

# Transient Ischemic Attacks Are More Than “Ministrokes”

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**Background and Purpose**—Transient ischemic attacks (TIAs) are warning signs of stroke. Recently, the hypothesis was raised that TIA bears a significant risk for death and dependence and requires the same complex diagnostic workup as a complete stroke.

**Methods**—We prospectively collected pre- and in-hospital procedures, symptoms, outcome, complications, and therapies from a representative sample of all stroke-treating hospitals (n=82) in southwest Germany. Follow-up was attempted 6 months after discharge. End points were death or dependence in activities of daily living (Barthel Index <95, modified Rankin Scale (mRS) of 3 to 6, or institutionalization in a nursing home).

**Results**—1380 TIA patients and 3855 stroke patients entered the database. During hospital stay, stroke incidence was 8% for TIA patients and another 5% within the first half-year. Similarly, for ischemic stroke (IS) patients these figures were 7% and 6% ( $P>0.05$ ), respectively. Two percent of TIA patients died in hospital (5% afterward) compared with 9% of stroke patients (10% afterward,  $P<0.001$ ). Seventeen percent TIA compared with 38% IS patients ( $P<0.05$ ) were dependent at follow-up. Whereas an estimated preexisting deficit (mRS  $>2$ ) was the strongest predictor for death or disability (baseline mRS odds ratio, 4.1; 95% CI, 2.3 to 7.2), admission to a stroke unit was a valid predictor for survival and independence (odds ratio, 0.4; 95% CI, 0.2 to 0.9).

**Conclusions**—These data from a large, multicenter, nonselected, observational study underscore the “not so benign” prognosis for TIA patients. There is a relevant individual risk of early stroke, death, or disability in TIA patients. Management and treatment strategies are similar for both TIA and acute stroke. (*Stroke*. 2004;35:2453-2458.)

**Key Words:** cerebrovascular accident ■ disease management ■ ischemic attack, transient ■ stroke, acute

An estimated 4.9 million people in North America do not seek medical advice despite reported transient ischemic attack (TIA) symptoms.<sup>1</sup> These “ministrokes” are usually of short duration (from minutes to a few hours) and, therefore, are considered benign with no need for emergency workup.<sup>2-6</sup> The traditional concept of TIA adds to this belittlement, although the short-term risk for any adverse event after TIA, either cerebrovascular or cardiovascular, is greater than previously assumed,<sup>7-9</sup> and the long-term risk, too, is substantial.<sup>8-12</sup> Because of this and the inability to differentiate TIA from stroke in the hyperacute stage, where thrombolysis is now the state-of-the-art emergency treatment, the term “brain attack” for both, either in combination with cerebral imaging information<sup>13,14</sup> or not, seems a more adequate approach to improve therapy, mandatory workup, and prediction of prognosis. Other authors advocate a new definition or replacement of the term.<sup>15,16</sup>

In a stroke quality assessment study, we compared a large representative cohort of hospitalized TIA and stroke patients. Diagnostic workup, length of hospital stay, in-hospital complications, and outcome (including death or disability) at discharge and after 6 months were documented. We hypothesized that differences were significant between stroke and

TIA patients, but that the diagnostic procedures will be comparable and the risk of death or disability clinically relevant in both groups.

## Patients and Methods

A prospective, multicenter, observational study was conducted in southwest Germany (35 752 km<sup>2</sup>, 10.6 million inhabitants). For 6 months, data were prospectively collected from a representative sample of 82 medical centers treating acute stroke in this area, recruiting 5668 stroke patients to provide evidence on hospital referral and in-hospital organization, diagnostic workup and time-management, risk factors, and prognosis for TIA, ischemic stroke (IS), and parenchymal hemorrhage (excluding subarachnoid hemorrhage). All hospitals had to report stroke cases treated per year before the start of the study, and data from hospitals that recruited <50% of reported patients were excluded from further analysis because of possible selection bias.

