Treatment and Outcome of Patients With Acute Myocardial Infarction and Prior Cerebrovascular Events in the Thrombolytic Era

The Israeli Thrombolytic National Survey

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Background: Patients with a history of stroke presenting with acute myocardial infarction (MI) are often excluded from thrombolytic therapy owing to fear of intracranial hemorrhage. Few data, however, are available on the risks vs the benefits of thrombolysis in patients with an acute MI and a prior cerebrovascular event (PCE).

Methods: Data were derived from 2 nationwide surveys of 2012 consecutive patients with acute MI admitted to all 25 coronary care units in Israel during 1992 and 1994. Thrombolytic therapy was given to patients with a PCE at the discretion of the treating physicians. Outcomes were compared between patients with an acute MI with and without a PCE and between patients with a PCE treated with or excluded from thrombolysis.

Results: Patients with a PCE (n=115 [6%]) were older, with higher rates of atherosclerotic risk factors and in-hospital complications than their counterparts without a prior event (n=1897). They were treated less often with thrombolysis (n=1897). They were treated less often with thrombolysis than their counterparts without a prior event (n=46). In-hospital intracranial hemorrhage did not occur in either group. The 1-year mortality rates were 2-fold higher among patients who had not undergone thrombolysis compared with those who had (33% vs 18%; adjusted hazard ratio, 2.44; 95% confidence interval, 0.78-7.64).

Conclusions: These findings, derived from 2 nationwide surveys of consecutive patients with acute MI, suggest that patients with PCEs have an adverse outcome attributable to their older age and less favorable risk profile. Thrombolytic therapy, however, based on our preliminary data, may be beneficial in selected patients with an acute MI with a nonrecent PCE.

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SUBJECTS AND METHODS

The Israeli Thrombolytic National Survey included 2012 consecutive patients with a confirmed acute MI admitted to all 25 operating coronary care units in Israel during 2-month periods (January and February) in both 1992 (n=1012) and 1994 (n=1000). In 1992, the coronary care units followed uniform guidelines for thrombolytic treatment as participants in the International Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial. The survey included all patients who had an acute MI (n=1012), regardless of their status in the GUSTO trial, including those treated by thrombolysis outside the GUSTO protocol. In 1994, none of the coronary care units participated in a thrombolytic or reperfusion randomized study. Thus, thrombolytic therapy and invasive procedures were used at the discretion of each center, and the main thrombolytic agent administered was streptokinase (in 85% of cases).

The diagnosis of acute MI was based on the presence of 2 of the following: typical chest pain lasting at least 30 minutes, unequivocal new electrocardiographic changes (Q/QS- and/or ST-segment and T-wave changes), an increase in at least 2 of the serum cardiac enzyme levels (creatine kinase, aspartate aminotransferase, and lactate dehydrogenase) to more than 1.5 times the upper limit, or a concomitant increase in the creatine kinase MB isoenzyme level. Demographic and clinical data were systematically collected for all patients with acute MI.

A history of stroke or TIA was reported by study physicians, based on patients’ reports and available clinical data at the time of hospitalization. Thrombolytic therapy was given to patients with a PCE at the discretion of the treating physicians. Data regarding the timing of the PCE and whether it was clinically a stroke or a TIA were systematically collected from the discharge records or the hospital charts and were available for 80% of patients. Data on brain imaging of the PCE or its severity were not available.

Among the patients who were treated with thrombolysis, the PCE was a stroke in 80% and a TIA in 20%, while all PCEs leading to exclusion from thrombolysis were strokes. The distribution of the timing of the cerebrovascular events prior to the index MI was comparable. The PCE occurred in the year prior to the index MI in 19% of the thrombolysis-treated patients vs 18% of the patients excluded from thrombolysis. The minimal period prior to the index MI was 3 weeks for a minor stroke (and 1 week for a TIA) among the patients treated with thrombolysis, compared with 2 weeks among the patients excluded from thrombolysis. Streptokinase was the thrombolytic agent used among patients with PCEs.

