REVIEW

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The complexity of atrial fibrillation newly diagnosed after ischemic stroke and transient ischemic attack: advances and uncertainties

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Purpose of review
Atrial fibrillation is being increasingly diagnosed after ischemic stroke and transient ischemic attack (TIA). Patient characteristics, frequency and duration of paroxysms, and the risk of recurrent ischemic stroke associated with atrial fibrillation detected after stroke and TIA (AFDAS) may differ from atrial fibrillation already known before stroke occurrence. We aim to summarize major recent advances in the field, in the context of prior evidence, and to identify areas of uncertainty to be addressed in future research.

Recent findings
Half of all atrial fibrillations in ischemic stroke and TIA patients are AFDAS, and most of them are asymptomatic. Over 50% of AFDAS paroxysms last less than 30 s. The rapid initiation of cardiac monitoring and its duration are crucial for its timely and effective detection. AFDAS comprises a heterogeneous mix of atrial fibrillation, possibly including cardiogenic and neurogenic types, and a mix of both. Over 25 single markers and at least 10 scores have been proposed as predictors of AFDAS. However, there are considerable inconsistencies across studies. The role of AFDAS burden and its associated risk of stroke recurrence have not yet been investigated.

Summary
AFDAS may differ from atrial fibrillation known before stroke in several clinical dimensions, which are important for optimal patient care strategies. Many questions remain unanswered. Neurogenic and cardiogenic AFDAS need to be characterized, as it may be possible to avoid some neurogenic cases by initiating timely preventive treatments. AFDAS burden may differ in ischemic stroke and TIA patients, with distinctive diagnostic and treatment implications. The prognosis of AFDAS and its risk of recurrent stroke are still unknown; therefore, it is uncertain whether AFDAS patients should be treated with oral anticoagulants.

Keywords
atrial fibrillation, diagnosis, ischemic stroke, prevention, transient ischemic attack

INTRODUCTION

Increasing physicians' awareness about atrial fibrillation and substantial improvements in cardiac monitoring technologies [1] have led to an increase in the number of patients diagnosed with atrial fibrillation after ischemic stroke and transient ischemic attack (TIA) [2▪]. Up to one-quarter of patients who are believed to be atrial fibrillation free before the stroke and subsequently undergo cardiac monitoring are newly diagnosed with atrial fibrillation [2▪]. After the diagnostic work-up of ischemic stroke and TIA patients, heart rhythm falls into three main categories: patients with previously known atrial fibrillation (KAF), atrial fibrillation newly detected after stroke and normal sinus rhythm (NSR). However, these three categories

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KEY POINTS

- AFDAS comprises a heterogeneous mix of AF, possibly including cardiogenic and neurogenic types, and a mix of both.
- The current knowledge gaps about the significance of AFDAS should be acknowledged when deciding the best secondary preventive strategies.
- Much research is needed to clarify the risk of recurrent stoke and death associated with AFDAS, and to identify potential strategies aimed at preventing neurogenic types.
- AFDAS burden should be considered as a key target for future research, as it may help to better stratify stroke risk.
- Future research should target the prevention of AFDAS among ischemic stroke and TIA patients, and the reduction of the risk of atrial remodeling in those already diagnosed with AFDAS.

constitute an oversimplification, as some patients with atrial fibrillation newly detected after stroke had undiagnosed AF prior to the stroke and in others it is a new-onset arrhythmia (Fig. 1). Preexisting but newly diagnosed atrial fibrillation is most likely caused by prestroke cardiac structural changes, and thus, the arrhythmia could be considered as predominantly 'cardiogenic'. Newly diagnosed atrial fibrillation may be the consequence of the stroke itself and therefore could be regarded as primarily 'neurogenic' [1,3]. Most likely, a considerable proportion of atrial fibrillation detected after stroke and TIA cases have a combination of cardiogenic and neurogenic mechanisms. Due to the intermittent nature of atrial fibrillation in some patients, many cases of atrial fibrillation in ischemic stroke and TIA patients may go undiagnosed without thorough screening [2▪]. This complexity explains the current lack of understanding of the pathophysiology of atrial fibrillation detected after stroke and why there are sizeable uncertainties regarding its