TIA was defined as a sudden onset of a focal neurological deficit or amaurosis fugax, suspected to be of cerebrovascular origin, usually lasting a few minutes but definitely remitted within 24 hours (traditional definition). The date of inception was defined as the time of symptom onset, which was no longer than 24 hours before admission in 92% of patients (and within 36 hours in 100%). All diagnostic and therapeutic measures were documented by the local study coordinators and controlled by the central study coordinators. Telephone follow-up was 6 months after hospital discharge and

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performed by blinded study nurses. Clinical end points were death or dependence (defined as a Barthel index of <95, modified Rankin Scale (mRS) of 3 to 6, or institutionalization in a nursing home) at discharge and during follow-up. After 6 months, the information about death and dependence was abstracted from patient's statements, relatives, general practitioners, or from nursing home personnel as available. Other end points were social status at home, stroke recurrence, and the patient's subjective feeling of recovery. Baseline and discharge data of patients lost to follow-up (censored patients) were analyzed and compared with patients with complete follow-up for estimation of censorship bias. In univariate analysis, we compared TIA and IS patients with  $\chi^2$  statistics for dichotomized variables. A multivariate analysis was performed to test the predictive value of the documented variables within the TIA and IS patient population. Odds ratios (ORs) and 95% CIs were used to express the probability of being dead or dependent at the end of follow-up using SPSS 11.5 statistical packages.

## Results

From a group of 5668 stroke patients, 1424 (25%) had a TIA and 3855 (68%) had an IS (406 patients had a cerebral hemorrhage; these data were not further analyzed for this report; in 3 patients the final diagnosis remained unclear). 1380 TIA patients fulfilled the inclusion criteria for further analysis.

### Patient's Baseline Data and Risk Factors

Baseline demographic data and risk factor distribution differed significantly in TIA and stroke patients (Table 1). TIA patients were slightly younger than IS patients ( $71 \pm 13$  years versus  $73 \pm 12$  years,  $P < 0.001$ ), and TIA patients had slightly less hypertension (69% versus 72%,  $P = 0.028$ ), diabetes mellitus (25% versus 32%,  $P < 0.001$ ), or atrial fibrillation (18% versus 26%,  $P < 0.001$ ). On the whole, IS patients were more severely affected on presentation: mono- or hemiparesis were the predominant symptoms on presentation both in TIA and IS patients (44% versus 74%,  $P < 0.001$ ) followed by dysphasia (41% versus 64%,  $P < 0.001$ ) and impaired consciousness (12% versus 27%,  $P < 0.001$ ). Twenty-five percent of TIA patients had no symptoms at all on arrival.

### Stroke Details

As expected, TIA patients disclosed significantly fewer visible infarctions on computed tomography (CT) scans (22% versus 70%,  $P < 0.001$ ). Atherothrombotic and cardioembolic stroke were among the most frequently found pathophysiologies in patients with completed stroke (36% and 28%, respectively); structural lesions in TIA patients were mainly classified as of unknown or microangiopathic etiology (28% and 26%, respectively) according to the Trial of Org 10172 in Acute Treatment (TOAST) criteria<sup>17</sup> (Table 1).

### Diagnostic Workup, Therapy, and Length of Stay

Fifty-two percent of TIA and 44% of IS patients arrived at the hospital within 3 hours of symptom onset or were already admitted ( $P < 0.001$ ); 92% of the TIA patients (and 86% IS patients) arrived within 24 hours (and all patients arrived within 36 hours; Table 1). Thirty-seven percent of TIA patients were admitted to a stroke unit (versus 36% of IS patients). Most TIA patients received a CT or MRI scan of the brain, but frequency was less than in IS patients (85% versus 91%,  $P < 0.001$ ). Doppler/duplex sonography

was done in  $\approx 90\%$  in both groups. Echocardiography was accomplished in 64% of TIA and 60% of IS patients ( $P = 0.019$ ). There were no significant differences in therapy; 64% of TIA patients received any form of antiplatelet therapy (versus 62% of stroke patients,  $P = 0.206$ ), and 56% were treated with low-dose heparin (versus 60% of IS patients,  $P = 0.009$ ). Length of stay differed between both groups: there was a median of 10 days in TIA and 15 days in IS patients ( $P < 0.001$ ).

### Complications

A significant number of TIA patients experienced 1 or more complications during their hospital stay. Eight percent of TIA patients and 19% of stroke patients had pneumonia or urinary tract infection ( $P < 0.001$ ). Two percent of TIA patients had a cardiovascular event (4% of IS patients,  $P = 0.037$ ), but 8% of TIA patients had a subsequent stroke during their hospital stay, leaving a significant disability compared with a similar 7% of IS patients ( $P = 0.092$ ). In-hospital mortality was significantly lower for TIA patients (2.2%) than for IS patients (8.6%,  $P < 0.001$ ).

