Relationship of Cardiac Disease to Stroke Occurrence, Recurrence, and Mortality

Joseph P. Broderick, MD; Stephen J. Phillips, MD; W. Michael O’Fallon, PhD; Robert L. Frye, MD; and Jack P. Whisnant, MD

Background and Purpose: This is a study of cardiac diseases associated with the 1,382 cases of first cerebral infarction in residents of Rochester, Minn., during 1960–1984.

Methods: This is a population-based study in Rochester, Minn., for which the medical record-linkage system was used to identify cardiac disease among patients with first cerebral infarction.

Results: There were 318 patients (23%) who had at least one major potential cardiac source of emboli. The proportion of patients with a cardiac source of emboli was significantly higher among patients older than age 75 years (29%) than among younger patients (17%). The 30-day stroke recurrence rate among patients with a cardiac source of emboli (2%) was not significantly different than that among those without a cardiac source of emboli (2%). Among patients with a cardiac source of emboli, there was no difference in the probability of stroke at 30 days and at 90 days for those treated or not treated with anticoagulants. During the first 30 days after cerebral infarction, the risk of death in patients with a cardiac source of emboli (23%) was 14 times that of recurrent stroke. The risk of death at 30 days in patients without a cardiac source of emboli was 8%.

Conclusions: Significant independent predictors of death (Cox proportional-hazards analysis) were age, prior myocardial infarction, atrial fibrillation present at onset of stroke, congestive heart failure before the stroke, and an age x congestive heart failure interaction. The only significant independent predictors of recurrent stroke were cardiac valve disease and congestive heart failure. (Stroke 1992;23:1250–1256)

Key Words • cardiovascular diseases • cerebral infarction • mortality

The concept that cardiogenic cerebral embolism is a frequent cause of stroke has gained increasing prominence during the past 20 years.1-6 However, in practice it is difficult to establish a definite diagnosis of cardioembolic stroke because of the absence of a benchmark diagnostic test, differing opinions over which cardiac conditions are embolic,,1-6 and the frequent occurrence of an alternative mechanism of cerebral infarction in the same patient.3-6,10-14 Estimates of the proportion of cerebral infarctions due to cardiogenic embolism vary from 9% to 29%,3-6,10-14 The risk of early stroke recurrence after cardioembolic stroke is reported to vary from 1% to 22%.3,5,10 Differences in the types of patients studied and in the definitions of cardioembolic stroke probably account for most of this variation.

Population-based studies are most likely to provide estimates that are free of referral bias. This article reports the survival and recurrence rates of stroke patients among residents of Rochester, Minn., who had a cerebral infarct and a cardiac disorder that might produce an embolus.

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Subjects and Methods

The Rochester Epidemiology Project17 medical records and records-linkage system were used to retrieve the records of all residents of Rochester who had a first cerebral infarct between 1960 and 1984. The methods used to identify these cases have been published previously.18 The diagnosis of cerebral infarction was based on clinical data, computed tomography of the head, or autopsy data. The few patients for whom there was inadequate information to judge the type of focal stroke were considered to have had a cerebral infarct. Data concerning cardiac diseases were abstracted by one of two physicians using criteria (Appendix 1) that were designed to separate those patients in whom a diagnosis was evident by history, physical examination, electrocardiogram (ECG), and chest radiograph from those in whom other diagnostic procedures (e.g., echocardiography) were necessary to make the diagnosis. Chest radiograph alone was not used as the basis for any diagnosis. A cardiac diagnosis had to have been made before the onset of stroke or at the time of first evaluation for the stroke. For example, a patient who was found to have new onset of atrial fibrillation during the evaluation was considered to have had atrial fibrillation at stroke onset. Definitions of hypertension and diabetes are also given in Appendix 1.

Cases were placed into one of two groups on the basis of the presence or absence of specific cardiac conditions.

