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Morbidity and Mortality Associated With Transient Ischemic Attack (TIA)

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Transient ischemic attack (TIA) is defined as "an episode of focal loss of brain function attributed to ischemia that lasts less than 24 hours, is localized to a portion of the brain supplied by one vascular system, has no persistent deficit, and is not attributable to any other cause."[1] Most TIAs are caused by small thromboemboli that originate in atheromatous areas in neck vessels or the heart. Other mechanisms include nonatherosclerotic vascular diseases, mitral valve prolapse, hematologic diseases, and abnormal blood pressure fluctuations. Even in series of fully investigated cases, there remains a group in which no cause can be found. The great majority of TIAs are extremely brief. In one series, 24% ended within 5 minutes, 39% in 15 minutes, 50% in 30 minutes, and 60% in 1 hour.[2]
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Morbidity And Mortality Following TIA

Community-based studies generally provide the best estimates of long-term prognosis after TIA. Two such studies have been reported. The Oxfordshire Community Stroke Project (United Kingdom) followed 184 subjects who had a TIA between 1981 and 1986 and who were initially seen by general practitioners in the rural and urban Oxfordshire area.[3] None of the cohort had suffered a stroke prior to enrollment, although some had experienced other TIAs in the past. Mean age was 69.4 years (56% male). Surviving patients were followed for an average of 3.7 years (range 2 days to 7 years). Mortality comparisons were based on age- and sex-specific mortality rates for Oxfordshire.

The majority of deaths were due to cardiac disease. The overall mortality rate was high but only slightly greater than for people without a history of TIA. Excess mortality was highest in the first year. Mortality ratios were greater for women and for people under the age of 75. Stroke risk was very high in the first 12 months. For patients alive 12 months after the TIA, the risk of stroke during the next 5 years averaged 5.3 times the risk of the control population.

The second community-based study was conducted by the Mayo Clinic (Rochester, Minnesota).[4] 330 subjects who had a first TIA between 1955 and 1979 and no history of prior stroke were followed for 10 years to determine survival and relative risk of stroke compared to an age- and sex-matched population. Survival free from stroke and overall survival were reduced in subjects with a prior TIA compared to the general population (Table 1). This pattern was observed in the first 12 months after TIA and during the subsequent 4 years. Only a few independent factors could be identified. Older age was a predictor of subsequent stroke; the stroke risk increased 45% for each 10 years of increased age. There was also a suggestion that multiple TIAs (especially 5 or more) before medical attention increased the risk of subsequent stroke, but most of the extra risk was confined to the first 6 months. Young women had the best overall survival and older women had the worst overall survival among the age-gender groups. For men, the relative death risk peaked at age 50 and decreased thereafter.

Four large hospital-based studies provide additional information concerning mortality after TIA, although the data may not be generalizable to all cases of TIA within a community. Two studies reported that mortality following TIA was significantly greater compared to the general population. A third series found that post-TIA patients with more than one vascular risk factor had significantly increased mortality, while survival in those with no risk factors was similar to the general population. The prognosis was more favorable in the fourth report; this was probably related to the low average age of the cohort (49 years)[3].

Bowman Gray School of Medicine (North Carolina) initiated a prospective study in 1964 to

Table 1: Survival Free From Stroke And Overall Survival Rates For Patients With First TIA Compared To An Age-And Sex-Matched Populations

Survival Data	Absolute Rate (%)	Relative To Expected (%)
Survival Free From Stroke		
1 year after stroke	86	87
5 years after stroke	72	75
Overall Survival		
1 year after stroke	89	94
5 years after stroke	65	87

Source: Evans et al.[4]

determine the natural history of TIA and identify factors affecting prognosis.[5] Follow-up averaged 5.25 years for untreated and medically treated patients, and 5.6 years for the surgically treated group. Relative to death rates in United States 1969-71 Population Tables, mortality ratios by treatment group were as follows: medical- 162%; surgical- 264%; medical plus surgical- 238%; and untreated- 343%.6

