Epidemiology of Transient Ischemic Attacks Using Time- or Tissue-Based Definitions

A Population-Based Study

Diana Degan, MD; Raffaele Ornello, MD; Cindy Tiseo, MD; Federica De Santis, MD; Francesca Pistoia, MD, PhD; Antonio Carolei, MD; Simona Sacco, MD

Background and Purpose—Transient ischemic attack (TIA) epidemiology may have changed in recent years as a consequence of improved identification and treatment of vascular risk factors. Our aim was to provide updated information about TIA epidemiology in Italy.

Methods—Cases of first-ever TIA were ascertained from January 1, 2011, until December 31, 2012, in a population-based prospective registry. All residents in the L'Aquila district with an incident TIA were included and followed up to 2 years after the event. Outcome events were recurrent TIA, nonfatal and fatal stroke, nonfatal and fatal myocardial infarction, and all-cause mortality.

Results—A total of 210 patients with a TIA according to the traditional time-based definition were included (51.4% women); 151 patients (71.9%) with transient symptoms and negative brain neuroimaging were broadly considered as tissue-based TIA, 29 patients (13.8%) had transient symptoms and evidence of a congruous acute ischemic lesion, and 30 patients (14.3%) had an acute neurovascular syndrome. The crude annual incidence rate for traditional time-based TIA was 35.2 per 100 000 (95% confidence interval, 30.6–40.3) and 28.6 per 100 000 (95% confidence interval, 24.1–33.5) when standardized to the 2011 European population. The incidence peaked in subjects aged ≥85 years, in both sexes. At 2 years, outcome events occurred in 50 patients (23.8%) including 15 patients (7.1%) with nonfatal or fatal strokes.

Conclusions—Our population-based study found a low annual TIA incidence rate and a fair TIA prognosis confirming the effectiveness of preventive strategies for cardiovascular diseases. We also proved the nonfitting applicability of the tissue-based definition in our district. **(*Stroke*. 2017;48:530-536. DOI: 10.1161/STROKEAHA.116.015417.)**

Key Words: cerebrovascular disease ■ epidemiology ■ incidence ■ stroke ■ transient ischemic attack

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Available crude annual incidence rates of transient ischemic attack (TIA) range between 29.0 and 61.0 cases per 100 000 in Western countries.[1,2] TIA is a known predictor of subsequent ischemic stroke with risk estimates within 3 months ranging between 7.5% and 17.3%; a half of those events were described to occur within 48 hours.[3,4] TIA epidemiology may have changed in recent years as a consequence of improved identification and treatment of vascular risk factors.[5]

According to the traditional time-based definition, TIA is a focal neurological dysfunction of brief duration, presumed to be of vascular origin and confined to an area of the brain or eye perfused by a specific cerebral artery and of a duration <24 hours.[6–8] Several studies have shown that diffusion-weighted imaging (DWI) alterations in clinically appropriate locations are present in about one third of patients with transient neurological symptoms, suggesting that the 24-hour criterion may allow the inclusion of patients with an acute ischemic cerebral tissue injury.[9–11]

A redefinition of TIA has alternatively been proposed.[12] According to this tissue-based definition, TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction. So far, to the best of our knowledge, no attempts were made to test the applicability of this definition in population-based studies.

We, therefore, performed a prospective population-based study to obtain data on TIA incidence and prognosis according to the traditional time-based definition. We also deemed useful to evaluate if the tissue-based TIA definition was suitable for the same context.

Methods

Study Design

Cases of TIA were ascertained from January 1, 2011, until December 31, 2012, in a prospective population-based registry of patients residing in the L'Aquila district, central Italy. To be included in the study, patients had to reside in the district at the time of the event and had to

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From the Institute of Neurology, Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, Italy.

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Correspondence to Antonio Carolei, MD, Institute of Neurology, Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, via Vetoio, 67100 L'Aquila, Italy. E-mail antonio.carolei@univaq.it; a_carolei@yahoo.com

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present a first-ever TIA according to the traditional time-based definition. The study was approved by the local Ethics Committee and because of its observational design no informed consent was required.

Study Population

The L'Aquila district is a mountainous area of 5034.46 km^2 with 108 towns. The population is served by 4 public hospitals, 5 private hospitals, 266 general practitioners, 78 on-call physicians, and the service known as the 118 emergency medical service. At the 2011 census, the total resident population was 298 343 (2% nonwhite).[13] Medical care is free of charge for hospitalized patients, allowing easy access to medical services, whereas the payment of a fee is required for outpatient visits and ancillary investigations.

Definitions of TIA

For the purpose of this study, the time-based definition of TIA applied was a focal neurological dysfunction of brief duration, presumed to be of vascular origin and confined to an area of the brain or eye perfused by a specific cerebral artery and of a duration <24 hours.[6–8] On the basis of the results of the available neuroimaging studies, those TIA patients were classified as tissue-based TIA, acute neurovascular syndrome (ANS), and patients with transient symptoms with evidence of an acute and congruous ischemic lesion. The presence of an acute infarction had to be proven preferentially on brain magnetic resonance imaging (MRI) with DWI. However, in our study, the choice of brain neuroimaging examination and when to do it was entrusted to the treating physician and depended on local MRI machine availability. Accordingly, when brain DWI-MRI could not be done, brain computed tomography (CT) was considered a valid option according to the Recommendations of the American Heart Association/American Stroke Association Stroke Council.[12] The tissue-based definition applied was a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.[12] We diagnosed an ANS in patients with symptoms suggesting a TIA and lacking brain neuroimaging studies or who had undergone brain CT earlier than 24 hours from symptom onset.[12] Patients with isolated vertigo, dysarthria, diplopia, bilateral blindness, drop attacks, confusion, dysphagia, loss of consciousness, transient global amnesia, malaise and fatigue, migraine, epilepsy, hypoglycemia, neurotic disorders, metabolic disorders, and hypotension were not considered as TIAs (Table I in the online-only Data Supplement).[8]

