Prognosis After Transient Ischemic Attack and Ischemic Stroke in Young Adults

José M. Ferro, MD; Manuela Crespo, MD

Background and Purpose  We undertook this study to describe the risk of stroke recurrence and functional and occupational status in the long-term follow-up of young adults with ischemic strokes and to identify possible predictors for stroke recurrence, disability, and working status.

Methods  A cohort of 215 patients aged ≤45 years with ischemic cerebral events (43 transient ischemic attacks, 135 minor strokes, 37 major strokes), evaluated at our institution from May 1985 through March 1992, was followed for a mean of 43.1 months (SD, 39.7 months; range, 1 to 228 months). Information on death and recurrent cerebral vascular events, functional disability (Rankin Scale), retirement, and working status was obtained from direct observation, mail questionnaire, and telephone interviews.

Results  Four patients (2%) with major strokes died acutely. Information on stroke recurrence and disability was available for 184 (87%) of the survivors and on retirement and working status for 140 (67%) of the patients. Two patients died from cancer. Seven transient ischemic attacks and eight strokes (two hemorrhagic) occurred during follow-up. Patients with strokes of unknown cause experienced no recurrent strokes, contrasting with two deaths and eight strokes in those whose stroke cause was identified (difference between proportions: 8%; 95% confidence interval, 3 to 13). Eighty-eight patients had a complete recovery, and only 21 were disabled (Rankin grades 4 or 5). Logistic regression analysis identified the severity of the initial stroke (Rankin grade >3) as the only significant predictor of disability (odds ratio, 10.7; 95% confidence interval, 0.8 to 3.4). The majority of patients return to an active professional life. Severity of the initial stroke is the major predictor of independence. The relation between disability and return to work or retirement is less clear. (Stroke. 1994;25:1611-1616.)

Key Words  • cerebral ischemia • prognosis • young adults

May 1985 through March 1992, demographic and clinical data and results of ancillary procedures were registered on a standard form and stored on a database. Etiologic investigation was pursued following the usual guidelines. Brain imaging was obtained by computed tomography (CT) or magnetic resonance imaging (MRI). Duplex/transcranial Doppler sonography and/or angiography were used to investigate extracranial and intracranial vessel disease, while transthoracic and more recently transesophageal echocardiograms were performed to rule out a cardiac source of emboli. When these investigations were negative, immunologic, hematologic (including proteins C and S, antithrombin III, lupus anticoagulant, and anticardiolipin antibodies), syphilis, and other serologies or appropriate tests to identify rare causes of stroke were carried out.

Functional disability was graded following the modified Rankin Scale at both (1) discharge from acute hospitalization or at the first outpatient visit and (2) the last follow-up. Strokes were classified as minor if the Rankin grade was ≤3 and as major if Rankin grade was >3.

Follow-up  For patients that were regularly followed at our outpatient clinic, follow-up data was obtained from direct observation and chart review. During 1993 a mail questionnaire and telephone interviews were used to obtain information from the remaining patients. We specifically collected the following data: (1) number and dates of any of the following events: death, stroke, transient ischemic attack (TIA), and myocardial infarction (all patients who reported new vascular events were reexamined, and CT was repeated, if they had not been admitted to our department in the acute phase); (2) functional disability (modified Rankin Scale); and (3) occupational status, categorized as workers (subjects having a part- or full-time job) or unemployed.
TABLE 2. Young Adults With Ischemic Cerebral Vascular Events Examined From May 1985 Through March 1992

