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REVIEW

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Atrial fibrillation and stroke

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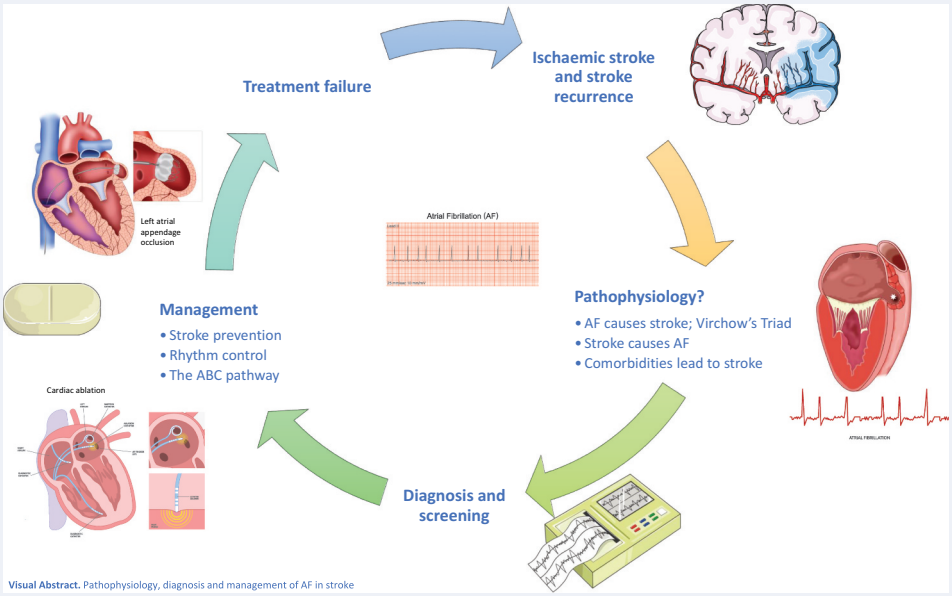
ABSTRACT

Introduction: Stroke is one of the leading causes of mortality and morbidity globally. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is set to reach epidemic proportions. AF is associated with a five-fold increase in risk of stroke. Strokes caused by AF more often are fatal or result in severe disability. Even though the incidence of stroke has been significantly reduced by oral anticoagulation, AF is thought to account for a significant proportion of cryptogenic strokes where no etiology is identified.

Areas covered: This article reviews the literature related to AF and stroke, pathophysiological insights, diagnosis of AF in stroke patients, and its management (Graphical Abstract).

Expert opinion: The pathophysiology of thrombogenesis that links AF and stroke is not well understood and is an area of active research to identify new therapeutic targets to prevent AF and stroke. As the nature of AF and stroke is multifaceted, an integrated care approach to managing AF and stroke is increasingly essential.



Visual Abstract. Pathophysiology, diagnosis and management of AF in stroke

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KEYWORDS
atrial fibrillation; cryptogenic stroke; embolic stroke; integrated care approach; oral anticoagulation; rhythm control; stroke prevention

1. Introduction

Stroke is one of the leading causes of mortality, morbidity, and long-term disability worldwide [1]. It is the second highest cause of death globally after ischemic heart disease [1]. Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults increasing the risk of stroke five-fold and represents a growing epidemic and public health burden [2]. Of note, AF has an estimated prevalence of 1% to 4% in Australia, Europe, and the United States [3–9], with a lower prevalence (0.49% to 1.9%) in Asian countries [10]. Its prevalence increases markedly with age and cardiovascular comorbidities, reaching up to 17% among adults aged 80 or older [11,12].

The lifetime risk of developing AF is approximately one in four [13,14]. With an aging population and improved

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Article highlights

- Atrial fibrillation (AF) is a common cause of ischemic stroke, and AF-related stroke is associated with higher severity and mortality than non-AF stroke.
- A better understanding of the interplay between pathophysiological mechanisms of thrombogenesis, AF, and stroke will help to identify new targets for treatment and stroke prevention in patients with AF.
- Although AF is diagnosed on surface ECGs, the increasing use of several screening modalities and predictive models that adopt multimodal biomarkers will enhance our ability to detect new AF during follow-up for acute ischemic stroke.
- Although oral anticoagulation following ischemic stroke in AF patients is crucial for prevention of recurrent strokes, the optimal time for starting or restarting anticoagulation remains to be determined by several RCTs comparing early to late initiation of oral anticoagulants.
- Adopting an early rhythm control strategy including ablation early in the diagnosis of AF after stroke may lower the risk of recurrent stroke.
- A holistic integrated care approach associated with reduction in adverse outcomes, such as the Atrial fibrillation Better Care (ABC) pathway, will continue to be essential.

management of cardiovascular diseases, the estimated worldwide prevalence of AF during the next 30 years is projected to increase by 66% reaching 62.5 million cases [15]. In the United States per se, the prevalence of AF is projected to rise from 5.1 million in 2000 to 12.1 to 15.9 million by 2050 [16]. The estimated prevalence of AF in the European Union in 2010 was 8.8 million individuals over 55 years and is projected to double to 17.9 million by 2060 [17].

AF is the most important cause of cardioembolism, representing 35% of patients with non-lacunar strokes and 15% to 24% of all ischemic strokes [18,19]. AF-related ischemic stroke is almost twice as likely to be fatal, usually more severe, or recurs more frequently than non-AF stroke [20,21]. Oral anticoagulation (OAC), comprised of vitamin-K antagonists (VKA) and non-vitamin K antagonist oral anticoagulants (NOAC), is the treatment of choice, significantly reducing the risk of stroke or systemic embolism, as well as mortality [22–26].

Due to patients' and physicians' deeper awareness of AF, the increasing use of several AF screening modalities, as well as improved control of modifiable stroke risk factors, there has been a trend toward proportionally higher incidence of cardioembolic strokes, compared to other stroke subtypes [27–30].

Despite an extensive diagnostic work-up during the acute or chronic phase of ischemic stroke, the cause of ischemic stroke remains unexplained for 20% of patients, termed cryptogenic stroke [31,32]. A subgroup of patients with cryptogenic stroke, in which despite an extensive diagnostic work-up, no potential cause is recognized, have what is described as embolic stroke of undetermined source (ESUS) [33]. Although occult AF and atrial cardiomyopathy may be a potential source of embolism in these patients, low-degree atherosclerotic stenosis, patent foramen ovale, left ventricular disease and others, may serve as potential embolic sources, which frequently overlap [34]. Due to its dynamic nature, identifying occult AF may be challenging in clinical practice, although it may be present in a significant proportion of patients presenting with cryptogenic stroke [35–37].

2. Pathophysiology of AF in stroke and insights into stroke risk

Despite the clear mechanistic association between AF and systemic thromboembolism, AF may also represent a marker of cardiovascular burden in the continuously aging contemporary population [38]. Moreover, stroke may affect the autonomic nervous system [39], which in turn is thought to play a role in triggering cardiac arrhythmia, most commonly, AF [40]. However, there is a paucity of data to explain the clinically important difference between the brief new-onset AF following a stroke and the long-standing AF, in terms of future stroke recurrence [41,42].

The pathophysiology of thrombogenesis in AF is multifaceted and complex. The pathogenic mechanisms of thrombus formation in the left atrium and left atrial appendage are incompletely understood and best framed by Virchow's triad [43]. Evidence that the processes described in Virchow's triad to explain thrombogenesis in vascular disease, namely (i) vessel wall abnormalities, (ii) abnormal blood flow, and (iii) hypercoagulability from abnormal hemostasis, platelet function, and fibrinolysis, are active in AF is well documented [44–46]. Moreover, several studies suggested the presence of these alterations among patients with AF-related strokes, fostering their association to thrombus formation and subsequently to systemic embolism (Tables 1 and 2). However, the precise interplay between those pathophysiological elements, AF, and ischemic stroke is not fully understood. Improved insights into those components and how they lead to stroke in AF patients will facilitate improved stratification and understanding of stroke risk and prognosis, and the development of management therapies and new targets for treatment strategies in the future.

2.1. Abnormal atrial wall structural changes

As to the first limb of Virchow's, abnormal changes in the structure and anatomy of the left atrial wall may lead to the development of atrial fibrillation and contribute to promoting a prothrombotic environment (Table 1) [47–57].

Masawa et al. [47] described a 'rough endocardium' attributable to a wrinkled appearance of the left atrial endocardium due to edema and fibrous thickening in autopsy patients with AF and cerebral embolism. Almost all patients identified with 'rough endocardium,' had changes of mural microthrombi on light microscopy. These changes in AF patients may suggest endocardial injury and represent the established knowledge that AF is associated with structural remodeling of the left atrium, the hallmark of which is atrial fibrosis. The pathogenesis of atrial fibrosis is highly complex and thought to involve numerous mechanisms on a cellular and neurohormonal level, which are not fully understood. There is an important interplay of the previously neglected innate immunity pathways, through the local activation of inflammasome [58], a process that leads to cardiac inflammation and myocyte loss, leading to abnormal activation and proliferation of cardiac fibroblasts and differentiation into myofibroblasts, followed by the excessive synthesis and deposition of

Table 1. Pathophysiology of thromboembolism in AF and stroke: vessel wall abnormalities and abnormal blood flow.

