Predictors of Cerebrovascular Events and Death Among Patients With Valvular Heart Disease
A Population-Based Study

George W. Petty, MD; Bijoy K. Khandheria, MD; Jack P. Whisnant, MD; JoRean D. Sicks, MS; W. Michael O’Fallon, PhD; David O. Wiebers, MD

Background and Purpose—There is little population-based information on cerebrovascular events and survival among valvular heart disease patients. We used the Kaplan-Meier product-limit method and the Cox proportional hazards model to determine rates and predictors of cerebrovascular events and death among valve disease patients.

Methods—This population-based historical cohort study in Olmsted County, Minnesota, reviewed residents with a first echocardiographic diagnosis of mitral stenosis (n=19), mitral regurgitation (n=528), aortic stenosis (n=140), and aortic regurgitation (n=106) between 1985 and 1992.

Results—During 2694 person-years of follow-up, 98 patients developed cerebrovascular events and 356 died. Compared with expected numbers, these observations are significantly elevated, with standardized morbidity ratio of 3.2 (95% CI, 2.6 to 3.8) and 2.5 (95% CI, 2.2 to 2.7), respectively. Independent predictors of cerebrovascular events were age, atrial fibrillation, and severe aortic stenosis. The risk ratio of severe aortic stenosis was 3.5 (95% CI, 1.4 to 8.6), with atrial fibrillation conferring greater risk at younger age. Predictors of death were age, sex, cerebrovascular events, ischemic heart disease, and congestive heart failure, the greatest risk being among those with both congestive heart failure and cerebrovascular events (risk ratio=8.8; 95% CI, 5.8 to 13.4). Valve disease type and severity were not independent determinants of death.

Conclusions—The risk of cerebrovascular events and death among patients with valve disease remains high. Age, atrial fibrillation, and severe aortic stenosis are independent predictors of cerebrovascular events, and age, sex, cerebrovascular events, congestive heart failure, and ischemic heart disease are independent predictors of death in these patients.

(Approximately 50 000 US residents with valvular heart disease develop a first stroke each year, and valve disease is an important risk factor for stroke recurrence.1–3 Despite the decline of rheumatic fever, valve disease will remain a frequent cause of stroke in the United States and especially abroad.4–6 Yet there is little modern information on the risk of cerebrovascular events among patients with hemodynamically significant mitral and aortic stenosis and regurgitation. Many previous studies appeared before advances in medical and surgical treatment and introduction of echocardiography as an accurate noninvasive means of diagnosing valve disease. Moreover, earlier longitudinal studies did not use multivariate analyses to identify independent determinants of morbidity and mortality and were derived largely from observations made on patients referred to tertiary care centers, an important source of bias.7–22 We undertook a large population-based historical cohort study of all residents of Olmsted County, Minnesota, who had a first 2-dimensional color Doppler echocardiographic diagnosis of hemodynamically significant mitral or aortic stenosis or regurgitation made between 1985 and 1992 to estimate rates and model determinants of the development of cerebrovascular events and to quantify the influence of cerebrovascular events on survival among these patients.

Subjects and Methods
This study used the population-based data resources of the Rochester Epidemiology Project medical records linkage system23 and the Mayo Echocardiography Laboratory database. Virtually all medical care in the community is supplied by the Mayo Clinic and its 2 hospitals or by Olmsted Medical Center and its hospital. All medical diagnoses made for a resident of Olmsted County are entered on a master sheet in the patient’s medical record, which is then entered into a central computer index. Funding of the Rochester Epidemiology Project 30 years ago permitted expanding this index to include other medical practices from surrounding communities, the University of Minnesota, and the Veterans Administration Hospital in Minneapolis, where Olmsted county residents may have received medical care.

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medical care. The medical record contains all inpatient and outpatient data, including information regarding emergency department visits, nursing home care, autopsies, and death certificates. All echocardiograms obtained at medical care facilities in Olmsted County, Minnesota, have been performed and interpreted by a single unified Mayo Clinic Echocardiography Laboratory since 1970. The echocardiography database includes detailed information on >300,000 echocardiographic examinations performed at the Mayo Clinic since 1975. From 1985 onward, virtually all patients studied at the Mayo Clinic had 2-dimensional echocardiograms, and >90% had Doppler and color-flow imaging. Approximately 1 in 5 residents of Olmsted County, Minnesota, underwent echocardiography each year for differential diagnostic assessment of cardiovascular-related conditions during the period of this study.24

Verification of residence was based on information obtained from city and county directories or earlier medical records. Patients were included only if their residence was established in Olmsted County, Minnesota, at least 1 year before their first echocardiographic diagnosis of valve disease. Those who apparently moved to the county to facilitate diagnosis or treatment were excluded. Population-based studies in Rochester and Olmsted County are approved by the Mayo and Olmsted Medical Center Institutional Review Boards.

