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Temporary Is Not Always Benign: Similarities and Differences Between Transient Ischemic Attack and Angina

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Abstract

The introduction of the tissue-based definition of transient ischemic attack (TIA), according to which TIA may be diagnosed only in the absence of an infarction on brain neuroimaging, prompts reflections about similarities and differences between TIA and angina. Both share transitory symptoms in the absence of tissue damage, whereas stroke and myocardial infarction are associated with tissue necrosis. Apart from this, TIA and angina are widely different with respect to pathophysiology, natural history, prognosis, and response to specific medical treatments. In general terms, it could be argued that TIA differs from angina as the brain differs from the heart in structure, physiology, metabolism, and performance. Most importantly, in TIA and angina, the reversible nature of symptoms cannot be assumed as a favorable prognostic indicator. In fact, reversibility of stable angina denotes a low-risk condition, whereas in TIA and unstable angina reversibility may suggest plaque instability and relevant risk of ischemic recurrences.

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The revised definition of transient ischemic attack (TIA) prompts renewed considerations on the comparability of TIA and angina.[1] The time-based definition of TIA of a duration less than 24 hours was originally proposed because of difficulties in separating seizures, migraine, and other short-duration events before the availability of modern imaging.[2,3] It was later replaced by the tissue-based definition, according to which a clinical episode may be diagnosed as a TIA only if signs of brain infarction, as revealed by neuroimaging techniques, are excluded.[1] Conversely, the evidence of brain damage, irrespective of the duration and persistence of neurologic symptoms, supports the diagnosis of stroke.[1] Apart from the new definition, it may be useful to consider that TIA diverges from stroke exactly as angina differs from myocardial infarction. Both TIA and angina are characterized by transient symptoms in the absence of tissue damage, whereas stroke and myocardial infarction are associated with tissue necrosis. Although intriguing, whether the comparison is convincing is the subject of this review.

DEFINITIONS

Transient Ischemic Attack

One of the first descriptions of a TIA was provided in 1841 by the French novelist Stendhal:

> All of a sudden I forget all French words […]. I watch myself with curiosity: apart from the ability to use words, I keep all the natural properties of the animal. Ideas are fine, but without words. It lasts eight to ten minutes. Then, slowly, the memory of words comes back, and I am tired.[4]

Brilliantly, Stendhal described the short-lived speech impairments he repeatedly experienced before eventually dying of a fatal stroke (whether from infarction or hemorrhage is unknown). The nature of those events, which were supposed even then to predispose patients to major vascular events, was recognized long before the definition of TIA was entered into the medical literature. In 1958, C. Miller Fisher introduced the term *intermittent cerebral ischemia*, anticipating the term *transient ischemic attack*.[5] Both defined a sudden, focal neurologic

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deficit 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. His observations suggested that the duration was only of minutes, typically 10 to 15. These observations aside, the extension to less than 24 hours was endorsed by others at the Fourth Princeton Conference in 1965 and became the definition in the National Institutes of Health classification in 1975.[6,7] The basis for this time frame definition was the general agreement (in the period when modern imaging had not yet had its effect) that symptomatic duration for 24 hours would mean a stroke; events resolving before that time were possibly explained as migraine, seizure, or other less threatening causes. Despite the definition of less than 24 hours for TIA, numerous cases had complete symptomatic resolution within a day or within 3 weeks, leading to a plethora of additional definitions, such as stroke with full recovery, reversible ischemic neurologic deficit, prolonged reversible ischemic neurologic deficit, or protracted TIA.[7-9]

The time-based definition was used for many decades without critical reappraisals for change in part because of the lack of imaging for assessment of brain disease. This lack forced a plan to infer stroke from those with persisting symptoms. The strength of this clinically based definition lay in allowing the inference that TIA was a fading condition supposed to cause no damage to the brain parenchyma vs stroke, a permanent disease caused by tissue necrosis and leading to a variable degree of neurologic impairment or death. Indeed, the initial limited imaging of brain computed tomography (CT), in the absence of any specific treatment for acute stroke, contributed to the long-lasting use of those criteria. Later, introduction of positron emission tomography and magnetic resonance imaging (MRI) allowed the mapping of the *dark continent*, as the central nervous system was termed.[10] Imaging introduced evidence that clinical syndromes matching the diagnosis of TIA were not exclusively due to ischemia but also reported from small hemorrhages; small, deep infarcts (lacunes); tumors; aneurysms; and even chronic subdural hematomas.[11]

New imaging techniques also revealed that former assumptions of absence of brain damage in TIA were often in error: using modern brain CT, up to 20% of the patients clinically diagnosed as having TIA were found to have evidence of ischemic necrosis of the brain.[12-14] The proportion was higher among patients investigated with brain CT and MRI performed in the same time frame.[15-17] Those observations forced reconsiderations of the accuracy of the time-based definition of TIA and prompted the need of introducing a tissue-based definition.[1] Accordingly, TIA was redefined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, with clinical symptoms lasting less than 1 hour and without evidence of acute infarction. Conversely, stroke should be considered in the presence of persistent clinical signs and neuroimaging abnormalities.[1]

According to the revised definition, the only patients we may diagnose reliably as having TIA are those without radiologic evidence of cerebral infarction. Patients who have objective evidence of brain infarction are reclassified as having a stroke, regardless of the duration of their symptoms (Figure). The presence or absence of a cerebral infarction, as revealed by brain MRI, represents the unique divide among patients with ischemic symptoms. The tissue-based definition encourages the performance of brain magnetic resonance diffusion-weighted imaging (DWI) sequences to look for early tissue damage, whose absence allows a diagnosis of TIA. The sensitivity of the DWI-based approach is demonstrated by the high proportion of DWI abnormalities in patients with classically defined TIA. Prevalence rates of DWI abnormalities in these patients range from 11% to 49%.[15-22] In addition, the proportion of patients with DWI lesions increases according to the increasing duration of TIA symptoms, from 30% with symptoms wearing off within 30 minutes to 71% with symptoms lasting up to 24 hours.[23]