First Author (Year) (Ref #)	Study Type	N	Population	Key Findings
Left atrial wall abnormalities, atrial fibrosis and endothelial damage				
Masawa et al. (1993) [47]	Observational	398	31 autopsies of cases of cerebral embolism (including 21 cases with AF) and 7 autopsy controls	Macroscopic changes of a "rough endocardium" (RE) due to a granular, wrinkled appearance of the LA endocardium associated with edematous and fibrous thickening, was seen in 81% of cases of AF and none of cases with no AF and in none of 7 autopsy controls. Statistically significant correlation between AF and atrial thrombosis, and between RE and atrial thrombosis
Conway et al. (2003) [48]	Prospective	994	NV AF patients receiving aspirin	vWF nonsignificant independent predictor of vascular events including IS
Ehrlich et al. (2011) [57]	Prospective	278	Any type of AF	MMP-2, and sVCAM-1 but not vWF (endothelial dysfunction) associated with cardiovascular events (MI, stroke, peripheral embolism)
Daccarett et al. (2011) [50]	Observational	387	AF or paroxysmal AF patients including 36 with history of stroke, and received cardiac DE-MRI of LA	Higher percentage of LA fibrosis in patients with previous strokes, and those with higher CHADS2 score. LA fibrosis independently predicted cerebrovascular events using logistic regression
Akoum et al. (2013) [52]	Retrospective	178	AF patients who underwent TOE and cardiac LGE-MRI prior to ablation or cardioversion	12 LAA thrombus; 19 SEC. Higher atrial fibrosis in patients with LAA thrombus or SEC compared to without LA thrombus or SEC. High fibrosis significant predictor of LAA thrombus or SEC using multivariate logistic regression
Krishnamoorthy et al. (2013) [49]	Prospective	423	NV AF patients	High vWF associated with increased risk of adverse events including IS
King et al. (2017) [51]	Retrospective	1,228	AF patients who underwent cardiac LGE-MRI followed up for 5 years	More severe LA LGE associated with increased risk of MACCE (stroke/TIA, MI, acute decompensated HF, and CV death)
Fonseca et al. (2018) [53]	Observational	111	IS patients including 17 CE associated with AF, 52 with undetermined cause, 42 had other stroke causes	Patients with an undetermined cause of IS had higher percentage of LA fibrosis than patients with other stroke causes, and similar values of atrial fibrosis as CE stroke patients
Tandon et al. (2019) [54]	Observational case-control	30	10 patients with ESUS (without AF), 10 patients with AF (without stroke) and 10 controls (no stroke, no AF)	Patients with ESUS had more atrial fibrosis on LGE-MRI than controls, and similar fibrosis compared to patients with AF
Bifulco et al. (2021) [56]	Observational	90	45 post-stroke ESUS and 45 pre-ablation AF patients recruited to undergo cardiac LGE-MRI for reconstruction of 3D patient-derived atrial models for simulated computational assessment of fibrotic substrate's arrhythmogenic potential through induction of reentrant drivers	More atrial fibrosis in inducible models than non-inducible models. Similar fibrosis levels in inducible ESUS and AF models indicating intrinsic pro-arrhythmic substrate properties indistinguishable between ESUS and AF models
Kühnlein et al. (2021) [55]	Prospective	203	100 patients with AF (50 with and 50 without prior stroke) and 103 patients without AF (35 healthy controls, 15 with lacunar strokes, 53 with ESUS) underwent LGE-MRI for evaluation of atrial fibrosis. ESUS patients followed-up for mean of 19 months for recurrent IS, incident AF or death	Significantly higher atrial fibrosis in patients with ESUS compared to healthy controls or patients with lacunar stroke, and comparable fibrosis (non-significant) to AF patients with or without prior stroke. Patients with recurrent stroke and/or incident AF had higher degree of atrial fibrosis (≥12%) compared with patients without recurrent events
Abnormal blood stasis				
SPAF Investigators (1992) [69]	Observational	568	Patients with NV AF assigned to placebo in SPAF study	LV dysfunction and LA size from M-mode echocardiograms strongest independent predictors of later TE
Chimowitz et al. (1993) [72]	Observational	82	42 patients with SEC (34 AF or MS), 40 controls (with AF or MS)	SEC highly associated with previous stroke or peripheral embolism in patients with AF or MS
Briley et al. (1994) [73]	Observational	50	Patients with acute stroke or chronic cerebrovascular disease	In patients with acute stroke or chronic cerebrovascular disease, higher grade of SEC associated with significantly greater percentage of patients with AF and larger LA size. Severity of SEC related to elevated fibrinogen
Leung et al. (1994) [85]	Prospective	272	Patients with NV AF undergoing TOE with mean follow-up of 17.5 months	SEC positive predictor of subsequent stroke or embolic events and associated with reduced survival
Kochi et al. (1999) [78]	Observational	44	Patients with NV AF studied with TOE and non-invasive imaging	LA SEC highly related to attenuation or occlusion on MRA and imbalance of cerebral blood flow on TCD in MCA territory
Okura et al. (1999) [79]	Observational	77	Patients with IS >70 years old undergoing TOE including 40 in AF and 37 in SR	In elderly stroke patients, LA SEC and thrombus more commonly detected in patients with AF

(*Continued*)

Table 1. (Continued).

First Author (Year) (Ref #)	Study Type	N	Population	Key Findings
SPAF Investigators Committee on Echocardiography (1999) [84]	Prospective	382	Patients with AF at high risk of TE, participating in SPAF-III, randomized to warfarin vs low-intensity warfarin plus aspirin	Subsequent rates of TE correlated with dense SEC, LAA thrombus, and complex aortic plaque
Kamp et al. (1999) [68]	Prospective	88	Patients with paroxysmal AF or chronic AF undergoing TOE followed up for 1 year	LA SEC and particularly low LAA peak flow velocity related to subsequent TE events and increased risk of TE in AF patients
Kumagai et al. (2014) [77]	Observational	98	Patients suspected of acute embolic brain infarction (including 46 patients with AF, 10 with TIA)	SEC important risk factor associated with LA thrombus in patients suspected of embolic brain infarction independent of AF
Yaghi et al. (2015) [71]	Prospective	655	First IS patients	Moderate to severe LA enlargement independent marker of recurrent CE or cryptogenic stroke in multi-ethnic cohort of IS patients
Hamatani et al. (2016) [70]	Retrospective	2713	Patients with AF with median follow-up 976.5 days	LA enlargement independently associated with higher risk of stroke/SE
Yoo et al. (2016) [76]	Observational	440	Stroke patients with NV AF undergoing TOE	Stroke severity increased in AF patients with SEC than in those without SEC (NIHSS median, 5 vs 3). Presence of SEC predictive of poor long-term functional outcome
Zhao et al. (2016) [80]	Prospective	206	Patients with NV AF receiving TOE followed up for 2 years	Video intensity of LA SEC higher in patients with stroke compared to those without stroke
Ohya et al. (2019) [81]	Retrospective	348	Patients with ESUS undergoing TOE followed up for paroxysmal AF (PAF)	SEC, LAA flow by TOE, enlargement of LA dimension by TTE, more frequent in patients with PAF compared to those without PAF. Specificity of SEC and/or LAA flow with enlarged LA dimension increased up to 90%

AF = atrial fibrillation; CE = cardioembolic; CV = cardiovascular; DE-MRI = delayed enhancement magnetic resonance imaging; ESUS = embolic stroke of undetermined source; HF = heart failure; IS = ischaemic stroke; LA = left atrium or left atrial; LAA = left atrial appendage; LGE = late gadolinium enhancement; LGE-MRI = late gadolinium enhancement magnetic resonance imaging; LV = left ventricular; MACCE = major adverse cardiovascular and cerebrovascular events; MCA = middle cerebral artery; MI = myocardial infarction; MMP-2 = matrix metalloproteinase-2; MRA = magnetic resonance angiography; MS = mitral stenosis; NV = non-valvular; SE = systemic embolism; SEC = spontaneous echo contrast; SPAF = The Stroke Prevention in Atrial Fibrillation; SR = sinus rhythm; sVCAM-1 = soluble vascular cell adhesion molecule-1; TCD = transcranial colour Doppler imaging TE = thromboembolic or thromboembolism; TIA = transient ischaemic attack; TOE = transoesophageal echocardiogram; TTE = transthoracic echocardiogram; vWF = Von Willebrand factor.

Table 2. Pathophysiology of thromboembolism in AF and stroke: abnormal blood constituents.