The cohort in this study is defined as all residents of Olmsted County, Minnesota, who had a first-time 2-dimensional color Doppler echocardiographic diagnosis of moderate or severe mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation, or any combination thereof made from January 1, 1985, through December 31, 1992, who did not have a history of cerebrovascular events (stroke, transient ischemic attack, or amaurosis fugax) before or at the time of the echocardiogram. We did not include patients diagnosed with valve disease by 2-dimensional color Doppler echocardiography before 1985 to avoid bias that could accrue to differential selection of patients for referral for this type of echocardiogram during earlier years before the use of this technology was routine in our laboratory. Patients with a history of cerebrovascular events were excluded from the cohort because the aim of the study was to determine rates of occurrence of incident cerebrovascular events after diagnosis of valve disease and to assess the impact of the development of cerebrovascular events on survival among these patients. Such an approach also limits bias that could accrue to inclusion of patients with a history of cerebrovascular disease in the years before the period of the study who had characteristics that guaranteed survival. Patients with only trivial or mild mitral or aortic stenosis or regurgitation were excluded from this study.

Echocardiographic diagnosis of valve disease was specifically chosen as the criterion for diagnosis and inclusion in the cohort because of the superiority of this technology over the clinical examination in accurately identifying and quantifying the type and severity of valvular disease.25–29 However, patients with a nonechocardiographic diagnosis of valve disease before the date of the echocardiographic diagnosis were included, in which case the date of first diagnosis was noted. Individual definitions of valve disease are as follows.

Aortic regurgitation was defined as the presence of diastolic flow through the aortic valve detected on color flow imaging or Doppler echocardiography. Aortic regurgitation was graded semiquantitatively by looking at the width of the jet in the left ventricular outflow tract as well as the jet area in the short-axis view of the aortic valve.30 Severe aortic stenosis was defined as a mean pressure gradient of >30 mm Hg. Moderate aortic stenosis was defined as a mean pressure gradient of 20 to 30 mm Hg. Severe aortic stenosis was defined as a mean pressure gradient of >30 mm Hg. Mean gradient was used to judge the severity of aortic stenosis since aortic valve area calculations were not available in all patients.

Mitral regurgitation was defined as the presence of systolic flow through the mitral valve detected on color flow imaging and Doppler echocardiography. Semiquantitative assessment of severity of mitral regurgitation was made by visual estimate of the regurgitant jet size as a percentage of the left atrial size.31

Moderate mitral stenosis was defined as mitral valve area of 1.1 to 1.4 cm². Severe mitral stenosis was defined as mitral valve area ≤1.0 cm².

Definitions of cerebrovascular events, as follows, are identical to those used in previous Rochester Epidemiology Project population-based studies of stroke incidence and recurrence.1,2,31

Ischemic stroke was defined as the acute onset, over minutes to hours, of a focal neurological deficit persisting for >24 hours, with or without CT or MRI documentation, and due to altered circulation to a limited region of the cerebral hemispheres, brain stem, or cerebellum. Persons with only persistent sensory symptoms and minimal sensory signs or mild impairment of dexterity with preservation of strength were included in the patient was aware of such symptoms being present for >24 hours. Patients with only deep tendon reflex changes or other minor signs without any functional impairment or awareness of the deficit were excluded. CT, MRI, or autopsy did not show evidence of intracerebral hemorrhage. Hemorrhagic infarction found on radiological imaging was classified as infarction. Without clinical evidence of stroke, a case of ischemic stroke detected at autopsy was excluded unless noted pathologically as a recent infarct, in which case the date of onset was estimated. Nonhemorrhagic infarctions from hematologic cause, vasculitis, or hemostatic factors were included. Persons with an area of probable infarction on CT without any associated clinical symptoms were not included.

Intracerebral hemorrhage was defined as the acute or progressive onset of a focal neurological deficit possibly associated with headache, vomiting, altered level of consciousness, signs of meningeval irritation, or blood-stained cerebrospinal fluid. If performed, CT, MRI, or autopsy demonstrated a parenchymal hemorrhage. Rupture of a lesion resulting in parenchymal hemorrhage that was not associated with hemorrhage into the subarachnoid space was classified as an intracerebral hemorrhage. A case of intracerebral hemorrhage detected at autopsy was included if described as a recent intracerebral hemorrhage, in which case a date of onset could be estimated. Traumatic and neonatal intracerebral hemorrhages were excluded.

