ORIGINAL ARTICLE

One-Year Risk of Stroke after Transient Ischemic Attack or Minor Stroke

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ABSTRACT

BACKGROUND

Previous studies conducted between 1997 and 2003 estimated that the risk of stroke or an acute coronary syndrome was 12 to 20% during the first 3 months after a transient ischemic attack (TIA) or minor stroke. The TIAregistry.org project was designed to describe the contemporary profile, etiologic factors, and outcomes in patients with a TIA or minor ischemic stroke who receive care in health systems that now offer urgent evaluation by stroke specialists.

METHODS

We recruited patients who had had a TIA or minor stroke within the previous 7 days. Sites were selected if they had systems dedicated to urgent evaluation of patients with TIA. We estimated the 1-year risk of stroke and of the composite outcome of stroke, an acute coronary syndrome, or death from cardiovascular causes. We also examined the association of the ABCD^2 score for the risk of stroke (range, 0 [lowest risk] to 7 [highest risk]), findings on brain imaging, and cause of TIA or minor stroke with the risk of recurrent stroke over a period of 1 year.

RESULTS

From 2009 through 2011, we enrolled 4789 patients at 61 sites in 21 countries. A total of 78.4% of the patients were evaluated by stroke specialists within 24 hours after symptom onset. A total of 33.4% of the patients had an acute brain infarction, 23.2% had at least one extracranial or intracranial stenosis of 50% or more, and 10.4% had atrial fibrillation. The Kaplan–Meier estimate of the 1-year event rate of the composite cardiovascular outcome was 6.2% (95% confidence interval, 5.5 to 7.0). Kaplan–Meier estimates of the stroke rate at days 2, 7, 30, 90, and 365 were 1.5%, 2.1%, 2.8%, 3.7%, and 5.1%, respectively. In multivariable analyses, multiple infarctions on brain imaging, large-artery atherosclerosis, and an ABCD^2 score of 6 or 7 were each associated with more than a doubling of the risk of stroke.

CONCLUSIONS

We observed a lower risk of cardiovascular events after TIA than previously reported. The ABCD^2 score, findings on brain imaging, and status with respect to large-artery atherosclerosis helped stratify the risk of recurrent stroke within 1 year after a TIA or minor stroke. (Funded by Sanofi and Bristol-Myers Squibb.)

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*A complete list of the TIAregistry.org investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Previous studies conducted between 1997 and 2003 estimated that the risk of stroke or an acute coronary syndrome was 12 to 20% during the first 3 months after a transient ischemic attack (TIA) or minor stroke.[1,2] Since then, there have been major changes in the management of TIA, including urgent management in specialized units, implementation of immediate investigations, and rapid treatment with antithrombotic agents and other stroke-prevention strategies.[1-4] Given these changes, the current prognosis of patients who have had a TIA and the role of risk-scoring systems in patients receiving urgent care are unclear.[5-11] Current guidelines recommend triage of patients on the basis of the risk of stroke as assessed by the ABCD^2 (age, blood pressure, clinical findings, duration of symptoms, and presence or absence of diabetes) score. Scores range from 0 to 7, with higher scores indicating a greater risk of stroke; an age of 60 years or older, a blood-pressure level of 140/90 mm Hg or higher, a clinical finding of unilateral weakness or speech impairment, a duration of symptoms of 10 to 59 minutes, and diabetes are each assigned 1 point, and a duration of symptoms of 60 minutes or more is assigned 2 points. Urgent care of patients with TIA within 24 hours after symptom onset is recommended when the ABCD^2 score is 4 or more.[12,13] However, ABCD^2 scores of 4 or more do not identify all patients needing immediate treatment.[14-16] The widespread introduction of emergency services for patients who have had a TIA or minor stroke in most developed health care systems makes it important to reassess prognosis and risk stratification.

The TIAregistry.org project was designed to describe the contemporary profile, etiologic factors, and short-term (1-year) and long-term (5-year) outcomes in patients with a TIA or minor ischemic stroke and to refine risk assessment in the context of modern stroke prevention and management. Here we report 1-year follow-up data.

METHODS

STUDY DESIGN AND OVERSIGHT

The TIAregistry.org project is an international, prospective, observational registry of patients who have had a recent TIA or minor stroke, involving 5 years of clinical follow-up. The protocol was approved by local institutional review boards. All patients gave written or oral informed consent according to country regulation.