First Author (Year) (Ref #)	Study Type	N	Population	Key Findings
Platelet abnormalities				
Shah et al. (1985) [126]	Comparative	58	10 CE stroke, 13 TE stroke (primarily carotid disease), 10 CE or TE stroke, 10 lacunar stroke, 10 TIA patients	BTG significantly elevated in acute phase of CE and TE stroke. No correlation between BTG and infarct volume
Woo et al. (1988) [88]	Comparative	372	Acute cerebral infarction: 116 atherosclerotic thrombotic, 36 CE, 96 lacunar infarcts; 16 TIA; and 73 normal and 35 patient controls	BTG significantly elevated in acute phase of atherosclerotic thrombotic and CE infarcts, but normal for lacunar infarcts. In atherosclerotic thrombotic infarcts, BTG tended to correlate with infarct size
Gustafsson (1990) [90]	Cross-sectional	100	40 NV AF patients (20 with previous IS and 20 without previous stroke), 20 stroke patients with SR, and 40 healthy controls	Higher BTG in NV AF patients (with and without previous stroke), and increased PF4 in NV AF patients with previous IS
Nagao et al. (1995) [89]	Observational	36	17 patients with CE stroke and chronic AF and 19 healthy controls	BTG and PF4 not enhanced in acute stage of CE stroke with NV AF. In contrast, coagulation system indicators TAT and D-dimer were markedly elevated
Heppell (1997) [122]	Case-control	109	AF patients including 88 without and 19 with LA thrombus	Increased BTG and PF4 in patients with LA thrombus compared with patients without thrombus
Feinberg et al. (1999) [87]	Prospective	1531	Participants of SPAF III study	F1 + 2 (prothrombotic), BTG, fibrinogen, and factor V Leiden not independent, clinically useful predictors of stroke
Yip et al. (2007) [102]	Observational	141	61 NV AF patients after AIS, 50 NV AF controls, 30 healthy controls	CD62p expression, which reflected increased BIV, significantly higher in NV AF patients in acute-phase of IS and substantially declined thereafter. BIV predictive of unfavorable intermediate-term outcomes
Ha et al. (2011) [91]	Prospective	200	Patients with AF followed up for mean follow-up of 15.1 months for IS event	A higher MPV predictive for stroke independent of age, gender, and other CHADS2 score components
Turfan et al. (2013) [94]	Retrospective	227	63 stroke patients with AF, 77 AF patients without stroke, and 87 healthy controls	A high MPV associated with increased risk of stroke in AF patients
Bayar et al. (2015) [127]	Retrospective	90	Patients with paroxysmal AF. 31 had history of stroke/TIA	Elevated MPV levels related to increased risk of stroke/TIA in patients with paroxysmal AF
Choi et al. (2017) [92]	Prospective	352	Patients with AF and mean follow-up of 35.4 months for a composite of ISE and incidental LA thrombus	High MPV and AT-III deficiency independent predictor for stroke or LA thrombus in patients with NV AF
Gul and Gozke (2018) [95]	Observational	297	170 patients with AIS with AF, and 127 controls with AIS without AF	MPV levels significantly higher in patients with AIS and AF than those without AF
Tarnowski (2018) [128]	Observational	108	28 AF patients with detected LA thrombus, 80 AF patients without detected LA thrombus	LA thrombus associated with significantly increased MPA, sCD40L, and D-dimer, but not sP-sel
Lyu et al. (2019) [97]	Observational	150	AF patients with stroke, and AF patients without stroke	Higher PDW in AF with stroke group compared with AF without stroke group. PDW is a risk factor for stroke in AF patients
Zheng et al. (2020) [93]	Prospective	370	Patients with AF followed up for AIS	MPV of stroke group higher than MPV of control group. The ISE rates significantly increased in highest MPV tertile compared to lowest. MPV predictor of IS
Zhu et al. (2020) [96]	Observational	371	Patients with AIS, including 177 with AF-related stroke and 194 with LAA stroke	MPV and MPV/PIt ratio much higher in AF group than LAA group
Abnormal changes in coagulation and haemostasis				
Gustafsson (1990) [90]	Cross-sectional	100	40 NV AF patients (20 with previous IS and 20 without previous stroke), 20 stroke patients with SR, and 40 healthy controls	Higher vWF and D-dimer in NV AF patients (with or without previous stroke) compared with stroke patients with SR or 40 healthy controls
Heppell (1997) [122]	Observational	109	AF patients including 88 without and 19 with LA thrombus	Increased D-dimer, vWF and TAT in LA thrombus compared with patients without thrombus
Kahn (1997) [98]	Cross-sectional	117	75 NV AF patients (50 without and 25 with prior embolic event) and 42 controls (patients in SR) (31 without and 11 with prior thrombotic stroke)	vWF and fibrinogen higher in AF with prior embolic event compared with controls without prior stroke, and similar to controls with prior thrombotic stroke.
Soncini et al. (1997) [123]	Observational	64	Patients with congestive HF, half with chronic NV AF; grouped into AF and stroke, AF alone, stroke alone, SR without stroke	F1 + 2 higher and TAT marginally higher in patients with AF and stroke than in those without stroke. Higher TAT in patients with previous stroke (irrespective of AF). Higher TAT and F1 + 2 in AF patients. TAT significantly higher in patients with SEC
Topcuoglu et al. (2000) [124]	Observational	131	95 patients with first time non-lacunar MCA IS (24 CE stroke due to lone AF, 21 other CE stroke, 50 stroke from LAA) and 36 controls (including 15 patients with lone AF and 21 with SR)	Higher TAT and marginally higher F1 + 2 in patients with CE stroke from all sources than those with LAA stroke. PAI-1 marginally higher in stroke patients with lone AF and LAA stroke
Conway et al. (2003) [48]	Prospective	994	NV AF patients receiving aspirin 325 mg/day as part of SPAF III study, followed up for 2 years	vWF (as marker of endothelial damage and dysfunction) nonsignificant independent predictor of vascular events (IS, MI, or vascular death)
Vene et al. (2003) [113]	Prospective	113	Patients with chronic AF	High D-dimer and tPA during oral anticoagulant therapy significant predictors of combined CV events (stroke, MI, peripheral vascular occlusion, vascular death)

(*Continued*)

Table 2. (Continued).

First Author (Year) (Ref #)	Study Type	N	Population	Key Findings
Heeringa et al. (2006) [129]	Retrospective	486	162 AF and 324 SR participants in Rotterdam Study	Although association between vWF and sP-sel and cardiac mortality, no associations between vWF, sP-sel and fibrinogen and stroke
Lip et al. (2006) [103]	Prospective	994	AF patients enrolled in SPAF III study followed up for rates of IS and vascular events	Addition of vWF to clinical risk stratification further refined risk stratification for stroke
Nozawa et al. (2006) [114]	Prospective	509	Patients with NV AF (263 treated with warfarin, 163 with antiplatelet drugs), with average follow-up of 2 years for cerebral infarction, TIA, or embolism of peripheral arteries	D-dimer (as marker of fibrinolysis) (but not F1 + 2 (as marker of coagulation)) in combination with clinical risk factors predictive of subsequent TE events in patients with NV AF even when treated with warfarin
Sato et al. (2006) [104]	Observational	183	AIS patients, including 40 with AF and 143 without AF	vWF higher in AF group than non-AF group and in patients with SEC in LA. vWF correlated with IS severity, outcome and infarct size (though, in AF group, difference in vWF between small and large infarcts was not significant)
Turgut et al. (2006) [99]	Observational	75	55 patients with AIS (26 with NV AF, 29 with SR), and 20 healthy controls	Higher F1 + 2 in stroke patients with AF than in stroke patients without AF or controls. Fibrinogen lower in controls than in stroke patients. D-dimer not significantly different between groups
Yip et al. (2007) [102]	Observational	141	61 NV AF patients after AIS, 50 NV AF controls, 30 healthy controls	vWF did not change or increase in NV AF during acute-phase of IS or up to 90 days after
Pinto et al. (2009) [105]	Prospective	373	Patients with AF, followed up for 36 months	Baseline vWF, TNF-α, and IL-6 predictors of new onset IS in patients with chronic AF
Sadanaga et al. (2010) [115]	Prospective	245	Patients with NV AF treated with warfarin, followed up for an average of 756 days	Elevated D-dimer and CHADS2 ≥ 3 associated with TE events
Sadanaga et al. (2010) [116]	Prospective	269	109 chronic AF and 160 paroxysmal AF patients treated with warfarin, with average follow up of 756 days	Patients with elevated D-dimer levels had higher TE and combined CV events
Krarup et al. (2011) [120]	Prospective	382	Patients with AIS and documented AF	D-dimer and F1 + 2 not associated with stroke progression, recurrent stroke or death in patients with AIS and AF
Roldán et al. (2011) [106]	Prospective	829	Permanent AF patients stabilized on oral anticoagulant therapy, with median follow-up of 829 days	High plasma vWF (but not D-dimer) independent risk factor for adverse events (mainly TE including stroke/TIA, ACS, acute HF, and cardiac death) in anticoagulated permanent AF patients
Ząbczyk et al. (2011) [125]	Observational	62	Patients with permanent AF, 19 with history of previous thrombotic event (11 stroke, 8 MI, 3 PE) and 43 without	Higher PAI-1 in patients with AF and history of previous thrombotic events
Freynhofer et al. (2013) [107]	Prospective	269	AF patients	A high ratio of vWF/ADAMTS13 independently predicts MACE in AF patients
Krishnamoorthy et al. (2013) [49]	Prospective	423	NV AF patients with median follow-up of 19 months	High vWF and sE-sel associated with increased risk of adverse events (AMI, IS and all-cause mortality) in AF patients
Matsumoto et al. (2013) [112]	Observational	124	Patients with IS and NV AF	D-dimer significantly associated to infarction volume on multivariate regression analysis. Worse outcome in highest D-dimer tertile
Christersson et al. (2014) [117]	Prospective	18,201	Patients with AF randomized to apixaban or warfarin, with median follow-up of 1.8 years	Higher D-dimer levels associated with increased frequencies of stroke, SE, and death
Siegbahn et al. (2016) [118]	Prospective	6202	Patients with AF randomized to dabigatran or warfarin in RE-LY trial	Baseline D-dimer independently related to risk of stroke/SE and CV death, with a higher rate of stroke/SE and CV death among patients with higher D-dimer levels. Addition of D-dimer to established clinical risk factors improved prediction of stroke/SE and CV death
García-Fernández et al. (2017) [108]	Prospective	1215	NV AF patients treated with VKA followed up over almost 7 years	Significant associations between vWF and CV events, stroke, mortality. Addition of vWF to CHA_2DS_2-VASc improved its predictive value but c-indexes not significantly different
Ancedy et al. (2018) [109]	Prospective	122	Patients with hospitalized NV AF, with median 5.4 years of follow-up	Higher vWF independently associated with increased risk of stroke and all-cause death
Roldán et al. (2018) [110]	Prospective	1361	AF and paroxysmal AF patients on optimal anticoagulation with VKA, with median follow-up of 2375 days	Although addition of HsT, NT-proBNP, IL-6, and vWF enhanced predictive value of CHA_2DS_2-VASc for long term CV events (composite of stroke/SE, ACS, acute HF and CV death) and death, overall improvement was modest and conferred only marginal predictive advantage. Only vWF remained significant for stroke when analyzed separately