Transient ischemic attack was defined as an episode of focal neurological symptoms with abrupt onset and rapid resolution, lasting <24 hours, and due to altered circulation to a limited region of the brain. Transient visual disturbances associated with monocular retinal ischemia were defined as amaurosis fugax (see below). Transient symptoms such as syncope, unexplained loss of consciousness, and dizziness or wooziness were excluded unless associated with other symptoms of brain stem ischemia. Symptoms such as vertigo, dysarthria, or diplopia, which occur in isolation without other symptoms of brain stem ischemia, were excluded. Focal symptoms associated with migraine were excluded.

Amaurosis fugax (transient monocular blindness) was defined as an episode of transient monocular visual disturbance, with abrupt onset and rapid resolution, lasting <24 hours, and due to altered circulation to the retina. The patient may have had total or partial loss of visual acuity affecting all or part of the visual field in that eye. Visual symptoms associated with migraine were excluded.

Syncope alone was not considered a cerebrovascular end point.

The medical records of all residents of Olmsted County, Minnesota, who had a 2-dimensional color Doppler echocardiogram and a diagnosis of valve disease during the period of the study were screened by a nurse abstractor under the supervision of a cardiologist and neurologist to identify individuals meeting criteria for inclusion in the cohort as well as to verify exclusion criteria. The entire medical record of those meeting inclusion criteria was then abstracted to record the presence or absence of hypertension, congestive heart failure, ischemic heart disease (myocardial infarction, angina pectoris), atrial fibrillation at the time of the echocardiogram, the date of subsequent development of these risk factors if not present at the time of the echocardiogram, and the date of subsequent development of transient ischemic attack, amaurosis fugax, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, death, or date of last follow-up or date of last contact before migration from Olmsted County. Treatment with oral anticoagulant agents after echocardiographic diagnosis of valvular heart disease was also recorded, as were dates of aortic or mitral valve surgery, replacement, or valvuloplasty.
TABLE 1. Risk Factors Among 729 Residents of Olmsted County, Minnesota, With Valvular Heart Disease Diagnosed Echocardiographically Between 1985 and 1992

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Before Valve Disease Diagnosis</th>
<th>After Valve Disease Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>509 (69.8)</td>
<td>19 (2.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>335 (46.0)</td>
<td>118 (16.2)</td>
</tr>
<tr>
<td>Intermittent atrial fibrillation</td>
<td>179 (24.6)</td>
<td>78 (10.7)</td>
</tr>
<tr>
<td>Persistent atrial fibrillation</td>
<td>145 (19.9)</td>
<td>58 (8.0)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>280 (38.4)</td>
<td>51 (7.0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>178 (24.4)</td>
<td>45 (6.2)</td>
</tr>
</tbody>
</table>

*Risk factor diagnosed on or before date of first 2-dimensional color Doppler echocardiographic diagnosis of moderate or severe mitral or aortic regurgitation or stenosis.
†Risk factor diagnosed after date of first 2-dimensional color Doppler echocardiographic diagnosis of moderate or severe mitral or aortic regurgitation or stenosis.

In addition to ischemic cerebrovascular events (ischemic stroke, transient ischemic attack, amaurosis fugax), we included intracerebral hemorrhage as a cerebrovascular end point because case-control studies have demonstrated that treatment with anticoagulant agents (which were frequently administered because of the diagnosis of valvular disease in our cohort) is an independent risk factor for intracerebral hemorrhage in our community (D.O. Wiebers, MD, et al, unpublished data, 2000). Subarachnoid hemorrhage was not treated as an end point because it has no etiologic relationship to valvular heart disease or its treatment.

All valve disease diagnoses were validated by the study echocardiographer, and all cerebrovascular events were validated by the study neurologist using the definitions outlined above. Because of the retrospective nature of the study, the study cardiologist and neurologist were not masked to the type of valve disease or other cardiovascular event or to the subsequent development of cerebrovascular events or death. Information regarding possible systemic (non–central nervous system) embolization was not collected because of the unreliability of clinical diagnosis of these events and infrequent validation of clinical diagnoses using radiographic or surgical techniques in our community.

