Early Coronary Revascularization Diminishes the Risk of Ischemic Stroke With Acute Myocardial Infarction

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Background and Purpose—Ischemic stroke is an uncommon but devastating complication of myocardial infarction (MI). It is possible that delay in the acute revascularization of these patients influences the risk of peri-MI ischemic stroke independent of size of infarction or residual ventricular function. The influence of the timing and type of revascularization on risk of ischemic stroke in the patient with MI has not previously been assessed.

Methods—We used the National Registry of Myocardial Infarction 3 and 4 databases to identify 45 997 subjects who received thrombolytic therapy and 47 876 patients who were treated with primary percutaneous transluminal coronary angioplasty for MI. In-hospital ischemic stroke occurred in 248 (0.54%) and 150 (0.31%) patients in the two groups, respectively. Patients were stratified based on time from presentation to initial therapy.

Results—A statistically significant linear relationship between time to revascularization therapy and risk of in-hospital ischemic stroke was seen on univariate analysis. A multivariate model incorporating 26 other variables showed thrombolytic therapy within 15 minutes was associated with a lower risk of ischemic stroke (odds ratio, 0.58; 95% CI, 0.36–0.94). Primary angioplasty within 90 minutes of arrival was associated with a nonsignificant trend toward lower stroke risk (odds ratio, 0.68; 95% CI, 0.41–1.12). Interestingly, this benefit of early reperfusion therapy did not appear to be related to improvements in left ventricular function.

Conclusion—Risk of in-hospital ischemic stroke with MI is closely tied to the time to revascularization with both thrombolytic and percutaneous transluminal coronary angioplasty therapies. Early revascularization is independently predictive of a lower risk of ischemic stroke, but the mechanism of this does not appear to be related to improved cardiac function. The records of 45 997 subjects who received thrombolytic therapy and 47 876 patients who were treated with primary percutaneous transluminal coronary angioplasty for myocardial infarction were analyzed to determine the relationship between time to revascularization and the occurrence of ischemic stroke. A statistically significant linear relationship between time to revascularization therapy and risk of in-hospital ischemic stroke was seen on univariate analysis. A multivariate model incorporating 26 other variables showed thrombolytic therapy within 15 minutes of presentation was associated with a lower risk of ischemic stroke, and angioplasty within 90 minutes was similarly associated with a nonsignificant trend toward lower stroke risk. (Stroke. 2006;37:2546-2551.)

Key Words: angioplasty ■ myocardial infarction ■ stroke ■ thrombolysis

Ischemic stroke is an uncommon but devastating complication of acute myocardial infarction (MI). In older series, the risk of thrombotic stroke was as high as 3.7%.1,2 but this has diminished in recent years, possibly related to improved reperfusion or more aggressive perinfarction antithrombotic therapy. In the GUSTO-I population, 0.6% of patients experienced ischemic stroke during hospitalization and of these, 17% died.3,4

Previous studies have found that risk factors for ischemic stroke associated with MI include large, akinetic segments of myocardium5 and the presence of left ventricular thrombus6 plus other concomitant states that predispose to stroke such as atrial fibrillation, advanced age, history of cerebrovascular disease, hypertension, diabetes mellitus, and coronary artery bypass graft surgery. In addition to these established risk factors, there are also several plausible mechanisms that may contribute to ischemic stroke after an MI. During an acute MI, there is increased activity of the coagulation cascade that may lead to enhanced platelet aggregation and activation on top of diffuse vasoconstriction from released catecholamines. Thus, this state of hypercoagulability after an MI may lead to increased thrombosis and subsequent thromboembolic events, including stroke. Emboli may come from aorta or carotid arteries or even from the left atrium or left ventricle. There is also
release of inflammatory cytokines in the vasculature after an MI. The circulatory inflammatory cytokines may then incite a cascade of events in the cerebral circulation leading to plaque rupture and thrombogenesis with resultant thromboembolic events. As evidence of this, complex and presumably unstable carotid plaques are found to be common in patients with acute coronary syndrome (42% with unstable angina versus 8% with stable angina,  \( P = 0.002 \)).