(*Continued*)

Table 2. (Continued).

First Author (Year) (Ref #)	Study Type	N	Population	Key Findings
You and Tang (2018) [121]	Retrospective	323	78 inpatients with NV AF and stroke, 245 NV AF inpatients without stroke	D-dimer independent risk factor for IS by logistic regression, and positively correlated with risk stratification of IS, but has no predictive value on occurrence of stroke in patients with NV AF
Kneihsl et al. (2019) [119]	Prospective	429	Patients with IS including 115 CE (103 AF-related) strokes, 143 CS and 171 non-cardiac strokes	NT-proBNP, and to a lesser extent D-dimer and AT-III, associated with AF-related stroke. NT-proBNP seems helpful in selecting CS patients for extended cardiac monitoring for detection of occult AF
Paulin et al. (2019) [100]	Observational	455	Patients with NV AF including 143 with first onset stroke and 312 non-stroke	D-dimer not associated with and not independent risk factor of stroke in NV AF patients (but BNP and HsT are (via multivariate logistic regression))
Harpaz et al. (2021) [101]	Observational	515	IS patients including 75 CE, 131 LAA, 247 lacunar, 62 undetermined; 31 pre-existing AF, 44 new-onset paroxysmal AF	Higher NT-proBNP, IL-6, and cortisol in stroke patients with new-onset AF and CE stroke, whereas D-dimer was unchanged in CE stroke. Biomarkers including NT-proBNP significant predictors of new-onset AF (by logistic regression analysis)
Wysokinski et al. (2021) [111]	Prospective	414	NV AF patients followed up for 3 years	vWF predictive of TE (in univariate but not multivariate analysis) and independent predictor of poor outcomes including death and a composite of death and TE

ACS = acute coronary syndrome; ADAMTS13 = a disintegrin and metalloprotease with thrombospondin type 1 repeats-13; AF = atrial fibrillation; AIS = acute ischaemic stroke; AMI = acute myocardial infarction; AT-III = antithrombin III; BIV = brain infarct volume; BNP = B-type natriuretic peptide; BTG = β-thromboglobulin; CE = cardioembolic; CS = cryptogenic stroke; CV = cardiovascular; F1 + 2 = prothrombin fragments 1 + 2; HF = heart failure; HsT = high sensitivity troponin; IL-6 = interleukin 6; IS = ischaemic stroke; ISE = ischaemic stroke event; LA = left atrial or left atrium; LAA = large artery atherosclerosis; MACE = major adverse cardiovascular events; MCA = middle cerebral artery; MI = myocardial infarction; MPA = monocyte-platelet aggregates; MPV = mean platelet volume; MPV/Plt ratio = mean platelet volume/ platelet count (MPV/Plt) ratio; NT-proBNP = N-terminal-pro-brain natriuretic peptide; NV = non-valvular; PAI-1 plasminogen activator inhibitor-1; PDW = platelet distribution width; PE = pulmonary embolism; PF4 = platelet factor 4; sCD40L = soluble CD40 Ligand; SE = systemic embolism; SEC = spontaneous echo contrast; sE-sel = soluble E-selectin; sP-sel = soluble P-selectin; SPAF = The Stroke Prevention in Atrial Fibrilltion; SR = sinus rhythm; TAT = thrombin-antithrombin complexes; TE = thromboembolic or thromboembolism; TIA = transient ischaemic attack; TNF-α = tumour necrosis factor α; tPA = tissue plasminogen activator; VKA = vitamin K antagonist(s); vWF = Von Willebrand factor

extracellular matrix (ECM) proteins [59,60]. The abnormal ECM homeostasis is reflected in the upregulation of matrix metalloproteinases (MMPs) and downregulation of tissue inhibitors of metalloproteinases (TIMPs) [59,61]. The increased expression of collagen forms a proarrhythmogenic substrate for the initiation and perpetuation of AF. Abnormal levels or ratios of MMPs and TIMPs as markers of atrial remodeling and endothelial dysfunction have been demonstrated in AF with some contradictory results [61,62]. Although elevated MMP-2 has been associated with stroke, MMPs and TIMPs have not been generally studied in patients with stroke associated with AF.

Elevated Von Willebrand factor (vWF) as a marker of endothelial damage and dysfunction is associated with an increased stroke risk in AF patients [48,49]. CRP marking the role of inflammation in AF has been shown to be positively correlated to stroke risk [63]. Whether atrial fibrosis is the causative link to AF or merely a marker of underlying disease, and whether atrial fibrosis leads to ischemic stroke is unclear, since the nature of the relationship between atrial fibrosis, AF, and stroke has not been fully elucidated [64].

Nevertheless, there is growing evidence of the association between left atrial fibrosis (as detected in cardiac magnetic resonance imaging) and stroke in patients with AF, and that in this group of patients, atrial fibrosis is a predictor of cerebrovascular events [50,51] or atrial thrombosis [52]. In particular, a greater amount or severity of left atrial fibrosis correlates with an increased risk of stroke or thrombus [50–52]. Compared to patients with ischemic stroke from other causes, patients with cryptogenic stroke were found to have a higher percentage of left atrial fibrosis similar to that found in patients with cardioembolic stroke [53]. Recent studies have found that even in the absence of AF, patients with ESUS had high atrial fibrosis, supporting the notion that atrial substrate changes may precede the development of AF and atrial fibrosis may be associated with cardioembolism independently of the presence of AF [54,55]. In patient-derived simulated models for the evaluation of the arrhythmogenic potential of fibrotic substrate in post-stroke-ESUS patients and in pre-ablation AF patients, similar fibrosis levels were found in inducible ESUS models as in AF models suggesting similar substrate properties in the two groups of patients [56]. Changes in atrial wall including atrial fibrosis, which may precede the clinical identification of AF and be linked to ischemic stroke are collectively described as atrial cardiopathy [65,66]. Its clinical correlation and the effect of oral anticoagulation in these patients are currently being investigated in the AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke (ARCADIA) randomized trial [67].

2.2. Abnormal blood flow

Abnormal blood flow or abnormal blood stasis in the left atrium promotes an environment for thrombogenesis (Table 1) [68–81]. Left atrial enlargement, which may represent the burden of atrial wall changes in patients with AF, is a common finding in patients with prolonged AF and promotes blood stasis [82,83]. Reduced left atrial appendage flow suggests aberrant blood stasis and may be associated with an increased risk of thrombus formation and subsequent thromboembolism [68]. Several studies suggested that left atrial enlargement may be associated with an increased risk of stroke [69,70] and may serve as a potential marker of recurrent cardioembolic or cryptogenic stroke in ischemic stroke patients [71].

Abnormal blood stasis may be reflected and visualized in the form of spontaneous echo contrast (SEC), an active smoke-like signal seen in the left atrium on transesophageal echocardiogram [72]. The identification of SEC and increased density of SEC have been associated with increased risk of thromboembolic events and stroke in patients with AF [68,72,73,75,84]. SEC may be predictive of subsequent stroke and poor long-term outcome following stroke [85] [76]. The identification of both SEC and left atrial enlargement has been associated with death from stroke [86]. SEC has been associated with left atrial thrombus as an important risk factor in suspected cardioembolic stroke that is independent of AF [77].