Cases of stroke complicating the index acute MI were reported by study physicians within each coronary care unit. The 1-year postdischarge mortality rates were assessed from the medical charts and by matching the identification number of patients with the Israeli National Population Registry. Characteristics, management, and outcome were compared between the patients with an acute MI and a PCE and those with an acute MI but no PCE. A further comparison was made between the patients with an acute MI and the patients (6%) with acute MI. The clinical characteristics, in-hospital complications, and procedures of patients with and without PCEs are presented in Table 1. Patients with PCEs were on average 5 years older, had hypertension, diabetes mellitus, and prior MI more frequently, but were cigarette smokers less frequently than patients with acute MI and no PCE. During hospitalization, the patients with
PCEs developed slightly more congestive heart failure or pulmonary edema and, twice as often, paroxysmal atrial fibrillation. Stroke complicating the index acute MI occurred in 3 patients with PCE (2.6%), compared with 12 patients without such a prior event (0.6%) (P = .05).

Patients with a history of PCEs received thrombolysis less often than their counterparts without a history of PCEs (25% vs 46%; P = .001). Other reperfusion therapies, ie, coronary angioplasty and coronary artery bypass surgery, were also used less frequently in these patients (8% vs 14%; P = .05), and coronary angiography was performed less often (14% vs 26%; P = .003). Aspirin and anticoagulation were used at similar rates in both groups (Table 1).

The 30-day and 1-year mortality rates were higher among patients with a PCE (Table 2). After adjustment for age and other clinical characteristics, the excess mortality, however, vanished. The adjusted HR for 1-year mortality following acute MI, after adjustment for clinical characteristics, reperfusion therapy, and in-hospital complications (see the “Subjects and Methods” section) among patients with a PCE compared with those without was 1.08 (95% CI, 0.75-1.55). The adjusted survival curves of patients with and without PCEs are depicted in Figure 1. The differences in 1-year mortality rates between groups were also not evident in a model that was adjusted for age and clinical characteristics (adjusted HR, 1.13; 95% CI, 0.78-1.63).

**COMPARISON BETWEEN THROMBOLYSIS- AND NON–THROMBOLYSIS-TREATED PATIENTS**

Twenty-nine (25%) of 115 patients with PCEs were treated with thrombolysis (all received streptokinase) and were compared with 46 patients found ineligible for thrombolysis (all received streptokinase) and were excluded from thrombolysis because of their PCE (n = 46). Other reperfusion therapies, ie, coronary angioplasty and coronary artery bypass surgery, were also used less frequently in these patients (8% vs 14%; P = .05), and coronary angiography was performed less often (14% vs 26%; P = .003). Aspirin and anticoagulation were used at similar rates in both groups (Table 1).

A comparison of the baseline characteristics and in-hospital complications of patients with an acute MI and a PCE who were treated with thrombolysis (n = 29) and those excluded from thrombolysis because of their PCE (n = 46) is given in Table 3. The patients who were treated with thrombolysis tended to be older (mean age, 72 vs 66 years) with anterior wall infarcts twice as often. Rates of in-hospital complications in both groups were comparable. The patients who were treated with thrombolysis were more often also treated with aspirin (76% vs 57%), anticoagulants (72% vs 39%), and β-blockers (52% vs 13%) (Table 4). No cases of intracranial hemorrhage occurred among the 115 patients with PCEs. One episode of ischemic stroke occurred among the patients treated with thrombolysis (n = 29), as well as 1 among patients excluded from thrombolysis because of their PCE (n = 46) and 1 among those excluded for other reasons (n = 40).

Early (7-day) mortality rates were comparable in both groups, while 30-day mortality rates were higher among the patients who were excluded from thrombolysis.
The present study, based on 2 nationwide surveys of consecutive patients with acute MI admitted to all coronary care units in Israel, assesses the treatment and outcome of patients with PCEs in clinical practice. The main findings of this study are (1) patients with an acute MI and a PCE also had a substantially higher rate of recurrent stroke complicating their acute MI, and no increase in the proportion of hemorrhagic vs ischemic stroke was found.15 In unselected cohorts of patients with acute MI, the prevalence of silent cerebral infarcts is expected to be substantially higher. The vast majority of strokes, especially among patients with coronary heart disease, are ischemic in origin.20 Indeed, cerebral infarction and MI share common risk factors and common pathophysiologic antecedents, atherosclerosis, and thrombus formation.

