ATRIAL FIBRILLATION

Definitions and Classification

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation without effective atrial contraction.[1, 2] On the ECG, AF is characterized by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing, (when visible, usually in lead V_1, the atrial length is variable and <200 ms, ie >300 bpm), associated with an irregular ventricular response. QRS complexes may also be of variable amplitude (Table 1). Regular R-R intervals are possible in the presence of AV block or AV junctional or ventricular tachycardia. The 4 stages of atrial arrhythmias progression to AF are presented in Figure 1.

Paroxysmal AF is defined as AF that terminates spontaneously or with intervention within 7 days of onset.[1, 2] Usually, self-termination occurs within 48 h. After this the likelihood of spontaneous conversion is low. Approximately 8% of patients with paroxysmal AF progress to persistent forms annually.[3]

Persistent AF that is continuous and sustains for >7 d and requires intervention. Of note, patients with persistent AF who, with therapy, become paroxysmal should still be defined as persistent as this reflects their original pattern and is more useful to predict outcomes and define substrate.[1]

Long-standing persistent AF is AF that has lasted for ≥1 year.

Permanent AF refers to the situation when the presence of the arrhythmia is accepted by the patient and physician. Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Acceptance of AF represents a therapeutic decision and does not represent an inherent pathophysiological attribute of AF.

AF burden encompasses both frequency and duration and refers to the amount of AF that an individual has. AF burden has been defined differently across studies. For the purpose of this guideline, AF burden will be defined as the durations of an episode or as a percentage of AF duration during the monitoring period depending on how it was defined in the individual studies.[1]

Obsolete terms

Chronic AF has variable definitions and should not be used.

Lone (idiopathic) AF has been variously defined but generally applies to young individuals (under 60 y of age) without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension. Increasing knowledge about the pathophysiology of AF shows that in almost every patient a cause is present.

Nonvalvular AF AHA/ACC/HRS define nonvalvular AF as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair. The ESC has defined

nonvalvular AF as AF not related to mitral stenosis or prosthetic heart valves, and discourages the use of the term. The ACC/AHA also considers the term obsolete.[1]

The term *clinical AF* has been used in several trials that required electrocardiographic documentation of the arrhythmia for inclusion and most patients presented for clinical evaluation and/or therapy of the arrhythmia.

Subclinical AF refers to AF identified in individuals who do not have symptoms attributable to AF and in whom there are no previous ECGs documenting AF. It usually indicates short-lasting (5 or 6 min), asymptomatic high-rate episodes of atrial fibrillation detected by implanted devices.

Although in certain cases AF is vagally mediated (ie after meals or habitual aerobic training), whereas in others follows sympathetic overactivity, the terms *vagal* and *adrenergic* AF are oversimplifications, since the balance between sympathetic and parasympathetic influences is as important as absolute tone.

Epidemiology

AF is the most common sustained arrhythmia in humans and affects 1–3% of the general population worldwide (Figure 2). According to the first global assessment of AF, conducted within the framework of the Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2010 Study), the estimated global prevalence of AF in 2010 was 33.5 million (20.9 million men and 12.6 million women),[4] and from 1990-2019, it doubled globally to 59.7 million in 2019.[5] In the USA its prevalence is estimated to 5.2 million people, and this is expected to rise to 12.1 million in 2030.[6] In Asian countries it is slightly lower.[7, 8] In 2019, there were an estimated one million new cases of AF while 15.7 million people live with AF, in the 57 Mediterranean ESC member countries.[9] The prevalence of AF increases with age, from approximately 3% in the general population, to 5–15% at 80 years.[10, 11] The lifetime risk of developing AF has been calculated 20-25% in those who have reached the age of 50, and is about 37% after 55 years of age,[12] although this may be partly due to enhanced surveillance.[13] Older studies from 1–2 decades ago found that women with AF were at much higher ischaemic stroke risk compared with men but in more contemporary years, the sex difference in AF-related stroke risk is less evident.[14] Whites have an increased risk of AF compared to blacks, Asians or Hispanics.[15] Studies on long-term monitoring with implantable loop-recorders reveal that approximately one of third of patients with previously undiagnosed AF but with risk factors for AF and stroke (see "AF in specific conditions").[16] In patients with chronic coronary syndromes the incidence new-onset atrial fibrillation has been reported as 1.12 per 100 patient-years, with a cumulative incidence of 5% at 5 years.[17] AF demonstrates a strong circadian rhythm. In a posthoc analysis of the LOOP study, onset during night time was common and the majority of episodes started before noon.[18] Cluster analyses revealed distinct AF phenotypes and patients with onset mostly from midnight to morning

AF and its associated morbidity represent a significant socio-economic burden on the healthcare system (Figure 3). A study examining public and private health insurer records in the USA from 1996 to 2016 reported that AF was 33rd in spending for health conditions with an estimated $28.4 billion out of a total of 3.1 trillion dollars for health care in general.[19] Between 1999 to 2013 median Medicare inpatient expenditure per beneficiary increased from $2932 to $4719 per stay, and this was associated with improved outcomes.[20] In Denmark, the 3-year societal costs of AF were approximately €20,403 to €26,544 per person and €219 to €295 million as a whole.[21]

Aetiology

The most prominent risk factor for AF is **chronological age** (Table 2). However, **epigenetically measured biological aging** is suggested to partially account for the association between chronological aging and AF. Epigenetic ageing (or clocks) refers to mathematical algorithms involving epigenetic modifications, specifically 5-cytosine methylations within CpG dinucleotides, that have been shown to predict chronological age with remarkable accuracy.[22] **Hypertension** is the most common causes of hypertension encountered in clinical practice, estimated to be present in >70% of AF patients, followed by ischemic heart disease.[23, 24] Approximately 30% of patients with **heart failure** or **valve disease** have AF. Patients with **coronary artery disease, diabetes** or **COPD** are at higher risk for AF (15-20%), and AF shares many of the causes of atherosclerotic cardiovascular disease.[25, 26] Up to 40% of patients with **heart failure** develop AF, and heart failure occurs in more than one third of individuals with AF. AF precedes and follows HF with both preserved and reduced ejection fraction.[27, 28] **Diastolic dysfunction** presents a potentially important link between many common risk factors, such as hypertension, age, obesity, and diabetes, and the development of AF.[29] Postulated mechanisms risk are increased atrial afterload, atrial myocyte stretching, and atrial wall stress. **Frequent atrial ectopy** (more than 2 APBs per hour), have been associated with increased risk of AF. [30] **Atrial infarction may** also cause intra-atrial conduction delay and AF,[31] and the role of **atrial cardiomyopathy** is important.[32] The risk of AF in children and young adults with **congenital heart disease** is 22 times higher than that in matched control subjects.[33] **Obesity,**[34, 35] **chronic kidney disease and albuminuria,**[36] **metabolic syndrome,**[37] **hyperuricaemia**,[38] **and alcohol consumption (>1.2-2 drinks a day),**[39-42] are associated with an increased prevalence of AF in adults. Current alcohol consumption is also associated with an increased risk of ischaemic stroke in patients with newly diagnosed AF.[43] Prospective cohort studies suggest a beneficial association between total **fish** intake and new-onset AF, while others show no association or even a U-shaped relationship with the lowest AF risk associated with a fish intake of 40 g/day. The inconsistency of data from available prospective cohort studies and lack of relevant RCTs make it challenging to determine whether consuming fish influences new-onset AF risk.[44] Trials on **supplementation of omega-3 fatty acids** have produced controversial results such as increase of AF

in REDUCE-IT,[45] no effect in VITAL.[46] In a study on participant-level data from a global consortium of 17 prospective cohort studies, higher circulating and tissue omega-3 fatty acid biomarkers were not associated with an increased incidence of AF, [47] whereas in a meta-analysis marine omega-3 fatty acid supplementation was associated with a significant increased risk of AF. The incremental risk appeared to be greater in trials testing >1gr per day of omega-3 fatty acid supplementation.[48] Consumption of **extravirgin olive oil** (at least 50 mg or 4 tablespoons) in the context of a Mediterranean dietary pattern may also reduce the risk of atrial fibrillation.[49] A reduction in new-onset AF risk with habitual **caffeine** intake has been shown.[44, 50] Ground and instant but not decaffeinated coffee is associated with reduced atrial and ventricular arrhythmias,[51] although an acute effect of increased premature ventricular contractions has also been detected.[52] In the DECAF RCT of coffee drinkers after successful cardioversion, allocation to consumption of caffeinated coffee averaging 1 cup a day was associated with less recurrence of AF or atrial flutter compared with abstinence from coffee and caffeinated products.[53] Consumption of more than L per week of **sugar-sweetened beverages** and **artificially sweetened beverages** is associated with increased risk of AF.[54] **Polycystic ovarian syndrome** is associated with increased long-term risk of cardiac arrhythmias such as AF, atrial flutter and cardiac arrest.[55] **Thyroid disease** is a recognized factor,[56] although less common than previously thought, and higher free thyroxine level are associated with AF in euthyroid patients.[57] Senile amyloidosis, either wild-type due to transthyretin (ATTRwt) or isolated atrial amyloidosis, plays an important role plays an important role in the development of AF.[58] **ASD** are associated with increased incidence of AF regardless of treatment, and persistent AF is unlikely to be affected by ASD closure. Transcatheter ASD closure may also trigger AF. **Interatrial conduction block**, ie conduction delay between the left and right atria through Bachmann's bundle, is an independent predictor of atrial arrhythmias, including AF.[59] Atrial biopsy revealed amyloid deposits in 7% of patients undergoing AF ablation, identifying early-stage **cardiac amyloidosis**.[60] There is a higher incidence of AF in patients with **cancer**, and an increased incidence of cancer in patients with AF, likely because of shared risk factors.[61] Most **chemotherapy agents** such as anthracyclines (at a rate of 2-10%), and melphalan (7-12%), and cisplatin (12-32%), particularly with intrapericardial use, may cause AF.[61, 62] **Methamphetamine, cocaine, opiate**, and **cannabis** use are associated with increased risk of developing incident AF.[63, 64] Moderate to severe **sleep apnoea** is an independent risk factor for AF.[65] Both current and lifetime **night shift exposures** are associated with increased AF risk.[66] **Coronavirus disease** is associated with arrhythmias, mostly atrial including AF.[67] **Psoriasis** is associated with increased risk of AF and ischaemic stroke.[68] **Exercise intensity** has a U-shaped relationship with AF.[69] Long-term vigorous exercise predisposes to AF especially in professional athletes,[70, 71] but light to moderate physical activities, particularly leisure-time activity and walking, are associated with significantly lower AF incidence in older adults,[69] and there is an inverse relationship between cardiorespiratory fitness and cardiovascular complications or incident AF, especially among obese patients.[72] Regular physical activity is beneficial in patients with established AF.[73] In the UK Biobank

Cohort, regular physical activity 500-1500 MET-min/wk) was associated with a lower incidence of both atrial and ventricular arrhythmias.[74] Long working hours are also a risk factor for AF.[75] **Daytime napping** frequency has been associated with an increased risk of cardiac arrhythmias including AF and atrial flutter, ventricular arrhythmia, and bradyarrhythmia.[76] **Hypokalaemia** is an established risk factor for AF.[77] Low serum **magnesium** is also associated with the development of AF even in persons without cardiovascular disease.[78]. Recently, a J-shaped association was found between **QTc interval** duration and risk of AF. This association was strongest with respect to the development of lone AF.[79] **Autoimmune** AF may be due to $K_{ir}3.4$ (inwardly rectifying potassium channel subunit 3.4) autoantibodies that are detected in patients with unexplained AF.[80] **Epilepsy** is associated with higher risk of AF and other cardiac arrhythmias, especially among those using **carbamazepine** and **valproic acid**.[81] **Parental AF** increases the future risk for offspring AF,[82] and a family history of AF is associated with substantial risk of lone AF,[83] thus supporting a genetic susceptibility to developing the arrhythmia.[84] Atrial tachycardia or AF may also be **device-triggered** due to competitive atrial pacing.[85] However, atrial pacing minimization in patients with sinus node dysfunction does not reduce the incidence of atrial fibrillation.[86] **Stressor-associated AF**, defined as newly diagnosed AF occurring in the setting of a reversible, acute physiological stressor, accounts for nearly one-third of incident AF diagnoses and is associated with risk factors such as age and heart failure.[87] AF stressors span a broad range of exposures, including cardiac and noncardiac surgery, infection, and acute cardiovascular or pulmonary illness.

Several gene mutations have been associated with AF (Table 3).[88] Mutations that cause loss of function of the sodium channel (mainly in SCN5A), gain of function of the potassium channels (KCN), or affect connexins and transcription factors, as well as others, are mainly responsible.[88, 89] A loss of function mutation in the sarcomere gene *MYL4 also* causes early-onset familial atrial fibrillation, and suggests a contribution of the cardiac contractile system to cardiac conduction and AF.[90] Novel genetic loci for AF are continually discovered by genome-wide association studies.[91]

Pathophysiology

Structural remodeling of the atria due to heart disease (Figure 4), atrial wall stretch, genetic causes or other non-identified mechanisms results in electrical dissociation between muscle bundles and local conduction heterogeneities that facilitate the initiation and perpetuation of AF. [92] Structural atrial abnormalities consist of areas of patchy fibrosis, enhanced connective tissue deposits juxtaposed with normal atrial fibers, inflammatory changes, intracellular substrate accumulation, and disruption of cell coupling at gap junctions with remodeling of connexins (ie transmembrane ion-channel proteins in the gap junctions).[93] Connexin gene variants are associated with AF, and connexin gene transfer in animal studies has prevented AF.[94] Fibrosis and inflammatory changes, identified by biopsy and delayed enhancement magnetic resonance, have also been documented in patients with lone AF.[95]

After the onset of AF, changes of atrial electrophysiological properties, and mechanical function occur within days (>24 h). Shortening of the atrial effective refractory period results from abbreviation of the atrial action potential duration, which is caused by a decrease in the calcium channel current (I_{Ca}), and an increase in the potassium channel current (I_{K1}) and the constitutively active acetylcholine-sensitive current (I_{KACh}).[93] Increased diastolic sarcoplasmic reticulum Ca2+ leak and related delayed after-depolarizations/triggered activity promote cellular arrhythmogenesis.[96] Ryanodine receptor type 2–mediated sarcoplasmic reticulum calcium leak also drives AF progression.[97] Down-regulation of the Ca^{2+} inward current and impaired release of Ca^{2+} from intracellular Ca^{2+} stores cause loss of contractility and increased compliance with subsequent atrial dilation. Electrical remodeling of the atria is, therefore, perpetuated by AF itself in a way that "AF begets AF".[98] Restoration of sinus rhythm results in recovery of normal atrial refractoriness within a few days. LA structure and function are increasingly abnormal with a greater electrical burden of AF, and LA dysfunction may be present despite normal LA size and sinus rhythm.[99] A fast fibrillatory rate is associated with worse prognosis in patients without structural heart disease, due to adverse atrial remodeling and prolonged episodes, but in patients with heart failure a low fibrillatory rate indicates poor prognosis probably due to adverse remodeling and atrial fibrosis.[100] New-onset AF is independently associated with diastolic dysfunction, indicating the presence of potentially overlooked HFpEF in symptomatic patients.[101]

Data from the Framingham Heart Study indicate that AF recurs in most individuals, including those diagnosed with secondary precipitants. [102] Increasing age, mitral regurgitation, aortic stenosis, left ventricular hypertrophy, and left atrial dilatation are associated with progression to persistent AF.[3] Assessment of AF progression depends on duration of rhythm monitoring and underlying substrate. Reported annual rates of paroxysmal AF progression range from <1% to 15% (up to 27 - 36% in studies with >_10-year follow-up).[32]

Electrophysiologic Mechanisms

The initiation and perpetuation of AF requires both triggers for its onset and a substrate for its maintenance.