Major potential cardiac source of emboli (CSE). Patients in this group had one or more of the following
conditions present: 1) congestive heart failure at stroke onset, 2) myocardial infarction (MI) ≤2 months prior to stroke onset, 3) mitral valve disease (stenosis, regurgitation, or mixed disease—mitral valve prolapse not included), 4) prosthetic mitral valve, 5) prosthetic aortic valve, 6) atrial fibrillation or flutter (hereafter termed atrial fibrillation) present at onset of cerebral infarction, 7) cardiomyopathy, 8) congenital heart disease, 9) recent systemic arterial emboli, 10) stroke <48 hours after coronary artery bypass operation, 11) stroke <48 hours after left ventricular aneurysm operation, 12) stroke related to cardiac catheterization or pacemaker installation, 13) left ventricular aneurysm, 14) intracardiac thrombus or valvular vegetations, 15) sinus node dysfunction (sick sinus syndrome), 16) autopsy evidence of recent MI (dated at the time of or prior to the cerebral infarction), 17) autopsy evidence of rheumatic heart disease, 18) autopsy evidence of recent systemic arterial emboli (dated at the time of or prior to the cerebral infarction), and 19) autopsy evidence of embolic occlusion of an intracerebral vessel with little or no evidence of carotid or intracranial arterial disease. Conditions 1 through 12 were diagnosed by clinical history, physical examination, ECG, and findings from chest radiographs. Diagnosis of conditions 13 through 19 required additional ancillary information from echocardiography, coronary angiography, ambulatory ECG monitoring, and autopsy if death occurred within 2 months after the first stroke.

No major potential cardiac source of emboli. Patients in this group had none of the conditions described for the CSE group.

During 1960–1964, 67% of all patients with a cerebral infarction had an ECG at the time of their evaluation for stroke. By 1970–1974, 88% of all patients had an ECG, and this proportion changed little during the next two 5-year periods. Although echocardiography was first introduced in 1968, it was used sparingly during the 1970s for evaluation of patients with stroke. However, during 1980–1984, 43% of patients had an echocardiogram at the time of evaluation for stroke or at some time prior to their stroke. Tests of cardiac enzymes were introduced as follows: serum glutamic-oxaloacetic transaminase in 1955, serum lactate dehydrogenase in 1963, and serum creatine kinase in 1964. Radionuclide ventriculography was introduced in 1981, cardiac catheterization for angiography in 1960, and ambulatory ECG monitoring in 1969.

Estimates of the probability of survival and the probability of stroke recurrence were determined for both groups of patients by the Kaplan-Meier product-limit method. The analyses were performed using data from the period 1975–1984 when echocardiography, coronary angiography, and ambulatory ECG monitoring were used most frequently. The estimates of probability of survival were compared with expected survival from an age- and sex-matched 1970 US white population.

Follow-up of patients was accomplished through the medical record-linkage system for residents of Rochester. The last follow-up date for living patients was the last medical note indicating that the person was alive. Patients who moved from Rochester or those who did not seek medical attention were not contacted individually. There were no living patients whose last follow-up was in the first month after onset of stroke, and there were six living patients whose last follow-up was in the first year after onset of stroke.

Probability of survival and probability of stroke recurrence, given 7-day survival, were estimated for the patients with a CSE who were treated with anticoagulants after the stroke and for those who were not treated. This was not part of the initial design but was added to determine whether recurrent stroke rates for patients with a CSE might have been affected by anticoagulant treatment. A trained nurse abstractor obtained the information from the medical record concerning use of anticoagulant agents.