Statistical Analysis

The Kaplan-Meier product-limit method was used to estimate rates of cerebrovascular events and death after the date of first echocardiographic diagnosis of valve disease. Patients were censored at the date of last information in the medical record as an Olmsted County resident in the survival analysis. Patients were censored at the time of death in the analysis of rates of development of cerebrovascular events. We calculated standardized morbidity ratios (SMRs) for cerebrovascular events and survival by dividing the number of observed events in the cohort by the expected number using age- and sex-appropriate rates from the population. CIs on the SMRs were obtained by assuming that the number of observed events has a Poisson distribution. Rates of observed events were compared with reported rates by a 1-sample log-rank test.

The Cox proportional hazards model was used to assess the impact of several potential risk factors on the occurrence of cerebrovascular events and death. Both baseline (at diagnosis of valvular heart disease) and time-dependent (possibly developing during follow-up) risk factors were considered. The baseline risk factors were age, sex, time from clinical to echo diagnosis of valvular heart disease, and treatment of valvular heart disease. The time-dependent variables included angina, myocardial infarction, hypertension, congestive heart failure, atrial fibrillation, and, in the survival model only, cerebrovascular events.

Univariate analyses of each of these variables were followed by multivariate analyses to identify risk factors making independent contributions to the development of cerebrovascular events or survival. This was done with the use of stepwise and backward selection procedures that involved not only the basic variables but also their interactions.

To compare death and cerebrovascular event rates among the different valve disease types (aortic stenosis, mitral stenosis, mitral regurgitation), 4 variables indicating the presence or absence of each of the 4 types of valve diseases were added to the multivariate proportional hazards models. The results of the variable selection process for the final models incorporating valve disease type and severity were validated by resampling (bootstrapping) methods, in which 500 multivariate proportional hazards regression analyses were performed on 500 data sets generated by random resampling from the original observations. Variables were validated for inclusion in the final model if they were included in >70% of these analyses at the 0.05 level.

The influence of anticoagulants on the development of cerebrovascular events was assessed with the use of a nested case-control design in which patients in the primary cohort who developed events (subsequent transient ischemic attack, amaurosis fugax, ischemic stroke, or intracerebral hemorrhage) served as cases. Each case was matched to a member of the cohort of the same age and sex who survived event free for the same length of time as the case had been event free. The odds ratio for treatment with warfarin at any time before the event and at the time of the event was derived by conditional logistic regression analyses.

**Results**

During the period of the study, 740 residents had a first 2-dimensional color Doppler echocardiographic diagnosis of valvular heart disease and 277 residents (37.5%) had at least one cerebrovascular event. The probability of cerebrovascular events and death were higher in the cohort of residents with valvular heart disease than in the general population (SMR 6.2; 95% CI 5.0–7.6) and the study cohort (SMR 2.4; 95% CI 2.0–2.9).

### TABLE 2. Kaplan-Meier Estimates of Rates of Cerebrovascular Events and Death Among 729 Residents of Olmsted County, Minnesota, After a First Echocardiographic Diagnosis of Valvular Heart Disease Made Between 1985 and 1992

<table>
<thead>
<tr>
<th>Time After First Echocardiographic Diagnosis of Valvular Heart Disease</th>
<th>Cerebrovascular Events</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage of Patients Developing Cerebrovascular Events</td>
<td>95% CI</td>
</tr>
<tr>
<td>6 mo</td>
<td>2.9</td>
<td>1.6–4.1</td>
</tr>
<tr>
<td>1 y</td>
<td>4.9</td>
<td>3.3–6.6</td>
</tr>
<tr>
<td>2 y</td>
<td>8.0</td>
<td>5.9–10.1</td>
</tr>
<tr>
<td>3 y</td>
<td>11.2</td>
<td>8.7–13.8</td>
</tr>
<tr>
<td>5 y</td>
<td>17.5</td>
<td>13.9–21.3</td>
</tr>
<tr>
<td>7 y</td>
<td>23.1</td>
<td>18.2–28.7</td>
</tr>
</tbody>
</table>
Cerebrovascular Events

