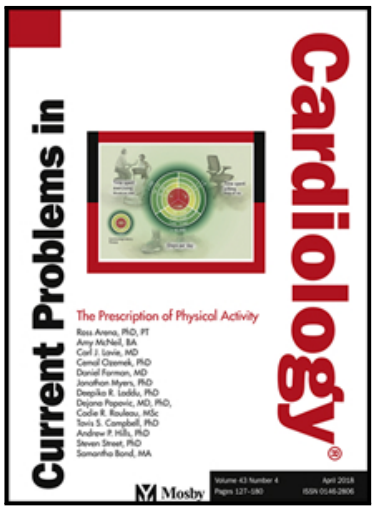

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Atrial Fibrillation and Stroke:

State-of-the-art and future directions

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Introduction

Stroke is a major complication of atrial fibrillation (AF). About 25% of ischaemic stroke are cardio-embolic in origin; AF is the most common cause of those[1]. Nonvalvular AF carries a 5-fold increased risk of stroke[2], while AF related to mitral stenosis increases the risk of stroke by 20-fold[3]. The attributable risk of stroke for AF increases with age unlike other factors such as hypertension for instance[4].

When the AF is asymptomatic but detected on a cardiac implantable electronic device (CIED) or a wearable monitor, it is described as being subclinical. It is suspected that subclinical AF might be the cause of cryptogenic strokes (i.e., strokes of unknown aetiology)[5]. While previous studies showed that atrial high-rate events (AHREs) detected on a CIED were associated with increased risk of stroke[5,6], treating such episodes with anticoagulation has not been shown to reduce the risk of stroke. In fact, anticoagulation in these cases resulted in higher incidence of a composite of death or major bleeding, mainly driven by the increased risk of bleeding[7].

Not only that AF can cause stroke and vice versa[8], but stroke patients with AF were shown have higher stroke severity and mortality compared to those without[9]. The effect of AF on mortality rate was primarily driven by stroke severity[9]. The worse clinical and imaging outcome in AF-related strokes was attributed to bigger volumes of more severely hypo-perfused tissues, resulting in larger infarct size and higher risk of haemorrhagic transformation[10].

In this narrative review article, we provided an overview of the burden of AF and stroke, the complex interplay between the two conditions, as well as the treatment and secondary prevention of stroke in patients with AF. We comprehensively discussed the current evidence and the ongoing conundrums, and highlighted the future directions on the topic.

Epidemiology

Atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia[11,12], and one of the most common cardiovascular conditions in men and women[12]. Its prevalence (1–2% of the total population) continues to increase with advancing age, reaching around 10% in those above 75 years of age[12]. It remains a major cause of morbidity and mortality, with an estimated five million incident cases globally[13]. Approximately eighteen million of people in Europe are estimated to have AF by 2060[11].The condition is therefore considered an epidemic[14,15] and a major public health challenge.

There are interracial differences in the incidence and prevalence of AF[3,16–18]; with higher rates seen in European descendance individuals compared to Asians and those of African descendance (despite the higher burden of comorbidities seen in the latter)[3,17]. These observations were also recorded in the Analysis of the Atherosclerosis Risk in Communities (ARIC)[18] study where African-Americans had a 41% lower adjusted risk of developing AF compared to whites. Factors such as limited access to health care with resultant lower AF detection rates, more frequent paroxysmal AF, and evidence of smaller left atrium size in

African-Americans were suggested as an explanation for their lower incidence of AF compared to similar age adjusted white population[17]. Genetic predisposition was another hypothesis put to explain the interracial differences. In a meta-analysis by Marcus et al. [19], the cohort of whites and African-Americans in the Cardiovascular Health Study (CHS)[20] and ARIC Study[18] were reviewed, and the percentage European ancestry in African-Americans was calculated with 1747 ancestry informative markers from the Illumina custom ITMAT-Broad-CARe array. The meta-analysis found that for every 10% increase in European ancestry, the risk of AF increased by 13%[19]. This trend persisted even after correction for potential confounders, indicating a clear role of genetic variants in development of AF. A difference in mortality between ethnic groups might account for some of the discrepancy in AF prevalence between them: both all-cause and cardiovascular disease mortality are higher among African-Americans compared to whites, leaving a disproportionate smaller African-American population surviving to be at risk of developing AF[18].

In the Framingham Heart Study population, the lifetime risk of developing AF was estimated to be 1 in 4 for men and women at an index age of 40 years or older[21]. The lifetime risk for developing AF remained high at 1 in 6 even in the absence of prior or concurrent known history of myocardial infarction or congestive heart failure[21]. In 2017, the estimated number of individuals with AF/flutter globally was 19.8 million men (95% uncertainty interval (UI) 17.2-22.4 million) and 17.8 million women (95% UI 15.3-20.2 million)[22].

The Global Burden of Disease (GBD) report confirmed the increasing prevalence of AF over the years. By 2019, the prevalence of AF and atrial flutter appears to have increased by more than double (+120.7%) since 1990 with the larger growth registered in middle-income

countries (+146.6% in lower-middle- and +145.2% in upper-middle-income countries)[23]. The absolute global prevalence of AF/ atrial flutter reached nearly 60 million of cases in 2019 compared to about 28 million of cases in 1990[23]. A few factors have been suggested to explain this trend; including an increased incidence of hypertension particularly in low-, lower-middle-, and upper-middle-income countries, as well as increased incidence of obesity in all income groups[15,23]. Another theory is improved management strategies for cardiovascular conditions closely related to AF, such as heart failure and ischaemic heart disease, resulting in surviving aging population at high risk of developing AF[15]. Improving AF diagnosis and detection rates is another contributing factor[15,24].

The financial burden of AF on public health is considerable. The cost of AF to health and social services, including that of outpatient and general practitioner consultations, hospitalization and drug treatment (including the cost of anticoagulation treatment and monitoring) was first evaluated in the UK in 1995[25]. In 2000, Stewart et al. used contemporary and extrapolated data[25] and estimated that the direct cost of AF during 2000 (excluding nursing home costs and admissions with a secondary AF coding) was £459 million, 0.88% of total National Health Service (NHS) expenditure[25].This figure does not consider related conditions such as aspirin or warfarin related brain haemorrhage, stroke rehabilitation, or digoxin toxicity[25]. It has been predicted that between 0.9% and 1.6% of NHS expenditure in 2020 was on AF, mostly from primary admissions. The predicted direct cost spent in the NHS on AF is £1,435 m-£2,548 m (depending on AF prevalence). The total direct costs of AF are expected to increase to 1– 4% of NHS expenditure over the next two decades[26].

Alongside increasing age, a few chronic conditions have been linked to the development and increased risk of AF including the following: hypertension, diabetes, heart failure, ischaemic heart disease, valvular disease, hyperthyroidism, obesity, alcohol consumption, chronic kidney disease and lung diseases[3,17,27].

Stroke

Three main pathological domains fall under the umbrella term "Stroke", and these are: ischaemic strokes (87%), intracerebral haemorrhage (ICH) (10%), and subarachnoid haemorrhage (SAH) (3%)[28][29].

Stroke is the most common neurological disease[30] and the second most common cause of death globally[28,30]. It has a lifetime risk of at least 1in 6[30]. It is a major cause of disability, and accounted for about 116 million global disability adjusted life-years (DALYs) lost in 2016(40). In 2016, the global stroke prevalence was 80.1 million (95% confidence interval [CI] 74.1–86.3), with higher female prevalence (41.1 million (38.0–44.3)) compared to male[29]. In the same year, the number of incident new strokes raised to 13.7 million (95% CI 12.7–14.7); 87% of these were ischaemic strokes(40). In 2017, stroke prevalence increased by 19.3%, incidence by 5.3%, disability-adjusted life-years by 2.7%, and mortality by 5.3%(42). It is projected that by 2030, 3.9% of the adult population in the US would have had a stroke and absolute stroke mortality would increase by 50%, translating to 64,000 additional stroke deaths per year compared to 2012(40).

There is also an ethnic variation in the stroke incidence, that is, 1.91 per 1,000 in African-American population vs 0.88 per 1,000 in the white population(40). This racial variation is

also seen in the distribution of ischaemic stroke subtypes: large artery atherosclerosis is the leading cause of ischaemic stroke in the Asian population (33%), while cardio-embolism is the leading cause in the white population (28%)(40).

Variation in availability of resources worldwide also bears an effect on the stroke burden and outcomes, for example, the stroke case-fatality rate at 30 days ranged from about 10% in Dijon, France (2000-2004) to as high as 42% in Kolkata, India (2003-2010)(40). In addition, the age at first stroke tends to be lower in low- and middle-income countries, resulting in the relatively higher proportion of strokes and the higher burden of DALYs lost in the developing world.(40).

Ischaemic stroke subtypes

Multiple studies have looked into classifying strokes. Subtyping strokes is useful for clinical, epidemiological and genetic studies, and can serve classifying patients for therapeutic decision-making in daily practice[32]. In addition, stroke outcomes, including recurrent stroke, and strategies for secondary stroke prevention differ by stroke subtype(44).

The Harvard Cooperative Stroke Registry[34] was formed in 1972. The initial report from the prospective registry was published in 1978 and included 694 patients. Among those, 233 patients were given a diagnosis of thrombosis of a large artery, 131 were diagnosed with lacunes, 215 with embolism, 70 with intracranial hematoma, and 45 with aneurysm-arteriovenous malformation. However, only a small percentage of those patients had angiography or computed tomography (CT) (106 patients of those diagnosed with embolic stroke had angiography and only 49 of them had CT)[34].

In 1989, a classification of stroke according to causal mechanisms, the Stroke Data Bank [35], was developed. While strokes due to haemorrhage included parenchymal haemorrhage and subarachnoid haemorrhage, strokes due to infarction included: large-artery atherosclerosis, lacune, cardio-embolic, infarction with tandem arterial pathology, and infarction of undetermined cause or infarction with a normal angiogram[35]. A CT scan was documented in 98% of patients with infarction and angiography was performed in 27%. The strict diagnostic scheme used helped identifying stroke subtypes that would have otherwise been classified as infarcts of undetermined cause (IUC). Nevertheless, 28.1% of total strokes (39.9% of infarcts) in the study were still classified as IUC[35].

