CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Transient Ischemic Attack

Pierre Amarenco, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 54-year-old man presents 2 hours after sudden weakness in his left arm prevented him from turning the steering wheel while driving. His symptoms lasted for 30 minutes. He has hypertension and hyperlipidemia, for which he takes an angiotensin-receptor blocker and a statin, and he is a smoker with a 30 pack-year history. On examination, the blood pressure is 156/96 mm Hg. How should this patient be further evaluated and treated?

THE CLINICAL PROBLEM

Approximately 20 to 25% of ischemic strokes are heralded by transient ischemic symptoms[1] (Table 1). These symptoms usually last for seconds or minutes and typically last less than 1 hour.[2] An older, time-based definition of transient ischemic attack (TIA) (based on symptoms lasting <24 hours) has been revised owing to the identification of an infarct on brain imaging in many patients with symptoms that last more than 10 minutes and given that many patients who arrive at the hospital within 6 hours after the onset of symptoms are considered for urgent revascularization. The new definition of TIA is now "tissue-based." An ischemic lesion is not visible on brain imaging in a patient with TIA,[3-5] and a patient with transient symptoms who has even a tiny ischemic brain lesion on imaging is considered to have had a minor ischemic stroke.[3-5] Since TIA and minor ischemic stroke generally have the same clinical manifestations (except for neuroimaging findings) and management, they are clinically considered together.[4-6]

Symptoms of a TIA, if recognized as such, provide a critical opportunity to quickly find and treat the cause in order to prevent a devastating stroke.[2,7] Without treatment, the risk of stroke is as high as 20% at 3 months, and most of this risk occurs within the first 10 days, particularly within the first 2 days.[8-10] Observational data indicate that prompt clinical diagnosis and immediate preventive measures are associated with a decrease of up to 80% in the 3-month risk of stroke.[11,12] The multinational TIAregistry.org project[10,13] collected data from TIA clinics in Europe, Asia, and Latin America, where patients with suspected TIA or minor stroke were rapidly triaged, evaluated, and treated. This project reported a 3-month risk of stroke of approximately 5%, but the risk was front-loaded during the early days after the TIA. Urgent evaluation of these patients[14,15] is best performed in a TIA clinic[10] with round-the-clock access or in an emergency department, depending on local practices.

From the Department of Neurology and Stroke Center, Assistance Publique–Hôpitaux de Paris, SOS-TIA Clinic, Bichat Hospital, Laboratory for Vascular Translational Science, INSERM Unité 1148, Département Hospitalo Universitaire–Fibrose Inflammation Remodelage, University of Paris, Paris. Address reprint requests to Dr. Amarenco at the Department of Neurology and Stroke Center, Bichat Hospital, 46 rue Henri Huchard, Paris 75018, France, or at pierre.amarenco@aphp.fr.

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KEY CLINICAL POINTS

TRANSIENT ISCHEMIC ATTACK

- Cerebral or retinal symptoms consistent with transient ischemic attack (TIA) usually last for seconds or minutes and typically last less than 1 hour.
- A suspected TIA should be evaluated urgently in a TIA clinic or in an emergency department where appropriate specialist expertise and imaging are available.
- Diffusion-weighted imaging of the head is now the preferred test for patients with a suspected TIA and should be performed immediately.
- If possible, immediately after the onset of symptoms, the patient should take aspirin at a dose of 300 mg, followed by 75 to 100 mg daily; clopidogrel should be added to aspirin during the first 21 days after the TIA (at a 300-mg loading dose, followed by 75 mg per day).
- The long-term prevention of stroke after TIA typically includes antiplatelet or anticoagulant treatment (depending on etiologic findings), blood-pressure lowering, lipid lowering, glycemic control, smoking cessation, and counseling regarding diet and lifestyle. Carotid endarterectomy should be performed if appropriate.