Cox proportional-hazards analysis also was performed for all patients whose cerebral infarction occurred between 1975 and 1984 to determine which factors known to be present at or before the time of stroke onset were significant independent predictors of death or stroke recurrence. The variables considered were age, sex, calendar year of stroke, hypertension, diabetes, and each individual cardiac diagnosis. Mitral valve disease, aortic valve disease, and mitral or aortic valve surgery were combined into one variable called cardiac valve disease. The frequency distribution for these variables in the 594 patients in 1975–1984 was very similar to the distribution of the same variables for the 1,382 patients in 1960–1984 (Table 1). Diagnoses for which there were fewer than 20 patients were not considered in the analysis. These included mitral valve prolapse (n=16), left ventricular aneurysm (n=2), dilated cardiomyopathy (n=2), congenital heart disease (n=2), sick sinus syndrome (n=9), permanent pacemaker (n=12), intracardiac thrombus or valvular vegetation (n=6), systemic arterial emboli (n=6), and cardiovascular surgery or procedure within 2 days prior to the stroke (n=4). In the multivariate analysis, variables were first considered each as an individual variable and then were entered into or removed from the model in a stepwise fashion.

Carotid artery disease, determined by the presence of a bruit, positive noninvasive studies, or carotid angiography, was noted for patients with and without a CSE. A $\chi^2$ analysis was performed on the differences between the two groups.

Results

During the years 1960–1984, 1,382 cases of first cerebral infarction were identified in the population of Rochester, Minn. Eight patients previously noted to have had a first infarct in 1960–1984 were reclassified as having had a mild stroke prior to 1960 rather than a transient ischemic attack. Table 1 shows the frequency of all associated cardiac conditions diagnosed on the basis of clinical history, examination, ECG, and chest radiographs. Angina, MI, atrial fibrillation, left ventricular hypertrophy, and congestive heart failure were the most commonly associated cardiac diagnoses.

Of the 1,382 cases of cerebral infarction, 318 (23%) had a cardiac diagnosis that met the criteria for a CSE (conditions 1–12). Atrial fibrillation, with or without an associated cardiac diagnosis, was by far the most common cardiac diagnosis, occurring in 19% of all cases. The proportion of cases with atrial fibrillation and without any other cardiac diagnoses increased significantly with age for both men and women (Table 2).
TABLE 1. Frequency Distribution of Cardiac Conditions Among 1,382 Patients With Cerebral Infarction, 1960–1984

<table>
<thead>
<tr>
<th>Cardiac diagnosis</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.*</td>
</tr>
<tr>
<td>Angina</td>
<td>285</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>&gt;2 mo before stroke</td>
<td>157</td>
</tr>
<tr>
<td>≤2 mo before stroke</td>
<td>59</td>
</tr>
<tr>
<td>Total</td>
<td>216</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td></td>
</tr>
<tr>
<td>With other cardiac diagnoses</td>
<td>174</td>
</tr>
<tr>
<td>With hypertension only</td>
<td>67</td>
</tr>
<tr>
<td>Without other cardiac diagnoses or prior</td>
<td>25</td>
</tr>
<tr>
<td>hypertension</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>266</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>193</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Past history</td>
<td>116</td>
</tr>
<tr>
<td>At stroke onset</td>
<td>55</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
</tr>
<tr>
<td>Aortic valve disease</td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>7</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>6</td>
</tr>
<tr>
<td>Mixed</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td></td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>6</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>46</td>
</tr>
<tr>
<td>Mixed</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
</tr>
<tr>
<td>Recent systemic arterial emboli</td>
<td>18</td>
</tr>
<tr>
<td>Other cardiac dysrhythmias</td>
<td>39</td>
</tr>
<tr>
<td>Mitral valve prolapse (clinical)</td>
<td>10</td>
</tr>
<tr>
<td>Artificial mitral valve</td>
<td>9</td>
</tr>
<tr>
<td>Artificial aortic valve</td>
<td>9</td>
</tr>
<tr>
<td>Sinus node dysfunction (sick sinus syndrome)</td>
<td>10</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>7</td>
</tr>
<tr>
<td>Permanent cardiac pacemaker</td>
<td>13</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>2</td>
</tr>
</tbody>
</table>

Cardiac conditions diagnosed by clinical, electrocardiographic, and chest radiographic findings also included diagnoses that did not meet the criteria for a cardiac source of emboli (e.g., angina).