The Trial of Org 10172 in Acute Stroke Treatment, (TOAST) system[36] was proposed in 1993, classifying ischaemic strokes into large-artery atherosclerosis, cardio-embolism, small-vessel occlusion (lacunes), stroke of other determined aetiology (such as non-atherosclerotic vasculopathies, hypercoagulable states, or haematological disorders), and stroke of undetermined aetiology (which also includes patients with two or more potential causes of stroke). Besides the use of clinical features and brain imaging (CT or magnetic resonance imaging [MRI]), arteriography, cardiac imaging (such as echocardiography), duplex imaging of extracranial arteries, and laboratory assessments for a pro-thrombotic state were also used to reach a diagnosis. Without supportive findings on diagnostic testing, a diagnosis of a specific subtype of stroke could not be made based on suggestive historical and physical features. Such strict rules increased the specificity of the system reducing the likelihood of misclassification at the expense of decreased sensitivity and increased number of strokes classified as strokes of undetermined aetiology[36].

In 2005, the Stop Stroke Study TOAST (SSS-TOAST) system[33] was designed based on the original TOAST algorithm. Each causative category within the TOAST system was subdivided based on the weight of evidence as "evident, (when one stroke mechanism adhering to a single causative category was identified)," "probable, (when more than one "evident" stroke mechanisms were identified, but one mechanism seemed more probable than the other based on certain characteristics)," or "possible (when no evident cause has been identified)." The main 5 mechanisms of ischaemic stroke according to this algorithm include: large artery atherosclerosis, cardio-aortic embolism, small artery disease, other causes, or undetermined causes. Under the category of undetermined causes two subtypes were identified: cryptogenic strokes (where no "evident" or "possible" criteria for the other causes have been identified) or unclassified (when there is more than one evident mechanism but with probable evidence for each or with no probable evidence to be able to establish a single cause). This classification improved the interobserver reliability (kappa (κ) value) of the original TOAST from 0.78 to 0.90, and reduced the number of patients originally assigned to the "undetermined-unclassified" class by the original TOAST system from 38–40% to 4%[33]. The computerised automated version of the SSS-TOAST system was released in 2007 and is known as the Causative Classification System (CCS)[37].

Both TOAST and CCS limited large artery disease to patients with carotid stenosis and did not consider high plaque burden (measured by total plaque area)[38]. Total plaque area is known to be a stronger predictor of poor outcomes (including stroke, MI and death) than stenosis measured by Doppler velocities[39]. The combined 5-year risk of stroke, MI, and vascular death was 19.5% when the carotid plaque area was 1.19 to 6.73 cm^2(51). Published in 2014, Bogiatzi et al. developed the Subtypes of Ischaemic Stroke Classification System (SPARKLE) as an adaptation of the SSS-TOAST that included total plaque area

measurements in the definition of large artery atherosclerosis[38]. This reduced the number of strokes previously classified as of an undetermined aetiology allowing for more specific treatment of underlying causes. Eighteen patients with large artery disease in SPARKLE were classified as undetermined in SSS-TOAST and TOAST (**Figure 1**)[38]. Also, 131 cases with either multiple causes of stroke/TIA or high total plaque area without carotid stenosis and otherwise large artery disease in SPARKLE were classified under the undetermined category in TOAST. This classification showed a substantial inter-rater reliability ($\kappa = 0.76$) and an excellent rater consistency over time ($\kappa = 0.91$)[38].

Stroke as a cause of AF

Associations between abnormal autonomic innervation and AF have been established(67), and insults to the central nervous system (as in stroke) are believed to play an important role in the pathogenesis of AF(58). In the acute post-stroke period, various forms of electrocardiographic and arrhythmic changes, including AF are detected.

AF is diagnosed in about 7% of patients with acute ischemic stroke within the first 3-5 days post-stroke[42]. The percentage of diagnosed AF increases to 25% with prolonged cardiac monitoring [43]. This has recently been termed AF diagnosed after stroke (AFDAS)[44]. Various studies have previously focused on AF as a previously undetected arrhythmia and failed to appreciate AF as a consequence of stroke. The earlier the appearance of AF post-stroke suggests that it might be a consequence of rather than a cause of stroke [45]. However, less incidence of AF post-haemorrhagic stroke doesn't support this notion. Signs of cardiac involvement are usually lacking in those who develop AF as a result of stroke. One study found that AFDAS was associated with less recurrent stroke (6.6%) compared to those with

previous diagnosis of AF (9.6%)[46]. More recently, a retrospective, registry-based cohort study[47] classified AFDAS into two different categories: ECG-detected AF and AF detected on a prolonged cardiac monitor [PCM-detected AF] (which is usually asymptomatic and of lower burden). The differences in the baseline characteristics between ECG- and PCM-detected AF in this study resembled those found between known AF and AFDAS. Furthermore, ECG-detected AF in this study was associated with 5-fold higher adjusted recurrent ischemic stroke risk compared to PCM-detected AF. This suggests that ECG-detected AF is likely pre-existent but hadn't been diagnosed before the stroke due to the lack of symptoms or the insufficient interaction with the health care system[47].

Several mechanisms have been postulated for the development of AF post-stroke:
There is evidence that development and maintenance of AF is linked to imbalances in cardiac autonomic nervous system (ANS), particularly following acute stroke. A disruption of regulation of heart rate and blood pressure leading to increased cortisol and catecholamines levels is a contributor[48]. ANS imbalance after stroke mainly manifests as sympathetic overactivation and may contribute to development of AF.

Location of the stroke within the brain has been shown to be associated with development of AF. Insular cortical damage is associated with 7-fold increased risk of AF[49][50]. Other locations of stroke have been linked to occurrence of AF post stroke including periaqueductal grey matter, hypothalamus, amygdala and other locations. While these locations are thought to produce AF via affecting ANS, the exact mechanism linking certain brain locations to development of AF is not known[45].

Additional mechanism leading to AF occurrence post stroke involves a 'catecholamine surge hypothesis'. Catecholamines released from adrenal glands and sympathetic system lead to higher occurrence of arrhythmias.

More recently, the entity of Stroke-Heart syndrome has been recognized[42]. Stroke-Heart syndrome manifestations tend to be transient, however, both short and potentially long-term outcomes can be poor for a subgroup of patients [42]. This syndrome encompasses all of the mechanisms described above; however, more evidence is required to delineate its exact pathophysiology and identify therapeutic targets to enable individualised patient care[42].

Acute ischaemic stroke is known to induce an inflammatory response both at the myocardial and systemic levels. Changes in the atria at the molecular and structural level have been detected, both in animal and human models. Multiple cytokines and inflammatory mediators such as tumour necrosis factor (TNF)-alpha and interleukin (IL)-6 are overexpressed leading to systemic inflammation[45][51].

Finally, AFDAS is a complex entity, and until further evidence is available, patients with AFDAS should receive anticoagulation as per current clinical practice[51].

Mechanisms of stroke in AF

While AF is an independent risk factor for stroke[52], the biological gradient between AF burden and stroke risk is not well established(61). In older patients with vascular risk factors, an episode of subclinical AF increases the risk of stroke by 2-fold(55), while clinically

apparent AF in young and otherwise healthy individuals with CHA_2DS_2-VASc score of 0 does not seem to pose a clinically important increase in stroke risk(62).

One of the proposed mechanisms of stroke in AF is that the impaired atrial contractility seen in AF leads to uncoordinated myocyte activity with resulting stasis and increased risk of thromboembolism[53]. Nevertheless, the evidence suggests the absence of survival benefit or difference in stroke risk between those treated with rhythm control or rate control strategies[55][56]. Hence, dysrhythmia and resultant stasis and thrombosis cannot be the only mechanism of stroke in AF. On the other hand, early rhythm control in selected patients with recent onset AF appears to be associated with improved clinical outcomes compared to usual care[57]. The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST AFNET 4) was an international, investigator-initiated, parallel-group, open, blinded-outcome assessment trial, which randomised AF patients diagnosed within a year of enrolment to rhythm control or usual care. This trial included 2789 patients, and its primary end point was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome. The primary outcome occurred less in patients assigned to early rhythm control. Notably, this trial was stopped at the third interim analysis for efficacy at 5.1 years follow up. Baseline characteristics were equal between groups, and treatments received were equal too. In comparison to previous trials, EAST AF-NET 4 enrolled patients with a new diagnosis of AF, more than half of which were in sinus rhythm when they entered the study[57].

Aortic arch atheroma often found in AF patients have also been associated with increased risk of stroke, and increased risk of stroke in AF may partially represent embolism from undetected aortic arch lesions[58]. However, not all AF-related strokes are embolic; in the

study by Loddler et al.(64) AF was prevalent in 10% of patients with lacunar infarcts thought to be non-cardioembolic, arising from the occlusion of a single perforating artery.

The interplay between AF and stroke is complex (**Figure 2**)[8]. While abnormalities of atrial substrates such as endothelial dysfunction, fibrosis, impaired myocyte function, chamber dilatation, and mechanical dysfunction in the left atrial appendage are often seen in AF, they have also been found associated with stroke risk independently of AF. This suggests that AF might in fact be a lagging marker of atrial abnormality(63).

In addition, comorbidities associated with increased risk of AF, such as hypertension, diabetes, congestive heart failure, dyslipidaemia, coronary heart disease, sleep apnoea, tobacco and obesity[3,17,27], have also been established as risk factors for stroke(66). Such systemic vascular risk factors result in an abnormal atrial substrate or atrial cardiomyopathy, and this itself can cause both AF and thromboembolism. Once AF develops, the atrial contractile function, and subsequently the underlying atrial cardiomyopathy worsen, increasing the thromboembolic risk and explaining the increase in stroke risk after the onset of AF(63).