Focal electrical activity contributing to the initiation and perhaps perpetuation of AF has been identified at pulmonary veins (PV) ostia.[103] Due to shorter refractory periods, as well as complex three-dimensional mural architecture, the venoatrial junctions have a stronger potential to initiate and perpetuate atrial tachyarrhythmias.[104, 105] Mechanisms of focal activity might involve increased local automaticity, triggered activity, and micro-reentry. Apart from the PVs, other cardiac veins and certain areas of the posterior left atrial wall may have a profibrillatory role.[106] Localized anisotropic reentry leading to rotors with a high dominant frequency, and fibrillatory conduction may also play a role in maintaining AF.[107] Wave fronts emanating from foci and breakthrough sites without reentrant mechanisms has also been demonstrated in persistent AF.[108]

According to the ***multiple wavelet hypothesis***, proposed by Moe and colleagues, AF is perpetuated by continuous conduction of several independent wavelets propagating through the atrial musculature in a seemingly chaotic manner. Fibrillation wavefronts continuously undergo wavefront–waveback interactions, resulting in wavebreak and the generation of new wavefronts, while block, collision, and fusion of wavefronts tend to reduce their number. As long as the number of wavefronts does not decline below a critical level, the multiple wavelets will sustain the arrhythmia.

Areas rich in ***autonomic innervation*** may be the source of activity that triggers AF (Figure 5).[109, 110] Ganglionated plexi that can be identified around the circumference of the left atrial-PV junction may also contribute to induction and perpetuation of AF.[106] These plexi are usually located 1-2 cm outside the PV ostia, they mediate both sympathetic and parasympathetic activity, and their ablation (autonomic denervation)) has been found efficacious when added to antral PV isolation .[111]

These mechanisms are not mutually exclusive and may co-exist at various times. While in most patients with paroxysmal AF localized sources of the arrhythmia can be identified, such attempts are often not successful in patients with persistent or permanent AF. This can be interpreted within the context of the multi-factorial aetiology of AF.

Hemodynamic Consequences

Loss of atrial contraction and atrioventricular synchrony, irregular ventricular response, rapid heart rate, and impaired coronary arterial blood flow affect the hemodynamic function during AF. Loss of atrial contraction, especially when diastolic filling is impaired may reduce cardiac output up to 15%. Up to 40% of patients with heart failure develop AF, and heart failure occurs in more than one third of individuals with AF.[27, 28] Irregular ventricular response affects both myocardial contractility and coronary flow. Rapid ventricular rates may compromise coronary flow and exacerbate MR. Atrial cardiomyopathy plays an important role in the development of AF,[32] and reduced AF burden by successful AF ablation may not restore LV function, thus suggesting an occult cardiomyopathy as a cause of AF.[112] A persistently elevated ventricular rate (>130 bpm) is also a known cause of tachycardia-induced cardiomyopathy. Ventricular response is limited by the intrinsic refractoriness of AV node and its atrial inputs, and is being affected by concealed conduction to the nose and autonomic tone. AF is also a cause of functional MR due to atrial dilatation.[113] Individuals with AF associated with a potentially reversible cause have a lower risk of heart failure but similar risks of stroke and mortality over follow-up as compared to individuals without such precipitants.[102] Nearly 33% patients with AF develop moderate-to-severe TR, and this is associated with poor long-term survival.[114] AF is a causal risk factor for kidney function impairment.[115]

Thromboembolism

Thrombotic material in AF usually arises in the left atrial appendage due to decreased flow and stasis, possible endothelial dysfunction, potentially even in anticoagulated patients, and a hypercoagulable state as indicated by increased fibrinogen, D-dimer, thromboglobulin, and platelet factor 4 levels.[116, 117] AF, in general, is associated with a 5-fold increased risk for stroke, a 2-fold increased risk for

dementia, and a tripling of risk for heart failure.[27, 118-120] AF genetic risk is strongly associated with cardioembolic stroke.[84] In the Framingham Study the percentage of strokes attributable to AF increases steeply from 1.5% at 50-59 years of age to 23.5% at 80-89 years of age. [121] In the Danish National Patient Registry, the 5-year risk of stroke for men aged 50 years with no risk factors was 1.1%, and with AF alone without additional risk factors 2.5%, with the great majority not being anticoagulated. In men aged 70 years, the corresponding risks were 4.8% and 6.6%.[119] In the Swiss-AF cohort, 5.5% of AF patients developed new brain infarcts after 2 years of follow-up. The great majority (85%) of these infarcts was clinically silent and occurred in anticoagulated patients.[122]
In patients with AF and a risk factor of stroke, treated with aspirin alone, the reported stroke rate is 3% per year.[123] Event rates vary by population, ie age, risk factors, and ethnicity. Female AF patients who have additional stroke risk factors (particularly older age) have been considered to be at greater risk than men of having a stroke, but recent data refute this notion.[124] Patients with a CHA_2DS_2-VASc score 0 in men or 1 in women usually have an event rate <1%/year, whereas in the presence of a CHA_2DS_2-VASc score>=6 the risk exceeds 9%. [119, 121] Each year, 17 million people worldwide have a stroke.[16] Approximately 24% of all strokes are due to AF,[118] and 10% of ischemic strokes are associated with AF first diagnosed at the time of stroke.[125] Approximately 7.5% of patients with embolic stroke of undetermined source develop atrial fibrillation over the next 19 months.[126]

Patients with ischemic stroke or TIA should have continuous ECG monitoring after a stroke for at least 72 hours.[127] In post-stroke monitoring trials, at least 75% of AF episodes were asymptomatic (CRYSTAL-AF and EMBRACE),[128, 129] and subclinical episodes of AF are associated with silent cerebral infarcts, particularly in diabetics.[130 131] Subclinical AF is associated with clinical AF and an elevated risk of stroke although lower than the risk of clinical AF [132] (see "Device-detected atrial high rate episodes"). Numbers of AF-related incident ischemic strokes at age ≥80 years have trebled over the last 25 years, despite the introduction of anticoagulants, and are projected to treble again by 2050.[133] Paroxysmal AF is a risk-factor for stroke,[134] although the risk of stroke depends on the burden of AF,[135] and permanent and persistent AF are probably associated with a higher risk of thromboembolism than paroxysmal AF,[136] and this true for both non-anticoagulated,[137] and anticoagulated patients. [138, 139] The risk is similar in patients with or without valvular disease.[140]
AT/AF episodes of duration >5min seem to increase the risk of stroke,[130 141] as opposed to very short episodes (<20 sec).[142] Serial ECGs, Holter monitoring mobile outpatient telemetry, external loop recorders, and implantable loop recorders detect post-stroke AF in 23.7% of patients. [118] However, AF early after stroke can be caused by a transient neurogenic mechanism, and AF several months post-stroke can be an incidental finding; therefore, it cannot be concluded that the cause of cryptogenic stroke has been identified in all patients found to have post-stroke AF.[118]

Prior embolic events, intracranial haemorrhage, myocardial infarction, vascular disease, hypertension, diabetes, female gender, and advancing age, but not thyroid disease, are independent risk factors for stroke.[143] Renal impairment (CrCl <60 mL/min) doubles the risk of stroke and

increases the risk of major bleeding by almost 60% in anticoagulated patients with AF.[144] The morphology of the left atrial appendage may affect the risk of stroke.[145] High-sensitivity troponin, N-terminal pro-brain natriuretic peptide, and growth differentiation factor 15 (GDF-15) are predictive of stroke and death in AF.[146]

Extracranial systemic embolic events constitute 11.5% of clinically recognized thromboembolic events in patients with AF and are associated with a high morbidity and mortality, comparable to that of ischemic stroke.[147] AF is the main cause of coronary embolism, being independently associated with an increased risk of myocardial infarction, especially NSTEMI in women. [148, 149]

Mortality

AF is independently associated with a twofold increased risk of all-cause mortality in women and a 1.5-fold increase in men, with an overall 3.5-fold mortality risk increase.[32] Patients hospitalized for AF or flutter had high death rates with an average 2.6-year loss in life expectancy.[150] In a the large Swedish registry, AF was an independent risk factor of all-cause mortality, and the highest relative risk of mortality was seen in women and in the youngest patients.[151] In a European registry (EORP-AF), one-year mortality was 5.7% despite good adherence to anticoagulation.[152] Earlier diagnosis of AF is associated with a higher hazard ratio of subsequent myocardial disease and shorter life expectancy.[153] AF is independently associated with a 3-fold increased risk of VF.[154] In the ARIC trial, incident AF was associated with an increased risk of sudden and non-sudden cardiac death in the general population.[155] In the RE-LY trial, <10% of deaths were attributed to stroke; main causes of death were sudden cardiac death (22%), and heart failure (15%).[156] In the ARISTOTLE trial, sudden cardiac death and heart failure also accounted for the majority of cardiovascular causes of death in patients with oral anticoagulation.[157] Compared with paroxysmal AF, nonparoxysmal AF is associated with higher prevalence and incidence of HF and higher risk of mortality.[158] Patients with AF or heart failure have a significantly higher risk of postoperative mortality following noncardiac surgery than patients with coronary artery disease, and even minor procedures carry a risk.[159]

Diagnosis

Patients may present with palpitations or the arrhythmia may be an incidental finding.[125] The diagnosis of AF needs to be confirmed by a conventional 12- lead ECG tracing, or rhythm strip showing AF for >_30 s (Table 4). The diagnostic yield increases with duration, dispersion, and number of screenings. Serial long-term (7–14 day) intermittent monitors accumulating at least 28 days of annual monitoring provide estimates of AF burden comparable with implantable loop recorders, which, however, outperform intermittent monitoring and are the gold standard for clinical trials (Figure 6 and Table 5).[160, 161] Several methods and devices are now available for screening.[162] Wrist-worn, optically based heart rate monitors are user-friendly but appropriate validation of the device

used is imperative.[163] In mechanocardiography, mechanical cardiac activity is recorded with accelerometers and gyroscopes, standard components of modern smartphones. High sensitivity and specificity of this method for AF detection with the use of smartphones has been reported.[164] Smartphone technologies have been developed that can assess heart rate and rhythm using either photoplethysmography or single-lead ECG but usually provide only a brief rhythm assessment without information on AF duration or burden.[165-167] In a recent comparison, an FDA-cleared AF-sensing watch (Apple Watch with KardiaBand) that allows a patient to record a 30-second lead I rhythm strip, was found highly sensitive for detection of AF and assessment of AF duration in an ambulatory population when compared with an insertable cardiac monitor (Reveal).[168] In an evaluation of an Apple Watch Application study, the probability of receiving an irregular pulse notification was low. Among participants who received notification of an irregular pulse, 34% had atrial fibrillation on subsequent ECG patch readings and 84% of notifications were concordant with atrial fibrillation.[169] However, in the VITAL-AF RCT, AF screening using a handheld single-lead ECG (AliveCor KardiaMobile) at primary care visits did not affect new AF diagnoses among all individuals aged 65 years or older compared with usual care.[170]

Regardless of the type of hardware and software being used, critical interpretation of available tracings is required to avoid unnecessary interventions from misdiagnosis. Obtaining additional leads in a single-lead device allows for the accurate differentiation of atrial flutter from atrial fibrillation (Figure 7).[171] High-amplitude PVCs may also be registered as R waves, and the sensing threshold will dynamically adjust itself relative to the PVC amplitude, leading to undersensing of true sinus QRS complexes (Figure 7).[172] This can be resolved either by lowering the programmed sensitivity to a level that allows sensing of the true QRS complexes while still avoiding P wave oversensing or by increasing the blanking period, which can minimize oversensing of PVCs.

Frequent atrial ectopy, atrial tachycardia, and atrial flutter may present with rapid irregular RR intervals and mimic AF or diagnosed in patients with AF. Most atrial tachycardias and flutters show longer atrial cycle lengths ≥200 ms, but patients on antiarrhythmic drugs may have slower atrial cycle lengths during AF. When the ventricular rate is fast, atrioventricular nodal blockade during the Valsalva maneuver, carotid massage, or intravenous adenosine administration can help to unmask atrial activity. Extremely rapid ventricular rates (> 200 bpm) suggest the presence of an accessory pathway or ventricular tachycardia.

In the absence of a prior history of the arrhythmia, AF can be detected by ECG monitoring in approximately one-quarter of all patients with acute ischemic stroke by routine monitoring followed by an intensified or prolonged AF search.[127] Machine learning, in particular deep neural networks, can predict new-onset AF from the 12-lead ECG in patients with no previous history of AF.[173]

Investigations

Complete **history** (including family and social history), **physical examination**, **12-lead ECG**, **blood pressure measurement**, **echocardiography**, and basic laboratory investigations (**full blood count, renal, liver and thyroid function, electrolytes, including calcium and magnesium, glucose and lipid profile**) are mandatory in every patient who presents with first detected AF (Figure 8, and Table 6). Biomarkers such as high-sensitivity **TnT, BNP** and **NT-proBNP**, and **GDF-15** are useful for risk stratification.[157] Elevated **FGF-23** is a new biomarker associated with AF.[174] The CHA_2DS_2-VASC score should be evaluated in all patients with AF. The quality of life of the patient should be also assessed using either the modified EHRA (Table 7),[32] or the Canadian Cardiovascular Society[175] scales.