STRATEGIES AND EVIDENCE

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Transient symptoms can be motor (in the frontal lobe or pyramidal tract), sensory (in the parietal area), or visual (monocular [transient monocular blindness] with retinal ischemia or binocular [e.g., hemianopia due to intracerebral visual tract or parietal, temporal, or occipital involvement]), or they can involve speech disturbance (aphasia or dysarthria). Other types of transient symptoms (e.g., vertigo, diplopia, dizziness, unsteady gait, or amnesia) can also occur with transient ischemic brain injury, although uncommonly, the occurrence of these symptoms or signs in isolation is explained by ischemia (Table 1).[16,17]

Several other conditions (termed "TIA mimics") may alternatively explain transient neurologic symptoms. Most common among these are migraine aura, peripheral vertigo, epilepsy (e.g., parietal-lobe epilepsy), hypoglycemia, transient global amnesia, and postural hypotension. Transient neurologic symptoms may also occur in patients who have myasthenia, cervical arthrosis, peripheral-nerve injury, multiple sclerosis, or hypokalemia, and, rarely, in those who have cerebral amyloid angiopathy, subdural hematoma, or subarachnoid or brain hemorrhage.

NEUROIMAGING

Immediate diffusion-weighted imaging assessed with magnetic resonance imaging (MRI) is the current preferred test for patients with a suspected TIA,[4,14] since its sensitivity in detecting brain ischemia is much higher than that with computed tomography (CT). In up to 50% of patients with suspected TIA, a bright spot on diffusion-weighted imaging[18] indicates ischemia (Fig. 1); this finding is particularly useful when the transient symptoms are of borderline significance or when the symptoms are atypical (Table 1).[17,19,20] Although CT of the head generally cannot be used to diagnose ischemia, when diffusion-weighted imaging is not available, CT should be performed to rule out another cause of the symptoms.[14]

If diffusion-weighted imaging is negative and there is a strong clinical suspicion of TIA, perfusion-weighted imaging may be performed during the same MRI examination; in 30% of cases, a focal perfusion deficit is identified in the brain area corresponding to the symptoms.[21,22] Arterial spin labeling MRI (which involves simply adding another sequence to the MRI) may increase the yield of perfusion-weighted imaging for the detection of acute ischemic lesions.[23]

OTHER EVALUATIONS

The causes of TIA or minor ischemic stroke are similar to those of all ischemic strokes. If the knowledge of intracranial steno-occlusive disease would alter management, the extracranial and intracranial arteries should be routinely assessed with the use of noninvasive imaging (carotid-artery ultrasonography, CT angiography, or magnetic resonance angiography) of the cervical vessels and of the intracranial vasculature to diagnose a proximal intracranial stenosis, occlusion, or both.[4,14] Additional evaluations should include electrocardiography (ECG), inpatient

Table 1. Common Symptoms Suggestive of TIA.*

Definite TIA
Focal cerebral or retinal symptoms lasting for seconds or minutes and typically lasting <1 hr
Motor weakness in two limbs or in one limb and the face
Sensory deficit in two limbs or in one limb and the face
Visual-field defect (homonymous hemianopia) or monocular blindness
Aphasia or dysarthria
Possible TIA†
Unsteady gait
Diplopia
Vertigo, dizziness
Dysphagia
Usually not a TIA‡
Amnesia
Confusion
Incoordination of limbs
Partial sensory deficit (abnormal sensation or deficit in one limb or only in the face)
Unusual cortical visual symptoms (lone bilateral blindness and bilateral positive visual phenomena)§
Transient loss of consciousness
Headache
Phosphenes, photopsias, complex visual hallucinations, and palinopsia

* TIA denotes transient ischemic attack.
† When combined, at least two of these symptoms suggest definite TIA; when isolated, they suggest possible TIA.
‡ "Bizarre spells" or isolated atypical symptoms are nonfocal or not clearly focal transient neurologic events for which the type of onset, topography, and course of symptoms do not fulfill the criteria for definite or possible TIA or another definite or possible neurologic syndrome (e.g., epilepsy or migraine).
§ Brief positive visual phenomena affecting one or both eyes or one hemifield are often described as flashes of light, stars, colored spots, or swirls of light. Transient positive visual phenomena involving both eyes include a variety of symptoms such as distortion, tilt of images, trails of images, and formed or unformed visual hallucinations.