Some concerns were raised immediately after the tissue-based definition was tentatively introduced, fostering an intense debate about its operational role in clinical practice. The main argument in favor of the revised definition was the more accurate demarcation between patients with and without tissue infarction, which encourages prompt diagnostic examination despite symptoms that are supposed to be transient. Arguments against the revised definition included the heterogeneous diffusion of brain MRI, which so far is not available in all centers and is often not performed on emergency admission, and the reference to the 1-hour temporal cutoff, which may not always demarcate events

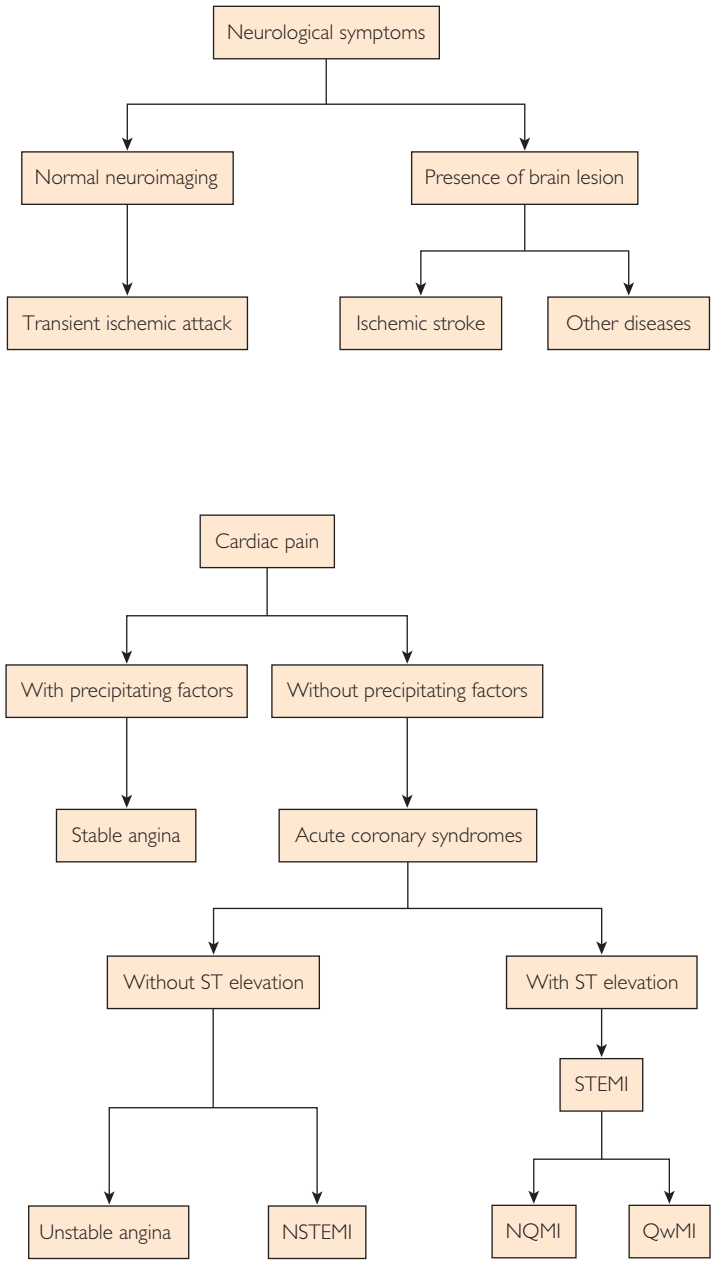

FIGURE. Algorithm for transient symptoms suggestive of transient ischemic attack or angina. NQMI = non–Q-wave myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; QwMI = Q-wave myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

with and without tissue infarction. A further update was proposed by the American Heart Association/American Stroke Association, which definitively abolished any temporal cutoff and identified TIA as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without imaging evidence of acute infarction.[24] These changes have imposed some major classification problems in the conduct of clinical trials for which neurologic events are not the primary focus. One result was a proposal to extend the clinical definition of TIA to any event clinically resolving within 72 hours; however, this definition has not been accepted. Far from settled, definitions of TIA continue to undergo evolution. In any case, a major benefit of these revised definitions has been the adopted practice of assuming, within the hours after symptoms, that the patient may have evolving infarction and be eligible for medical or instrumental efforts at recanalization, as in cases of coronary heart disease.

Stable Angina and Acute Coronary Syndromes

Contrary to what has been the case for TIA, not much has changed over the years in the definition and classification of angina and acute coronary syndromes (ACSs). Many of the clinical features seem similar in duration and resolution to those of TIA.

The first description of a case of chest pain was reported in the 17th century by Edward Hyde, a member of the British Parliament and a writer.[25] Talking about his father, he wrote:

> He was constantly seized on by so sharp a pain in the left arm for half a quarter of an hour, or near so much, that the torment made him as pale as if he were dead; and he used to say that he had passed the pangs of death, and he should die in one of those fits. As soon as it was over, which was quickly, he was the cheerfullest man living.[25]

A century later this clinical picture was termed *angina pectoris* (Latin for strangling, choking) by William Heberden, who, talking about patients with angina, wrote:

> They who are afflicted with it are seized while they are walking with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue; but the moment they stand still, all this uneasiness vanishes.[26,27]

The transition from rest angina to crescendo angina is also presaged by Heberden's words:

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> After it has continued some months it will not cease so instantaneously upon standing still and will come on not only when the persons are walking but when they are lying down.[26,27]

More recently, it became clear that a wide spectrum of clinical conditions, including angina, can reflect myocardial ischemia, from stable angina to myocardial infarction, all of which share a variable degree of discrepancy between oxygen need and availability within the cardiac muscle. Currently, patients with myocardial ischemia are diagnosed as belonging to 2 main groups, those with stable angina and those with ACSs, the last group including unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Moreover, STEMI may include non–Q-wave myocardial infarction and Q-wave myocardial infarction (Figure).