It is unknown whether the timing of revascularization, with thrombolytic therapy or angioplasty, results in a lower risk of ischemic stroke in the weeks immediately after MI. It is conceivable that early interruption of myocardial injury may attenuate thromboembolic stroke risk as a result of improved myocardial salvage and a subsequent decrease in akinetic wall segments leading to a lower likelihood of ventricular thrombus formation. Additionally, infarction itself may increase the risk of ischemic stroke independent of the ultimate postinfarct architecture and function of the left ventricle such as through endocardial inflammation. We sought to investigate the link between the duration of ischemia in patients with MI and the risk of ischemic stroke while attempting to control for the extent of MI-related myocardial damage.

Methods

The National Registry of Myocardial Infarction (NRMI) 3 and 4 registries are prospective, observational databases of patients with acute MI; the registry’s data collection process has been described elsewhere. Briefly, the NRMI database is a registry that primarily collects detailed information regarding the immediate cardiac care of patients presenting to the hospital with acute MI. Multiple data points are collected during each patient’s hospitalization, but because this is an inpatient registry, information relating to posthospital care and outcomes is not available. Stroke is defined by NRMI as “hemorrhagic,” “nonhemorrhagic,” or “unknown.” Clinical testing that allows for the diagnosis of stroke type (eg, CT, etc) is not recorded. The patients included in this study were admitted to one of 1607 participating hospitals between April 1, 1998, and January 31, 2002. Hospitals that participated in the registry enrolled all consecutive patients with MI, resulting in a total of 838 267 participants. Patients transferred into or out of a NRMI-participating center were excluded. Patients were also excluded if they had a stroke event that occurred before arrival, were missing stroke information, had a stroke classified as hemorrhagic or unknown, or were missing electrocardiographic information. After implementing exclusionary criteria, the final patient count was 455 502 patients enrolled from 1607 hospitals. In this group, 45 997 patients were treated with thrombolytic therapy (45 997) or PTCA (47 876). Ischemic stroke occurred during hospitalization in a total of 398 patients (0.42%): 248 patients (0.54%) who received thrombolytic therapy and in 150 patients (0.31%) who underwent PTCA. The characteristics of these patients are presented in Tables 1 and 2 and are well matched within all time divisions with the exceptions noted. Atrial fibrillation was present more frequently in the patients in whom primary revascularization was initiated later, although this difference was statistically significant only among those treated with PTCA.

Increase delay in revascularization was associated with an increasing incidence of ischemic stroke in both thrombolytic and angioplasty-treated patients (Figure 1). Patients who underwent revascularization with minimal delay had a significantly lower risk of stroke than those who received therapy later. This relationship remained statistically significant for all time divisions.

By multivariate analysis, thrombolytic therapy within 15 minutes of arrival in the emergency department was associated with an improvement in ischemic stroke risk compared with the group receiving therapy after 45 minutes (OR, 0.35; 95% CI, 0.14–0.88) (Figure 2). Similar therapy delivered 16 to 45 minutes into hospitalization resulted in a nonsignificant, linear trend toward diminished thrombotic stroke risk when compared with thrombolytic therapy after 45 minutes. In the subset of patients undergoing primary PTCA, the risk of stroke rose linearly as the time from presentation to first balloon inflation increased, but this trend was not statistically significant between the time interval groups in the multivariate analysis.

To determine whether the relationship between early revascularization and decrease ischemic stroke risk was associated with improved left ventricular function, several markers of infarct size were included in the multivariate analysis: the number of electrocardiographic leads with ST-segment elevation; the presence of congestive heart failure or cardio-
The pathophysiology that leads to ischemic stroke in the chronic phase is somewhat elusive. The traditional explanation for this association implicates the role of an akinetic segment of left ventricular myocardium that predisposes to mural thrombus and subsequent embolism to the cerebral circulation. This progression of events is supported mainly by the findings of smaller trials showing that the presence of ventricular mural thrombus is a marker for an increased risk of ischemic stroke along with showing that the presence of ST-segment depression, presence of left bundle branch block, cardiac catheterization; †Pearson P value; ‡119 subjects in this group.