### Patients Lost to Follow-Up

Complete follow-up was done with 1150 TIA patients (83%) and 3038 IS patients (79%). To estimate possible censor bias, a comparison of baseline and discharge data of patients lost and not lost to follow-up was performed. Patients lost to follow-up presented with slightly more severe symptoms. Thirty-eight percent of lost follow-up TIA patients had a Rankin score on admission  $> 2$  compared with 30% of not TIA patients followed ( $P = 0.006$ ) and were more likely to have impaired consciousness at admission (15% versus 10%,  $P = 0.004$ ). IS patients lost to follow-up were also older than those not lost to follow-up and had more complications during their hospital stay (data not shown).

### Outcome and Prognostic Factors

Seventeen percent of 1150 TIA patients were dependent after 6 months of follow-up, half of whom had experienced a new stroke during the hospital stay, and 5% had a stroke after discharge (Table 2). For IS patients, stroke recurrence was 6% after discharge ( $n = 181$ ). Five percent of TIA patients had died during follow-up compared with 10% of IS patients ( $P < 0.001$ ). In multivariate analysis (Figure 1), baseline- and discharge-mRSs were the strongest predictors for death or dependency of TIA patients after 6 months (baseline mRS OR, 4.1; 95% CI, 2.3 to 7.2). Other independent predictors included age  $> 60$  years (OR, 2.8; 95% CI, 1.7 to 4.7), cardiogenic embolism (OR, 2.3; 95% CI, 1.0 to 5.0), and new visible infarction on CT or MRI (OR, 1.8; 95% CI, 1.1 to 3.1). Admittance to a stroke unit (OR, 0.4; 95% CI, 0.2 to 0.9) was a predictor for being alive and independent at follow-up. Almost all predictors for outcome of IS patients matched that of the TIA patients completely. The only exception was the detection of a new corresponding structural lesion in the CT, which did not, however, distinguish the outcome in IS patients (Figure 2).

TABLE 1. Comparison of TIA and Ischemic Stroke Patients

	TIAs (%)	Ischemic Stroke (%)	<i>P</i>
Baseline data			
No.	1380 (100)	3855 (100)	
Age mean±SD	71±13 y	73±12 y	<.001
Female gender, %	687 (50)	1955 (51)	0.573
Age >60 y, %	1105 (80)	3297 (86)	<0.001
Prior TIA/stroke	347 (25)	1035 (27)	0.218
Hypertension	945 (69)	2761 (72)	0.028
Diabetes	348 (25)	1243 (32)	<0.001
Atrial fibrillation	253 (18)	1018 (26)	<0.001
Impaired consciousness	157 (12)	1028 (27)	<0.001
Paresis	599 (44)	2864 (74)	<0.001
Dysphasia, dysarthria	559 (41)	2468 (64)	<0.001
mRS >2	446 (32)	2699 (70)	<0.001
Stroke details			
Infarction on scan	205 (22)	2008 (70)	<0.001
Anterior circulation	1038 (79)	2734 (76)	0.002
Atherothrombotic	336 (24)	1293 (36)	<0.001
Cardioembolic	251 (18)	1077 (28)	<0.001
Microangiopathic	355 (26)	749 (19)	<0.001
Unknown etiology	392 (28)	535 (17)	<0.001
Diagnostic workup, therapy, and length of stay			
Arrival <3 h from onset	491 (52)	989 (44)	<0.001
Arrival 3–24 h	378 (40)	952 (42)	0.205
Admitted to stroke unit	511 (37)	1368 (36)	0.305
CT/MRI done	1178 (85)	3507 (91)	<0.001
Echocardiography	859 (64)	2245 (60)	0.019
Heparin high	390 (28)	1132 (29)	0.439
Heparin low	776 (56)	2323 (60)	0.009
Antiplatelets	881 (64)	2387 (62)	0.206
Warfarin	87 (6)	194 (5)	0.072
Carotid surgery	14 (1)	37 (1)	0.455
Length of stay, median	10d	15d	<0.001
In-hospital complications			
Any	207 (15)	1251 (33)	<0.001
Cardiovascular	33 (2)	137 (4)	0.037
Infection	105 (8)	737 (19)	<0.001
Recurrent stroke	105 (8)	266 (7)	0.092
Dead	31 (2)	330 (9)	<0.001

## Discussion

The aim of this study was to demonstrate a substantial risk for early subsequent stroke, risk of death, or disability not only in IS but also in TIA patients. Therefore, we prospectively assessed diagnostic workup, length of stay, in-hospital complications, and early/late outcome in TIA and IS patients admitted within 24 hours of symptom onset in a large, multicenter, observational study; similar standards of diagnosis and treatment were obtained.<sup>1,8,9</sup>

