**Stroke in Atrial Fibrillation and Other Atrial Dysrhythmias**

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**Abstract**

**Purpose of review:** Atrial fibrillation (AF) is a major risk factor for systemic embolism and ischaemic stroke. Furthermore, AF-related strokes are associated with higher mortality, greater disability, longer hospital stays, and lower rates of hospital discharge than strokes caused by other reasons. The aim of this review to summarize the existing evidence on the association of AF with ischemic stroke and provide insights on the pathophysiological mechanisms and the clinical management of patients with AF in order to reduce the burden of ischemic stroke.

**Recent findings:** Beyond Virchow’s triad, several pathophysiological mechanisms associated with structural changes in the left atrium, which may precede the identification of AF, may contribute to the increased risk of arterial embolism in AF patients. Individualized thromboembolic risk stratification based on CHA2DS2-VASc score and clinically relevant biomarkers, provide essential tool towards a personalised holistic approach in thromboembolism prevention. Anticoagulation remains the cornerstone of stroke prevention moving from vitamin K antagonists (VKA) to safer non-vitamin K direct oral anticoagulants in the majority of AF patients. Despite, the efficacy and safety of oral anticoagulation, still the equilibrium between thrombosis and hemostasis in AF patients remains suboptimal and future directions in anticoagulation and cardiac intervention may provide novel treatment options in stroke prevention.

**Summary:** This review summarizes the pathophysiologic mechanisms of thromboembolism, aiming the current and potential future perspectives in stroke prevention in AF patients.

**Keywords:** stroke; atrial fibrillation; risk stratification; anticoagulant.

**Introduction**

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a significant global health burden1 which has been increasing during the last 50 years.2 The global prevalence of AF has been estimated around at 38 million cases and is expected to rise by more than 60% by 2050.3 AF is a well-established cardioembolic risk factor with a 3-fold higher risk of ischaemic stroke4 and is also associated with higher mortality and morbidity rates, and longer hospital stays compared to non-AF-related strokes.5 As a result, the risk of death is double and the cost of care is 1.5 times more in stroke patients with AF compared to those without.6 Taken together, the increasing prevalence of AF represents a considerable public health burden, with untreated AF still accounting for a considerable proportion of ischaemic strokes7.

Oral anticoagulant treatment, especially in the era of non-vitamin K antagonists (NOAC), is the mainstay therapy for stroke prevention in patients with AF.8 A careful stratification of the thromboembolic and bleeding risk is essential in stroke prevention among AF patients, providing the ability to identify those patients who may benefit from alternative therapeutic approaches.9

In this review, we summarise the potential mechanisms of AF-related stroke, epidemiology and temporal trends of AF and AF-related stroke. We highlight thromboembolic risk stratifications and outline serum biomarkers, electrocardiogram (ECG) findings and imaging parameters which are potential predictors of stroke in patients with AF. We also discuss the prevention and intervention therapies relevant to AF-related stroke, and the challenge of anticoagulant treatment failure.

**Prevalence and time trends of atrial fibrillation**

AF has been described as a growing major public health problem given the increasing prevalence and incidence, and the ageing population with multimorbidity. AF is often asymptomatic and may first be diagnosed following presentation with an AF-related complication; hence, the calls for increasing efforts directed at AF screening.10

The prevalence of AF, following the increasing trends of ageing and cardiovascular risk factor accumulation11, is expected to double over the next 30 years reaching 4% by 2050, with a lifetime risk of AF in 1 out of 7 individuals over 20 years of age.4 In the Framingham Heart Study (FHS), over the last 50 years among 9511 individuals (202,417 person-years) the age-adjusted prevalence of AF significantly increased in both men and women, with a concomitant age-adjusted incidence increase from 3.7 to 13.4 new cases per 1000 person-years in men and from 2.5 to 8.6 new cases per 1000 person-years in women.2 In a population based study based on electronic healthcare records of 3.4 million people, from 1998 to 2017 the incidence of AF increased by 30% (247 to 322 per100.000 person-years; adjusted incidence rate ratio [IRR] 1.30, 95% CI 1·27–1·33), associated with a significant increase of the comorbidity burden at AF diagnosis12. In the same study, AF incidence was significantly correlated with socioeconomical status, being more common in deprived individuals, reflecting the association of socioeconomic status with the prevalence of comorbidities and unequal health-care access13. Another population-based study showed that after adjustment for age and sex, the incidence of AF increased significantly with a relative increase of 12.6% over 21 years14. Interestingly though, a recent population-based study among 15,343 men and women aged 45 to 64 years over a mean (SD) follow‐up of 22 years (8.4), showed that although the IRs of AF increase as age increases affecting the overall prevalence of AF, after adjustment for sex, race, and age group, the rate of new AF diagnosis did not change significantly from 1987 to 1991 compared with 2012 to 2017 (incidence rate ratio, 1.10 [95% CI, 0.88–1.36])15.