*Number of cases in column adds up to more than 1,382 because a patient may have had more than one cardiac diagnosis.

TABLE 2. Cases of Cerebral Infarction Associated With Atrial Fibrillation or Flutter and Without Other Cardiac Diagnoses

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;35</th>
<th>35–44</th>
<th>45–54</th>
<th>55–64</th>
<th>65–74</th>
<th>75–84</th>
<th>85+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Of these patients, 73% also had diagnosis of hypertension.

For 1975–1984, by using all sources of information (for example, echocardiography, angiography, and autopsy findings), 290 of 594 cases of cerebral infarction (49%) had at least one associated cardiac condition (for men 55%, for women 44%). Of the 594 cases, 154 (26%) had a cardiac diagnosis that met the criteria for a CSE (conditions 1–19). This could be an underestimate because echocardiography was performed on a minority of cases.

For 1975–1984, the postinfarction survival of patients with a CSE (conditions 1–19) was 77% at 30 days, 56% at 1 year, and 23% at 5 years. The postinfarction survival of patients without a CSE was 92%, 82%, and 57%, respectively. The difference in survival between the two groups was highly significant ($p<0.0001$). Comparable survival figures for the age- and sex-matched 1970 US white population were 99%, 92%, and 65%. The ratio of the observed survival to the expected survival (which corrects for the difference in age) for each group is shown in Figure 1.

In the proportional-hazards model, the variables that were significant independent predictors of death within 5 years after the stroke were age, MI at any time before the stroke, atrial fibrillation present at the time of stroke, congestive heart failure diagnosed at any time prior to the stroke, and an age × congestive heart failure interaction (Table 3). The effect of the age × congestive heart failure interaction is shown in Table 3 as the hazard ratio of age with and without congestive heart failure. This indicates that there is less of an increased risk with age in those with congestive heart failure than...
in those without, which should be interpreted as a higher relative risk of death from congestive heart failure at younger ages. Cardiac disease was a frequent cause of death in patients with a CSE (42%) as well as in patients without a CSE (25%) (p<0.01) (Table 4).

During 1975–1984, 40 of the 154 patients with a CSE (conditions 1–19) had at least one recurrent stroke during 294 person-years of observation. Of the 440 patients without a CSE, 94 had a recurrent stroke during 1,508 person-years of observation. The probability of recurrent stroke, given survival, for patients with a CSE was 2% at 30 days, 5% at 1 year, and 32% at 5 years (Figure 2). Those same probabilities for patients without a CSE were 2% at 30 days, 9% at 1 year, and 26% at 5 years. There was no significant difference in stroke recurrence rates between the two groups. In the Cox proportional-hazards model, variables that were significant independent predictors of recurrent stroke were cardiac valve disease and congestive heart failure diagnosed at any time prior to the stroke (Table 5).

Among the 37 patients without a CSE who died in the first 30 days after the first stroke, three died of recurrent stroke, whereas none of the 35 patients with a CSE who died within 30 days had a recurrent stroke.

Among the 133 adult patients with a CSE in 1975–1984 who survived 7 days, 69 were started on heparin, warfarin, or both within the first 7 days after the stroke. Given 7-day survival, the probability of stroke recurrence at 30 days after the stroke was 3% for those who were treated and 2% for those who were not treated with anticoagulants. At 90 days these rates were 5% for those who were treated and 2% for those who were not treated. These were not significantly different. There was a significant difference in survival at 90 days (p=0.02) favoring the treated patients, presumably related to greater severity of stroke in those who were not selected for treatment.

Discussion

This study showed that major potential cardiac sources of emboli were present in about a quarter of all persons who had a cerebral infarct and were found more frequently in the elderly. The proportion of cerebral infarcts associated with a CSE in this study is similar to that of other population-based and cohort studies, particularly the Oxfordshire Community Stroke Project and earlier reports of the Framingham Study (Table 6).