Additional tests in selected cases are:

- **Chest radiography** to exclude lung disease or before starting amiodarone.
- **Ambulatory ECG monitoring** to document AF episodes and detect other initiating arrhythmia. They are not useful in patients with infrequent episodes. Implantable or wireless loop recorders, and smartphone applications may be needed for subclinical AF detection (see Diagnosis).
- **Six-minute walk test** or **treadmill exercise test** to assess rate control.
- **Ischemia testing** if coronary artery disease is suspected.
- **Ambulatory blood pressure monitoring** in case of borderline hypertension.
- **Transesophageal echocardiography** to exclude left atrial appendage thrombus or mobile aortic plaques when cardioversion is planned.
- **Electrophysiology study** when other supraventricular arrhythmia that initiates AF is suspected or when presumed AF presents as a wide-QRS tachycardia
- **Sleep study** when sleep apnea is suspected.
- **Coronary angiography** if CAD is suspected**.**
- **Brain CT/MRI when a stroke is suspected** when sleep apnea is suspected.
- **LGE CMR of the left atrium** to detect fibrosis or atrial cardiomyopathy.[32]

Genetic testing is not generally indicated. It may be considered in patients with multigenerational family members with AF, or in suspicion of inherited cardiomyopathies or channelopathies. In addition (EHRA/HRS/APHRS/LAHRS 2022 Consensus Statement on genetic testing), an analysis of SCN5A, KCNQ1, MYL4 and truncating TTN variants may be performed in all index patients in whom the diagnosis of familial (young = age < 60) AF, is established, based on examination of the patient's clinical history, family history, and ECG characteristics. Variant-specific genetic testing may also be recommended for family members and appropriate relatives following the identification of the disease-causative variant, and predictive genetic testing in related children may be considered in specific settings.[88]

Risk stratification

The main complications of AF are thromboembolism, and impairment of LV function. Reduced LV function predisposes to thromboembolism, and may evolve into tachycardiomyopathy. Baseline echocardiography, therefore, is essential for initial assessment of LA size and LVEF, and follow-up. . Arrhythmia-induced impairment of LV function should be considered with fast and persistently elevated ventricular rate. The ventricular rate that causes cardiomyopathy is not known, although rates>100 bpm for prolonged periods are considered to be responsible.[176]

Absolute stroke rates for nonanticoagulated patients vary between 1.5% to 10% depending on the presence of risk factors (Table 8). Prior stroke/TIA is the most powerful risk factor and reliably confers a stroke risk averaging 10% per year.[143] Patients <60 years, with lone AF, have a very low cumulative stroke risk, estimated to be 1.3% over 15 years. The probability of stroke in young patients with lone AF appears to increase with advancing age or development of hypertension. Asymptomatic AF may confer even a worse prognosis that symptomatic AF in this respect.[177]

Risk stratification schemes are based on the predisposing factors that have been discussed. The most frequently used score is the CHA_2DS_2VASc score (Table 9). [178] These schemes apply to patients with any form of AF (paroxysmal, persistent, or permanent). Additional scores such as the ATRIA, biomarker-based risk scores for predicting stroke in AF (such as the ABC-stroke score), and the ENGAGE AF-TIMI that has also considered patients on NOACs, and others have also been developed, and some of them have been found superior to CHA_2DS_2VASc score.[179-183] In most stages of chronic kidney disease, predictive performance of the majority of risk scores is poor. The Modified $CHADS_2$ score (six categories of age, sex, diabetes, history of stroke) has been found superior in a comparative study considering the predictive performance of the AFI, $CHADS_2$, Modified $CHADS_2$, CHA_2DS_2-VASc, ATRIA, and GARFIELD-AF risk scores.[184] Clinical risk scores only have a modest ability to predict events in AF, but since recent data suggest that women and men with AF have similar rates of thromboembolic events, excluding gender leads to better precision.[185] However, the use of risk stratification and precision medicine tools does not necessarily result in improved clinical outcomes in patients with AF. In a multicenter, registry-based, randomized, controlled, open-label study in patients with AF, a biomarker-based ABC-AF risk score–guided multidimensional treatment strategy did not improve long-term outcomes in patients with AF.[186]

Risk of bleeding and mortality in anticoagulated patients with AF are discussed under "Anticoagulation".

Therapy: General Principles

General recommendations are provided in Figures 9-11, and Tables 10 and 11.

Prevention of AF

Hypertension treatment is mandatory but the J-curve effect should be kept in mind. In the RE-LY cohort, the risk of major bleeding was increased at low systolic blood pressure values <110 mmHg, with the lowest risk around 120–130 mmHg.[187] Abstinence from alcohol in heavy drinkers (>120g of alcohol daily), reduces AF recurrences.[188] Treatment of sleep apnoea is mandatory.[65] Tirzepatide, a insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist, has been found beneficial in patients with moderate-to-severe obstructive sleep apnoea and obesity.[189] Upstream therapy to prevent or delay myocardial remodeling associated with hypertension, heart failure, or inflammation (e.g. after cardiac surgery) may deter the development of new AF (primary prevention) or, once established, its rate of recurrence or progression to permanent AF (secondary prevention).[190] Allopurinol is also protective in patients with hyperuricaemia.[38] There has been compelling evidence supporting the role of RAAS in the genesis and perpetuation of AF. Experimental studies have demonstrated the beneficial effects of ***ACEIs and ARBs*** on AF prevention; however, clinical studies on the efficacy of such therapeutic interventions have produced variable results depending on the clinical background of treated patients.[191] [192] In patients with heart failure and/or LV hypertrophy, ACEIs and ARBs appear particularly useful for primary prevention of AF. Although meta-analyses of secondary prevention trials also suggest a risk reduction after cardioversion with the use of ACEIs and ARBs, no effect was detected in large primary prevention trials,[193, 194] or in a meta-analysis for the prevention of postoperative AF.[195] These agents are indicated for primary prevention in patients with hypertension or heart failure, but their value in secondary prevention is unproven. In patients with systolic heart failure and mild symptoms, ***eplerenone*** has also reduced the incidence of new onset AF,[196] and in patients with chronic kidney disease and diabetes, ***finerenone*** reduced the risk of new-onset AF or flutter.[197] Despite experimental evidence for a potential role of ***statins,*** and ***steroids***, their clinical value as single therapeutic agents is not proven.[198] However, in the RACE 3 trial, targeted therapy of underlying conditions with simultaneous use of mineralocorticoid receptor antagonists, statins, ACEI/ARB, and cardiac rehabilitation including physical activity, dietary restrictions, and counselling improved sinus rhythm maintenance in patients with persistent AF.[199]

Recommendations for primary and secondary prevention are presented in Table 12 and Figure 12.

Acute Therapy

Cardioversion

Restoration of sinus rhythm by cardioversion or ablation reduces LA and RA volumes and mitral and tricuspid regurgitation and improves atrial and ventricular function in patients with AF.[200] However, in stable patients presenting to the emergency department with recent-onset, symptomatic atrial fibrillation, a wait-and-see approach is not inferior to early cardioversion in achieving sinus rhythm at 4 weeks, since atrial fibrillation often terminates spontaneously.[201]

Peri-cardioversion anticoagulation Atrial fibrillation patients undergoing cardioversion have an increased thromboembolic risk (up to 7%) that is present regardless of whether cardioversion was successful and whether or not oral anticoagulation or TOE were used prior to cardioversion.[202] In patients with AF<48 h from a definite onset a bolus of UFH (5,000 U IV) or LMWH (1mg/kg IV) should be given, especially if the patient is >65 years old or the CHA2DS2VASC score is >=2.[203] If AF occurred for more than 48 h a trans-oesophageal echocardiography (TOE) is necessary to exclude left atrial thrombus. Patients who have been on oral anticoagulation for at least 4 weeks before cardioversion with warfarin (and INR>2) or a direct oral anticoagulant (DOAC) may be subjected to cardioversion without previous TOE.[204] However, the prevalence of left atrial thrombus identified by transesophageal echocardiography even among anticoagulated patients anticoagulated with a DOAC or vitamin K antagonist for 3-4 weeks is 3-4%.[116, 117] Thus, a TOE should be performed. Following cardioversion, further anticoagulation depends on underlying risk factors for thromboembolism. In the absence of such risk factors (CHA_2DS_2-VASc score 0 for males or 1 for females), no oral anticoagulation is needed after cardioversion. In patients with AF>48 h or risk factors for thromboembolism, heparin is continued together with warfarin until the INR becomes 2-3, or a DOAC is administered immediately after cardioversion. Thereafter, anticoagulation is continued for 4 weeks and then further anticoagulation depends on the presence of risk factors. Recommendations are provided in Figures 13 and 14, and Table 13.

Direct current cardioversion (DCC) is indicated in hemodynamic instability (Table 14) or when pharmacologic cardioversion has failed. Biphasic, R-wave synchronized shock (at least 150-200 Joules to avoid repeated shocks and occurrence of shock-induced VF) is recommended. Anteroposterior electrode placement (at least 8 cm from a pacemaker battery, if present) had been found more efficient when monophasic shocks were used, but in a recent RCT using the more effective and safer biphasic shocks anterior–lateral electrode positioning was more effective than anterior–posterior electrode positioning. The superiority of the anterior–lateral electrode position was significant after both an initial low-energy shock and a final higher energy shock.[205] Ventricular arrhythmias (in digitalis intoxication or hypokalemia) are rare. A pacing catheter or external pacing pads may be needed in patients with sick sinus syndrome or in elderly patients with structural heart disease. Active compression of the anterior pad has been found more effective for persistent AF

cardioversion than standard anterior-posterior cardioversion.[206] Pretreatment with drugs such as ibutilide or amiodarone or flecainide may increase success rates.[207-209] In patients with an ICD, external cardioversion is more effective than internal cardioversion in restoring sinus rhythm.[210] Factors that predispose to AF recurrence are age, AF duration before cardioversion, number of previous recurrences, an increased LA size or reduced LA function, and the presence of coronary heart disease or pulmonary or mitral valve disease. Atrial ectopic beats with a long–short sequence, faster heart rates, and variations in atrial conduction also increase the risk of AF recurrence.

Pharmacological cardioversion is less effective than DCC. However, single oral dose Class 1C drugs are safe for cardioversion of recent-onset AF.[211] The same precautions for anticoagulation and thromboembolic risk prevention apply as in DCC. Drugs used are (Figure 15 and Tables 15 and 16):

- ***Flecainide*** (1.5-3 mg/kg IV over 10-20 min) or ***propafenone*** (2 mg/kg IV over 10 min) achieve SR in 67-92% and 41-91% of patients, respectively within the next 6 h. They are both contraindicated in patients with CAD or impaired LV function, and are not effective in atrial flutter or persistent AF. They may prolong QRS duration with resultant ventricular tachycardia (and flecainide also the QT) and inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles. Flecainide may be superior to propafenone.[211] Orally inhaled flecainide, 120 mg estimated total lung dose (eTLD) flecainide solution via nebulization at a flow rate of 5 L/min, may also achieve cardioversion in up to 47% of patients.[212]
- Self administered ***flecainide acetate oral inhalation*** solution using a nebulizer (60-120 mg) results in acute conversion of 35-44% of patients within 90 minutes from the start of inhalation. Cardiac adverse events such as postconversion pauses, bradycardia, and atrial flutter with 1:1 atrioventricular conduction are rare and transient. However, clinical experience is limited.[213]
- The ***"pill in the pocket"*** approach refers to oral flecainide (200-300 mg po) or propafenone (450-600 mg po) that may achieve SR in up to 45% of patients who present with a <7 days AF.[214] They can also be used outside the hospital, once treatment has proved safe in hospital for selected patients without sinus or AV node dysfunction, bundle branch block, QT-interval prolongation, the Brugada syndrome, or structural heart disease, and especially previous MI. Before antiarrhythmic medication is initiated, a beta blocker or nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs (<0.2%).
- ***Ibutilide*** is a Class III agent blocking the rapid component of the rectifier potassium channel (IKr), and also activating the slow inward sodium.[215] It is a moderately potent drug for acute conversion of AF. In one or two doses, achieves conversion within 90 min in approximately 50% of patients. It prolongs the QTc by approximately 60 ms and there is a 1% risk of torsades de pointes. Patients should be watched for abnormal T-U waves or prominent QT

prolongation, and should be monitored for a minimum of 4 hours if the QTc interval remains prolonged. Co-administration of magnesium (1-4 g) or beta blockade may increase efficacy and diminish the proarrhythmic risk.[216] It is more effective in atrial flutter.

- ***Amiodarone*** achieves cardioversion in 40-60% of patients (80-90% with pretreatment), but later than the other drugs. Hypotension and slow ventricular rate may be seen.
- ***Dofetilide*** is also a pure class III agent (selective Ikr blocking agent), that is moderately effective in cardioverting AF or Afl to SR (30%), and significantly effective in maintaining SR for 1 year (60%).[217] It is also effective even in AF >7 days duration but the response may be delayed. QTc prolongation also occurs and there is a small but not negligible risk of torsade de points that may translate into increased mortality.[218] In-hospital monitoring is recommended (FDA) when initiating dofetilide therapy to avoid torsade de pointes ventricular tachycardia, especially in patients with heart failure, hypertrophy, bradycardia and female gender.
- ***Vernacalant*** blocks early activating potassium channels (Ikur) and frequency-dependent sodium channels. It is relatively atrial selective because the density of I_{Kur} channels is higher in the atria and the effects on sodium channels are rate dependent. In a dose of 3mg/kg IV over 10 min, second infusion of 2 mg/kg IV over 10 min after15 min rest, may convert AF (of duration <=7 days or <=3 days after surgery) in up to 51% of patients within 90 min.[219] Vernakalant is contraindicated in patients with systolic blood pressure <100 mm Hg, severe aortic stenosis, heart failure (class NYHA III and IV), ACS within the previous 30 days, or QT interval prolongation (uncorrected QT>440 ms). Before its use, the patients should be adequately hydrated. The drug is not contraindicated in patients with stable coronary artery disease, hypertensive heart disease, or mild heart failure. Vernakalant is not approved in the USA.

Acute rate control

When AF cannot be cardioverted or cardioversion is contra-indicated (ie presence of left atrial thrombus), acute rate control (80-100 bpm) can be accomplished by IV

- ***b-blockers***, or
- ***non-dihydropyridine calcium antagonists***

In the setting of heart failure or hypotension, ***digitalis*** or ***amiodarone*** IV may be used (Table 17 and Figure 16). Adding intravenous magnesium to digoxin reduces fast ventricular response in acute onset atrial fibrillation.[220]

In preexcitation, only Class I drugs or amiodarone are safe. AF with slow ventricular rates may respond to atropine (0.5-2 mg IV) but temporary pacing may be required.

Chronic Therapy

General principles are presented in Figures 17-20.

Rhythm vs rate control

Despite the established haemodynamic and cardiac remodeling benefits achieved by restoration of sinus rhythm,[200] randomized control trials had failed to detect significant mortality and cardiovascular morbidity differences between patients with rate (ie controlling ventricular response with the patient in AF) vs rhythm (is maintenance of SR) control achieved with antiarrhythmic medication.[221-228] This is rather surprising in view of the deleterious effects of AF, and has been mainly attributed to the proarrhythmic effects of drugs, that may negate any benefits conferred by maintenance of SR.[229, 230] Assessment of quality of life was also rather inadequate in most trials. In the J-RHYTHM trial, fewer patients requested changes of assigned treatment strategy in the rhythm control vs the rate control group, which was accompanied by improvement in AF-specific quality of life scores.[225] Maintenance of SR also improved quality of life in the SAFE-T trial.[231] Finally, follow-up of most trials was relatively short. However, improved survival with maintenance of sinus rhythm was detected in the CHF-STAT trial (amiodarone in heart failure patients). [232] In an extensive population-based, observational trial, rhythm control therapy was associated with lower rates of stroke/TIA particularly among patients with moderate and high risk of stroke.[233] In the RAFAS RCT in patients with AF and ischaemic stroke, early rhythm control strategy (performed following a stepwise sequential approach with antiarrhythmic drugs, electrical cardioversion, and catheter ablation) decreased the sustained AF and recurrent stroke within 12 months without an increase in the composite adverse outcomes.[234] In the ATHENA trial, cardiovascular mortality was reduced by dronedarone (3.9% vs 2.7%, p=0.003).[235] However, dronedarone is contra-indicated in patients with heart failure,[236] and in permanent AF (see drugs for rhythm control).[237] Although initial trials suggested no advantage for a systematic rhythm control strategy in HF with reduced ejection fraction, recent data suggest that select patients may benefit from catheter ablation, by means of improving survival, quality of life, and ventricular function and reducing heart failure hospitalizations compared with antiarrhythmic drugs and rate control therapies.[28, 238, 239] Catheter ablation also appears more effective than drugs regardless of the presence of heart failure (see Catheter Ablation). In the EAST-AFNET 4 RCT, early rhythm control with either antiarrhythmic drugs or catheter ablation was associated with a lower risk of adverse cardiovascular outcomes than usual care during adequate rate control therapy among patients with early AF and cardiovascular conditions,[240] and especially in patients with signs or symptoms of heart failure,[241] or high morbidity burden (CHA_2DS_2-VASc scores ≥ 4).[242] This effect was mediated by attainment of sinus rhythm regardless of the way in which it is achieved.[243] In a retrospective population-based cohort study including 22 635 patients, early initiation of rhythm control was also associated with a lower risk of stroke and heart failure–related admission than rate control.[244]

Thus, increasing evidence supports early rhythm control for most patients with recently diagnosed AF as well as for those who are symptomatic.[245] Considerations for choosing are presented in Figure 21.