This study was an investigator-driven initiative and was supported by an unrestricted grant from Sanofi and Bristol-Myers Squibb, both of which had no involvement in the design or conduct of the study, the analysis or interpretation of the data, or the writing of the manuscript. SOS-Attaque Cérébrale Association (a not-for-profit organization) and the Charles Foix Group (an academic research organization for clinical trials in stroke at Université Paris-Diderot, Sorbonne-Paris Cité) were responsible for the conduct of the study.

STUDY POPULATION

Patients were eligible for enrollment if they were 18 years of age or older and had had a TIA or minor stroke within the 7 days before evaluation by stroke specialists. Eligible patients had focal retinal or brain ischemia with resolution of symptoms or minor strokes with a score on the modified Rankin scale (range, 0 to 6, with 0 indicating no symptoms, 1 no disability, and 6 death) of 0 or 1 when first evaluated by stroke specialists. The modified Rankin scale was used instead of the National Institutes of Health Stroke Scale as a pragmatic approach to rating minor focal neurologic events that had no effect on disability. Detailed descriptions of the potential residual neurologic deficits at admission were captured in the case-report forms.

Sites were selected in 21 countries on the basis of the existence of a dedicated system for the care of patients with TIA (with care delivered by stroke specialists) and a yearly volume of at least 100 patients during the previous 3 years. Emergency departments, stroke units, day clinics, and outpatient clinics were the care settings; the systems varied across centers except that at all centers, all patients were evaluated on an urgent basis by stroke specialists (most of them were neurologists, and the other physicians specialized in stroke care). (For additional details, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

EVALUATION

Stroke specialists collected patient data prospectively, using a standardized Web-based case-report form, during face-to-face interviews at the time of evaluation of the qualifying event (base-

line), at 1, 3, and 12 months after baseline, and every 12 months thereafter for 5 years. If the patient could not be reached for follow-up, a relative or family doctor was interviewed by telephone. At baseline, information was obtained on clinical symptoms during the qualifying event, the occurrence of clinical events after the qualifying event, and sociodemographic characteristics; a medical history was obtained and a physical examination performed; investigations (including brain and cerebral-artery imaging and cardiac investigations) were recommended; and management of care (e.g., medical treatment or revascularization procedure) was recorded. Patients were evaluated at follow-up for clinical events, medical treatment, and main risk factors (smoking status, blood pressure, and lipid profile).

DEFINITIONS OF CLINICAL EVENTS AND OUTCOMES

Any clinical event after the qualifying event (i.e., after the patient first sought medical attention), even if the event occurred before evaluation by a stroke specialist, was considered to be an outcome event, as judged by the individual investigators. Primary outcome events and bleeding events were reviewed by two of the investigators (the first and second authors) on the basis of narrative descriptions. The primary study outcome was defined as a composite outcome that included death from cardiovascular causes, nonfatal stroke (either ischemic or hemorrhagic), and nonfatal acute coronary syndrome (myocardial infarction with or without ST-segment elevation or unstable angina followed by urgent catheterization). Secondary outcomes included individual components of the primary outcome, TIA recurrence, death from any cause, and bleeding. Ischemic stroke was defined as one of the following: a new symptomatic neurologic deterioration lasting at least 24 hours that was not attributable to a nonischemic cause, or a new symptomatic neurologic deterioration that was not attributable to a nonischemic cause and was accompanied by neuroimaging evidence of new brain infarction. Hemorrhagic stroke was defined as acute extravasation of blood into the brain parenchyma. Death from cardiovascular causes included fatal acute coronary syndrome, fatal stroke, fatal intracranial hemorrhage, fatal pulmonary embolism, sudden death, and unobserved or unexpected death. Fatal stroke or acute coronary syndrome was defined as an event that was followed by death within 30 days. TIA was defined as new symptomatic neurologic deterioration lasting less than 24 hours with no new infarction on neuroimaging. Bleeding was categorized according to the Global Utilization of Streptokinase and Tissue Plasminogen Factor for Occluded Coronary Arteries (GUSTO) definitions.[17]

STATISTICAL ANALYSIS

We initially calculated that a sample size of 5000 would allow a 10% relative precision in the estimate of the rate of the primary outcome after a maximum follow-up of 5 years (corresponding to a maximum enrollment period of 4 years and a minimum follow-up period of 1 year), assuming an average annual risk of composite events of 2.5%. Because we decided to follow all patients for 5 years and to perform a short-term analysis at the 1-year follow-up, we calculated (using the Peto method for calculating the standard error of survival at a given time) that with a 25% attrition rate at 5 years, the relative precision of the estimates of the composite event rate would be 18% at 1 year and 9% at 5 years.

