

Mini Review

TIA as Acute Cerebrovascular Syndrome

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Abstract

Patients during early period after the onset of transient ischemic attack (TIA) are at high risk of stroke. Therefore, TIA in acute setting should be recognized to be an emergency requiring immediate evaluation and starting treatment. There is no meaning to differentiate TIA in acute setting from acute ischemic stroke (AIS) only by the duration of symptoms. Acute TIA and AIS are on the same spectrum of acute ischemic syndrome in the central nervous system. The concept of acute cerebrovascular syndrome (ACVS), which includes acute TIA and AIS, is important for the recognition of TIA in acute setting to be a medical emergency as well as AIS. TIA patients with high clinical risk scores such as ABCD2 score, positivity of diffusion weighted image on MRI, intracranial or extracranial arterial stenosis, multiple episodes of TIA, and hypercoagulability are at very high risk of subsequent stroke, and thus should be admitted. Dual anti platelet therapy in patients with non-cardio embolic TIA and direct oral anti coagulants in patients with atrial fibrillation may be useful for preventing early stroke recurrence. In patients with severe arterial stenosis and resistant to medical treatment, surgical or intravascular intervention may be necessitated. A TIA clinic might be very useful for immediate evaluation and management of acute TIA patients. The TIAregistry.org was conducted, which was an international multicenter cooperative prospective cohort study. Patients with TIA or minor stroke within 7 days of onset were recruited and followed up for 5 years. At 1 year, cumulative incidence of the composite outcome of stroke, acute coronary syndrome and cardiovascular death was less than half that expected from historical cohorts. The results of this registry suggest that urgent care for patients with a TIA or minor stroke either in specialized TIA clinics or dedicated care delivery units with stroke specialists undoubtedly works.

INTRODUCTION

Transient ischemic attack (TIA) is well known to be a prodromal syndrome of ischemic stroke. TIA is, however, easily neglected or underestimated by patients or their family's because the symptoms naturally disappear without any treatment [1]. Even by general physicians, TIA is non-prioritized since it is regarded just as minor stroke. However, during early period after the onset of TIA, patients are at very high risk of stroke [2]. Therefore, TIA should be recognized to be an emergency requiring immediate evaluation and starting treatment [3].

There is no global consensus in the definition of TIA. In the classical criteria, TIA is defined as focal neurologic brain or retinal ischemic symptoms which disappear within 24 hours [4]. However, according to the definition by the TIA working group in the United States, TIA had been defined as brain or retinal ischemic symptoms within one hour of the duration without responsible ischemic lesions [5]. Afterwards, the American Heart Association/American Stroke Association redefined TIA as transient focal ischemic symptoms in the brain, retina, or spinal cord without evidence of ischemic lesion regardless

duration of symptoms [6]. However, this tissue-based diagnosis is not possible without MRI diffusion weighted image (DWI). DWI would not be applicable in many hospitals or clinics an immediate examination for tissue-based differential diagnosis between acute ischemic stroke (AIS) and TIA.

Distribution of the duration of TIA with positive DWI is continuous without any specific cutoff point [1]. In addition, early risk of subsequent stroke is very high in patients with not only major stroke but also TIA or minor stroke [2]. Therefore, there is no meaning to differentiate TIA in acute settings from AIS neither by the duration of symptoms or by any other features. Acute TIA and AIS are on the same spectrum of acute ischemic syndrome in the central nervous system. After immediate examinations, antithrombotic therapy as well as risk factor management with anti hypertensive's, statins, and glucose-lowering drugs should be started in patients with not only AIS but also TIA.

The concept of acute cerebrovascular syndrome (ACVS), which includes TIA in acute settings and AIS, is comparable to acute coronary syndrome (ACS), which includes unstable angina and acute myocardial infarction (Figure 1) [1]. When a focal