Studies from China and Japan indicate that stroke is a relatively more common cause of post-TIA morbidity and mortality in Asian populations. Investigators in Beijing followed 71 subjects with TIA for 22 years.[7] Most of the 34 deaths were due to stroke (cerebral hemorrhage in 15 cases and cerebral infarction in 6 cases). There was only one death due to myocardial infarction. A higher incidence of stroke death and a lower incidence of generalized atherosclerosis was also observed in the 20-year prospective community study of TIA incidence in the rural community of Hisayama, Japan.[8] Of the original 1621 subjects, 18 people (11 men and 7 women) had a first-ever TIA at a mean age of 71.6 years. Strokes occurred in 50% of these patients, as compared to 11% of an age-matched control group. Nine deaths occurred in the subjects who had suffered a TIA (cancer- 3; stroke- 2; emphysema- 1; congestive heart failure- 1; accident- 1; infection- 1). Autopsies on the deceased subjects revealed 1 prior myocardial infarction, severe carotid atherosclerosis in 2 cases, and mild to moderate carotid stenosis in 1 patient. The authors remarked that atherosclerotic disease appeared to play a somewhat smaller role in the pathophysiology of TIA in Japanese patients as compared to Western populations. (It is likely this pattern will change due to the increasing prevalence of cigarette smoking and the adoption of a Western diet in some parts of Asia.)

A number of reports have observed a more favorable prognosis in patients with retinal TIAs (amaurosis fugax) compared to those with TIAs involving much larger areas of the brain (hemispheric TIAs).[9] The improvement in prognosis is relative; the incidence of stroke in patients with amaurosis fugax is still considerably higher than in the general population.[10]

The prognosis of patients with asymptomatic retinal cholesterol emboli was reported in a study from Albuquerque, New Mexico.[11] All subjects were men (mean age 69 years). The average annual stroke rate during the 3.4 year follow-up was approximately 13 times higher than that expected for men of similar age. The total mortality rate was only slightly higher than in the control population, perhaps because there was a high rate of comorbid vascular disease (e.g., hypertension, diabetes mellitus, ischemic heart disease, and prior stroke) in both study subjects and controls. In contrast, several other reports have found that patients with retinal cholesterol emboli had a higher mortality rate than did age- and sex-matched general population controls.[11]

A final study from London, Ontario is noteworthy because it suggests there is reason to be concerned about extra morbidity and mortality following TIA in middle-aged and elderly individuals even if a fairly detailed workup fails to detect any significant abnormalities.[12] Forty-three patients (26 men and 17 women) were followed for an average of 4.4 years after a TIA. Mean age was 55.6 years (range 24 to 72). Sixteen subjects had a single TIA and 27 had multiple TIAs. All of the participants had a normal four-vessel angiogram, a normal cranial computed tomography scan, normal cardiac findings (41 had echocardiography and 34 Holder monitoring), and normal hematologic findings. Angina pectoris later developed in 6 subjects, 2 of whom also experienced a myocardial infarction. No strokes occurred but 6 patients had recurrent TIAs. The authors were unable to identify any risk factor that could distinguish patients at risk

for future cardiac disease. They did note that subsequent vascular events were more common in the group with multiple TIAs, but the difference was not statistically significant.

Experience In A Young Population

A study from Copenhagen, Denmark reported the long-term prognosis of 46 young people (14 men and 32 women) with few or no underlying impairments who experienced a TIA between 1971 to 1980.[13] Mean age was 29 years (range 18 to 39 years) and follow-up averaged 10 years (range 5 to 15 years). All patients were hospitalized for a detailed medical evaluation. Excluded from the study were patients with a prior stroke, those in whom subsequent examination disclosed an intracranial lesion (e.g., tumor or vascular malformation), and those with a history of classic migraine (headache preceded by sensory, motor or visual symptoms). Seven subjects with common migraine (headache without preceding symptoms) were included. Approximately half the cohort had experienced other TIAs in the past.

Cardiovascular risk factors and/or diseases were uncommon: angina pectoris (1 patient), diabetes mellitus (1 patient; arteriosclerosis obliterans was also present), and hyperlipidemia (3 patients in the 29 for whom lipid data were available; one case was the patient with diabetes). There were no cases of hypertension, nonatherosclerotic heart disease, collagen disease, or blood dyscrasias. Twenty-seven patients had angiograms and only 4 showed abnormalities, all of which were located in vessels that could account for the TIAs. Ten of the 34 women used contraceptive pills and 6 were pregnant.

Twenty-six patients had no further TIAs, 2 patients had one, and 15 had two or more episodes. Eight patients developed migraine attacks (5 common, 3 classic). Four patients (3 men and 1 woman) had a stroke; none were fatal. Myocardial infarction occurred in three cases (all males). Two of the infarctions were fatal; one was preceded by a stroke. In summary, serious events during follow-up were limited to the 6 patients who experienced either a stroke or a myocardial infarction, or both. These events occurred 1 to 11 years after admission (mean 5 years).