Cerebrovascular events developed in 98 patients (13.4%) during follow-up, including 4 with amaurosis fugax, 20 with transient ischemic attack, 68 with ischemic stroke, and 6 with intracerebral hemorrhage. Table 2 presents the Kaplan-Meier estimates of rates of development of cerebrovascular events for the entire cohort. These rates were significantly greater than the corresponding age- and sex-adjusted rates for the community (SMR=3.2; 95% CI, 2.6 to 3.8; log-rank P<0.001; Figure 1). Rate estimates for the development of cerebrovascular events for each valve disease subtype are presented in Table 3. Differences in rates among the valve groups were not significant when adjusted for age and sex (P=0.6). Time-dependent proportional hazards regression analysis identified age and an interaction between age and intermittent or persistent atrial fibrillation as independent determinants of cerebrovascular events in this cohort, with atrial fibrillation imparting a greater risk of cerebrovascular events at younger ages (Table 4). Adjusted for age and atrial fibrillation, severe aortic stenosis (compared with moderate aortic stenosis) was also an independent determinant of the development of cerebrovascular events (risk ratio [RR]=3.5; 95% CI, 1.4 to 8.6). The time-dependent proportional hazards regression analysis was repeated with only ischemic cerebrovascular events used as end points (excluding the 6 intracerebral hemorrhages), and the model was unchanged.

Clinical diagnosis of valve disease before echocardiographic diagnosis was not a determinant of the subsequent development of cerebrovascular events, either in age-adjusted univariate analysis (RR=0.95; 95% CI, 0.63 to 1.43; P=0.8) or in the final multivariate model. One hundred twenty-two members of the cohort (16.7%) had aortic or mitral valve repair or replacement during follow-up. Valve repair or replacement was not a determinant of survival free of cerebrovascular events either in the univariate analysis (RR=1.64; 95% CI, 0.95 to 2.84) or in the final model.

Three hundred forty-five members of the cohort (47.3%) received anticoagulation after the diagnosis of valve disease, including 12 of the patients (63.2%) with mitral stenosis, 236 (44.7%) with mitral regurgitation, 67 (47.9%) with aortic

TABLE 3. Kaplan-Meier Estimates of Rates of Cerebrovascular Events Among Residents of Olmsted County, Minnesota, After a First Echocardiographic Diagnosis of Valvular Heart Disease Made Between 1985 and 1992*

<table>
<thead>
<tr>
<th>Type of Valve Disease</th>
<th>1 y (Percent 95% CI)</th>
<th>5 y (Percent 95% CI)</th>
<th>7 y (Percent 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral stenosis (n=19)</td>
<td>17 (8–35)</td>
<td>17 (0–48)</td>
<td>17 (0–48)</td>
</tr>
<tr>
<td>Mitral regurgitation (n=528)</td>
<td>5 (3–7)</td>
<td>19 (14–23)</td>
<td>24 (18–32)</td>
</tr>
<tr>
<td>Aortic stenosis (n=140)</td>
<td>7 (3–11)</td>
<td>19 (11–28)</td>
<td>22 (12–35)</td>
</tr>
<tr>
<td>Aortic regurgitation (n=106)</td>
<td>1 (0–3)</td>
<td>8 (1–15)</td>
<td>17 (5–30)</td>
</tr>
</tbody>
</table>

*Differences between valve disease groups are not significant when adjusted for age and sex (P=0.6). The sum of individuals assigned to the 4 valve groups is greater than the number of patients in the entire cohort because 63 members of the cohort had >1 type of valve disease.

TABLE 4. Cox Proportional Hazards Model of Independent Determinants of Cerebrovascular Events After First Echocardiographic Diagnosis of Valvular Heart Disease Among 729 Residents of Olmsted County, Minnesota, Between 1985 and 1992

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No AF</th>
<th>AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>1*</td>
<td>11.7 (2.5–55)</td>
</tr>
<tr>
<td>50</td>
<td>2.1</td>
<td>15.3 (3.6–65)</td>
</tr>
<tr>
<td>60</td>
<td>4.3</td>
<td>20.1 (5.1–79)</td>
</tr>
<tr>
<td>70</td>
<td>8.8</td>
<td>26.3 (7–100)</td>
</tr>
<tr>
<td>80</td>
<td>18.1</td>
<td>34.5 (9–130)</td>
</tr>
<tr>
<td>90</td>
<td>37.2</td>
<td>45.2 (12–177)</td>
</tr>
</tbody>
</table>

*The group of individuals aged 35–44 y without atrial fibrillation (AF) was used as the comparison.
stenosis, and 41 (38.7%) with aortic regurgitation. Nested case-control analysis, adjusted for age and atrial fibrillation, demonstrated no effect on the occurrence of cerebrovascular events for either current (odds ratio = 1.21; 95% CI, 0.57 to 2.58) or prior (odds ratio = 1.24; 95% CI, 0.64 to 2.39) treatment with warfarin. Three of the 6 intracerebral hemorrhages (50.0%) and 14 of the 68 ischemic strokes (20.6%) occurred among patients treated with warfarin.