Continuous variables are expressed as means and standard deviations or medians and interquartile ranges, and categorical variables are expressed as frequencies and percentages. Cumulative event curves were constructed for the primary outcome and selected secondary outcomes with the use of the Kaplan–Meier method. Crude event rates were determined from Kaplan–Meier rates and compared with the use of the log-rank test. For a given outcome, deaths from causes other than those included in the outcome were treated as censoring events. Data on patients with no information at 1 year were censored at the time of the last follow-up available. Events that occurred after the 1-year follow-up period were not included in the current analysis.

We estimated and compared the risk of stroke in subgroups of patients categorized according to the time from symptom onset to evaluation by a stroke specialist (≤24 hours vs. >24 hours), ABCD^2 score (≤3 vs. 4 or 5 vs. 6 or 7),[5] the number of acute (new) infarction-related lesions (0 vs. 1 vs. ≥1), and the probable cause of the initial TIA or minor stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (large-artery atherosclerosis, cardioembolism, small-vessel occlusion, other determined

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Value (N=4583)
Evaluated by stroke specialist within 24 hr after symptom onset — no. (%)	3593 (78.4)
Age — yr	66.1±13.2
Male sex — no./total no. (%)	2755/4574 (60.2)
Medical history — no./total no. (%)	
Hypertension	3174/4533 (70.0)
Diabetes	879/4494 (19.6)
Dyslipidemia	3194/4571 (69.9)
Former smoker	1105/4498 (24.6)
Current smoker	984/4498 (21.9)
Regular alcohol consumption	913/4492 (20.3)
Regular physical activity	979/4381 (22.3)
Stroke or TIA	803/4567 (17.6)
Coronary artery disease	565/4562 (12.4)
Peripheral artery disease	129/4540 (2.8)
Atrial fibrillation or flutter	388/4565 (8.5)
Congestive heart failure	124/4562 (2.7)
Clinically significant valvular disease or prosthetic heart valve	123/4566 (2.7)
Modified Rankin score — no./total no. (%)†	
0	3122/4475 (69.8)
1	1353/4475 (30.2)
Body-mass index‡	26.5±4.6
Blood pressure — mm Hg	
Systolic	146±24
Diastolic	81±13
Glucose — mg/dl	
Median	105
Interquartile range	92–128
Cholesterol — mg/dl	
LDL	119±39
HDL	50±16
Living alone — no./total no. (%)	1516/4472 (33.9)
Living in rural area — no./total no. (%)	634/4485 (14.1)
Unemployed — no./total no. (%)§	234/4375 (5.3)
Educational level — no./total no. (%)	
No education	240/4193 (5.7)
Primary education	1389/4193 (33.1)
Secondary education	1890/4193 (45.1)
Tertiary education	674/4193 (16.1)

* Plus–minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and TIA transient ischemic attack.

† Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no disability, and 6 death.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Excluded were students, persons receiving a disability pension, and the elderly receiving a pension.

cause, or undetermined cause). Given that the ABCD^2 score, acute infarctions on brain imaging, and TOAST classification have been previously reported to be associated with stroke recurrence,[7] a Cox proportional-hazards regression model was used to evaluate whether these three predictors were independently associated with stroke recurrence. The proportional-hazards assumption was verified with the use of Schoenfeld residuals. Owing to missing data on the ABCD^2 score, acute infarction lesions, and TOAST classification, we performed a sensitivity analysis with multiple imputation of missing values by means of chained equations (10 imputed data sets were generated with the use of all patient characteristics described in Table 1).[18]

Statistical testing was conducted at a two-tailed alpha level of 0.01 to account for multiple comparisons. Data were analyzed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