Compared to series of middle-aged and elderly TIA patients, this study was characterized by a predominance of women, a low prevalence of associated cardiovascular risk factors and/or diseases, few angiographic abnormalities, and a very favorable prognosis. The 15 patients (13 women, 2 men) with migraine attacks had a strikingly good prognosis; no major vascular event occurred during an observation period averaging 10 years. The 19 women in the nonmigraine group also fared well, the only vascular event being one stroke in a 27-year-old woman who was neither pregnant nor using contraceptive pills. In contrast, 5 of the 12 men without a history of migraine suffered either a stroke or a myocardial infarction. Four of these patients had cardiovascular risk factors and/or diseases at the time of the TIA. This high morbidity is comparable to that observed in series of elderly TIA patients.

Another study of young patients with TIAs included 38 Portuguese subjects aged 45 years or younger.[14] Follow-up averaged 33.4 months. Only 2 patients experienced recurrent cerebrovascular events (1 hemorrhagic stroke and 1 TIA). Some patients retired even though there was no functional impairment.

The relatively favorable morbidity and mortality in young people after TIA has been observed in other studies. The explanation is probably related to the absence of serious underlying impairments. It may also be that many TIAs at the younger ages, particularly in women with migraine, are caused by flow disturbances rather than by the thromboembolic process characteristic of TIA in the elderly.[13]

Risk Factors

There are conflicting reports in the medical literature regarding risk factors that predict outcome following TIA.[15] Various studies have reported that post-TIA survival is significantly decreased by older age, smoking, previous stroke, ischemic heart disease, peripheral artery disease, and diabetes mellitus. Hypertension was found to increase the risk of stroke in the joint study of carotid TIA, in an Italian study of reversible ischemic attacks, and in the North American Stroke Data Bank, but it did not influence the probability of stroke after TIA in two other reports. The varying importance of these variables probably reflects differences in the risk factor profiles of the study populations.

Outcome of TIA Compared To Minor Stroke

Patients with cerebral ischemia are usually classified according to the duration of symptoms:

- TIA- Symptoms completely reversible within 24 hours.

- RIND (reversible ischemic neurologic deficit)- Symptoms lasting more than 24 hours but completely absent after 6 weeks. Some investigators define the upper duration of RIND as 1, 3 or 4 weeks.[16,17]
- Stroke- Persisting symptoms or signs of cerebral infarction.

Advances in imaging technology have raised questions regarding the accuracy of this traditional clinical classification. One study documented CT (computed tomography) evidence of cerebral infarction in 39% of patients who had experienced a TIA.[2] Another report from the Dutch TIA Trial provided some of the best data on this subject.[18] Investigators performed CT scans on 606 patients with TIA, 422 patients with a reversible ischemic neurologic deficit, and 1054 patients with a minor stroke (no more than moderate disability, i.e., requiring some help but able to walk without assistance). Relevant ischemic lesions (i.e., lesions correlating with signs and symptoms of the ischemic episode) were found in 13% of TIAs (an incidence similar to the 12% found in the Oxfordshire Community Stroke Project but somewhat lower than in most other reports), 35% of RINDs, and 49% of minor strokes. Multiple infarcts (indicating prior strokes) were found in 3% of TIAs, 4% of RINDs, and 11% of minor strokes.

Cerebral infarctions were found in each time category, e.g., strokes occurred in 11% of patients with TIA symptoms of 1 to 30 minutes duration and in 30% of RINDs lasting 1 to 7 days (Table 2). Infarctions were also observed in 3 of 12 patients (not shown separately) with attacks lasting less than 1 minute. The increase in the frequency of infarcts with longer attacks was gradual and not related to the artificial boundaries of 24 hours (TIA), 24 hours to 6 weeks (RIND), or longer than 6 weeks (stroke). The authors concluded that TIA, RIND, and minor stroke should be regarded as a continuum of cerebrovascular disease rather than as distinct subgroups.