CHANGING EPIDEMIOLOGY

The epidemiology of cerebrovascular and cardiovascular diseases is constantly evolving because it is inextricably linked to the changing pattern and relevance of vascular risk factors and their management.[28] As a consequence of modern laboratory and imaging efforts in cardiology, there has been an epidemiologic shift across the spectrum of coronary syndromes. This transition has been characterized by a decline in STEMI incidence of approximately 62%,[29] with a proportionate increase in the proportion of patients with NSTEMI.[29,30] At the same time, a reduction in the incidence of unstable angina has been observed, with incidence rates of stable angina remaining almost unchanged over the years.[31] The introduction of troponin measurement in the late 1970s, which allows the diagnosis of coronary syndromes at a much earlier stage, has contributed to the reported reduction of infarctions associated with electrocardiographic (ECG) alterations (STEMI). Other factors may have had an influence, including the progressive aging of the population (elderly individuals are more likely to present with NSTEMI than younger individuals) and the wider use of preventive treatments (antithrombotics, statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers), which may reduce the risk of more severe infarcts and of unstable angina by promoting coronary plaque stabilization.[31] A decrease in cardiac mortality in the past decades has also been reported.[32,33] The overall mortality rate decreased by approximately 59% in recent years,[32] with in-hospital and 30-day mortality rates being reduced by 14% and 15%, respectively.[33] The shift from more severe to less severe manifestations of ACSs together with advances in medical, endovascular, and surgical treatments has certainly contributed to reducing mortality and improving outcomes.

Similar to what has been observed for coronary syndromes, TIA is currently undergoing an epidemiologic transition. As previously noted, the adoption of a tissue-based criterion prompted the reclassification of some ischemic events: if a tissue injury is present, events previously diagnosed as TIA were necessarily reclassified as ischemic strokes. The magnitude of the epidemiologic shifting in the incidence of TIA and stroke is changing current data in epidemiology. The reclassification of cerebral ischemic events also influences estimates of prognosis: when adopting the tissue-based criterion a change occurs in diagnosis across groups. Patients who would have been previously diagnosed as having TIA move from the TIA group to the stroke group if neuroradiologic signs of acute infarction are detected. This transition reduces the proportion of patients with stroke and permanent disability and, at the same time, causes the withdrawal from the TIA group of patients with infarction and a higher risk of subsequent stroke.[34] Therefore, the effect of reclassification on prognosis is paradoxical (the so-called Will Rogers phenomenon) because it results in an improved prognosis in both groups.[34]

Our knowledge about the mechanisms and the course of diseases may vary as a function of the adopted criterion in clinical studies. Findings from the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST), which compared carotid artery stenting vs endarterectomy for the treatment of symptomatic stenosis, could have been different if a tissue-based rather than a merely clinical criterion had been adopted for the diagnosis of stroke.[35] The troponin biomarker evaluation was accepted as a sufficient marker for myocardial infarction, but brain magnetic resonance DWI abnormalities were not accepted as signs of stroke unless patients had focal neurologic symptoms. Had magnetic resonance DWI signs

been accepted, wider attention might have been given to periprocedural strokes.[35]

All these observations suggest the necessity of reviewing the epidemiology of stroke and TIA in light of the revised criteria to differentiate when TIA represents a low-risk vs a high-risk condition, depending on its clinical characteristics and culprit lesion, and to better define the prognosis. In fact, studies based on revised criteria suggest that TIA carries a risk of early stroke that is lower than that expected (risk at 7 days, <1%), but, at the same time, they recognize that, in selected cases, TIA should sound as an alarm, especially in the presence of unstable and vulnerable plaques.[36,37]

SIMILARITIES AND DIFFERENCES

Pathophysiology

The maintenance of an adequate energy supply is critical for the normal functioning of heart and brain even if energy demand is differently satisfied by the two organs. The increased energy demand is counteracted by the autoregulation of blood flow (vascular reserve) in the heart and by the combination of autoregulation and increased oxygen extraction (metabolic reserve) in the brain.[38,39] This is the consequence of different oxygen extraction rates at rest in the heart (75%) and in the brain (40%). When vascular and metabolic reserves fail or are depleted, ischemic symptoms arise. Symptoms of myocardial ischemia may arise after physical exertion only as in stable angina or in rest conditions as in unstable angina and myocardial infarction.

Patients with stable angina usually have a nonvulnerable obstructive coronary lesion, which rarely encounters ulceration and superimposed thrombus formation and has a low tendency to embolize.[40,41] However, during an effort-based increase in oxygen demand, the lesion interferes with the vascular reserve and hinders the maintenance of adequate levels of oxygen in the bloodstream. Patients become familiar with the level of exertion that induces angina and learn to control it by modulating their physical efforts.

In contrast, patients with unstable angina and myocardial infarction usually have vulnerable plaques, which are liable to unpredictable complications, such as rupture, erosion, or hemorrhage.[42] These lesions may cause unpredictable ischemic symptoms as a result of a sudden reduction of coronary blood flow.[42] Indeed, if the condition of hypoperfusion is severe, symptoms of myocardial ischemia may be associated with signs of tissue necrosis, revealed by elevations of troponin and creatine kinase MB (CK-MB) without ECG changes (as in NSTEMI) or their combination (as in STEMI).

Transient ischemic attack may be caused by the migration of emboli from the brain-bound arteries or from or through the heart into the cerebral circulation or, as an alternative mechanism, by a hemodynamic failure due to a critical arterial narrowing by an atherosclerotic plaque.[43] The first mechanism is widely considered to account for most TIAs. Recurrent TIAs with a repetitive clinical pattern are considered to be the result of hemodynamic mechanisms, whereas isolated attacks are more frequently associated with a thromboembolic mechanism.[43] Similar to what was found for unstable angina and myocardial infarction, TIA occurs unpredictably, as unpredictable is the occurrence of future ischemic events.

Pathophysiologic similarities between TIA and angina also involve molecular and metabolic changes at the cellular level where perfusion is impaired and causes anoxia.