Patients with PCEs have a higher risk of sustaining a recurrent stroke during their index MI.27,28 In the present study, we found that patients with PCEs have a worse outcome after acute MI, but this is ascribed mainly to their older age and less favorable risk profile. The frequency of stroke during the index hospitalization is 4-fold higher among patients with PCEs. In the GUSTO megatrial, patients with PCE also had a substantially higher rate of recurrent stroke complicating their acute MI, and no increase in the proportion of hemorrhagic vs ischemic stroke was found.15

Reports from unselected cohorts of patients with acute MI suggest that patients with PCEs receive less aggressive treatment after acute MI. Thrombolytic was less likely to be used in patients with a history of stroke, even if the stroke occurred more than 3 months prior to their index MI.8,9,20,29,30 Our results from 2 national surveys concur with these findings and demonstrate that these patients are also less likely to receive alternative reperfusion therapies (coronary angioplasty or coronary artery bypass surgery).

Early recommendations from the National Institutes of Health Consensus Conference on Thrombolytic Treatment included withholding thrombolyis only if a stroke occurred within 2 months prior to the index MI.29 Recent guidelines, however, are more stringent.18,19,30 In the guidelines on the management of acute MI from the European Society of Cardiology, prior stroke is considered a contraindication to thrombolytic therapy, and a TIA in the preceding 6 months a relative contraindication.18 In recent guidelines from the American College of Cardiology and the American Heart Association for the treatment of patients with an acute MI, cerebrovascular events within 1 year are considered as absolute contraindications for thrombolytic therapy, whereas other PCEs are considered relative contraindications, and thrombolytic therapy should be administered with caution.30 Pre-

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**Table 3. Baseline Characteristics and Hospital Course of Patients With Acute Myocardial Infarction (MI) With Prior Cerebrovascular Events, Treated With or Excluded From Thrombolytic Therapy Owing to Their Prior Event**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Thrombolytic Therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=29)</td>
<td>No (n=46)</td>
</tr>
<tr>
<td>Men</td>
<td>22 (76)</td>
<td>34 (74)</td>
</tr>
<tr>
<td>Age, mean (±SD); y</td>
<td>72±10</td>
<td>66±10</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (24)</td>
<td>19 (41)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (59)</td>
<td>29 (63)</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (24)</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>10 (34)</td>
<td>17 (37)</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>25 (86)</td>
<td>36 (78)</td>
</tr>
<tr>
<td>Anterior site MI</td>
<td>19 (66)</td>
<td>14 (30)</td>
</tr>
<tr>
<td>In-hospital complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killip class 2 or more on admission</td>
<td>11 (38)</td>
<td>19 (41)</td>
</tr>
<tr>
<td>CHF/PE</td>
<td>6 (21)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>4 (14)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>3 (10)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (3)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*Values are presented as number (percentage) unless otherwise indicated. CHF/PE indicates congestive heart failure or pulmonary edema.*

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**Table 4. Treatment of Patients With Acute Myocardial Infarction With Prior Cerebrovascular Events, Treated With or Excluded From Thrombolytic Therapy Owing to Their Prior Event**

<table>
<thead>
<tr>
<th>Thrombolytic Therapy</th>
<th>Yes (n=29)</th>
<th>No (n=46)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>22 (76)</td>
<td>26 (57)</td>
<td>.99</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>21 (72)</td>
<td>18 (39)</td>
<td>.005</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>15 (52)</td>
<td>6 (13)</td>
<td>.001</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>4 (14)</td>
<td>11 (24)</td>
<td>.29</td>
</tr>
<tr>
<td>Digitalis</td>
<td>4 (14)</td>
<td>2 (4)</td>
<td>.20</td>
</tr>
<tr>
<td>Nitrates</td>
<td>22 (76)</td>
<td>29 (63)</td>
<td>.25</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>10 (34)</td>
<td>20 (43)</td>
<td>.44</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>4 (14)</td>
<td>6 (13)</td>
<td>.93</td>
</tr>
</tbody>
</table>