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>n (%)</th>
<th>Type of Stroke</th>
<th>Follow-up</th>
<th>Type of Study</th>
<th>Events During Follow-up (%)</th>
<th>Disability Score</th>
<th>Assessment of Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells and Timberger</td>
<td>1</td>
<td>77</td>
<td>I ?</td>
<td>1-30 mo</td>
<td>Retrospective</td>
<td>10</td>
<td>4</td>
<td>?</td>
</tr>
<tr>
<td>Haerer and Smith</td>
<td>2</td>
<td>207*</td>
<td>I+H</td>
<td>1-5.5 y</td>
<td>Retrospective</td>
<td>14-48%</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Abraham et al</td>
<td>3</td>
<td>110</td>
<td>I+H</td>
<td>1-50 mo</td>
<td>Prospective</td>
<td>11</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Hindfelt and Nilsson</td>
<td>4</td>
<td>60</td>
<td>I ?</td>
<td>51 mo</td>
<td>Prospective</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hindfelt and Nilsson</td>
<td>5</td>
<td>74</td>
<td>I ?</td>
<td>13-26 y</td>
<td>Prospective</td>
<td>12</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Grindal et al</td>
<td>6</td>
<td>34</td>
<td>I</td>
<td>2.7 y</td>
<td>Retrospective</td>
<td>3</td>
<td>7</td>
<td>?</td>
</tr>
<tr>
<td>Snyder and Ramirez-Lassepas</td>
<td>7</td>
<td>52</td>
<td>I</td>
<td>2.4-3 y</td>
<td>Retrospective</td>
<td>4</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Marshall</td>
<td>8</td>
<td>189*</td>
<td>I</td>
<td>Up to 15 y</td>
<td>Consecutive cases</td>
<td>6</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Srinivasan</td>
<td>9</td>
<td>46</td>
<td>I ?</td>
<td>2 y</td>
<td>Retrospective</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Bogousslavsky and Regli</td>
<td>10</td>
<td>38</td>
<td>I</td>
<td>48 mo</td>
<td>Consecutive cases</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Chancellor et al</td>
<td>11</td>
<td>59</td>
<td>I</td>
<td>36 mo</td>
<td>Retrospective</td>
<td>...</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lanzino et al</td>
<td>12</td>
<td>155*</td>
<td>I</td>
<td>5.8 y</td>
<td>Prospective</td>
<td>4</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Matjas-Guiu et al</td>
<td>13</td>
<td>386</td>
<td>I</td>
<td>34.1 mo</td>
<td>Prospective</td>
<td>12</td>
<td>64</td>
<td>...</td>
</tr>
<tr>
<td>Leno et al</td>
<td>14</td>
<td>81</td>
<td>I+H</td>
<td>1 y</td>
<td>Prospective</td>
<td>2</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Ref indicates reference; TIA, transient ischemic attack; I, ischemic; H, hemorrhagic; and ADL, activities of daily living.
*Includes TIAs (78*, 70*, 154:).
†Fatal strokes only.
‡Depending on the diagnosis.
§Includes mild disability.

Results

Description of the Assembled Cohort

During the study period (May 1985 through March 1992) 215 young adults (119 men, 96 women) with ischemic cerebral vascular accidents (Table 2) were examined in our unit. One hundred seventy-two were first-ever strokes, whereas 22 had been preceded by TIA, and 17 were recurrent strokes. Thirty patients were less than 30 years of age, 84 were between 31 and 40 years, and 101 were between 41 and 45 years of age.

Distribution of risk factors was as follows: hypertension, 82 (38%); diabetes, 13 (6%); current smokers, 86 (40%); hyperlipidemia, 64 (29%); alcohol abuse, 25 (11%); hematocrit ≥50%, 18 (8%); known cardiac disorders, 17 (8%); migraine, 27 (13%); and current or recent use of birth control pills, 18 (19% of the women). CT (198 cases) or MRI (16 cases) were performed in 214 patients. Duplex was performed in 88, transcranial Doppler in 24, and angiography in 134 (62%). Transforaminal echocardiogram was performed in 151 (70%) and transesophageal echocardiogram in 14 patients. Forty-five (21%) patients were classified as having stroke of nonspecified cause, and 27 patients (12%) were categorized as having stroke of unknown cause.

The more commonly identified etiologies were cardioembolic, 39 (19%); large-artery atheromatous disease (either extracranial, 18 [8%]; intracranial, 10 [5%]; or both, 5 [2%]); single-perforator disease, 22 (10%); multiple causes, 7 (3%); dissection, 16 (7%); arteritis, 10 (5%); hematologic disorder, 2 (1%); and other rare conditions, 14 (7%).

TABLE 2. Young Adults With Ischemic Cerebral Vascular Events Examined From May 1985 Through March 1992

<table>
<thead>
<tr>
<th>Type of Stroke</th>
<th>n (%)</th>
<th>Acute Death</th>
<th>Lost to Follow-up</th>
<th>Follow-up (%)</th>
<th>Death</th>
<th>Stroke (%)</th>
<th>TIA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>43 (20)</td>
<td>...</td>
<td>4</td>
<td>38 (88)</td>
<td>...</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>125 (63)</td>
<td>1 (1)</td>
<td>18</td>
<td>120 (90)</td>
<td>2 (2)</td>
<td>5 (5)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Major stroke</td>
<td>37 (17)</td>
<td>3 (6)</td>
<td>5</td>
<td>29 (85)</td>
<td>...</td>
<td>2 (7)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Total</td>
<td>215</td>
<td>4 (2)</td>
<td>27 (13)</td>
<td>184 (87)</td>
<td>2 (1)</td>
<td>8 (5)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.
Patients With Transient Ischemic Attacks at Inclusion

Six TTAs and seven recurrent strokes (six infarcts, one hemorrhage) occurred. One patient had both a TIA and a stroke. No myocardial infarction was reported.