In the heart, a shift from aerobic metabolism to anaerobic glycolysis is observed with the consequent intracellular increase of lactate and hydrogen ions and the reduction of adenosine triphosphate.[44] These modifications lead to metabolic acidosis, cytotoxic edema, and alterations of ionic gradients. The result is loss of cellular function, leading to the reduction of effective contraction, which may be reversible if the original perfusion and aerobic metabolism are promptly restored.[44] Reperfusion is characterized by reactive hyperemia, production of oxygen-derived free radicals, mitochondrial swelling, reduction of lactate, restored adenosine triphosphate synthesis, and pH normalization.[44] The result is a restoration of contractility, even if prolonged regional wall motion abnormalities may seldom persist. In fact, when reperfusion occurs within 20 minutes, myocardium is stunned, with temporary contractile failure even though alive and again aerobic.[44,45] Moreover, the tissue, preconditioned by the previous ischemia, is more likely to tolerate further ischemic events.[44] Conversely, in response to more prolonged or

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chronic anoxia or to multiple episodes of stunning, a condition of hibernating myocardium may develop, characterized by an adaptive reduction of the contractile function to temporarily maintain myocardial integrity and viability.[46,47] Both myocardial stunning and hibernation may be associated with angina and ACSs. Indeed, the phenomenon of ischemic preconditioning may favor the adaptation to exercise of patients with first-effort or warm-up angina.[48]

In the brain, similarly to what is observed in the heart, impaired perfusion causes both reversible and irreversible damages. Two critical perfusion thresholds are identified: one for reversible functional failure (denoting ischemic penumbra) and the other for irreversible energy failure and structural damage (denoting ischemic core).[49] If the blood flow is restored at a sufficient level and within a suitable time window, cerebral areas in ischemic penumbra may recover without residual morphologic damage.[49] The brain ischemic cascade involves sodium-potassium pump failure, increase in intracellular calcium, depolarization, spreading depression, generation of oxygen-derived free radicals, blood-brain barrier disruption, cytotoxic edema, inflammation, and apoptosis.[50] Magnetic resonance DWI identifies hyperacute alterations, including cytotoxic edema, within the first minutes of ischemia. Delayed modifications, including the increase of cytotoxic edema and intracellular $Ca2^{+}$, the activation of enzyme systems, and the damage of cell membranes, lead to cell death and produce signs that may be recognized on standard brain MRI within 12 to 24 hours.[50]

Finally, the presence of a preconditioning effect, resulting in a greater tolerance to ischemia, has been hypothesized also in the brain. Mechanisms of preconditioning are mainly based on the inhibition of apoptosis, the reduction of excitotoxicity, and the activation of endogenous antioxidant systems. However, whether ischemic tolerance might be induced by a preceding TIA is still the object of debate.[51]

Clinical Features

Angina and TIA share reversibility as a common clinical feature, but apart from this, clear-cut differences are recognizable. Angina commonly reveals itself through pain or angina-equivalent symptoms, including exertional dyspnea, diaphoresis, and fatigue, whereas TIA is characterized by focal neurologic symptoms. Pain in the form of a local headache is known to occur with balloon inflation during embolization therapies when the particle (or balloon) is large enough to stretch pain-sensitive structures but is not expected in TIA.[52,53] Patients with angina usually experience pain without decreases in heart performance, unless arrhythmias or stunning and hibernation phenomena occur, whereas patients with TIA may experience symptoms such as hemiparesis, paresthesias, numbness, dysarthria, aphasia, vision loss, vertigo, and imbalance, depending on the affected arterial territory.[43]

Contrary to what is commonly observed in thromboembolic TIA, symptoms of hemodynamic TIA may provide guidance for the identification of the underlying lesion. In fact, hemodynamic TIA usually reveals recurrent clinical manifestations that suggest the progressive narrowing of a specific artery by an atherothrombotic plaque.[43] Transient visual loss and limb shaking are specific indicators of severe carotid occlusive disease, whereas isolated vertigo, dysarthria, and diplopia may presage a vertebrobasilar artery occlusion. In these cases, preceding transient symptoms need to be promptly recognized to plan recanalization in the attempt to prevent more notable ischemic events.[43,54,55]

The duration of symptoms in TIA and angina, long considered different, have some similarities. Angina generally resolves within a few minutes. A TIA may also be brief, with symptoms subsiding within minutes, but those lasting up to 20 to 30 minutes are longer than from angina. The mean frequency of stable angina is approximately 2 episodes per week per patient, whereas the occurrence and recurrence of unstable angina and TIA are unpredictable.[40,43] The circadian rhythm of angina and TIA also have some similarities because their occurrence is greatest in the morning, during the first few hours after awakening.[40,56] Indeed, contrary to what is observed in TIA, some patients with chronic stable angina may experience episodes of asymptomatic ischemia as revealed by exercise testing and ECG monitoring.[40] Modifications of the angina threshold, as frequently observed in patients with diabetes mellitus, account for many of the silent manifestations.[40]

Additional differences between TIA and angina include the specific action of precipitating factors and the influence of comorbid conditions. The relationship between the presence of precipitating factors, including physical exertion and intense emotional involvement, is more evident for stable angina than for ACSs. However, it is generally agreed that the effect of such factors may also be cumulative, so a series of triggers, each of which is not strong enough to induce an ACS, might collectively be able to do so.[57] Precipitating factors may act by increasing the oxygen demand or causing a sympathetic overtone. They may induce transient physiologic changes, such as an increase in arterial pressure or coagulability, which, in the presence of a vulnerable coronary artery plaque, may contribute to angina, myocardial infarction, or sudden cardiac death.[58] Moreover, the presence of comorbid conditions, including anemia, hyperthyroidism, and hemorheologic alterations, may influence the clinical course of TIA and angina.[59,60] Finally, angina may be rapidly relieved by nitroderivatives, whereas there are no specific drugs to selectively reverse TIA symptoms.