Cardio-embolic stroke, cryptogenic stroke and embolic stroke of undetermined source (ESUS)

A significant overlap has been noted between the above three clinical terms but they are not synonymous.

Cardio-embolic stroke

In a prospective study using the TOAST criteria, cardioembolic strokes were found to account for about one third of ischaemic strokes(90). High risk sources of cardiac-embolism include: AF or atrial flutter, mechanical prosthetic valves, rheumatic heart disease, infective endocarditis, left atrial or ventricular thrombus, recent MI (<4 weeks), dilated cardiomyopathy, regional left ventricular akinesis, atrial myxoma, and patent foramen ovale (PFO) with thrombus in situ(63).

Clinically, cardio-embolic strokes are classically characterised by sudden onset of maximal neurological deficit, and the presence of cortical signs such speech disturbances and visual field defects(63,91). Decreased level of consciousness is also a predictor of embolic stroke(91,92).

From a neuro-imaging perspective, infarct pattern and distribution can give aetiological clues; e.g., infarcts along the borders between brain artery territories suggest systemic hypotension or multiple emboli, and a small deep infarct along with white-matter hyperintensities suggests intrinsic small-vessel disease(93). Tomographic features supportive of embolic stroke also include: the presence of a low-density zone corresponding to the territory of a single cerebral surface branch of a major cerebral artery(92), infarcts of different ages in a single territory (suggesting emboli of arterial origin)(93), evidence of cerebral or cortical infarct(45,92), or the presence of multiple territory acute infarcts(45)(suggesting emboli from a proximal aorto-cardiac source(93)). When angiography is performed, an abrupt vessel cut-off without significant atherosclerotic narrowing of the upstream vessel(63).

Previous studies suggested that recurrent embolism to the brain occurs within 2 weeks of an initial cardioembolic stroke in 10-20% of the cases(94). Immediate anticoagulation in this population has been controversial. The Cerebral Embolism Group showed a trend toward reduction of recurrent embolism with the use of early anticoagulation in this group in the absence of hypertension or evidence of haemorrhage on CT performed 24-48 hours after stroke(94).

Cryptogenic stroke

Cryptogenic stroke often refers to an ischaemic stroke where no probable cause has been identified despite adequate diagnostic work up(93). The term is also used to describe strokes with incomplete evaluation(63,93), and extends to include strokes where two or more plausible causes are found that the physician is unable to make a final diagnosis(48). It accounts for 10-40% of ischaemic strokes(93). Attempts to identify the mechanism(s) of stroke in this group is important for planning treatment strategy and secondary prevention(95).

Routine diagnostic work-up usually includes: echocardiography, inpatient cardiac telemetry or Holter monitoring, MRI or CT imaging, and MR or CT angiographic assessment of neck and brain arteries. More specialised tests reveal the cause of "cryptogenic" stroke in more than half of those cases(93). Such causes include occult atherosclerosis (such as non-stenosing but unstable plaques at intracranial and cervical sites or stenosing plaques at the thoracic origins of the common carotid and thoracic vertebral arteries); non-atherosclerotic arteriopathies, such as dissection or vasculitis; hypercoagulable states; cardio-embolism from medium-grade sources, such as low-burden paroxysmal atrial fibrillation or dilated

cardiomyopathy of moderate degree; or paradoxical embolism(93). Covert AF has been detected in 10-20% of patients with cryptogenic stroke who underwent extended (7-30 days) cardiac rhythm monitoring. However, the duration of paroxysmal AF was brief in many patients to justify the use of anticoagulation with certainty(96).

Embolic stroke of undetermined source (ESUS)

The term ESUS was introduced in 2014 to describe cryptogenic strokes that are likely caused by embolism after the exclusion of major-risk cardioembolic sources, proximal occlusive atherosclerosis, and lacunar strokes due to cerebral small artery disease (96). While antiplatelets are recommended for cryptogenic strokes, the subset of ESUS is likely to benefit from anticoagulation(96).

ESUS comprises 1 in 6 of all ischaemic strokes, with an annual stroke recurrence rate of about 4.5%(97). In the systematic review by Hart et al., ESUS patients were younger (with mean age 65 years), had lower rates of conventional vascular risk factors than non-ESUS patients with ischaemic stroke, and 42% were women(97). A certain stepwise approach has been suggested to reach a diagnosis of ESUS (**Figure 3**)[67,68].

While multiple trials found that AF may be detected in 30% of ESUS patients, its causal association with stroke remains uncertain(98). This was supported by the findings of the Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF RANDOMISED) trial, where among patients with cryptogenic stroke, there was no significant difference in the recurrent stroke rates between the intervention group (who had enhanced and prolonged monitoring, yielding AF detection rate of 13.5% at 12 months) and

the control group (who received stroke-unit telemetry for a median duration of 73 hours +/- additional Holter-ECG-monitoring for a median of 24 hours, yielding an AF detection rate of 6.1%)(99).

The role of patent foramen ovale (PFO) in cryptogenic stroke/ ESUS

PFO is the most common cause of a right-to-left cardiac shunt(93). It affects 25% of the adult population and is found in nearly 50% of patients with cryptogenic stroke (93,100,101). Nevertheless, not all patients with PFO develop stroke; and PFO is thought to be the likely the cause of approximately 5% of all ischemic strokes and 10% of those occurring in young and middle-aged adults(102).

It is presumed that the paradoxical embolus passing from the right to the left atrium through a PFO results in stroke(98,101). However, the absolute risk of stroke recurrence in PFO patients receiving medical therapy alone was low (1.27 per 100 person-years), and no higher risk of stroke recurrence was observed in patients who received antiplatelets only as opposed to oral anticoagulants (1.33% versus 1.30%)(103).

The Risk of Paradoxical Embolism (RoPE)(104) score was developed to assess the causality of PFO in cryptogenic strokes. It was validated in a multicentre study to predict the presence/absence of PFO in patients with ESUS, and subsequently identifying a likely pathogenic PFO which may benefit from closure. This study(104) also showed that patients with low RoPE score / incidental PFO had significantly higher rates of new incident AF (similar to those without PFO), while those with pathogenic PFO had a very low rate. A

PFO frequency of >60% was noted in patients with a RoPE ≥7, translating to a PFO-attributable fraction >80%(104).

Evidence suggests that PFO closure is may be superior to antithrombotic therapy with regard to the risk of stroke recurrence in patients of ≤60 years of age with cryptogenic stroke(103).

Considerations on AF-related stroke risks

Does the patterns of AF matter?

AF is considered paroxysmal AF when episodes last <7 days and spontaneously revert to normal sinus rhythm, persistent when they last ≥7 days, or permanent when AF rhythm is accepted and no further attempts to achieve normal sinus rhythm are made[76].

The role of AF pattern (paroxysmal, persistent or permanent) in relation to stroke risk has been the subject of controversy, as trials have shown conflicting evidence[77][78][79]. The analysis of incidence of stroke and systemic embolism in 6563 aspirin-treated patients with AF from the ACTIVE-A and AVERROES databases[77] showed that after adjusting for other independent risk factors, persistent and permanent AF has about two-fold higher rate of stroke or systemic embolism than paroxysmal AF. Similar findings were reported in other trials such as the ARISTOLE trial[78]. On the other hand, in the Stroke Prevention in Atrial Fibrillation (SPAF) studies, where patients treated with aspirin for intermittent AF and for sustained AF were assessed, stroke rates were found similar between both cohort groups[79].

Does AF duration matter?

(80)(81) of non-sustained AF episodes (defined as short-lasting <30-second-long irregular runs of supraventricular tachycardia) in stroke has not been proven yet[80]. In the retrospective study by Arvasa et al.[80] the rates of non-sustained AF were not higher in patients with cryptogenic strokes compared with those with other causes of stroke.

On the other hand, studies using data from implantable pacemakers suggest increased rates of embolic complications with total AF burden of >5 minutes, and even higher risk when the burden is >24hours[81][82]. In The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), subclinical atrial tachyarrhythmias (at heart rate of at least 190 beat per minute (bpm) for more than 6 minutes) detected on pacemakers/ implantable cardioverter defibrillators (ICD) independently increased the risk of ischaemic stroke or systemic embolism by 2.5-fold with a trend towards higher risk when the episodes are longer in duration[5]. Similarly, in the Report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST)[6], atrial high-rate events (AHREs) lasting more than 5 minutes in patients with sinus node disease (SND) who had received pacemakers were associated with increased risk of stroke as well as death. These patients were also 6 times more likely to develop AF compared to those without documented AHREs[6]. Treating patients with documented AHREs of at least 6 minutes with Edoxaban did not reduce the risk of stroke despite the inclusion of patients ≥,65 years of age with additional one or more risk factor for stroke. Furthermore, Edoxaban at stroke prophylaxis dose in these patients resulted in increased risk of major bleeding[7].

This suggests that the targets in AF therapy should be lower AF burden, less frequent episodes, and shorter AF duration.

Is rhythm control strategy better than rate control strategy?

Previously, various studies have looked into the difference in outcomes between rate control strategy and rhythm control strategy for treatment of AF and showed comparable outcomes between the two strategies[55][83][84][85][86][87]. In an intention-to-treat analysis of the results of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study[55], patients with AF at high risk of stroke or death who were treated with rhythm strategy had no survival benefit over those treated with rate control strategy. There was no difference in the incidence of stroke between the two study groups. The study also confirmed that anticoagulation (warfarin was used in this trial) reduced the risk of stroke in high-risk AF patients even when sinus rhythm had been restored and maintained. In a post-hoc analysis of the same trial using an "on-treatment analysis", the presence of sinus rhythm (when analysed as a separate variable to the use of antiarrhythmic drugs (AADs)) was also associated with reduced risk of death[83].