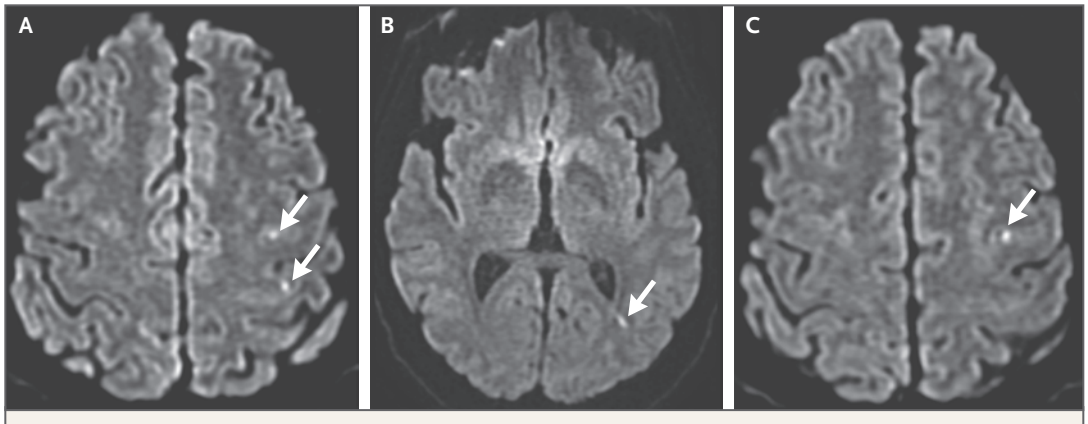


Figure 1. Neuroimaging Evaluation.
An axial section of a diffusion-weighted image of the brain shows multiple bright spots in the cortical territory of the right middle cerebral artery. Panel A shows two small brain infarctions (arrows), Panel B shows one small infarct (arrow), and Panel C shows one small infarct (arrow).

monitoring of the cardiac rhythm, and laboratory testing as clinically indicated (e.g., measurement of the C-reactive protein level and erythrocyte sedimentation rate in patients with findings such as headache or transient monocular blindness that are suggestive of giant-cell arteritis) (Fig. 2; and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