Case-Finding Procedures

The purpose of the study was explained in advance to all general practitioners and on-call physicians, who were asked to report all cases with neurological symptoms suggestive of TIA and to give information about patients with similar symptoms evaluated at home. During the study period, all subjects with a possible diagnosis of TIA were screened by 2 investigators (C.T. and R.O.). Events were identified by active monitoring of inpatient and outpatient health services in the district and in nearby areas. In addition, in each clinical ward, all patients admitted for transient focal neurological symptoms were identified and examined by a senior referral physician and thereafter by a consulting neurologist to validate the event. To avoid the omission of any TIA patient, the admission and discharge hospital lists were checked daily.[14] Nearby hospitals were regularly monitored to identify those residents who had cross-boundary medical care. The 118 emergency medical service, emergency rooms, neuroradiology, neurophysiology, and neurosonology services were systematically checked. Hot pursuit (active identification of all events as they occurred) and cold pursuit (retrospective identification of the same events) were combined in the ascertainment of cases to ensure the most complete identification of the events.[15]

Clinical and laboratory data were recorded on standardized forms and stored in a computerized database. Basic information included medical history, cardiovascular and neurological examination, and routine laboratory blood tests. Where available, it also included the results of ancillary investigations such as 12-lead electrocardiography, transthoracic echocardiography, transesophageal echocardiography, Doppler ultrasonography of neck vessels, transcranial Doppler, brain CT and brain MRI studies with DWI sequences, CT angiography and magnetic resonance angiography. Risk factors such as arterial hypertension, hypercholesterolemia, diabetes mellitus, atrial fibrillation, cigarette smoking, alcohol abuse, and coronary heart disease, together with carotid and vertebral–basilar stenosis and occlusion and stroke in medical history were also screened. Definitions of risk factors are reported in the online-only Data Supplement. As soon as patients came to medical attention, they were evaluated by means of the $ABCD_2$ score (age, blood pressure, clinical features, duration of TIA, presence of diabetes).[4] Every effort was made to maintain uniform diagnostic accuracy throughout the study period. Strict adherence to current guidelines for management of TIA patients was encouraged.

Follow-Up

All patients were evaluated with in-person visits whenever possible, or alternatively by a structured telephone interview, to record the occurrence of any outcome event at 30 days, 1 year, and 2 years. Outcome events were recurrent TIA, nonfatal and fatal stroke, nonfatal and fatal myocardial infarction, and all-cause mortality. Definitions of outcome events are reported in the online-only Data Supplement. All the available sources were checked monthly, including death certificates.

Statistical Analysis

Descriptive statistics are reported as absolute numbers with percentages, mean±SD, or median with interquartile range. Groups were compared with Student *t* test. Figures of the resident population in the L'Aquila district at the 2011 census were used to calculate incidence rates.[13] Crude annual incidence rate per 100 000 was calculated for all the included patients diagnosed according to the traditional time-based TIA definition and for tissue-based TIA. Rates were computed also according to age and sex groups. Ninety-five percent confidence intervals (CIs) were computed assuming a Poisson distribution of the events. Using the direct method, incidence rates were standardized by age and sex to the 2011 European population[16] (Table II in the online-only Data Supplement). The risk of outcome events at 30 days, 1 year, and 2 years was measured using the Kaplan–Meier method.

Results

Out of 804 screened patients, we excluded 21 patients with a first-ever TIA who were nonresident in the L'Aquila district and 573 patients with transient symptoms other than TIA (109 nonresidents and 464 residents). Two hundred and ten TIA patients diagnosed according to the traditional time-based definition were finally included (109 women [51.4%], mean [SD] age 73.3 [14.2] years). One hundred ninety-nine patients (94.8%) received brain neuroimaging; 169 patients (80.5%) were investigated with brain CT, and 30 patients (14.3%) with brain DWI-MRI. The flow chart of the study with details of received brain neuroimaging, and diagnoses is reported in Figure. One hundred ninety-nine TIA patients (94.8%) were referred to emergency departments or hospitalized; 11 patients (5.2%) were investigated as outpatients.

The final classification of the 210 TIA patients (Figure) was the following: 151 patients (71.9%) broadly defined tissue-based TIA patients, 29 patients (13.8%) with transient symptoms and evidence of an acute and congruous ischemic lesion, and 30 ANS patients (14.3%) either lacking brain neuroimaging (n=11) or having undergone brain CT within <24 hours from symptom onset (n=19). Only 16 of the 151 patients (10.6%) received brain DWI-MRI, whereas 135 patients (89.4%) received brain CT after 24 hours.