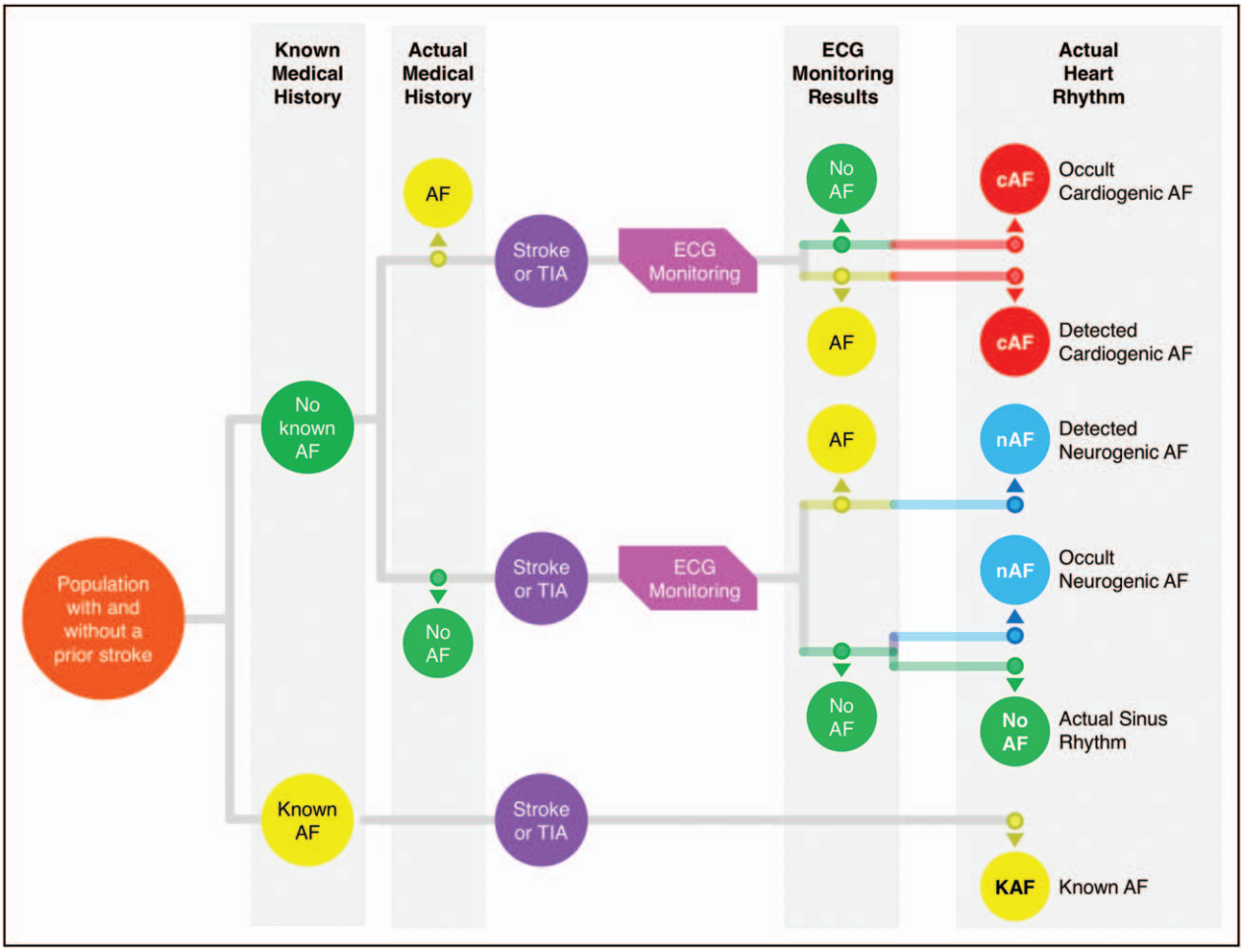

FIGURE 1. Apparent and actual heart rhythm before and after electrocardiographic monitoring in transient ischemic attack and ischemic stroke patients. AF, atrial fibrillation; cAF, cardiogenic atrial fibrillation; ECG, electrocardiographic; nAF, neurogenic atrial fibrillation; TIA, transient ischemic attack.

prognosis and suitable therapeutic approaches to prevent stroke recurrence.

NOMENCLATURE

Conceptually, atrial fibrillation detected after stroke is so complex that no currently used terminology fits adequately. 'Poststroke AF' implies that the atrial fibrillation is triggered by the stroke [1,2▪]. 'Newly-diagnosed AF' is not limited to atrial fibrillation diagnosed after a stroke or TIA. Indeed, it has been used for studies limited to stroke and TIA patients [4–6] as well as for nonselected cohorts [7]. 'Occult AF' [8] describes undiagnosed atrial fibrillation on any kind of patient, regardless of the patient's stroke history. 'Paroxysmal AF' describes the intermittent nature of atrial fibrillation [9], but it does not differentiate between patients who are diagnosed before or after stroke.

We propose the term AFDAS for Atrial Fibrillation Detected (or Diagnosed) after Stroke or TIA. AFDAS comprises all cases of atrial fibrillation (paroxysmal, persistent or permanent) detected after ischemic stroke or TIA by any ECG monitoring technology. AFDAS includes atrial fibrillation that existed, but was undiagnosed, prior to the stroke as well as incident atrial fibrillation beginning near the time or shortly after the stroke event. pAFDAS can specifically indicate paroxysmal forms of AFDAS, as not all AFDAS are paroxysmal [5].

