) experienced an acute stroke during hospitalization. The proportion of patients with AMI who developed a stroke increased through the 1980s and 1990s but declined slightly thereafter. Advanced age, female sex, a previous myocardial infarction (MI), and the occurrence of atrial fibrillation during hospitalization were associated with a greater risk of stroke. Receipt of a percutaneous coronary intervention during hospitalization was associated with a lower risk of stroke. Compared with patients who did not experience a stroke, patients developing a stroke in the 1990s were approximately 3 times more likely to die during hospitalization (odds ratio [OR], 2.91; 95% confidence interval [CI], 1.72-5.19), whereas those experiencing a stroke in the 2000s were 5 times more likely to die (OR, 5.36; 95% CI, 2.71-10.64).

Conclusions: Although the incidence rates of stroke complicating AMI have declined somewhat since 1999, there is not a corresponding decline in the odds of dying during hospitalization in those developing a stroke. Although contemporary therapies may be reducing the risk of stroke in patients with AMI, more attention should be directed to improving the short-term prognosis of these high-risk patients.

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Given the improved survival of patients hospitalized with acute myocardial infarction (AMI) during the past several decades,¹ an increasing pool of patients are at risk for serious complications of AMI, including ischemic and hemorrhagic stroke. Although stroke is a relatively infrequent complication of AMI, with approximately 1% to 2% of patients with AMI developing a stroke during their index hospitalization,² the occurrence of stroke in patients with AMI is associated with increased morbidity and mortality.³⁴ In addition, clinical and epidemiologic studies³⁴ reported an excess risk of stroke after myocardial infarction (MI) during the 1980s and 1990s, trends coincident with the increasing use of thrombolytic therapy for the hospital management of patients with AMI. The risk of in-hospital stroke complicating AMI has not been well characterized; however, particularly during recent periods, neither has the potentially changing association between the occurrence of stroke and hospital death rates.

Using data from a communitywide surveillance study of patients hospitalized with AMI in a large New England community,⁷⁻⁹ we examined 2-decade trends (1986-2005) in the incidence rates of stroke complicating AMI, patient and treatment characteristics associated with the occurrence of stroke, and the impact of stroke on hospital mortality. The study population consisted of 9220 residents of the Worcester metropolitan area hospitalized with AMI at all greater Worcester medical centers in 11 annual periods between 1986 and 2005.

Data for this study were derived from the Worcester Heart Attack Study. This is an ongoing population-based investigation that is examining long-term trends in the incidence, hos-
pital, and postdischarge case-fatality rates of AMI in residents of the Worcester metropolitan area hospitalized at all 16 greater Worcester medical centers. Fewer hospitals (n=11) have been included during recent study years due to hospital closures, mergers, and conversions to long-term care facilities. The details of this study have been described previously. In brief, the medical records of residents of the Worcester metropolitan area (2000 census estimate=478,000) hospitalized for possible AMI at all greater Worcester medical centers were individually reviewed, and a diagnosis of AMI was validated according to predefined criteria. Patients who developed AMI secondary to an interventional procedure or surgery were excluded from the study sample.

Because we were interested in examining changing trends in the magnitude of incident (initial) cases of stroke, patients with a history of stroke (N=1103) were excluded from the present study. The percentage of patients with AMI and a history of stroke increased slightly during the study period; 9.0% (n=273) of the study sample had a history of stroke in the 1980s, 10.8% (n=430) had a history of stroke among those hospitalized with AMI in the 1990s, and 12.1% (n=400) of patients with AMI had a history of stroke since 2000.