Rate control

- ***Beta blockers*** (such as metoprolol, bisoprolol, nebivolol, and carvedilol) are the most safe drugs.
- ***Verapamil*** and ***diltiazem*** are also safe but are contraindicated in heart failure. Verapamil may delay progression of paroxysmal AF, especially in patients with vagal AF.[246] Diltiazem has been found superior to carvedilol and metoprolol in patients with permanent AF and preserved LV function.[247]
- ***Digoxin*** is only effective at rest. Life-threatening proarrhythmia may occur, especially with overdosing in the elderly. In a recent analysis of the AFFIRM study, digoxin as a time-dependent covariate was associated with a significant increase in all-cause mortality in patients with AF after correcting for clinical characteristics and comorbidities, regardless of gender or of the presence or absence of HF.[248] This could be due to relatively high serum digoxin levels (≥1.0 ng/mL), required by the study for firm rate control. In another report on the AFFIRM with very careful propensity score matching, no evidence of increased mortality with digoxin was found in patients with paroxysmal or persistent AF,[249] and this was also the findings of a study on data from the ORBIT-AF registry.[250] However, increased mortality was seen in a retrospective analysis of the ROCKET-AF trial,[251] in an observation study on data from the TREAT-AF trial regardless of cardiovascular comorbidities and concomitant therapies,[252] in the retrospective ATRIA-CRVN study on patients without heart failure,[253] and the ARISTOTLE trial.[254] Increased mortality was also detected in a relevant meta-analysis.[255] Very low dose digoxin (serum digoxin concentration <1.2 ng/ml) seems to be safe. In the small RATE-AF RCT (160 patients, >= 60 years with AF and heart failure), digoxin (161 μg/od) resulted to an equal quality of life and less adverse effects compared to bisoprolol (3.2mg/od) at 6 months.[256] Thus, the issue is debatable.
- ***Amiodarone*** IV is the drug of choice (together with IV b-blockers) for slowing the ventricular rate in patients with acute coronary syndromes. In stable patients with AF should not be used for rate response due to its thyroid (in up to 20% of patients) and pulmonary toxicity (2%), unless all other drugs have failed.

Strict rate control (<80 bpm) has not been found superior to lenient rate control (<110 bpm). [257] However, resting heart rate >100 bpm should be avoided, especially in patients with heart failure.[258] Recommendations are presented in Figure 22, and Tables 17 and 18.

AV nodal modification

In patients in whom drug or pulmonary vein ablation therapy has failed or there are signs of tachymyocardiopathy, ***AV nodal catheter ablation or modification*** followed by ***ventricular*** or ***biventricular pacing*** may be necessary (Table 19 and Figure 23).[259] Septal RV or biventricular pacing if LVEF ≤ 35%, are superior to apical RV pacing in this respect.[260]

Rhythm control

In a meta-analysis of 44 randomized trials with 11,322 patients, the efficacy of drugs such as disopyramide, quinidine, flecainide, propafenone, amiodarone, dofetilide, and sotalol, for maintenance of SR was 40-60% per year. All drugs resulted in increased withdrawals due to side effects, and all except amiodarone and propafenone, increased proarrhythmia. No drug reduced mortality, whereas disopyramide and quinidine drugs increased mortality.[261] In a subsequent meta-analysis, a trend for increased mortality was identified for sotalol and, possibly, amiodarone.[262]

- ***Amiodarone*** is the most effective drug,[263] but its long-term use is limited by its toxic effects mainly on the thyroid, lungs and liver (especially at doses>200 mg od). The incidence of interstitial lung disease is 2-10% after 18-24 months of treatment but it may not always be of clinical significance.[264] The effect of amiodarone therapy on mortality has been controversial.[262, 264, 265] It is the drug of choice in heart failure NYHA III/IV. Proarrhythmia is rare but QT monitoring is advisable. Although it inhibits the clearance of warfarin, a paradoxical increase in stroke has been reported in anticoagulated patients.[266]
- ***Dronedarone*** is less effective as well as less toxic than amiodarone at least over one year follow-up (dronedarone vs placebo in ADONIS and EURIDIS trials).[267] It reduces hospitalization due to paroxysmal AF or atrial flutter (ATHENA trial),[235] even in the presence of ischemic heart disease.[268] It is contraindicated in NYHA III or IV or recently decompensated (<4 weeks) heart failure increased mortality in and early termination of the ANROMEDA trial),[236] and in patients with permanent AF (PALLAS trial).[237] The PALLAS trial on patients with >2 years AF, 70% of whom had NYHA I-III heart failure, was stopped due to increased cardiovascular mortality by the drug.[237] Thus, dronedarone is not indicated in patients who cannot or will not be converted into normal sinus rhythm, because it doubles the rate of cardiovascular death, stroke and heart failure. It may cause creatinine levels elevation (2.5% of patients) and, very rarely, severe hepatic impairment, although in a recent Swedish registry on patients with paroxysmal AF no increased risk of death or liver disease was detected. [269] Although it mildly prolongs the QT, the risk of torsades is neglible.[262] It may be given in patients with recurrent AF for the maintenance of sinus rhythm, and to reduce hospitalization for AF in patients in sinus rhythm with a history of non-permanent AF . Care is needed with concomitant administration of digoxin,[237] and this combination should be probably avoided.
- ***Beta blockers*** (other than sotalol) are safe but modestly effective.

- ***Sotalol*** a beta blocker with Class III properties at high doses, is equally effective with amiodarone in converting AF to AR (24% vs 27%, respectively) but less effective than maintaining SR (approximately 30% vs 47% at one year, respectively).[231] Sotalol should not be used in the presence of ventricular hypertrophy or significant repolarization abnormalities. The main concern is proarrhythmia due to QT prolongation and a trend towards increased mortality has been reported,[230, 262] although not validated in all studies.[265] Careful monitoring of the QT is advisable and discontinuation of the drug when the QT>500 ms.
- ***Flecainide*** approximately doubles the likelihood of maintaining sinus rhythm. It is contraindicated in coronary artery disease and LV dysfunction and cardiac hypertrophy or infiltration,[270] and should be stopped if the QRS increases by >25% (risk of monomorphic VT). There has been some indirect evidence from a retrospective, observational study that it might be safer in patients with non-obstructive, asymptomatic CAD, and in the absence of a recent acute coronary syndrome.[271] Concomitant administration of beta blockers reduces proarrhythmic risk and controls ventricular rate in case of conversion to atrial flutter.[272] [273] Caution is necessary when using sodium channel-blocking drugs as monotherapy in athletes with AF. These drugs may lead to (slow) atrial flutter, with 1 to 1 conduction to the ventricles during high sympathetic tone. Short-term flecainide administration (4 weeks) after cardioversion is less effective than is long-term treatment (80%), but can prevent recurrences of atrial fibrillation.[274]
- ***Propafenone*** is safer and has a mild beta blocking activity, but the same precautions as with flecainide should be taken.
- ***Dofetilide***, has also been found useful and safe in patients with AF and impaired LV function (DIAMOND trial), since mortality was not different compared to controls (>50% in 3 years).[275]

The primary goal of rhythm-control drug therapy is to selectively prolong the refractory period in the atrium and avoid the risk of ventricular proarrhythmia. ***Ranolazine*** is an anti-ischemic drug that was shown to reduce AF in the MERLIN-TIMI 36 trial. It blocks I_{Na}, I_{CaL}, and I_{Kr}, and it is postulated that the late sodium current contributes to the prolongation of the action potential duration associated with reduced I_{Kr} at slow heart rates.[276] Theoretically, inhibition of I_{Na} with ranolazine or vernakalant may reduce the risk of TDP associated with I_{Kr} inhibition by drugs such as dofetilide or sotalol.[277] Combination therapy with amiodarone plus ranolazine or dronedarone plus ranolazine has been shown experimentally to have marked synergistic effects that result in atrium-selective blockade of sodium channels and suppression of AF.[277] Other drugs are also being developed.[278] Recommendations for drug usage are presented in Tables 20 and 21, and Figures 24 and 25.

Anticoagulation

Adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and 20%, respectively, in patients with AF.[279] In general, oral anticoagulation is preferred in patients with CHA_2DS_2VASc score ≥ 2, and no anticoagulation in patients with score 0 (Table 22 and Figures 26 and 27). These criteria are superior for selection of anticoagulation than detection of atrial tachyarrhythmias by implantable devices such as ICDs.[280] Low risk patients (score 0 for male and 1 for female) have a low risk of stroke (<1% per year) and may be left without anticoagulation, since the benefit of anticoagulation does not outweigh the bleeding risk (net clinical benefit).[177] In patients with one stroke risk factor (CHA_2DS_2VASc score 1 for men and 2 in women), the risk of bleeding should also be considered, and anticoagulation should be individualized since there is a significant increase in events rate in the presence of an additional risk factor. [281, 282] In the SINGLE-AF RCT, among patients with AF at intermediate risk for stroke (1 in men and 2 in women), DOAC therapy led to a lower risk of stroke, systemic embolism, major bleeding, or death from cardiovascular causes at 24 months than no anticoagulation.[283] In a retrospect study of Swedish Registries, men and women with AF and CHA2DS2-VASc score 0 or 1 who were on anticoagulation had a lower risk of dementia than those who were not, and patients age >65 years benefited from anticoagulation irrespective of stroke risk score.[284] Oral anticoagulation is not associated with reduced risk of stroke/TE among patients with moderate/severe anaemia, whereas the risk of bleeding is increased.[285] Anaemia, therefore, should be treated in these patients. Patients older than 65 years, and especially women, are at high risk of ischemic stroke,[286] and anticoagulation reduces mortality.[287-289] The duration of AF is also important in patients with CHA_2DS_2VASc score >=2.[290] Older patients should receive anticoagulation when indicated.[291, 292] In the very elderly patients (>=85 years), the stroke-free survival improved by 3.5% along with an increased risk of ICH.[293] Therefore, risk stratification beyond CHA_2DS_2-VA is needed to identify patients who may not benefit from OAC therapy.

Aspirin

The protective value of acetylsalicylic acid as monotherapy has been questioned, and it may increase risk of stroke in the elderly (>75 years).[294 295] Warfarin is superior to aspirin in the elderly (>75 years) offering a 52% reduction in yearly risk of a combined end-point of stroke, intracranial haemorrhage and peripheral embolism, (1.8% vs 3.8%) (BAFTA trial).[288] Thus, aspirin for stroke prevention in AF should be limited to patients who refuse any form of oral anticoagulation. In addition, it might be useful in patients with subclinical AF detected by an implanted device, and CHA_2DS_2-VASc score< 4.[296] In patients on DOACs addition of aspirin is not beneficial without a clear indication.[297]

Aspirin with clopidogrel

They offer increased protection compared to aspirin alone, albeit at an increased risk of major bleeding,[298] and are preferred when warfarin is contraindicated. Still, however, aspirin and clopidogrel

offer less protection than warfarin (relative risk 1.44 for stroke, peripheral embolism, MI, and vascular death).[298] In patients who sustain an ischemic stroke despite INR 2-3, targeting a higher INR should be considered (3-3.5) rather than adding an antiplatelet agent, since major bleeding risk starts at INR>3.5.

Warfarin

Wafarin is a racemic mixture of isomers that inhibits synthesis of vitamin K–dependent coagulation factors (Table 23). The effective dose of warfarin varies significantly among individuals, due to genetic variations in its receptor, metabolism via the cytochrome P450 system, and interactions with other drugs, vitamins, and green vegetables. Despite anticoagulation of more elderly patients with AF, intracerebral haemorrhage is considerably lower than in the past, ranging from 0.1 to 0.6%. [299] The risk increases with INR>3.5. Recommended INR values for AF are 2-3. Pharmacogenetic testing for guiding doses, by means of genotyping for variants CYP2C9 and VKORG1 that are associated with reduced clearance and thus a decrease in warfarin requirement, is not clinically useful.[300] Patients initiating warfarin may be at an increased risk of stroke during the first 30 days of treatment, probably due to rapid deactivation of proteins S and C two endogenous anticoagulantas.[301] In high risk cases, warfarin should be started with concomitant LMW heparin administration for the initial 3-5 days of treatment. Increased levels of coronary calcification has been recently reported in patients on long-term therapy with vitamin K antagonists (VKA),[302] and an eventual more rapid deterioration of renal function may be resulting from warfarin-induced vascular calcification.[303] The efficacy of the treatment with VKAs is directly related to the time in therapeutic range (TTR), ie the percent time with international normalized ratio (INR) between 2.0 and 3.0. A target threshold TTR exists (estimated between 58% and 65%) below which there appears to be little benefit of OAC over antiplatelet therapy.[304]

The SAMe-TT2R2 [Sex (female); Age , 60 years; Medical history(more than two comorbidities); Treatment (interacting drug, e.g. Amiodarone); Tobacco use (doubled), and Race (doubled)] score is useful in identifying individuals who will not have good INR control (score>=2).[305] In the absence of bleeding, oral vitamin K is necessary when INR is >10.[306] If bleeding is present, IV vitamin K (5-10 mg) for major bleeding, or 2-5 mg oral vitamin K (or 1-2 mg of the IV preparation in a cup of orange juice) for non-major bleeding are given.[307] In major bleeding, four-factor prothrombin complex concentrate (4-PCC) is preferred to fresh frozen plasma, since >1500 mL of fresh frozen plasma are needed to achieve a meaningful increase in coagulation factor levels.[308, 309] In a trial for reversal of VKA-associated major bleeding, the reported efficacy of 4-PCCs was 72%, with 8% thrombotic events, and 6% mortality.[310] The additional use of vitamin K 5 to 10 mg administered by slow IV injection is helpful.[306]

Direct oral anticoagulants (DOAC)