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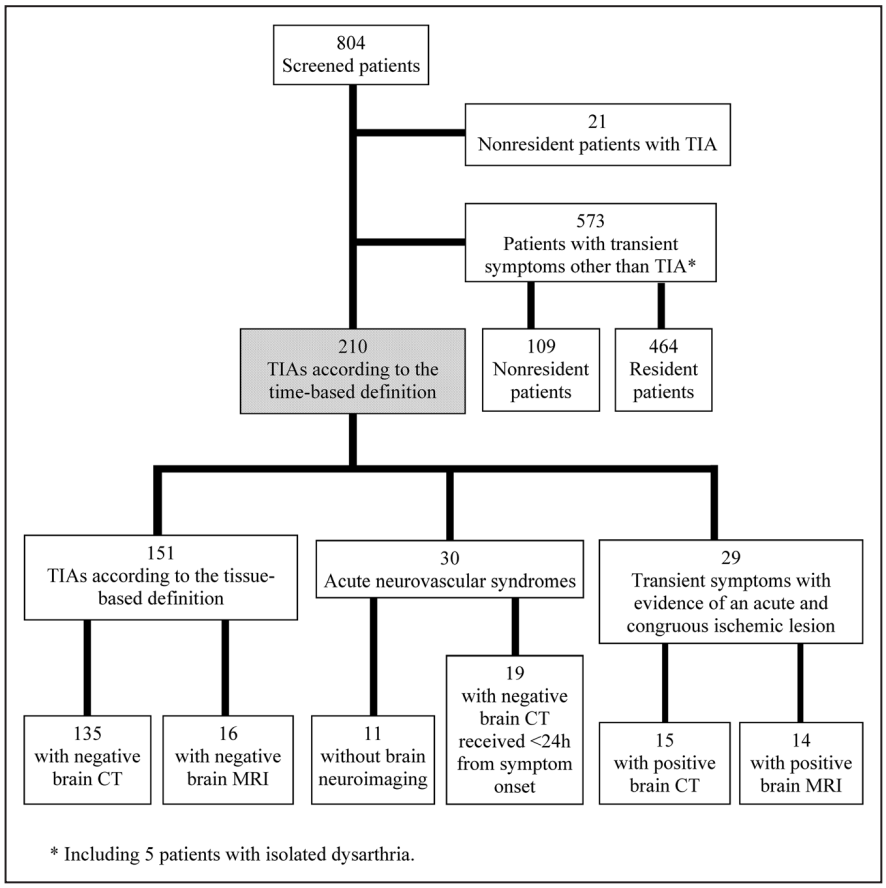

Figure. Flow chart of the study. CT indicates computed tomography; MRI, magnetic resonance imaging; and TIA, transient ischemic attack.

Baseline characteristics of the 210 TIA patients are reported in Table 1. Women (51.4%) outnumbered men; at TIA onset, mean [SD] age 75.0 [15.2] versus 71.4 [12.7] years was similar in women and men (P=0.062). Among all TIA patients, 168 patients (80.0%) had a carotid and 42 patients (20.0%) a vertebral–basilar TIA. The median $ABCD_2$ score was 5 (interquartile range, 5–6).

Crude annual incidence rate for the 210 TIA was 35.2 per 100 000 (95% CI, 30.6–40.3) and 28.6/100 000 (95% CI, 24.1–33.5) when standardized to the 2011 European population. TIAs were rare in young adults (<45 years) and fairly rare in subjects aged 45–64 years; thereafter, the incidence steeply increased, peaking in subjects aged ≥85 years, in both sexes (Table 2; Figure I in the online-only Data Supplement). Overall annual incidence rates were similar in men and women. Crude annual incidence rate for the broadly defined tissue-based TIA was 25.3 per 100 000 (95% CI, 21.5–29.6) and 20.0 per 100 000 (95% CI, 16.3–24.1) when standardized to the same European population.

No patient was lost to follow-up. Outcome events at 30 days and at 1 and 2 years are reported in Table 3. Overall outcome events at 2 years were 50 (23.8% of patients) in all the 210 TIA patients, including 15 patients (7.1%) with nonfatal or fatal strokes.

Discussion

According to standard criteria, we performed in the L'Aquila district a 2-year prospective population-based registry of patients with a first-ever TIA.[17] We found a fairly low crude annual incidence rate for TIA when comparing our results with those of comparable studies that were performed in the 1980s and in the 1990s including populations with different baseline characteristics. In Table 4, we reported annual standardized TIA rates from comparable studies ranging from 35.7 to 98.7 per 100 000.[1,2,18–21] Other studies lacking the data to allow standardization reported annual crude incidence rates ranging from 22.9 to 31.0 per 100 000, which were closer to those found in the present study.[22–25] Our data suggest that the burden of TIA, in line with that of ischemic stroke, is now reduced compared with the past. This difference may extend to other high income countries and may reflect changes in TIA epidemiology. Our low incidence rate might depend on inaccurate case-finding procedures compared with other studies. However, we consider this possibility unlikely, because we used multiple case-finding sources. Additionally, more stringent criteria may have contributed to the low incidence rate as we screened a large number of cases with transient symptoms, which, after careful evaluation, were attributed to diseases other than TIA (Figure). Because our study is the most recent among the available studies, the better control of known risk factors together with strong health promotion activities and improved preventive treatments of modifiable risk factors may have contributed to decrease figures of TIA incidence.[26] This possibility is also supported by a population-based study anticipating a decrease in incidence rates for both TIA and ischemic stroke.[25] Additionally, the relatively low crude incidence rate could reflect a lower baseline cardiovascular risk in our population, possibly depending on environmental factors including lifestyle and Mediterranean diet.