Even in patients with congestive heart failure, previous data showed that a rhythm control strategy did not reduce the risk of stroke or death from any causes[84]. Similarly, for post-operative new onset AF, rhythm control had no advantage over rate control strategy with regards to complication rates[85].

More recently, the EAST AFNET 4 trial [88] examined if early rhythm control (ERC) (defined as AF diagnosed within <12 months) would result in better outcomes compared to

usual care. This trial, which enrolled 2789 patients with a median time of 36 days from AF diagnosis, showed a significant reduction in its primary outcome (a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome) in favour of ERC versus usual care based on the current evidence-based AF treatments. Unlike previous trials of rhythm control, the EAST AFNET 4 used AF catheter ablation as well as AADs for rhythm control. The improved outcomes seen with ERC in this trial are attributable to the use of catheter ablation, the use of rate control therapies in both arms of the trial, the use of anticoagulation, as well as the management of comorbidities according to current standard practice guidelines.

Efficacy of ERC has been tested in several prespecified subgroup analyses of the EAST AFNET 4 trial. In patients with symptoms or signs of heart failure, ERC conferred benefit regardless of ejection fraction status[89]. Another prespecified subgroup analysis of the trial included patients with high comorbidity burden (defined as those with CHA2DSsVSc ≥ 4), in whom ERC should be considered as concluded. Those with less comorbidities were shown to derive less benefit from ERC[90]. The incurred benefit from ERC seen in the EAST AFNET 4 trial was also noted regardless of the AF pattern (i.e., first diagnosed, paroxysmal or persistent AF)[91].

The current European Society of Cardiology guidelines for the diagnosis and management of AF recommend rhythm control in patients with symptomatic AF[92], a recommendation which was mainly based on the lack of benefit from rhythm versus rate control based on earlier studies. In a separate sub-analysis of the EAST AFNET 4 trial, the primary outcome was not different between asymptomatic (those with European Heart Rhythm Association [EHRA] score of 1) and symptomatic patients, suggesting that ERC should be discussed with

all patients regardless of their symptom status[93]. It should be noted that the baseline characteristics and the rhythm control methods used were found comparable between the above analysis groups.

In a sex-based analysis of the EAST AFNET 4, no significant differences were demonstrated in the primary outcome based between males and females[94]. When sub-analysis was performed taking prior stroke status into account, the positive impact of ERC was maintained[95]. When genotyping was performed and polygenic risk scores were calculated for both AF and ischemic stroke, ERC was still found to be effective among the various genetic AF and stroke risk arrays[96]

Real-world data: rhythm control versus rate control

An observational study utilizing the National Health Claims Database (NHIS-2016-4-009) provided by the National Health Insurance Service (NHIS) of Republic of Korea for the period 2005-2015 was published in 2023. The population observed was similar to that of the EAST AFNET 4 trial, and included patients (total 20,611) who received rhythm or rate-control therapies within 12 months of AF diagnosis. The impact of frailty on outcomes of early rhythm control was assessed. The primary end point (a composite outcome of cardiovascular-related mortality, myocardial infarction, hospitalization for heart failure, and ischemic stroke) was lower in the early-rhythm control group who were non-frail, and a signal toward a lower risk of early rhythm-control was observed in the moderately frail and highly frail individuals[97].

When assessing the impact of sex on outcomes in the same Korean database population,

rhythm control compared to rate control was associated with lower risk of the described primary composite outcome in both sexes. However, the observed relative benefit was attenuated gradually in women and remained steady in men until 12 months[98].

When assessing the effect of early rhythm-control strategy for AF in a UK based population, using the UK BioBank database, 22,650 participants out of 28,174 with new diagnosis of AF of <1 year were eligible after applying the EAST AFNET inclusion and exclusion criteria. 12,329 were later excluded due to insufficient follow up data for outcome analysis. The composite efficacy outcome of cardiovascular death, stroke/transient ischemic attack (TIA) or hospitalization for worsening heart failure or acute coronary syndrome, and the composite safety outcome (stroke, death or serious adverse event related to rhythm control therapy) were significantly lower in the early rhythm-control group before propensity score matching of the study cohorts was performed. However, the matched analysis showed no difference between the compared groups in the primary efficacy or safety outcomes. Hence, it appears that early rhythm-control strategy for AF is safe in routine care[99].

In a European cohort of 10,707 AF patients derived from the EHRAESCEORP-AF General Long-Term Registry, the generalizability of the EAST AFNET 4 results was evaluated. Only 34% of this population met the eligibility criteria as stated in the EAST AFNET trial. While early rhythm control strategy was associated with higher use of health-care resources, it resulted in significantly lower rates of primary outcome (including cardiovascular death, stroke, acute coronary syndrome, and worsening of heart failure). This difference was not statistically significant in the fully adjusted analyses, suggesting that differences in baseline characteristics may have played a role in the initial outcome results[100].

The positive outcomes of early rhythm control strategy of the EAST AFNET 4 trial were also mirrored in the retrospective analysis by Dickow et al. which included 109,739 AF patients from the US administrative database, 72.9% of which met the EAST AFNET eligibility criteria[101].

In a systematic review and a meta-analysis of 5 pooled observational studies, early rhythm control strategy resulted in significantly reduced risk of a primary composite outcome of death, ischemic or haemorrhagic stroke, hospitalization with heart failure, or acute coronary syndrome. In addition, no significant interactions between RCT and real-world data regarding outcomes were observed[102].

Thus, unlike previous trials, EAST AFNET 4 trial as well as recent observational studies based on real-world patients' database are in favour of early rhythm-control strategy over rate-control strategy.

Sex differences in stroke risk in AF

AF is associated with a 1.5-1.9-fold increase in mortality in both sexes. Even though the conferred mortality risk with AF does not seem to increase with age, there is a clear discrepancy in the AF impact on mortality between sexes, and females seem to be more disadvantaged[103].

Female sex is also strongly associated with more severe strokes compared with male sex[104]. As females with AF have higher prevalence of Total Anterior Circulation Stroke indicating proximal vessel occlusion, it is hypothesized that biological differences, such as

the smaller diameter of intracranial and extracranial vessels in females compared with males, contribute to in their occlusion[104]. Differences in sex hormones and poorer quality anticoagulation control have also been suggested as causes, though they were not confirmed[104,105].

Female sex is also a strong risk modifier in AF, and the excess risk for women is particularly evident among those with ≥2 non-sex-related stroke risk factors[105].

Future directions: arterial calcification as a novel risk marker for AF and stroke

Vascular calcification is the deposition of minerals in the intimal and medial layers of the vessel wall secondary to processes such as aging, CKD, diabetes or certain hereditary conditions. It is associated with increased risk of adverse cardiovascular outcomes(80). Multiple mechanisms have been suggested for calcific vasculopathy including: inflammatory (affecting the intimal layer of the vessel; associated atherosclerosis), metabolic (affecting the media; associated with CKD and diabetes), genetic as in Marfan's syndrome(81). Various studies have looked into arterial calcification involving the intracranial arteries particularly the intracranial internal carotid artery, and the coronary arteries, and their association with adverse cardiovascular events(82)(83)(84)(41).

Calcification of the intracranial internal carotid artery (iICA) was the focus of research as well. It was previously perceived as a proxy for atherosclerosis which tends to affect the intimal layer. The iICA calcification is now rather known to be predominantly found in the medial layer of the artery. While intimal calcification is associated with vessel stenosis,

medial calcification results in arterial stiffness, increased pulse pressure and vascular resistance[110,111].

Intimal calcification and/ or medial calcification of the iICA and their severity are independent risk factors for stroke(84). ICA calcification was found to result in 75% of all strokes in middle-aged and elderly white population in the Rotterdam study(41). In addition, severe intracranial artery calcification has also been linked to worse stroke outcomes including recurrence and mortality, as well as certain aetiologies of stroke such as cardio-embolism or large vessel atherosclerosis[112]. Of note, iICA intimal calcification is also an independent risk factor for MI[110].

Coronary artery calcification (CAC) has also been studied. In the MESA cohort, CAC was strongly associated with the 10-year incident risk of atherosclerotic cardiovascular disease (ASCVD) which includes coronary heart disease death, non-fatal MI, fatal and non-fatal stroke[108].

In addition, CAC has also been associated with increased risk for AF[113], a risk that was higher for the younger compared with the older participants in the MESA cohort. The risk of AF also increased with higher levels of CAC progression[113].

In a retrospective case-control trial by Hillerson et al. an incidental finding of coronary artery calcification was also independently associated with increased risk of stroke and death in AF patients[114]. Similar findings were reported by Wang et al.[115]. This may call for further studies in order to incorporate CAC into stroke risk scores in AF patients.

Considerations on the acute management of ischaemic stroke in patients with AF

Thrombolytic therapy

Administered within 4.5 hours of symptoms onset, intravenous (IV) alteplase (recombinant tissue plasminogen activator [tPA]) improves the outcomes of ischemic stroke, with time-to-treatment dependent benefit[116]. This proportional benefit did not differ between younger patients and those older than 80 years of age and was evident irrespective of stroke severity[116]. The European Stroke Organisation (ESO) guidelines also recommend the use of IV Tenecteplase (as alternative thrombolytic agent) in patients with large vessel occlusion (LVO) stroke, who are candidates for mechanical thrombectomy (MT) and present within 4.5 hours of stroke onset[117].

Being on OAC is not an absolute contraindication to IV thrombolysis; the ESO guidelines recommend IV tPA for those already on VKAs if INR ≤1.7[118]. However, data for IV thrombolysis in patients who are on DOAC are conflicting.

Breakthrough stroke while on a Direct Oral Anticoagulant (DOAC) and use of reversal agents to facilitate thrombolysis

Patients on DOACs presenting with acute stroke present a challenge as ways of measuring DOACs activity are limited. A dilemma presents to the treating physician when thrombolysis is indicated in a patient who is already taking a DOAC, as the use of alteplase in patients

treated with a DOAC within 48 hours of stroke onset is associated with perceived increased risk of symptomatic intracranial haemorrhage[118].