The 30-day stroke recurrence rate in cases with a CSE (2%) was not significantly different from that in...
cases without a CSE (2%). This was not affected by anticoagulant treatment because the probability of stroke recurrence among patients with a CSE was not significantly different for those treated and those not treated with heparin, warfarin, or both. However, there is evidence that patients with less severe infarcts were more likely to be treated with anticoagulants, so these data should not be interpreted as providing any evidence about effectiveness of anticoagulant treatment in regard to recurrence of infarction.

Based on an aggregate analysis of 15 mostly retrospective studies, the Cerebral Embolism Task Force (CETF) estimated that about 12% of patients with a cardioembolic stroke will experience a second embolic stroke within 2 weeks.15 A follow-up review by the CETF in 1989 reported five additional studies with early stroke recurrence rates of 0-21%.16 The low recurrence rate in the present study compared with most of the prior reports probably is due to the fact that patients with first stroke in the population of Rochester and those summarized in the CETF report are quite different. The majority of reports summarized by the CETF were retrospective studies of cardioembolic stroke at tertiary referral centers and were not likely to be representative of first cardioembolic stroke in a general population. Most of these reports, including the only randomized prospective study (Cerebral Embolism Study Group),20 included patients who had previous embolic events including embolic stroke. In contrast, the Rochester study included all first cerebral infarcts in the population during the study period.

The marked variability in stroke recurrence rates among the various reports raises questions about which cardiac conditions are associated with an increased rate of stroke recurrence. In the present study, only cardiac valve disease and congestive heart failure diagnosed at any time prior to the stroke were significant independent predictors of recurrent stroke in the Cox proportional-hazards analysis.

During the first 30 days after a cerebral infarct, the risk of death in patients with a CSE was 14 times the risk of recurrent stroke. Although the 30-day recurrence rate for stroke among patients with and without a CSE was the same (2%), the 30-day mortality in patients with a CSE was nearly three times greater than in patients without a CSE (23% versus 8%). None of the patients with a CSE who died within the first 30 days had a recurrent stroke during that time. Only three of the deaths in the first 30 days in patients without a CSE were due to recurrent stroke within that time. The only recurrent strokes that would have been likely to have been missed were those for which medical care was not obtained and which were not subsequently reported to a physician. In this age group, about 95% of the population are seen by a physician within any 2-year period.

Treatment of patients with a CSE should focus primarily on decreasing cardiac morbidity and mortality, particularly that which is related to congestive heart failure and MI (Tables 3 and 4). Evaluation and treatment of cardiac risk factors in patients without a CSE are also important, as evidenced by the fact that 25% of the deaths in this group were due to cardiac disease, including sudden death (Table 4).

For our category CSE we chose cardiac conditions with a relatively well-defined risk of stroke, such as acute MI,21 rheumatic heart disease,22 and congestive

### Table 6. Frequency of Major Cardiac Sources of Emboli in Population-Based Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Time period</th>
<th>With infarct (No.)</th>
<th>With cardiac source of emboli No.</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham10</td>
<td>1949–1961</td>
<td>78</td>
<td>15 19</td>
<td>Sudden onset, AF, RHD, acute MI, systemic emboli</td>
</tr>
<tr>
<td>Framingham19</td>
<td>1949–1979</td>
<td>384</td>
<td>105 27</td>
<td>AF, RHD, cerebral embolism (other)</td>
</tr>
<tr>
<td>Oxfordshire6</td>
<td>1981–1983</td>
<td>244</td>
<td>43 18</td>
<td>AF, RHD, mitral regurgitation, MI &lt;6 wk, prosthetic valve, paradoxical embolism</td>
</tr>
<tr>
<td>Rochester10</td>
<td>1960–1984</td>
<td>1,382</td>
<td>318 23</td>
<td>AF, MI &lt;2 mo, congestive heart failure at onset, mitral valve disease, prosthetic valve, cardiomyopathy, congenital heart disease, recent systemic emboli, stroke related to coronary artery bypass graft or coronary catheterization</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; MI, myocardial infarction; RHD, rheumatic heart disease.