CHARACTERISTICS OF PATIENTS ENROLLED

From June 2009 through December 2011, a total of 4789 patients at 61 sites in 21 countries were enrolled in the TIAregistry.org project, of whom 4583 were included in the analysis; 173 patients did not meet inclusion criteria, and 33 had no follow-up data owing in almost all cases to the emergence of another cause for their TIA-like event (Fig. S1 in the Supplementary Appendix). A total of 4013 patients (87.6%) sought medical attention within 24 hours after symptom onset, and 89.5% of these (3593 patients, or 78.4% of those included in this analysis) were examined by stroke specialists within 24 hours (Table 1). The median length of hospital stay was 4 days. Baseline characteristics of the patients are shown in Table 1. The two most frequent clinical symptoms of the qualifying event were weakness (55.0%) and speech abnormalities (48.3%). Patients evaluated by a stroke specialist within 24 hours after symptom onset had a higher ABCD^2 score than patients seen after 24 hours; the mean (±SD) ABCD^2 score was 4.7±1.5 in patients seen within 24 hours, as compared with 3.8±1.6 in patients seen after 24 hours ($P<0.001$). (Additional details regarding the characteristics of the patients are provided in Tables S1 and S2 and Fig. S2 in the Supplementary Appendix.)

INVESTIGATIONS AND TREATMENTS

The main findings from investigations are listed in Table 2. Medications used before admission and at the time of discharge are listed in Table 3. During evaluation at baseline by a stroke specialist, 5.0% of the patients (199 of the 3960 patients for whom data were available) received a new diagnosis of atrial fibrillation, and 66.8% of these patients (133 patients) received anticoagulant therapy before discharge. A carotid stenosis of 50% or more was found in 15.5% of the patients (618 of 3993 patients for whom data were available), and 26.9% of them (166 patients) underwent carotid revascularization before discharge. The rates of self-reported medication use at 3 months and at 12 months were similar to the rates of use at the time of discharge, findings that support the accuracy of self-reported medication adherence (Table 3). At 12 months, the mean systolic blood pressure was 133±17 mm Hg, and the mean level of low-density lipoprotein cholesterol was 95±34 mg per deciliter (2.46±0.88 mmol per liter) (Table S3 in the Supplementary Appendix).

Table 2. Main Investigation Findings during Evaluation by Stroke Specialist and Key Urgent Treatment before Discharge.*

Investigation or Treatment	Value (N=4583)
Main investigations	
Brain imaging: CT or DWI	
Evaluated — no. (%)	4422 (96.5)
Any acute infarction — no./total no. (%)	1476/4422 (33.4)
Extracranial imaging: CT, MRA, or Doppler	
Evaluated — no. (%)	4028 (87.9)
≥1 Stenosis of ≥50% or occlusion — no./total no. (%)†	618/3993 (15.5)
Intracranial imaging: CT, MRA, or Doppler	
Evaluated — no. (%)	3659 (79.8)
≥1 Stenosis of ≥50% or occlusion — no./total no. (%)†	491/3633 (13.5)
ECG or 24-hr Holter ECG — no./total no. (%)	
Evaluated	4013/4428 (90.6)
Atrial fibrillation or flutter	410/3960 (10.4)
New diagnosis of atrial fibrillation or flutter	199/3960 (5.0)
Cardiac echography: TTE or TEE — no./total no. (%)	
Evaluated	2538/4325 (58.7)
≥1 Clinically significant abnormality	112/2521 (4.4)
Key urgent treatments	
Carotid revascularization — no. (%)	166 (3.6)
Anticoagulant agent for any atrial fibrillation — no./total no. (%)‡	315/3913 (8.1)
≥1 Antiplatelet therapy — no./total no. (%)	4046/4486 (90.2)

* Data on specific findings were missing for some patients who were evaluated. For example, 4028 patients underwent extracranial imaging, but data with respect to stenosis were available for only 3993 patients. CT denotes computed tomography, DWI diffusion-weighted imaging, ECG electrocardiography, MRA magnetic resonance angiography, TEE transesophageal echocardiography, and TTE transthoracic echocardiography.

† A total of 23.2% of the patients had at least one extracranial or intracranial stenosis of 50% or more.

‡ Any atrial fibrillation includes previously and newly diagnosed atrial fibrillation.

OUTCOMES

At the time of database extraction (July 24, 2015), patients had been followed for a median of 27.2 months (interquartile range, 12.4 to 48.1); 4200 patients (91.6%) had died or had had at least 1 year of follow-up. At 1 year, a total of 274 primary outcome events had occurred (25 deaths from cardiovascular causes, 210 nonfatal strokes, and 39 nonfatal acute coronary syndromes), corresponding to a Kaplan–Meier estimate of the primary outcome event rate of 6.2% (95% confidence interval [CI], 5.5 to 7.0) (Fig. 1). With respect to secondary outcomes, death from any cause occurred in 80 patients (Kaplan–Meier estimate, 1.8%), any recurrent stroke or TIA in 533 (12.0%), any acute coronary syndrome in 46 (1.1%), and any bleeding in 87 (2.0%), including 16 with moderately severe bleeding and 18 with major bleeding (Table 4, and Fig. S3 in the Supplementary Appendix).