They are direct thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban) inhibitors (Tables 23 and 24). Thrombin catalyses the final step in the coagulation cascade by converting fibrinogen to fibrin. Factor Xa, in conjuction with factor Va, mediates activation of prothrombin to thrombin. In patients with ***AF not in the context of rheumatic mitral disease or a mechanical valve***, standard-dose DOAC use results in lower incidence of stroke, death, and intracranial haemorrhage with no difference in major bleeding, compared to warfarin, and the benefit is also maintained in the elderly.[311, 312] Compared with warfarin, DOACs appear to have more favorable efficacy and safety profiles, especially in younger patients and patients with lower body weight or creatinine clearance.[312] There is no need for frequent laboratory monitoring and dose adjustments, and no effect on absorption by food. Actually it is enhanced with edoxaban, and, especially, rivaroxaban.[313] Results of clinical trials are presented in Table 25. Lower stroke rates (thromboembolic or haemorrhagic) 0.7% per year may be seen in lower risk patients in clinical practice,[314] and all DOAC are associated with a significant risk reduction of MI,[315] and osteoporotic fractures,[316] compared with VKA. In a meta-analysis of randomized trials, apixaban and edoxaban offered a reduced rate of gastrointestinal bleeding compared to warfarin the elderly (>=75 years), whereas dabigatran (both 150 mg bd and 110 mg bd) was associated with an increased risk of gastrointestinal bleeding compared to warfarin.[317] In patients, >75 years of age apixaban was the only DOAC that reduced systemic embolism as well as intracranial and major bleeding compared with warfarin, while major bleeding rates were the lowest with apixaban, intermediate with dabigatran, and highest with rivaroxaban.[311] In the largest comparison so far, apixaban was associated with lower risk for gastro-intestinal bleeding and similar rates of ischemic stroke or systemic embolism, intracranial haemorrhage, and all-cause mortality compared with dabigatran, edoxaban, and rivaroxaban. This finding was consistent for patients aged 80 years or older and those with chronic kidney disease.[318] In patients aged >=75 years, switching from wargarin to DOACs is beneficial.[319] A history of sporadic falls does not constitute a contraindication for DOAC therapy.[11] Women have a higher baseline endogenous factor Xa activity in comparison with men, but results from edoxaban-treated patients indicate that the efficacy of DOAC versus warfarin is preserved in women in comparison with men.[320] In an individual patient data meta-analysis of 71 683 patients with atrial fibrillation, standard-dose non–vitamin K oral anticoagulants reduced systemic embolic events risk by approximately 30% versus warfarin, a benefit not seen for ischemic stroke. Systemic embolic events accounted for approximately 10% of thromboembolic events and had mortality rates comparable with ischemic stroke.[321]

Specific antidotes such as idarucizumab, andexanet alfa, and ciraparantag have now been developed. However, the half-life of the DOACs is ~12 h, and thus even among patients with major bleeding, temporary interruption of the DOAC is usually an effective strategy for managing bleeding.[307, 313] Furthermore, with the development of specific antidotes, the main problem of DOACs is the considerably higher cost than warfarin. DOAC are indicated only in patients with nonvalvular

AF. There has been indirect evidence from observational studies that they may also be effective in patients with rheumatic mitral stenosis and AF,[322, 323] but in the INVICTUS RCT among patients with rheumatic heart disease–associated AF, vitamin K antagonist therapy led to a lower rate of a composite of cardiovascular events or death than rivaroxaban therapy, without a higher rate of bleeding.[324] They also appear safer and more effective compared with VKA in patients with non-valvular AF and concomitant aspirin therapy,[325] and are preferred to warfarin in the elderly, especially patients >=90 years old.[287, 326] However, in frail older patients already on warfarin, switching to an NOAC was associated with more bleeding complications without an associated reduction in thromboembolic complications (FRAIL-AF RCT).[327]

It should be noted that all major clinical trials have been tried in patients without severe renal impairment (CrCl<15-30 mL/min), and renal function should always be considered, especially with dabigatran. However, in patients with CrCl 25-30 mL/min, apixaban caused less bleeding than warfarin, with even greater reductions in bleeding than in patients with CrCl >30 mL/min.[328] Dabigatran and rivaroxaban are not indicated in patients on haemodialysis because they have been shown to precipitate inadvertent bleeding.[329] Apixaban is approved in the US (not in Europe) for stable, on dialysis patients, but at the usual dose of 5 mg bd it may lead to subtherapeutic levels.[330] Renal function declines with anticoagulation by approximately 1.16 ml/min GFR, and this is more pronounced with warfarin than DOAC due to inhibition of vitamin K-dependent gamma-carboxyglutamic acid (Gla/MPG).[303, 331]

Liver function testing is recommended once a year, but in clinical practice no excess hepatotoxicity, compared to vitamin K antagonists, has been demonstrated,[332] and DOACs might be safer than warfarin in this population (Figure 28).[333, 334] However, as opposed to warfarin, they are still contraindicated in significant liver disease (bilirubin or transamaninases >=2 ULN) including cirrhosis (Child-Turcotte-Pugh category C).[313, 335] DOAC do not interact with food, and rivaroxaban, in particular, shows increased bioavailability when taken with food.[336] They do interact with inhibitors (or inducers) of P-glycoprotein transporters and cytochrome P450 (CYP)3A4. Caution is required when they are co-administered with enzyme inducers and drugs such as verapamil, diltiazem, amiodarone and dronedarone.[337] The concomitant use of selective serotonin reuptake inhibitors with DOACs increased the risk of major bleeding, particularly in the first few months of use.[338] Direct-acting antivirals (such as those used for COVID-19) also inhibit DOAC transport through P-glycoprotein inhibition leading to a theoretical increase in bleeding risk. During their use anticoagulation with alternative drugs (such as LMWH) is recommended.[339]

Dabigatran is administered at a dose of 150 mg bd (CrCl >30 mL/min), or 75 mg bd (CrCl 15-30 mL/min) based on the results of the Re-LY trial (Table 25).[340] Doses of 75 mg twice daily were approved for patients with chronic kidney disease stage 4 (eGFR <30 but ≥15 ml/min). However, in the long-term RELY-ABLE trial, during 2.3 years of continued treatment with dabigatran, there was a higher rate of major bleeding with dabigatran 150 mg twice daily in comparison with 110 mg, and

similar rates of stroke and death.[341] The European Medicines Agency (EMA) has approved both the 110 mg bd and 150 mg bd doses for non-valvular AF. Dabigatran might be considered in valvular heart disease other than mitral stenosis and prosthetic heart valves where it is clearly contraindicated.[342, 343] Elective cardioversion may be performed in patients taking dabigatran for at least three weeks. Dabigatran is excreted via the kidneys and no dosing recommendation is given for clearance <15 mL/min. In the elderly a reduced dose is reasonable (75 mg bd), especially for those >80 years old. It can be safely used together with aspirin. [344] A higher risk of major and gastrointestinal haemorrhage compared to warfarin has been seen in African Americans and patients with chronic kidney disease, but still the risk of inrtracranial haemorrhage is lower.[345] In Asians, dabigatran has been associated with a lower risk of acute kidney injury compared to warfarin. [346] Main side effects are dyspepsia and stomach pain (11%), and transaminase elevations 0.9-2% although with a frequency similar to that caused by warfarin. There is no evidence of liver toxicity as happened with ximelagartan. Despite initial concerns, the risk of MI, if anything, is lower with dabigatran compared to warfarin.[315, 347] Dabigatran is contraindicated in combination with dronedarone, and its dose should be reduced in co-administration with verapamil.[348]

Measurement assays Diluted *thrombin time* and *ecarin clotting assay* are precise methods to assess the anticoagulant effect, and, consequently, expected plasma levels of dabigatran (Table 26). Plasma levels <30 ng/mL are considered sub-therapeutic.[313] *aPTT* and *PT*, measured in samples soon after the last dose, are prolonged by dabigatran but the correlation is not linear to guide dosage. However, in the presence of a normal aPTT dabigatran is unlikely to contribute to bleeding, and *aPTT* can be used in emergencies as a rough estimate.[307, 313]

Antidotes Due to the short half life of dabigatran, interruption of the drug is usually an effective strategy in cases of bleeding.[307, 313]

Non-specific haemostatic agents are prothrombin complex concentrates (PCC) and activated prothrombin complex concentrates (aPCC) in a dose of 50 units/Kg.[307] PCCs are plasma-derived products that contain 3 (factors II, IX, and X) or 4 (addition of factor VII) clotting factors in addition to variable amounts of heparin and the natural coagulation inhibitors protein C and protein S. aPCC contains mostly activated factor VII along with mainly nonactivated factors II, IX, and X. Prothrombin complex concentrates , and especially aPCC carry an absolute increase of thromboembolic events, and in practice they are rarely needed.[313] Fresh frozen plasma is no longer considered a useful reversal strategy.[313]

Specific antidotes are also available (see Bleeding on AC Therapy).[349] *Idarucizumab*, a monoclonal antibody fragment, completely reverses the anticoagulant effect of dabigatran within minutes and has been shown effective in initial clinical trials (2.5 g IV infusions no more than 15 min apart).[350] The achieved rate of haemostasis is approximately 76.7% and the mortality rate 17.4%. Thromboembolic events occur in 3.8% of patients.[351] *Ciraparantag (aripazine)* binds in a similar way to the new oral factor Xa inhibitors, and to dabigatran.

General measures are RBC substitution (if necessary), platelet substitution (in case of thrombocytopenia <=60 $x10^9$/L), tranexamic acid (1 g IV repeat every 6 h, if necessary), and desmopressin in special cases such as coagulopathy or thrombopathy (0.3 mg/kg IV infusion (max dose 20 mg). In emergencies, gastric lavage in recent drug ingestion, hemodialysis, oral charcoal within 2 hours following dabigatran ingestion can also be tried.

Apixaban an oral factor Xa inhibitor, is approved in Europe and by the FDA for nonvalvular AF, and is possibly the most cost-effective and safer new oral anticoagulant.[352, 353] Apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial haemorrhage in patients with non-valvular atrial fibrillation for whom vitamin K antagonist therapy was unsuitable (apixaban vs aspirin, AVERROES trial).[123] In the ARISTOTLE trial, apixaban was found superior to warfarin in preventing embolic or hemorrhagic stroke, and resulted in less bleeding and lower mortality (11% reduction, P=0.047).[354] Benefits were seen in both paroxysmal and persistent/permanent AF,[355] as well in a cohort of patients with valvular disease (mainly MR and TR).[356] Rates of intracranial bleeding were significantly lower in patients treated with apixaban than with warfarin regardless of renal function. Benefits of apixaban are irrespective of concomitant aspirin use,[357] or of patients' age.[358] A substudy of the ARISTOTLE trial has shown that cardioversion of AF can be safely performed in apixaban-treated patients.[359] The drug is metabolized in the liver via P450-depended and -independent mechanisms and 25% is excreted renally. It should not be used in severe hepatic impairment. The usual dose is 5 mg bd, but 2.5 mg bd should be used in patients with at least 2-dose reduction criteria, such as Cr ≥ 1.5 mg/dL, ≥ 80 years of age, and body weight ≤ 60 kg. In patients with only 1 dose-reduction criterion, 5 mg bd are appropriate.[360] Perhaps, it might be prudent to use the 2.5 mg dose in patients with stage 54/5 chronic kidney disease (eGFR<30mL/min/1.73 m^2).[361] Apixaban is not recommended in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-glycoprotein, such as azole antimycotics and HIV protease inhibitors, and should also be used with caution in patients taking rifampicin, phenytoin, carbamazepine, and phenobarbital. Diltiazem results in increased Xa inhibitor levels. There are limited clinical data on patients with a CrCl of 15 to 29 ml/min, and the drug is not recommended in patients with a CrCl of <15 ml/min. No dose reduction is needed in patients taking verapamil.[348]

Measurement assays *Anti- factor Xa assays* may be used as estimate of the anticoagulant effect, and, consequently, expected plasma levels of apixaban. Plasma levels <30 ng/mL are considered sub-therapeutic.[313] aPTT and PT are prolonged by apixaban but cannot be used to guide dosage, since the correlation is not linear.[307] *Diluted prothrombin time* appears as the best test to use in emergency situations.[362]

Antidotes. Due to the short half life of apixaban, interruption of the drug is usually an effective strategy in cases of bleeding.[307, 313] Xa inhibitors are not removed by dialysis, being protein bound. General measures are as described for dabigatran. aPCC and 4-F PCC may be used as non-specific agents.[363]

Andexanet alfa a recombinant protein that binds and sequesters factor Xa inhibitors has been successfully tried for apixaban and rivaroxaban (see Bleeding on AC Therapy).[349, 364] It is given as 300-800 mg IV bolus that can be followed by an infusion of 4mg/min for 120 min.[363] In a meta-analysis of trials and registries on the use of 4PCC, idarucizumab, and andexanet, the average rate of haemostasis was 78.5% and the mortality rate 17.7%. Thromboembolic events occurred in 4.6 % of patients, more frequently with andexanet (10.4%).[351] *Ciraparantag (aripazine)* reverses Xa inhibitors within 10 to 30 minutes. Sustained reversal was achieved with 60 mg ciraparantag for apixaban and 180 mg ciraparantag for rivaroxaban and was well-tolerated.[365] Ciraparantag also reverses dabigatran, edoxaban and enoxaparin.

Rivaroxaban, an oral factor Xa inhibitor, has been approved in Europe and by the FDA for nonvalvular AF. In the ROCKET-AF trial, rivaroxaban, was not inferior to warfarin (INR 2-3) in patients with nonvalvular AF for the prevention of stroke or systemic embolism, and offered a lower rate of intracranial bleeding, but a higher rate of non-fatal gastrointestinal bleeding.[366] In a substudy of this trial, rivaroxaban demonstrated equal safety and efficacy with warfarin in patients >75 year old.[367] However, in a large cohort of Medicare patients, rivaroxaban increased intracranial and extracranial bleeding and, in patients >75 years old mortality, when compared with dabigatran 150 mg bd.[368] The half-life of rivaroxaban is 7-11 hours, but factor Xa is inhibited for up to 24 hours, allowing once daily dosage. Its bioavailability increases with food. The drug is metabolized in the liver via P450-depended and -independent mechanisms, and is not recommended in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-glycoprotein inhibitors (see apixaban). The drug is not recommended in patients with a CrCl of <15 ml/min. No dose reduction is needed in patients taking verapamil.[348]

For assessment of anticoagulant effect and antidotes see Apixaban.

Edoxaban, was also noninferior to warfarin with respect to prevention of stroke or systemic embolism and was associated with significantly lower rates of bleeding and death from cardiovascular causes (ENGAGE AF-TIMI 48 trial), and is now approved by the FDA. Both the 30 and 60 mg doses were not inferior to warfarin, and in the intention to treat analysis with the 60 mg dose there was a trend favoring edoxaban both in men and women.[320] In elderly patients (≥80 years of age) and are not considered to be appropriate candidates for oral anticoagulant therapy, a once-daily 15-mg dose of edoxaban appears to be a safe option (ELDERCARE AF RCT).[369] Amiodarone increases edoxaban plasma levels via P-glycoprotein inhibition, and the lower dose should be used in patients on amiodarone.[370] Edoxaban appears to demonstrate greater efficacy compared with warfarin in patients who were vitamin K antagonists naive than vitamin K antagonists experienced. [371] The dose of edoxaban should be reduced in co-administration with dronedarone or verapamil.[348]

For assessment of anticoagulant effect and antidotes see Apixaban.