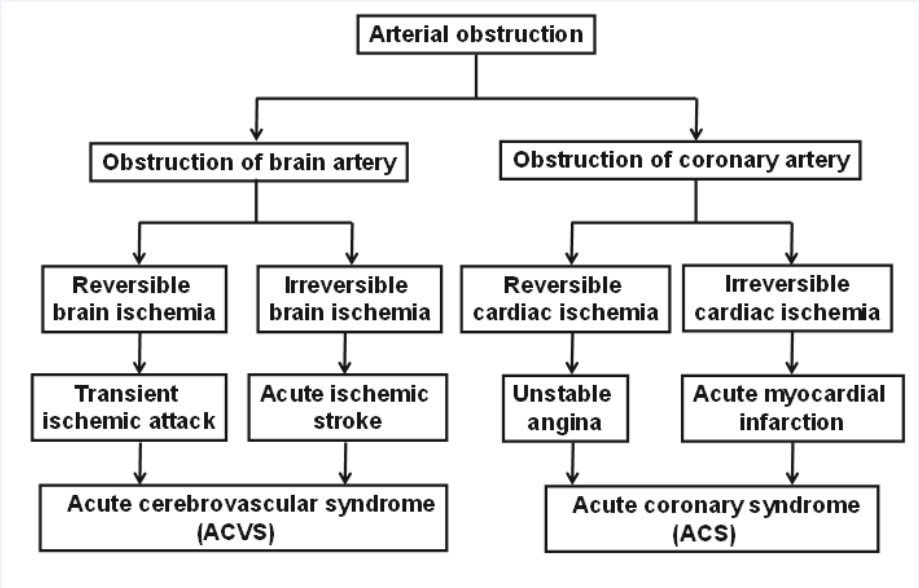


Figure 1 Concept of acute cerebrovascular syndrome (ACVS) in comparison with concept of acute coronary syndrome (ACS). Quoted from Reference 1. The concept of ACVS is comparable to the concept of ACS. In obstruction in coronary artery, if ischemia is reversible, it is termed unstable angina (UA), if it is irreversible it is termed acute myocardial infarction (AMI), and UA and AMI are categorized into ACS. Similarly, in obstruction of brain artery, if ischemia is reversible it is termed TIA, and if it is irreversible it is termed AIS, and TIA and AIS are categorized into ACVS. Therefore, TIA is comparable to unstable angina, which is an unstable ischemic syndrome of central nervous system.

symptomatic reversible ischemia occurs in the brain, it is called TIA, and when a focal symptomatic irreversible ischemia occurs in the brain, it is called AIS. Patients with ACS share a single pathophysiological mechanism, which is rupture of unstable plaque followed by formation of platelet-rich thrombi to plug up coronary arteries. Unlike ACS, the mechanism of ACVS is complicated, which is not only large artery atherosclerosis similar to ACS but also cardio embolism or small vessel occlusion. In addition, there is no measurable biomarker for ACVS, while there are practical biomarkers for ACS [1]. Nevertheless, the concept of ACVS is practical to emphasize the importance of immediate evaluation and starting treatment to prevent subsequent stroke in acute settings of TIA. Therefore, TIA in acute settings as well as AIS should be recognized as ACVS, which is a medical emergency. ACVS are a clinical concept but not a pathological diagnosis. The concept of ACVS is important for the recognition of TIA in the acute setting to be a medical emergency as well as AIS. Acute TIA is an unstable cerebral ischemic condition, which is a prodromal symptom before an irreversible thromboembolic event in the brain.

TIA is underestimated or overlooked, and even when it was recognized by physicians, they may not recognize the need to give anti thrombotics for stroke prevention [7]. TIA patients in acute settings are at very high risk of subsequent stroke, especially among those with high clinical risk scores such as ABCD² score, positivity of DWI, intracranial or extracranial arterial stenosis, multiple episodes of TIA, and hypercoagulability (Table 1) [1,3,8-10]. The TIA patients with these high risk factors for subsequent stroke should be admitted, and immediate brain and vascular imaging are required as well as blood testing and cardiac evaluation in order to detect vascular and cardiac risk factors (Table 2) [1]. After immediate examinations, antithrombotic

Table 1: TIA patients who require hospitalization.
High clinical risk scores such as ABCD ² score
Positivity of MRI diffusion weighted image
Intracranial or extracranial arterial stenosis
Multiple episodes of TIA including crescendo TIA
Non-valvular and valvular atrial fibrillation
Hypercoagulability such as antiphospholipid syndrome

Table 2: Radiological and physiological examinations for initial evaluation of acute TIA patients.
Brain magnetic resonance imaging including diffusion-weighted imaging
Intracranial and extracranial MR or CT angiography
Carotid and vertebral ultrasonography
Electrocardiography with continuous monitoring
Transthoracic and/or transesophageal echocardiography
Transcranial Doppler ultrasound

therapy as well as risk factor management with anti hypertensives, statins, and glucose-lowering drugs should be started (Table 3) [1,11]. As to antithrombotic therapy, dual anti platelet therapy maybe effective to prevent early stroke recurrence in patients with non-cardioembolic TIA for aggressive inhibition of platelet activation [12], and novel or direct oral anti coagulants for rapid inhibition of coagulation activation may be useful for preventing early stroke recurrence in patients with cardioembolic TIA due to atrial fibrillation [13]. In patients with severe arterial stenosis and resistant to medical treatment, surgical or intravascular intervention with carotid endarterectomy, carotid artery

Table 3: Initial managements in TIA patients.