The 2-day, 7-day, 30-day, 90-day, and 1-year rates of stroke according to the time from symptom onset to medical evaluation and according to ABCD^2 score are shown in Figure S4 in the Supplementary Appendix. Overall, strokes occurred in 67 patients (Kaplan–Meier estimate, 1.5%) within 2 days after the onset of symptoms in the qualifying event, in 95 patients (2.1%) within 7 days, in 128 patients (2.8%) within 30 days, in 168 patients (3.7%) within 90 days, and in 224 patients (5.1%) within 1 year. The risk of stroke tended to increase with a higher ABCD^2 score, with the 1-year risk ranging from 0% (score of 0) to 9.6% (score of 7). A total of 22% of strokes occurred in patients with an ABCD^2 score of less than 4 (Table S4 in the Supplementary Appendix).

Table 3. Medication Use.

Medication	Before Admission (N=4583)	At Discharge (N=4583)	At 3 Months (N=4086)	At 12 Months (N=3960)
	number/total number (percent)			
≥1 Antiplatelet agent	1225/4555 (26.9)	4046/4486 (90.2)	3293/4043 (81.4)	3052/3872 (78.8)
Aspirin	1069/4550 (23.5)	3015/4437 (68.0)	2445/3996 (61.2)	2239/3863 (58.0)
Other antiplatelet agent	272/4550 (6.0)	1542/4437 (34.8)	1274/3996 (31.9)	1141/3863 (29.5)
Aspirin and other antiplatelet agent	121/4550 (2.7)	593/4437 (13.4)	473/3996 (11.8)	336/3863 (8.7)
≥1 Anticoagulant agent	230/4552 (5.1)	791/4501 (17.6)	673/4035 (16.7)	672/3859 (17.4)
≥1 Antihypertensive agent	2495/4564 (54.7)	3075/4544 (67.7)	2779/4009 (69.3)	2739/3835 (71.4)
1	1048/4518 (23.2)	1416/4438 (31.9)	1210/3998 (30.3)	1147/3823 (30.0)
2	802/4518 (17.8)	904/4438 (20.4)	873/3998 (21.8)	920/3823 (24.1)
≥3	599/4518 (13.3)	609/4438 (13.7)	685/3998 (17.1)	662/3823 (17.3)
≥1 Lipid-lowering agent	1213/4559 (26.6)	3156/4521 (69.8)	2797/4006 (69.8)	2591/3838 (67.5)
Statin	1125/4551 (24.7)	3022/4490 (67.3)	2707/3995 (67.8)	2497/3829 (65.2)
Other lipid-lowering agent	125/4551 (2.7)	151/4490 (3.4)	127/3995 (3.2)	145/3829 (3.8)

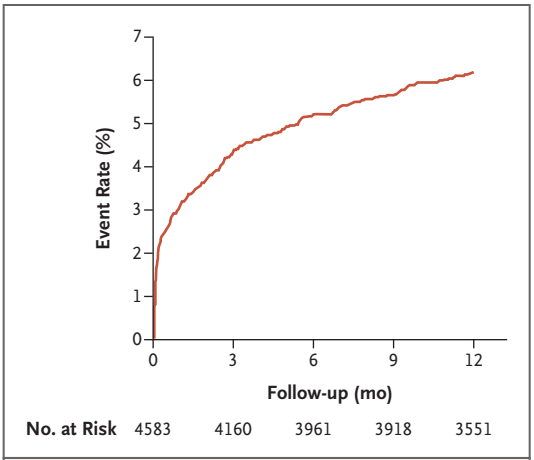


Figure 1. Cumulative Incidence of the Composite Outcome in the Overall Population.

The composite outcome included stroke, an acute coronary syndrome, and death from cardiovascular causes.