*Epidemiology of atrial fibrillation-related stroke*

The prevalence of AF among patients with ischaemic stroke is increasing, particularly among Caucasian and elderly patients16, associated with increased disability and extended in-hospital stay.17 Since 2010, the impact of AF on in-hospital mortality has been significantly reduced due to overall temporal improvements in hospital stroke care, with no evidence of sex or race-ethnic disparities in in-hospital mortality.16, 17 However, AF is still associated with increased morbidity and mortality, as well as increased cost and resource use.16

The FHS showed that after multivariable-adjustment there was a 74% (95% CI 50-86%) relative reduction in stroke risk (hazards ratio [HR] 3.77, 95% CI 1.98-7.20 in 1958-1967 compared with 1998-2007; ptrend=0.0001) and 25% (95% CI -3.1 - 46%) decrease in mortality (HR 1.34, 95% CI 0.97-1.86 in 1958-1967 compared with 1998-2007; ptrend=0·003) over a follow-up period of 20 years after AF diagnosis2. Accordingly, among patients admitted with ischaemic stroke between 1993 and 2012, there was an average annual increase in the proportion of AF patients who were prescribed anticoagulants [modified Rankin Scale (mRS)<4 (3.5%) and mRS: 4–5 (7.2%)], leading to an average annual reduction of stroke recurrences (5.8%, 95%CI: −8.6; −3.0%), cardiovascular events (6.5%, 95%CI: −8.3; −4.7%) and deaths (7.9%, 95%CI: −9.2; −6.5%)18.

Ageing, male sex, and Caucasian race are associated with increased risk of incident AF2, 19. Similarly aging increases the risk of stroke in patients with AF, with a three-fold increase in those older than 65 years of age.2, 20, 21 Although stroke is more common among men, AF-related stroke is more common among women. A meta-analysis of 30 studies including 4,371,714 patients, showed female sex was associated with a two-fold increase in the risk of stroke among patients with AF, compared to men.22

**Mechanisms of cardioembolism in atrial fibrillation**

AF is a major independent predictor of ischaemic stroke and systemic embolism, with an estimated lifetime risk ranging from 22% to 26%.23 Although the loss of atrial contraction is associated with blood stasis, it seems that thrombus formation is not limited only to that, since substantial evidence supports the presence of a prothrombotic or hypercoagulable state in patients with AF (Figure 1).24

1. *Structural and abnormal flow*

From a structural and pathological perspective, a narrow inlet of the left atrium, the left atrial appendage (LAA), is an atrium area associated with lower contractility and blood stasis, which predisposing to thrombus formation, especially in the loss of atrial contractility as in AF.25 The presence of non-valvular AF and loss atrial organised contraction is associated with progressive atrial dilatation leading to abnormal blood flow and stasis.26 Atrial dilation has been found to be an independent risk factor for stroke and has been shown that there is an association between atrial size and risk of stroke.27 In terms of abnormal blood stasis, another thromboembolic risk factor is LAA emptying flow. For example, Mügge *et al*28 showed that patients with non-valvular AF have an increased risk for thrombosis, particularly those with a low LAA emptying flow rate of <250mm/s. Also, they demonstrated that the incidence of thromboembolism in the low flow rate group was considerably higher (60%) compared to those with high flow (≥250 mm/s).28

1. *Endocardial and endothelial damage/ dysfunction, and hypercoagulability*

Endocardium damage/ dysfunction account for one of the components of Virchow`s triad. Certain structural changes in the atrium may lead to the development of AF and subsequently, contribute prothrombotic state via a variety of mechanisms.29-31 In a post-mortem study of the morphology of LAA, patients with AF had increased LAA volume and luminal surface area, reduced pectinate muscle volume and marked endocardial thickening with fibrous and elastic tissue.30 When these changes are combined with the loss of atrial contraction, they may cause abnormal blood stasis and subsequent thrombosis.32

Endothelial damage/ dysfunction is also suggested as a potential mechanism of thrombosis in patients with AF, by identifying several components representing endothelial disruption such as von Willebrand factor (vWf) and E-selectin.33, 34 The vWf is a glycoprotein which is secreted during the endothelial injury thereby, it is usually measured to assess endothelial damage, whereas E-selectin is an endothelial-specific adhesive molecule that is elevated in the bloodstream as a result of endothelial activation.35, 36 Increased levels of both vWf and E-selectin have been found in patients with AF suggesting a potential correlation between AF and endothelial dysfunction.37, 38 For example, Krishnamoorthy *et al* in a study with 423 patients with AF followed for approximately 2 years, showed that patients with elevated levels of vWf and E-selectin were at higher risk of thromboembolism 37. Aside from vWf, and E-selectin, high levels of asymmetric dimethylarginine (ADMA) also contribute to clot formation by inhibiting endothelial nitric oxide (NO) synthase. 39 NO is one of the principal endothelium derived vaso-active substances and plays a critical role in maintaining endothelial homeostasis.40 Low levels of NO are associated with impaired endothelial function and excess ADMA reduces NO levels by inhibiting endothelial nitric oxide synthase .40, 41 A study by Goette *et al* demonstrated that patients with AF had high levels of ADMA compared to those in sinus rhythm and also, that ADMA levels returned to normal within 24 hours after electrical cardioversion.42