PATHOPHYSIOLOGY OF NEUROGENIC ATRIAL FIBRILLATION DETECTED AFTER STROKE AND TRANSIENT ISCHEMIC ATTACK

The pathophysiology of KAF, which is primarily cardiogenic, has been extensively investigated and research on this topic is continuously updated [10]. In comparison, little is known about the pathophysiology of AFDAS, in particular neurogenic AFDAS. As neurogenic AFDAS is a potential target for stroke prevention (e.g. preventing AFDAS triggered by strokes may help prevent recurrent events), we have proposed a hypothetical pathophysiological model involving autonomic and inflammatory pathways consistent with current evidence but requiring rigorous empirical investigation to validate (or invalidate) [1].

The autonomic regulation of cardiac rhythm can be conceptualized as an integrated relay system (Fig. 2). The highest level is represented by the cerebral cortex, particularly the insula, although other areas such as the cingulate and the prefrontal cortices are also implicated [11]. In turn, bilateral projections connect the right and left insular

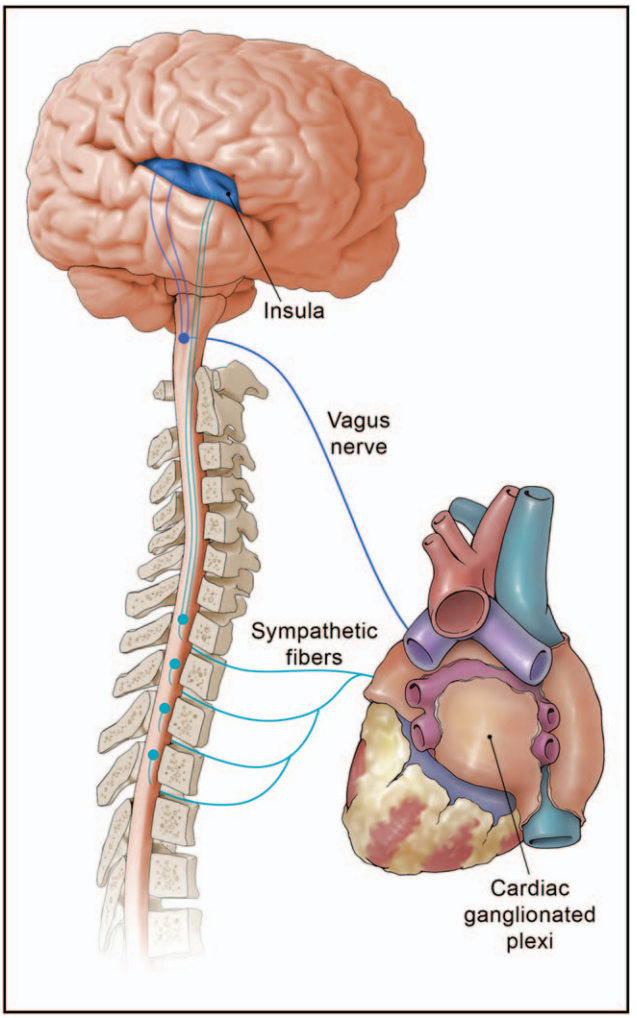

FIGURE 2. Integrated autonomic regulation of heart rhythm.

cortices with the hypothalamus, the limbic system and brainstem nuclei [11]. This higher component of the system is considered an overall 'extrinsic' or 'cerebral' regulation centre. The 'intrinsic' autonomic nervous system encompasses ganglionated plexi distributed along the ending of the pulmonary veins in the left atrium and within the pericardium [12]. This system is highly regulated by the extrinsic component [13]; thus, the loss of autonomic control mediated by damage to the insular cortex or its projections may result in AFDAS triggered at the ganglionated plexi. This concept is supported by current evidence: atrial fibrillation is triggered by focal firing of ganglionated plexi at pulmonary vein and nonpulmonary vein sites in the heart with high sensitivity to autonomic neurotransmission in up to 90% of the cases [1]; acute ischemia of the cerebral cortex, especially within the insula, generates major autonomic imbalances [14]; as shown by our group and others, the involvement of the insular cortex after ischemic stroke is more frequent among

patients with AFDAS than among those who remain in sinus rhythm [15–17].