Of the 7 patients who had strokes on follow-up, 3 were hypertensive, 4 were current smokers, 2 had hyperlipidemia, 1 had a hematocrit >50%, 2 abused alcohol, and 1 woman was taking birth control pills. Two patients had bilateral atheromatous carotid disease (carotid occlusion followed 19 months later by contralateral carotid thrombosis, bilateral carotid stenosis), 2 had a cardiac embolic condition (redundant mitral valve prolapse, large patent foramen ovale), 2 had arteritis (Behcet's disease, isolated central nervous system arteritis), and 1 had a lacunar infarction due to single-perforator disease and suffered a hemorrhagic stroke during follow-up.

Overall, patients with TIA and strokes of unknown cause experienced no serious events (only one TIA) contrasting with two deaths and eight strokes in those whose stroke cause was identified (difference between proportions: strokes or death, 8%; 95% CI, 3 to 13; any event including TIAs, 10%; 95% CI, 2 to 18). In part due to the small number of events, the log-rank comparison of curves for survival free of recurrent stroke showed no significant differences between patients with known versus unknown etiology ($\chi^2=2.55; P=.11$) or those with and without risk factors ($\chi^2=0.99; P=.32$) or between subjects with first-ever strokes and recurrent strokes at inclusion ($\chi^2=0.26; P=.60$). However, univariate Cox regression analysis showed that the risk of recurrence was significantly higher for strokes of identified etiology (coefficient $34.5$), and none of the other predictors significantly improved a multiple regression model of recurrence including only that variable.

Functional Recovery

At the end of the follow-up, 88 patients had a complete recovery, and only 21 were disabled (Rankin grade 4 or 5). Of those disabled, 13 had been included as major strokes and 7 as minor strokes. One patient had a TIA at inclusion but suffered a major stroke during follow-up. Disability at follow-up was more common among those included as major strokes (major stroke versus minor stroke/TIA, $\chi^2=31; P<.0001$).

In univariate logistic analysis (Table 3) severity at onset was the only significant predictor of disability (constant, −4; coefficient, 2.37). In multivariate analysis the introduction of any of the other three variables or their combinations did not improve the model including only severity at onset as predictor of disability at follow-up.

Occupational Status

At the end of the follow-up, 73% of the survivors were active (including full- or part-time workers, housewives, and students) (Table 4). Of the 25 patients who retired, 19 (76%) did so between the second and sixth year poststroke (the minimal bureaucratic delay for retirement due to illness is 2 years), and 6 (14%) retired between the sixth and the tenth year. Retirement was significantly more common among those drinking more than 60 g/d of alcohol ($\chi^2=5.62; P=.02$), among men (19/72; $\chi^2=6.09; P=.01$), among those with major strokes ($\chi^2=9.08; P=.003$), and patients still disabled at follow-up ($\chi^2=6.94; P=.008$).

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### Prospective Study

Four (2%) major stroke patients died acutely. Three had massive hemispheric infarcts, 1 due to carotid dissection, 1 on the first day before relevant etiologic information could be gathered, and 1 with both an appropriate carotid stenosis and a ventricular segmental akinesia due to an old myocardial infarction. The fourth death was due to brain stem infarction secondary to verteobasilar dissection.

Information on follow-up was available for 184 (87%) of the survivors. Follow-up information was obtained by direct observation in 79 and by mail or telephone interview in 106. Twenty-seven (13%) had moved to an unknown address and could not be reached by telephone. Mean duration of follow-up was 43.1 months (SD, 39.1 months; range, 1 to 228 months). Reliable information on occupational status and retirement could be gathered in only 140 (66%) of the subjects because some patients refused to answer those items, could not be reached, or had unknown address and could not be reached by telephone. Mean duration of follow-up in those with and without follow-up information had similar age (mean age: with follow-up, 37 years; without, 38 years) and sex (men/women: with follow-up, 2 years and 2 months after the initial TIA. The patient who suffered the hemorrhage was included because of a "lacunar" TIA (pure motor defect and appropriate lacune on CT).

### Recurrent Events

#### Patients With Transient Ischemic Attacks at Inclusion

Follow-up data (mean, 33.4 months; SD, 28.3 months; range, 1 to 143 months) was available for 38 of the 43 TIA subjects. Only 2 subjects experienced recurrent events: one hemorrhagic stroke and one TIA, respectively, 2 years and 2 months after the initial TIA. The patient who suffered the hemorrhage was included because of a "lacunar" TIA (pure motor defect and appropriate lacune on CT).