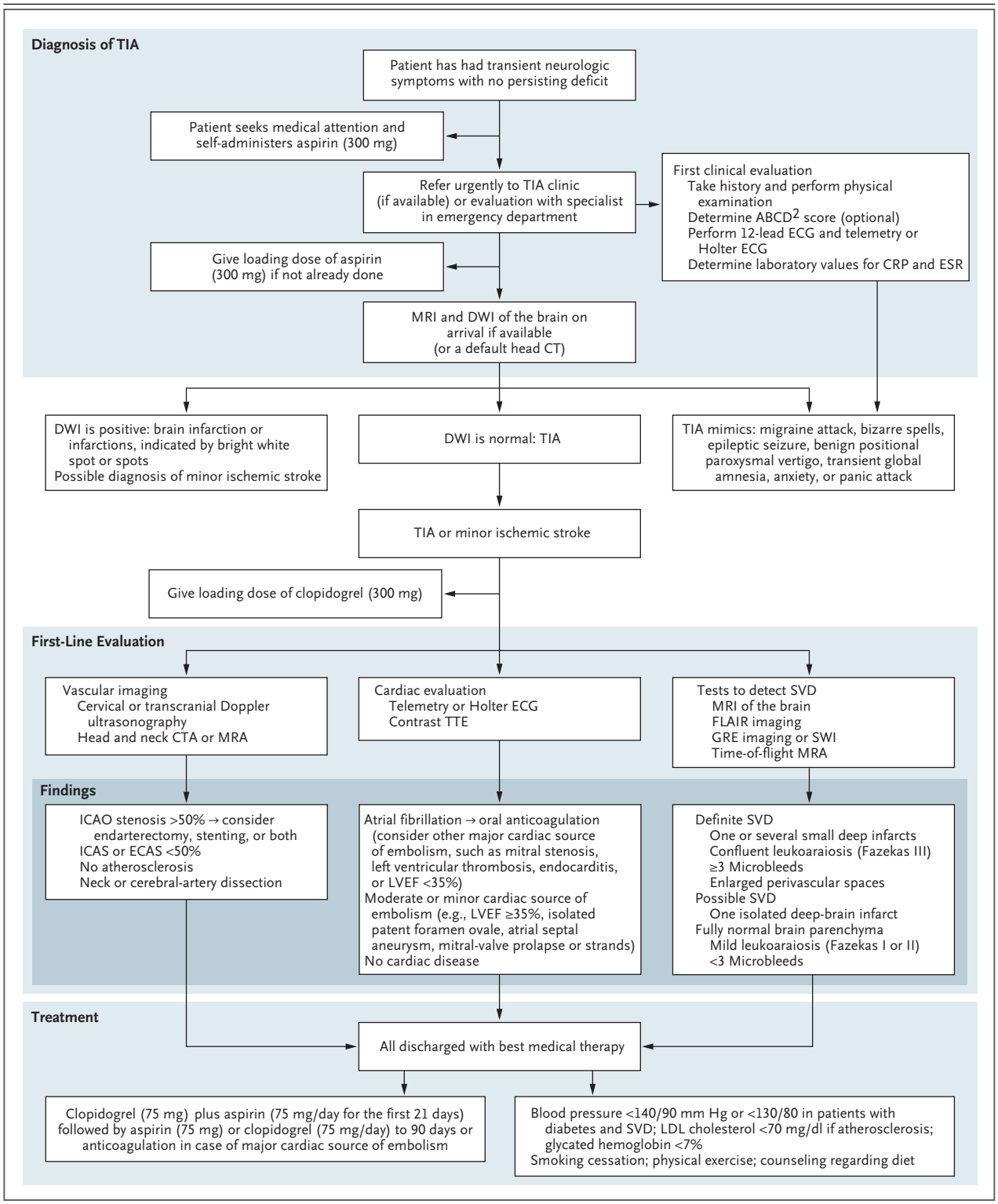
In patients in whom the origin of the TIA is unclear after initial brain imaging and ECG, further evaluation may include prolonged cardiac monitoring (Holter monitoring or the use of an implantable cardiac monitoring device).[4] Contrast transthoracic and transesophageal echocardiography to detect cardiac structural abnormalities such as patent foramen ovale, atrial thrombus, and valvular disease or atherosclerosis of the aortic arch as a source of cerebral embolism[24-26] may be performed if these findings will alter management.[4] Other tests may be performed in selected cases (e.g., to detect a *JAK2* mutation in a patient with suspected polycythemia vera).

Treatment to prevent a recurrent, potentially more severe ischemic event is the main initial goal and is guided by an assessment of the risk of such an event on the basis of the initial evaluation. The score on the ABCD^2 scale (calculated on the basis of age, blood pressure, the presence of clinical weakness or speech disturbance, the duration of symptoms, and the presence or absence of diabetes) is used to predict the risk of stroke. ABCD^2 scores range from 0 to 7, with higher scores indicating a greater risk of stroke (Table S2).[27] The ABCD^2-I score is a refined score that also includes findings on diffusion-weighted imaging of the brain. This score has been shown to improve risk prediction over the ABCD^2 score alone.[28] In one study, among 3206 patients in whom TIA or minor ischemic stroke was evaluated with the use of an ABCD^2 score and imaging, the 7-day risk of stroke was 7.1%, as compared with 0.4% among those who had positive findings on diffusion-weighted imaging.[29] The addition of carotid-artery stenosis of at least 50% or "dual" TIA (TIA prompting medical attention plus at least one TIA in the preceding 7 days) also improved the performance of the ABCD^3-I score.[30]

Figure 2 (facing page). Diagnosis, Evaluation, and Treatment of Transient Ischemic Attack and Minor Ischemic Stroke.