TIA patients experienced approximately half as many complications (cardiovascular, infections, etc) as stroke

patients both in-hospital as well as during 6 months follow-up. Mortality in-hospital (TIA=2% versus IS=9%) and mortality at 6 months (TIA=5% versus IS=10%) was lower in TIA than in stroke patients, closely related hereon because only a minority died because of a fatal stroke. Seventeen percent of TIA patients (38% of IS patients) were dependent in functions of daily living after 6 months, although initial symptoms resolved within 24 hours. However, almost the same rate of subsequent stroke or stroke recurrence occurred in TIA and IS patients (7% and 8%, respectively) both in-hospital and during follow-up. This

**TABLE 2. Outcome of TIA and Ischemic Stroke Patients at 6 Months**

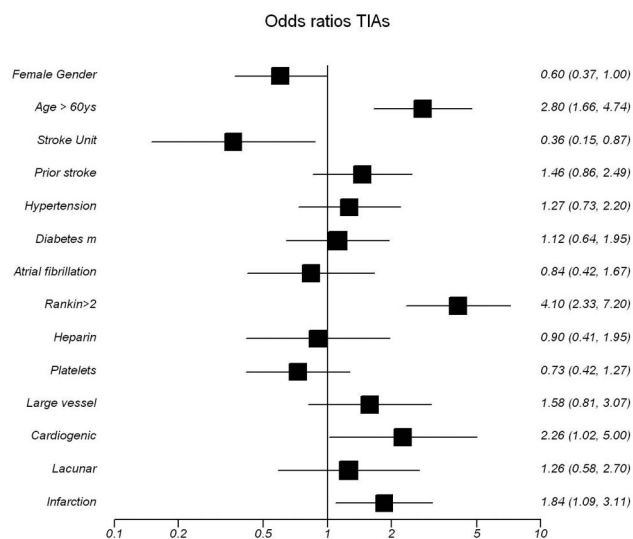
	TIA (%)	Ischemic Stroke (%)	P
No.	1150 (83)	3038 (79)	
Dead	61 (5)	307 (10)	<0.001
Dependent	198 (17)	892 (38)	<0.001
Recurrent stroke	54 (5)	181 (6)	0.092
On antiplatelet	663 (58)	1566 (52)	<0.001
On oral anticoagulation	135 (12)	363 (12)	NS

NS indicates not significant.

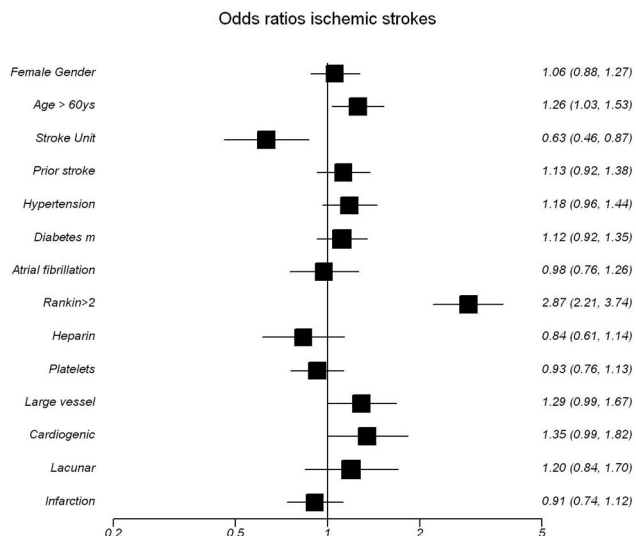
was largely because of almost the same rate of early stroke and subsequent stroke in TIA and IS patients both in-hospital and at follow-up (7% and 8%, respectively).