Diagnosis

The diagnosis of stable angina is based on the presence of chest pain, ECG changes, and the exclusion of pathologic elevations in cardiac biomarkers. Angina is defined as *typical* when all diagnostic criteria, including the presence of substernal chest pain, the induction by exertion or emotional distress, and the remission with rest or nitroderivatives, are satisfied. Conversely, angina is defined as *atypical* when only 2 of these criteria are fulfilled. The likelihood of an underlying coronary artery disease is high when clinical criteria are entirely fulfilled. However, the clinical diagnosis may be supported by additional tests to identify a condition of inducible ischemia, which is the pathophysiologic substrate of stable angina. Such tests may identify a cascade of ischemic abnormalities underlying angina, including ECG abnormalities revealed by exercise ECG testing, perfusion defects, and signs of diastolic and systolic dysfunction revealed by single-photon emission CT, MRI, contrast echocardiography, and exercise echocardiography. Invasive coronary angiography and multisection CT coronary angiography are indicated in selected cases to verify the location of coronary artery disease and to quantify its extent. High-resolution coronary MRI may provide qualitative information about the plaque characteristics in terms of vulnerability, proneness to rupture, and thrombogenicity. Lastly, coronary artery calcium score may further help to refine the risk stratification of patients.[61]

The diagnosis of unstable angina is based on the recognition of 3 possible clinical scenarios, including chest pain at rest, new-onset (<2 months) exertional angina causing severe limitations in daily activities, or recent acceleration (<2 months) of angina, as identified by a worsening in the Canadian Cardiovascular Society Classification.[42,62] Although the diagnosis is merely clinical, some patients with unstable angina may present with dynamic ECG changes (ST depression) indicative of transient ischemia or with a slight increase in cardiac biomarkers that are below the decision level for myocardial infarction.[42] Indeed, one-third of patients with a diagnosis of unstable angina have minor myocardial damage, as suggested by elevations in troponin in the absence of CK-MB changes.[42] Finally, a myocardial infarction is diagnosed when signs of tissue injury are detected in the clinical setting of acute ischemia. Stable elevations in cardiac biomarkers (troponin, CK-MB) and ECG changes (ST-segment elevation, T-wave inversion, abnormal QRS pattern) indicate myocardial necrosis. In STEMI the extent of the injured tissue may be estimated from the ST-segment deviation score.[63] The higher the ST-segment deviation score, the larger the injured area.[42] In addition, ECG may suggest the site of the occlusion in the coronary district, thus indicating the more appropriate management. However, not all patients with myocardial necrosis have abnormalities on ECG; consequently, the presence of normal ECG findings does not rule out the diagnosis of myocardial infarction.[64] Hence, sensitive cardiac markers are useful because they enable the early detection even of a myocardial necrosis too small to be associated with ECG changes. In unstable angina and myocardial infarction, the initial diagnosis may be supported by additional tests to recognize regional wall motion abnormalities (echocardiography) and the presence of an underlying coronary artery disease (conventional angiography, CT coronary angiography, and high-resolution MRI).

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The diagnosis of TIA is based primarily on the clinical interpretation of transient symptoms and signs.[65] In contrast to exercise-induced cardiac angina, the TIA event is rarely associated with activity and its duration not related to rest. Yet, the usual lack of relation to exercise appears more a sign of the availability of extensive collateral brain vessels in support of those threatened with ischemia. Efforts to identify examples of brain angina have rarely succeeded. The examples are almost entirely confined to the population with severe bilateral carotid stenosis or occlusive disease, in which expected collaterals from healthy adjacent territories are not available. Early efforts to trigger a TIA by deliberate transient hypotension via tilt-table tests and the like proved disappointing[66] and helped pave the way for the acceptance of embolism for most cases. However, only limited knowledge exists on the extent of the vascular disease during life. In modern settings, intervention is typically applied before vascular disease has reached extreme states, but a few patients have been described whose compensatory collateral is fully developed, and symptoms can be provoked by exercise of hyperventilation.[3] Such syndromes are well known in a setting of moyamoya, which came to clinical attention when young children with the disease became weak, then paralyzed by crying, and recovering within minutes when calmed.[67,68]

The clinical diagnosis of TIA is more challenging compared with the diagnosis of angina, and there is often disagreement about whether a given patient had a TIA or not. This is mainly because there are many conditions that may mimic TIA.[43,69] This is not the case for angina, which has fewer mimickers than TIA, so that the diagnosis is more straightforward. However, prompt brain neuroimaging with CT or MRI can eliminate the presence of other clinical conditions that may masquerade as a TIA, as well as revealing the presence of any area of cerebral infarction indicative of a stroke.[70] Additional examinations may provide information about the mechanism responsible for transient symptoms. Critical narrowing of the large arteries may be detected through ultrasound scanning of carotid and vertebral arteries and transcranial ultrasonography. Both CT and MRI angiography may add accuracy to extracranial and intracranial plaque characterization. Lastly, cardioembolic diseases may be recognized through ECG or transthoracic and transesophageal echocardiography. Contrary to what is commonly observed in ACSs, laboratory markers of brain necrosis, which should identify even a microscopic cerebral damage, are not currently available. The absence of biomarkers of the acute ischemic process does not allow attaining the divide between ongoing cerebral infarction and resolving cerebral dysfunction.

Natural History and Prognosis

The natural history and prognosis of stable angina, ACSs, stroke, and TIA are strictly linked with the characteristics of the underlying vascular disease.[42,43] In stable angina, periodic health checkups, appropriate lifestyle behavioral strategies, and medical treatments to contain vascular risk factors and to prevent precipitating events may be sufficient to reduce the risk of further complications. This is not the case for ACSs and TIA for which the absence of clearly recognized precipitating events hinders patients from controlling their risk and adopting behavioral strategies to avoid any recurrence of the attacks.

Therefore, if a prognostic comparison between TIA and manifestations of myocardial ischemia has to be made, the most reliable one is that between TIA and unstable angina. In both cases, a condition of ischemia that rapidly resolves may be a marker of hemodynamically important stenosis or plaque instability and could be taken as an indicator of a worse prognosis. However, some differences in the clinical course and natural history of the 2 diseases should be recognized based on the organs involved. Sudden death is more common in unstable angina than in TIA because unstable angina may predispose patients to fatal arrhythmias, which may abruptly interfere with cardiac performance and impair survival. Conversely, TIA reflects disease of a different organ system and is not directly a cause of a sudden death, even if it may predispose patients to further ischemic events and may potentially reduce life expectancy. The occurrence and timing of recurrent ischemic events are also different for TIA and angina. Myocardial infarction after stable angina is relatively frequent, especially in the presence of old age (hazard ratio, 1.45), smoking (hazard ratio, 1.39), diabetes (hazard ratio, 2.62), previous stroke (hazard ratio, 1.50), and