Hypercoagulability is primarily associated with activation of the coagulation cascade, increased platelet reactivity or impaired fibrinolysis. Patients with chronic AF have higher levels of coagulation factors (factor VIII:C, vWf and fibrinogen), platelet activation (plasminogen factor-4 and β- thromboglobulin) and secondary fibrinolysis (D- dimer).43 Several studies have shown that AF may induce a hypercoagulable state as measured by increased levels of D-dimer, Fibrinogen and prothrombin fragment 1+2 (F1+2).44, 45 Especially, fibrinogen plasma levels in AF patients have been significantly associated with ischaemic stroke implying that the coagulation system could be implicated in thrombosis-related ischaemic events of AF.46

1. *Atrial cardiopathy and fibrosis*

Atrial cardiopathy refers to structural and functional abnormalities of the atrium, which are evident also in patients with AF.47 Additionally, AF often arises as a consequence of underlying cardiac abnormalities,23 and then deteriorates these abnormalities through a variety of mechanisms including atrial remodelling, leading to the acknowledgment that AF is both a cause and consequence of atrial cardiopathy.48 Moreover, atrial cardiopathy is being considered an emerging risk factor for ischaemic stroke and systemic embolism, even in the absence of AF.49 Accumulating evidence suggests that is associated to changes in collagen degradation and impaired extracellular matrix degradation, which may also precede the identification of AF.50 The presence of inflammatory infiltration and the activation of fibrotic pathways via fibroblasts and transforming growth factor-β leads to structural remodelling of the atria.51

Atrial cardiopathy and subsequent fibrosis may be the result of several cardiovascular comorbidities which have been previously proposed to be associated with AF, including obesity, hypertension, and sleep apnoea.52 Fibrous tissue content and distribution in patients with AF are related not only to AF mechanisms but also to the risk for therapeutic failure and complications.53, 54

Several electrocardiographic, echocardiographic and serum biomarkers have been proposed to define atrial cardiopathy in the absence of AF. For example P-wave terminal force in lead V1 (PTFV1) on 12-lead ECG,55-57 the left atrial size on echocardiogram58 the serum amino terminal pro-B-type natriuretic peptide (NT-proBNP)59 and others.60 Moreover, in patients with ischaemic stroke, cardiac magnetic resonance imaging (MRI) have also been used to assess atrial fibrosis, which has been shown to be more common in patients with embolic stroke of undetermined source (ESUS).61 A post-hoc analysis of the Warfarin Aspirin Recurrent Stroke Study (WARSS) in patients with previous stroke and elevated serum biomarkers related to atrial cardiopathy, showed that warfarin reduced risk of stroke or death at 2 years compared to aspirin.62

Although there may be an important interplay between atrial cardiopathy and ischaemic stroke, anticoagulation treatment is currently not recommended in patients with stroke who have findings of atrial cardiopathy only.60 Ongoing randomised controlled trials investigate the optimal antithrombotic strategy. Specifically, the Atrial Cardiopathy and Antithrombotic Drugs in Prevention after Cryptogenic Stroke Trial (ARCADIA) investigates the hypothesis that a NOAC may be superior to aspirin for the prevention of recurrent stroke in patients with cryptogenic ischaemic stroke and atrial cardiopathy.63 Until the results of the trial become available, antiplatelet therapy is the recommended strategy in patients with previous ischaemic stroke and atrial cardiopathy.

In the primary prevention setting, it is still unclear whether any antithrombotic treatment is beneficial for stroke prevention in patients with atrial cardiopathy, as it is not known whether the potential benefit of stroke prevention exceeds the associated risk of antithrombotic-related bleeding events.

**Atrial fibrillation in acute stroke**

Whether post-stroke AF is a consequence of brain damage associated with several neurogenic mechanisms or represents the cause of stroke is not always certain. In stroke, especially with the involvement of insula64, brain ischemia and cell death may affect the autonomic nervous system.65 This neurogenic dysregulation following acute stroke, may lead to sympathetic overactivity66, 67 and inflammatory upregulation, which may also be associated with the development of AF.51, 68 Furthermore, this combination of local and distal inflammatory mechanisms, may lead to early cardiac complications, collectively described as Stroke-Heart syndrome, increasing the risk of secondary AF69-71.