*Values are presented as number (percentage). ACE indicates angiotensin-converting enzyme; β-blockers, β-adrenergic blocking agents.*

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**Figure 1. Survival curves of patients with and without prior cerebrovascular events, adjusted for age, sex, diabetes, hypertension, anterior site myocardial infarction, prior myocardial infarction, congestive heart failure or shock, paroxysmal atrial fibrillation, and reperfusion therapy (thrombolysis, coronary angioplasty, and coronary artery bypass grafting). Adjustment was done using the Cox proportional hazard model (SAS PHREG procedure, SAS Institute Inc, Cary, NC).**
vious hemorrhagic stroke at any time is an absolute contraindication for thrombolytic therapy in all guidelines.

The reason for excluding patients with a prior stroke from thrombolytic therapy is fear of an intracranial hemorrhage. However, evidence-based data are scarce regarding the treatment of patients with prior ischemic strokes who present with an acute MI, as patients with a history of stroke are mostly excluded from clinical trials.31-33 Patients with PCEs in the 6 months preceding their index acute MI were excluded from the Thrombolysis in Myocardial Infarction Phase II Pilot and Clinical Trial,31 which involved treatment with high doses (150 mg) of tissue plasminogen activator. In an early phase of the study, since 3 (10%) of 30 patients with a history of TIA, stroke, or other neurological disease had intracerebral hemorrhages, compared with 8 (1.2%) of 639 without such a history, the protocol was changed to make all patients with a history of PCEs ineligible for the study. On the other hand, in the Thrombolysis in Myocardial Infarction Study Group experience, no strokes occurred among the 18 patients with PCEs who were given tissue plasminogen activator (all more than 6 months prior to the index MI).12 Data from the large thrombolytic trials for acute MI demonstrate that treatment with tissue plasminogen activator is associated with a higher risk of intracranial hemorrhage than treatment with streptokinase.45

In the absence of data from randomized trials, observational data can be used to supplement our knowledge on the risks vs the benefits of treating patients with PCE with thrombolysis. In the present national survey, none of the 29 patients with PCEs treated with thrombolysis (streptokinase) experienced an intracranial hemorrhage. Moreover, 1-year mortality rates were almost half among patients treated with thrombolysis compared with those who were not treated with thrombolysis, even though these patients tended to be older, with large anterior wall infarcts. These preliminary results suggest that patients with a history of nonrecent ischemic stroke should not be categorically excluded from thrombolytic therapy.

Early thrombolytic therapy (intravenous tissue plasminogen activator administered within 3 hours) was also shown to improve outcome after acute ischemic stroke.34 Patients presenting with a hyperacute ischemic stroke should be considered for thrombolysis, according to the recent recommendation of the American Heart Association Stroke Council, if they have a more than 3-month-old history of prior ischemic stroke.35 Indeed, the pathological evolution of a cerebral infarction reaches its end stage within 3 or 4 months,36 suggesting that the main increased risk of hemorrhage may be within this time frame.

Since the study is based on national surveys, it represents the clinical practice in the different coronary care units at that period, and the decision to use thrombolysis was not randomized but made at the treating physicians’ discretion. In the absence of randomized trial data, however, valuable information can be drawn from observational data. We collected data on the timing of the PCE and whether it was clinically a stroke or a TIA to try to overcome possible bias in selection for treatment. Given the nature of such a survey and the number of patients with PCE and their profiles, we could not assess the risk of intracranial bleeding associated with thrombolytic therapy for different time points of the PCE.

Our findings suggest that thrombolytic therapy may be beneficial in selected patients with a PCE who present with an acute MI. Thus, patients with a PCE should not categorically be excluded from thrombolytic therapy. Careful individual assessment of potential benefits vs risks should guide decisions regarding therapy. Extensive evaluation of patients with acute stroke, including brain imaging and a variety of ancillary tests, is becoming widespread. Therefore, data on the type and severity of a prior stroke in patients presenting with an acute MI should be part of any subsequent prospective studies. Future studies are needed to assess in which circumstances alternative therapies should be used among patients with a history of stroke who present with an acute MI.
The Israeli Thrombolytic National Survey Group

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