TABLE. Predictive Variables in ABCD2 and TIMI Score

ABCD2 score	TIMI score
Age 60 years or older	Age 65 years or older
Blood pressure ≥140/90 mm Hg	At least 3 risk factors for coronary artery disease
Clinical features of TIA Weakness Speech impairment	Prior coronary stenosis of 50% or more
Duration, min ≥60 10-59	ST-segment deviation on ECG at presentation
Diabetes	At least 2 anginal events in prior 24 hours Use of aspirin in prior 7 days Elevated serum cardiac markers

ECG = electrocardiography; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction.

positive coronary angiographic findings in multiple districts.[71] The risk of death or myocardial infarction after unstable angina is higher, especially when a pattern of myocardial necrosis, revealed by an increase in troponin, is immediately recognized (hazard ratio, 10.6 at 30 days and 3.7 at 2 years).[72,73] Myocardial infarction after unstable angina may frequently occur within a short time from the index event, whereas stroke after TIA is usually more delayed. The risk of stroke after a classically defined TIA is more than 10% in the 90 days after the event, with half of the strokes occurring within the first 2 days.[74,75] However, the risk of stroke after a TIA decreases significantly in tissue-based studies, revealing a 7-day stroke rate of approximately 0.4% and a 90-day stroke rate of approximately 1.2% in tissue-negative patients.[36]

Clinical scores for risk assessment at presentation have been developed for both TIA and ACSs. The most reliable ones are the ABCD2 score, which predicts the risk of stroke after a TIA, and the Thrombolysis In Myocardial Infarction risk score for angina, which predicts the risk of death and ischemic events after ACS (Table).[76,77] As a result of the increasing use of the tissue-based definition of TIA, the ABCD3 score, also incorporating the parameters of TIA together with brain and carotid imaging criteria, has been recently proposed to further refine risk stratification.[78,79] Advantages of including carotid imaging criteria into the risk stratification model are clear, considering that even a carotid bruit in asymptomatic patients is a clue of altered blood flow pattern and is associated with a higher risk of stroke.[79-81]

Therapy

Therapeutic targets of angina include limitation of the number, severity, and consequences of pain attacks, protection against future potentially more lethal ischemic syndromes, and reduction of the risk of progressive atherosclerosis.[40,41] Treatment strategies include the reduction of vascular risk factors, the prevention of myocardial infarction through antithrombotic agents, and the stabilization of vulnerable plaques through statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. β-Blockers and calcium antagonists are also used to reduce myocardial oxygen consumption and to improve cardiac performance. Finally, nitroderivatives are used to reverse acute symptoms because of their ability to reduce myocardial oxygen consumption and improve perfusion. When a myocardial infarction occurs, thrombolysis or myocardial revascularization through percutaneous coronary intervention or coronary artery bypass graft surgery is recommended.

Therapeutic interventions in the management of TIA are more limited. Therapy with antithrombotics has to be promptly started to prevent a further TIA or stroke. Statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers may be used to stabilize vulnerable plaques and to improve the long-term prognosis. Indeed, the patient may undergo carotid endarterectomy or endovascular treatment if a relevant stenosis is detected. Unlike in the case of angina, no treatments are available that can accelerate the remission of the acute symptoms of TIA. When a stroke occurs, thrombolysis is recommended within 3 to 4.5 hours from onset, whereas endovascular revascularization strategies, despite their implementation, still represent off-label procedures currently under investigation.

CONCLUSION

The absence of tissue damage and the reversibility of clinical symptoms account for most of the similarities between TIA and angina. Stable angina sounds as a *claudication* of the heart, as it occurs during activity and it is relieved by rest. It represents a warning to the patient to stop activities that may cause

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further ischemic damage. Although the same could exist for TIA, most such events occur without pain and usually without precipitating factors.

Although TIA and angina share some clinical features, they are, from a pathogenic perspective, a long way apart. Their natural history and prognosis, as their response to specific medical treatments, are extremely different. In general terms, TIA differs from angina as the brain differs from the heart in structure, physiology, metabolism, and performance.

Most importantly, the reversible nature of each of these distinctive symptoms is not a favorable prognostic sign. Reversibility of stable angina denotes a low-risk condition, whereas, in unstable angina and TIA, reversibility may, in some cases, suggest plaque instability and denote a bad prognosis. In any case, transitory should not be taken to mean benign. As evidence of this we should remember that in one of his last publications, C. Miller Fisher argued that TIA [like angina] should "sound an alarm."[43]

Abbreviations and Acronyms: **ACS** = acute coronary syndrome; **CK-MB** = creatine kinase MB; **CT** = computed tomography; **DWI** = diffusion-weighted imaging; **ECG** = electrocardiography; **MRI** = magnetic resonance imaging; **NSTEMI** = non—ST-segment elevation myocardial infarction; **STEMI** = ST-segment elevation myocardial infarction; **TIA** = transient ischemic attack