Systemic inflammation also seems to play an important role in AFDAS generation by mechanisms comprising both focal firing (autonomic cascade) and re-entry circuits (atrial myocarditis) [1]. Focal firing at the ganglionated plexi could be initiated by poststroke systemic inflammation resulting in autonomic dysfunction [1]. A short-lasting inflammatory response including cytokines [e.g. interleukin (IL)-1 and IL-6], adhesion molecules (e.g. intercellular adhesion molecule-1 and E/P-selectins) and chemokines (e.g. CXCL16) released into the blood stream immediately follows acute ischemic stroke [18]. Furthermore, compared with other subtypes of ischemic stroke, patients with cardioembolic ischemic stroke have significantly higher plasma levels of tumour necrosis factor-alpha (TNF-α), IL-1β and IL-6 [19]. Interestingly, all these inflammatory markers have also been implicated in the genesis of atrial fibrillation [20] and have been shown to be related to autonomic imbalance [21]. In fact, elevated levels of IL-6 and C-reactive protein have been associated with decreased heart rate variability, a marker of autonomic dysfunction [21–23]. A prolonged inflammatory response can result in atrial remodeling and atrial fibrillation perpetuation through re-entry circuits, further contributing to the prothrombotic state of atrial fibrillation [1,20].

SCREENING FOR ATRIAL FIBRILLATION DETECTED AFTER STROKE AND TRANSIENT ISCHEMIC ATTACK: THE ROLE OF RAPID INITIATION AND DURATION OF CARDIAC MONITORING

Currently, there are several technologies available for atrial fibrillation screening after stroke for both in-hospital and ambulatory settings. The technologies vary significantly in their invasiveness from the perspective of the patient and the normal duration of monitoring. The most frequently used devices are conventional ECG, in-patient and outpatient telemetry, Holter monitoring, external loop recording and internal loop recording [2▪]. Newly available self-monitoring devices and wearable technologies have shown promising results [24,25].

We recently estimated the atrial fibrillation detection yield for various inpatient and outpatient screening methods, separately and when used sequentially [2▪]. Overall, we found that AFDAS can be detected in up to 23.7% of ischemic stroke and TIA patients without known atrial fibrillation by sequentially combining technologies [2▪]. Considering that about 20% of ischemic stroke and TIA patients have KAF [26], we can estimate that approximately 40% ($20 + 0.8 \times 23.7$) of patients with a history of stroke have atrial fibrillation, and that AFDAS accounts for half of all atrial fibrillation cases in patients with ischemic stroke and TIA.

Recent studies have struggled to compare the diagnostic yield of different technologies [27]. The lack of a gold standard has made these efforts challenging and has sometimes led to misleading conclusions [28]. Despite this limitation, the early initiation and the total duration of monitoring seem to be the most reliable determinants of AFDAS diagnostic yield [5,29].

The early initiation of cardiac monitoring is crucial for improving atrial fibrillation diagnosis after stroke and TIA, with over 70% of cases being diagnosed within the first 3 days after admission [5]. Furthermore, the odds of detecting AFDAS is over five-fold higher when continuous cardiac monitoring is initiated at a mean of 27 days after stroke than a mean of 75 days [2▪]. It is unknown whether the higher atrial fibrillation diagnostic yield immediately after ischemic stroke and TIA is explained by a greater number or a longer duration of atrial fibrillation paroxysms. Regardless, delays in the initiation of cardiac monitoring after stroke may result in missed AFDAS paroxysms.

Up to 95% of atrial fibrillation paroxysms in patients with AFDAS are asymptomatic [5,30] and half of them last less than 30 s [31]. Not surprisingly, paroxysmal atrial fibrillation detection in ischemic stroke and TIA patients is highly determined by the duration of cardiac monitoring and atrial fibrillation burden. The latter is defined as the total time a patient spends in atrial fibrillation and is calculated by adding the duration of all atrial fibrillation paroxysms in a given period of cardiac monitoring (e.g. three paroxysms totalizing 5.3 h of atrial fibrillation in 24 h of monitoring) [32▪]. Two recent prospective studies have confirmed that prolonged cardiac monitoring results in substantial increases in the proportion of patients diagnosed with AFDAS [30,33]. Consistent with these findings, the American Heart Association recommendations support poststroke cardiac monitoring for up to 30 days [34]. However, the ideal sequence of technologies and the optimal duration of atrial fibrillation screening remain a matter of intense debate [8,35–43].

MARKERS OF ATRIAL FIBRILLATION DETECTED AFTER STROKE AND TRANSIENT ISCHEMIC ATTACK

The identification of patient characteristics for predicting AFDAS has become critical for the appropriate tailoring of monitoring allocation and duration

such that patients with the highest odds of having atrial fibrillation are monitored for longer, whereas those who are at a low risk for atrial fibrillation are not subjected to unnecessary testing. As a result, in the recent years, there have been an overwhelming number of efforts to assess different candidate markers [6,44–61] and several scores [62–71] (HATCH, STAF, CHA2-DS2-Vasc, CHADS2, etc.) to improve the accuracy of AFDAS prediction.