The score on the ABCD^2 scale is calculated on the basis of age, blood pressure, the presence of clinical weakness or speech disturbance, the duration of symptoms, and the presence or absence of diabetes. "Bizarre spells" are nonfocal or not clearly focal transient neurologic events for which the type of onset, topography, and course of symptoms do not fulfill the criteria for definite or possible TIA or another definite or possible neurologic syndrome such as epilepsy or migraine. Fazekas scores range from 0 (no leukoariosis) to III (confluent leukoariosis). After the first-line evaluation, a second-line evaluation can be performed on an outpatient basis and may include more precise vascular imaging (e.g., high-resolution magnetic resonance imaging [MRI] of the cerebral artery, catheter-guided angiography of cerebral arteries, tests to detect arteritis, or lumbar puncture), further cardiac tests (e.g., 3-week Holter electrocardiography [ECG], the use of an implantable cardiac monitoring device, or transesophageal echocardiography), and tests to determine rare causes of the symptoms (e.g., alpha-galactosidase A deficiency, *JAK2* mutation, and antiphospholipid antibodies). To convert values for low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586. CRP denotes C-reactive protein, CT computed tomography, CTA CT angiography, DWI diffusion-weighted imaging, ECAS extracranial carotid-artery stenosis, ESR erythrocyte sedimentation rate, FLAIR fluid-attenuated inversion recovery, GRE gradient echo, ICAO internal carotid-artery origin, ICAS intracranial carotid-artery stenosis, LVEF left ventricular ejection fraction, MRA magnetic resonance angiography, SVD small-vessel disease, SWI susceptibility-weighted imaging, TEE transesophageal echocardiography, and TTE transthoracic echocardiography.

The ABCD^2 score was previously recommended for use in triage. For example, previous National Institute for Health and Care Excellence (NICE) guidelines called for immediate hospitalization of patients with an ABCD^2 score of 4 or higher but allowed up to 8 days for evaluation in patients with scores lower than 4, provided that aspirin was immediately initiated.[6] However, subsequent data have called this strategy into question. In some studies involving large cohorts of patients presenting with TIA, serious findings on evaluation (e.g., clinically significant extracranial-artery stenosis, intracranial-artery stenosis, or atrial fibrillation) were detected in 20% of those with an ABCD^2 score lower than 4, and the 3-month risk of stroke among these patients was similar to that among



patients with a score of 4 or higher.[10,31,32] In one of these cohorts (in the TIAregistry.org project study), the strongest predictors of a new vascular event were carotid stenosis, atrial fibrillation, multiple ischemic spots on diffusion-weighted imaging, and an ABCD^2 score of 6 or 7.[10] Hence, when a patient is evaluated urgently, the scoring system is not relevant, since treatment decisions are based on etiologic findings. NICE guidelines that were updated in 2019 no longer recommend the clinical use of scoring systems such as ABCD^2 for triage,[33] although scores remain useful in research (e.g., for the selection of patients at high risk in a randomized, controlled trial) and in areas where urgent evaluation that includes specialist input is not readily available, since no useful blood biomarker has been validated for TIA.

TREATMENT

ANTIPLATELET THERAPY

In patients with noncardioembolic ischemic stroke, aspirin is the most effective treatment to reduce the risk of recurrent stroke during the first 90 days, and it is the only antiplatelet treatment that has been shown to reduce the risk of recurrent disabling ischemic stroke (i.e., ischemic stroke in patients with a score on the modified Rankin scale of 2 or more (scores range from 0 [no symptoms] to 6 [death]) during that period.[34] However, beyond 3 months, the efficacy of aspirin has been less clear.[34] On the basis of clinical trials that have shown effectiveness, a loading dose of aspirin (300 mg orally) should be administered as soon as possible after TIA symptoms,[5] before admission or on arrival for urgent care. The patient should be encouraged to take aspirin immediately at home if possible.[34] Aspirin should then be continued at a dose of 75 to 100 mg per day for 90 days.[5]

Two trials have shown that dual antiplatelet treatment (a loading dose of 300 mg of clopidogrel plus 300 mg of aspirin, followed by a maintenance dose of 75 mg of clopidogrel and 75 mg of aspirin during the first 21 or 90 days after TIA or minor ischemic stroke) reduced the risk of stroke by 25%, as compared with aspirin alone. There was a 3.5-percentage-point and 1.5-percentage-point absolute reduction in the risk of stroke and a 0-percentage-point and 0.5-percentage-point absolute excess of major hemorrhage in the two trials, respectively.[35-37] Post hoc analyses of these trials showed that the benefit of the combination treatment was seen during the first 21 days, without a significant increase in major hemorrhage complications.[37,38]

Previous trials have shown that anticoagulant treatment was not superior to aspirin in patients with noncardioembolic TIA or stroke. If atrial fibrillation is detected after the TIA, oral anticoagulant treatment should be initiated without delay.