Several approaches have been suggested to managing patients on DOACs requiring thrombolysis. Major international guidelines [119] state that if a DOAC has been received >48 hours, then IVT can be administered [119]. Use of blood tests (e.g., calibrated anti-Xa-activity for factor Xa inhibitors, thrombin time for dabigatran, or the DOAC blood concentrations) is referred to in some guidelines with limited evidence supporting these recommendations, this is in addition to its cost and limited availability in most settings[120]. Although various studies have suggested cut-off levels for the use of specific anticoagulants assays, these have not been validated except for rivaroxaban (< 20ng/ml)[121].

Use of specific DOACs reversal agents including Andexanet for Apixaban and Rivaroxaban, or Idarucizumab for Dabigatran, can facilitate the use of thrombolysis. Limited data are available in this context. Andexanet can effectively reverse effects of apixaban and rivaroxaban, with its main use being the control of life-threatening or uncontrolled bleeding [122]. In patients presenting with stroke however, a major limitation to its use is that it requires about 2 hours to administer. Considering the 4.5-hour window for thrombolysis, its clinical utility is thus significantly limited. There is also a concern about its potential for causing rebound thrombosis with a rate of 10% at 30 days [122]. Another concern is the increased incidence of thromboembolic events and risk of cardiac events [123]. Based on this evidence, ESO cautions against the use of Andexanet for reversal of apixaban or rivaroxaban in patients eligible for thrombolysis [121].

Idarucizumab on the other hand, can be used to reverse dabigatran used within 48 hours. There is again a fear of its prothrombotic effects particularly in patients with acute stroke. European stroke society, was therefore, unable to recommend for or against its use in patients otherwise eligible for IVT [119]. A recent meta-analysis has suggested that use of reversal agents in patients with acute ischemic stroke while on DOACs is safe, however, more data are required to prove this [124].

The recent international multicenter study by Meinel et al.[125] tried to address many of the above-mentioned concerns. In this study, adults with acute ischemic stroke who were treated with IVT (with or without MT) were included if they ingested a DOAC within the preceding 48 hours (total number was 832). The control group was formed of 32 375 patients with acute ischemic stroke receiving IVT without history of prior anticoagulation treatment (defined as being on DOAC treatment or on VKA with therapeutic INR >1.7). Data on selection strategy within the DOAC group were also gathered: 355 (42.7%) were treated with IVT without measurement of DOAC plasma levels or administration of a reversal agent, 252 (30.3%) received DOAC reversal prior to IVT (idarucizumab was the only agent used in patients taking dabigatran), and 225 (27.0%) had DOAC plasma levels measured. The primary outcome was symptomatic ICH (sICH); defined as any ICH occurring up to 36 hours after IVT, with associated ≥4 point-increase in NIHSS score attributable to radiographically evident haemorrhage. The unadjusted rate of sICH was 2.5% (95% CI, 1.6-3.8) in the DOAC group compared with 4.1% (95% CI, 3.9-4.4) in the control group. Even after adjusting for stroke severity and other predictors of sICH, recent DOAC ingestion was not associated with increased risk of sICH (adjusted odds ratio: 0.57; 95% CI: 0.36-0.92, P: 0.02). There was no statistical difference between the selection strategies[125]. While the study had its limitations, such as the likely selection bias towards patients with a low probability for sICH

(when IVT was given without measurement of DOAC plasma levels or use of a reversal agent), it provided new and crucial evidence signalling the safety of IVT in ischemic stroke patients who had recently ingested a DOAC.

Mechanical thrombectomy for stroke and the impact of AF

Mechanical thrombectomy (MT) is the goal standard for treatment in ischemic stroke with large vessel occlusion (LVO)[126]. It is recommended in addition to best medical management (including IVT, if indicated) [127]. It improves the functional outcome in those presenting within 6 hours of symptoms onset [126]. Careful patient selection using advanced imaging has also allowed more patients to receive MT up to 24 hours of symptoms onset[128][129].

Some data suggest that patients with AF, who received MT for stroke, tend to have worse 90-day outcomes with significantly higher mortality rates and significantly lower rates of functional independence, even in the setting of comparable rates of successful reperfusion to those without AF. This could possibly be attributed to the older age of AF population and the associated co-morbidities seen in this group [130]. The presence of AF itself was not found to affect the good short-term outcome or the short-term and long-term mortality in patients with acute ischemic stroke who were treated with MT[131]. Hence, these findings should not deter MT on patients with AF and concomitant LVO, irrespective of anticoagulant treatment.

Anticoagulation timing after stroke in AF

The optimal timing for (re-)starting OAC after an acute ischemic stroke in patients with AF has been unclear. The concerns regarding the risk of recurrent stroke in this group must be balanced against the perceived competing risk of secondary haemorrhagic transformation. The current European guidelines suggest considering (re-)initiation of OAC at 1 or 1-3 days after TIA (depending on findings on brain imaging), or at ≥ 3, ≥6-8, or ≥12-14 days after a mild, moderate, or severe ischaemic stroke with no evidence of haemorrhagic transformation, respectively[132]. This approach has also been supported by a study of the data from the National Health Insurance Research Database of more than 12000 AF patients hospitalised for ischaemic stroke in Taiwan[133].

The Early Versus Delayed Non–Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation (TIMING) trial[134] assessed the noninferiority of early versus late initiation of DOAC after an ischaemic stroke in 34 stroke units in Sweden. Stroke patients were randomised within 72 hours of symptom onset to early (≤4 days) or delayed (5–10 days) DOAC initiation. Early initiation was noninferior to delayed initiation with respect to the primary outcome (a composite of recurrent ischemic stroke, symptomatic ICH, or all-cause death at 90 days). Numerically lower rates of ischemic stroke and death were noted in the early initiation group. No symptomatic ICH was recorded in either of the study groups during 90 days of follow-up. However, the study was underpowered, and while a sample size of 1451 per group was calculated to assess noninferiority with a power of 80% using a significance level of 5%, only 888 patients were included in the final cohort and assigned to each group[134].

The recently published Early versus Late Initiation of Direct Oral Anticoagulants in Post-ischemic Stroke Patients with Atrial Fibrillation (ELAN) trial[135], was an international

multicenter trial involving 103 stroke centers in Europe, the Middle East, and Asia. It compared the early (within 48 hours after a minor or moderate stroke or on day 6 or 7 after a major stroke) versus late (day 3 or 4 after a minor stroke, day 6 or 7 after a moderate stroke, or day 12, 13, or 14 after a major stroke) initiation of DOAC in patients with AF. There was no statistically significant difference between the early-treatment group and the later-treatment group in the rates of the primary outcome (a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic ICH, or vascular death within 30 days after randomization). The two groups did not differ either in the risk of recurrent ischemic stroke, ICH or vascular death at 30 and 90 days)[135]. The trial suggested no excess harm with the early use of DOAC after ischemic stroke and may advise an important change in clinical practice and guidelines.

The Optimal Timing of Anticoagulation after Acute Ischemic Stroke (OPTIMAS) trial (ClinicalTrials.gov number, NCT03759938) have opened in multiple centres in the UK since December 2021 and is still ongoing. It looks at assessing the non-inferiority of early versus late initiation of DOAC in patient with AF after an acute ischemic stroke, with a non-inferiority margin of 2 percentage points.

Mitigating the long-term risk of stroke in AF

The conundrum of antithrombotic therapy for secondary prevention of stroke in AF patient already on OAC treatment

Despite our best efforts at stroke prevention, patients with AF still have an annual ischemic stroke risk of 1-3% while on effective OAC treatment [136]. In a pooled data analysis of 7

prospective cohort studies, patients with AF developing stroke whilst on OAC were found to have a higher stroke recurrence risk compared to those who were OAC-naïve despite similar CHA_2DS_2-Vasc and HAS-BLED scores[137]. In such cases of breakthrough strokes, the optimal antithrombotic strategy had been uncertain.

In the pooled analysis by Seiffge et al.[137], the final cohort of about 5000 patients were followed up for at least 3 months post ischemic stroke or TIA. Changing the type of OAC after the index event in this cohort was not associated with a decreased risk of further strokes.

More recently, Ip et al.[138] studied the antithrombotic strategies for patients with AF already on DOAC at the time of an ischemic strokes. The potential strategies included: continuing on the same DOAC (DOAC-same), DOAC-to-warfarin switch, DOAC-to-DOAC switch (DOAC-switch), or addition of antiplatelet agents. Bonaventure Ip et al. compared the clinical outcomes of patients in each of those 4 groups over a median follow up period of 16.5months. The strategy of continuing the same DOAC was associated with the lowest annual risk for recurrent stroke (8.7%). DOAC-switch and the DOAC to warfarin switch strategies were associated with increased risk of recurrent stroke compared to the DOAC-same strategy (adjusted hazard ration[aHR]1.96, 95% CI 1.29–3.02, p = 0.002, and aHR 1.62, 95% CI 1.25–2.11, p < 0.001 respectively). Adjunctive antiplatelet treatment among the DOAC-same group did not reduce the risk of recurrent ischemic stroke (aHR 1.28, 95% CI 0.88–1.84, p = 0.188), ICH (aHR 1.20, 95% CI 0.54–2.68, p = 0.654), or death (aHR 1.09, 95% CI 0.84–1.41, p = 0.512). On the other hand, the risk of ICH and death was not significantly different between the groups[138].

Non-medical options for prevention of stroke in AF patients

While oral anticoagulation is the main pillar of secondary prevention post stroke in AF patients[52,77,79,139,140], left atrial appendage occlusion or exclusion might provide a reasonable alternative or adjunctive therapy in certain cases.

Left atrial appendage occlusion devices

In non-valvular AF, an embolic stroke is believed to be secondary to a thrombus formed in the left atrial appendage (LAA)[141]. Percutaneous LAA occlusion with Watchman Left Atrial Appendage System was investigated in the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) study, and was found non-inferior to warfarin therapy in prevention of stroke in AF patients, though it was associated with higher rate of adverse safety events in the intervention group mainly secondary to periprocedural complications[141,142]. It is also important to note that the non-inferiority was mainly driven by reduction in rates of haemorrhagic strokes and not ischemic strokes.