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Table 1. Baseline Characteristics of All TIA Patients

Baseline characteristics	(n=210)
Women, n (%)	109 (51.4)
Hospitalized patients, n (%)	199 (94.8)
$ABCD_2$ score (median, IQR)	5 (5–6)
Mean age ± SD at onset, y	
Overall	73.3±14.2
Men	71.4±12.7
Women	75.0±15.2
Age range, y	19–100
Symptoms, n (%)	
Unilateral weakness	118 (56.2)
Speech disturbance without weakness	27 (12.8)
Duration of symptoms <60 min	64 (30.5)
Duration of symptoms >60 min	146 (69.5)
Carotid TIA	168 (80.0)
Vertebral–basilar TIA	42 (20.0)
Transient monocular blindness	4 (1.9)
Risk factors, n (%)	
Arterial hypertension	151 (71.9)
Hypercholesterolemia	66 (31.4)
Diabetes mellitus	48 (22.8)
Atrial fibrillation	28 (13.4)
Coronary heart disease	15 (7.1)
Cigarette smoking	29 (13.8)
Alcohol abuse	18 (8.6)
Ipsilateral carotid stenosis ≥50%	20 (9.5)
Ipsilateral carotid stenosis <50%	81 (38.6)
Ongoing treatment at symptom onset, n (%)	
Statins	63 (30.0)
Antihypertensives	157 (74.8)
Antiplatelets	87 (41.4)
Anticoagulants	17 (8.0)
Treatment after TIA diagnosis, n (%)	
Statins	73 (34.8)
Antihypertensives	157 (74.8)
Antiplatelets	170 (80.9)
Anticoagulants	26 (12.4)
Endarterectomy	9 (4.3)

$ABCD_2$ indicates age, blood pressure, clinical features, duration of TIA, presence of diabetes; IQR, interquartile range; and TIA, transient ischemic attack.

Table 2. Age- and Sex-Specific Annual Incidence Rates per 100 000 for All TIA Patients

Age Group, y	At Risk	N	Rate	95% CI
Men				
0–44	150 716	3	2.0	0.4–5.8
45–54	44 680	11	24.6	12.3–44.1
55–64	39 955	14	35.0	19.2–58.8
65–74	28 223	25	88.6	57.3–130.8
75–84	20 225	32	158.2	108.2–223.4
85+	6732	16	237.7	135.8–386.0
Crude rate	290 531	101	34.8	28.3–42.2
Standardized rate*			29.1	22.8–36.4
Women				
0–44	144 808	6	4.1	1.5–9.0
45–54	45 650	6	13.1	4.8–28.6
55–64	40 450	9	22.2	10.2–42.2
65–74	30 948	17	54.9	32.0–87.9
75–84	29 401	38	129.2	91.5–177.4
85+	14 642	33	225.4	155.1–316.5
Crude rate	305 899	109	35.6	29.3–43.0
Standardized rate*			28.1	22.1–35.1
Total				
0–44	295 524	9	3.0	1.4–5.8
45–54	90 330	17	18.8	11.0–30.1
55–64	80 405	23	28.6	18.1–42.9
65–74	59 171	42	71.0	51.2–95.9
75–84	49 626	70	141.0	110.0–178.2
85+	21 374	49	229.2	166.8–298.1
Crude rate	596 430	210	35.2	30.6–40.3
Standardized rate*			28.6	24.1–33.5

CI indicates confidence interval; and TIA, transient ischemic attack.
*Rates standardized to the 2011 European population.

In the present study, the proportion of TIA patients who were not referred to the emergency departments or hospitalized (5.2%) was low. The high rate of hospital care can be attributed to the lack of TIA clinics and to the preferred hospitalization to overcome delay in performing the necessary exams as outpatients because of overloaded waiting lists. Besides, hospital care in our district provide 24/7 clinical and diagnostic assessment without fees for the patient and is the healthcare resource preferred by general practitioners for the management of TIA patients.

To the best of our knowledge, this is the first epidemiological study that sought to test the applicability of the tissue-based definition of TIA. We also found that using the broad tissue-based TIA definition, there was only a slight change in incidence as compared with the traditional time-based definition. The strictly MRI-dependent tissue-based definition, however, was not applicable to our population-based setting, which, like many other populations, lacks universal access to MRI for TIA patients. Because of the observational population-based study design, the choice to perform brain CT scan or brain DWI-MRI was entrusted to the treating physician and

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Table 3. Outcome Events at 30 Days, at 1 Year, and at 2 Years for All TIA Patients

Outcome Event	n=210		
	n	%	95% CI
30 d			
TIA recurrence	4	1.9	0.1–3.8
Nonfatal and fatal stroke	5	2.4	0.3–4.4
Nonfatal and fatal myocardial infarction	2	1.0	0.0–2.3
All-cause mortality	2	1.0	0.0–2.3
Overall	13	6.2	2.9–9.5
1 y			
TIA recurrence	7	3.3	0.9–5.8
Nonfatal and fatal stroke	8	3.8	1.2–6.4
Nonfatal and fatal myocardial infarction	7	3.3	0.9–5.8
All-cause mortality	8	3.8	1.2–6.4
Overall	30	14.3	10.0–19.0
2 y			
TIA recurrence	11	5.2	2.2–8.3
Nonfatal and fatal stroke	15	7.1	3.7–10.6
Nonfatal and fatal myocardial infarction	10	4.8	1.9–7.6
All-cause mortality	14	6.7	3.3–10.0
Overall	50	23.8	18.1–30.0