2.3. Platelet and coagulation abnormalities

The third limb of Virchow's triad, abnormal blood constituents, specifically proteins involved in the coagulation cascade and platelet aggregation, is well supported in AF (Table 2) [48,49,87–129]. However, no single plasma marker has been shown to reliably predict stroke in AF. In AF, enhanced platelet activation, by a prevalent increase of β-thromboglobulin, platelet fragment 4, P-selectin, and platelet microparticles, is well described [87,130,131]. However, the importance and clinical correlation of these factors in patients with AF and ischemic stroke is unclear [87–90,126].

Mean platelet volume (MPV) has been associated with increased platelet reactivity and aggregation in patients with myocardial infarction [132] and those with previous ischemic stroke or transient ischemic attack (TIA) [133]. Among patients with AF, several studies suggest that higher levels of MPV significantly increased risk of ischemic stroke [91–96]. Similarly, platelet distribution width (PDW) was associated with an increased risk of stroke in patients with AF [134]. Although these studies suggest that MPV and PDW may serve as potential new and cost-effective biomarkers for prediction of stroke risk in AF patients [93,97], their validity and clinical relevance remains unclear.

Several studies suggested a potential association of von Willebrand factor (vWF) and D-dimer among patients with AF and ischemic stroke [90,98–102]. Among AF patients, vWF increase was associated with higher risk of ischemic stroke and adverse cardiovascular events [48,49,103–111,135,136], while both D-dimer and vWF have been associated with ischemic stroke severity and prognosis [104,112]. Still, the evidence related to the clinical significance of D-dimer levels in patients with AF is conflicting [106,113–121]. Other coagulation markers such as fibrinogen [98], thrombin-antithrombin complexes [122–124], prothrombin fragments 1 + 2 [99,123,124], plasminogen activator inhibitor-1 [125], and antithrombin III [119] have been associated with higher risk of stroke in AF patients, yet their clinical significance remains unclear.

3. Diagnosis and screening

Atrial fibrillation is a dynamic arrhythmia with a broad spectrum of clinical and electrophysiological findings. Although AF diagnosis is based on surface ECGs [137], the increasing use of several screening modalities, especially among patients with cryptogenic stroke, significantly increased our ability to identify atrial fibrillation during follow-up.

An important proportion of patients with cryptogenic stroke might have undiagnosed asymptomatic AF [37]. It is suggested that stroke patients should undergo at least 24 to 72 hours ECG ambulatory monitoring to identify potential AF episodes [137,138]. In patients with ESUS, a 72 hours Holter monitor is used to further investigate the presence of AF, and although no consensus has been reached regarding prolonged monitoring, several non-invasive or implantable monitors can considerably increase the detection of AF following a stroke [36,139,140]. Indeed, clinical guidelines have issued recommendations for more prolonged monitoring following cryptogenic stroke [137,141], including a Class IIa recommendation from the European Society of Cardiology (ESC) for either longer term ECG monitoring or an insertable cardiac monitor [137]. As it is thought that the proportion of strokes associated with AF may be higher than estimated, by sequentially combining the various methods of cardiac monitoring using a tiered approach, it might be possible to detect new AF in almost one-quarter of patients with stroke or TIA [142].

Although systematic screening of the population for AF is not generally recommended largely due to considerations concerning cost-effectiveness and net-benefit, some guidelines suggest screening in groups at high-risk of stroke or in those aged 75 and over [137,143]. Otherwise, opportunistic screening for AF by pulse check and 12-lead ECG has been recommended for patients aged 65 and over, or those in high-risk groups such as hypertensive patients [137]. With the unfolding of new technologies, new portable and wearable devices, such as patch sensors, smartphones, smartwatches, wristbands, and rings, could develop into useful tools for screening for AF and lead to increased detection of AF [144–146].

3.1. Device-detected and subclinical AF

Modern cardiac implantable electronic devices (CIED), which include dual chamber permanent pacemakers, cardiac resynchronization therapy devices, implantable cardioverter-defibrillators, and implantable loop recorders (ILR), are capable of monitoring and recording atrial tachyarrhythmias. Stored episodes have been found to be well correlated with AF, particularly when they have an atrial rate of more than 250 complexes per minute or a duration exceeding 5 minutes [147]. Such atrial asymptomatic tachyarrhythmias, in patients who have no previous history of clinical or documented AF, are known as atrial high-rate episodes (AHRE), a term often used interchangeably with 'subclinical AF.' Several studies have shown that AHRE are associated with an increased risk of stroke and thromboembolism (Table 3) [148–160], while patients with AHRE are at increased risk of developing clinical AF [148,151,160].

Current data suggest that AHRE increase the risk of stroke or systemic embolism when they last for at least 30 seconds in patients with CIED [161–163]. Among patients with previous cryptogenic stroke who undergo continuous monitoring with ILR, AHRE lasting greater than 2 minutes significantly increased the risk of future stroke or systemic embolism [161,164,165]. However, it is still unclear, especially in primary stroke prevention, whether the potential benefits of OAC will not be outweighed by the risks of bleeding [166,167]. AF burden greater than 5 minutes is associated with an increased risk of both clinical AF and stroke [168]. A high burden of AHRE of 5.5 hours or more, occurring within 30 days of stroke, doubled the risk of thromboembolism compared to a lower burden of AHRE [150]. The risk was found to be highest in the initial period of 10 days after the AHRE and rapidly diminished after longer periods [154,169].

Several studies have found the lack of any temporal relationship between the detected AHRE and stroke, with few patients having AHRE within the month before their stroke or patients were not in AF at the time of the stroke [152,156,170,171], raising the inference that the pathogenesis of stroke and thromboembolism may involve mechanisms other than AF [156]. Rather, AF may represent the marker of other mechanisms or conditions leading to stroke instead of a risk factor for stroke [172,173]. However, the studies were open to several biases including the lack of any adjudication of strokes to cardioembolic or non-cardioembolic strokes [174].

The apparent lack of a temporal association between subclinical AF and stroke adds to the controversy surrounding the burden or length of duration of subclinical AF that would justify commencing anticoagulant therapy [175], until we have the results of a number of randomized controlled trials evaluating the implications. The ESC guidelines [137] suggest that anticoagulant therapy may be considered in selected patients with longer durations of AHRE of at least 24 hours who are at high risk of stroke if a net clinical benefit can be expected [137].

3.2. Prediction of incident AF in cryptogenic stroke

Although various scores have been proposed to predict the onset of new AF, including the Framingham Heart Study score [176] and CHARGE-AF score [177], they have not been widely used in practice. The scores were designed to allow early identification of patients at risk who would benefit from timely targeted intervention and prevention. Similarly, risk scores have been proposed for post-stroke patients, particularly cryptogenic stroke patients. As clinical and radiological methods lack sensitivity for identifying patients suspected of having had a cardioembolic stroke, attempts at devising an algorithm to guide management and investigation, selection of patients for longer-term monitoring, and stroke prevention have been made in a number of observational studies.

These published scores include the STAF [178], LADS [179], NDAF [180], Intermountain AF [181], HAVOC [182], CHA_2DS_2-VASc [183], C_2HEST[184], AS5F [185], CHASE-LESS [186], AF-ESUS [187], Decryptoring [188], Brown ESUS-AF [189], Graz AF Risk [190] and SAFE [191] scores for predicting AF, and iPAB [192] and Fujii [193] scores for predicting paroxysmal AF in

Table 3. Subclinical AF, AHRE, and stroke risk.

