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Review Article

Challenges and misconceptions in the aetiology and management of atrial fibrillation-related strokes

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ABSTRACT

Strokes, whether ischaemic or haemorrhagic, are the most feared complications of atrial fibrillation (AF) and its treatment. Vitamin K antagonists have been the mainstay of stroke prevention. Recently, direct oral anticoagulants have been introduced. The advantages and disadvantages of these treatment strategies have been extensively discussed. In this narrative review, we discuss dilemmas faced by primary care clinicians in the context of stroke and transient ischaemic attack (TIA) in patients with AF. We discuss the classification of stroke, the different types of stroke seen with AF, the prognosis of AF-related strokes, the early management after AF-related stroke or TIA and the therapeutic options after anticoagulant-associated intracerebral haemorrhage. Most importantly, we aim to dispel common misconceptions on the part of non-stroke specialists that can lead to suboptimal stroke prevention and management.

1. Epidemiology of stroke and atrial fibrillation

About one in four people will develop atrial fibrillation (AF) during their lifetime [1]. The risk for AF increases with age, the presence of obesity, diabetes, hypertension and cardiac disease. When AF is newly diagnosed, 3% of patients will develop a stroke within the next year, and 13% will either die or have a stroke if anticoagulants are not prescribed [2].

AF increases the risk of stroke four- to five-fold. Recent data demonstrate that permanent and persistent AF confers a higher risk of stroke than paroxysmal AF [3]. The risk of stroke varies widely according to the presence of concomitant risk factors. Risk scores can help in stratifying the risk of future stroke [4].

Stroke in patients with AF may not always be clinically evident: the prevalence of covert brain infarcts ranges from 14.7% to 48% [5]. Their presence increases the risk of clinically obvious stroke and may contribute to the cognitive impairment that is commonly observed in AF [6].

The lifetime risk of having a stroke in people of European descent is about one in six for men and one in five for women [7]. Most strokes are ischaemic in nature with haemorrhages representing only about 8–13% of all cerebrovascular events (Fig. 1) [8–10]. In contemporary trials of patients with AF who were treated with warfarin for stroke prevention, ischaemic strokes were at least three times as common as intracerebral haemorrhages [11–13]. Although the incidence of stroke is on the decline in the Western world, the same is not true in the developing world where the incidence is rising steeply [14].

2. A new definition of stroke

Recently, new definitions for cerebrovascular diagnoses have been proposed that emphasise the role of neuroimaging and de-emphasise the duration of symptoms as seen in previous classification systems (Table 1) [15]. The major change compared with the previous classification system is that imaging evidence of a brain infarction leads to a diagnosis of ischaemic stroke, regardless of the duration of symptoms. In the previous classification system, symptoms lasting shorter than 24 h were classified as a TIA, even in the presence of a brain infarction on computerised tomography (CT) or magnetic resonance imaging (MRI) scans.

Recent studies using advanced imaging indicate that a high proportion of patients' transient neurological symptoms are associated with brain injury, and these patients are at high risk of stroke [16]. Given the large number of patients, it is important to identify and target those at highest risk for early recurrence.

2.1. Ischaemic stroke

An ischaemic stroke occurs when brain tissue is permanently damaged by reduced blood perfusion within the territory of an occluded cerebral artery. Stroke can be subtyped by location, affected vascular territory, size and aetiology. The causes of vessel occlusion are diverse.

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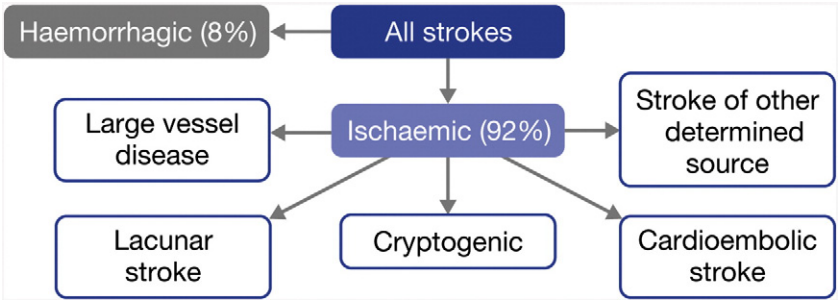

Fig. 1. Subtypes of stroke. The majority of strokes are ischaemic in nature; the rest are haemorrhagic. Ischaemic strokes can be further classified depending on the cause of the stroke [8,10,33]. Adapted, with permission, from H-C Diener, SJ Connolly, JD Easton et al. Rationale, Objectives and Design of a Secondary Stroke Prevention Study of Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source (RE-SPECT ESUS). Presented at the 23rd European Stroke Conference, Nice, France, 6–9 May 2014 [10].