CI indicates confidence interval; and TIA, transient ischemic attack.

was influenced by the availability of MRI machines in only 2 public hospitals within our district (L'Aquila and Avezzano). We had a low proportion of MRI-DWI brain examinations (10.6%) and a high proportion of brain CT scans (89.4%). This prevented us from accurately excluding the presence of acute brain ischemia in a notable proportion of patients but enabled diagnosis according to a broad tissue-based working definition of TIA. If we had to rely only on brain MRI-DWI, we could have diagnosed as TIA only 16 patients, and we would have been unable to adequately define the remaining 135 patients with negative brain CT. In fact, the proportion of tissue-based diagnoses of TIA depends on the timing and type of neuroimaging. The diagnosis of TIA has for a long time been based only on clinical symptoms (anamnestic or clinically present and relevant). The advent of brain neuroimaging has led to their inclusion in differential diagnosis to distinguish TIA from concurrent disorders and, more recently, from stroke or minor stroke. The tissue-based definition undoubtedly represents a step forward for the characterization of cerebrovascular events. Clearly, from a clinical point of view, a diagnosis without neuroimaging is different from one that includes extensive neuroimaging. Consequently, although the time-based diagnosis of TIA is still exclusively based on the 24-hour time limit, the tissue-based diagnosis depends on the availability of brain DWI-MRI neuroimaging to identify small ischemic lesions. In everyday practice and across different hospital settings, tissue-based diagnosis of a TIA episode may vary not only qualitatively (brain CT versus brain DWI-MRI) but also quantitatively depending on the availability of brain MRI machines. The tissue-based definition is more conveniently applicable in advanced hospital settings than in population-based studies because it requires brain neuroimaging and preferentially brain DWI-MRI. For this reason, our epidemiological data are not generalizable to districts where tertiary stroke centers or dedicated TIA clinics are available. However, we must remember that brain CT still represents the mainstay in most emergency departments and primary-level hospitals, so a broad definition of tissue-based TIA that relies on high proportions of brain CT should be acceptable where there is not access to brain MRI for TIA.

In our patients, the risk of stroke after TIA was closer to the risk reported by more recent population-based studies and lower than those reported in less recent studies.[5,19,20,27,28] Globally, all the available data suggest that TIA prognosis is improving over time. Our figures are also in line with data about the unchanged risk of death after a TIA.[19,28]

Our study had a prospective design and was based on a rigorous identification of TIA patients. It also took due account of patients with ANS and of patients with transient symptoms and evidence of an acute and congruous ischemic lesion. We duly recognize that our study suffers from limitations shared with other epidemiological studies. The ascertainment of all incident first-ever TIA cases is challenging because in some instances

Table 4. Crude and Standardized Annual Incidence Rates per 100 000 in Selected Studies

Study	Inclusion Period	Included TIA, n	Crude Incidence Rate	95% CI	Standardized Incidence Rate*	95% CI
Novosibirsk[1]	1996–1997	89	28.7	23.1–35.1	44.5	38.9–50.6
Oxfordshire[18]	1981–1986	184	34.9	30.1–40.2	51.3	45.3–57.9
Porto[20]	1998–2000	141	67.0	45.0–104.0	63.2	52.7–73.7
Rochester[2]	1985–1989	202	61.3	53.2–70.1	98.7	90.2–107.6
Segovia[21]	1992–1994	103	35.0	28.0–42.0	35.7	28.8–42.6
Udine[19]	2007–2009	178	52.5	44.8–61.0	42.3	36.9–48.3
L'Aquila (present study)	2011–2012	210	35.2	30.6–40.3	28.6	24.1–33.5

CI indicates confidence interval; and TIA, transient ischemic attack.
*Rates standardized to the 2011 European population.

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the spontaneous resolution of symptoms within a short time interval can lead patients not to seek medical care. It is common experience that patients with a rapid and complete recovery are less likely to report, or in some cases even to recall, their TIA symptoms. In 5.2% of the patients, the diagnosis of TIA had to rely on medical history only, as they missed brain neuroimaging examinations. Ultimately, the number of TIA patients who do not seek medical care is not determinable, and this is another common problem in the epidemiology of TIA. As brain DWI-MRI is more sensitive than CT in identifying ischemic lesions, the high proportion of patients who received only brain CT after 24 hours (89.4%) might have led to the underestimation of the presence of ischemic lesions, a bias that might have increased the proportion of tissue-based TIA.

Finally, we also included patients with ANS (5.2%) who were not hospitalized and did not undergo brain neuroimaging studies; we cannot exclude that some of those patients might have had symptoms not related to vascular lesions. Nevertheless, the low proportion of these events should not have affected the overall results. By strictly applying clinical diagnostic criteria, we excluded from our registry patients with isolated vertigo, dysarthria, diplopia, bilateral blindness, confusion, and dysphagia. We are aware that isolated or pure dysarthria could be otherwise considered as an unascertained TIA or as the consequence of an atypical lacunar syndrome[8,29] or, as recently proposed, could also represent an uncommon TIA presentation.[30] Regarding follow-up data, we have only scarce information about the adherence of our patients to the treatment that was prescribed after the TIA. Strict adherence to the prescribed treatment may partially explain the lower rate of outcome events that we found in our study (globally 23.8% of included patients at 2 years) with respect to rates reported in previous studies. Less probably, we might have included patients with transient symptoms other than TIA.