These results confirm recent observations from other studies. Johnston et al found a slightly higher stroke incidence of 10.5% in 1707 TIA patients (half of which occurred in the first 2 days after TIA) at a similar mortality of 2.6% within 90 days.<sup>8</sup> The German Stroke Database reported a mortality of 1.7% at 90 days, and an additional 14% had a moderate to severe handicap.<sup>18</sup> The Oxfordshire Community Stroke Project (OCSP) cohort (a community-based study) experienced a 8.6% short-term risk of stroke in the first week (and 12% within 30 days) if the patient was seen early enough after symptom onset.<sup>9</sup>

Furthermore, in our study the most important and significant predictors for being dead or dependent at follow-up in TIA patients were (1) >60 years old, (2) a mRS of >2 on admission, (3) a cardiogenic source of emboli with early complete cardiovascular workup in more than two thirds of patients admitted, and (4) a visible infarction on CT or MRI associated with acute signs or symptoms. This is important in light of the discussion of the new TIA concept separating patients with evidenced brain tissue damage on magnetic resonance diffusion-



**Figure 1.** Multivariate analysis for death and dependency at follow-up for TIA patients.



**Figure 2.** Multivariate analysis for death and dependency at follow-up for IS patients.

weighted imaging (MR-DWI)<sup>16</sup> from patients without it. Although there is good evidence of early infarcted brain tissue in TIA patients,<sup>19-22</sup> little is known about the clinical relevance of such findings and their correlation with outcome. Although, in our large trial, MRI studies were performed only in <10% of patients, the significant association of early infarction with a worse outcome in TIA patients further supports the idea to separate TIA patients with and without evidence of tissue damage. The Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence (FASTER) study<sup>23</sup> is an ongoing trial that aims to identify patients with MR-DWI lesions at high-risk for subsequent stroke. Other studies have been recently designed to investigate the appropriateness of long versus short symptom duration in anticipating high risk versus low risk independent from MR-DWI.<sup>16</sup>

Eighty two (60%) of the hospitals treating acute stroke in this area contributed to the study.<sup>24</sup> The study centers were identified in cooperation with the Regional Medical Association with regard to serving rural or urban areas. Follow-up was complete in 83% of TIA and 79% of IS patients. Patients lost to follow-up were comparable in baseline and outcome data in both evaluation terms. We, therefore, consider this study representative for acute hospitalized TIA and IS patients. Hypertension is by far the most important risk factor for both TIA (69%) and IS (72%) patients.<sup>25</sup> The study was not designed to document individual blood pressure values on admission, at discharge, or during follow-up, rather patients with hypertension were classified when on continuous medication per definition. This is probably the reason why our study failed to demonstrate differences for outcome in TIA and IS patients when compared with earlier studies with a variable compliance of treatment.<sup>26</sup> Admission to a dedicated stroke unit was the only positive predictor for being alive and independent at the end of follow-up for both TIA and

IS patients. This parameter emphasizes the similarity of prognosis and predictive factors in both cerebrovascular conditions, as well.

Patients lost to follow-up may bias the results of the study as far as late results are concerned.<sup>27,28</sup> Budget constraints and the location of the study in central Europe, with a high mobility area, and many immigrants reflecting modern urban societies are certainly factors. We accepted this rather than investigate populations less representative for our industrialized countries. Nevertheless, 83% of TIA and 79% of IS patients had a near complete follow-up. Data directly from the patient or next of kin was complete in 70% of TIA and 64% of IS patients; all other information was supplied by the treating general practitioner or nursing homes. An analysis of the hospital data of patients who were later lost to follow-up revealed that lost patients were more likely to have had more severe symptoms at baseline (mRS >2, impaired consciousness), whereas all other variables were not significantly different. Assuming that these patients had a worse outcome than patients with complete follow-up, one can conclude that the mortality as well as the rate of dependency would have been higher. Our results, therefore, may even underestimate the prognosis of TIA and stroke patients.<sup>12,29,30</sup>

In a hospital setting, it is often overlooked that the diagnostic procedures of TIA patients are de facto identical to that of (uncomplicated) IS patients, and sometimes health authorities blame hospitals for that. The current concept that TIA and IS are different entities could support such statements and argue for a less expensive clinical management in TIA patients. As a consequence, reimbursement of TIA patients is roughly 40% of that of IS patients, and TIA patients are, in fact, in an economic sense (diagnosis-related group) not worth being diagnosed early and thoroughly.<sup>30–32</sup> This study shows that both TIA and IS patients indeed have similar risk and benefit relationships. With this background, in our opinion, the acute diagnosis always has to be “brain attack,” and patients are to be evaluated immediately and similarly, whether the properly validated symptoms have been resolved early or not.

### Conclusions

These data from a large multicenter cohort reveal the “not so benign” prognosis for TIA patients. Although they have a better outcome, the individual risk for death or disability is still remarkable, and diagnostic workup is comparable to stroke patients. “TIAs” are the same as strokes, incidents in the progressive course of a generalized vascular disease; they merit the same attention, and the resources used and the costs should be compensated for accordingly.

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