DATA COLLECTION
Demographic, medical history, and clinical data were abstracted from the hospital medical records of geographically eligible patients with confirmed AMI by trained study physicians and nurses. Information was collected about patient age, sex, and body mass index; comorbidities (eg, angina, diabetes mellitus, hypertension, stroke, and atrial fibrillation); AMI order (initial vs previous), type (Q wave vs non-Q wave), and location (anterior vs inferior or posterior); hospital treatment approaches; and hospital discharge status. Information was collected about the occurrence of clinically significant in-hospital complications, including stroke, atrial fibrillation, heart failure, and cardiogenic shock. The occurrence of acute stroke was defined as the development of neurologic changes consistent with a stroke based on information in medical records and reviewed by a team of nurse and physician abstractors. Since 1991, information about the type of stroke (hemorrhagic or ischemic) has been recorded. Information about whether the stroke was confirmed by a neurologist or by diagnostic imaging studies was not recorded. Survival status after hospital discharge was ascertained through a review of the medical records for additional hospitalizations and a statewide and national search of death certificates for residents of the Worcester Standard Metropolitan Statistical Area.

DATA ANALYSIS
We examined differences between patients who developed vs did not develop an acute stroke during hospitalization for AMI regarding their demographic and clinical characteristics, treatment practices, and hospital outcomes using $\chi^2$ and t tests for discrete and continuous variables, respectively. Three logistic regression models were performed to identify variables independently associated with the development of stroke. The first model controlled for age and sex only, the second model included previous comorbidities (history of angina, documented coronary artery disease, diabetes mellitus, atrial fibrillation, or hypertension), and the third model included AMI-associated characteristics, occurrence of in-hospital complications (development of atrial fibrillation, heart failure, or cardiogenic shock), and information about thrombolytic therapy and hospital procedures (cardiac catheterization, percutaneous coronary intervention [PCI], and coronary artery bypass surgery).

Logistic regression analysis was used to examine changes across time in the odds of developing an acute stroke, simultaneously controlling for the previously described demographic and clinical factors associated with the risk of stroke. Multivariate logistic regression analysis was also used to examine the association between occurrence of an acute stroke and hospital mortality using the 3-model regression approach described previously herein.

RESULTS
Of the 9220 patients (mean age, 69 years; 42.3% were women) hospitalized with confirmed AMI at all greater Worcester hospitals without previous stroke during the study period (1986-2005), 132 patients (1.4%) experienced an acute stroke during hospitalization. Overall, 72.8% of all strokes occurring between 1991 and 2005 were ischemic. In the 1990s, approximately three-quarters of strokes complicating AMI were ischemic and, since 2000, approximately two-thirds of all strokes in the setting of AMI were ischemic ($P = .18$).

FACTORS ASSOCIATED WITH ACUTE STROKE
Patients who experienced a stroke were significantly older, were more likely to be women, were more likely to have a medical history of atrial fibrillation or a do-not-resuscitate (DNR) order, and were more likely to have their hospital stay complicated by atrial fibrillation (Table 1). Patients with stroke were less likely to have undergone cardiac catheterization or a PCI.

Physiologic data at the time of hospital admission were available in a subsample of patients from the mid-1990s to the most recent year under study. Patients who experienced an acute stroke had lower serum hematocrit findings, total serum cholesterol levels, and estimated glomerular filtration rates (eGFRs) but higher heart rates, systolic blood pressure (BP) at admission, and peak systolic and diastolic BP levels during their hospital stay compared with those without an acute stroke (Table 1).

After adjusting for demographic factors, comorbid conditions, AMI-associated characteristics, and clinical complications of AMI, advanced age ($\geq 75$ years), female sex, a previous MI, and the development of atrial fibrillation during hospitalization were associated with significantly increased odds of acute stroke (Table 2). The odds of stroke were unchanged when thrombolytic therapy and in-hospital interventions were controlled for in the regression analyses. When we controlled for length of hospital stay and use of DNR orders, the present results did not change materially. Use of DNR orders (odds ratio [OR], 2.88; 95% confidence interval [CI], 1.80-4.60) and longer hospital stay (OR, 1.03; 95% CI, 1.03-1.05) were associated with a significantly greater risk of experiencing an acute stroke.