In conclusion, we found a low overall TIA annual incidence rate, in line with the reduction of ischemic stroke incidence, and a fair TIA prognosis possibly because of improved health promotion activities and of the wider diffusion of preventive treatments of modifiable risk factors for cardiovascular diseases. We also proved that using the broad tissue-based TIA definition, there is only a slight change in incidence as compared with the traditional time-based definition, whereas the strictly MRI-based tissue-based definition was not applicable to our population-based setting as to other populations that lack universal access to brain MRI for TIA patients.

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Disclosures

None.

References

1. Feigin VL, Shishkin SV, Tzirkin GM, Vinogradova TE, Tarasov AV, Vinogradov SP, et al. A population-based study of transient ischemic attack incidence in Novosibirsk, Russia, 1987–1988 and 1996–1997. *Stroke*. 2000;31:9–13.
2. Brown RD Jr, Petty GW, O'Fallon WM, Wiebers DO, Whisnant JP. Incidence of transient ischemic attack in Rochester, Minnesota, 1985–1989. *Stroke*. 1998;29:2109–2113.
3. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369:283–292. doi: 10.1016/S0140-6736(07)60150-0.
4. Coull AJ, Lovett JK, Rothwell PM; Oxford Vascular Study. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ*. 2004;328:326. doi: 10.1136/bmj.37991.635266.44.
5. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284:2901–2906.
6. Fisher CM. Intermittent cerebral ischemia. In: Wright IS, Millikan CM. *Cerebral Vascular Disease*. New York, NY: Grune & Stratton; 1958:81–97.
7. Millikan CH, Siekert RG, Whisnant JP. *Cerebral Vascular Disease*. 4th ed. New York, NY: Grune & Stratton; 1965:194.
8. Ad Hoc Committee on Cerebrovascular Diseases. A classification and outline of cerebrovascular diseases. *Stroke*. 1975;6:564–616.
9. Brazzelli M, Chappell FM, Miranda H, Shuler K, Dennis M, Sandercock PA, et al. Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Ann Neurol*. 2014;75:67–76. doi: 10.1002/ana.24026.
10. Al-Khaled M. Magnetic resonance imaging in patients with transient ischemic attack. *Neural Regen Res*. 2014;9:234–235. doi: 10.4103/1673-5374.128211.
11. Redgrave JN, Schulz UG, Briley D, Meagher T, Rothwell PM. Presence of acute ischaemic lesions on diffusion-weighted imaging is associated with clinical predictors of early risk of stroke after transient ischaemic attack. *Cerebrovasc Dis*. 2007;24:86–90. doi: 10.1159/000103121.
12. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al; American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40:2276–2293. doi: 10.1161/STROKEAHA.108.192218.
13. 15th Population and Housing Census. Italian National Institute of Statistics (ISTAT) website. http://dati.istat.it. Accessed December 10, 2015.
14. World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*. 9th ed. Geneva, Switzerland: WHO; 1977:1.
15. Feigin V, Hoorn SV. How to study stroke incidence. *Lancet*. 2004;363:1920. doi: 10.1016/S0140-6736(04)16436-2.
16. The 2011 Population and Housing Census. Directorate-General of the European Commission (EUROSTAT) website. 2011. http://ec.europa.eu/eurostat. Accessed December 10, 2015.
17. Sudlow CL, Warlow CP. Comparing stroke incidence worldwide: what makes studies comparable? *Stroke*. 1996;27:550–558.
18. Dennis MS, Bamford JM, Sandercock PA, Warlow CP. Incidence of transient ischemic attacks in Oxfordshire, England. *Stroke*. 1989;20:333–339.
19. Cancelli I, Janes F, Gigli GL, Perelli A, Zanchettin B, Canal G, et al. Incidence of transient ischemic attack and early stroke risk: validation of the ABCD2 score in an Italian population-based study. *Stroke*. 2011;42:2751–2757. doi: 10.1161/STROKEAHA.110.612705.
20. Correia M, Silva MR, Magalhães R, Guimarães L, Silva MC. Transient ischemic attacks in rural and urban northern Portugal: incidence and short-term prognosis. *Stroke*. 2006;37:50–55. doi: 10.1161/01.STR.0000195209.26543.8f.
21. Sempere AP, Duarte J, Cabezas C, Clavería LE. Incidence of transient ischemic attacks and minor ischemic strokes in Segovia, Spain. *Stroke*. 1996;27:667–671.
22. Lai SM, Alter M, Friday G, Sobel E, Gil-Peralta A, McCoy RL, et al. Transient ischemic attacks: their frequency in the Lehigh Valley. *Neuroepidemiology*. 1990;9:124–130.
23. Fratiglioni L, Arfaioli C, Nencini P, Ginanneschi A, Iaquinta L, Marchi M, et al. Transient ischemic attacks in the community: occurrence and