**TABLE 2.** Clinical Characteristics of Patients Treated With Primary Percutaneous Coronary Intervention Who Experienced an Ischemic Stroke, Stratified by Time From Presentation to Initiation of Therapy

<table>
<thead>
<tr>
<th>Clinical Variable*</th>
<th>0–90 Minutes (n=25)</th>
<th>91–120 Minutes (n=29)</th>
<th>&gt;120 Minutes (n=96)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), mean</td>
<td>68.0</td>
<td>70.8</td>
<td>68.6</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>40.0</td>
<td>38.0</td>
<td>52.0</td>
<td>NS</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>8.0</td>
<td>17.2</td>
<td>16.7</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>28.0</td>
<td>65.5</td>
<td>64.6</td>
<td>0.030</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>72.0</td>
<td>65.5</td>
<td>64.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>32.0</td>
<td>17.4</td>
<td>38.5</td>
<td>NS</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>40.0</td>
<td>17.2</td>
<td>14.6</td>
<td>0.016</td>
</tr>
<tr>
<td>Prior congestive heart failure, %</td>
<td>0.0</td>
<td>17.2</td>
<td>3.1</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST elevation, %</td>
<td>88.0</td>
<td>89.7</td>
<td>61.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Leads with ST elevation, mean</td>
<td>3.8</td>
<td>4.0</td>
<td>3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior infarct, %</td>
<td>32.0</td>
<td>55.2</td>
<td>43.8</td>
<td>NS</td>
</tr>
<tr>
<td>Inferior infarct, %</td>
<td>64.0</td>
<td>44.8</td>
<td>39.6</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral infarct, %</td>
<td>20.0</td>
<td>20.7</td>
<td>17.7</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>0.0</td>
<td>27.6</td>
<td>29.2</td>
<td>0.009</td>
</tr>
<tr>
<td>Cardiogenic shock, %</td>
<td>20.0</td>
<td>20.7</td>
<td>17.7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>84.0</td>
<td>93.1</td>
<td>87.5</td>
<td>NS</td>
</tr>
<tr>
<td>Heparin, %</td>
<td>96.0</td>
<td>86.2</td>
<td>83.3</td>
<td>NS</td>
</tr>
<tr>
<td>GP Iib/IIa inhibitor, %</td>
<td>68.0</td>
<td>65.5</td>
<td>67.7</td>
<td>NS</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor, %</td>
<td>20.0</td>
<td>20.7</td>
<td>16.7</td>
<td>NS</td>
</tr>
<tr>
<td>β blocker, %</td>
<td>60.0</td>
<td>65.5</td>
<td>59.4</td>
<td>NS</td>
</tr>
<tr>
<td>Intraaortic balloon pump, %</td>
<td>20.0</td>
<td>34.5</td>
<td>25.0</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery, %</td>
<td>16.0</td>
<td>13.8</td>
<td>18.6</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Discharge</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction &lt;0.40, %</td>
<td>16.0</td>
<td>27.6</td>
<td>33.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Not listed here, but also included in the multivariate analysis, were the following variables: presence of ST-segment depression, presence of left bundle branch block, cardiac catheterization; †Pearson P value; ‡119 subjects in this group.

NS indicates not significant.

of these clear risk factors, the relationship between acute MI and subsequent development of ischemic stroke is somewhat elusive. The traditional explanation for this association implicates the role of an akinetic segment of left ventricular myocardium that predisposes to mural thrombus and subsequent embolism to the cerebral circulation. This progression of events is supported mainly by the findings of smaller trials showing that the presence of ventricular mural thrombus is a marker for an increased risk of ischemic stroke along with studies that strengthen the association between low EF and stroke in the chronic phase. Anticoagulation after MI reduces the chance of ischemic stroke, but it is not known if this intervention decreases stroke rate solely by...
diminishing the likelihood of the formation of mural thrombus or by limiting its embolic potential.

Our data suggest that the risk of thromboembolic stroke increases linearly with prolonged myocardial ischemia and that this risk seems to persist regardless of the extent of myocardial damage. Early revascularization, whether by thrombolytic therapy or PTCA, confers protection against the development of ischemic stroke during the index hospitalization. The relationship between delay in revascularization and ischemic stroke appears to be independent of size of infarction, the presence or absence of shock or congestive heart failure, and EF seen at time of discharge and therefore invokes the possibility of a mechanism for stroke risk that does not depend on ventricular structure. We note that an infarction of the inferior wall of the ventricle was far more common in the 0- to 15-minute thrombolytic group, but this factor was considered in the multivariate analysis and seemed to not affect the predictive power of early thrombolytic therapy on stroke risk.