PREDICTORS OF OUTCOMES

Figure 2 shows the unadjusted risk of stroke according to the time from symptom onset to evaluation by a stroke specialist, $ABCD^2$ score, finding on brain imaging, and cause of stroke. In multivariable Cox regression analysis that included imaging findings, $ABCD^2$ scores, and cause of stroke according to TOAST classification, the following three variables were independently associated with 1-year stroke risk: multiple acute cerebral infarctions on brain imaging (hazard ratio for the comparison with no infarctions, 2.16; 95% CI, 1.46 to 3.21; P<0.001), an $ABCD^2$ score of 6 or 7 (hazard ratio for the comparison with a score of 0 to 3, 2.20; 95% CI, 1.41 to 3.42; P<0.001), and large-artery atherosclerosis (hazard ratio for the comparison with undetermined cause, 2.01; 95% CI, 1.29 to 3.13; P=0.002) (Fig. S5 in the Supplementary Appendix). The results were similar when the Cox regression model was refitted by introducing $ABCD^2$ score as a continuous variable (hazard ratio per point, 1.23; 95% CI, 1.10 to 1.37; P<0.001), multiple acute infarctions as a binary variable (hazard ratio, 2.07; 95% CI, 1.43 to 3.00; P<0.001), and large-artery atherosclerosis as a binary variable (hazard ratio, 1.54; 95% CI, 1.11 to 2.11; P=0.008). After imputation of missing data for $ABCD^2$ score, finding on brain imaging, and TOAST classification, the estimates were similar. Sensitivity analyses restricted to patients who underwent diffusion-weighted imaging or to 90-day stroke risk yielded similar results (data not shown).

DISCUSSION

The TIAregistry.org project included 4789 patients who were enrolled over the course of 2.5 years at 61 TIA clinics; 78% of the patients were evaluated by a stroke specialist within 24 hours

after symptom onset. At 1 year, the Kaplan–Meier estimate of the risk of the composite outcome of major fatal or nonfatal cardiovascular events was 6.2%, and the estimate of the risk of stroke was 5.1%. The risk of recurrent stroke at 2 days, 7 days, 30 days, 90 days, and 1 year was less than half that expected from historical cohorts; for example, the risk of stroke and other vascular events at 90 days in the historical cohorts was 12 to 20%,[3,4] as compared with 3.7% in our cohort. The lower event rates in our cohort may be explained by better and faster implementation of secondary stroke prevention strategies (e.g., immediate initiation of antiplatelet drugs, oral anticoagulation in the event of atrial fibrillation, urgent revascularization in patients with critical carotid stenosis, and other secondary prevention measures such as treatment with statins and blood-pressure–lowering drugs) in contemporary TIA clinics than in settings where historical cohorts received care.[3,4]

The findings from the current multicenter registry suggest that the low risk of stroke reported by single-center registries[1,2] in patients who had a TIA or minor stroke and who received care in TIA clinics that were organized for fast-track evaluation (reported 1-year stroke risk of 1.95% in the SOS-TIA trial[1] and 3-month stroke risk of 2% in the Early Use of Existing Preventive Strategies for Stroke [EXPRESS] study[2]) may be achievable in a large range of settings as long as patients are evaluated and treated for acute TIA and minor stroke on an urgent basis. The efficacy of early, intensive treatment with antithrombotic agents has also been shown in the recent Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, which included patients with a TIA or minor stroke who were treated within 24 hours after symptom onset.[19] It is evident from the Kaplan–Meier plot showing the stroke events over time in the CHANCE trial that most of the benefit of dual antiplatelet therapy as compared with monotherapy was achieved within 8 days after symptom onset.[19]

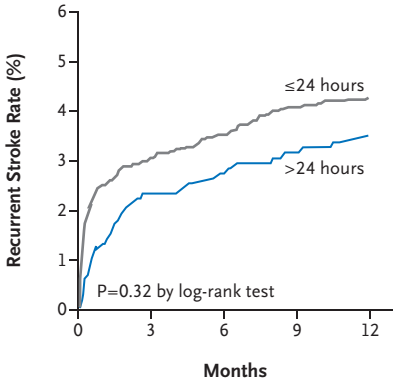
The good outcomes seen in the TIAregistry.org project are not explained by a population that was at lower risk than the population in historical cohorts. More than two thirds of the cohort had an ABCD^2 score of 4 or more, and the risk that we observed was low in each stratum of the ABCD^2 score (Fig. S4B in the Supplementary Appendix). More than 75% of the patients were examined within 24 hours after symptom onset, which ensured that early recurrent events were identified. The median length of hospital stay of 4 days did not reflect the severity of the TIA, because 70% of the patients had a modified Rankin score of 0 and the rest had a modified Rankin score of 1. Patients had good adherence to treatment recommendations as evaluated at the time of discharge and at 1 year (Table 3), with rates of treatment that were similar to those reported in the SOS-TIA and EXPRESS registries, which makes it plausible that the risk observed during the follow-up was the risk of stroke that remained after treatment of risk factors, such as anticoagulation therapy for atrial fibrillation and antihypertensive and statin med-