Based on previous work identifying a diastolic BP greater than 90 mm Hg, GFR, and heart rate as factors associated with the risk of stroke, we included these physiologic variables in the regression models. The associations among age, sex, and risk of stroke were attenuated, perhaps owing to the inclusion of these variables in the calculation of estimated GFR, whereas the physi-
After declines in the frequency of incident stroke between 1986 and 1990, stroke rates increased through the 1990s, peaking in 1999 (Figure). Beginning in 2001, stroke rates began to decline slightly, with the incidence rate falling to 1.4% in 2005, similar to the rate observed in the initial study year of 1986.

After controlling for demographic factors, comorbid conditions, AMI-associated characteristics, and hospital complications, the odds of experiencing a stroke during hospitalization for AMI were significantly higher in 1997 and 1999 than in the index year of 1986 (Table 3). In the other study years, the odds of stroke were not significantly different from that observed in the initial 2 study years of 1986 and 1988.

There were few changes across time in the demographic and clinical characteristics of patients who experienced an acute stroke. Patients with an AMI who experienced a stroke during recent study years were more likely to have a history of hypertension and were less likely to have developed a Q-wave or anterior AMI during their index hospitalization. Greater Worcester residents experiencing a stroke in the 2000s were less likely than those experiencing a stroke in earlier years to have received thrombolytic therapy during their acute hospitalization ($P < .05$ for all).

### HOSPITAL CASE-FATALITY RATES OF ACUTE STROKE AND FACTORS ASSOCIATED WITH A POOR HOSPITAL PROGNOSIS

Patients who experienced an acute stroke during hospital admission for AMI were significantly more likely to die during hospitalization compared with those who did not experience a stroke (34.1% vs 11.6%, $P < .001$). In the fully adjusted regression model, patients with AMI who experienced a stroke were nearly 4 times more likely to die during their acute hospitalization compared with those who did not experience a stroke (OR, 3.76; 95% CI, 2.51-5.65). In addition to stroke, increasing age, a medical history of hypertension, development of an anterior AMI, and receipt of a DNR order were associated with a higher risk of dying, whereas undergoing a PCI was associated with a lower risk of dying during hospitalization (data not shown). When patients with a DNR order were excluded from the analysis, the results did not materially change, and patients who experienced an acute stroke were significantly more likely to die compared with those who did not experience a stroke (OR, 2.3; 95% CI, 1.2-4.4).

Of patients who developed a stroke since 1991 (n=114), those who experienced a hemorrhagic stroke were significantly more likely to die during hospitalization compared with those who experienced an ischemic stroke (OR, 4.14; 95% CI, 1.47-11.71). There were no differences in hospital death rates in patients who developed an acute stroke according to selected demographic characteristics, clinical factors, or previous comorbidities.

In examining potentially changing trends in the odds of dying after a stroke, in the 1980s, patients who experienced a stroke were 5 times more likely to die during hospitalization (adjusted OR, 4.91; 95% CI, 1.21-19.84); in the 1990s, patients who experienced a stroke were nearly 3 times more likely to die (adjusted OR, 2.91;
95% CI, 1.72-5.19); and in the 2000s, patients with a stroke were more than 5 times more likely to die (adjusted OR, 5.36; 95% CI, 2.71-10.64) compared with those who did not experience a stroke. Expressed in another manner, compared with patients who experienced a stroke in the 1980s, those who developed a stroke in the 1990s were less likely to die during hospitalization for AMI (adjusted OR, 0.65; 95% CI, 0.28-1.26). The risk of dying during hospitalization was similar for patients experiencing a stroke in the 2000s compared with those who developed a stroke in the 1980s (adjusted OR, 1.04; 95% CI, 0.32-3.32).

Because the length of hospital stay has declined across time, we also examined 30-day death rates in patients who did and did not develop a stroke according to time. The 30-day death rate after hospital admission was significantly higher in patients who experienced a stroke than in those who did not (37.9% vs 14.2%, P < .001). The 30-day death rate increased slightly during the study in patients who experienced an acute stroke (Table 4).