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clinical characteristics. A population survey in the area of Florence, Italy. *Neuroepidemiology*. 1989;8:87–96.
24. Matias-Guiu, Oltra A, Falip R, Martin R, Galiano L. Occurrence of transient ischemic attacks in Alcoi: descriptive epidemiology. *Neuroepidemiology*. 1994;13:34–39.
25. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al; Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet*. 2004;363:1925–1933. doi: 10.1016/S0140-6736(04)16405-2.
26. Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Carlsson M, Mathiesen EB. Time trends in incidence and case fatality of ischemic stroke: the Tromsø study 1977–2010. *Eur J Intern Med*. 2014;25:e50–e51.
27. Sundararajan V, Thrift AG, Phan TG, Choi PM, Clissold B, Srikanth VK. Trends over time in the risk of stroke after an incident transient ischemic attack. *Stroke*. 2014;45:3214–3218. doi: 10.1161/STROKEAHA.114.006575.
28. Li OL, Silver FL, Lichtman J, Fang J, Stamplecoski M, Wengle RS, et al. Sex differences in the presentation, care, and outcomes of transient ischemic attack: results from the Ontario Stroke Registry. *Stroke*. 2016;47:255–257. doi: 10.1161/STROKEAHA.115.010485.
29. Arboix A, López-Grau M, Casasnovas C, García-Eroles L, Massons J, Balcells M. Clinical study of 39 patients with atypical lacunar syndrome. *J Neurol Neurosurg Psychiatry*. 2006;77:381–384. doi: 10.1136/jnnp.2005.071860.
30. Beliavsky A, Perry JJ, Dowlatshahi D, Wasserman J, Sivilotti ML, Sutherland J, et al. Acute isolated dysarthria is associated with a high risk of stroke. *Cerebrovasc Dis Extra*. 2014;4:182–185. doi: 10.1159/000365169.

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Epidemiology of Transient Ischemic Attacks Using Time- or Tissue-Based Definitions: A Population-Based Study

Diana Degan, Raffaele Ornello, Cindy Tiseo, Federica De Santis, Francesca Pistoia, Antonio Carolei and Simona Sacco

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SUPPLEMENTAL MATERIAL

For manuscript entitled:
Epidemiology of transient ischemic attacks using time- or tissue-based definitions: a population-based study

Authors:
Diana Degan, MD
Raffaele Ornello, MD
Cindy Tiseo, MD
Federica De Santis, MD
Francesca Pistoia, MD, PhD
Antonio Carolei, MD, FAHA
Simona Sacco, MD

Affiliation: Institute of Neurology, Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, 67100 L'Aquila, Italy

Supplemental Table I. Other diagnoses in 464 resident patients with transient symptoms other than TIA.

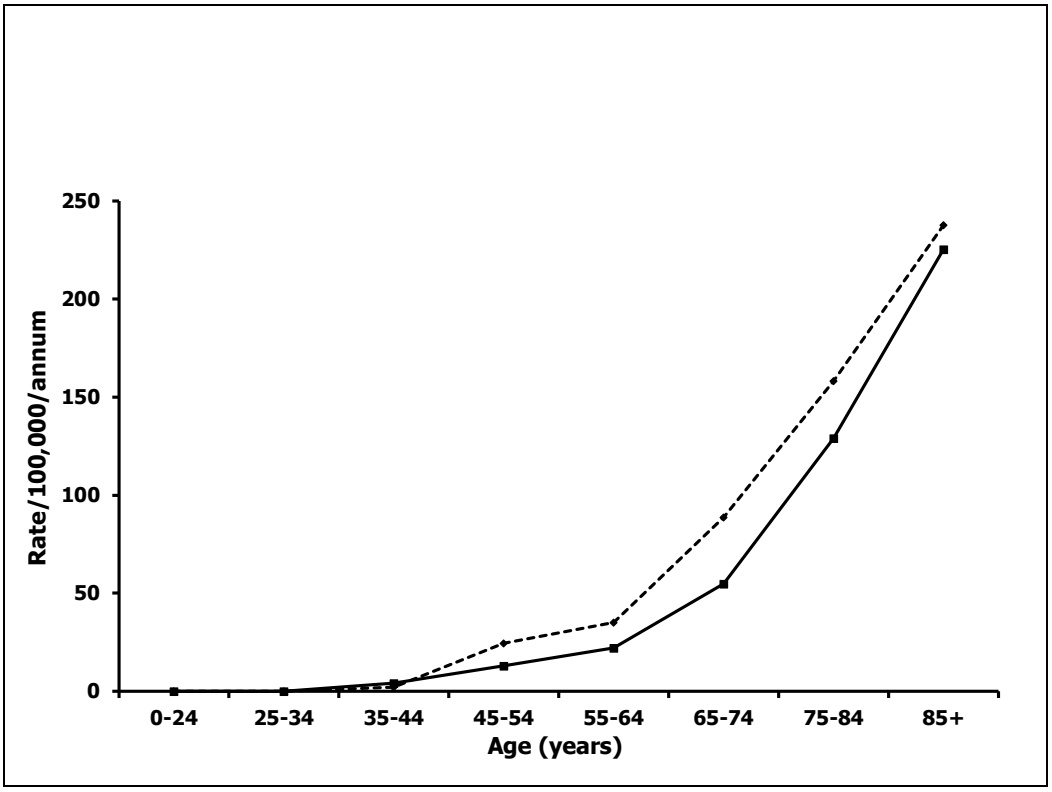
ICD-9-CM code	Other diagnosis	Patients	
		n	%
293.0	Acute confusional state	66	14.3
345	Epilepsy	94	20.3
780.2	Syncope and collapse	81	17.5
780.4	Dizziness and giddiness	43	9.2
Other codes	Other diagnoses	180	38.7
Total		464	100.0

ICD-9-CM= International Classification of Diseases, 9th Revision, Clinical Modification; TIA=Transient Ischemic Attack.

Supplemental Table II. Italian 2011 and European 2011 populations by age and gender groups.