TREATMENT OF ASSOCIATED RISK FACTORS

In patients with TIA, long-term treatment involves blood pressure–lowering and lipid-lowering therapy[4,39] and control of diabetes. Smoking cessation and lifestyle changes are also recommended. It is reasonable to target blood pressure to less than 140/90 mm Hg; a target below 130/80 mm Hg is appropriate for patients with lacunar stroke or diabetes[5] and is appropriate more generally if the patient can achieve these levels without adverse effects. Randomized trials involving patients with recent ischemic stroke or TIA have shown significant decreases in the risk of stroke and overall cardiovascular events with high-dose statins[39] or those specifically targeting a low-density lipoprotein (LDL) cholesterol level of less than 70 mg per deciliter (1.8 mmol per liter).[40] Thus, intensive statin therapy is recommended when an atherosclerotic origin of the TIA is presumed, regardless of the baseline LDL cholesterol level.[5]

All patients should be screened and treated for diabetes mellitus and should receive counseling regarding lifestyle (e.g., diet, weight loss, smoking cessation, and the importance of three to four exercise sessions per week).[5] Screening for sleep apnea is also recommended.[5]

Carotid endarterectomy or stenting should be considered in patients in whom the underlying cause of TIA is ipsilateral internal-carotid-artery stenosis of 50% or more.[5] Stenting of intracranial stenosis is not usually recommended.[5]

TIA EVALUATION

TIA can be a challenging diagnosis even for experienced vascular neurologists, and careful and rapid evaluation is needed even for atypical symptoms, given the potentially catastrophic risks of a missed diagnosis.[7,11,41,42] On the basis of observational data showing associated decreases in

the 3-month risk of stroke and length of stay and cost, as well as improved patient satisfaction,[11,12,43] TIA clinics with round-the-clock evaluation have been promoted and developed as an addition to many comprehensive stroke centers, particularly in Europe, Australia, and Canada.[6,15,33,42] Alternatively, urgent evaluation can be performed in emergency departments where stroke expertise and imaging are readily available.

AREAS OF UNCERTAINTY

Without findings on neuroimaging, the diagnosis of TIA is often uncertain, particularly in patients with isolated, "bizarre," or nonfocal symptoms (Table 1). ("Bizarre spells" or isolated atypical symptoms are nonfocal or not clearly focal transient neurologic events for which the type of onset, topography, and course of symptoms do not fulfill the criteria for definite or possible TIA or another definite or possible neurologic syndrome such as epilepsy or migraine.) Research is needed to identify blood biomarkers or new neuroimaging techniques that might improve the diagnosis.

TIA and minor ischemic stroke are both characterized by the absence of disability (score on the modified Rankin scale, 0 or 1). Many ischemic events that were previously considered to be TIAs (according to the time-based definition) are now considered to be "minor strokes" on the basis of the presence of a bright spot or spots on diffusion-weighted imaging (Fig. 1). This definition may complicate interpretation of the results of clinical trials in which stroke outcomes include these events along with major strokes that cause disability.

A meta-analysis of individual patient data[34] from trials of antiplatelet therapy for secondary prevention of TIA and minor ischemic stroke showed a considerable early benefit (in the first 2 weeks) of aspirin (93% relative reduction in the risk of early recurrent stroke). This finding supports a benefit of a loading dose (300 mg) of oral aspirin as soon as possible after the first TIA symptoms occur. If possible, patients should take aspirin before they seek clinical care[34] (Fig. 2), but this strategy has not been formally evaluated.