Betrixaban has also been found equivalent to warfarin.[372]

Transition between DOAC/Warfarin

Transitioning from one anticoagulant to another is a high-risk period for both strokes and bleeding. A reasonable strategy is to reduce the DOAC to half dose, start warfarin and stop the DOAC when the INR is >=2. When the patient is on warfarin, the DOAC is started after cessation of therapy and three-daily INR measurements to detect a value<2.[373, 374]

XI Inhibitors

Inhibition of XI, a factor that resides in the intrinsic pathway where it is activated by FXIIa or thrombin with significant affinity to thrombotic mechanisms but with a limited role in haemostasis (ie contributing to clot progression but not to clot consolidation), is under clinical evaluation. [375] XIa factor inhibition is promising since it attenuates thrombosis with minimal disruption of hemostasis, thus theoretically being associated with less risk of hemorrhagic complications. However, the first comparison RCT (OCEANIC-AF RCT) was stopped prematurely because asundexian, an XIa inhibitor, was associated with a higher incidence of stroke or systemic embolism, albite fewer major bleeding events, than apixaban in patients with AF.[376] Factor XI pathway inhibition may prove to be particularly attractive in patients with atrial fibrillation who require concomitant antiplatelet therapy. Abelacimab reduced bleeding compared with rivaroxaban in patients with concomitant antiplatelet therapy, but the efficacy of this agent is still unknown (AXALEA-TIMI 17 RCT).[377]

Perioperative anticoagulation

The bleeding risk depends on the type of surgery.

Warfarin Usually major surgical procedures require an INR of at least <1.5. Warfarin has a half-life of 36-42 h and should be stopped for 3-4 days before surgery when the INR is <2, and 5 days when it is >2.[378] In urgent cases oral or IV vitamin K (for dosing see Warfarin) may be considered. In need of urgent reversal, prothrombin plasma concentrates may also be added, and is preferable to fresh frozen plasma.[308, 309] Bridging to UFH or LMWH that is discontinued >=12 h before and restarted 24 h after the operation, has been recommended only in patients with certain mechanical heart valves and high risk of thrombosis. In a meta-analysis, however, heparin bridging for invasive procedures and surgery in patients receiving vitamin K antagonists for AF, prosthetic heart valves, or VTE, conferred a >5-fold increased risk for bleeding, whereas the risk of thromboembolic events was not significantly different between bridged and nonbridged patients.[379] The use of therapeutic dose LMWH was associated with an increased risk of bleeding compared with prophylactic or intermediate dose.[379] Thus, bridging is usually not required (see chapter 70).[380-382] In the continued-warfarin group, the INR in the day of surgery should be <=3, except for patients with one or more mechanical valves, for whom an INR <= 3.5 is permitted (BRUISE CONTROL trial).[383] In patients with AF, normal renal function, and platelet count platelet count >100 × 10^9/L, even major surgery can be safely accomplished with warfarin cessation without bridging when the INR is <1.8 (BRIDGE trial).

Warfarin is then resumed the evening after the procedure.[381] It has been postulated that during minor surgery, hemostasis is primarily dependent on capillary and platelet function as opposed to the coagulation cascade itself, and antithrombotic drugs that interfere with the former (e.g., heparin and antiplatelet drugs) are less well tolerated than those that do not. Another explanation is the concept of an "anticoagulant stress test." That is, if patients undergo surgery while receiving full-dose anticoagulation therapy, any excessive bleeding will be detectable and appropriately managed while the wound is still open.[384] There are limited data on safety of cardiac surgery or other major surgery with a very high risk of thromboembolism and bleeding, in patients who are on warfarin. Currently, these patients are bridged with heparin prior to surgery. In the need of emergent CABG, fresh frozen plasma, and vitamin K may be used to reduce the risk of bleeding.

Non-vitamin K anticoagulants Pre-operative interruption of DOAC depends on the risk of bleeding and renal function.[378] In low-risk patients with normal renal function 24-48h interruption of dabigatran and 24h interruption of Xa inhibitors is sufficient. In patients at high bleeding risk dabigatran is interrupted 120 h (Cr Cl<30 ml/min) to 48 h (CrCl>80 ml/min), and Xa inhibitors 72h (CrCl<30 ml/min) to 48 CrCl>30 ml/min).[378] There has been evidence that continuation or short-interruption of DOAC are safe strategies for most invasive procedures (BRUISE CONTROL-2 RCT).[385] Bridging with heparin is, on most occasions, not necessary and may increase the risk of bleeding. [386] In an analysis of data from the RE-LY trial, interruption of dabigatran (2 days) or warfarin (5 days) for allowance of surgery was not associated by a significant occurrence of stroke and systemic embolism although heparin bridging was used in <80% of patients on dabigatran, and major bleeding was not different in the two treatment groups.[387] However, discontinuation of rivaroxaban in the ROCKET AF for at least 3 days was associated with a higher incidence of stroke compared to discontinuation of warfarin.[388] Thus, in patients with a $CHADS_2DS_2VASC$ score >4, ie >5% annual risk of stroke, bridging therapy with LMWH should be considered. Procedures with low haemorrhagic risk (dental extraction, skin biopsy, cataract surgery) can be safely performed without interruption of NOACs, especially if they are carried out 12 h after last dosing. For pacemaker and ICD implantation, a 24 h discontinuation with reinitiation 48 h after implantation (24 h in patients with a $CHADS_2DS_2VASC$ score >4) is appropriate.

If urgent surgery or intervention is required, the risk of bleeding must be weighed against the clinical need for the procedure. Surgery or intervention should be deferred, if possible, until at least 12 h and ideally 24 h after the last dose. Specific agents are now available for urgent reversal of anticoagulation. Non-specific agents, such as prothrombin complex concentrates should not be given for prophylactic reversal due to their uncertain benefit-risk. Reinitiation of these agents should be delayed for 24-48 hours and once complete hemostasis is assured, since within 1 to 2 hours of reinitiation the patient will be anticoagulated. For procedures with immediate and complete haemostasis NOACs can be resumed 6-8 h after the intervention. Recommendations are provided in Tables 26 and 27, and Figures 29-33.

Bleeding on Anticoagulant Therapy

Risk factors for bleeding with anticoagulant and antiplatelet therapy are presented in Table 28 and Figure 34.

The risk of bleeding is assessed by several schemes such as the HAS-BLED, ATRIA, $HEMORR_2HAGES$, ORBIT.[389] [390] The most popular is the HAS-BLED where a score ≥ 3 or an indicates "high risk" (Table 28). The ABC-bleeding score, using age, history of bleeding, and three biomarkers, haemoglobin, cTn-hs, and GDF-15 (growth differentiation factor-15) has been shown to perform better than HAS-BLED and ORBIT scores in this respect, and predicts the risk of death in anticoagulated patients.[182, 391] The DOAC score has been developed for patients taking DOAC and has also outperformed the HAS-BLED. A score >=5 indicates moderate risk whereas a score >=10 high risk (Table 28).[392] A history of falls should not be considered an absolute contraindication to anticoagulation.[281] Nonsteroidal anti-inflammatory drugs (NSAID) increase the risk of both serious bleeding and thromboembolism in anticoagulated patients with AF.[393] Nuisance bleeding, ie bruising, haemorrhoidal bleeding, is not associated with a higher risk of major bleeding, and ,thus, not a reason for interrupting anticoagulation.[394] In anticoagulated patients with AF, bleeding is associated with new cancer diagnoses. It is important to proceed to timely investigations in patients with bleeding after anticoagulation for AF, rather than attributing bleeding as an expected adverse effect.[395]

Antidotes and general measures are summarized in Table 29 and Figures 35 and 36. Anticoagulation may be restarted within one week after an episode of GI bleeding.[396]

Management of stroke

Risk factors for thromboembolic complications and recurrent intracranial haemorrhage are presented in Table 30.

Ischaemic stroke

AF-related ischaemic strokes are often fatal or disabling, with increased risk of early recurrence within 48 h to 2 weeks, or haemorrhagic transformation, especially in the first days after large cardio-embolic lesions and acute recanalization therapy.[32, 397] Non-contrast computed tomography is the most sensitive and specific method for detecting ischemic stroke and excluding intracerebral haemorrhage.[398] Detection of only severe hypoattenuation on CT is a contraindication for fibrinolysis. High burden (>10) of cerebral microbleeds on diffusion-weighted magnetic resonance may also be a contraindication, but routine use of MRI to exclude cerebral microbleeds before administration of IV alteplase is not recommended.[398] The CT hyperdense middle cerebral artery sign should not be used as a criterion to withhold IV alteplase.[398]

If the patient is fully anticoagulated, fibrinolysis should not be performed due to the risk of haemorrhage, and endovascular treatment should be considered. Intraarterial, catheter-based treatment administered within 6-12h hours after acute ischaemic stroke using aspiration and stent retrievers has

improved neurologic recovery, and reduced mortality compared to IV fibrinolysis, especially in the presence of a proximal cerebral arterial occlusion on CT or MRI perfusion scan.[399, 400] It can be delivered with or without concomitant IV fibrinolysis, and there is emerging evidence that following CT perfusion or MRI perfusion-diffusion confirmation of the diagnosis, it might be useful up to 16 h after symptoms onset.[401, 402] Low-intensity monitoring is non-inferior to standard monitoring (that is burdensome for nurses and disrupts the sleep of patients) in patients with a mild or moderate level of neurological impairment who receive thrombolysis treatment for acute ischaemic stroke.[403]

Anticoagulation does not increase the risk of intracerebral hemorrhagic complications when INR is <=1.7.[348] In patients who present with stroke while taking new anticoagulants, if the aPTT is prolonged in a patient taking dabigatran or the prothrombin time with an Xa inhibitor, it should be assumed that the patient is anticoagulated, and thrombolysis should probably not be administered. However, in recent studies on patients with a ischemic stroke and a DOAC taken within the last 48 h, thrombolysis with rt-PA or intra-arterial treatment had similar risk of symptomatic intracranial haemorrhage to that in patients on subtherapeutic VKA treatment (INR<1.7) or in those without previous anticoagulation.[404 405] Thus, patients with a last DOAC intake 24-48 h earlier or with plasma levels <30 ng/mL can treated with fibrinolysis.[313] Of note, age>80 years is not an exclusion criterion, provided it can be given within the first 3 hours. Anticoagulants and antiplatelet agents should be withheld the first 24-48 h following fibrinolysis. However, tirofiban infusion in patients who underwent thrombolysis within 4.5 hours after onset increased the likelihood of an excellent functional outcome but at the expense of a relatively low increase (1.7%) of intracranial hemorrhage.[406]

Eligible patients presenting within 4.5 h after the onset of ischaemic stroke should be considered for IV alteplace (tPA, 0.9 mg/Kg, with 10% bolus, and the remainder over 60 min, maximum dose 90 mg). In addition, in patients in whom a small core volume of cerebral infarction is disproportionate to a larger area of hypoperfusion (defined on perfusion MRI or CT a ratio >1.2 between the volume of hypoperfusion and the volume of the ischemic core, an absolute difference in volume > 10 ml, and an ischemic-core volume < 70 ml), the time for fibrinolysis can be extended to 9h.[399, 407] Tenecteplase (0.25 mg per kilogram, administered as a single bolus, with a maximum dose of 25 mg), a more fibrin-selective agent, is superior to alteplace in patients subjected to fibrinolysis within 6 h after the onset of ischemic stroke,[408] but this was not verified in another comparison within 4.5 h after stroke.[409] Reteplase (a bolus of 18 mg followed 30 minutes later by a second bolus of 18 mg) may also be superior to alteplace.[410] Fibrinolysis offers recanalization rate of < 50%, and large thrombi in vessels such as the distal internal carotid artery or the first segment of the middle cerebral artery respond poorly.[411] Beyond 4.5 hours and up to 24 hours after stroke onset, treatment with tenecteplase has resulted in less disability and similar survival as compared with standard medical treatment, but at a higher incidence of symptomatic intracranial hemorrhage.[412]

Thrombectomy is superior to medical therapy, especially in young patients.[412, 413]

Although alteplace combined with thrombectomy has not been found superior to thrombectomy alone, tenecteplace plus thrombectomy in patients with acute ischemic stroke due to large-vessel occlusion and who had presented within 4.5 hours after onset, offered a higher percentage of patients with functional independence at 90 days. Symptomatic intracranial hemorrhage within 48 hours occurred in 8.5% of the patients in the tenecteplase–thrombectomy group and in 6.7% of those in the thrombectomy-alone group; mortality at 90 days was 22.3% and 19.9%, respectively (BRIDGE-TNK RCT).[414]

Labetalol (10–20 mg IV over 1–2 minutes, may repeat 1 time), or nicardipine (5 mg/h IV, titrate up by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h) are recommended only when the blood pressure exceeds 180/110 mm Hg. [415] However, in patients who are not candidates for fibrinolysis, blood pressure lowering in acute stroke is not established to be useful with systolic blood pressure of 140 to 220 mm Hg and without evidence of nonstroke end-organ damage, with the possible exception of an early (<6h) BP lowering strategy. [416] Thus, treatment of hypertension in this setting should be individualized. In patients who are candidates for fibrinolysis a pretreatment BP<180/110 mm Hg is mandatory.

Anticoagulation should be started within 48h after a minor or moderate stroke or on day 6 or 7 after a major stroke (ELAN RCT).[417] Late initiation (> 48h for minor, 3–4 days for moderate, 12–14 days for major stroke) might be preferable in patients with parenchymal haemorrhage due to haemorrhagic transformation of the stroke.[418, 419] In patients with a TIA, anticoagulation, with either a vitamin K antagonist or a DOAC, can be initiated 1 day after the onset of neurological symptoms. [313, 348] In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or haemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days (AHA/ASA 2014 GL for prevention of stroke IIa-B).[420] If anticoagulation is unsuitable or not feasible, dual antiplatelet therapy is recommended for secondary prevention (CHANCE trial).[421] Since dabigatran 150 mg bd resulted in a significant reduction in both ischaemic and haemorrhagic stroke, should the acute ischaemic stroke occur whilst the patient is taking dabigatran 110 mg bd, or rivaroxaban or apixaban(neither of which significantly reduced ischaemic stroke compared with warfarin, in their respective trials), the use of dabigatran 150 mg bd instead, may be reasonable, but no direct data exist. Elective noncardiac surgery may best be avoided for 9 months following a stroke, if possible.[422]

In patients suffering an ischaemic stroke despite anticoagulation, switching from one DOAC to another or from a DOAC to warfarin has not been proven of benefit (Table 31).