A prospective hospital-based study from Malmö, Sweden compared the morbidity and mortality of TIA and minor stroke.[19] Seventy-eight patients with TIA (mean age 66.9 years) and 45 patients with minor stroke (mean age 68.8 years) were followed for 3 years. Comorbid vascular diseases were common in both groups. Mortality and cardiovascular morbidity were significantly greater in the TIA cohort than in patients with minor stroke. In the TIA group, myocardial infarction was the most common cause of death, and recurrent TIAs and nonfatal myocardial infarctions were more common than in subjects with minor stroke. There was no difference between the groups in the incidence of future stroke.

In the longest prospective study of its kind in Spain, investigators compared morbidity and mortality in patients with TIA (65 cases), RIND (37 cases), and minor stroke (41 cases)[17]. The group included 112 men and 31 women. Mean age was 57.8 years (range 24 to 82 years), and follow-up averaged 5.2 years. Cardiovascular risk factors were common, as was a prior history of cardiovascular and/or cerebrovascular disease. Morbidity and mortality were high, but there were no significant differences in outcome among the 3 groups except that disabling stroke was less frequent in patients with a history of minor stroke compared to

Table 2: Frequency of Relevant Cerebral Infarct on Computed Tomography According to Duration of Attack

Disorder	Relevant Cerebral Infarct (%)
TIA	
1-30 minutes	11
31-60 minutes	8
1-4 hours	13
5-24 hours	23
RIND	
1-7 days	30
1-6 weeks	39
Minor Stroke	49

Source: Koudstaal et al.

those with TIA or RIND. This latter observation may seem puzzling, but it is analogous to the observation that elderly patients who survive a non-Q-wave myocardial infarction have a higher death rate during the remainder of the year than patients with a Q-wave infarction.[20] In each case - TIA and non-Q-wave infarction - there is still an area at risk for infarction.

A final study from Giessen, Germany reported the prognosis of 381 patients (mean age 59.5 years) hospitalized with a cerebellar or brain stem TIA or minor stroke.[15] Follow-up averaged 3.9 years. Subjects with a history of minor stroke had a significantly higher risk of death, myocardial infarction, or recurrent stroke compared to those with TIA. This finding differs from studies cited earlier. The explanation is probably related to differences in risk factors among the study populations.

Underwriting Considerations

Mortality

Mortality following TIA is significantly greater than in the general population, especially in the first year.

The 5% to 6% annual mortality rate following TIA is mainly due to myocardial infarction. This percentage is similar to the 4% annual cardiac mortality rate in patients with stable angina pectoris.[21]

Excess mortality is greater at younger ages.

Some studies have reported a less favorable prognosis in patients with multiple cardiovascular risk factors and/or other cardiovascular impairments.

Stroke

- The risk of stroke after TIA varies depending on the population. Overall, post-TIA stroke risk is approximately 5% during the first month, 12% during the first year, and 30% during the next 5 years.[21] In community studies, the risk of stroke after TIA averages 12% in the first year and 7% per year thereafter. This risk is approximately 7 times higher than in a general population of the same age.[22]
- The risk of stroke is generally higher in patients with TIAs that cause extensive neurologic deficit (hemispheric TIAs), recent or increasingly frequently TIAs, or TIAs associated with high-grade carotid stenosis.[23]

Young People (ages to 39 years)

- In young people with a history of TIA, prognosis is generally favorable if a detailed medical evaluation fails to find a cause for the TIA other than migraine, and if there are no associated cardiovascular risk factors and/or diseases.
- Outcome is very favorable if the TIA was due to migraine, especially in women.
- Young patients with cardiovascular risk factors and/or diseases at the time of the TIA, particularly men, experience morbidity and mortality that is comparable to a more elderly population.
- Some young patients retire following a TIA even though there is no functional impairment.

TIA Compared To Minor Stroke

- Computed tomography scans indicate that strokes often occur in patients with a clinical diagnosis of TIA.
- Transient ischemic attack, reversible ischemic neurologic deficit, and minor stroke represent a continuum of cerebrovascular disease rather than distinct subgroups.
- Patients with TIA and minor stroke experience similar morbidity and mortality.

General Comments

- Stroke is a relatively more common cause of post-TIA morbidity and mortality in Asian populations.
- Prognosis is somewhat better for patients with amaurosis fugax and asymptomatic retinal cholesterol emboli, but still considerably less favorable than in the general population.
- The underwriting evaluation should focus on known cardiovascular risk factors and/or impairments, adequacy of the post-TIA medical evaluation, and the possibility of undetected cardiac disease.

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