Table 4. One-Year Event Rates.*

Outcome	Patients (N = 4583)
	no. (%)
Primary outcome	
Major cardiovascular events	274 (6.2)
Death from cardiovascular causes	25 (0.6)
Nonfatal stroke	210 (4.7)
Nonfatal acute coronary syndrome	39 (0.9)
Secondary outcomes	
Death from any cause	80 (1.8)
Stroke or TIA	533 (12.0)
Stroke	224 (5.1)
TIA	326 (7.4)
Intracerebral hemorrhage	16 (0.4)
Acute coronary syndrome	46 (1.1)
Myocardial infarction	16 (0.4)
Bleeding	87 (2.0)
Moderately severe bleeding†	16 (0.4)
Major bleeding‡	18 (0.4)

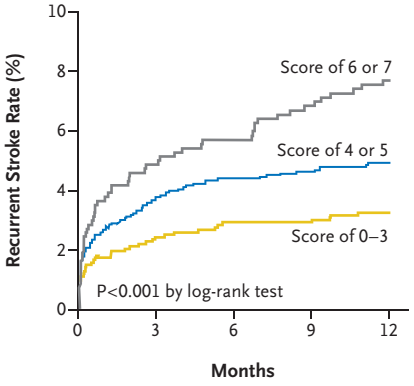
* Percentages are Kaplan–Meier estimates.
† Moderately severe bleeding was defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Factor for Occluded Coronary Arteries (GUSTO) definition: bleeding that requires transfusion of blood but does not lead to hemodynamic compromise requiring intervention.
‡ Major bleeding was defined according to the GUSTO definition for severe bleeding: documented intracranial hemorrhage or bleeding that causes hemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assistance devices, surgical intervention (other than vascular site repair), or cardiopulmonary resuscitation to maintain a sufficient cardiac output.

A Rate of Recurrent Stroke According to Time from Symptom Onset to Evaluation by Stroke Specialist



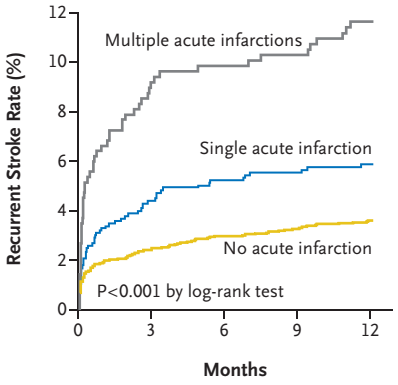
No. at Risk					
≤24 hours	3593	3289	3101	3067	2965
>24 hours	990	926	888	881	850

B Rate of Recurrent Stroke According to ABCD² Stroke Risk Score



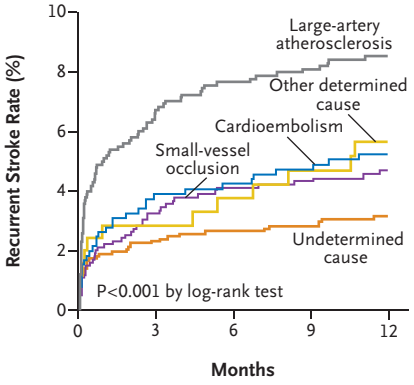
No. at Risk					
Score of 0–3	1294	1221	1175	1166	1063
Score of 4 or 5	1851	1701	1633	1625	1484
Score of 6 or 7	745	684	657	642	596

C Rate of Recurrent Stroke According to Finding on Brain Imaging



No. at Risk					
No acute infarction	2946	2699	2570	2542	2289
Single acute infarction	995	926	894	885	821
Multiple acute infarctions	481	414	397	394	357

D Rate of Recurrent Stroke According to Cause of TIA or Minor Stroke (TOAST Classification)



No. at Risk					
Large-artery atherosclerosis	987	892	863	853	799
Small-vessel occlusion	983	905	862	857	790
Cardioembolism	641	584	570	561	494
Other determined cause	244	214	205	198	184
Undetermined cause	1354	1263	1206	1199	1085

Figure 2. Unadjusted Kaplan–Meier Event Curves for Stroke Recurrence from the Time of the Qualifying Event to 1 Year.