Intracerebral haemorrhage

Forms of intracranial haemorrhage are presented in Figure 37. Intracerebral haemorrhage is generally associated with higher mortality and morbidity than recurrent ischaemic stroke. Anticoagulation-related intracranial haemorrhage is associated with > 40% mortality,[423] and it is probably lower with DOAC than VKA.[298] The risk is higher in patients with hypertension and, especially, cerebral amyloid

angiopathy which in the elderly is associated with cognitive impairment and spontaneous lobar haematomas.[424] In the case of intracerebral haemorrhage, reversal of anticoagulation (INR<1.3) is needed with vitamin K 10 mg IV, to be repeated if the INR remains >1.4 at 24 to 48 h.[425] If INR remains >1.4, four-factor PCCs are preferred to fresh frozen plasma. In patients receiving a DOAC, a specific antidote such as idarucizumab for dabigatran and andexanet alfa for Xa inhibitors are preferable. PCCs, both activated (aPCC) and 4-factor, are a reasonable treatment for the management of apixaban- or rivaroxaban-related intracerebral haemorrhage when a target-specific antidote is not available.[426] In patients with severe bleeding, particularly intracranial haemorrhage, during treatment with DOACs, failure to achieve effective hemostasis after administration of either 4PCC or specific reversal agents (idarucizumab or andexanet alfa) is associated with considerable mortality (20.2% vs 15.4% for extracranial haemorrhage.[351]

Protamine (1 mg for every 100 units of UFH) is used for unfractionated as well as for LMW heparin, and cryoprecipitate should be administered to patients who have received thrombolytics. Platelet transfusions are not recommended for patients who take antiplatelet agents, and may be detrimental (PATCH trial).[427] Thrombocytopenia is treated with transfusions if platetlet count is <50,000/μl, (or 100,000/μl, if neurosurgical procedures are needed).[425] Tranexamic acid administration causes a reduction in early deaths and serious adverse events, but does not affect functional status 90 days after intracerebral haemorrhage (TICH-2 trial).[428] Tranexamine and amionocaproid acid are alternatives if blood products are being refused by the patient.[429] Intensive treatment to lower the blood pressure with a target systolic level of <180 mm Hg is recommended, [430] but there has been evidence that values <160-140 mm Hg may reduce haematoma enlargement and improve functional outcomes.[431] [432] After documentation of cessation of bleeding low-dose heparin may be started 1-4 days from onset. [430] The timing of resumption of oral anticoagulant is controversial but for most patients waiting 4-8 weeks is prudent.[419] It may be started after 2 weeks since in certain patients it is associated with a significant reduction in ischemic stroke/all-cause mortality rates.[433, 434] DOAC are probably preferred if the haemorrhage happened on warfarin. In Asian patients, where the prevalence of intracranial haemorrhage is much higher than in non-Asians, warfarin was found beneficial following an event only in patients with CHA_2DS_2-VASc score>=6.[435]

Catheter ablation

There is strong evidence for improved rhythm control and quality of life after catheter ablation in appropriately selected patients (Table 33). Ablation offers improved rates of SR maintenance compared to antiarrhythmic therapy, being more beneficial in younger patients. Is effective both in men and women, although a greater reduction in AF burden occurs in men.[436] It is indicated in AF-induced tachycardiomyopathy,[437] and is usually associated with improved left ventricular function and reduced hospitalizations and mortality compared to antiarrhythmic therapy in patients with AF and

heart failure with or without reduced ejection fraction. Its effect on mortality in patients without heart failure is not established in RCTs, However, in meta-analyses, compared with medical therapy, catheter ablation appeared to reduce risks for ischemic stroke after 30 days, mortality, and heart failure (HF) and hospitalization , but at the expense of an increased risk for perioperative stroke.[239, 438] Data mainly from registries and observational studies indicate that average success rates following AF (70% paroxysmal) ablation are approximately 60% and 70% after a single and multiple procedures, respectively, with an average follow-up of 14 months, compared to 50% with antiarrhythmic drug therapy. [439-441] In the CABANA RCT, in the intention-to-treat analysis, over a median follow-up of 48.5 months, catheter ablation did not significantly reduce the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest that occurred in 8.0% (n = 89) of patients in the ablation group vs 9.2% (n = 101) of patients in the drug therapy group (P = 0.30).[442, 443] The main problem in interpreting this trial is the high rate of treatment crossovers.[444] This, together with the lower-than-expected event rates suggest that, in clinical practice, a reduction in the composite endpoint of all-cause mortality, stroke, major bleeding, or cardiac arrest by catheter ablation may be seen in patients who meet the CABANA eligibility criteria but not in lower-risk patients.[445] Over 5 years of follow-up, AF recurrence was reduced by approximately 50% in catheter ablation patients compared with drug therapy, regardless of their baseline AF type.[446] In adult patients with congenital heart disease the one-year success rate is 40%.[447] Cryoballoon ablation has also resulted in a significantly lower rate of AF recurrence than antiarrhythmic drug therapy over a follow-up period of one to three years in three recent randomized trials (EARLY-AF, STOP-AF, and Cryo-FIRST).[448-450] Compared to sham procedures, catheter ablation has been found superior in reducing arrhythmia recurrences and burden and improving quality of life using cryoballoon or PFA techniques (SHAM-PVI and PFA-SHAM RCTs).[451, 452] However, in the PVI-SHAM-AF RCT, catheter ablation did not demonstrate superiority over a sham procedure for improving atrial fibrillation-related quality of life at 6 months.[453]

In the AVANT GUARD RCT, in patients with persistent AF (continuous AF for 7 days to 365 days), the risk of recurrence of atrial arrhythmia was significantly lower among those who received PV and posterior wall isolation with a PFA catheter than among those who received antiarrhythmic therapy with Class I or III, drugs (excluding amiodarone).[454] Catheter ablation has also been found superior to drug therapy in delaying the progression from paroxysmal to permanent AF (ATTEST RCT).[455]

We should acknowledge that antiarrhythmic drugs may also affect the arrhythmogenicity of the pulmonary veins.[456, 457] In meta-analyses of randomized clinical trials including 1212 patients with paroxysmal atrial fibrillation, catheter ablation use was associated with a significant reduction in atrial arrhythmias (average 30%) and hospitalizations compared with use of antiarrhythmic drugs, without increasing risk of serious adverse events.[458, 459] Registries data also suggest that ablation may decrease thromboembolic events and, possibly, mortality in patients at high thromboembolic risk.[460] The

RAFAS RCT in patients with AF and ischaemic stroke also suggested that catheter ablation is beneficial by means of reducing recurrent stroke.[234]

Long-term (>= 10 years) success rates range from 25 to 80% in paroxysmal AF multiple ablation procedures and antiarrhythmic drugs..[461-464] Success rates are lower (52-69%) in patients with persistent AF.[465-467] However, recurrences following catheter ablation for persistent AF are most commonly (63%) paroxysmal in nature.[468] According to data from the Danish Register, over the last 8 years, the risk of recurrent AF after ablation has almost halved. Hypertension, female sex, cardioversion 1 year prior to ablation, and AF duration for more than 2 years all increased the associated risk of recurrent AF. Patients with diabetes, chronic kidney disease, AF duration over 2 years, and patients with heart failure all experienced no improvement in risk of recurrent AF over time.[469] Patients with CMR-detected atrial fibrosis have a higher risk of recurrence following ablation.[470]

Lifestyle modification (sleep apnoea test, weight reduction, alcohol reduction, smoking cessation, and optimal hypertension and hypercholesterolaemia therapy) before catheter ablation reduces both repeat ablations and direct current cardioversions by half until 12 months after index ablation.[471]

Techniques

Current catheter ablation strategies fall into 2 broad categories: pulmonary vein isolation (and, perhaps, ablation of non-PV triggers) to prevent AF initiation, and atrial substrate modification to impede AF perpetuation. PV isolation is achieved with PV antral ablation assisted by dedicated circumferential catheters, or circumferential PV isolation with the assistance of electroanatomic mapping or by cryoablation with a balloon. Irrigated-tip RF ablation, irrigated-tip catheter using a contact force-sensing, and cryoballoon ablation have been reported to yield similar outcomes after AF ablation (FreezeAF, FIRE AND ICE, CIRCA-DOSE, and RACE-AF trials).[472-475] Radiofrequency energy might be associated with fewer patients developing persistent AF on a 3-year follow-up.[476] Nonthermal pulsed field ablation is a novel approach with preliminary results showing durable efficacy, apparently eliminating oesophageal damage. The most common adverse events reported for PFA are pericardial effusion, vasovagal response, and hemolysis, compared with pericardial effusion, ischemic stroke, and esophageal damage for RF ablation.[477] No significant difference in 1-year freedom from atrial arrhythmias between thermal (radiofrequency/cryoballoon) and pulsed field ablation has been shown (ADVENT RCT).[478] In the SINGLE SHOT CHAMPION RCT with continuous rhythm monitoring, PFA was associated with a lower recurrence rate of atrial arrhythmia than cryoablation (37 vs 50%, P=0.046) at 1 year among patients with PAF.[479]

The coronary sinus is another potential arrhythmogenic source but in a randomized comparison, empirical isolation of the coronary sinus with both endo- and epicardial lesions as an adjunct to pulmonary venous isolation and roofline ablation was not associated with improved freedom from atrial arrhythmias.[480] Superior vena isolation has also failed to improve outcomes, and

at the expense of increased complications (CAVAC AF RCT).[481] Additional linear ablation from the superior vena cava to the right atrial septum and cavotricuspid isthmus ablation may improvs the rhythm outcome of patients with persistent AF undergoing cryoballoon PVI (CRALAL RCT). However, this trial only included patients with LA diameter ≤45 mm, and intermittent rhythm monitoring techniques were used.[482] The left atrial appendage has also been described as a potential site of atrial arrhythmia and atrial fibrillation initiation but recent data do not support an empirical left atrial appendage isolation strategy for patients with recurrent atrial fibrillation after previous ablation.[483]

Additional linear lesions along the roof of the left atrium connecting the superior aspects of the left and right upper PV isolation lesions, along the region between the mitral annulus and the left inferior PV (mitral isthmus) and the intervenous ridge, or ablation of complex fractionated electrograms carry a potentially increased risk of complications or proarrhythmia, and none of them has been conclusively demonstrated to be beneficial.[484] There has been evidence that posterior wall lines, especially as part of a low voltage (<0.5 mV) ablation approach may be beneficial in addition to PVI.[467, 485] Most RCTs, [486-491] but not all of them,[492, 493] have refuted this possibility, and the extended approach may even be associated with stroke. These approaches carry a potentially increased risk of complications or proarrhythmia, and none of them has been conclusively demonstrated to be beneficial.[484, 494-499]

Thus, substrate modification is unlikely to add benefit in patients with paroxysmal atrial fibrillation without structural atrial disease. In patients with advanced persistent atrial fibrillation and significant atrial remodeling, the effect of this approach is still under study.[489]

Other techniques such as autonomic denervation by targeting areas of the major ganglionated autonomic plexi, the ligamend of Marshall, and renal denervation are also under study.[500, 501]

Oral amiodarone treatment for two months following ablation reduces atrial arrhythmia related hospitalization and cardioversion rates during the blanking period but does not significantly reduce recurrence of atrial tachyarrhythmias at the 6-month follow-up.[502] Freedom from AF recurrence during the blanking period is highly predictive of longer-term success in catheter ablation.[503]

Hybrid ablation techniques combine minimally invasive epicardial surgical ablation with endocardial catheter ablation and has been proposed for long-standing, persistent AF. Previous observational studies indicated equal efficacy with conventional ablation and a higher complication rate.[504, 505] The CONVERGE RCT on patients with paroxysmal or persistent AF did report a higher efficacy of hybrid ablation albeit at the cost of a non-statistically significant higher complication rate.[506] Similar results were reported by other randomized and observational trials.[507, 508]

Following ablation, aggressive control of weight, blood pressure, lipids, blood sugar, and sleep apnea is important for a favorable outcome.[509] Current guidelines state that ***anticoagulation*** should be continued indefinitely after atrial fibrillation ablation on the basis of the patient's

stroke risk profile and not the apparent success of the procedure.[1, 2] Sustained anticoagulation is recommended in patients with a CHA_2DS_2-VASc score of ≥2.[510] However there has been recent evidence that among patients who had had successful catheter ablation for atrial fibrillation at least 1 year earlier and had risk factors for stroke, discontinuation of anticoagulation resulted in a lower risk for the composite outcome of stroke, systemic embolism, and major bleeding (ALONE-AF RCT),[511] while continuation of rivaroxaban did not result in a significantly lower incidence of a composite of stroke, systemic embolism, or new covert embolic stroke than treatment with aspirin (OCEAN RCT).[512]

Complications

Complications of catheter ablation occur in approximately 4% of cases and are mainly dependent on the operators experience (<25 procedures per year), age of the patient (>80 years), female gender, CHADS2 score of ≥2, and adopted techniques (Table 34).[11, 513, 514] The average mortality rate due to complications associated with the AF ablation procedure is 0.04 - 0.3%, depending on the technique, and is mainly due to stroke, atrio-oesophageal fistulae, tamponade, and pneumonia.[478, 513-516] Pericarditis occurs in up to 3.7% of patients, with RF ablation and younger age as risk factors.[517] Tamponade occurs in 0.67% (in men) to 1.24% (in women) of patients, 16% of which require surgical intervention.[518] Asymptomatic cerebral emboli may be detected in up to 25% of patients,[519] and stroke and TIA in 0.1 to 0.3%.[478, 513] Post-procedure neurocognitive dysfunction may be seen in up to 14% of patients, depending on ablation techniques and anticoagulation strategies, but is usually transient, with complete recovery at 12 months.[520] In the AXAFA-AFNET 5 trial, acute ischemic brain lesions or chronic white matter damage detected on magnetic resonance imaging were detected in 26% of patients subjected to RF or cryo-ablation, but not associated with cognitive decline at 3 months after first ablation on uninterrupted oral anticoagulation. Cognitive dysfunction 3 to 6 weeks before and 3 months after ablation was linked to older age.[521] Pulmonary vein stenosis used to occur with ostial ablation but not with antral or circumferential lesions. Atrio-oesophageal fistula occur in approximately 0.04% of all patients with RF, (0.001% with cryoablation), and carry a 65% mortality depending on immediate surgical repair. Fever is the most common initial symptom and the diagnosis is established by chest CT.[522] Circumflex coronary artery injury may result following extensive ablation near the distal coronary sinus and the base of the left atrial appendage as well as in the anterior left atrium. It may result in VF or sinus dysfunction requiring permanent pacing.[523] Iatrogenic arrhythmias may occur in 4-20% of cases, being higher with linear or fractionated electrogram ablation techniques, but they do not always require repeat ablation.[524]

Cryoballoon-mediated PV isolation might reduce thromboembolic complications and oesophageal injury, but is associated with an *approximately* 4% risk of phrenic nerve pulse that is usually reversible within the next 12 months (up to 97%).[472-475, 525] Cough and haemoptysis following bronchial injury are very rare.[526]

Pulsed field ablation appears to avoid esophageal damage.[527] Reported mortality is 0.04%. Other major reported complications are pericardial tamponade (0.16%), vascular events (0.30%), coronary arterial spasm (0.10%) and stroke (0.10%). Acute kidney injury related to haemolysis is a rare complication of PFA, and haemolysis-related acute renal failure necessitating hemodialysis in 0.02%.[516] A threshold of 70,[528] or even 54 PFA deliveries per procedure,[529] has been found to be associated with the highest haemolysis severity, particularly in patients with baseline glomerular filtration rate <50 mL/min. Thus, prompt careful titration of PFA deliveries, and fluid infusion of >= 2 L normal saline immediately after the procedure,[530] are necessary for the safety of this approach. Prophylactic nitroglycerin is needed when delivering pulsed field ablation near coronary arteries (ie cavotricuspid and mitral isthmus) to avoid spasm.[531] A possibly higher risk of stroke with PFA (0.25%) versus RFA (0.16%) was detected in the EMBOL-AF Registry,[532] and in a high-volume, single-center registry, PFA was associated with a significantly higher risk of stroke/TIA at 30 days (0.47%) compared with RFA (0.2%). However, patients receiving PFA were twice as likely to undergo posterior wall isolation.[533]