Table 2. Factors Associated With the Occurrence of Stroke in Patients With AMI (Worcester Heart Attack Study)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<tr>
<td>Age, y</td>
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<tr>
<td>55-64</td>
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<td>65-74</td>
<td>1.82 (0.88-3.74)</td>
<td>2.35 (1.00-5.51)</td>
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<td>≥75</td>
<td>2.81 (1.43-5.53)</td>
<td>3.37 (1.49-7.62)</td>
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<td>Female sex</td>
<td>1.66 (1.15-2.39)</td>
<td>1.92 (1.28-2.86)</td>
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<tr>
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<td>1.41 (0.84-2.39)</td>
<td>1.14 (0.53-2.45)</td>
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<tr>
<td>Coronary artery bypass surgery</td>
<td>...</td>
<td>...</td>
<td>1.53 (0.51-4.63)</td>
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</table>

Abbreviation: AMI, acute myocardial infarction.

The respective referent categories are age younger than 55 years, male sex, absence of selected medical history variables, previous AMI, non-Q-wave AMI, inferior or posterior AMI, absence of selected clinical complications, absence of selected prescribed medications, and absence of selected in-hospital therapies and procedures.

Figure. Changes across time in the incidence rates of acute stroke in patients with acute myocardial infarction (Worcester Heart Attack Study).
The results of this communitywide study of greater Worcester residents hospitalized with AMI between 1986 and 2005 suggest that the incidence rates of initial stroke events increased from the mid-1980s through the late 1990s but have declined somewhat thereafter. These results also suggest that, although the occurrence of stroke complicating AMI seems to be decreasing during recent study years, there is not a corresponding decline in the hospital death rates of those developing an acute stroke. We identified several demographic and clinical factors associated with a greater risk of developing, and dying after, a stroke in residents of the Worcester metropolitan area hospitalized with AMI at all area medical centers.

INCIDENCE OF STROKE COMPLICATING AMI

Previous work has shown that the hospital incidence rates of stroke complicating AMI range from 1% to 2%. Despite the morbidity and mortality associated with this devastating condition, little published information is available that has examined changing trends in the magnitude of stroke complicating AMI. Data from the population-based Rochester (Minnesota) Epidemiology Project showed increased rates of stroke after AMI from the late 1970s through the 1980s, with a leveling off in the 1990s. Findings from the multinational Global Registry of Acute Coronary Events project suggest that the occurrence of stroke in patients hospitalized with acute coronary disease at approximately 100 medical centers throughout the United States, Europe, and South America between 1999 and 2005 remained relatively stable. Previous findings from the Worcester Heart Attack Study suggested declines in the frequency of stroke complicating AMI from the middle through the late 1980s followed by an increase through the late 1990s. The present study extends the earlier findings and suggests slightly declining rates of acute stroke in the setting of AMI during recent years.

Although we do not have data in the present study to support the speculated hypothesis, the recently observed declines in the incidence rates of acute stroke suggest that contemporary management strategies for patients hospitalized with AMI may be favorably lowering the risk of cerebrovascular complications. The decreased rate of stroke observed in this study population during the past 5 years is coincident with marked declines in the use of thrombolytic therapy in this patient population, and increased use of PCI, which may reduce the risk of hemorrhagic stroke in patients with AMI. It remains important to continue to monitor changing trends in the magnitude and outcomes of stroke in patients hospitalized with AMI as the therapeutic management of these patients continues to evolve.