*No criteria specifically listed in report.
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heart failure. We also included atrial fibrillation as a CSE even though its associated independent stroke risk is more controversial, varying from a fivefold increase in the Framingham Study to a 1.5-fold nonsignificant increase in a Rochester, Minn., cohort study. In the Framingham Study, 62 of the 68 persons with strokes who had atrial fibrillation had hypertension, either definite or borderline, at some time prior to the onset of atrial fibrillation. Of the 169 patients in the Rochester cohort study who had atrial fibrillation during the study, only 41 did not have coexistent coronary or hypertensive heart disease, and a recurrent stroke developed in only one of the 41. In another population-based study in Shibata, Japan, 20 of the 25 stroke cases with prior atrial fibrillation had a history of hypertensive cardiovascular disease, three had a history of congestive heart failure, and one each had a history of rheumatic heart disease and coronary heart disease.

Even though atrial fibrillation was present in 19% of the patients with cerebral infarction in the present study, it was not a significant independent predictor of stroke recurrence. Of the 25 stroke patients in the present study with atrial fibrillation but no other cardiac diagnoses or prior history of hypertension, only two had a recurrent stroke during 98 person-years of observation; one recurrent stroke occurred at 109 days, and the second was at 7 years after the first stroke. Atrial fibrillation was an independent predictor of death following stroke with a hazard ratio of 1.7, which is similar to that in a hospitalized case series in Italy. These data from diverse populations emphasize that the relationship of atrial fibrillation to stroke is difficult to separate from the effects of hypertension and other cardiac disease. In light of the recently reported benefits of anticoagulation and possibly aspirin therapy in patients with atrial fibrillation, identification of those patients who are at particularly high or low risk of stroke is critical for deciding whom to treat and with what antithrombotic therapy.

The present study indicated a higher risk of stroke recurrence in those patients with a history of congestive heart failure and those with cardiac valvular disease but does not address the effect of antithrombotic therapy for these conditions.

Our study showed a similar frequency of carotid artery occlusion or severe stenosis in stroke patients with and without a CSE, as judged by noninvasive testing. However, only 3% of those with a CSE had angiography whereas 25% of those without a CSE had angiography, probably indicating a negative selection bias for angiography, determined by the presence of a CSE. The observation that there is an overlap of potential stroke mechanisms confirms previous reports.

Appendix 1

Definitions

Congestive heart failure. Coexistence of at least four of the following criteria: 1) dyspnea on ordinary exertion (not due to pulmonary disease), 2) paroxysmal nocturnal dyspnea, 3) acute pulmonary edema described in hospital records, 4) distended neck veins (in other than in the supine position and in the absence of venous obstruction), 5) bilateral ankle edema (not known to be due to some other condition), 6) hepatomegaly (not due to liver disease), 7) rales in the absence of pulmonary disease, 8) third heart sound, and 9) radiographic evidence of pulmonary congestion (pulmonary venous congestion, prominent pulmonary veins, or pleural effusion).

Myocardial infarction. A clinical diagnosis of acute myocardial infarction was the critical requirement for diagnosis. With few exceptions, the clinical diagnosis was supported by electrocardiographic (ECG) changes and/or increased serum concentrations of glutamic-oxaloacetic transaminase, lactate dehydrogenase, and creatine kinase. "Silent" myocardial infarction (i.e., ECG changes suggestive of myocardial infarction that were not associated with clinical symptoms and increased serum enzyme concentrations) was not included. Non-Q-wave myocardial infarction was included.