First Author (Year) (Ref #)	Study Type	N	Population	Key Findings
Glotzer et al. (2003) [148]	Prospective	312	Patients with DDDR or VVIR PPM for SND in SR, followed-up for median of 27 months	Patients with SND with AHRE detected by pacemakers more than twice as likely to die or have a stroke, and 6 times as likely to develop AF than similar patients without AHRE
Capucci et al. (2005) [149]	Prospective	725	Patients with dual chamber PPM, and a history of symptomatic atrial tachyarrhythmias, followed up for median of 22 months. Permanent AF excluded	In patients with bradycardia and AF, arterial embolism was common in patients with ischemic CM; HTN, DM; and known stroke risk factors. AF longer than 1 day independently associated with embolic events
Botto et al. (2009) [157]	Retrospective	568	Patients with PPM and SND associated with AF (tachycardia-bradycardia variant)	*2.5%* of patients had IS. Risk stratification of patients with recurrent AF can be improved by combining $CHADS_2$ score with AF presence/duration
Glotzer et al. (2009) [150]	Prospective	2486	Patients with PPM and ≥ 1 stroke risk factor, followed up for a mean of 1.4 years. Permanent AF excluded	TE rate low compared with similar traditional AF patients. AT/AF burden >5.5 hours on any of 30 prior days appeared to double TE risk
Daoud et al. (2011) [156]	Prospective	40	TRENDS subgroup of 40 patients with PPM who had CVE/SE for whom 30 days monitoring prior to CVE/SE available. Permanent AF excluded	AT/AF detected *prior* to CVE/SE in 50% of patients. 73% of patients with CVE/SE had no AT/AF burden within 30 days prior to CVE/SE. 70% of patients with AT/AF detected prior to CVE/SE were not in AT/AF at diagnosis of CVE/SE
Healey et al. (2012) [151]	Prospective	2580	Patients with PPM, with HTN and no history of AF, followed up for mean of 2.5 years	Subclinical atrial tachyarrhythmias, without clinical AF, occurred frequently (10.1% by 3 months) in patients with PPM and were associated with 2.5-fold increased risk of IS or SE, and of clinical AF
Shanmugam et al. (2012) [152]	Prospective	560	HF patients with CRT devices in SR (178 with prior history of AF) followed up over median of 370 days	In high-risk cohort of HF patients, device-detected atrial arrhythmias associated with higher incidence of TE events. Patients with AHRE >3.8 hours over 24 hours were 9 times more likely to develop TE complications compared with patients without detected AHRE. 73% of patients did not show a temporal relationship between the detected atrial episode and adverse event (with mean interval 46.7 +/- 71.9 days (range 0–194) before the TE complication)
Boriani et al. (2014) [153]	Prospective	10,016	Patients with CIED without permanent AF	43% had >1 day with >5 min of AF burden. Device-detected AF burden associated with increased risk of IS in relatively unselected population of CIED patients
Brambatti et al. (2014) [170]	Prospective	2580	Patients with PPM, with HTN and no history of AF, followed up for mean of 2.5 years	8% had SCAF detected within 30 days before IS or SE. Although SCAF associated with increased risk of IS and SE, very few patients had SCAF in month before their event
Martin et al. (2015) [167]	Randomized trial	2718	Patients with ICD or CRT-D devices, $CHADS_2$ > 1, randomized to start and stop OAC based on remote monitoring vs usual care	Trial stopped after 2 years median follow-up. In patients with implanted defibrillators, strategy of early initiation and interruption of anticoagulation based on remotely detected AT did not prevent TE and bleeding
Turakhia et al. (2015) [154]	Case-Crossover	9850	187 patients with acute IS and CIED, and no prior AF. 19 OAC at baseline	Little or no AF in vast majority. AF burden >5.5 hours raised short-term risk of stroke 4- to 5-fold, with risk highest in initial 5 to 10 days after AF episode and rapidly diminished after longer periods.
Witt et al. (2015) [155]	Observational	394	Patients with CRT and no AF, followed up over median of 4.6 years	20% had early detected AHRE. In patients without AF, early detected AHRE after CRT implantation associated with significantly increased risk of clinical AF and TE events, particularly where AHRE longer than 24 hours. Risk of mortality not higher with early detected AHRE (but not significant). Only 37% of TE events associated with AHRE within 2 months before TE event.
Kawakami et al. (2017) [158]	Retrospective	343	Patients with PPM followed up over median of 48 months	Association of AHRE detected by PPM with IS/SE in Japanese population observed only in the high TE risk group
Sandgren et al. (2018) [159]	Retrospective	678	Patients with dual chamber PPM for SND or AV block/BBB (including 411 without AF and 267 with known AF at implant (62% on OAC))	2.1% annual incidence of stroke in patients with known AF, as compared with 1.9% in patients who developed silent AF during follow-up, and 1.4% in patients without AF. Stroke risk in incident silent AF group may have been decreased due to OAC
Li et al. (2019) [171]	Retrospective	594	CIED patients followed up over mean of 4.2 years	29.5% developed AHRE. 5.5% of patients with AHRE developed TE events. TE risk in CIED patients mainly driven by comorbidity burden, i.e. CHA_2DS_2-VASc score, rather than AHRE. No temporal relationship between AHRE and TE events
Park et al. (2021) [160]	Retrospective	496	Patients with PPM without pre-existing AF followed up over median of 5.2 years	High-burden SCAF (>24 hours in 1 device analysis) closely associated with increased risk of composite adverse outcomes, particularly the progression to clinical AF and IS
Singer et al. (2021) [169]	Case-crossover	466,635	891 patients with CIED and IS identified	Stroke risk most increased in days 1 to 5 following AF episode of >5.5 hours and declined rapidly thereafter. AF >23 hours on a given day associated with clearest increase in stroke risk

AF = atrial fibrillation; AHRE = atrial high rate events or episodes; AT = atrial tachycardia; AV = atrioventricular; BBB = bundle branch block; CM = cardiomyopathy; CIED = cardiac implanted electronic devices; CRT = cardiac resynchronisation therapy; CRT-D = cardiac resynchronisation therapy defibrillator; CVE = cerebrovascular event(s); DM = diabetes mellitus; HF = heart failure; HTN = hypertension; ICD = implantable cardioverter-defibrillator; IS = ischaemic stroke; OAC = oral anticoagulation; PPM = permanent pacemaker; SCAF = subclinical atrial fibrillation; SE = systemic embolism or emboli; SND = sinus node disease; SR = sinus rhythm; TE = thromboembolic or thromboembolism

acute ischemic stroke patients. As the risk scores identified performed variably in their discriminative ability and the utility of these scores to predict newly detected AF in clinical practice remains uncertain [194], none have been generally adopted in current clinical practice.

A tailored approach to patient selection for longer-term cardiac monitoring or comprehensive predictive models that adopt multimodal biomarkers for predicting newly detected AF after cryptogenic stroke may be more discriminating [195]. The markers can range from clinical, ECG, and blood-based biomarkers [195,196] to echocardiographic and brain imaging biomarkers [188–193]. Clinical variables associated with greater likelihood of newly detected AF following cryptogenic stroke include older age, female sex, hypertension, heart failure, ischemic heart disease, diabetes, treatment with statin, being a non-smoker, higher National Institutes of Health Stroke Scale or modified Rankin Scale scores, and IV thrombolysis treatment [195,196].

ECG markers linked with higher likelihood of AF detection include frequent premature atrial contractions, left ventricular hypertrophy, atrioventricular block, as well as more prolonged PR interval, P-wave duration, P-wave dispersion, P-wave index, and QTc interval [195,197,198]. Associated blood biomarkers include NT-proBNP [188,190,192,193,195,199] and high-density lipoproteins [195]. Echocardiographic and radiological biomarkers linked with AF detection after cryptogenic stroke include left atrial enlargement [189–191,193], decreased left atrial strain [188,200], reduced left ventricular ejection fraction [198], prior cortical or cerebellar infarction [37,190], cortical topography [191], intracranial large vessel occlusion [191], and multi-territory brain infarction [190].

AF as the suspected cause of cryptogenic stroke may never be found. However, commencing OAC for stroke thromboprophylaxis for suspected cardioembolic stroke in such cases is not recommended. Two randomized controlled trials, the Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients with Recent Embolic Stroke of Undetermined Source (NAVIGATE ESUS) and the Dabigatran Etexilate for Secondary Stroke Prevention in Patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS), evaluated OAC for the prevention of recurrent stroke following ESUS. In the NAVIGATE ESUS trial, rivaroxaban was found to be non-superior to aspirin for prevention of recurrent stroke after an initial ESUS but was associated with a higher risk of bleeding [201]. The RE-SPECT ESUS trial made similar findings regarding the non-superiority of dabigatran compared to aspirin, though non-major bleeding events but not major bleeding events were greater [202]. The results might be explained by the heterogeneity of the ESUS population involved in the studies where patients were even included who had large artery atherosclerosis resulting in less than 50% occlusion or aortic atherosclerosis [203].

4. Management

4.1. Stroke prevention

4.1.1. Stroke risk stratification

Stroke risk is not homogenous but dependent on various risk factors, which have been incorporated into clinical stroke risk stratification algorithms, all of which have only modest predictive value for identifying patients at high risk of stroke. However, being based on clinical risk scores, they are appealing for their simplicity and convenience for use in daily clinical practice and decision-making. The most commonly adopted stratification scores are $CHADS_2$ and CHA_2DS_2-VASc [204], which have been widely validated [205,206]. Low-risk patients, those having a CHA_2DS_2-VASc score of 0 in men or 1 in women, with a rate of stroke of less than 1% per year do not require any antithrombotic therapy. Any score above that due to the presence of at least one stroke risk factor triggers the requirement to consider OAC with either a VKA or NOAC. Clinical risk scores do not remain static over time but are dynamic and likely to change with additional comorbidities and age.

Prior to commencing OAC, an evaluation of bleeding risk using a validated bleeding risk score such as the HAS-BLED score is recommended with the goal of reducing modifiable bleeding risk factors (such as uncontrolled hypertension, labile INR, excessive use of alcohol, or concomitant drugs predisposing to bleeding). Patients with a high HAS-BLED score will benefit from more frequent review. A high HAS-BLED score by itself is rarely a cause to avoid OAC [207].