The hypothesis of “neurogenic” AF has been supported by several studies, especially in episodes of AF identified during the early days after the ischemic stroke.72 Evidence from observational data suggest that self-terminated episodes of AF are associated with lower risk of stroke recurrence or major adverse cardiovascular events compared to sustained AF73-76 Towards this notion several clinical observations suggest that post-stroke AF lacks accompanying features of long-standing AF.72, 77 Still, it is uncertain whether post-stroke episodes of AF are the cause or a consequence of stroke.

**Thromboembolism in atrial high-rate episodes**

Current technological devices and artificial intelligence methods including from cardiac implanted electronic devices (CIED), such as pacemakers, implantable defibrillators, implantable loop recorders (ILR) and wearable devices provide the ability to assess the burden and the types of atrial arrhythmias burden. Even short episodes of sub-clinical AF and other atrial tachyarrhythmias, summarized under the term atrial high-rate episodes (AHRE) can be identified by such CIEDs.

Although AF was traditionally considered as a binary risk factor for thromboembolism, especially related to treatment decisions, growing evidence from several studies suggest that AHREs >30 seconds may significantly increase the risk of ischaemic stroke or systemic embolism.78 Based on a pathophysiological perspective, changes in left atrium and atrial endocardium dysfunction which may precede the identification of AF, may increase the risk of thromboembolism.79 Accordingly, AHREs may represent an early state of AF, which based on the same pathophysiological and structural changes, increase the risk of thromboembolic events. It is still unclear whether these patients would benefit from anticoagulation to reduce their risk of stroke.80

The ongoing ARTESIA (Rationale and design of the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) and the NOAH-AFNET (Probing oral anticoagulation in patients with atrial high rate episodes: Rationale and design of the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes) trials in patients with CIEDs, may eventually provide essential information on the use of anticoagulation in patients with subclinical atrial fibrillation.81, 82

**Thromboembolic risk assessment**

*Clinical risk stratification tool*

The risk of stroke and thromboembolism in patients with AF are not homogenous and associated with presence of several risk factors (Figure 2). These risk factors have been used to develop several risk stratification tools. Among them initially CHADS2 and then CHA2DS2-VASc scores including simple clinical factors provide the ability to discriminate patients with AF into low and high risk for thromboembolic events categories.83, 84 Anticoagulation is now recommended for patients with a CHA2DS2-VASc score of 1 or higher unless the score is solely based on female sex, in which case another risk factor is required.85 Several studies have shown that CHA2DS2-VASc have similar or slightly higher sensitivity than the CHADS2 score and other proposed clinical risk scores.86, 87 Currently, CHA2DS2-VASc is recommended as the stroke stratification tool in the most of major guidelines. 88-90

Clinical stroke risk scores in general are not dynamic and work on the assumption that all patients have the same risk profile. Often, the stroke risk scores lack generalisability and appreciation of various individual risk factors. In addition, although female sex is a risk modifier for stroke in patients with AF; its value is prominent in the presence of other clinical risk factors of stroke, since if the female sex is the only risk factor, it does not confer a CHA2DS2-VASc score of 1.91

*Biomarkers in risk stratification*

Beyond clinical assessment tools, biomarkers can improve stroke risk stratification in patients with AF and evidence on how they can refine clinical risk stratification are present more than 10 years ago.92 Since then, many biomarkers have been studied, with the natriuretic peptides and cardiac troponins have emerged as the most promising to date.93 Nonetheless, many biomarkers are non-specific at being predictive of clinical outcomes beyond stroke (or bleeding) in patients with AF.94

The biology of natriuretic peptides is complex, they are synthesised and secreted in response to myocyte which occurs under pressure or volume overload.95 Moreover, B-type natriuretic peptide (BNP) and the N-terminal fragment of BNP have been associated with AF diagnosis and the identification of AF in patients acute ischaemic stroke.96, 97 Furthermore, in patients with AF associated stroke, elevated BNP is predictive of recurrent events98 and higher BNP levels were associated with suspected cardioembolic stroke rather than with non-cardioembolic stroke.99 In the sub-analysis of RE-LY 100 and ARISTOTLE trial 101 it was shown that patients with NT-proBNP levels in the highest quartile had a significantly elevated risk of stroke or systemic embolism.