RISK FACTORS FOR STROKE COMPLICATING AMI

We identified several patient characteristics independently associated with a greater risk of stroke, including advanced age (≥75 years), female sex, development of atrial fibrillation during hospitalization, and a previous MI. These findings are consistent with the results of previously published studies. Advanced age and occurrence of atrial fibrillation have been consistently identified as risk factors of hospital stroke in the setting of AMI. On the other hand, there is conflicting published evidence regarding therapeutic regimens possibly associated with the development of stroke complicating AMI; much of this previous work has focused on the potentially adverse effects associated with the administration of thrombolytic therapy or has been conducted in the setting of clinical trials of prescribed therapies. We found that undergoing a PCI was associated with a lower risk of stroke after controlling for a variety of demographic and clinical factors. These results are consistent with findings from the Rochester Epidemiology Project, which reported a lower risk of stroke in the setting of AMI in patients who received a PCI. A meta-analysis of more than 20 published studies, however, did not identify any therapies associated with a reduced risk of stroke in patients hospitalized with AMI. The present findings suggest that patients at increased risk of a stroke can be identified in advance. Increased surveillance, and use of targeted therapies, where indicated, are warranted in these high-risk patient groups.
HOSPITAL CASE-FATALITY RATES

The death rates associated with acute stroke in patients with AMI are high, with patients who experience a stroke being 2 to 4 times more likely to die during hospitalization than those who do not experience a stroke. In a review of the literature, we did not find other studies that have examined changing trends in hospital death rates in patients with AMI who developed a stroke. In the present study, we found that the odds of dying during hospitalization for MI in patients with an acute stroke were higher in more recent years than in the late 1990s. Although hospital case-fatality rates in patients with acute coronary disease are declining, and the rate of stroke complicating AMI is declining in this hospitalized cohort, the odds of an acute stroke being fatal are not showing similar declines.

It is possible that contemporary therapies for AMI may be reducing the risk of stroke complications. However, the occurrence of stroke may be increasingly important regarding short-term mortality risk after AMI. The higher odds of dying during hospitalization, and 30 days after hospital admission, in patients experiencing an acute stroke since 2000 compared with the odds in the 1990s is especially important given recent reports of decreasing mortality rates associated with stroke in a variety of communitywide studies.

Although death rates in patients who experienced a stroke did not differ according to various demographic characteristics, clinical factors, or comorbidities of AMI, patients who experienced an ischemic stroke were less likely to die than were those who developed a hemorrhagic stroke. Since stroke subtype has been shown to affect the risk of dying in patients with AMI, changes across time in the relative magnitude of hemorrhagic compared with ischemic strokes may be playing a role in the changing epidemiologic features of stroke and associated short-term case-fatality rates. Other contributory factors may include changes in the natural history of stroke or may be due to the less aggressive treatment of these high-risk patients. The latter may be due, in part, to the increasing prevalence of important comorbidities or to the increasing use of DNR orders in these high-risk patients.

STUDY STRENGTHS AND LIMITATIONS

The strengths of this study include the generalizability of the population-based study design that included all patients hospitalized with AMI from a well-characterized urban New England community. All cases of possible AMI were independently validated according to standardized criteria. Moreover, because patients’ medical history and hospital care were well characterized, we could control for a variety of potentially confounding factors in examining changing trends in the magnitude and impact of stroke in patients hospitalized with AMI. The limitations of this study include that the diagnosis of stroke was not always confirmed by a neurologist or by imaging studies and that we did not have information available about the severity of the acute stroke, availability of a stroke team, or withdrawal of mechanical support. In addition, because we could not determine whether in-hospital treatment approaches were prescribed either before or after the acute stroke, we did not adjust for receipt of in-hospital medications in the multivariate-adjusted regression models. We did not examine the role of other risk factors for stroke, such as cigarette smoking, and information on cause-specific death rates was not available.

The results of this study in residents of a large New England community suggest that the risk of stroke complicating AMI has declined somewhat since the late 1990s, but the short-term death rates of those experiencing stroke are not showing a corresponding decrease. Understanding factors associated with the risk of stroke after AMI, particularly those associated with fatal stroke, remains an important issue for the more optimal care of the increasing number of patients at risk for serious complications of AMI.

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