### Survival

During follow-up, 356 patients died. The cause of death was congestive heart failure in 90, myocardial infarction in 47, stroke in 22, and sudden unexplained death in 3. The other deaths were due to other noncardiovascular causes (193 patients) or unknown cause (1 patient). The Kaplan-Meier estimates of rates of death after first echocardiographic diagnosis of valvular disease are presented in Table 2. These rates were significantly worse than the age- and sex-adjusted rates for the population (SMR = 2.5; 95% CI, 2.2 to 2.7; P < 0.001, Figure 2). Estimates of rates of death for the individuals types of valve disease, adjusted for age and sex, were not significantly different (P = 0.1) (Table 5).

Time-dependent Cox proportional hazards regression analysis univariately identified ischemic heart disease (RR = 1.71; 95% CI, 1.38 to 2.12), atrial fibrillation (intermittent RR = 1.46; 95% CI, 1.13 to 1.90; persistent RR = 1.35; 95% CI, 1.05 to 1.74), congestive heart failure (RR = 4.19; 95% CI, 3.18 to 5.52), cerebrovascular events (RR = 2.44; 95% CI, 1.82 to 3.27), and clinical diagnosis of valve disease before echocardiogram (RR = 0.77; 95% CI, 0.62 to 0.95) as possible determinants of survival after adjustment for age and sex. Multivariate time-dependent proportional hazards regression analysis resulted in a final model in which independent predictors of death were age, sex, cerebrovascular events, ischemic heart disease, and congestive heart failure, which interacted with each other as described in Table 6. After adjustment for these variables, the type and severity of valve disease were not important determinants of survival. Valve repair or replacement was not a determinant of survival either in the univariate analysis (RR = 1.01; 95% CI, 0.72 to 1.41) or in the final model.

### Discussion

The significance of our study is that it reports rates, identifies determinants of cerebrovascular events, and quantifies the impact of cerebrovascular events on survival among all residents with newly echocardiographically diagnosed valve disease in a defined population. The population-based nature of our study limits bias that could have affected measurements of cerebrovascular events and survival in previous natural history studies involving patients referred to tertiary centers from outside a community. In contrast to many earlier studies addressing the risk of stroke among patients with valve disease, our study included only patients with newly echocardiographically diagnosed valve disease and without a history of cerebrovascular events, thus eliminating possible bias from inclusion of patients referred for echocardiographic evaluation of single or multiple cerebrovascular events or from inclusion of patients with a history of stroke in earlier years who had guaranteed survival to the time of echocardiography. In addition to providing new insights into the relationship between valve disease and cerebrovascular events, the uniform echocardiographic diagnostic criteria and large number of patients in our study allowed us to develop and validate multivariate models, which more precisely quantify the relative risks of cerebrovascular events and death.

### TABLE 5. Kaplan-Meier Estimates of Rates of Death Among 729 Residents of Olmsted County, Minnesota, Between 1985 and 1992

<table>
<thead>
<tr>
<th>Type of Valve Disease</th>
<th>1 y</th>
<th>5 y</th>
<th>7 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral stenosis (n=19)</td>
<td>16 (0–32)</td>
<td>28 (7–49)</td>
<td>27 (7–60)</td>
</tr>
<tr>
<td>Mitral regurgitation (n=528)</td>
<td>18 (15–22)</td>
<td>51 (47–56)</td>
<td>60 (54–66)</td>
</tr>
<tr>
<td>Aortic stenosis (n=140)</td>
<td>21 (14–27)</td>
<td>57 (47–66)</td>
<td>71 (61–81)</td>
</tr>
<tr>
<td>Aortic regurgitation (n=106)</td>
<td>11 (5–17)</td>
<td>40 (29–50)</td>
<td>50 (38–63)</td>
</tr>
</tbody>
</table>

**Percent (95% CI) Dying**

* Differences between valve groups are not significant when adjusted for age and sex (P = 0.1).