#### Patients With Stroke at Inclusion

Two patients died from cancer during follow-up. Only six TTAs and seven recurrent strokes (six infarcts, one hemorrhage) occurred. One patient had both a TIA and a stroke. No myocardial infarction was reported.

Of the 7 patients who had strokes on follow-up, 3 were hypertensive, 4 were current smokers, 2 had hyperlipidemia, 1 had a hematocrit >50%, 2 abused alcohol, and 1 woman was taking birth control pills. Two patients had bilateral atheromatous carotid disease (carotid occlusion followed 19 months later by contralateral carotid thrombosis, bilateral carotid stenosis), 2 had a cardiac embolic condition (redundant mitral valve prolapse, large patent foramen ovale), 2 had arteritis (Behcet's disease, isolated central nervous system arteritis), and 1 had a lacunar infarction due to single-perforator disease and suffered a hemorrhagic stroke during follow-up.

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incidence between 0.7% and 1.8%. These discrepancies range from 1.7% to 20.6%, and the recurrent stroke death rate ranges from 2.6% to 12%, the annual death rate between 0.7% and 12%, the recurrent stroke incidence between 0.7% and 1.8%. These discrepancies are related mainly to methodological differences: age limits for inclusion, type, setting and geographic location of the studies, and length of follow-up. Some studies were undertaken in the pre-CT era. In other series CT and/or MRI were not performed in all cases. Some series included both infarcts and hemorrhages. The prognosis of hemorrhage in the young adult should be studied separately because these patients have a higher mortality and a worse functional prognosis than those with infarcts. Long-term stroke prognosis can be adversely influenced if a series is biased toward systemic causes of stroke or includes many cases of valvular rheumatic heart disease. In our study there were only five cases of valvular rheumatic heart disease.

Information on the prognosis of TIA in young adults is scarce. In our series of 38 TIA's, the prognosis was benign. This agrees with the reports of Levy, Tippin et al, and Johnson and Skre, who followed young adults who experienced a transient central nervous system deficit, amaurosis fugax, and presumed TTAs from a population screening, respectively. The high rate of recurrence (5%) found by Marshall is probably due to a referral bias because in England many stroke patients are not referred to neurologists.

Although stroke of unknown cause occurs in a heterogeneous group of patients, our study confirms that its outcome is benign and that potentially dangerous preventive measures (such as long-term anticoagulation) probably should be avoided. As the number of subjects for each of the other etiologic categories was small, no firm conclusion can be drawn concerning the relative risk for stroke recurrence in each category. In accordance with other series and except for basilar artery dissection, dissection of either carotid or vertebral arteries had a favorable outcome and no recur-

### Table 3. Univariate Logistic Regression for Disability (Rankin Scale Grade >3) and Retirement

<table>
<thead>
<tr>
<th>Dependent Variable-Predictor</th>
<th>Disability</th>
<th>Retirement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR</strong></td>
<td><strong>95% CI</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>Age, &lt;30/30-40/&gt;40 y</td>
<td>0.71</td>
<td>0.37-1.39</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>0.55</td>
<td>0.19-1.59</td>
</tr>
<tr>
<td>Alcohol, &gt;60/&lt;60 g daily</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Severity at inclusion, major stroke/TIA/minor stroke</td>
<td>10.71</td>
<td>3.75-30.59</td>
</tr>
<tr>
<td>Etiology, unknown/known</td>
<td>0.74</td>
<td>0.17-3.29</td>
</tr>
<tr>
<td>Disability at follow-up, Rankin &gt;3/≤3</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; and TIA, transient ischemic attack.

### Table 4. Follow-up: Occupational Status

<table>
<thead>
<tr>
<th></th>
<th>TIA</th>
<th>Minor</th>
<th>Major</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Working</td>
<td>22 (68)</td>
<td>56 (64)</td>
<td>8 (40)</td>
<td>86 (61)</td>
</tr>
<tr>
<td>Housewife/student</td>
<td>2 (6)</td>
<td>12 (14)</td>
<td>2 (10)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Absent/ill/unemployed</td>
<td>4 (13)</td>
<td>7 (8)</td>
<td>2 (10)</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Retired</td>
<td>4 (13)</td>
<td>13 (15)</td>
<td>8 (40)</td>
<td>25 (18)</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.
ferences. Two subjects with lacunar infarcts suffered intracerebral hemorrhages during follow-up, a finding that is unusual in prospective lacunar series.23,34

The majority of the subjects regained full independence. The major predictor of independence was the severity of the initial stroke measured by the Rankin Scale at discharge. Figures on disability (available for only nine studies) are difficult to compare (Table 1) because the type of functional assessment is not specific-1,2,5,9,10,12 or the categories of disability and dependency are not uniformly defined. The percentage of disabled survivors ranges from 2% to 38% and of dependents from 0% to 17% in different series. Few investigators addressed the question of the variables that influence recovery. Age and etiology were not found to affect it significantly. The severity of the initial strokes was found to be important by Haerer and Smith.2 Hemiplegia and aphasia35 are indicated by others to adversely affect independence but were not specifically addressed in our study.