	Italy			Europe		
Age group (years)	Male	Female	Total	Male	Female	Total
0-14	4,285,033	4,041,015	8,326,048	40,192,263	38,180,657	78,372,920
15-24	3,036,127	2,885,687	5,921,814	30,272,098	29,068,875	59,340,973
25-34	3,524,422	3,532,488	7,056,910	33,845,878	33,315,282	67,161,160
35-44	4,649,839	4,709,928	9,359,767	36,897,666	36,492,341	73,390,007
45-54	4,381,588	4,536,985	8,918,573	35,837,152	36,210,748	72,047,900
55-64	3,613,816	3,851,853	7,465,669	30,272,051	32,132,704	62,404,755
65-74	2,909,563	3,322,989	6,232,552	21,163,651	24,766,494	45,930,145
75-84	1,831,636	2,629,630	4,461,266	12,551,513	18,597,031	31,148,544
85+	513,483	1,177,662	1,691,145	3,270,305	7,634,044	10,904,349
Total	28,745,507	30,688,237	59,433,744	244,302,577	256,398,176	500,700,753

Supplemental Figure I. Age- and sex-specific crude annual incidence rates per 100,000 in time-based TIA patients in the L'Aquila district.



Supplemental Figure I Legend: --▪-- Men –▪– Women.

Supplemental Methods

Participating centers

Together with the general practitioners, the following centers participated in the study:
Public hospitals: *Ospedale San Salvatore*, L'Aquila; *Ospedale Civile Santi Filippo e Nicola*, Avezzano (Coordinating center); *Ospedale Santissima Annunziata*, Sulmona; *Ospedale Civile*, Castel di Sangro.
Private hospitals: *Casa di Cura Istituto Neurotraumatologico Italiano (I.N.I.)*, Canistro; *Casa di Cura L'Immacolata*, Celano; *Casa di Cura San Raffaele*, Sulmona; *Casa di Cura di Riabilitazione Nova Salus*, Trasacco; *Casa di Cura privata Di Lorenzo*, Avezzano.
Nearby hospitals: *Ospedale Santo Spirito*, Pescara; *Ospedale Santissima Trinità*, Popoli; *Ospedale Civile Giuseppe Mazzini*, Teramo; *Ospedale Civile Maria Santissima dello Splendore*, Giulianova.

Risk factors

Arterial hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg (systolic blood pressure >130 mmHg and/or diastolic blood pressure >80 mmHg in diabetic patients) on at least two different occasions, or history of hypertension confirmed in medical records. [1]
Hypercholesterolemia was defined as fasting total cholesterol serum level ≥200 mg/dL and/or fasting low density lipoprotein (LDL) cholesterol serum level >129 mg/dL at recruitment, or history of hypercholesterolemia that was confirmed in medical records and/or use of lipid-lowering medications. [2]
Diabetes mellitus was defined as fasting blood glucose >6.0 mmol/L, and/or use of insulin/oral hypoglycemic agents and/or history of diabetes that was confirmed in medical records.[3]
Atrial fibrillation was defined as a cardiac arrhythmia with the following characteristics: the surface ECG shows 'absolutely' irregular RR intervals (AF is therefore sometimes known as arrhythmia absoluta), i.e. RR intervals that do not follow a repetitive pattern; there are no distinct P waves on the surface ECG; some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1; the atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 ms (>300 bpm).[4]
Cigarette smoking was defined as never, current smoker and former smoker of any kind of tobacco. Patients were defined as smokers if they were current smokers or they had stopped smoking at least 6 months before the index transient ischemic attack and as former smokers when smoking was stopped earlier.
Alcohol abuse was diagnosed in the presence of a daily alcohol consumption of more than two alcohol units.
Coronary heart disease was defined as a history of acute myocardial infarction or angina pectoris.

Outcome events

Stroke was defined as rapidly developing signs of focal or global disturbance of cerebral function lasting longer than 24 hours or leading to death with no apparent cause other than that of vascular origin.[5]
Transient ischemic attack (TIA) recurrence was defined as a new focal neurological dysfunction of brief duration, presumed to be of vascular origin and confined to an area of the brain or eye perfused by a specific cerebral artery and of duration less than 24 hours.[6-8]
Myocardial infarction was diagnosed in the presence of rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischemic symptoms; b) development of pathologic Q waves on the ECG; c) ECG changes indicative of ischemia (ST segment elevation or depression); or d) coronary artery intervention (e.g., coronary angioplasty).[9]

Cardiovascular death included death from myocardial infarction,[9] congestive heart failure,[10] acute pulmonary edema and systemic embolism.

Supplemental References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–72.

2. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation.* 2002;106:3143–421.

3. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care.* 2003;26:3160–7.

4. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J.* 2010;31:2369-429.

5. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ.* 1980;58:113-30.

6. Fisher CM. Intermittent cerebral ischemia. In: Wright IS, Millikan CM, eds. Cerebral vascular disease New York, NY: *Grune & Stratton*. 1958:81-97.

7. Millikan CH, Siekert RG, Whisnant JP, eds. Cerebral vascular disease 4th ed. New York, NY: *Grune & Stratton*. 1965:194.

8. Ad Hoc Committee on cerebrovascular diseases. A classification and outline of cerebrovascular diseases. *Stroke*. 1975;6:564-616.

9. Thygesen K, Alpert JS, White HD; on behalf of the joint ESC/ACCF/AHA/WHF task force for the redefinition of myocardial infarction. *J Am Coll Cardiol.* 2007;50:2173-95.

10. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al; ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail*. 2008;10:933–89.