Scores on the ABCD² stroke risk scale range from 0 to 7, with higher scores indicating a greater risk of stroke; an age of 60 years or older, a blood-pressure level of 140/90 mm Hg or higher, a clinical finding of unilateral weakness or speech impairment, a duration of symptoms of 10 to 59 minutes, and diabetes are each assigned 1 point, and a duration of symptoms of 60 minutes or more is assigned 2 points. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification indicates the probable cause of the initial transient ischemic attack (TIA) or stroke; the five main categories are large-artery atherosclerosis, cardioembolism, small-vessel occlusion, other determined cause, and undetermined cause.

ications to lower levels of blood pressure and lipids to recommended targets. The choice of evaluating the primary outcome not only at 90 days, which is commonly used as the follow-up time point in trials of TIA or minor stroke, but also at 1 year was driven by the expected low event rates after 90 days of follow-up. The 1-year risk still represents a short-term risk as far as lifelong stroke prevention is concerned.

In this study, brain imaging showing multiple infarctions, an $ABCD^2$ score of 6 or 7, and large-artery atherosclerosis were each associated with more than a doubling in the risk of stroke. Despite a much lower event rate than in historical cohorts, we found that the $ABCD^2$ score was still effective at stratifying risk in this urgently and intensively treated cohort (Fig. S5 in the Supplementary Appendix), but we also observed that 22% of recurrent strokes occurred in patients with $ABCD^2$ scores of less than 4 and with preventable underlying causes such as atrial fibrillation and ipsilateral internal-carotid-artery stenosis of 50% or more (Table S4 in the Supplementary Appendix).[14,15]

Other factors independently helped stratify the risk of recurrent stroke, such as the presence of multiple infarctions on neuroimaging — a new finding of this registry. This finding may be explained by plaque rupture with multiple distal emboli[20] or a cardiac source of embolism. Our findings also suggest that large-artery atherosclerosis is a stroke subtype that is associated with a significantly higher risk than the risk with other etiologic stroke subtypes ($P<0.001$) (Fig. 2D, and Fig. S5 in the Supplementary Appendix). In the event of cardiac disease (e.g., atrial fibrillation), anticoagulant therapy in addition to risk-factor control is so effective that the residual risk of stroke after these interventions is probably very low.[13] In patients with small-vessel disease, blood-pressure–lowering therapy is very effective when combined with other risk-factor management and antiplatelet therapy.[21]

This registry has important limitations. First, sites were not chosen at random but rather were chosen on the basis of the existence of a TIA clinic or dedicated care for patients with TIA, with at least 100 TIAs evaluated per year during the previous 3 years. The median number of patients enrolled per site was 54, with a range of 1 to 640 (many sites joined the registry late in the study). This suggests that either investigators overestimated their annual recruitment rate or not all patients were included in the registry. However, 4789 patients enrolled in 2.5 years at 61 sites represents a much higher average inclusion rate per site than that in most of the current clinical trials involving the same population. Our registry was biased toward more specialized stroke physicians and possibly enrolled a cohort of patients that had characteristics that differed from those of patients in a population-based study but that probably represents patients whom clinical trials are recruiting. Second, owing to resource constraints, we were able to audit only 10% of the data for accuracy. Although primary outcome events and major bleeding events were adjudicated, primary outcome events may have been underreported in the registry. For this reason, our primary outcome included only hard end points, which are unlikely to be missed. Third, of 4583 patients analyzed, 4200 (91.6%) had 1-year follow-up data available at the time of this analysis. The fact that data were missing for more than 380 patients may have partially affected the 1-year event rate.

In the TIAregistry.org project, we observed a lower rate of cardiovascular events after a TIA or minor stroke than that in historical cohorts. Our findings probably reflect the contemporary risk of recurrent cardiovascular events among patients with a TIA or minor stroke who are admitted to TIA clinics and who receive risk-factor control and antithrombotic treatment as recommended by current guidelines. Although we found that the $ABCD^2$ score was a good predictor of risk, our findings suggest that limiting urgent assessment to patients with a score of 4 or more would miss approximately 20% of those with early recurrent strokes. Multiple infarctions on neuroimaging and large-artery atherosclerotic disease were also strong independent predictors of recurrent vascular events. These results may help in the design and interpretation of future randomized trials.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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