Studies of stroke in young adults that investigated the ability to return to work show comparable figures (60% to 90%). Black-Shader and Osberg35 found a low Barthel Index score, aphasia, and alcohol consumption to be negative predictors. We could confirm the negative effect of heavy alcohol ingestion. Concerning the influence of disability, although we found that the proportion of retired people was higher among those with higher Rankin grades at discharge, this relation was less clear than for independence. Hindfelt and Nilsson5 also noticed that only 8 of their 17 retired patients had moderate or severe neurological handicaps. In our series some patients with TIs and minor strokes were retired at the end of the follow-up period. The high retirement rate among young adults with TIs or minor strokes may be related to misinformation concerning prognosis and recurrence risk as understood by general practitioners and doctors working for medicolegal institutions. Except in a few cases where stroke represents the first or one manifestation of a systemic disease, ischemic stroke in young adults is often a relatively benign episodic event. Functional recovery is good, even for subjects disabled at discharge from the hospital. Reassurance of the low risk of recurrence and encouraging early return to work appear to be important recommendations to improve the quality of life of young stroke survivors.

Appendix: Definitions

Vascular Risk Factors

Hypertension and diabetes were defined according to the World Health Organization criteria (hypertension: systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg on two different occasions or subjects on antihypertensive treatment; diabetes: fasting glucose >140 mg/dL or random glucose >200 mg/dL). Hypercholesterolemia was said to be present if fasting cholesterol was >240 mg/dL; hypertriglyceridemia was present if fasting triglyceride levels were >200 mg/dL, and the hematocrit was high if >50%. Smokers were defined as patients who were current smokers at the time of the stroke. Alcohol abuse was considered consumption >120 mg/dL. Migraine was defined following the criteria of the International Headache Society.25

Etiologic Classification

A. Cardioembolic stroke was present if (1) a cardiac disease with a high emboligenic potential (mitral stenosis, prosthetic valve, dilated cardiomyopathy, atrial fibrillation, endocarditis, myxoma, intracardiac thrombus) or (2) if a cardiac disorder with a low emboligenic potential (mitral valve prolapse, atrial septal aneurysm, patent foramen ovale) was disclosed and extracranial or intracranial vessel pathology and a systemic cause of stroke were excluded.

B. Stroke due to large-vessel atheromatous disease was present if stenosis or occlusion of an appropriate extracranial or intracranial vessel was demonstrated by angiography or duplex or transcranial Doppler sonography. The finding of an isolated intracranial occlusion required the exclusion of cardioembolic disease.

C. Stroke related to single-perforator disease (lacunar infarction) was present if the patient presented with one of the recognized clinical lacunar syndromes (pure motor or pure sensory, sensory-motor, ataxic hemiparesis, and dysarthria clumsy-hand syndromes), normal intracranial and extracranial vessels, and either an appropriate lacunar infarction (<15 mm diameter) on CT/MRI or a normal CT.

D. Dissection was present if the symptomatic vessel presented the typical angiographic features of arterial dissection.

E. Systemic disease was present if stroke was symptomatic of arteritis, hematologic disease, or other systemic cause of stroke.

F. Mixed etiology was defined as any combination of the above.

G. Stroke of unknown cause was assigned if despite adequate investigation the etiology could not be ascertained; this group included patients with vascular risk factors, but no documented evidence of extracranial or intracranial arterial disease, and not fulfilling the criteria for single-perforator disease.

H. Nonspecified cause was assigned for patients who did not have a complete etiologic investigation (eg, vertebrobasilar distribution and lacunar strokes for which intracranial circulation was not studied by transcranial Doppler/angiography, low embolicgenic cardiac conditions without vessel studies, and intracranial occlusions without echocardiogram).

Events

TIA27 was defined as a focal neurological deficit occurring suddenly in a cerebrovascular territory, resolving within 24 hours, with causes other than vascular excluded.

Stroke28 was defined as a focal neurological deficit occurring suddenly in a cerebrovascular territory and lasting more than 24 hours in surviving patients. For recurrent strokes an increase of handicap at the time of the event was required.

Myocardial infarction was defined as at least two of the following: typical pain, new electrocardiographic changes, and enzyme elevation.

References


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