Most recently identified markers comprise age [45,48,52,57,63,67,68]; female sex [6,67]; brain natriuretic peptide (BNP) [56,58,59,62,64]; troponin-I [53,60]; premature atrial complexes [44,52,54,55,61,72], prolonged PR interval [48] and QRS duration and total atrial conduction time [51] on ECG; preexisting heart disease or cardiac structural abnormalities (e.g. echocardiographic evidence of left atrial enlargement, left atrial function, impaired systolic function, left ventricular hypertrophy, mitral valve disease and epicardial fat) [6,44–47,52,62–65,68,69,73▪]; history of congestive heart failure [67] and coronary artery disease [57,68]; duration of stroke symptoms [57]; stroke severity [62,63,67]; prior cortical [50,65], anterior circulation [54], and posterior circulation [50] infarctions; white matter lesions [52], haemorrhagic transformation [45,65], susceptibility sign [65] and multiple infarcts [45] on brain MRI; and free fatty acid and triglyceride levels [65]. In patients with acute atrial fibrillation, there is depletion of lymphocytes, possibly due to excessive apoptosis mediated by inflammatory responses and decreased survival modulated by catecholamines [20]. As such, an increased neutrophil to lymphocyte ratio seems to predict incident and postprocedural atrial fibrillation; however, it has never been investigated as a marker of AFDAS to the best of our knowledge [74].

The large number of potential markers and the diversity of findings across studies reveal a great deal of remaining uncertainty. Inconsistency is due to methodological diversity, small study sample sizes limiting the adjustment of analyses for the multiple factors implicated in the genesis of atrial fibrillation and heterogeneity of AFDAS with regard to its pathophysiological mechanisms (e.g. cardiogenic vs. neurogenic). For instance, although classic markers of atrial fibrillation such as cardiac structural abnormalities would certainly predict cardiogenic AFDAS [6], their role, if any, in neurogenic AFDAS is controversial [15].

The search for biomarkers should not be limited to identifying patients at a higher risk of AFDAS. Other markers, such as specific characteristics of neurogenic AFDAS (e.g. autonomic dysfunction, strokes involving the insular cortex and lack of cardiac structural changes) [1] and predictors of cardiac remodeling (e.g. endothelin-1 and matrix metalloproteinase) [75–77] could be useful for identifying additional targets for the timely initiation of preventive strategies aimed at avoiding AFDAS perpetuation and stroke recurrence that could be tested in experimental studies (Fig. 3) [78–86]. Patients with acute neurogenic AFDAS may evolve to recurrent paroxysmal or even chronic or permanent AFDAS mediated by atrial remodeling, possibly representing a group at particularly high risk of recurrent stroke. Indeed, short paroxysmal episodes of atrial fibrillation can lead to atrial fibrillation perpetuation if they become recurrent through structural changes that take place in the atrial myocardium leading to remodeling [87–89]. The timely identification of patients at a higher risk of atrial remodeling may allow the rapid initiation of treatments aimed at preventing it.

ENDOTHELIAL DYSFUNCTION, ATRIAL FIBRILLATION DETECTED AFTER STROKE AND TRANSIENT ISCHEMIC ATTACK BURDEN, STROKE SEVERITY AND THE RISK OF STROKE RECURRENCE

AFDAS burden very likely influences its detection. Little evidence on the relationship between AFDAS burden and stroke risk and severity is available. First, the existing literature focuses on patients with KAF. No study has investigated the relationship between atrial fibrillation burden and the risk of recurrence or stroke severity exclusively in the AFDAS population. Second, most data about atrial fibrillation burden and stroke risk are not generalizable because the study cohorts comprised highly selected populations with considerable heart disease (e.g. with pacemakers or implantable cardiac defibrillators) [32▪]. Third, current knowledge about the relationship between atrial fibrillation and cerebrovascular disease comes from studies based on single or a few ECGs used to detect atrial fibrillation before or/and after stroke [90▪]. The limitation of these studies is that short-duration monitoring, such as ECG, is more likely to detect high-burden atrial fibrillation, thus biasing the characteristics of the newly diagnosed atrial fibrillation population towards patients with highly recurrent or permanent/chronic atrial fibrillation. Furthermore, most studies have not considered paroxysms of less than 30 s as relevant in their analyses because of technical limitations. Interestingly, these episodes seem to be 10-fold more frequent than those more than 30 s when systematically screened by using 24-h Holter monitoring in patients with ischemic stroke of undetermined source [91]. This bias may have systematically influenced the atrial fibrillation