Angina pectoris. Chest discomfort or pain that: 1) was described as heavy, tight, constricting, crushing, pressing, or squeezing; 2) might radiate into the neck, jaw, shoulder, or upper arm; 3) was often related to, or precipitated by, exertion, stress, excitement, or exposure to cold or wind; 4) was of short duration, usually lasting less than 5 minutes; and 5) was promptly relieved by rest or nitroglycerin. It was not required that the clinical diagnosis of angina pectoris be supported by positive results of an exercise ECG.

Left ventricular aneurysm. A frankly dyskinetic segment of the left ventricle was demonstrated by cardiac angiography, echocardiography, or radionuclide ventriculography.

Hypokineti/cinekinetic segment. A segment of left ventricular hypokinesis or akinesis, not amounting to an aneurysm, was demonstrated by cardiac angiography, echocardiography, or radionuclide ventriculography.

Mitral valve disease. A clinical diagnosis of mitral stenosis was made if the subject had a rumbling diastolic murmur audible at the cardiac apex. A clinical diagnosis of mitral regurgitation was made if the subject had an apical pansystolic or late systolic murmur radiating into the axilla. A clinical diagnosis of mixed mitral valve disease was made if the criteria for both mitral stenosis and regurgitation were present. It was not required that the clinical diagnosis be supported by evidence from echocardiography, cardiac angiography, or autopsy.

Mitral valve prolapse. This was defined clinically as the presence of single or multiple systolic clicks, with or without a mid-to-late systolic murmur, and no evidence of other valvular disease. Cases in which the diagnosis was made incidentally at the time of echocardiography or cardiac angiography were included. Those subjects who had both clinical and ancillary evidence of mitral valve prolapse were also included.

Aortic valve disease. A clinical diagnosis of aortic sclerosis was made if a subject had a systolic ejection murmur audible at the apex or aortic area, or both, that radiated into the neck. The diagnosis of aortic stenosis required the presence of an aortic sclerotic murmur and a diminished, slow carotid upstroke at physical examination. A clinical diagnosis of aortic regurgitation was made if a subject had a high-pitched, early diastolic murmur best heard along the left sternal border. A diagnosis of mixed aortic valve disease was made if the clinical criteria for both aortic stenosis or sclerosis and regurgitation were present. It was not required that the clinical signs be supported by evidence from echocardiography or cardiac angiography.

Left ventricular hypertrophy. Coded as present when documented in an ECG report.

Cardiomyopathy. Dilated cardiomyopathy was diagnosed when congestive heart failure (defined above) occurred in the absence of evidence of ischemic, hypertensive, congenital, valvular, or pericardial disease. It was not required that cases diagnosed on the basis of clinical and chest radiographic findings have the diagnosis supported by other ancillary tests.

Congenital heart disease. The diagnosis of congenital heart disease was based on the clinical findings of a cardiologist and appropriate ancillary investigations.

Atrial fibrillation or flutter. Atrial fibrillation or atrial flutter had to be documented in an ECG report. Episodes of atrial
fibrillation that alternated with periods of sinus rhythm were judged to have been present if the diagnosis was made by a cardiologist on the basis of clinical and ancillary findings.

Sinus node dysfunction (sick sinus syndrome). This was defined by the absence of any other cardiac condition as determined by history, physical examination, ECG, or chest radiograph.

Other cardiac dysrhythmias. These included ECG-documented severe ventricular ectopy, ventricular tachycardia or fibrillation, second- or third-degree heart block, and supraventricular tachycardia.

Intracardiac thrombus. This diagnosis required documentation by cardiac catheterization, echocardiography, or autopsy.

Hypertension. The presence of hypertension was determined by a clinical diagnosis of hypertension or by two blood pressure determinations with a diastolic blood pressure of ≥95 mm Hg, a systolic blood pressure of ≥160 mm Hg, or both.

Diabetes. The diagnosis of diabetes mellitus was determined by criteria from the National Diabetes Data Group. Only those patients whose diagnosis of diabetes was made prior to stroke onset or within 1 month after the onset of the stroke were considered to have diabetes.

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