Vessel occlusion occurs most commonly through emboli originating from the heart (cardioembolic stroke), from emboli from atherosclerotic plaques in the aorta or internal carotid artery or intracranial vessels (categorized under the heading of large vessel disease) or from in situ occlusion of small penetrating arteries originating from large intracranial vessels (leading to lacunar infarcts). A precise mechanism is often difficult to pinpoint, hence the term cryptogenic stroke, which refers to infarction in patients in whom no source/cause can be identified despite a thorough etiological workup. Ischaemic stroke within the context of AF will be further discussed later in the article.

2.2. Haemorrhagic stroke

The term haemorrhagic stroke can lead to confusion among non-stroke specialists. The term includes subarachnoid haemorrhage, parenchymal or intracerebral haemorrhage (ICH) and haemorrhagic transformation (Fig. 2 and Table 1). Urgent neuroimaging, either with CT or MRI, is essential to the diagnosis of ICH, as stroke subtypes cannot be reliably distinguished on clinical grounds alone.

2.3. Primary intracerebral haemorrhage

Primary ICH refers to spontaneous, non-traumatic bleeding from intraparenchymal blood vessels, pathologically altered by the effects of long-standing hypertension or cerebral amyloid angiopathy [17]. Intracerebral haemorrhage is the second most common and the most lethal form of stroke, with 30-day mortality rates of 30–55%. The majority of survivors are left with significant, long-term disability. Approximately 10–20% of events are associated with a vascular malformation, neoplasm or coagulopathy and are therefore referred to as secondary ICH.

The most common sites of bleeding in ICH are the basal ganglia (42%), lobar regions (40%), cerebellum (8%), brain stem (6%) and thalamus. Clinicians often infer aetiology from the location of the haemorrhage. Hypertension is associated with ICH in the basal ganglia, thalamus, brain stem and cerebellum, whereas amyloid angiopathy is often presumed to be the cause of lobar haemorrhage, particularly when recurrent. It should be noted, however, that in the absence of tissue pathology, aetiology cannot be definitively determined.

2.4. Haemorrhagic transformation or haemorrhagic infarction

Haemorrhagic transformation (HT) refers to secondary bleeding into a cerebral infarct, related to impaired blood vessel integrity following the ischaemic insult (Fig. 3). HT is the most feared and common complication of thrombolysis for acute ischaemic stroke. It can also be associated with early (<1 week) oral or parenteral anticoagulation after ischaemic stroke. Haemorrhagic complications vary, from peripheral petechiae within the infarct to parenchymal haematomas with mass effect. Haemorrhagic transformation can be classified as symptomatic/asymptomatic, on the basis of contemporaneous clinical deterioration and radiological evidence of bleeding [18]. The definition of symptomatic HT can be somewhat subjective, however, as the clinical impairment often fluctuates in acute stroke patients, regardless of the presence of haemorrhage. Objective anatomic–radiological definitions of HT, based solely on post-treatment imaging, have been developed. Haemorrhagic transformation can be classified as haemorrhagic infarction, which is limited to petechial bleeding, or parenchymal haemorrhage [19].

The term 'haemorrhagic infarct' is often used by radiologists to accurately describe these findings, but it also leads to confusion among non-stroke specialists. In many cases, the emphasis for the treating clinician is on *haemorrhage*, rather than *infarct*, leading to delays in initiating, or even avoidance of, anticoagulation (Fig. 3). In

Table 1
Terminology used in the classification of cerebrovascular diseases.

Stroke[a]	Subtype	Pathological finding	Typical imaging finding	Analogy with acute coronary syndrome
Acute ischaemic cerebrovascular syndromes:				
Episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia				
	TIA	No lesion	Absence of hyperintensity on DWI	Angina
	Ischaemic stroke (Figs. 2 and 4)	Brain infarction	Presence of hyperintensity on DWI	Acute myocardial infarction
Haemorrhagic strokes:				
Rapidly developing clinical signs of neurological dysfunction or headache due to non-traumatic brain haemorrhage				
	Parenchymal haemorrhage or ICH (Fig. 2)	Focal collection of blood within the brain parenchyma or ventricular system	Hyperdensity in ventricles or parenchyma on CT	–
	SAH (Fig. 3)	Bleeding into the subarachnoid space	Hyperdensity in subarachnoid space on CT	–
	Haemorrhagic infarction (Fig. 3)	Bleeding into initial infarcted tissue	Hyperdensity within infarction on CT	–

CT, computerised tomography; DWI, diffusion-weighted imaging; ICH, intracerebral haemorrhage; SAH, subarachnoid haemorrhage; TIA, transient ischaemic attack.
[a] Stroke is characterised as an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, ICH and SAH.