Randomized trials are needed to determine the best antithrombotic strategy for patients with TIA (or minor ischemic stroke). Dual antiplatelet therapy of aspirin and clopidogrel for 21 days is considered by many experts to be the standard of care,[44] yet clopidogrel is less effective or not effective in patients who are carriers of *CYP2C19* loss-of-function alleles (as many as 20 to 40% of the population, depending on ethnic group),[45] and screening for clopidogrel resistance has not been validated for clinical use. Ongoing randomized trials involving patients with previous TIA or stroke are assessing the benefits and risks of ticagrelor, an alternative, directly-acting antiplatelet agent that does not need to be metabolized, in combination with aspirin, as compared with aspirin alone (ClinicalTrials.gov number, NCT03354429), triple antithrombotic strategies (a dual antiplatelet agent plus a short-term oral anticoagulant) (NCT03766581), and an intravenous tissue plasminogen activator in patients with intracranial large-vessel occlusion (NCT02398656). Randomized trials have shown a benefit of antiinflammatory agents in decreasing the incidence of cardiovascular events among patients with previous myocardial infarction[46,47]; colchicine is currently under study in patients who have had a TIA or stroke (NCT02898610).

There is uncertainty as to whether, beyond 90 days, lifelong treatment with aspirin is useful in low-risk patients with TIA (i.e., those in whom brain-tissue damage has not been detected on diffusion-weighted imaging, with no documented stenosis in the ipsilateral cerebral artery, no major cardiac source of embolism, no small-vessel disease, and an $ABCD^2$ score of <4). Similarly, investigation is needed of the benefit of aspirin beyond 90 days relative to bleeding risk among patients with isolated diplopia, amnesia, visual defect, vertigo, dizziness or gait instability, dysarthria, or isolated aphasia or weakness in the leg, arm, or both lasting less than 10 minutes.

Aggressive lowering of LDL cholesterol levels (e.g., to <55 mg per deciliter [1.4 mmol per liter]) has been shown to reduce cardiovascular risks after the acute coronary syndrome and ischemic stroke.[40,48-50] Studies to determine the role of this strategy in patients with TIA are warranted.

The length of hospitalization for low-risk patients (e.g., those with an $ABCD^2$ score of <4) is uncertain. Whether these patients should be admitted for evaluation and treatment for less than 1 day, as reported by the SOS-TIA researchers,[11] or whether longer hospitalization for in-hospital cardiac monitoring is required is unclear.

GUIDELINES

The American Heart Association and the American Stroke Association (AHA–ASA),[4] NICE,[6,33] and the European Stroke Organization[51] have published guidelines for the evaluation and treatment of patients with TIA or minor ischemic stroke. All the guidelines recommend that patients should be evaluated and receive treatment as soon as possible and within 24 hours after the onset of symptoms, although they do not specify the setting (e.g., a TIA clinic or an emergency department). The 2019 update of the 2018 AHA–ASA guidelines[44] recommends the use of dual antiplatelet therapy in patients with TIA or minor ischemic stroke during the first 21 days after the onset of symptoms if there is no indication for oral anticoagulation (e.g., atrial fibrillation). The current recommendations are generally concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette presented with symptoms consistent with a motor TIA. Had I spoken with him by telephone before he presented, I would have recommended that he take 300 mg of aspirin if possible. In this case, when he arrived at the TIA clinic without having self-administered aspirin, I would have administered the aspirin as well as 300 mg of clopidogrel. In a prompt assessment of diffusion-weighted imaging on brain MRI, the finding of a bright spot in the right hemisphere would confirm ischemia. I would then prescribe clopidogrel at a dose of 75 mg plus aspirin at a dose of 75 mg for 21 days, followed by long-term aspirin monotherapy (75 mg). If ipsilateral right carotid stenosis were detected on imaging of the extracranial and intracranial vasculature, I would recommend prompt carotid endarterectomy. I would also perform a cardiac evaluation including 3-week ECG monitoring to detect paroxysmal atrial fibrillation that would warrant long-term oral anticoagulation instead of antiplatelet therapy, particularly in the absence of severe carotid stenosis or another potential direct cause of TIA. I would review with the patient his increased risk of stroke and provide guidance regarding control of risk factors, including smoking cessation and lifestyle changes.

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