As more predictors of stroke risk become known, they may be reflected in risk stratification schemes to make scores more discriminating. For example, echocardiographic markers (such as spontaneous echo contrast on transesophageal echocardiography and left ventricular systolic dysfunction on transthoracic echocardiography) and blood biomarkers may be relevant, as well as electrocardiographic markers of atrial cardiomyopathy such as abnormal p-wave axis [208,209]. Potential new markers of stroke risk are being recognized with time. White matter changes and chronic intracranial arterial calcification are being recognized as risk factors for stroke [210,211]. Mitral annular calcification was found to be an independent predictor of cardioembolic stroke in elderly patients with AF [212].

4.1.2. Appropriate antithrombotic therapy

The cornerstone of management of AF is stroke prevention. In patients with AF, the use of OAC, such as a VKA like warfarin or a NOAC, is recommended, reducing the risk of stroke by approximately 60% and lowers all-cause mortality [213]. Multicenter Phase III randomized controlled trials (RCTs) have confirmed that NOACs are as efficacious as warfarin, providing a safety profile for patients with AF [22–25]. In these trials, individual NOACs provided comparable results in terms of efficacy and safety compared to warfarin. Despite the signs of potential superiority of one NOAC compared to others in relation to their effectiveness and safety [214] including in AF patients with chronic kidney disease [215], the lack of head-to-head comparison in RCTs and the diverse patients' characteristics in RCTs and observational studies do not allow for safe conclusions.

Nevertheless, the risk of bleeding remains an impediment to the use of and adherence to OAC. There exists developing evidence that activated coagulation factor XI (factor XIa) may provide a target for a next-generation NOAC with advantages over conventional factor X inhibitors in terms of lower risk of major bleeding. A recent randomized Phase II dose-finding

study of asundexian, a direct inhibitor of factor XIa, observed significantly lower rates of bleeding with asundexian compared to apixaban in patients with AF [216]. The trial paves the way for larger studies exploring the efficacy, safety, and incidence of major bleeding events in factor XIa inhibition in patients with AF at risk of stroke.

Even in the presence of stable coronary artery disease, OAC monotherapy is effective in preventing both stroke or systemic embolism and new coronary artery events. Recently, rivaroxaban monotherapy was found to be noninferior to a combination of rivaroxaban and antiplatelet treatment in patients with AF and stable coronary artery disease, for the composite outcome of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause (HR: 0.72; 95% CI, 0.55 to 0.95; $P < 0.001$ for noninferiority), while it was associated with a significantly lower risk of major bleeding (HR: 0.59, 95% CI, 0.39 to 0.89; $P = 0.01$ for superiority) [217]. This was also confirmed in meta-analysis including both randomized and observational studies, where OAC monotherapy was as effective as OAC combined with antiplatelet, but significantly associated with a reduced risk of bleeding [218]. The position is less clear where other stable vascular diseases (such as carotid artery or peripheral artery disease) co-exist with AF. Although It is thought that OAC monotherapy should suffice, actual practice may differ between clinicians [219].

Although anticoagulation treatment and stroke prevention in AF might be straightforward, in the acute and early post-stroke phase, the decision to start anticoagulation may vary. In the early post-stroke period, especially in patients with AF, the risk of a recurrent event is significantly high [220]. Despite this increased risk of recurrent event, anticoagulation in the acute and early phase of ischemic stroke is contraindicated, especially in patients with large ischemic strokes due to the risk of hemorrhagic transformation. Hence, the optimal time in which the risk of recurrent stroke outweighs the bleeding risk and subsequently when to start anticoagulation in these patients is still not clear. This might be answered by several RCTs, comparing the early to late initiation of NOACs in patients with AF-related ischemic strokes [221–224]. One of the RCTs has published its results. In the Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial (TIMING), a study involving 888 patients with AF, early initiation of NOAC at 4 days or less from onset of acute ischemic stroke was noninferior to delayed start at between 5 and 10 days from stroke onset [225]. In TIMING, no patient suffered a symptomatic intracerebral hemorrhage in either the early or delayed groups and the early group had a numerically lower rate of recurrent stroke and death. While waiting for the results of all the RCTs, there are also observational cohort data suggesting that the relative risk of recurrent stroke and symptomatic intracerebral hemorrhage may be highest in the first 2 days after a stroke before attenuating to become constant over time. Thus, early introduction of OAC 2–3 days after a stroke was associated with considerably fewer recurrent stroke events over the ensuing weeks without excess risk of symptomatic intracerebral hemorrhage [226].

The European Heart Rhythm Association of the European Society of Cardiology (EHRA-ESC) introduced the '1–3–6–12 days rule' in 2013, depending on the neurologic deficit of the stroke patient [227]. Nevertheless, in view of the lack of solid evidence on the time of OAC initiation, current guidelines suggest that OAC should be initiated or re-initiated as soon as possible, usually within the first 2 weeks following an acute stroke [137].

Although NOACs have predictable pharmacokinetic properties with rapid onset and need for dose adjustment in special populations such as patients with chronic kidney disease, the elderly, and those with low bodyweight that need to be considered to optimize their benefit-risk profile, the pharmacokinetic modeling of NOACs has rarely been studied in a post-stroke population in contrast to the data gathered from healthy subjects [228–232]. In the earlier Phase III RCTs comparing individual NOACs with warfarin, as patients who had experienced a stroke within days of randomization were excluded from those studies, the efficacy and safety of NOACs in acute stroke patients who may commonly be older, or have renal impairment associated with the effects of acute ischemic stroke, is unknown [232]. Limited observational data in a small study examined the anticoagulation intensity of rivaroxaban in stroke patients in Japan, the majority of whom were enrolled soon after stroke onset and commenced rivaroxaban within a median of 5 days [232]. The ongoing RCTs comparing the early to late initiation of NOACs after acute ischemic stroke in AF patients may shed light on the pharmacokinetic implications and efficacy and safety of individual NOACs and dosing regimens in an acute ischemic stroke setting.

Notwithstanding OAC therapy, there remains a residual risk of treatment failure. Observational data suggests that patients with AF who suffer a stroke while on treatment with OAC are at high risk of recurrent ischemic stroke. Furthermore, changing the type of OAC by switching between VKA and NOAC or from one NOAC to another was not associated with a decreased risk of recurrent ischemic events. Thus, the optimal approach to secondary prevention to reduce the risk of further recurrent events in this high-risk group of patients remains uncertain [233–235]. Although there may be a benefit from alternative strategies, such as left atrial appendage occlusion, there is currently limited evidence on the benefits. However, The Left Atrial Appendage Occlusion Versus Novel Oral Anticoagulation for Stroke Prevention in Atrial Fibrillation Multicenter Randomised Clinical Trial (Occlusion-AF), currently recruiting, will compare left atrial appendage occlusion to NOAC treatment for secondary stroke prevention in patients with AF and a recent stroke or TIA at high risk of recurrent thromboembolic events [236].

4.1.3. Left atrial appendage occlusion

In patients who are unable to tolerate OAC, left atrial appendage occlusion (LAAO) may be a potential alternative treatment modality in patients with AF, especially after an ischemic stroke. Patients who do not have a contraindication to short-

term antithrombotic use may be suitable. The WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation (PROTECT AF) and the Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients with Atrial Fibrillation (AF) Versus Long Term Warfarin Therapy (PREVAIL) trials showed that LAAO was non-inferior to warfarin in stroke prevention in patients with AF [237,238]. In the more recent Interventional Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in High-risk Patients With Atrial Fibrillation (PRAGUE-17) trial, LAAO using an Amulet or Watchman device was noninferior to NOAC in preventing major cardiovascular, neurological, and bleeding events related to AF in high-risk patients [239].

During the period of endothelialization following implantation of an LAAO device, antithrombotic therapy is essential for reducing the risk of thromboembolism. The optimal post-procedural antithrombotic regime, however, is unclear, and clinical practice has tended to vary, with registries indicating majority use of dual antiplatelet therapy (DAPT) in Europe, and OAC plus antiplatelet in contemporary U.S. practice [240,241]. However, recent studies suggest that OAC monotherapy may potentially be considered as an alternative post-procedural antithrombotic strategy. A randomized pilot study found reduced thrombin generation following LAAO in patients treated with reduced-dose rivaroxaban rather than DAPT [242]. In a meta-analysis, including mainly single-arm studies, OAC had a better efficacy and safety profile than antiplatelet therapy favoring OAC over DAPT as anti-thrombotic therapy following LAAO [243]. In a recent study, post-procedural OAC without concomitant aspirin was associated with lower risk of adverse outcomes [241].

4.2. Rhythm control

Rhythm control may be achieved through pharmacological and non-pharmacological means. Antiarrhythmic drugs are commonly used for restoration and maintenance of sinus rhythm. Catheter ablation is an alternative to medical therapy for rhythm control in AF. Catheter ablation of AF is usually performed through the standard approach of pulmonary vein isolation. The two most frequently used techniques for pulmonary vein isolation are radiofrequency ablation and cryoablation [244]. Radiofrequency ablation is the most common method and involves the application of a radiofrequency current to heat tissue and achieve cellular necrosis. Cryoablation entails the application of cryogenic energy with a balloon to induce tissue necrosis by freezing.