### TABLE 6. Cox Proportional Hazards Time-Dependent Model of Determinants of Death After First Echocardiographic Diagnosis of Valvular Heart Disease Among 729 Residents of Olmsted County, Minnesota, Between 1985 and 1992

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 y)</td>
<td>1.52</td>
<td>1.37–1.69</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without ischemic heart disease</td>
<td>0.91</td>
<td>0.63–1.29</td>
</tr>
<tr>
<td>With ischemic heart disease</td>
<td>1.54</td>
<td>1.16–2.03</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.12</td>
<td>0.85–1.47</td>
</tr>
<tr>
<td>Male</td>
<td>1.90</td>
<td>1.33–2.70</td>
</tr>
<tr>
<td>Cerebrovascular events*</td>
<td>4.34</td>
<td>2.38–7.95</td>
</tr>
<tr>
<td>Congestive heart failure*</td>
<td>4.42</td>
<td>3.23–6.04</td>
</tr>
<tr>
<td>Cerebrovascular events and congestive heart failure*</td>
<td>8.80</td>
<td>5.80–13.35</td>
</tr>
</tbody>
</table>

*Compared with no cerebrovascular events and no congestive heart failure.
attributable to various cardiovascular comorbidities among patients with valvular heart disease.

Studies of the relationship between valve disease and stroke derived from patients followed at referral centers during earlier decades focused on the importance of mitral stenosis as a source of thromboembolism, particularly when accompanied by atrial fibrillation. Aortic stenosis is presumed to be uncommonly associated with stroke, but its role in valve disease, whether atrial fibrillation simply becomes a stronger determinant of stroke risk attributable to valvular atrial fibrillation before the echocardiographic diagnosis of valve disease, we cannot determine whether the greater impact on cerebrovascular events, even after adjustment for age and atrial fibrillation (RR = 3.5). Our study suggests that hemodynamically significant aortic valve disease may be an underrecognized source of embolism among patients with valvular heart disease. Alternatively, hemodynamically severe aortic valve disease may be a marker for other conditions that increase stroke risk in valve disease patients, such as atherosclerosis or prothrombotic tendencies.

Another important finding of our study that differs from earlier studies of stroke risk among patients with valvular heart disease is the interaction between age and atrial fibrillation. Prior reports indicated either no difference in stroke risk among young and old patients with valvular disease and atrial fibrillation or an increased risk with age. Our multivariate model demonstrates that atrial fibrillation has a far stronger impact on the risk of cerebrovascular events among younger patients with valve disease (Table 4). Because we did not collect information on duration of atrial fibrillation before the echocardiographic diagnosis of valve disease, we cannot determine whether the greater impact on the risk of stroke attributable to valvular atrial fibrillation at younger ages is due to an increased risk primarily among patients with new-onset atrial fibrillation, as suggested by Szekely, or whether atrial fibrillation simply becomes a relatively less important mechanism of stroke in older patients with valve disease as other stroke risk factors become more prevalent, despite the increase in atrial fibrillation prevalence with age in the general population.

Our study also provides new quantitative evidence on the relative importance of cardiovascular comorbidities that influence survival in patients with valve disease: age, ischemic heart disease, and congestive heart failure. Our multivariate survival model (Table 6) demonstrates that congestive heart failure is a far more important determinant of death among patients with newly diagnosed valvular heart disease than ischemic heart disease. Congestive heart failure alone confers a 4-fold risk of death among patients with valve disease, regardless of sex, whereas ischemic heart disease confers a 2-fold increased risk of death among men with valve disease and no significant increase in risk of death among women with valve disease.

A unique and striking aspect of our study is the documentation of a nearly 9-fold increased risk of death among valvular heart disease patients with congestive heart failure who develop cerebrovascular events. This finding is an illustration of the power of multivariate modeling to identify biological interactions that strongly influence disease outcomes and suggests that prospective randomized studies to identify interventions to prevent cerebrovascular events and death among valve disease patients with congestive heart failure may be especially indicated, regardless of the presence or absence of atrial fibrillation.

In contrast to the findings in the cerebrovascular event analysis, we found that among the various types and severities of aortic and mitral disease, none were independent predictors of death after adjustment for age, sex, ischemic heart disease, congestive heart failure, and cerebrovascular events. These findings suggest that clinical comorbidities of ischemic heart disease, congestive heart failure, and cerebrovascular events are more important determinants of survival among patients with valvular heart disease than the particular type and severity of valve disease.

Despite the decline in rheumatic valve disease and recent advances in medical and surgical therapy for cardiac disease, our study demonstrates that the relative risks of cerebrovascular events and death in valve disease patients remain disturbingly high, at 3.2 and 2.5 times, respectively, the age- and sex-adjusted rates for the general population. In fact, death rates in our community for individual types of valve disease (Table 5) are similar to those reported from a referral center by Rapaport 25 years ago. Although earlier nonpopulation-based studies may have overestimated death rates by inclusion of patients selected for referral because of comorbidity profiles that negatively influence survival, our findings suggest that randomized treatment trials for patients with valve disease may be indicated to determine interventions that will improve outcomes in these patients.