Management of risk factors	Single or dual antihypertensives
	Lipid lowering with statins
	Blood glucose lowering drugs
Antithrombotic therapy	Dual or single antiplatelet therapy
	Direct oral anticoagulants or warfarin
Resistance to medical therapy	Carotid endarterectomy
	Carotid artery stenting
	Intracranial bypass surgery

stenting or bypass surgery as an emergency procedure may be necessitated [14].

A TIA clinic might be very useful for immediate evaluation and management of acute TIA patients, as it accepts TIA patients 24 hours a day, 365 days a year [11,15]. In the field of cardiology, ACS terminology including unstable angina and acute myocardial infarction was used for the campaign to save lives from cardiac death, which was very successful in reducing the death rate. In the field of neurology, ACVS terminology is expected to be helpful for reducing the risk of stroke, which is the leading cause of death or disability worldwide.

Based on these backgrounds, the TIAregistry.org was conducted, which was an investigator-driven, international multicenter cooperative prospective cohort study [16]. Patients with TIA or minor stroke within 7 days of onset were recruited and followed up for 5 years. Among 4583 patients analyzed, 78% of patients were evaluated by stroke specialists within 24 hours after symptom onset. Adherence to treatment recommendations according to guidelines was very good at discharge and at 3 and 12 months. At 1 year, cumulative incidence of the composite outcome of stroke, ACS and cardiovascular death was less than half that expected from historical cohorts (Figure 2) [16]. Because, one-year rate of major cardiovascular events was 6.2%,

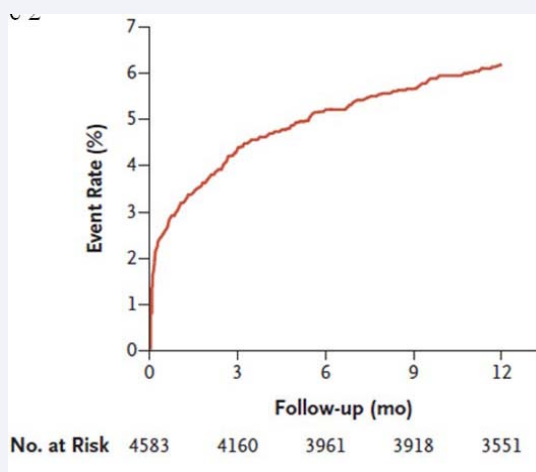


Figure 2 Cumulative incidence of composite outcome in the overall population of TIAregistry.org. Quoted from Reference 14. The composite outcome included stroke, acute coronary syndrome, and cardiovascular death. The incidence was less than a half that expected from historical cohorts.

and stroke rate was 5.1%. The rate of recurrent stroke was significantly higher in ABCD² score 6 or 7 than 0-3, although the threshold score to increase risk of stroke was raised up when compared with the score 10 years ago, which had been score 4 (Figure 3) [16]. Rate of recurrent stroke was significantly higher in patients with multiple acute infarctions than in those without acute infarction or with single acute infarction (Figure 4) [16]. Rate of recurrent stroke was significantly higher in patients with large artery atherosclerosis than in those with other subtypes of ACVS (Figure 5) [16].

According to our nested case-control analysis to evaluate pre-

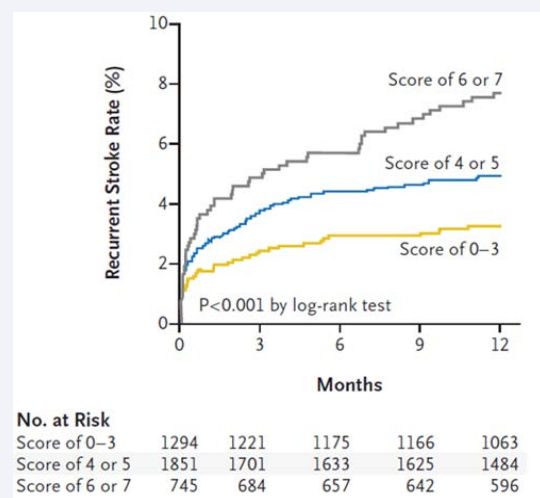


Figure 3 Rate of recurrent stroke according to ABCD² score. Quoted from Reference 14. The rate was significantly higher in ABCD² score 6 or 7 than in 0-3. The threshold score to increase the risk of stroke was raised up when compared with the score in 10 years ago, which was score 4.