Although there is an association between these biomarkers and stroke, whether this association relies on the accumulation of concomitant cardiovascular comorbidities or has a direct association with thromboembolic risk is unclear. Therefore, the use of biomarkers to improve risk stratification of stroke in patients with AF has been a longstanding topic of discussion. A study which investigated the potential additional effect of several biomarkers (vWf, high-sensitivity troponin T, NT-proBNP, IL-6, fibrin monomers and β-trace protein) to CHA2DS2-VASc, found that the addition of consecutive biomarkers did not improve its predictive performance for ischaemic stroke102. On the other hand, another study found that adding four blood biomarkers (high-sensitivity troponin T, NT-pro-BNP, IL-6, vWf) enhanced the predictive accuracy of CHA2DS2-VASc in well anticoagulated and stable AF patients; however, the overall accuracy remained modest with only marginal addition to the current stratification tools.103 Furthermore, a study which investigated the addition of vWf to CHA2DS2-VASc on anticoagulated AF patients found that adding vWf statistically improved the predictive value of CHA2DS2-VASc score.104 The ABC score including age, biomarkers (NT-pro-BNP, high-sensitivity troponin) and clinical history (prior stroke/transient ischaemic attack), was proposed to predict stroke in AF.105 However, in anticoagulated patients with AF the ABC score did not offer significantly better predictive performance compared to the CHA2DS2-VASc score and more importantly the CHA2DS2-VASc score was better in identifying low risk patients.106

Several observational studies suggested additional biomarkers which may help in the identification of AF patients at higher risk of cardioembolic strokes, such as cardiac troponin,100 C-reactive protein,107 or even interleukin-6,108 but whether these biomarkers are effective taking into consideration their availability and cost needs to be investigated in prospective real world studies.

Although in some studies the addition of biomarkers to clinical risk scores results in better prediction of stroke risk in patients with AF, it may delay the treatment by adding another step to an already hectic clinical environment. Moreover, most of the biomarkers are non-specific; hence, they might be a reflection of other conditions/diseases in patients with multiple health issues.94 Beside these limitations, there are also issues with timing of blood samples, establishing normal ranges of biomarkers, and expensive costs.109

*Imaging and ECG parameters for risk stratification*

A structural evaluation of the heart may provide additional information about stroke aetiology. Left atrial size, LAA morphology and left atrial fibrosis are potential predictors of stroke associated with AF. Transthoracic echocardiography (TTE) is a simple and commonly performed modality to evaluate the structural and functional integrity of the heart, and it can provide valuable information to aid in stroke assessment. Studies demonstrated that left atrial enlargement is associated with higher thromboembolic risk and recurrent events among patients with cryptogenic stroke.58, 110 Echocardiogaphic findings have been associated also with structural changes in LA. Increased LA volume has been associated with higher atrial fibrosis, however this correlation is not linear, and some patients demonstrated severe fibrosis while still showing modest increases in atrial volume.111 Furthermore, according to a study on patients without evident AF, left atrial volume was found to be an independent risk factor for stroke, suggesting that LA changes related to higher thromboembolic risk may precede the identification of AF.112

Several ECG markers associated with atrial or AV nodal abnormalities have been associated with stroke. P wave duration and P wave terminal force in electrocardiogram lead V1 on surface ECG, have been shown to be associated with stroke independent of the presence of AF.56, 57 In addition to these, P wave area is related to an increased risk of stroke.113 Furthermore, a study with 146 patients found that a prolonged P wave interval of >120 ms was also associated with an increased risk of stroke.114 Imaging and ECG parameters may provide valuable information about stroke risk; however, using them for risk stratification still remains uncertain.

**Thromboembolism prevention**

The prevention of systemic embolism and stroke is the cornerstone of AF management representing the initial and most essential part of an integrated and holistic approach to the treatment of patients with AF115, tailored by the characteristics and comorbidities of each patient.116

*Medical therapy*

For decades, anticoagulant monotherapy for stroke prevention in AF patients, was vitamin K antagonists (VKAs), such as warfarin or acenocoumarol. Various studies have shown the effectiveness of warfarin in reducing thromboembolic events in individuals with AF compared to antiplatelets.117, 118 However, adherence to VKAs and the time spend in therapeutic range of prothrombin time were found to be optimal in less than the half of the patients who were enrolled in multiple trials, due to the medication's onerous monitoring requirements and numerous drug and dietary interactions.119, 120

In recent years, non-vitamin K oral anticoagulants (NOACs), which do not require routine coagulation monitoring and have rare drug-to-drug interactions121, have been compared to VKA for the prevention of stroke in patients with non-valvular AF. These trials are supported by real world studies showing that anticoagulation therapy with NOAC is associated with lower rates of ischaemic stroke and major bleeding when compared to warfarin.122, 123 Several meta-analyses found that NOACs are associated with 15% reduction in thromboembolic events, almost 10% reduction in all-cause mortality and a 50% reduction in intracranial haemorrhage.121, 124-126 Despite the effectiveness and safety of NOACs, VKA are still in the frontline of thromboembolism prevention in patients with valvular AF or concomitant mechanical valve, where NOACs were not found to be effective.127, 128 Current international guidelines suggest the use of anticoagulation in patients with AF at risk of thromboembolic events based on CHA2DS2-VASc score, antiplatelets are now not suggested for the prevention of stroke in AF.89, 129, 130 Despite the use of anticoagulation there is still significant residual risk of stroke and mortality in patients with AF. In order to lessen this residual cardiovascular risk, the recent ESC guidelines, suggest a holistic approach in the treatment of patients with AF focusing in the management of concomitant long-term conditions in order to reduce the risk of stroke and cardiovascular events 89.