Similar outcome was seen in the Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy: The PREVAIL Trial[143]. In this trial, non-inferiority was only achieved after isolating periprocedural events, and LAA occlusion was noninferior to warfarin for prevention of ischemic stroke or systemic embolism >7 days post-procedure. Neither PROTECT AF nor PREVAIL compared the safety and efficacy of LAA occlusion to NOAC or in patients who have contraindication to oral anticoagulants (OACs).

Those with contraindications to OAC were assessed in the ASAP Study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology)[144]. Comparing the outcomes rates in this trial's intervention group to the annual stroke/TIA risk using $CHADS_2$ score, showed that the LAA closure with the Watchman device can provide a reasonable alternative in patients at high risk for stroke but with contraindications to OACs.

OAC vs LAA closure was studied in the PRAGUE-17 trial (using Amulet or the Watchman device), and OACs were found non-inferior to LAA occlusion in the prevention of major AF-related cardiovascular, neurological, and bleeding events in patients known to have high bleeding and stroke risk[145], **Table 1** summarizes the trials studying percutaneous LAA occlusion.

In the real-world data, the frequency of in-hospital adverse outcomes associated with percutaneous LAA closure is slightly higher at 24.3% than in clinical trials[146]. Currently, the ESC guidelines suggest a class IIb indication for consideration of LAA occlusion in AF patients at risk of stroke but with contraindication for long-term OAC[147].

Surgical LAA occlusion or exclusion surgery

The Left Atrial Appendage Occlusion Study II (LAAOS II)[148] was a cross-sectional study and a pilot trial that included 51 AF patients undergoing cardiac surgery. The primary end point (a composite of death, MI, stroke, non-cerebral systemic emboli, or major bleeding) occurred in 15.4% in the occlusion arm and 20.0% in the no-occlusion (relative risk [RR], 0.71; 95% confidence interval [CI], 0.19-2.66; $P = 0.61$). The predominant component of the

composite was stroke, with 1 in the occlusion arm and 3 in the no-occlusion arm. Nevertheless, the study confirmed feasibility of the procedure.

LAA exclusion using a double ligation technique (with both a polydioxanone (PDS) II endosnare and a running 4-0 Prolene pledgeted suture) was studied and it yielded positive results among 808 trial participants[149]. The technique was associated with lower rates of in-hospital and 30-day mortality without an increase in perioperative complications. There was a trend towards less post-operative AF (19.4% vs 22.9%, P = 0.07).

The LAAOS III trial[150] is the only randomised controlled trial assessing the efficacy of surgical LAAO in patients undergoing cardiac surgery. All participants had AF with CHA2DS2-VASc score of 2 or above. They all received anticoagulation after surgery. Concomitant occlusion of the LAA during cardiac surgery was more effective than standard therapy alone in reducing the risk of ischaemic stroke in these patients. On the other hand, the procedure was found safe and did not increase the risk of bleeding or death. The current ESC guidelines suggest class IIb indication for surgical LAA occlusion or exclusion for stroke prevention in AF patients undergoing cardiac surgery[147].

The Atrial Fibrillation Better Care (ABC) pathway

The ABC pathway was suggested in 2017 for a streamlined management of AF, and was subsequently adopted in the European Society of Cardiology (ESC) guidelines[147,151]. ‘A’ stands for avoid stroke, ‘B’ is for better symptom management, and ‘C’ is for cardiovascular and comorbidity risk reduction[151]. Such integrated care approach was introduced to allow a structured management for AF that can be applied by the general practitioner or any

hospital-based specialist (even the non-cardiologists)[152]. It also facilitates discussion and patient engagement on the principles of AF care ("easy as ABC…")[152].

ABC pathway in AF patients has been supported by posthoc analysis of trial data as well as prospective randomised controlled trial data[153–155].

Integrated care post-stroke in relation to incident cardiovascular events, including AF

Stroke-heart syndrome is a term used to describe the cardiac manifestations occurring as a consequence of brain ischaemia[156]. New onset major adverse cardiovascular events (MACE), including acute coronary syndrome, heart failure, and arrhythmias has been reported at a rate of up to 20% in the acute phase of ischaemic stroke[156]. It is suggested that they have the same underlying autonomic and inflammatory mechanisms as stroke[157]. In a retrospective cohort study of 365 383 patients with stroke, 11.1% developed acute coronary syndrome, 8.8% AF/flutter, 6.4% heart failure, 1.2% severe ventricular arrythmia, and 0.1% Takotsubo syndrome within 4 weeks of the index stroke. Those with stroke and newly diagnosed cardiovascular complications had worse prognosis and >50% prevalence of recurrent stroke at 5 years[157]. The risk of subsequent cardiovascular events is similar between incident haemorrhagic and ischemic stroke[158].

A post-stroke ABC pathway has been proposed to provide a more holistic approach to integrated stroke care. Its main pillars are: "A" for appropriate antithrombotic therapy, "B" for better functional and psychological status, and "C" for cardiovascular risk factors and comorbidity optimization (including lifestyle changes)[152]. The European Society of Cardiology Council on Stroke issued a consensus statement in support of this approach[159].

In a systematic review and metanalysis assessing the impact of 'Atrial Fibrillation Better Care' pathway on the clinical outcomes of AF patients, patients treated according to the ABC pathway had a lower risk of all-cause death (odd ration (OR): 0.42; 95% CI: 0.31–0.56), cardiovascular death (OR: 0.37; 95% CI: 0.23–0.58), stroke (OR: 0.55; 95% CI: 0.37–0.82) and major bleeding (OR: 0.69; 95% CI: 0.51–0.94)[160].

Management of large vessel disease and AF

Existing data suggest that the presence of asymptomatic carotid artery stenosis increases the risk of stroke by 50%[161]. However, the risk gradient between the severity of asymptomatic lesions causing 50% luminal narrowing or more and stroke is less clear[162]. In these patients, triple medical therapy with anti-thrombotic, anti-hypertensive and LDL cholesterol-lowering agents decreases the risk of stroke, myocardial infarction and death[162]. In patients with AF and coexisting carotid artery stenosis, there is no evidence that adding aspirin to OAC reduces the risk of recurrent stroke[162,163].

Detection of AF after stroke

Risk scores for predicting AF in patients with stroke

AF-related strokes tend to be associated with worse functional deficit, poor survival and higher recurrence rate within 12 months compared to strokes in non-AF individuals[164]. Hence, early detection of AF in stroke patients is vital for secondary prevention.

In a large prospective multicenter study by Grond et al.[52] stroke patients with otherwise undiagnosed AF (silent AF) were of older age and less functional disability before their index stroke, but sustained a more severe neurological deficit. Radiologically, there was no clear preference for a specific vascular territory involvement in undiagnosed AF patients compared to those in sinus rhythm, and imaging features suggestive of cardioembolic mechanism (i.e., multiple infarctions) were not more common in the former group either[52].

Various studies have looked into predicting AF in patients who have had an acute stroke or TIA (**Table 2**)[165–175]. Predicting AF in such high-risk groups can identify the subset of patients who need more extensive investigations and guide the screening strategy for AF. The generated scores or models have not been formally incorporated into clinical guidelines as yet, although position papers or consensus documents have advocated simple scores such as the C_2HEST score.

In the Score for the Targeting of Atrial Fibrillation (STAF) study[165], 4 variables were used to calculate the STAF score of 0-8. These were: age >62 years (2 points); the National Institutes of Health Stroke Scale (NIHSS) ≥8 (1 point); left atrial dilatation (2 points); absence of symptomatic intra or extra-cranial stenosis ≥50%, or clinico-radiological lacunar syndrome (3 points). A total score of 5 or more had 89% sensitivity and 88% specificity in detecting AF. In this trial, TIA patients were excluded.

The LADS system on the other hand was developed to identify both stroke and TIA patients who may have AF[166]. This includes: Left atrial diameter (0–2 points), Age (0–2 points),

Diagnosis of stroke (0–1 point), and Smoking status currently (0–1 point). A score of 4 or greater had a sensitivity of 85.5% and a specificity of 53.1%.

The C_2HEST score was originally developed and validated to assess the individual risk of developing AF in the Asian population without structural heart disease[171].Variables included in this score were: (coronary artery disease or chronic obstructive pulmonary disease [1 point each]; hypertension [1 point]; elderly [age ≥75 years, 2 points]; systolic HF [2 points]; thyroid disease [hyperthyroidism, 1 point]), total points of 0-8. The score was then tested in a post stroke white European population in a French nationwide study by Li et al.(71). The annual incidence rates of AF in this study were 3.19% in the low-risk group (0 or 1 point), 7.15% in the medium-risk group (2 or 3 points), and 14.64% in the high-risk group (≥4 points).

Another scoring system for identifying those at risk of developing AF among patients with cryptogenic stroke or TIA is the HAVOC score[169] (**h**ypertension [2 points], **a**ge [2 points], **v**alvular heart disease [2 points], peripheral **v**ascular disease [1 point], **o**besity (body mass index (BMI) of >30) [1 point], **c**ongestive heart failure [4 points], and **c**oronary artery disease [2 points]); a total of 0-14 points. 3 risk categories were developed: low risk (scores 0–4), medium risk (5–9), and high risk (10–14), and AF rates were 2.5%, 11.8%, and 24.9% respectively, and AF rates >30 days after the stroke in the validation cohort were 2.6%, 11.1%, and 20.3% respectively. In an external assessment of the performance of HAVOC score in predicting incident AF in patients with embolic stroke of undetermined source (ESUS) (72), low-risk HAVOC score had a specificity of 88.7% in identifying patients without incident AF, a negative predictive value of 85.1%, and an accuracy of 78.0%.