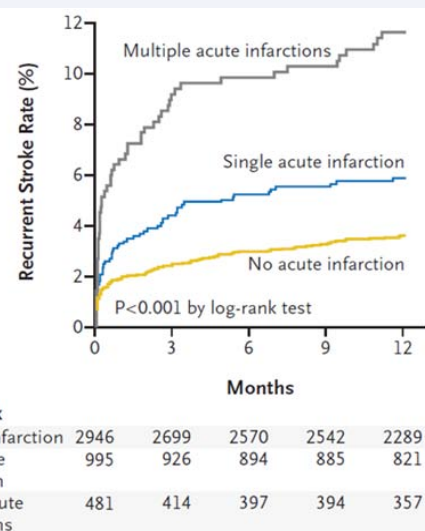


Figure 4 Rate of recurrent stroke according to finding on brain imaging. Quoted from Reference 14. Rate of recurrent stroke was significantly higher in patients with multiple acute infarctions than in those without acute infarction or with single acute infarction.

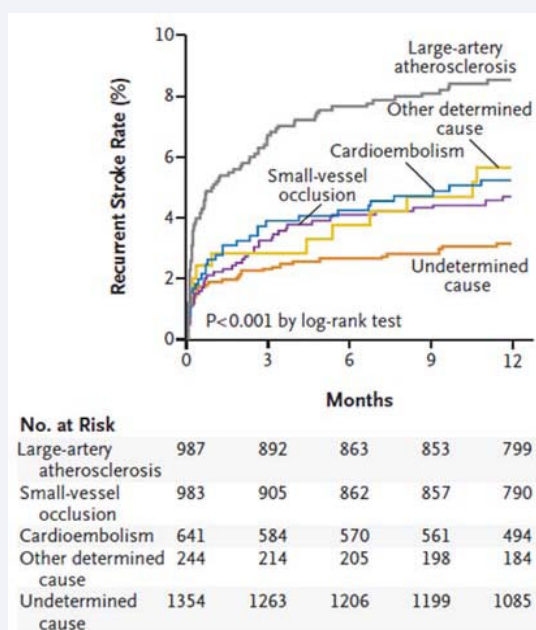


Figure 5 Quoted from Reference 14. Rate of recurrent stroke according to cause of TIA or minor stroke. Rate of recurrent stroke was significantly higher in patients with large artery atherosclerosis than in those with other types.

and post-carotid endarterectomy (CEA) or carotid artery stenting (CAS) in patients enrolled to TIA registry.org, patients with CEA/CAS had a higher 1-year risk of major vascular events than other patients [17]. The results suggest that atherothrombosis is a poly-vascular disease and residual risk of systemic vascular events remain high even after local interventions, which can reduce only the risk of stroke corresponding to the arteries [18]. On the other hand, it is also true that there are considerable ethnic or regional differences in risk factors, etiology, prevalence of intracranial and extracranial arterial stenosis, and type of recurrent stroke [19,20]. These differences should be taken into consideration for the management of patients.

CONCLUSION

In conclusions, under an urgent or emergency, modern secondary stroke prevention strategy in TIA and minor AIS patients, the residual risk is much lower than previously reported, but risk stratification tools such as ABCD² score and MRI are still effective. Large artery atherosclerosis has higher residual risk than other subtypes of ACVS. However, ethnic differences should also be taken into consideration. Because prevalence of intracranial artery and extracranial artery stenoses as well as etiologies of TIA and subtypes of recurrent stroke may considerably differ between individual ethnicities.

Prof. Ralph Sacco stated in the Editorial of the New England Journal of Medicine, "Urgent care for patients with a TIA or minor stroke either in specialized TIA clinics or dedicated care delivery units with stroke specialists undoubtedly works. Both early institution and sustained adherence of evidence-based stroke-prevention treatments are necessary to achieve better outcomes. Stroke prevention and treatment have come a long way. This

study should prompt health care providers and policymakers to make necessary changes in systems of stroke care in order to deliver the most effective care not only to patients with acute stroke, but also to those with a TIA or minor stroke. The TIA registry.org results support the value of organizing specialized units for the care of patients with a TIA or minor stroke where rapid diagnostic evaluations and evidence-based preventive treatments by stroke specialists can be initiated promptly and lead to reduced early and late risks of stroke" [21].

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