In a pursuit to balance the equilibrium between thrombosis and haemostasis, recent evidence revealed the association of factor XI (FXI) with thrombogenesis rather haemostasis.131 Recently in a Phase II trial, Asundexian, a novel inhibitor of the activated coagulation factor XIa, was found to significantly reduce the primary endpoint of major or clinically relevant non-major bleeding among patients with AF compared to apixaban, with similar rates of adverse events.132 Similarly, several novel anti-FIX or FIXa antibodies or inhibitors are in development or being in phase I or II clinical trials for patients with AF, making the future of thromboembolism prevention in patients with AF intriguing.133

*Interventional therapy*

Percutaneous closure of LAA was first introduced in 2001 as alternative option for thromboembolic risk reduction in patients who cannot tolerate anticoagulation.134 Several observational studies have shown that LAA occlusion might be a safe and effective alternative in patients with AF, especially in those at higher bleeding risk.135, 136 The PROTECT AF137 (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation) and PREVAIL138 (Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy) trials demonstrated the non-inferiority of WATCHMAN device to warfarin in terms of reduction of all cause stroke and systemic thromboembolism.139 Real world studies have been less reassuring, with a high prevalence of device-related thrombus140 and a high mortality post LAAO implantation (for example, 1in 6 patients, in a recent analysis).141

Recently, in the Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation (Prague-17) among patients with AF and history of cardio-embolism under NOAC, or clinically-relevant bleeding, or both high risk of bleeding and thromboembolism (HASBLED ≥2 and CHA2DS2-VASc ≥3), LAA closure was found to be noninferior to NOACs for the composite clinical outcomes.142 The WATCHMAN device is now approved in clinical usage in both USA and Europe for the patients at risk of stroke, recommended and deemed suitable for OACs but have and appropriate reason to consider a non-pharmacological alternative to warfarin. As a result of the limited data comparing LAAO with NOACs and the increased stroke risk under LAAO compared to VKA, the recommendations for LAAO are rather weak(Class IIb in ESC and AHA guidelines). According to the ESC and AHA guidelines,89, 130 LAAO may be considered for stroke prevention in patients with AF and contraindications for long term anticoagulant therapy (Class IIb). In addition to this, ESC guidelines also recommend that LAAO may be considered for stroke prevention in patients with AF undergoing cardiac surgery (Class IIb). 89

**Anticoagulant failure**

Our best efforts at AF-related stroke prevention sometimes fail, either because patients are not offered appropriate treatment or because treatment is not anyway completely effective.143 This is often regarded as a treatment failure. Patients on warfarin may have suboptimal outcomes due to an inadequate time in therapeutic range especially in the presence of concomitant comorbidities.144 As a result, the quality of therapy is frequently inadequate, and despite monitoring and dose adjustments patients may be outside the therapeutic range in more than one-third of the time144 which represents an indirect anticoagulant failure.

NOACs offer important advantages compared to VKAs, not requiring routine coagulation monitoring, by not having a specific dietary requirement or usual drug-drug interactions.121 Despite these benefits, low adherence to NOAC treatment and dosages has been challenge in real world.145 Even in developed countries, patients with AF were usually under-treated.146, 147 For example, in the USA, in 2011, only 43% of AF patients were initiated OAC after discharge.148 According to the findings of an Australian AF study with 1471 new users of NOACs and 1348 new users of warfarin, 9% of NOACs users failed to collect first repeat prescriptions and 30% discontinued within 12 months, while the corresponding percentages for warfarin were 14% and 62% respectively.149

On the other hand, the optimal use of NOACs in real life remains a challenge. Different dosage regimens for various indications, especially in older patients, those with renal insufficiency and drug-to-drug interactions, may affect the effectiveness and safety of these drugs in real life.150 According to the findings of a study that evaluated the appropriateness of prescribing dabigatran and rivaroxaban in patients with non-valvular AF, one out of four patients was prescribed the incorrect dosage.151 According to a recent questionnaire about use of NOACs in clinical practise, 43% of patients with AF and impaired renal function were potentially overdosed and had a higher risk of major bleeding, while 13% of patients with normal renal function were potentially underdosed had a higher risk of stroke.152

Apart from pitfalls in the dosage regimens and adherence which may affect anticoagulants success, even in the well-controlled randomised trials, characterized by robust follow-up and treatment according to protocol, among AF patients treated with oral anticoagulants the annual rate of ischaemic stroke was 1-2% per year.153-156 In observational studies, among patients with previous ischaemic stroke and AF treated with anticoagulants, the risk of recurrent event was approximately 3%-5% following the index stroke.157, 158 Although, ischaemic stroke recurrences among AF patients treated with anticoagulants were 4.9% during the first year after the initial stroke, this is not always attributed to AF, emphasising the multifactorial aetiological mechanism of ischaemic stroke.159 Thus, in patients with AF, who are experiencing an ischaemic stroke or a recurrent thromboembolic event, we should always take into consideration patients’ adherence, correct dosage, concomitant diseases and after excluding other potential causes of ischaemic stroke, such as large vessel atherosclerosis or stroke due to low-flow, in order to attribute a recurrent event to pure anticoagulant failure.