The earliest therapy with a thrombolytic agent appears to confer the greatest relative advantage in stroke prevention. This is likely the result of the very rapid reperfusion attendant with aggressive thrombolytic therapy and is not related to any direct effect of the drug on inhibition of cerebral thromboembolism. If the latter were true, we would observe a lower stroke rate among patients receiv-
ing thrombolytic therapy across all intervals of time to treatment (Figure 1).

Myocardial infarction is known to accompany a diffuse hematologic milieu of enhanced thrombosis and amplified inflammatory mediators. It is conceivable that ischemia itself induces a systemic procoagulant effect, thereby facilitating thrombus formation and embolization from the aorta or carotid arteries, or even from the left ventricle (irrespective of the degree of sustained wall motion abnormality). In patients with acute coronary syndromes—but not in patients with stable coronary disease—markers of a hypercoagulable state such as prothrombin fragment 1+2 and fibrinopeptide A become elevated and remain so for months.

Alternatively, ischemia may provoke the release of inflammatory cytokines that trigger the destabilization and rupture of plaques in the remote cerebral circulation. Even short periods of ischemia are adequate to stimulate the activation of neutrophils and the synthesis of acute phase reactants. In unstable angina, the presence of diffuse inflammation of the coronary vasculature has been suggested by the finding of diminished neutrophil myeloperoxidase in serum samples extracted remote to the affected coronary segment. Acute mediators of inflammation may serve as both markers of plaque instability and propagators of it. C-reactive protein has been shown to exhibit both a procoagulant effect—by stimulating PAI-1 expression and tissue factor expression—and a direct proinflammatory effect. Serum C-reactive protein levels rise in response to myocardial injury to a degree that is attenuated by early patency of the infarct related artery. Direct evidence that hematologic factors stimulated by ischemia or injury have a direct bearing on endothelial structure is suggested by the finding of diffuse plaque instability in remote coronary segments of patients with acute MI and the presence of multiple fissured, complex plaques in patients with non-ST-elevation acute coronary syndromes. Consideration should be given to the possibility that enhanced thrombotic tendency or diffuse intravascular inflammation contribute to thrombus formation inside or outside the ventricular cavity with subsequent cerebral embolization or rupture of a vulnerable plaque in the remote cerebral circulation and that these dynamic factors are potentiated by progressively longer periods of myocardial ischemia.

**Limitations**

Despite the large number of patients in the NRMI databases, the absolute number of patients in this analysis who underwent primary revascularization and subsequently suffered ischemic stroke is relatively small with a combined total of only 398. Further subdivision into intervals of treatment delay results in the small sample sizes noted in this analysis and constitutes the chief weakness of this study.

We used surrogate features—such as the degree of ST-segment elevation on electrocardiogram, the presence of shock, and the ventricular EF on hospital discharge—to estimate the extent of myocardial injury. A more ideal measure would be the absolute value of cardiac-specific enzyme elevation, but this information was not available as part of the NRMI databases we queried. However, a close correlation has been shown to exist between the number of leads exhibiting ST-segment elevation and total serum creatine kinase in acute MI.

The NRMI databases provide only limited information regarding our main end point: stroke. We are unable to elucidate how the diagnosis was made in each instance (clinically, CT, other imaging, etc), the location and extent of the stroke, and what type of therapies were used in response to the cerebral event. Finally, the NRMI databases tracks the hospital phase of care only. The details of long-term, out-of-hospital events and treatments are not available.

**Conclusion**

The risk of ischemic stroke with acute MI appears to be at least partly related to the time from initial presentation to primary revascularization therapy both in patients undergoing PTCA and in those receiving thrombolytic therapy. Early thrombolytic therapy is strongly independently predictive of a lower risk of ischemic stroke regardless of the ultimate degree of ventricular myocardial preservation.

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**Disclosures**

None.

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