Guidelines have historically recommended rhythm control for improvement of symptoms and quality of life in symptomatic patients with AF [137]. Until recently, rate control was thought to be equivalent to rhythm control. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial demonstrated that rhythm control (using an antiarrhythmic drug and, if necessary, cardioversion) offered no survival benefit over rate-control [245]. Similarly, the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial demonstrated that rate control is not inferior to rhythm control for preventing cardiovascular death and morbidity in patients with recurrent persistent AF after cardioversion [246].

However, the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) RCT showed that, among 2789 patients with early AF diagnosed within 12 months who were randomized to either early rhythm control or usual care, a rhythm control strategy was associated with a lower risk of stroke, hospitalization for heart failure, and cardiovascular death [247]. Following the landmark EAST-AFNET 4 trial, clinical practice now tends to favor adopting an early rhythm control strategy including ablation therapy early in the diagnosis of AF. Nevertheless, an ancillary analysis from the ESC-European Heart Rhythm Association (EHRA) EURObservational Research Programme (EORP) AF (ESC-EHRA EORP-AF) General Long-Term Registry, conducted to evaluate real-world applicability and impact of the EAST-AFNET 4 study, showed a lower rate of major adverse events, but no significant difference in the primary outcome of cardiovascular death, stroke, acute coronary syndrome, and worsening of heart failure [248]. Although cardioversion seems beneficial in patients with AF, whether patients with paroxysmal AF detected after stroke benefit from cardioversion is still not clear. An observational study showed that sinus rhythm restoration, either with the use of antiarrhythmic medication or in patients with self-terminated paroxysmal AF, was associated with a 36% reduction of overall mortality and led to reduction in both stroke recurrence and MACE by 46% [249]. Similarly, the Risk and Benefits of Urgent Rhythm Control of Atrial Fibrillation in Patients With Acute Stroke (RAFAS) randomized trial recently showed that post-stroke early rhythm control significantly reduced recurrent events within 1 year [250]. These findings suggest that even in the early post-stroke phase, cardioversion and sinus rhythm restoration may benefit future cardiovascular outcomes.

When comparing pharmacological antiarrhythmic therapy with ablative therapy for rhythm control, no clear difference in reduction of stroke risk has been demonstrated. Although several observational studies found that catheter ablation reduces the risk of stroke compared to antiarrhythmic drug therapy in high-risk patients, no difference in stroke risk has been observed in randomized trials [251]. The recent Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA) showed that compared to antiarrhythmic drug therapy, catheter ablation did not significantly lower the primary composite end point of disabling stroke, death, bleeding, or cardiac arrest [252]. Only randomized controlled trials have demonstrated mortality benefit from catheter ablation in patients with heart failure with left ventricular systolic dysfunction [251].

Until recently, catheter ablation has been recommended for rhythm control after failed antiarrhythmic drug therapy. However, recent evidence from the randomized trials Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF), Catheter Cryoablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation (Cryo-FIRST), and STOP AF First: Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation

(STOP AF First) demonstrates that ablation is superior to antiarrhythmic drug therapy for reducing recurrence of AF [253–255]. Similarly, the Atrial Fibrillation Progression Trial (ATTEST) suggests radiofrequency ablation is superior to antiarrhythmic drugs for delaying the progression of paroxysmal AF to persistent AF [256].

4.3. Integrated care in AF and in stroke: Atrial fibrillation Better Care (ABC) pathway

Although stroke is relatively infrequent in anticoagulated patients, even in large and well-conducted anticoagulation RCTs, the annual rate of ischemic stroke in AF patients despite OAC was 1–2% [257–261], while observational studies suggest that this might be higher reaching 5% [262,263]. Also, mortality associated with AF doubled between 1990 and 2010 [264]. Due to its multifactorial background and the coexistence of several cardiovascular risk factors in patients with AF, a more holistic or integrated care approach in AF management has been promoted in recent years [265–267].

The Atrial fibrillation Better Care (ABC) holistic pathway (the ABC pathway) is an example of such approach and is increasingly recommended by International guidelines [137,265,268–270]. The three pillars of the ABC pathway are 'A' – Anticoagulation/Avoid stroke, 'B' – Better symptom control (with patient centered, symptom directed decisions on rate or rhythm control), and 'C' – Cardiovascular risk factors and Comorbidities management, including lifestyle changes. It has consistently been shown that the ABC pathway is associated with improved clinical outcomes and a significant reduction in adverse outcomes [271–277].

In accordance with this notion, a recent position paper of the European Society of Cardiology Council of Stroke proposed an integrated care approach for optimization of 'general' stroke management and associated cardiovascular disease in the form of a post-stroke ABC pathway [219]. Along the lines of the AF ABC pathway, the post-stroke ABC pathway includes three pillars of care: 'A' – Appropriate Antithrombotic therapy, 'B' – Better functional and psychological status, and 'C' – Cardiovascular risk factors and Comorbidity optimization (including lifestyle changes) [219]. In the context of AF, NOACs are preferred over VKAs due to their favorable safety profile, while patients should undergo a multidisciplinary evaluation to recognize post-stroke depression and dementia, together with the optimization of cardiovascular comorbidities and risk factors [219].

5. Expert opinion

More research is needed into the paradigm of interaction between AF, thrombogenesis and stroke, and the pathways that lead to abnormal development of the atrial substrate that favors the generation of arrhythmia. The hope is that the knowledge gained will help to identify novel markers of stroke risk for refining current models of risk stratification and new molecular targets for treatment and stroke prevention. The renin-angiotensin-aldosterone system may play an important role in the development of atrial fibrosis, as has already been shown in experimental canine models, where angiotensin-converting enzyme inhibition suppressed atrial fibrosis [278,279], while sacubitril/valsartan was associated with reduction in atrial fibrosis in mice [280]. Recently, the new coronavirus 2019 pandemic brought up the importance of angiotensin-converting enzyme 2 (ACE 2), which, apart from serving as the virus' functional cell receptor [281], among others, may provide important information on pathophysiology of several cardiovascular diseases including AF and atrial fibrosis [282]. These data may provide further knowledge on the evaluation and treatment of patients with AF or atrial fibrosis [283–285].

Accumulating evidence and the expanding research interest associated with the use of artificial intelligence (AI) and machine learning (ML) may provide future perspectives for risk stratification and stroke prevention in patients with AF. As multimorbidity risk factors and AF predispose to stroke in a dynamic way, AI technics may help in the optimization of the preventive and treating pathways. Research continues to take advantage of AI and ML techniques for identifying and recognizing imaging and electrocardiographic markers of stroke risk. In silico models are proving highly useful to simulate computational models to predict outcomes, providing a way to examine the effect of several interventions based on artificial models. For example, to assess the pathophysiological link between atrial fibrillation and stroke, potential pro-arrhythmic substrate properties of fibrosis have been assessed through patient- and magnetic resonance imaging-derived inducible in silico models to computationally predict the presence of triggers, and re-entrant drivers, needed for perpetuation of AF [56].

Although many cases of cryptogenic stroke are suspected to be caused by AF, these patients will never get the chance to reduce their further thromboembolic risk if they will not undergo an extensive search for AF. More research is much needed in this area, along with more refined RCT evidence for the efficacy of NOACs in stroke prevention in ESUS. In the meantime, advancements in information technology and the increasing use of smartwear and smartphones by the general public will provide more opportunities for detecting arrhythmias. As demonstrated in the Apple Heart Study (Assessment of Wristwatch-Based Photoplethysmography (PPG) to Identify Cardiac Arrhythmias) [145], the Mobile Health Technology for Atrial Fibrillation Screening Using Photoplethysmography-Based Smart Devices (The HUAWEI Heart Study) [144] and the Fitbit Heart Study (Detection of Atrial Fibrillation in a Large Population Using Wearable Devices) [146], continuous monitoring with PPG-based smartwear could be feasible for screening and early detection of AF in large populations. In the Apple Heart Study, notifications of an irregular pulse had an 84% positive predictive value for concurrent AF, while in the HUAWEI Heart Study, 91.6% of PPG-positive signals were confirmed as AF. In the Fitbit Heart Study, the PPG software algorithm for Fitbit devices resulted in a positive predictive value of 98.2%.

As mortality associated with AF remains high and there is still a five-fold increased risk of having a stroke in patients with AF, a holistic integrated care approach to managing AF and stroke prevention will continue to be essential, with greater development of multidisciplinary inputs. Care may involve

more sophisticated and structured lifestyle programs such as weight reduction, diet, and physical exercise programs to address the pro-arrhythmic consequences of obesity. More integrated involvement of sleep disorder units and specialists in treatment of conditions like obstructive sleep apnea will be important. With the advent of more sophisticated smart technology, mobile health apps are likely to feature, which will help enhance patients' knowledge of their own conditions, and encourage greater involvement in their clinical care[286]. Nevertheless, there is a recognition that OAC therapy is still underused in practice in the contemporary high-risk population of stroke survivors with AF, especially individuals of older age or those affected by socioeconomic deprivation. Thus, there is a need to identify barriers to OAC and develop strategies to improve prescription of OAC treatment [287].

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