Because we included amaurosis fugax and transient ischemic attack as cerebrovascular end points, the question could arise as to whether patients with known valvular heart disease might be more vigilant regarding medical symptoms and thus more likely to notice and seek medical attention for transient symptoms than individuals in the general population, thus resulting in an overestimation of the standardized morbidity ratio for cerebrovascular events. We believe this is not the case for 2 reasons. First, we have shown previously that our methods of ascertainment identify virtually all instances of transient ischemic attack and amaurosis fugax that occur in our community. Second, the proportion (24 of 92, 26.1%) of amaurosis fugax and transient ischemic attack among all incident ischemic events in our cohort is actually lower than the proportion in the community (34.4%). This observation is also consistent with the findings of previous case-control studies in our community, which suggest that valvular heart disease is less likely to be associated with cerebral ischemic episodes that are brief enough to be called transient ischemic attack than other mechanisms of cerebral ischemia.

Our study does have some limitations. The community is largely white, and the prevalence of cardiovascular risk factors may not be the same as in more ethnically diverse communities. Although demographic factors may influence overall assessment of determinants of cerebrovascular events and survival for the population in general, we believe they are probably less important in assessing the determinants of these
end points within a defined cohort of individuals with valve disease. Although our study is population based, most patients were evaluated by physicians in a tertiary referral center. Replication of our study in a setting remote from a tertiary referral center could give different results. Inclusion of autopsy-ascertained cerebrovascular events could have biased our findings toward a higher RR for cerebrovascular disease as a determinant of death. On the other hand, exclusion of autopsy-ascertained events would not have been consistent with the population-based design of our study and could have resulted in underestimation of cerebrovascular event rates.

Because of the retrospective and observational nature of the study, there was no standard echocardiographic follow-up, and we were therefore unable to assess the impact of hemodynamic progression of valvular disease or severity of congestive heart failure on outcomes. The smaller number of patients and end points within each subgroup of valve disease, especially mitral stenosis, did not permit modeling of interactions between different types and severities of valve disease or modeling of determinants of cerebrovascular events and survival within individual valve disease subgroups. We did not examine the effect of the specific etiology of valve disease on survival and cerebrovascular events in the cohort, although we did control for the presence or absence of other cardiovascular diseases that might play a role in the genesis of valve disease in some patients. The relative infrequency with which new diagnoses of mitral stenosis were made in our community during the period of our study is probably attributable in part to the decline in the incidence of rheumatic fever and rheumatic mitral valve disease. We do not have information on ischemic stroke subtypes and therefore cannot determine whether the increased cerebrovascular risk attributable to severe aortic stenosis is due to embolism or due to associated atherosclerotic arterial occlusive disease or atherosclerotic aortic debris. The observational nature of our study somewhat limits our ability to speculate on why, despite treatment advances, survival in these patients remains so poor. For example, we did not find any influence on outcomes for valve replacement or repair in time-dependent multivariate analysis, nor could we detect a protective effect of treatment with warfarin with respect to the occurrence of cerebrovascular events (adjusting for age and atrial fibrillation) in the nested case-control analysis. However, we do not believe that the results of this historical cohort study can be interpreted as indications of lack of efficacy or safety of these treatments, because patients were selected and treated in a nonrandomized, nonstandardized fashion, using criteria for which our models cannot completely control. For example, patients who were not selected for anticoagulation may have had risk factor profiles that guaranteed better outcomes than those who were selected for treatment. Therefore, inferences regarding treatment recommendations should not be made on the basis of these observations. Finally, because ours is a historical cohort study of patients with hemodynamically significant valvular heart disease diagnosed echocardiographically, the qualitative and quantitative information that our study provides about risk factors and their interactions is applicable to patients with valvular heart disease, not to patients in the general population without valvular heart disease.

In summary, despite advances in medical and surgical therapy for valve disease and its complications over the last several decades, the risk of cerebrovascular events and death among these patients remains high. Age, atrial fibrillation, and the presence of severe aortic stenosis are the most important determinants of cerebrovascular events in patients with valvular heart disease. Age, sex, ischemic heart disease, congestive heart failure, and cerebrovascular events are the most important determinants of death, with the poorest survival being among those valvular heart disease patients with congestive heart failure who develop cerebrovascular events. These findings predict a continuing significant burden of morbidity and mortality attributable to valve disease, especially in developing countries where the prevalence of valve disease is highest.

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