In the CHARGE-AF, variables including age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive medication, diabetes, and history of myocardial infarction and heart failure were used to create and validate a 5 year predictive model of AF in 5 community-based US and European cohorts (the Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), the Rotterdam Study (RS), and the Age Gene/Environment Susceptibility-Reykjavik (AGES) Study)[172]. Even though the model was tested in community-based cohorts (AGES and RS) rather than in post-stroke patients, it proved good discrimination (C-statistic, 0.765; 95% CI, 0.748 to 0.781). In a report comparing the CHARGE-AF versus CHA_2DS_2-VASc risk score, the CHARGE-AF had a C-statistic of 0.757 (95% CI, 0.741–0.772) as opposed to C- statistics of CHA_2DS_2-VASc score of 0.712 (95% CI, 0.693–0.731)[173]. Reports from the multi-ethnic study of atherosclerosis (MESA) studies also suggest that the CHARGE-AF risk score is superior to the CHA_2DS_2-VASc risk score in the prediction of incident AF in community-based cohorts[174].

Predictors of newly diagnosed AF (NDAF) in cryptogenic stroke patients were also studied by Bugnicourt et al.[175], who developed a score including the following variables: age ≥72 years (2 points), history of coronary artery disease (1 point) or stroke (1 point), and left atrial area ≥16 cm^2 (2 points); a total score ranging from 0 to 6. A score of 0 or 1 was highly predictive of the absence of NDAF during the one-year follow-up period.

In a systematic review by Kishore et al.[176] the performance of most of the above-mentioned scores, and others, was assessed. Such scores tend to have a high negative predictive value, however, no score performed consistently better than another, and their usefulness in decision making remains uncertain[176].

Randomised controlled trials assessing the risks and benefits of AF screening as a public health strategy to prevent stroke may have signalled reductions in stroke or systemic embolism with screening, but were statistically nonsignificant[177]. This is because of the inherent challenges of screening studies and the need for a very large sample size. Hence, they are often statistically underpowered[177]. Therefore, a systematic review and a metanalysis is important to achieve the sample size and power needed to answer such question. A systematic review and a metanalysis is currently underway by McIntyre et al. to address this area of interest[177].

Improving the detection rate of AF after stroke

As AF can be paroxysmal, its detection can be challenging but remains of paramount importance as it can guide change in management. Detection of AF in post-stroke patients can instruct initiation of anticoagulation therapy proved to reduce risk of thrombo-embolism in AF[178]. In the study by Elijovich et al., rhythm monitoring with a 30-day event recorder changed the management of one fifth of patients with otherwise cryptogenic stroke due to the detection of intermittent AF on those monitors that had not been picked up on 12-lead electrocardiogram (ECG) or during a period of telemetry during their hospital stay[179]. New AF detection rate from a 12-lead ECG after an ischemic stroke or transient ischemic attack (TIA) is estimated to be about 2-5%, while the detection rate from a 24-hour monitor is about 2-6%[180]. Detection rates are noted to increase by 2% to 4% with each additional 24 hours of monitoring as reported in the meta-analysis by Kishore et al.[180].

Several studies have assessed the optimum duration of rhythm monitoring post-stroke. In a prospective multicenter cohort study conducted in Germany, extending the period of Holter ECG monitoring in stroke survivors to 72 hours almost doubled the detection rate of AF[181]. The AF detection rate in patients with otherwise presumed cryptogenic stroke was even higher at 23% with the use of Mobile Cardiac Outpatient Telemetry (MCOT) system. Eighty-five percent of those detected AF episodes were short and <30 second long. The overall higher detection rate in this study was attributed to longer monitoring period (up to 21 days after stroke), patient selection and inclusion of all new onset AF[182].

Insertable cardiac monitors (ICM), such as Reveal XT (Medtronic Inc, Minneapolis), which were originally designed to investigate syncope were subsequently refined to incorporate algorithms detecting AF[183]. In the study by Ritter et al., ICM had a 17% AF detection rate as opposed to 1.7% for 7-day Holter monitoring[183]. Similarly, Israel et al. studied the use of implantable loop recorder (ILR) in patients labelled with embolic stroke of unknown source (ESUS), and AF was detected in about 25% of those patients within one year of ILR monitoring and daily remote interrogation[184].

In the Cryptogenic Stroke and Underlying AF (CRYSTAL-AF) trial[185], ECG monitoring with ICM was found superior to conventional follow up in detection of AF after cryptogenic stroke. AF detection rate was significantly higher in the ICM group compared to the control group at 6 months and 12 months (8.9% vs 1.4%, and 12.4% vs 2% respectively).

Future directions in AF detection using wearable devices and artificial intelligence (AI)

With advancing technology, new means of detecting AF have come to light. As low detection rate and non-adherence continue to be major obstacles in the management approach to suspected AF, use of mobile health devices may help and facilitate continuous home monitoring[186]. In the Apple Heart Study[187], participants who self-reported not having AF were enrolled. They gave consent via their smart phone (Apple iPhone) application (App). Those who received an "irregular heart pulse" notification via the smart watch were mailed an ECG patch from telemedicine. About half a million of participants were enrolled, only 0.52% received an irregular pulse notification. The positive predictive value for AF was 84% (95% CI, 76 to 92%).

The use of smart device–based photoplethysmography (PPG) technology in detection of AF was also studied in a large population in China with the use of a wristband (Honor Band 4) or wristwatch (Huawei Watch GT, Honor Watch, Huawei Technologies Co., Ltd., Shenzhen, China)[186]. When a "possible AF" alert is sent, further assessment is carried out by health providers among the MAFA (mobile AF App) Telecare center and network hospitals in order to confirm AF with clinical evaluation, ECG, or 24-hour Holter monitoring [186]. Out of 186,956 participants, 0.2% had a suspected AF notification, and 87% of those had AF confirmed by doctors. 95.1% then entered the MAFA integrated care program based on the Atrial fibrillation Better Care (ABC) pathway. The positive predictive value of PPG signals was 91.6% (95% CI: 91.5% to 91.8%). The study showed the feasibility of PPG-based smart devices as a screening tool for AF patients.

The Liverpool-Huawei Stroke Study (Identifier: https://doi.org/10.1186/ISRCTN30693819) is actively recruiting patients with stroke to evaluate the feasibility and clinical effectiveness of using the Huawei smart band in detection of incident and prevalent AF[188].

Other technologies investing in the use of artificial intelligence (AI) methods such as deep learning (DL) have been explored. Models have been proposed to predict the likelihood of a person having underlying undiagnosed AF from an 'apparently normal' ECG without any additional information[189]. In one study, the ability of AI-ECG model to predict AF in ESUS patients was measured against the results of prolonged ambulatory cardiac rhythm monitoring[190]. While the AF probability by AI-ECG was not associated with ESUS, the probability of AF by AI-ECG in ESUS patients was associated with a higher probability of AF detection by ambulatory monitoring (P = 0.004)[190].

In a study by Khurshid et al.[191], a convolutional neural network was trained to draw the 5-year incident AF risk using 12-lead ECGs in patients receiving longitudinal primary care in a state in the USA. The overall performance of the model was tested in the UK Biobank data and it showed a comparable performance to the CHARGE-AF risk score[191]. This suggested the potential comparable predictive utility of these innovative tools to clinical risk factor models, though more testing and clinical trials are needed in the future before any conclusions are drawn and generalized.

Conclusions

Reducing the risk of recurrent stroke is a primary goal in the therapeutic journey after a stroke, identifying covert AF is crucial to advise on the need for anticoagulation treatment. Several risk scores have been developed to predict AF after stroke, thereby identifying individuals where prolonged rhythm monitoring periods might be necessary. However, their

applicability in clinical practice remains uncertain, and they are yet to be implemented in any clinical guidelines.

Breakthrough strokes in patients with AF already on DOACs have presented a clinical conundrum. It has recently emerged that the early (re-)initiation of OAC in for secondary prevention in patients with AF is not associated with increased risk of recurrent ischemic stroke or ICH.

Advancing technologies such as the use of smart wearables have been studied with promising results, but their use and clinical effectiveness in the high-risk post stroke population is yet to be validated. Novel predictors of AF and markers of stroke risk in AF such as arterial calcification of the coronary and the intracranial arteries have been explored but not yet incorporated into any clinical risk models.

With advancing technology, innovative algorithms leveraging AI to interpret ECGs have been developed. However, more work and large-scale testing is still required. Appropriate validation and testing in large randomized trials are also needed before these tools can be widely used and applied in clinical practice.

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Figure 1. A schematic description of the results of the study by Bogiatzi et al.

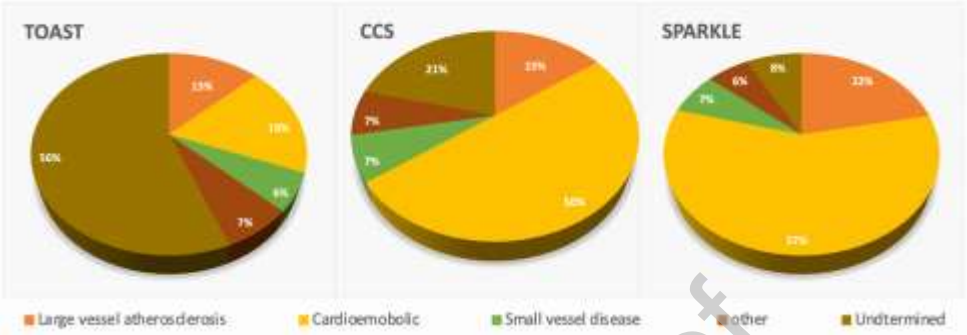

Figure 2. A schematic description of the results of the study by Bogiatzi et al. The figure shows the five ischaemic stroke subtypes comparing SPARKLE, CCS and TOAST. Please note the higher percentage of cardioembolic and large artery atherosclerosis strokes and the lower percentage of strokes of undetermined etiology using SPARKLE classification compared to TOAST or CCS. TOAST, Trial of Org 10172 in Acute Stroke Treatment. CCS, Causative Classification System. SPARKLE, Subtypes of Ischaemic Stroke Classification System.