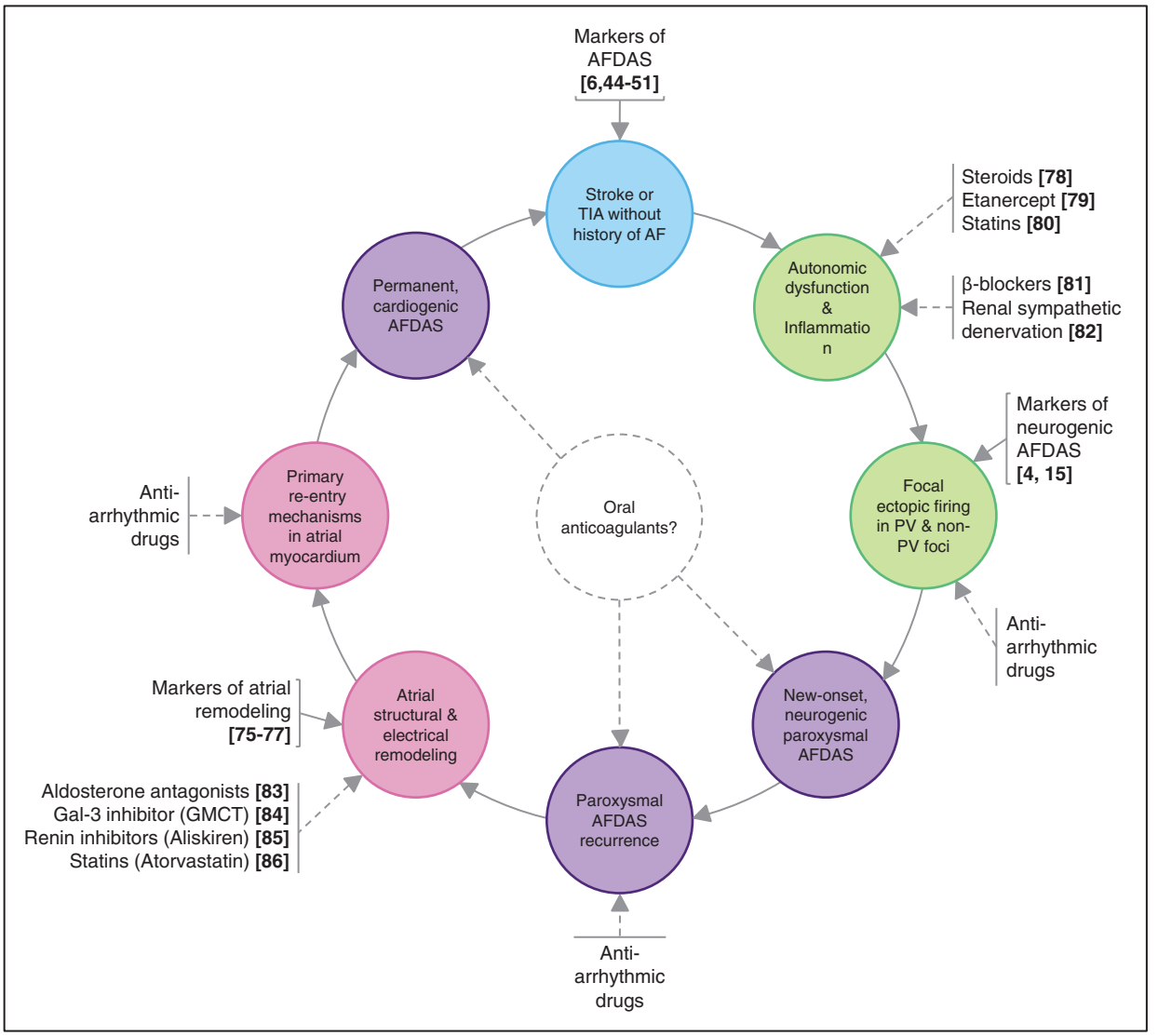

FIGURE 3. Role of markers and potential therapeutic interventions to prevent stroke recurrence in patients at risk of paroxysmal atrial fibrillation detected after stroke or transient ischemic attack. AF, atrial fibrillation; AFDAS, atrial fibrillation detected after stroke or transient ischemic attack; GMCT, galectin-3 inhibitor GM-CT-01; OACs, oral anticoagulants; PV, pulmonary veins; TIA, transient ischemic attack. Green circles: acute poststroke steps related to focal ectopic firing mechanisms. Pink circles: subacute/chronic steps related to atrial remodeling and primary re-entry mechanisms. None of the potential treatments shown in the figure have been prospectively studied in randomized controlled trials. Only antiarrhythmic drugs have been proven to be effective in preventing arrhythmias in patients with known AF, although they have never been used to prevent AFDAS in ischemic stroke and TIA patients.

literature; therefore, shaping the current atrial fibrillation clinical paradigm with concepts such as 'atrial fibrillation is more frequent in moderate/severe strokes than in minor strokes and TIAs' [92], and 'atrial fibrillation related ischemic strokes have worse outcomes and higher recurrence rates than most nonatrial fibrillation ischemic strokes' [93,94].

In this context and with the availability of improved cardiac monitoring technologies, the relationship between paroxysmal atrial fibrillation and stroke needs to be revisited. Studies have shown that even a few hours of atrial fibrillation are enough to result in thrombus formation in the left atrium. Within the first 24 h and in the context of endothelial dysfunction, the left atrium undergoes remodeling shortly after paroxysmal atrial fibrillation onset resulting in a highly thrombogenic state [95▪▪]. Indeed, the endocardium of atrial fibrillation patients is highly prothrombotic and proinflammatory [96]. Atrial fibrillation itself stimulates platelet

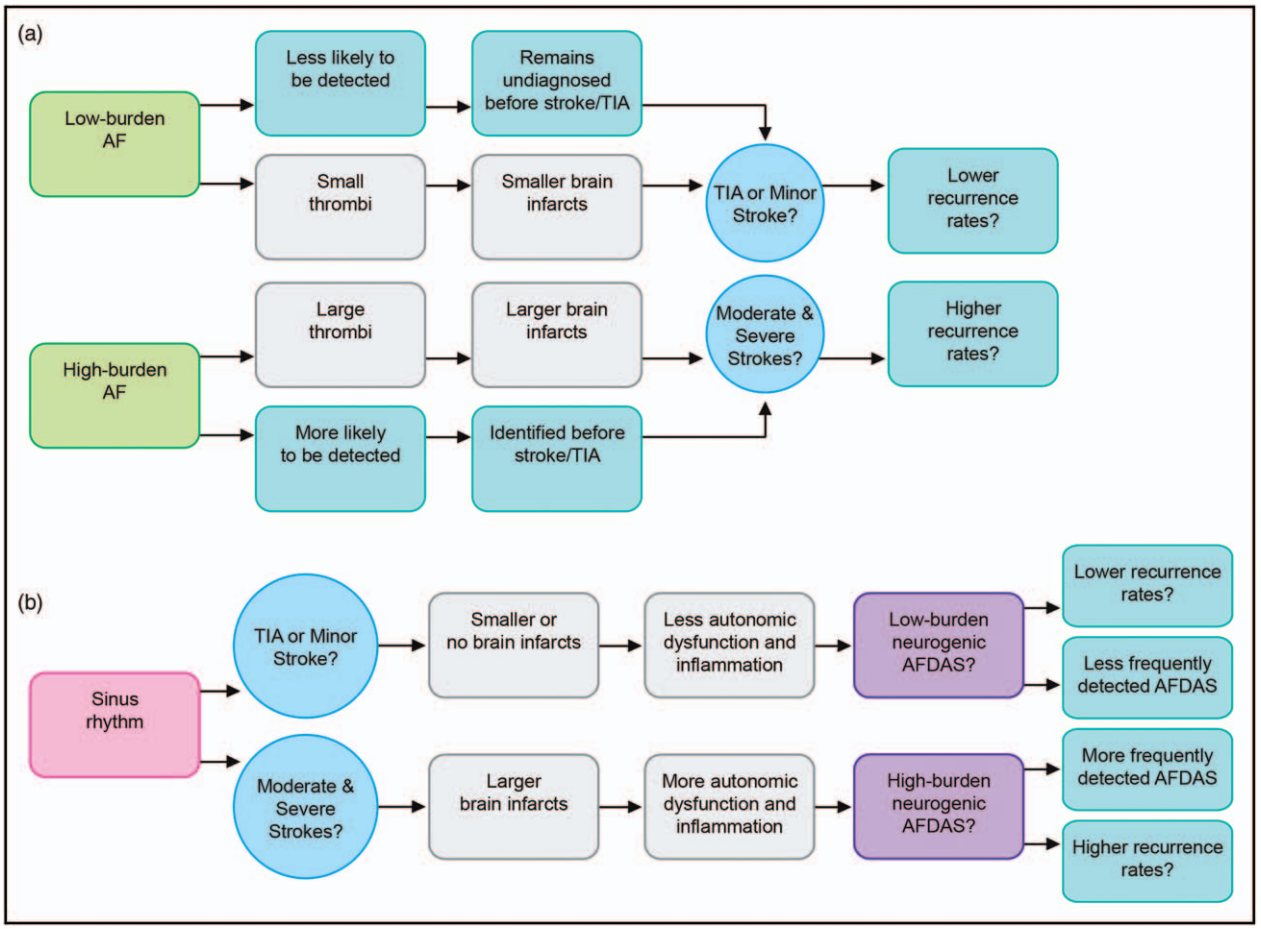

FIGURE 4. Relationship between atrial fibrillation burden and stroke severity and recurrence. (a) Preexisting AF burden and its relationship with stroke severity and risk of recurrence. (b) Burden of AF detected after stroke and its relationship with stroke severity and risk of recurrence. Turquoise boxes: potential diagnostic and prognostic consequences of AF burden. Grey: thrombus and infarct size (a) or infarct size and associated pathophysiological mechanisms (b).