**Conclusion**

AF is and will continue to be a challenge for healthcare systems. AF-related stroke remains important due to the increased risk of mortality, morbidity and longer hospital stays. In patients with AF, effective risk stratification (for example using CHA2DS2-VASc score) and appropriate thromboprophylaxis (with VKA or NOACs; or if OACs are contraindicated, LAA occlusion) are essential for stroke prevention. Anticoagulant failure also contributes to the burden of AF-related stroke; thus, it is important to identify cause(s) of treatment failure and tailor therapies to individual patients.

**Declarations**

**Conflict of Interest**

Dr Sagris reports receiving research support by the ESC council on Stroke.

Prof Lip reports being a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are received personally.

The other authors report no conflicts of interest.

**Human and Animal Rights and Informed Consent**

This article does not contain any studies with human or animal subjects performed by any of the authors.

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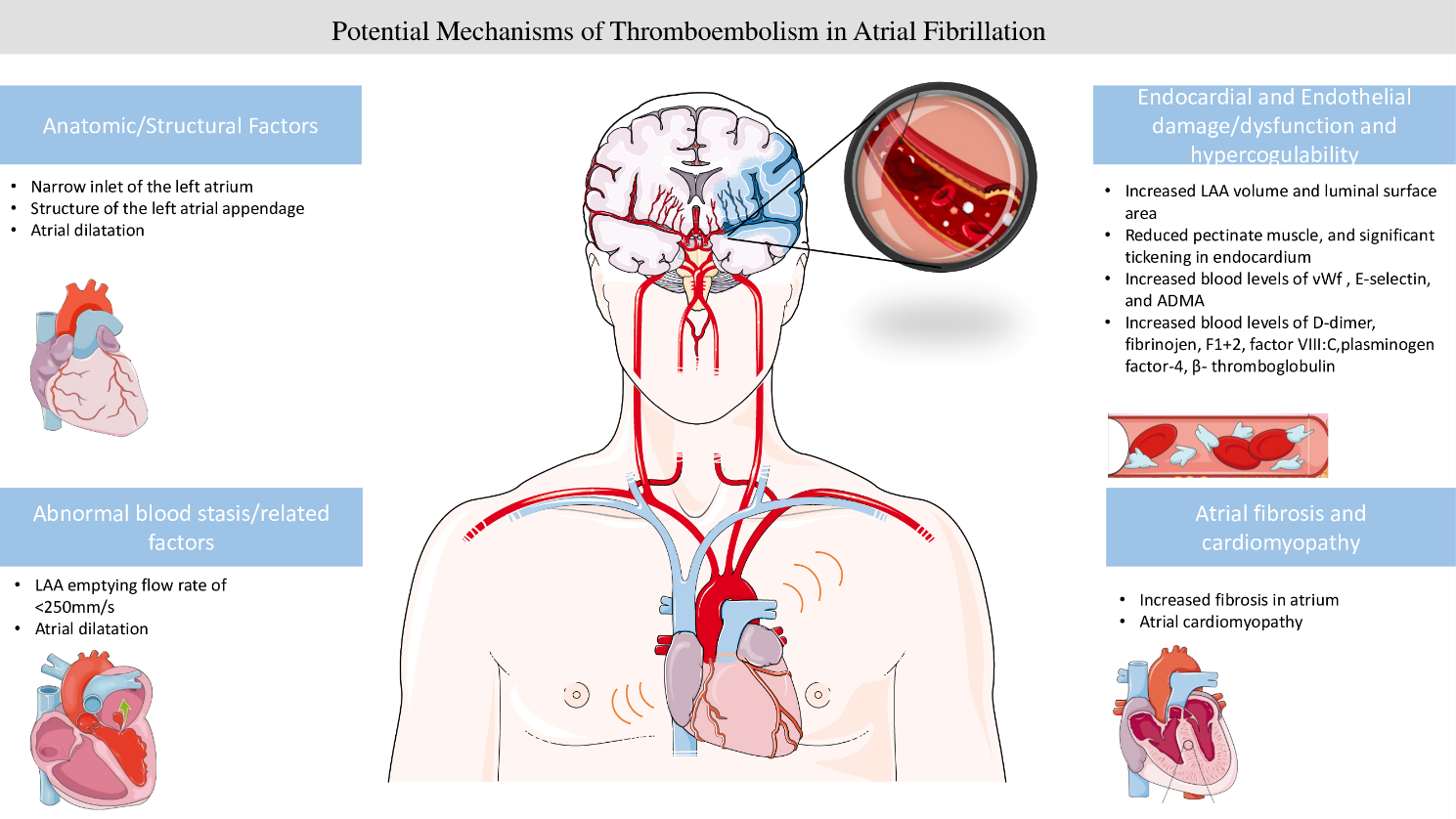
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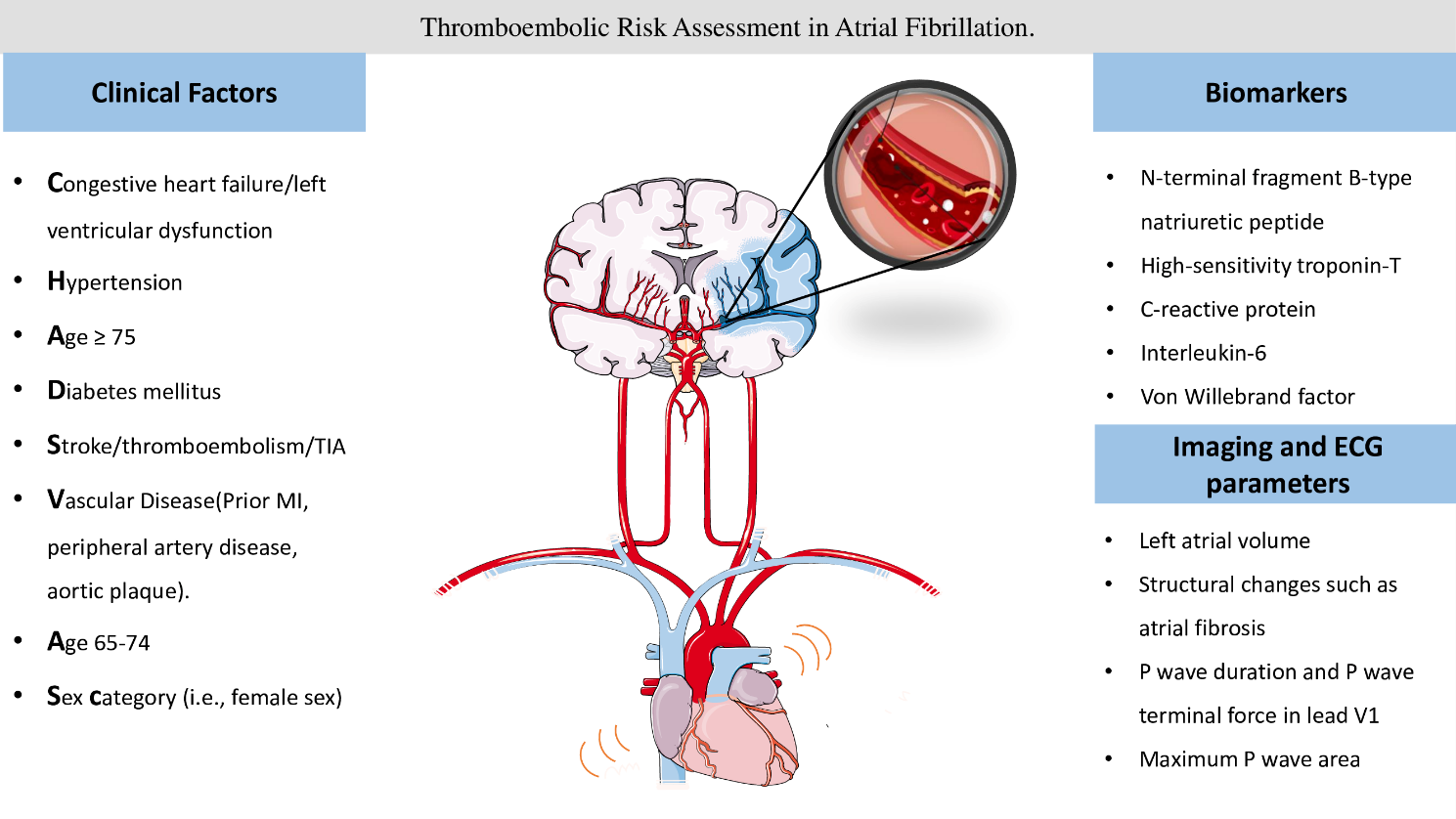
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Figures



**Figure 1:** Potential mechanisms of thromboembolism in atrial fibrillation; LAA: left atrial appendage, vWF: von-Willenbrand Factor, ADMA: asymmetric dimethylarginine. Servier Medical Art images were used for this figure (https://smart.servier.com).



**Figure 2:** Thromboembolic risk assessment in atrial fibrillation. Clinical factors, circulating biomarkers, ECG and imaging markers. ECG: electrocardiogram. Servier Medical Art images were used for this figure (https://smart.servier.com).