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; JoRena 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.

Key Words: atrial fibrillation ▪ cerebral embolism and thrombosis ▪ echocardiography ▪ heart valve diseases ▪ stroke

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. The medical record contains all inpatient and outpa-
tient data, including information regarding emergency department
visits, nursing home care, autopsies, and death certificates. All
echocardiograms obtained at medical care facilities in Olmst-
ked 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 resi-
dents of Olmsted County, Minnesota, underwent echocardiogra-
phy 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. Popula-
tion-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 Dop-
pler echocardiographic diagnosis of moderate or severe mitral steno-
sis, 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 echocar-
diogram 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 nonecho-
cardiographic 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 semiquantita-
tively 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

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
cm. 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.32

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 preserva-
tion of strength were included if 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 head-
ache, vomiting, altered level of consciousness, signs of meningeal
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 classi-
ﬁed as an intracerebral hemorrhage. A case of intracerebral hemor-
rhage 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 conscious-
ness, and dizziness or wooziness were excluded unless associated
with other symptoms of brain stem ischemia. Symptoms such as
vertigo, dysthria, 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.
Transient symptoms associated with migraine were excluded.

Syncope alone was not considered a cerebrovascular end point.

The medical records of all residents of Olmsted County, Minne-
sota, 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 ab-
stracted to record the presence or absence of hypertension, conges-
tive 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, replace-
ment, 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>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 neurologists 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, aortic regurgitation, mitral stenosis, mitral regurgitation), 4 variables indicating the presence or absence of each of the 4 types of valve diagnoses and 8 variables to differentiate moderate and severe hemodynamic designations among the 4 valve disease types 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...
moderate or severe valve disease. Eleven patients declined to give consent to have medical records reviewed for this study, resulting in a cohort of 729 patients. Nineteen patients had mitral stenosis, 528 had mitral regurgitation, 140 had aortic stenosis, and 106 had aortic regurgitation, with 63 having >1 type of valve disease. Valve disease was classified as hemodynamically severe in 2 patients (10.5%) with mitral stenosis, 46 (8.7%) with mitral regurgitation, 55 (39.3%) with aortic stenosis, and 7 (6.6%) with aortic regurgitation. Combinations of mixed valve disease were mitral regurgitation and aortic stenosis in 29 patients; mitral regurgitation and aortic regurgitation, 22; aortic stenosis and aortic regurgitation, 8; mitral stenosis and mitral regurgitation, 1; mitral stenosis and aortic stenosis, 1; mitral stenosis and aortic regurgitation, 1; and mitral regurgitation, aortic stenosis, and aortic regurgitation, 1.

The mean (±SD) age of patients in the entire cohort was 72.3±15.8 years, and the age range was 13 to 107 years. Four hundred twenty-four of these patients (58.2%) had a nonechocardiographic diagnosis of valve disease before the date of the first echocardiographic diagnosis. Cardiovascular risk factors among these patients are presented in Table 1. The entire cohort was followed for a total of 2694 person-years. Median follow-up was 3.5 years.

### 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</th>
<th>5 y</th>
<th>7 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral stenosis (n = 19)</td>
<td>17 (8–35)</td>
<td>17 (0–38)</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>8.3</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.
Type of Valve Disease

<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


Kaplan-Meier estimates of rates of death after first echocardiographic diagnosis of valve disease. SMR indicates standardized morbidity ratio.
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. In our study of patients with valvular heart disease newly diagnosed by echocardiography, atrial fibrillation was, in fact, associated with rates of development of cerebrovascular events similar to those for mitral stenosis (Table 3) and was an independent determinant of the development of cerebrovascular events, even after adjustment for age and atrial fibrillation. 

Another important finding of our study that differs from some 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 valve 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 non-population-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 endpoints, 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.

Acknowledgment
This study was supported by the National Institute of Neurological Disorders and Stroke (grant NS06663).

References


Predictors of Cerebrovascular Events and Death Among Patients With Valvular Heart Disease: A Population-Based Study
George W. Petty, Bijoy K. Khandheria, Jack P. Whsnant, JoRean D. Sicks, W. Michael O'Fallon and David O. Wiebers

Stroke. 2000;31:2628-2635
doi: 10.1161/01.STR.31.11.2628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/31/11/2628

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/