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REFERENCES

1. Albers GW, Caplan LR, Easton JD, et al; for the TIA Working Group. Transient ischemic attack proposal for a new definition. *N Engl J Med*. 2002;347(21):1713-1716.
2. Marshall J. The natural history of transient ischaemic cerebrovascular attacks. *Q J Med*. 1964;33(3):309-324.
3. Harrison MJ, Marshall J, Thomas DJ. Relevance of duration of transient ischaemic attacks in carotid territory. *Br Med J*. 1978; 1(6127):1578-1579.
4. Bogousslavsky J, Assal G. Stendhal's aphasic spells: the first report of transient ischemic attacks followed by stroke. *Front Neurol Neurosci*. 2010;27:130-142.
5. Fisher CM. Intermittent cerebral ischemia. In: Wright IS, Millikan CM, eds. *Cerebral Vascular Disease*. New York, NY: Grune & Stratton; 1958:81-97.
6. Millikan CH, Siekert RG, Whisnant JP, eds. *Cerebral Vascular Diseases*. 4th ed. New York, NY: Grune & Stratton; 1965:194.
7. Ad Hoc Committee on Cerebrovascular Diseases. A classification and outline of cerebrovascular diseases. *Stroke*. 1975;6(5): 564-616.
8. Loeb C, Gandolfo C. Transient ischemic neurologic deficits. In: Vinken PJ, Bruyn GW, Klawans HL, eds. *Handbook of Clinical Neurology*, Vol. 53, revised series 9, part 1. Philadelphia, PA: Elsevier; 1988:257-290.
9. Carolei A, Candelise L, Fiorelli M, et al; for the National Research Council and Rome Study Groups. Long-term prognosis of transient ischemic attacks (TIAs) and reversible ischemic neurologic deficits (RINDs): a hospital-based study. *Cerebrovasc Dis*. 1992;2(5):266-272.
10. Bull JWD. The history of neuroradiology. *Proc R Soc Med*. 1970; 63(6):637-643.
11. Loeb C. Protracted transient ischemic attacks. *Eur Neurol*. 1980; 19(1):1-11.
12. Dávalos A, Matías-Guiu J, Torrent O, et al. Computed tomography in reversible ischaemic attacks: clinical and prognostic correlations in a prospective study. *J Neurol*. 1988;235(3): 155-158.
13. Dennis M, Bamford J, Sandercock P, et al. Computed tomography in patients with transient ischaemic attacks: when is a transient ischaemic attack not a transient ischaemic attack but a stroke? *J Neurol*. 1990;237(4):257-261.
14. Evans GW, Howard G, Murros KE, et al. Cerebral infarction verified by cranial computed tomography and prognosis for survival following transient ischemic attack. *Stroke*. 1991;22(4): 431-436.
15. Kidwell CS, Alger JR, Di Salle F, et al. Diffusion MRI in patients with transient ischemic attacks. *Stroke*. 1999;30(6): 1174-1180.
16. Engelter ST, Provenzale JM, Petrella JR, et al. Diffusion MR imaging and transient ischemic attacks. *Stroke*. 1999;30(12): 2762-2763.
17. Mohr JP, Biller J, Hilal SK, et al. MR vs CT imaging in acute stroke. *Stroke*. 1995;26(5):807-812.
18. Miyagi T, Uehara T, Kimura K, et al. Examination timing and lesion patterns in diffusion-weighted magnetic resonance imaging of patients with classically defined transient ischemic attack. *J Stroke Cerebrovasc Dis*. January 22, 2013. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2012.12.007.
19. Al-Khaled M, Matthis C, Münte TF, et al; for the QugSS2-Study. The incidence and clinical predictors of acute infarction in patients with transient ischemic attack using MRI including DWI. *Neuroradiology*. 2013;55(2):157-163.
20. Carpentier N, Edjlali M, Bouhafs F, et al. Serial brain MRI in TIA patients. *J Neuroradiol*. 2012;39(3):137-141.
21. Förster A, Gass A, Kern R, et al. Brain imaging in patients with transient ischemic attack: a comparison of computed tomography and magnetic resonance imaging. *Eur Neurol*. 2012;67(3): 136-141.
22. Tong T, Zhenwei Y, Xiaoyuan F. Transient ischemic attack and stroke can be differentiated by analyzing the diffusion tensor imaging. *Korean J Radiol*. 2011;12(3):280-288.
23. Saver JL, Kidwell C. Neuroimaging in TIAs. *Neurology*. 2004; 62(8, suppl 6):S22-S25.
24. Easton JD, Saver JL, Albers GW, et al. 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. *Stroke*. 2009;40(6):2276-2293.
25. Clarendon EH. *The Life of Edward, Earl of Clarendon, Lord High Chancellor of England and Chancellor of University of Oxford: Continuation of History of Grand Rebellion*. Oxford, England: Clarendon Press; 1857.
26. Silverman ME. William Heberden and some account of a disorder of the breast. *Clin Cardiol*. 1987;10(3):211-213.
27. Heberden W. Pectoris dolor. In: *Commentaries on the History and Cure of Diseases*. Boston, MA: Wells & Lily; 1808.
28. Marini C, Triggiani L, Cimini N, et al. Proportion of older people in the community as a predictor of increasing stroke incidence. *Neuroepidemiology*. 2001;20(2):91-95.

29. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362(23):2155-2165.
30. Rogers WJ, Frederick PD, Stoehr E, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J*. 2008;156(6):1026-1034.
31. Ruff CT, Braunwald E. The evolving epidemiology of acute coronary syndromes. *Nat Rev Cardiol*. 2011;8(3):140-147.
32. Fox CS, Evans JC, Larson MG, et al. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study. *Circulation*. 2004; 110(5):522-527.
33. Mandelzweig L, Battler A, Boyko V, et al; for the Euro Heart Survey Investigators. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. *Eur Heart J*. 2006;27(19):2285-2293.
34. Mullen MT, Cucchiara BL. Redefinition of transient ischemic attack improves prognosis of transient ischemic attack and ischemic stroke: an example of the Will Rogers phenomenon. *Stroke*. 2011;42(12):3612-3613.
35. Brott TG, Hobson RW II, Howard G, et al; for the CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363(1):11-23.
36. Giles MF, Albers GW, Amarenco P, et al. Early stroke risk and ABCD2 score performance in tissue- vs time-defined TIA: a multicenter study. *Neurology*. 2011;77(13): 1222-1228.
37. Barrett KM. Early stroke risk: tissue is the issue. *Neurology*. 2011; 77(13):1214-1215.
38. Braunwald E. Control of myocardial oxygen consumption: physiologic and clinical considerations. *Am J Cardiol*. 1971; 27(4):416-432.
39. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. *Ann Neurol*. 1991;29(3):231-240.
40. O'Rourke RA. Alternative strategies for the management of chronic stable angina. *Curr Probl Cardiol*. 2010;35(8): 384-446.
41. Kones R. Recent advances in the management of chronic stable angina I: approach to the patient, diagnosis, pathophysiology, risk stratification, and gender disparities. *Vasc Health Risk Manag*. 2010;6:635-656.
42. Thygesen KA, Alpert JS. The definitions of acute coronary syndrome, myocardial infarction, and unstable angina. *Curr Cardiol Rep*. 2001;3(4):268-272.
43. Fisher CM. Transient ischemic attacks. *N Engl J Med*. 2002; 347(21):1642-1643.
44. Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 1. *Circulation*. 2001;104(24):2981-2989.
45. Heusch G, Schulz R. Characterization of hibernating and stunned myocardium. *Eur Heart J*. 1997;18(suppl D): D102-D110.
46. Heusch G, Schulz R. Endogenous protective mechanisms in myocardial ischemia: hibernation and ischemic preconditioning. *Am J Cardiol*. 1997;80(3A):26A-33A.
47. Heusch G, Schulz R. Hibernating myocardium: a review. *J Mol Cell Cardiol*. 1996;28(12):2359-2372.
48. Tomai F. Warm up phenomenon and preconditioning in clinical practice. *Heart*. 2002;87(2):99-100.
49. Heiss WD. The ischemic penumbra: correlates in imaging and implications for treatment of ischemic stroke: The Johann Jacob Wepfer award 2011. *Cerebrovasc Dis*. 2011; 32(4):307-320.
50. Kanekar SG, Zacharia T, Roller R. Imaging of stroke: part 2, pathophysiology at the molecular and cellular levels and corresponding imaging changes. *AJR Am J Roentgenol*. 2012;198(1): 63-74.
51. Weber R, Diener HC, Weimar C; for the German Stroke Study Collaboration. Why do acute ischemic stroke patients with a preceding transient ischemic attack present with less severe strokes? insights from the German Stroke Study. *Eur Neurol*. 2011;66(5):265-270.
52. Fisher CM. Unusual vascular events in the territory of the posterior cerebral artery. *Can J Neurol Sci*. 1986;13(1):1-7.
53. Nichols FT III, Mawad M, Mohr JP, et al. Focal headache during balloon inflation in the internal carotid and middle cerebral arteries. *Stroke*. 1990;21(4):555-559.
54. Knoflach M, Matosevic B, Meinhart M, et al. Prognostic relevance of limb shaking in symptomatic carotid artery occlusion. *Cerebrovasc Dis*. 2011;32(1):35-40.
55. Paul NL, Simoni M, Rothwell PM; for the Oxford Vascular Study. Transient isolated brainstem symptoms preceding posterior circulation stroke: a population-based study. *Lancet Neurol*. 2013;12(1):65-71.
56. Gallerani M, Manfredini R, Ricci L, et al. Chronobiological aspects of acute cerebrovascular diseases. *Acta Neurol Scand*. 1993;87(6):482-487.
57. Muller JE, Abela GS, Nesto RW, et al. Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. *J Am Coll Cardiol*. 1994;23(3):809-813.
58. Tasch C, Larcher L. Can triggers be cumulative in inducing heart attack in soccer game spectators? *Wien Med Wochenschr*. 2012; 162(15-16):337-339.
59. da Silveira AD, Ribeiro RA, Rossini AP, et al. Association of anemia with clinical outcomes in stable coronary artery disease. *Coron Artery Dis*. 2008;19(1):21-26.
60. Sacco S, Marini C, Olivieri L, et al. Contribution of hematocrit to early mortality after ischemic stroke. *Eur Neurol*. 2007;58(4): 233-238.
61. Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA*. 2010;303(16): 1610-1616.
62. Campeau L. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. *Can J Cardiol*. 2002; 18(16):371-379.
63. Wellens HJ, Gorgels AP. The electrocardiogram 102 years after Einthoven. *Circulation*. 2004;109(5):562-564.
64. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med*. 2000;342(16):1163-1170.
65. Carolei A, Marini C, Fieschi C. Transient ischemic attacks. In: Ginsberg MD, Bogousslavsky J, eds. *Cerebrovascular Disease — Pathophysiology, Diagnosis and Management*. Vol II. Cambridge, MA: Blackwell Science; 1998:941-960.
66. Denny-Brown D. Recurrent cerebrovascular episodes. *Arch Neurol*. 1960;2:194-210.
67. Fukuyama Y, Suzuki Y, Segawa M. Acute recurrent transient hemiplegia in children with special reference to cases presenting telangiectasis-like anomalous vascularity at the base of brain. *No To Shinkei*. 1965;17(8):757-760.
68. Sano K. Cerebral juxta-basal teleangiectasia. *Brain Nerve*. 1965; 17(8):748-750.
69. Panagos PD. Transient ischemic attack (TIA): the initial diagnostic and therapeutic dilemma. *Am J Emerg Med*. 2012; 30(5):794-799.
70. Cucchiara BL, Kasner SE. All patients should be admitted to the hospital after a transient ischemic attack. *Stroke*. 2012;43(5): 1446-1447.
71. Clayton TC, Lubsen J, Pocock SJ, et al. Risk score for predicting death, myocardial infarction, and stroke in patients with stable angina, based on a large randomised trial cohort of patients. *BMJ*. 2005;331(7521):869.
72. Reichlin T, Twerenbold R, Maushart C, et al. Risk stratification in patients with unstable angina using absolute serial changes of 3 high-sensitive troponin assays. *Am Heart J*. 2013;165(3): 371-378.

73. Harper RW, Kennedy G, De Sanctis RW, et al. The incidence and pattern of angina prior to acute myocardial infarction: a study of 577 cases. *Am Heart J*. 1979;97(2):178-183.

74. Kleindorfer D, Panagos P, Pancioli A, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke*. 2005;36(4):720-723.

75. Johnston SC, Gress DR, Browner WS, et al. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284(22):2901-2906.

76. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284(7):835-842.

77. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369(9558):283-292.

78. Merwick A, Albers GW, Amarenco P, et al. Addition of brain and carotid imaging to the ABCD2 score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. *Lancet Neurol*. 2010;9(11):1060-1069.

79. Song B, Fang H, Zhao L, et al. Validation of the ABCD3-I score to predict stroke risk after transient ischemic attack. *Stroke*. 2013;44(5):1244-1248.

80. Heyman A, Wilkinson WE, Heyden S, et al. Risk of stroke in asymptomatic persons with cervical arterial bruits: a population study in Evans County, Georgia. *N Engl J Med*. 1980;302(15):838-841.

81. Carolei A, Marini C, Nencini P, et al; National Research Council Study Group. Prevalence and outcome of symptomatic carotid lesions in young adults. *BMJ*. 1995;310(6991):1363-1366.