Figure 3. The complex mechanistic interplay between AF and stroke.

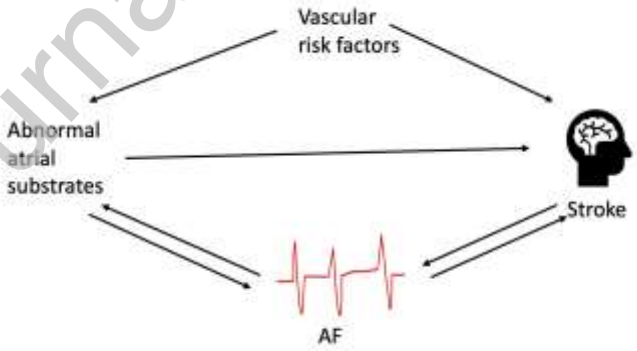

Figure 4. The complex mechanistic interplay between AF and stroke. AF, atrial fibrillation.

Figure 5. ESUS diagnosis as proposed by Hart et al.

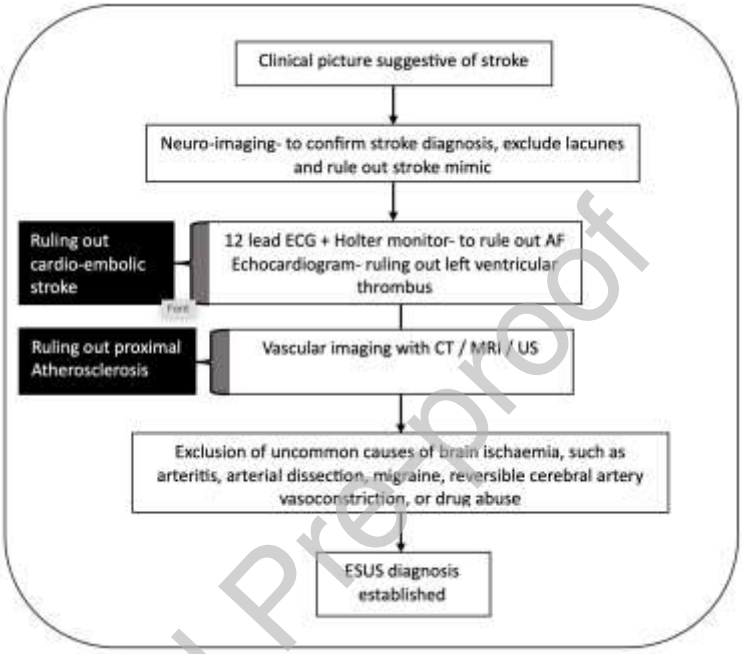

Figure 6. ESUS diagnosis as proposed by Hart et al. ESUS, embolic stroke of undetermined source. ECG, electro-cardiogram. CT, computed tomography. MRI, magnetic resonance imaging. US, ultrasound.

Table 1. Trials studying percutaneous left atrial appendage occlusion (LAAO)						
Study	**Study Design**	**Population**	**Comparison**	**Primary Outcome**	**Safety end points**	**Conclusions**
PROTECT AF Holmes et al(141), 2009	Randomised controlled trial	1. Non-valvular AF 2. Additionally, has at least one of the following: - Prior TIA/Stroke - CCF - DM - HTN - Age > 75 years	Non-inferiority design testing LAAO device (Watchman device) (n = 463) vs warfarin (n = 244)	Composite of: stroke, cardiovascular death, and systemic embolism	Major bleeding (Intracranial or gastrointestinal), pericardial effusion, and device embolization	LAAO device was non-inferior to warfarin though at expense of increased safety end point events in the LAAO group
PROTECT AF Reddy	Randomised controlle	2.3 follow up of PROTECT	As above	As above	As above	LAA occlusion device

et al(142), 2013	d trial	AF trial (Holmes et al, 2009)				continued to be non-inferior to warfarin, yet with an increased incidence of primary safety end point
ASAP study Reddy et al(144), 2013	Non-randomised, prospective study	1. Non-valvular AF 2. and $CHADS_2 \geq 1$ 3. Anticoagulation is contraindicated	Use of LAAO device (Watchman) in patients with contraindications to anticoagulation (n = 150)	Composite of: Ischemic stroke, haemorrhagic stroke, systemic embolism, and cardiovascular/unexplained death	Procedure and device related complications	LAA occlusion device is a safe alternative when OAC is contraindicated
PROTE	Random	4-year	Described	Described above	Described	LAA

CT AF, Reddy et al(192), 2014	ised controlled trial	follow up of PROTECT AF trial	above		above	occlusion device met both non-inferiority and superiority criteria compared to warfarin
PREVAIL trial, Holmes et al(143), 2014	Randomised controlled trial	1. Non-valvular AF 2. And $CHADS_2 \geq 2$, or ≥ 1 and another risk factor including: female aged ≥75 years, baseline ejection	Compare safety and efficacy of the Watchman LAA closure device (n = 269) vs warfarin (n = 139)	composite of: Stroke, systemic embolism, and cardiovascular/unexplained death	Composite of: all-cause death, ischemic stroke, Systemic embolism, or device-/procedure-related events requiring open cardiovascular surgery	LAA closure device was non-inferior to warfarin for ischemic stroke prevention or systemic embolization >7 days post procedure

		fraction ≥30% but <35%, age 65 to 74 years and either diabetes or coronary disease. and age ≥65 years with CCF			or major endovascular intervention between randomization and within 7 days of the procedure or during the index hospitalization	
PRAGUE-17, Osmancik et al (145), 2020	Randomised controlled trial	1. nonvalvular AF 2. with an indication for OAC 3.and had -a history of bleeding requiring interventio	Comparison of LAA closure device [Amulet or Watchman/Watchman- FLX] (n = 201) vs NOAC (n = 201)	Composite of: stroke, TIA, systemic embolism, cardiovascular death, major or nonmajor clinically relevant bleeding, or procedure-/device- related complications	Safety end points are part of the primary composite point	-LAAO was noninferior to NOAC in preventing major AF-related cardiovascular, neurological, and bleeding

		n or hospitalization, - a history of a cardioembolic event while taking OAC, - and/or a CHA2DS2-VASc of ≥ 3 and HAS-BLED of >2.				events

AF, Atrial fibrillation. TIA, transient ischemic attack. CCF, congestive cardiac failure. DM, diabetes mellitus. HTN, hypertension. LAAO, left atrial appendage occlusion. N, number. OAC, oral anticoagulation. NOAC, non-vitamin K oral anticoagulant.

Table 2. Risk scores for predicting AF in stroke patients

Score/ Study Name	Reference	Population Tested	Variables	Score/ Total Score	Reported Predictive value/ Sensitivity & Specificity in Detecting AF/ AF rates / C-Statistic
STAF	Suissa et al.(165)	Stroke	Age >62 years	2 points	A score of ≥5 had: 89% sensitivity 88% specificity
			NIHSS ≥8	1 point	
			LA dilatation	2 points	
			Absence of symptomatic intra or extra-cranial stenosis ≥50%, or clinico-radiological lacunar syndrome	3 points	
LADS	Malik et al.(166)	Stroke/ TIA	LA diameter (mm)	0-2 points	A score ≥4 had: 85.5% sensitivity 53.1%. specificity
			Age (years)	0-2 points	

			Diagnosis (stroke/TIA)	0-1 point	
			Smoking within the previous year	0-1 point	
C_2HEST	Li et al.(171)	Stroke	Coronary artery disease or chronic obstructive pulmonary disease	1 point each	1. Low risk group (0-1 point): annual AF incidence of 3.19%,
			Hypertension	1 point	2. Medium-risk group (2 or 3 points): annual AF incidence of 7.15%,
			Elderly [age ≥75 years]	2 points	
			Systolic heart failure	2 points	3. High-risk group (≥4 points): annual AF incidence of 14.64%
			Thyroid disease [hyperthyroidism]	1 point	
HAVOC	Kwong et al.(169)	Stroke/TIA	Hypertension	2 points	1. Low risk (0–4 points): AF rate of 2.5%,
			Age	2 points	

			Valvular heart disease	2 points	2. Medium risk (5–9 points): AF rate of 11.8%,
			Peripheral vascular disease	1 point	
			Obesity (BMI of >30)	1 point	3. High risk (10–14 points): AF rates of 24.9%,
			Congestive heart failure	4 points	
			Coronary artery disease	2 points	
CHARGE-AF	Alonso et al.(172)	Community	Age	A 5-year predictive model is created	C-statistic: 0.765; (95% CI, 0.748 to 0.781)
			Race		
			Height		
			Weight		
			Systolic and diastolic blood pressure		

			Current smoking		
			Use of antihypertensive medication		
			Diabetes		
			History of myocardial infarction and heart failure		
CHA_2DS_2-VASc	Lip et al. (193)	Stroke	Congestive Heart Failure or left ventricular ejection fraction of □ 40%	1 point	C- statistic: 0.712 (95% CI, 0.693–0.731) [Christopherson et al.(173)]
			Hypertension	1 point	
			Age □ 75 years	2 points	
			Diabetes	1 point	
			Stroke / TIA/	2 points	

			thromboembolism		
			Vascular disease history (prior MI, peripheral artery disease, or aortic plaque)	1 point	
			Age 65-74 years	1 point	
			Female gender	1 point	
NDAF	Bugnicourt et al.(175)	Stroke	Age ≥72 years	2 points	A score of 0 or 1 has high negative predictive value for NDAF at one year
			History of coronary artery disease	1 point	
			History of stroke	1 point	
			LA area ≥16 cm^2	2 points	

AF, atrial fibrillation; NIHSS, The National Institutes of Health Stroke Scale; LA, left atrial; TIA, transient ischaemic attack; BMI, Body mass index; MI, myocardial infarction;

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: