Chapter 6
Atrial Fibrillation and Stroke

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6.1 Epidemiology

Atrial fibrillation is a supraventricular tachyarrhythmia characterized by an uncoordinated atrial electrical activation that produces an ineffective atrial contraction. It is a highly prevalent cardiac arrhythmia affecting 2–4% of global population [1]. In 2017, the global incidence and prevalence were 403 new cases and 4977 cases per million inhabitants, respectively, a significant increase relative to 1997 (309 new cases and 3751 cases per million) [2]. The incidence of AF is expected to continue growing in future years [1–3]. Population studies from the USA and Europe have estimated a 2.3-fold increase in the prevalence of the disease in the next few decades [3, 4].

The most prominent risk factor for AF is age, with a yearly prevalence increase of approximately 5% after the age of 65 [5], and older cohort studies indicate an OR of 2.1 for every extra decade of life [6]. The risk of developing AF depends on genetic predisposition and clinical risk factor's burden [7–10]. Males have a slightly

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increased risk of developing AF compared to females, with a ratio of 1.11 [2]. There are also racial differences on prevalence, with being AF less frequent in non-Caucasians compared with Caucasians [11–13]. The lifetime risk of AF in the European ancestry population is 1 out of 3 (37%), and 1 out of 5 in the black and Asian population [14–17]. Genetic polymorphisms have shown an association with incidence of AF after adjusting for other factors [7, 18].

Modifiable risk factors typically associated with cardiovascular disease have demonstrated association with AF in several different studies: smoking, alcohol abuse, obesity, and inappropriate nutritional behaviour. Physical activity has a bimodal association, since both, a sedentary lifestyle and intense physical activity, are associated with the disease [17, 19–21]. There is interest in the reduction of these risk factors to help reduce the burden of the disease [22]. Additionally, diseases like hypertension, diabetes, coronary artery disease (CAD), heart failure, valvular heart disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and sleep-disordered breathing (SDB), and acute illnesses or surgery have been associated with AF [17, 20, 23–28].

Estimating death rates for AF-related mortality is challenging, given that patients usually do not die from the arrythmia itself, but from associated complications. AF is associated with an increased risk of death [29]. The mortality risk from AF seems to be higher in women than in men [30], and in patients with comorbidities such as CAD, heart failure, end-stage renal disease (ESRD), diabetes, sepsis, among others [7].

AF-related costs range from 1% of the UK's health budget [31] to 26 billion dollars per year in the USA, equivalent to 10% of all cardiovascular disease expenses [32]. Yearly AF-related patient-based costs for high-income, upper-middle-income, and lower-middle-income countries are 41.420, 12.895, and 8.184 international dollars [33].

The association between AF and stroke has been clearly established, with early studies showing a 3 to 5 times higher risk of stroke in patients with AF, and the presence of AF in around 1 in 3 patients with stroke [6, 34, 35]. Contemporary studies have shown AF-associated stroke (known or newly detected) in 28% of stroke patients, with higher prevalence in North American and European populations and lower prevalence in Latin America (35%, 33%, and 17%, respectively) [36].

6.2 Pathophysiology

The association between AF and stroke is currently considered to have three explanations [37]:

- AF is a direct cause of stroke.
- Stroke can trigger AF.
- AF and stroke share risk factors.

AF pathogenesis in stroke patients can be considered as two distinct entities: AF as a consequence of an abnormal atrial substrate, also known as cardiogenic AF, that could be later on associated with a cardioembolic stroke; or AF as a consequence of stroke-induced heart injury (SIHI), also known as neurogenic AF. Additionally, stroke and AF can co-exist without being etiologically related in two contexts: a non-cardioembolic stroke in a patient with AF, known as a bystander AF; and stroke and AF both as the consequence of an abnormal atrial substrate, known as atrial cardiopathy.

In the next sections, we are going to expand these ideas and clarify some of the evidence behind these concepts.

6.2.1 Cardiogenic AF

The left atrium (LA) has many functions in the cardiovascular system. It initiates and transmit the electric stimulus for myocardial contractions employing the pacemaker cells in the sinus node, intra atrial conduction pathway and the AV node. It also acts as a blood reservoir that is filled during ventricular systole, and then is emptied into the left ventricle during ventricular diastole. There are also atrial homeostatic functions mediated by the secretion of atrial natriuretic peptides (**ANP**) and brain natriuretic peptides (**BPN**), which contribute to systemic volume regulation [38]. The atrium is very sensitive to both intrinsic and extrinsic injury, which can affect its normal functioning with subsequent irregular beating and loss of contractile function [39, 40].

AF is an electrophysiological state characterized by poor contractility, increased automaticity, decreased refractoriness, and re-entry activity [18, 39, 41]. The physiopathology involves a complex interplay of several contributors, facilitators, and perpetuators that lead to atrial remodelling and, eventually abnormal atrial substrate. It has been previously resumed with four interconnected loops, all producing positive feedback to each other [41]:

1. Electrical loop.
2. Triger loop.
3. Hemodynamic loop.
4. Structural loop.

There are important mechanisms that are central to these loops and deserve additional explanation

- Ion channel dysfunction via K+ and Ca2+ currents produce a facilitated depolarization and a decreased refractoriness, facilitating re-entry [42, 43].
- Ectopic activity with rapid focal firing can act on vulnerable tissue creating re-entry circuits or discrete rotors that help maintain the rapid firing activity [39, 43]. This is the most frequent mechanism initiating AF.
- Structural remodelling, primarily fibrosis but also changes in cellular ultrastructure, alter the electrophysiological characteristics of the LA, producing hypocon-

tractility, dilatation, and conduction disturbances; which facilitates unidirectional blocks and re-entry circuits [39, 44–47].

- Atrial myocardial stretch secondary to atrial overload is considered a main contributor to the structural remodelling [48].
- Autonomic dysfunction via vagal and adrenergic dysregulation produces shortening of action potential duration and promotes delayed afterdepolarizations mostly via Ca++ currents, levels and sensitivities (both in transmembrane and sarcoplasmic reticulum channels and pumps) [39, 42, 49].

The development and perpetuation of AF constitutes a dynamic process over time: atrial remodelling secondary to age, underlying heart disease and the AF itself are associated with increasing arrhythmia burden [38, 50–52], and the abnormal rhythm potentiates all pathological mechanisms, increasing the abnormal atrial substrate and producing a positive loop between both entities [38, 41].

Finally, genetics have been recently recognized as having a significant role in AF pathogenesis. A series of genes implicated in ion channels, transporters, myocytes structural components, and others factors have been associated with the disease (PITX2, TTN, MYL4, HCN4, ZFHX3, KCNN3) [18, 53–57]. There is familial aggregation even in the absence of risk factors, and the calculated heritability from a study in twins was 62% [58, 59] (Fig. 6.1).

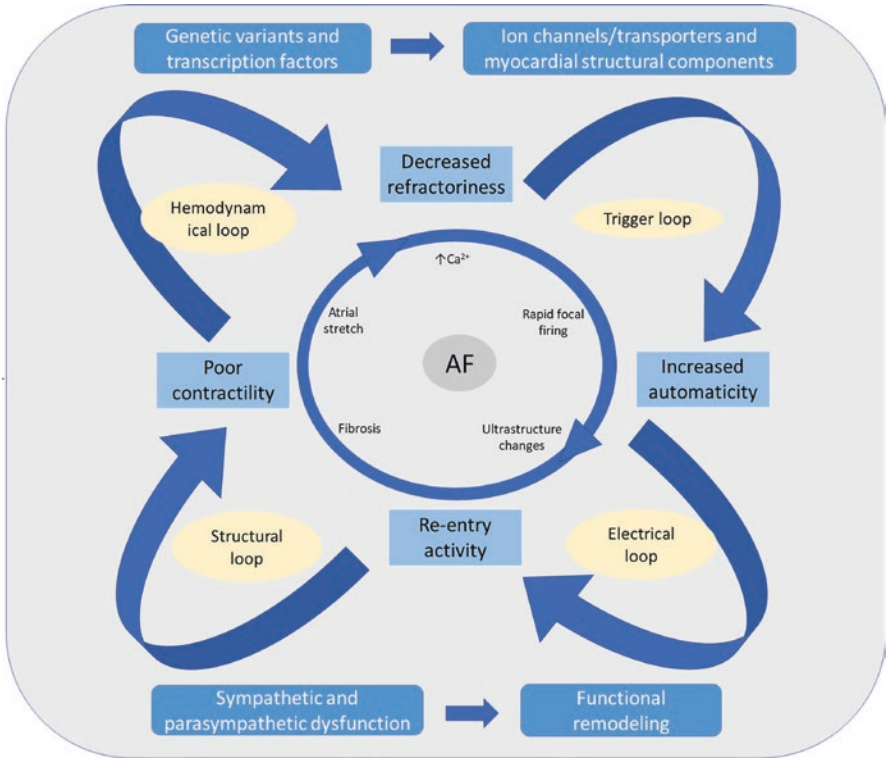

Fig. 6.1 Resumed AF loops

Subject to genetic predisposition, autonomic dysfunction and atrial cardiopathy, four distinct pathophysiological loops act synchronously and interdependently in the onset and maintenance of AF.

6.2.2 Neurogenic AF

In some cases, AF can be a manifestation of neurogenic myocardial damage on the context of the recently described stroke-heart syndrome [60–62]. This kind of AF is called neurogenic AF [63]. Based on population-based data showing a time-varying risk of cardiovascular complications post-stroke in patients without known heart disease, current timeframe for heart-brain syndrome is 30 days after the stroke, with the peak on the first 72 hours, so only AF first detected in this period of time could fix into this category [61, 63, 64].

There are three described mediators in the stroke-heart syndrome:

- Immunological: increased systemic inflammatory response, myocardial proinflammatory cytokines and macrophage infiltration [65].
- Humoral: increased systemic norepinephrine and cardiac catecholamine production [66].
- Neuronal: lesions in the insula or the broadly distributed central autonomic network have been described to produce autonomic tone disbalance and secondary cardiogenic damage [67, 68].

The neuronal mechanism and the so-called cardiac neuronal network have been widely studied in recent decades. The heart has important autonomic innervation via the vagus nerve, the cervicothoracic ganglia and the cardiac ganglionated plexus. Brain damage in certain regions such as a stroke in the insular cortex has been associated with increased sympathetic and reduced parasympathetic function [69], but increase in both sympathetic and parasympathetic outflow has also been linked to arrhythmias [70]. Studies in humans and animals have found evidence of autonomic dysregulation after a stroke including increased serum norepinephrine, increased heart catecholamine-driven transcription, and abnormal autonomic reflexes [71–75]. This autonomic disbalance is considered associated with development and propagation of AF via increased calcium in presynaptic neurons and subsequent increased action potential frequency, shortening of action potential duration via potassium channel modulation, and vagal induced conduction delays [76]. In this context, the use of autonomic modulation with betablockers have been proposed to prevent SIHI and stroke-heart syndrome, but clinical evidence this is needed [61].

6.2.3 The AFDAS Concept

Atrial fibrillation detected after stroke (AFDAS) is a unique type of AF, with different characteristics and prognosis compared to AF known before stroke occurrence (KAF).

- Age: AFDAS patients may be younger than KAF patients [77].
- Heart disease: AFDAS patients have less frequently LA enlargement, prior myocardial infarction, coronary artery disease or heart failure than KAF patients [77–79].
- Stroke location: AFDAS patients have stroke in the insular territory more frequently [77].
- Stroke severity: AFDAS is found more frequently on stroke than on transient ischaemic attack (TIA) patients [80, 81]. AFDAS related stroke has higher NIHSS and LVO than KAF [82].
- Risk of stroke recurrence: AFDAS risk of recurrent stroke is lower than that of KAF [78].
- AF burden: AFDAS patients have lower AF burden, lower rates of sustained AF and higher rates of spontaneous conversion to sinus rhythm [82–84].

While KAF is understood as mediated primarily by intrinsic cardiac factors (hypertension, structural heart disease, ischaemic heart disease, etc.), AFDAS can be triggered by the same cardiac mechanisms (cardiogenic AFDAS) or stroke-related neurogenic mechanisms (e.g., autonomic dysfunction or inflammation). However, it is challenging to differentiate if an AF episode after a stroke is neurogenic, or if it is a previously unrecognized cardiogenic AF. The pathogenesis of these two entities is clearly different, and so seem to be patients' characteristics and stroke risk profiles [77]. Moreover, a dichotomous classification is probably wrong in most patients. The concept of AF detected after stroke (AFDAS) has been proposed with the aim of acknowledging and better characterizing the pathophysiological and prognostic differences related to the timing of AF diagnosis in patients with ischaemic stroke and transient ischaemic attack (TIA).

AFDAS phenotypes constitute a spectrum of AF-related risk, with each patient representing a specific combination of multiple factors, including but not limited to (a) the severity of atrial substrate, (b) the basic underlying mechanism (cardiogenic vs. neurogenic), (c) the burden of AF, and (d) the overall demographic and risk factor profile (age, sex, hypertension, etc.). The risk of subsequent stroke depends on the interplay of these characteristics [37, 78, 83].

Extensive research has identified reliable markers of atrial cardiopathy. These markers have also been associated with the risk of AFDAS. The most consistent makers are left atrial (LA) strain, LA size, p-wave terminal force in V1, natriuretic peptides, and cardiac troponin [63, 85, 86]. The severity of atrial cardiopathy seems

to be related to the risk of cardiogenic AFDAS, similarly to what has been found in patients without stroke. Also, a "rise and fall" pattern of cardiac troponin (acute myocardial injury) instead of chronically increased troponin (chronic myocardial injury) is a candidate biomarker to differentiate neurogenic vs cardiogenic AFDAS [83].

6.2.4 AFDAS as an Incidental Finding and Its Potential Bystander Role

A multitude of cardiovascular risk factors are independently associated with both AF and stroke [39, 87]. Patients with AF can have non-cardioembolic strokes, for example secondary to small vessel disease or carotid atherosclerosis, so AF would be a bystander [88]. These patients could have a stroke without temporal relationship to AF episodes [89–92]. This is supported by the findings of the Stroke of Known Cause and Underlying Atrial Fibrillation (STROKE-AF) study, in which patients with strokes attributed to small or large vessel disease undergoing implantable loop recording (ILR) had a strikingly high AFDAS detection rate [93].

On the other hand, atrial cardiopathy, a potential cause and consequence of AF, can also be a source of atrial embolic strokes independently of AF rhythm; hence, AF and stroke could potentially share a common precursor [94]. This abnormal atrial substrate could be secondary to AF, ageing, cardiovascular disease, metabolic risk factors, or other systemic comorbidities [37]. Patients with both AF and atrial cardiopathy have an even higher risk of ischaemic stroke compared with patients with just one of them [37, 95]. Evidence supporting this concept comes from several different studies, for example:

- Rhythm control does not eliminate the risk of stroke in AF patients [96].
- There is no temporal relationship between AF episodes and incident ESUS [97, 98] (Table 6.1).

Table 6.1 Risk factors for AF. Risk factors for AF can be classified as modifiable and non-modifiable. Many of the risk factors are also risk factors for cardiovascular disease

Non-modifiable	Modifiable		
Age	Valve disease	Obesity	Endurance exercise or sedentarism
Male sex	Heart failure	Smoking	Diabetes
White/European race	Coronary artery disease	Obstructive sleep apnoea	Thyroid disease
Genetics	Hypertension	Alcohol consumption	Diet

6.3 AF and Thrombus Formation

Thrombogenesis in AF is no longer though to be secondary only to blood stasis, and it is now considered that it follows the same three principles Virchow described more than a century ago: hypercoagulability, blood stasis, and prothrombotic endothelial (in this case endocardial) changes [99].

6.3.1 Prothrombotic Endocardial Remodelling

In atrial cells of patients with AF, the excess of cytosolic calcium produces a chain reaction [100]:

- Increased generation of reactive oxygen species (ROS).
- Proinflammatory effect on the endocardium.
- Increased synthesis of prothrombotic molecules.
  - Plasminogen activator inhibitor 1 (PAI1).
  - Von-Willebrand factor (vWF).
  - ICAM, VCAM, selectins.

This endocardial remodelling is not exclusive to AF but is also independently associated with the same cardiovascular risk factors that produce the AF [100].

6.3.2 Blood Stasis

The atrial dilation in the context of AF, and the ineffective atrial contraction during AF rhythm, contribute to incomplete atrial voiding and blood stasis. It has also been described that even in sinus rhythm, the atrial contraction of AF patients is impaired, so this mechanism is enduring even in paroxysmic AF [100–103]. The blood pooling happens preferentially at the left atrial appendage (LAA), a 1.2–4.5 cm pouch-like structure with great size and shape variability. The LAA is the most common location of atrial thrombus formation both in AF and non-AF patients [38, 104]. Indeed, 90% of thrombi in AF patients are found in the LAA.

There have been several prothrombotic LAA markers described: pulse wave doppler phenotype, lower LAA flow velocity, non-'chicken-wing' morphology (especially 'cauliflower' morphology), larger orifice area, fibrosis, and spontaneous echocardiographic contrast [105–107]. LAA and LA can also have a discordance in rhythm (LAA pulse wave despite sinus rhythm in ECG) [105]. A high-risk LAA phenotype may explain a portion of the embolic events in AF patients with otherwise low stroke risk [104].

6.3.3 *Hypercoagulability*

There is increasing evidence for hypercoagulability in AF. The finding of spontaneous echo contrast (SEC) on LA or LAA during an AF paroxysm is a marker of blood stasis, but it is also considered a marker of fibrinogen-erythrocytes interaction and is associated with stroke risk [99, 108]. Prothrombin fragment 1 + 2 is a marker of active coagulation and is higher on stroke patients with AF than in other stroke patients [109]. Other coagulation and endothelial markers such as fibrinogen, Von-Willebrand factor or soluble P-selectin, have a linear correlation with FA burden markers such as LA volume and permanent instead of paroxysmal AF [110, 111]. Nitric Oxide Synthetase (NOS) levels are downregulated and oxidative stress is higher, and the thrombogenic Plasminogen Activator Inhibitor-1 (PAI-1) is upregulated in cardiomyocytes of AF patients [112, 113]. Finally, platelet activation and thrombin generation are increased in patients with rapid atrial rate or AF [99, 114, 115].

6.4 Diagnosis of AF

There are multiple definitions that need to be stablished first:

- AF rhythm: Supraventricular tachyarrhythmia with irregular R-R intervals, absence of distinct repeating P waves and irregular atrial activations.
- Atrial high-rate episodes (AHRE): Event of atrial beating at ≥175 bpm for ≥5 min detected with a cardiac implantable electronic device (CIED) with an atrial lead or sensor (cut-off values are not standardized).
- Subclinical AF (SCAF): Event of AHRE or device-detected AF (implantable cardiac monitor (ICM) or wearable) that has been confirmed by a physician's review of the recorded intracardiac electrogram or ECG-recorded rhythm.
- Clinical AF: AF rhythm documented for at least the entire duration of a 12-lead ECG, or 30 s of an ECG tracing (telemetry, Holter, wearable monitor with a recorded ECG…).
- Excessive supraventricular ectopic activity (ESVEA): Holter-detected premature supraventricular contractions (PSC) ≥30/h or an episode of PSC longer than ≥20 beats. Usually considered a surrogate of AF.

AHRE/SCAF events (AHRE and SCAF are not the same but in the literature are often use together or even interchangeable) require that the patient remains asymptomatic during the episode and that a diagnosis of AF has not been previously made. A clinical AF diagnosis can be made in either symptomatic or asymptomatic patients. An asymptomatic AF event that found in a patient with a previous stroke is not asymptomatic anymore [116] and should not be named SCAF.

6.4.1 Screening for AF

There are many different options available for screening for AF. They can be classified depending on how invasive vs non-invasive the strategy is and on whether intermittent vs permanent monitoring is intended. There is not a consensus on how intense or which methods we should be used for screening for AF in stroke patients. Longer monitoring will also detect patients with a lower AF burden [117–119].

If an asymptomatic patient is detected to have an AHRE, a SCAF, or an irregular rhythm on pulse palpation, oscillometry or photoplethysmography, then a 12-lead ECG or at least a single-lead ECG tracing longer than 30 s should be done in order to make a definitive diagnosis of clinical AF [1, 120].

In post-stroke patients, early start of continuous cardiac monitoring improves the detection of AF (in this case: AFDAS) and increases the rate of anticoagulation [121–123]. In this population, a staircase approach can result in an overall detection rate of approximately 24 [124]. However, it remains unknown if this approach is timelier, more clinically effective, or more cost-effective than skipping Phases 2 and 3 by applying an ILR immediately after stroke with a less stringent selection process.

- Phase 1: emergency room ECG.
- Phase 2: serial ECG, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry, and in-hospital Holter monitoring.
- Phase 3: Ambulatory Holter.
- Phase 4: Mobile cardiac outpatient telemetry, external loop recording, and implantable loop recording.

Some wearable monitors such as smartwatches, belts or smartphones have proven efficacy for detecting AF patients and are new option for screening [1]. There are clinical risk cores that could help identify patients with high probability of AF such as C2HEST score that has been validated in cohorts with stroke history [125] (Table 6.2).

6.4.2 The Burden Of AF

The burden of the arrythmia is a measure of how often and for how long a patient has the abnormal rhythm. It can be measured or reported in several different ways: number of episodes per day, amount of time with an abnormal rhythm over a period, longest arrhythmia event during monitoring... Continuous monitoring devices allow for a precise determination of the arrythmia burden, while intermittent monitoring tend to underestimate it.

There is a classification based on the temporal pattern of abnormal rhythm in AF has been historically used [1].

- First diagnosed: AF not diagnosed before, irrespective of duration or symptoms.

Table 6.2 Screening methods for AF. Many different screening methods can be used to detect possible AF. The sensitivity increases with more prolonged and continuous screening time, and specificity increases with more invasive techniques

	Least invasive		More invasive
Intermittent	• Pulse palpation • Oscillometric pressure cuff	Wearable belt In-hospital telemetry monitoring	
	Photoplethysmogram or Intermittent ECG rhythm strip on smartphone or device	• Long-term holter •1-2 week continuous ECG patches	
Continuous	Photoplethysmogram on smartwatch/ wearable		• Implantable cardiac monitor • Cardiac implanted electronic devices

ICM: single-lead bipolar surface ECG
CIED: atrial lead can monitor atrial rhythm and store the tracings (pacemakers, implantable cardioverter defibrillator (ICD), biventricular pacemakers, and cardiac loop recorders)

- Paroxysmal: episodes terminating within 7 days of onset.
- Persistent: AF continuously sustained beyond 7 days but less than 12 months.
- Long-standing persistent: AF continuously sustained beyond 12 months.
- Permanent: Continuous AF without any further attempts of rhythm control.

The method of the AF episode termination (after medical treatment or spontaneous) is not relevant for the classification.

The AF burden is supposed to be related to the stroke risk, but it remains unclear if this relationship is linear and what the AF burden threshold to warrant anticoagulation is, especially in subclinical patients. The risk of stroke is smaller in AHRE/SCAF than in paroxysmal AF, and is smaller in paroxysmal AF than in non-paroxysmal AF (persistent, long-standing or permanent) [50, 91, 126–129]. Non-paroxysmal AF patients tend to have higher risk profiles than patients with paroxysmal AF [130], but the increased stroke risk persists even after adjusting for risk factors. Paroxysmal AF is more often associated with stroke because its more prevalent than non-paroxysmal AF and its more frequently undiagnosed [131]. It has been proposed that AF newly detected with a short monitoring technique such as a 12-lead ECG is generally considered as high burden [132]. Lastly, SCAF is a strong predictor of clinical AF, the burden of both clinical and subclinical AF tend to increase over time, and high initial burden is a stronger predictor of subsequent burden increase [133–135].

Studies with implantable devices have found a cutoff value of >1 h/day of AF burden as a predictor of stroke, with increasing risk as the burden increases [127]. It has been proposed that AF burden is especially predictive of the stroke risk in patients with low cardiovascular risk [91, 136].

AF rhythm events shorter than 30 s are a matter of controversy; these episodes represent more than half of AF rhythm episodes detected in monitoring after a

stroke, and it is not clear if they entail a significant risk of stroke. Stroke neurologists are twice as likely to consider these short events as clinical AF [116, 137–139].

The role of low-burden AHRE/SCAF in stroke is also controversial as the temporal association of these events with an incident stroke is not always clear, and several studies have shown no association of short events (<20 s) with stroke [98, 140]. Some authors argue that these episodes should be considered as stroke risk markers instead of a direct cause of stroke [97, 141]. Recent studies have shown that high-intensity screening of AF with implantable devices increases the rate of AF detection and the rate of treatment with anticoagulation, but there is no impact on reducing stroke incidence [142, 143]. This reflects the fact that AF detected only after long monitoring is probably low burden, and as such, the risk of stroke is not as high [117, 118]. High intensity screening should be reserved for high-risk patients, for which there is evidence of benefit of prolonged cardiac monitoring for the reduction of ischaemic stroke [144].

6.4.3 Neuroimaging in AF

There are distinctive patterns of stroke distribution in patients with cardioembolism: bilateral, multiple vascular territories, larger size. Other characteristics such as lesion shape or anterior/posterior distribution has not been proven different from non-cardioembolic stroke [145, 146]. About 1 in 6 patients with classic lacunar syndromes have been found to have cardioembolic looking strokes in MRI [147]. Other differential etiologies of multiple territory infarcts such as hypercoagulability, cancer, vasculitis, and multiple arterial dissections should be kept in mind.

6.5 Approach to Treatment of AF

Multiple guidelines recommend the 'Atrial fibrillation Better Care Pathway (ABC)' to treat AF patients: **A**nticoagulation/**A**void stroke, **B**etter symptom management, **C**ardiovascular and **C**omorbidity optimization. This approach has evidence for better results than standard care [148, 149].

6.5.1 Stroke Prevention

6.5.1.1 Oral Anticoagulation

Current recommendations for preventing thromboembolism with oral anticoagulation (OAC) in clinical AF are not based on the AF burden but on the calculated stroke risk [126, 150–152]. This stroke risk assessment can be made with different

tools such as GARFIELD-AD, ATRIA, or ABC-stroke, but the most widely recommended and used is the CHA2DS2-VASc score [1, 153].

The CHA2DS2-VASc score is based exclusively on clinical data (age, sex, and comorbidities), but it does not include any measures of AF burden or atrial cardiopathy biomarkers [126, 154]. Patients with high-risk CHA2DS2-VASc scores have an overall high risk of cardiovascular events, not only secondary to AF episodes [89]. In general, the higher the thrombotic risk, the higher the benefit or OAC [155]. Real-world studies have shown that each item of the CHA2DS2-VASc score imply a different weight for stroke risk [156]. Patients with low scores (CHA2DS2-VASc score of 0 for males or 1 for females) have a low thromboembolic risk that is no different from that of people without AF, and the recommendation is to not use OAC [38, 157]. In male patients with CHA2DS2-VASc scores ≥1 or females with scores ≥2 most guidelines recommend OAC to prevent stroke [1, 150, 151]. Another important aspect of using the CHA2DS2-VASc score is that it can increase over time, as patients age and develop new risk factors or comorbidities.

In the context of AFDAS, even though it carries a lower burden of AF, fewer comorbidities and fewer rate of complications than KAF, it is clear that it implies a higher stroke risk compared with non-AF patients [83], so the current recommendation is to treat AFDAS the same as KAF, and they should receive OAC unless contraindicated [1, 150, 151, 158]. Future research may find a way to identify lower-risk individuals with AFDAS, such as low-burden self-limited neurogenic AFDAS, that may not need life-long anticoagulation [124]. Careful monitoring of AF burden and determination of atrial cardiopathy probably will be helpful to establish the subsequent risk of stroke in these patients [132, 152]. It is recommended that FA detected on admission ECG should not be considered AFDAS, as it is probably a previously undiagnosed AF [83].

In patients without diagnosis of clinical AF, but a diagnosis of AHRE/SCAF, the decision to start anticoagulation is more difficult. It is clear that the burden of both AHRE and SCAF is associated with the risk of stroke and death [94, 116, 159–161], but the amount of burden where the risks of stroke are large enough to warrant anticoagulation is not clearly established because the studies have used different cut off values (>5 min, >1 h, >5.5 h, >24 h). Current guidelines and expert consensus recommend an individualized approach based on the burden of AHRE/SCAF and the individual's calculated stroke risk based on CHA2DS2-VASc score to make the decision for anticoagulation [1, 135, 162, 163] (Table 6.3).

Warfarin was the standard of treatment for stroke prevention in AF for decades until the direct oral anticoagulants (DOACs) entered the market. These newer anticoagulants not only prevent strokes, with a risk reduction of around 2/3 [164], but they also diminish the severity of incident strokes [165, 166]. DOACs: rivaroxaban, dabigatran, apixaban, edoxaban; have a similar efficacy than warfarin for stroke prevention (slightly better reduction of ischaemic stroke or systemic embolism), but the risk of ICH is lower with DOACs than with warfarin [167]. There main results of pivotal randomized clinical trials suggest the following:

Table 6.3 When to start OAC dependent on AF burden and stroke risk score. AF burden and clinical risk factors for stroke can be used to determine the threshold of benefit for anticoagulation in AF. The exact threshold is not fully elucidated, and more research is needed

	Burden				
CHA2DS2-VASc	AHRE/SCAF			AF	
	<1 h/day	1–24 h/day	>24 h/day	Neurogenic AFDAS	Cardiogenic AFDAS or KAF
Low risk: 0(m), 1 (f)	NO	NO	NO	NO	NO
Intermediate risk 1(m), 2(f)	NO	NO	MAYBE	YES (maybe self-limited)	YES
High risk ≥2 (m), ≥3(f)	NO	MAYBE	YES	YES	YES
Consider atrial cardiopathy markers (imaging, biomarkers, etc.)					
In AHRE/SCAF: Always review electrograms to exclude false positives					

Source: Based on ESC 2020 guideline on AF diagnosis and treatment

- Warfarin safety and efficacy rely on a good INR control (time in therapeutic range > 70%) [168].
- Dabigatran 150 mg has a higher risk of gastrointestinal bleeding than warfarin [169].
- Rivaroxaban 20 mg has a higher risk of gastrointestinal bleeding than warfarin [170].
- Apixaban 5 mg was superior to warfarin in preventing ischaemic stroke or systemic embolism [171].
- Reduced-dose regimens of DOACs have worst efficacy and safety results than full-dose regimens, but reduced- and full-dose regimens have consistent results compared to warfarin [172].
- In patients with AF and any mechanical heart valve or mitral moderate or severe stenosis, warfarin is the only OAC recommended as DOACs have not shown clear benefit in these patients [173].

It is clear that both single antiplatelet therapy (SAPT) with AAS, and dual antiplatelet therapy (DAPT) with AAS and clopidogrel, are inferior in the prevention of thromboembolic events in patients with AF compared to anticoagulation [174]. It should be noted that the level of protection is around 22% with SAPT compared with no antithrombotic medication [175].

6.5.1.2 LAA Occlusion

In patients with AF, device-occlusion of the LAA seems to be non-inferior for ischaemic stroke prevention and have a lower risk of haemorrhagic stroke compared to warfarin [104, 176–178], although some considerations need to be made regarding the inclusion criteria and outcomes used in some randomized clinical trials. This discussion is beyond the scope of this chapter. No studies have been conducted comparing this technique versus DOACs [104]. It is usually reserved for patients

with high bleeding risk or contraindications for OAC use. There is no randomized evidence for the selection of antithrombotic treatment after LAA occlusion, long-term SAPT or temporary OAC are commonly used [1, 179, 180].

6.5.1.3 Assessment of Bleeding Risk

The best tool for the prediction of bleeding risk in AF patients is the HASBLED score [181]. Guidelines recommend using this score to identify modifiable risk factors for bleeding, and also, depending on the risk level, the clinician should establish the frequency of follow-ups. This score should not be used to hold back anticoagulation, as patients with high bleeding risk based on HASBLED usually also have high thrombotic risk based on CHA2DS2-VASc [182], and unless there is an absolute contraindication, patients should receive OAC. Both scores should be reassessed regularly as the risks of patients are not static and could prompt adjustment in treatments [183–185].

6.5.1.4 Rhythm Control

Based on current evidence [96], most guidelines consider symptom control to be the only indication of rhythm management in AF patients, as it seems to be of no benefit in preventing thromboembolic events. Guidelines usually recommend rate-control measures as first line of treatment, and others antiarrhythmic medication in patients with residual symptoms, leaving ablation of the arrhythmogenic loci for refractory patients. Detailed rate or rhythm management and cardioversion in AF is beyond the scope of this chapter [1, 150, 151].

Some trials have shown that rhythm control may be beneficial compared to rate-control in slowing AF progression [186]. Recently, a subgroup analysis of a large, randomized trial on patients with recently diagnosed AF (<12 months) showed that early rhythm control was superior to usual care for the prevention of cardiovascular death, stroke, and hospitalization in patients with a history of stroke. It is yet to be seen if this will change current guidelines [187, 188].

6.5.1.5 Cardiovascular Comorbidities

All cardiovascular comorbidities and risk factors should be treated, controlled, or optimized to improve outcomes in AF patients. There should be a focus on metabolic control, avoidance of alcohol, weight loss, cardiovascular fitness, SAHOS and hypertension treatment [189–192].

6.5.2 Special Interest Circumstances

6.5.2.1 Haemorrhagic Stroke

Patients with AF and an intracranial haemorrhage (ICH) have a high risk of ischaemic stroke if antithrombotics are withheld. Observational evidence in this population has shown that OAC (including warfarin) protects against ischaemic stroke compared to antiplatelets or no treatment without a significant increase in ICH recurrence [193–195]. The safer risk profile of DOACs has been proven in this scenario in randomized trials and should be the OAC of choice over warfarin [167, 196]. Patients with traumatic ICH or ICH without evidence of cerebral amyloid angiopathy are the subgroups that benefit the most from OAC [197]. Reversible risk factors for bleeding such as high blood pressure or problematic drug interactions, should be controlled.

There is no clear evidence on the optimal time to (re-)start OAC after ICH and patient selection should be made on a personalized basis after a thorough discussion with them or their substitute decision-makers. Guidelines usually suggest waiting 4 to 8 weeks, but in patients with high thrombotic risk (for example, with a mechanical heart valve), starting as early as after 2 weeks or LAA occlusion could be considered [1, 198, 199]. Observational evidence on patients with ICH and mechanical heart valve found that OACs increase the haemorrhagic risk when initiated before day 14, but balancing the ischaemic and haemorrhagic risks suggests that the earliest possible OAC resumption is in day 6 [200]. Small randomized controlled trials have not provided definite evidence yet.

6.5.2.2 AF and Concurrent Acute or Chronic Coronary Syndrome

Coronary artery disease is present in 1/3 of patients with AF, and it is not infrequent that these patients require percutaneous coronary intervention (PCI) and stenting, for which antiplatelets are required to prevent stent thrombosis [201]. Current guidelines recommend the use of triple therapy (ASS + clopidogrel + DOAC) for 1 to 4 weeks, then dual therapy (preferable clopidogrel + DOAC) until 6 to 12 months after the PCI, and then continue monotherapy with a DOAC unless there's a new coronary event. Full-dose regimens should be used unless patient weight and renal function do not allow it [202–206].

6.5.2.3 Recent TIA or Ischaemic Stroke

Patients with recent brain ischaemia are considered to have a transient increased risk of haemorrhagic transformation, so OAC is usually withheld temporally. The risk is considered to be related to the stroke size, so this is usually the marker used to decide when to (re-) start OAC [206]. Evidence in this matter is lacking. Some

guidelines recommend (re-)starting OAC in the 4–14 days after the stroke based on prospective observational data [207, 208]. Other guidelines recommend a 1–3–6-12-days rule according to the initial stroke severity (TIA, NIHSS <8, NIHSS 8–15, and NIHSS >15, respectively) based on expert recommendations [209].

Recent trials are trying to update these recommendations in the context of DOACs, probably allowing an earlier start than with warfarin. A non-randomized trial using database information formulated the 1–2–3–4-day rule using the same NIHSS cutoffs as for the 1–3–6–12 rule. It showed increased efficacy without increasing the haemorrhagic risk [210]. A more recent randomized trial showed no difference in early (<4 days) vs late (5–10 days) OAC initiation in a population of mostly low and moderate severity strokes [211]. However, this was a small trial and we await the results of other ongoing randomized controlled trials.

Bridging with low-molecular-weight heparin is associated with more bleeding and more ischaemic strokes, so it should not be used [212]. Antiplatelet bridging is recommended in some guidelines and could be used based on the small protection against ischaemic stroke in AF conferred by these medications [213].

6.5.2.4 Kidney and Liver Disease

The efficacy and safety of DOACs in AF patients with CrCl 30–49 mL/min is similar compared with patients with normal renal function [214, 215]. Apixaban safety profile compared to warfarin is even greater in patients with CrCl 25–30 mL/min than in patients with CrCl >30 mL/min [216]. Different guidelines disagree on the management of patients with AF and CrCl <15 mL/min or in dialysis, some recommend apixaban or warfarin, and other recommend no antithrombotic treatment (considering that patients on dialysis receive anticoagulation for the procedure) [150, 151, 217]. A randomized trial comparing apixaban to warfarin in AF patients on haemodialysis could not find differences between groups, but bleeding events were tenfold more frequent than ischaemic events [218]. Depending on the bleeding and thrombotic risks LAA closure may be an option for these patients [218].

Cirrhotic patients have high risk of devolving AF and of haemorrhagic complications. DOACs have shown consistent benefit and safety in patients with active liver disease [219], but evidence in severely impaired liver function is poor as they were not included in the pivotal trials. Based on mostly retrospective data, DOACs has shown safety superiority compared to warfarin in cirrhotic patients with AF [220].

6.5.2.5 Postoperative AF

Even though the risk of stroke in postoperative AF (OPAF) is not as high as other forms of AF, it is still associated with an increased risk of late AF and with both early and late stroke. In this patients OAC is protective against embolic stroke and should be used [221, 222].

6.5.2.6 Atrial Flutter

Auricular flutter (AFL) patients have higher risk of stroke compared with sinus rhythm patients, but lower compared with AF patients. AFL patients can also progress to have AF. All recommendations for management of patients with AF also apply for AFL patients [1, 151, 223].

6.5.2.7 Atrial Cardiopathy

There are many proposed markers of atrial cardiopathy that are currently under extensive research to establish if they could be used to detect patients that could benefit from anticoagulation even in the absence of confirmed AF. They could also help increase the accuracy of stroke risk estimation in AF, the risk of progression to AF in AHRE/SCAF or the risk of stroke in neurogenic AFDAS [128, 132, 154, 224–227].

- Indexed LA volume.
- Spontaneous LA contrast.
- Reduced LA strain.
- Low peak LAA velocity.
- LA fibrosis.
- Troponin I.
- P-wave terminal force in lead V1.
- Premature atrial complexes.
- Supraventricular tachycardia.
- Clinical scores.

The ARCADIA trial has been recently stopped and we are awaiting the presentation of its results.

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