aggregation and coagulation mediated by beta-thromboglobulin [97], platelet factor 4 [98], von Willebrand factor [98] and increased expression of procoagulant genes [99] among other factors. On the basis of this evidence, we speculate that low-burden atrial fibrillation produces small thrombi, leading to minor strokes and TIAs, whereas high-burden atrial fibrillation results in larger thrombi, causing more severe strokes (Fig. 4). This would explain, at least in part, why AFDAS is less frequently diagnosed among TIA and minor stroke patients (low-burden atrial fibrillation) compared with those with moderate/severe strokes (high-burden atrial fibrillation). Indeed, a recent large study showed a lower proportion of atrial fibrillation (KAF and AFDAS) among TIAs than ischemic strokes [92]. Likewise, a recent meta-analysis also found that AFDAS is less frequently diagnosed after continuous cardiac monitoring in cohorts limited to TIA patients compared with those including TIA and ischemic stroke participants (4% vs. 6.3–11.5%) [100]. These results may also be explained by our mechanistic hypothesis of neurogenic AFDAS generation, as after a TIA or minor stroke, there is only minimal structural brain damage, which could result in less severe dysautonomia and lower magnitude inflammatory responses, thus causing fewer 'neurogenic' AFDAS (Fig. 4) [15]. Accordingly, lower levels of BNP have been found in TIA patients than in those with ischemic stroke, potentially indicating a lesser impact of brain damage on cardiac function in TIA patients [101].

KNOWLEDGE GAPS AND FUTURE PERSPECTIVES

We have identified at least six major knowledge gaps regarding AFDAS:

(1) The characterization of neurogenic and cardiogenic AFDAS;
(2) How and when neurogenic atrial fibrillation is triggered;
(3) The identification of reliable markers to predict atrial fibrillation in patients with recent stroke and no history of atrial fibrillation, as well as predictors of atrial fibrillation perpetuation and stroke recurrence in patients with AFDAS;
(4) The effect of KAF and AFDAS burden on stroke severity and recurrence;
(5) Whether the risk of AFDAS in terms of stroke recurrence and death warrants the use of oral anticoagulants. There is general expert agreement in that AFDAS patients should be started on oral anticoagulants to prevent stroke and systemic embolism [2▪]. As such, most patients with AFDAS are treated with oral anticoagulants [102]. However, the expert agreement relies largely on what is known about atrial fibrillation diagnosed prior to stroke, which may disproportionately be symptomatic, higher burden or occurring in patients with concomitant illnesses that made their atrial fibrillation diagnosis more likely (such as other forms of heart disease). Patients with AFDAS may have a lower risk of recurrent stroke and their recurrent strokes may be less severe compared with patients with KAF. If this is true, their risk–benefit profile for oral anticoagulants may be different, and thus, specifically tailored risk stratification may be necessary to facilitate patient-centred care.
(6) The role of AFDAS as a mechanism of embolization. AFDAS could be just a marker of endothelial dysfunction, atrial hypercoagulability and increased risk of embolism, but not the embolizing mechanism itself [10]. Endothelial dysfunction and atrial hypercoagulability are consequences of vascular risk factors and age, which could be acutely enhanced by ischemic strokes involving the insula, leading to substantial changes in cardiac structure, such as subendocardial haemorrhage, ischemic damage and subendocardial oedema [103].

Ongoing studies such as Detection of Silent Atrial Fibrillation aFter Ischemic StrOke (SAFFO) [104], Impact of Standardized Monitoring for Detection of Atrial Fibrillation in Ischemic Stroke (MonDAFIS) [105], Finding Atrial Fibrillation in stroke patients – Randomized (Find-AF Randomized) [106], Detection of occult paroxysmal atrial fibrillation by implantable long-term ECG monitoring in cryptogenic stroke and TIA [107] and PAthophysiology and Risk of Atrial fibrillation Detected after Ischemic StrokE (PARADISE) will probably address many of the currently unknown aspects of AFDAS.

CONCLUSION

New cardiac monitoring technologies have dramatically improved the detection of atrial fibrillation in stroke and TIA patients revealing a large number of patients whose atrial fibrillation prognosis may not be well understood. Ongoing research will fill in some of the gaps. Improved understanding of neurogenic atrial fibrillation may contribute to a broader understanding of the heart and brain connection and of neurogenic causes of cardiac arrhythmias. Furthermore, the rapid integration of new knowledge about AFDAS into patient-centred care will improve the selective use of long-term monitoring and will help to tailor treatment regimens to patient risk profiles, ultimately improving health outcomes.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

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