Surgical ablation

Since its introduction, the MAZE procedure has gone through 4 modifications (Maze I-IV) using cut-and-sew techniques that ensure transmural lesions to isolate the PV, connect these dividing lines to the mitral valve annulus, and create electrical barriers in the RA that prevent macro-reentrant rhythms from becoming sustained.[534] The Cox MAZE IV procedure is now mainly used either as concomitant ablation in patients undergoing cardiac surgery or as a stand-alone procedure. In a meta-analysis of 23 RCTs, concomitant AF surgery, usually combined with left atrial appendage exclusion or excision was shown to result in increased freedom from AF without affecting the risk of stroke or reducing mortality.[535] However, reports on registries and an analysis of the STS database have suggested a reduced incidence of stroke and mortality following surgical ablation of AF.[536] Series on the stand-alone Cox MAZE IV have shown success rates of 70-90%. Risks include death (less than 1% when performed as an isolated procedure), the need for permanent pacing (with right-sided lesions), recurrent bleeding requiring reoperation, impaired atrial transport function, transient ischemic attacks delayed atrial arrhythmias (especially atrial flutter), and atrioesophageal fistula. Variations of the maze procedure using minimally invasive thoracoscopic approaches and hybrid techniques utilizing radiofrequency or cryoablation energy have also been successfully used.[514]

Surgical ablation of AF may also be considered in patients with symptomatic AF undergoing cardiac surgery, especially when mitral valve procedures are undertaken in experienced centers (Figure 38, and Table 40). In patients with persistent or long-standing persistent AF undergoing rheumatic cardiac valve surgery, biatrial maze ablation has provided better rhythm control than left atrial maze ablation without increasing the risk of permanent pacemaker implantation (ABLATION

RCT).[537] The value of minimally invasive surgical ablation (thoracoscopic) of AF without concomitant cardiac surgery after failure of or compared to conventional catheter ablation is not established.[538 539, 540] The Society of Thoracic Surgeons 2017 Guidelines recommend surgical ablation in patients undergoing cardiac surgery (Class I-A/B) or as a stand-alone operation (Class IIa-B).[534] Recommendations are provided in Table 35 and Figure 38.

Left atrial appendage closure

The left atrial appendage (LAA) is considered the main (but not the only) site of thrombus formation in AF, and various surgical techniques have been used for ligation, excision or stapling of the LAA in patients with AF. Minimally invasive epicardial techniques and interventional trans-septal techniques have been developed for occlusion of the appendage orifice to reduce the stroke risk.[541] The Watchman FLX and the Amulet devices are both U.S. FD, and European Medicines Agency approved and are the 2 most-used devices for percutaneous closure worldwide. The Watchman FLX is a single-closure system device consisting of a self-expanding nitinol cage covered with a flat, porous polyethylene terephthalate membrane on the atrial surface secured with twelve "J"-shaped fixation anchors in 2 rows located circumferentially. The Amulet is a double-closure system consisting of a self-expanding nitinol lobe surrounded by 6 to 10 pairs of stabilizing wires and connected by means of an articulated waist to an external disc that seals the LAA orifice. Concerns have also been raised about device-related thrombus that may be detected in 3.7 to 7.2% of patients and require immediate anticoagulation due to the increased risk of stroke,[542, 543] and a procedure-related mortality of up to 0.56%.[544] Hypercoagulability disorders, renal insufficiency, nonparoxysmal AF, and device implantation depth >10 mm from the pulmonary vein limbus are more important predictors of device-related thrombus.[543] Peri-device leak detected by TEE following implantation are associated with adverse events, primarily thromboembolism.[545] In the PRAGUE-17 RCT, left appendage occlusion was non-inferior to DOACs in high risk patients, but one procedural death (0.5%) was reported.[546] At 4-years follow-up, rates of stroke, cardiovascular death, and bleeding were similar in the two treatment groups.[547] In the Amulet Observational Study using the Amplatzer Amulet device, the ischaemic stroke rate was reduced by 67% compared to the predicted risk. Major adverse events (≤7 days post-procedure) occurred in 4.0%, including death (0.3%), stroke (0.4%), major vascular (1.3%), and device embolization (0.2%).[548] In the ADVENT RCT, among patients who underwent catheter-based atrial fibrillation ablation, left atrial appendage closure was associated with a lower risk of non-procedure-related major or clinically relevant nonmajor bleeding than oral anticoagulation and was noninferior to oral anticoagulation with respect to a composite of death from any cause, stroke, or systemic embolism at 36 months.[549] Improvement in implantation techniques has led to a reduction of peri-procedural complications (EVOLUTION and CAP Registries).[550-552] In the CLOSURE-AF in patients with AF at high risk for stroke and bleeding, left atrial appendage closure was not

noninferior to medical care with regard to a composite end point of stroke, systemic embolism, major bleeding, or cardiovascular or unexplained death.[553] In the CHAMPION-AF RCT, among relatively lower-risk patients with AF who were candidates for anticoagulation, device-based left atrial appendage closure with different devices was noninferior to NOAC therapy with respect to a composite of death from cardiovascular causes, stroke, or systemic embolism and was superior to NOAC therapy for non–procedure-related bleeding at 3 years.[554] In the SWISS-AREPO RCT, Amulet with a dual sealing system appeared less prone to side leaks, yet to greater intradevice leaks and pericardial effusions, compared to Watchman 2.5 or FLX devices.[555] At three years follow-up there was no difference in ischaemic stroke, but there was a lower composite of cardiovascular death, stroke, transient ischemic attack, or systemic embolism at 3 years in the Amulet group.[556] In the Amulet IDE RCT, the 5-year clinical outcomes were similar between the Amulet and Watchman 2.5 devices, including the composite of ischemic stroke or systemic embolism (approximately 7%), although strokes in patients with the Amulet were less severe.[557]

Percutaneous closure is indicated in patients with a relative or absolute contraindication to anticoagulation and AF in the context of a CHADS2 score of ≥1 or CHA2- DS2-VASc score ≥2.[558-561] In a meta-analysis of 6 RCTs enrolling 7004 patients, closure was associated with a higher risk of ischemic stroke, but a significantly lower risk of nonprocedural bleeding compared with OAC.[562] It seems that closure is beneficial in patients with high bleeding risk and low stroke risk, whereas the benefit is uncertain in patients with high stroke risk.[563] Surgical excision of the LAA may be considered in patients undergoing open heart surgery. LAA closure during routine cardiac surgery is significantly associated with an increased risk of early post-operative AF,[564] and may [565, 566] or may not [564] reduce the risk of stroke. In a retrospective analysis, left atrial appendage exclusion performed during isolated coronary artery bypass graft surgery in patients with AF significantly reduced 30-day readmissions for strokes, but it increased the risk of 30-day readmission along with an increased risk of respiratory failure and acute kidney injury, postoperatively, apparently due to the loss of the hormonal and hemodynamic effects of the LAA.[567] However, in the LAAOS II RCT, among patients with AF who were scheduled to undergo cardiac surgery for another indication, occlusion of the left atrial appendage during surgery was associated with improved outcomes in terms of ischemic stroke or systemic embolism,[568] independent of the use of anticoagulation.[569] Similar results were provided by the ATLAS trial.[541] In valvular patients with CGADS-VASC score >=2 but without AF, routine prophylactic left atrial appendage closure is not beneficial.[570] Short-term anticoagulation (approximately6-8 weeks) may be given after occlusion. In this setting, DOAC monotherapy may be a safer than DOAC plus aspirin after LAA occlusion,[571] and a DOAC may be safer than DAPT.[572, 573] Recommendations are presented in Tables 36 and 37.

Atrial Pacing

Atrial-based pacing is associated with a lower risk of AF and stroke than ventricular-based pacing in patients requiring pacemakers for bradyarrhythmias, but the value of pacing as a primary therapy for prevention of recurrent AF has not been proven (Table 38).[574] Pacing in the interatrial septum instead of the appendage, as well as antitachycardia algorithms for suppression of ectopic activity have produced promising results,[575, 576] but the evidence is still inconclusive. There is no hard data to support the use of bi-atrial or multisite right atrial pacing for prevention of AF.

AF in Specific Conditions

Post-operative AF

AF is the most common complication after cardiac surgery, 30% after CABG, 40% after valve surgery, and 50% after combined CABG and valve surgery, with a peak incidence of post-operative AF between post-operative days 2 and 4. [577-579] After noncardiac surgery, depending on the type of the operation, 3% to 16% of patients develop acute AF.[579] Post-operative AF is associated with increased mortality and risk of stroke,[580, 581] and anticoagulation is necessary for AF persisting longer than 48h. In general, minimization of inotropes and optimization of fluid and electrolyte status (especially hypokalemia and hypomagnesemia) has been proposed for all patients.[582] However, in a meta-analysis the benefits of anticoagulation in patients developing post-operative AF after coronary artery bypass grafting were questioned.[583] ***b-Blocker*** therapy is most effective when provided both before and after cardiac surgery; [584, 585] withdrawal of b-blockers is a significant risk factor for the development of post-operative AF and should be avoided. Treatment should be started at least 1 week before surgery with a b1-blocker without intrinsic sympathomimetic activity. However, in an analysis of the STS database, preoperative β-blockade within 24 hours of isolated coronary artery bypass surgery has been found to be associated with a small but finite increase in the rate of postoperative AF without a reduction of morbidities or mortality.[586] Beta blockers are not recommended for non-cardiac surgery.[585] Prophylactic ***amiodarone*** started orally before the operation also decreases the incidence of postoperative AF and reduces the incidence of stroke in most [584, 587] but not all studies.[588] IV amiodarone is the drug of choice for pharamacologic conversion of post-operative AF.[582] Recently, perioperative infusion of ***carpetide*** a renin-angiotensin-aldosterone system inhibitor with strong natriuretic activity, reduced postoperative AF.[589] ***IV magnesium***, and ***steroids*** have also been beneficial,[590, 591] and IV magnesium may increase the success of cardioversion in patients in whom amiodarone was ineffective.[577] ***Colchicine*** (1 mg bd the third post-op day followed by 0.5 mg bd (0.25 bd in patients <70 kg) for one month reduced the incidence of AF by 45% (COPPS substudy),[592] but not in the COP-AF RCT.[593] Use of ***statins*** has also been found to reduce post-operative AF.[594] There has also been limited evidence that routine of atrial or bi-atrial pacing reduces AF.[595] Recommendations are provide in Figures 39-41 and Table 39.

Device-detected atrial high rate episodes

European and US guidelines recommend opportunistic screening for atrial fibrillation in people aged >=65 years, especially when they are at high risk of stroke.[32, 596] The cause of stroke remains unexplained in 20% to 40% of cases. Among these unexplained strokes, 10% to 30% may be caused by AF that has eluded detection.[16] Discovery of subclinical AF usually defined as high-rate episodes of atrial tachyarrhythmias of at least 180 bpm with a duration of at least 5-6 minutes detected by implantable devices and wearable monitors[16] is common, especially in populations known to have an increased risk of stroke (or recurrent stroke). Atrial high rate episodes may be detected in up to 10% of patients with ICDs or pacemakers and hypertension but no history of AF,[130] and could be as high as 30% in patients with additional risk factors for AF.[597] The detected incidence also depends on the monitoring time. In patients with nonspecific symptoms potentially compatible with AF, such as fatigue, dyspnea, and/or palpitations, and a CHADS score>=3, implantable cardiac monitors detect AF in 30-40% of them within the next 18 to 30 months (REVEAL AF study).[598] Detection of AT/AF episodes of duration >=5min appears to increases the risk of stroke by approximately 1.2%.[599, 600] However, the effect of brief AF episodes of <5 min on stroke risk has not been rigorously evaluated and remains unknown, but less than that of clinical AF. [142, 158] Longer AF duration times, at least 5.5 h,[601] or 24h,[602] are associated with stroke, and in a meta-analysis subclinical AF (detected in up to 35% of patients with a pacemaker) was strongly associated with clinical AF and an elevated risk of stroke although lower than the risk of clinical AF.[132] In the STROKESTOP RCT, screening for AF (>30 s) detected by a hand-held single-lead electrocardiogram showed a significant benefit by reducing hard clinical outcomes.[603] However, in the LOOP RCT, screening for AF (>6 min) with an implantable loop recorder resulted in a three-times increase in AF detection and anticoagulation initiation but no significant reduction in the risk of stroke or systemic arterial embolism.[604] It seems that the CHA_2DS_2-VASC score impacts stroke risk much more than the duration of detected AF episodes.[605] The potential benefit of anticoagulation in patients with atrial high rate episodes is under study (Figure 42 and Table 40). [16] In the NOAH-AFNET 6 RCT on patients with device-detected high rate atrial episodes, anticoagulation with edoxaban failed to reduce the incidence of a composite of cardiovascular death, stroke, or systemic embolism but increased the risk of bleeding.[600] However, in the ARTESIA trial, among patients with subclinical atrial fibrillation (at least 1 episode of ≥6 minutes, but no episodes >24 hours) CHA_2DS_2-VASc score >= 3, apixaban resulted in a lower risk of stroke or systemic embolism (0.78% per patient-year) than aspirin (1.24%) but a higher risk of major bleeding (1.71 vs 0.94 %).[599] A meta-analysis of these two trials found that oral anticoagulation with edoxaban or apixaban reduces the relative risk of stroke by approximately 32% and increases the relative risk of major bleeding by approximately 62%, without any effect on cardiovascular or total mortality.[606]

Cryptogenic stroke

Routine anticoagulation in patients with acute ischaemic or embolic stroke of undetermined aetiology is not recommended, since neither rivaroxaban or dabigatran have been found superior to aspirin

(NAVIGATE ESUS and RESPECT-ESUS RCTs. [607] Search for AF in these patients should be performed (Table 41), but it should be noted that new-onset AF is identified in approximately 13% of stroke patients during the in-hospital phase,[118] and in these patients anticoagulation may not be indicated.[608] Clinical risk scores such as the C2HEST (CAD/COPD (1 point each), Hypertension (1point), Elderly (>_75 years, 2 points), Systolic heart failure (2 points), and Thyroid disease (hyperthyroidism, 1 point), have been proposed for the detection of patients prone to AF.[609]

Acute coronary syndromes

Recommendation for the management of AF in patients with an ACS and stable CAD are discussed in the relevant Chapters.

Heart failure

The prevalence of atrial fibrillation in heart failure is 5-50% depending on its severity, and is associated with increased mortality. For a detailed discussion and recommendations see the Chapter on HF.

Adult congenital heart disease

Atrial arrhythmias (AF, atria tachycardia and atrial flutter) occur in 15-40% of patients with congenital heart disease, especially after surgical repair (see ACHD).[610] In patients with sustained AF, anticoagulation is recommended in most patients.[32, 611] Recommendations are presented in Table 42.

Valve disease

AF is frequently seen in mitral and progressed aortic valve disease. Paroxysmal or persistent AF constitutes an indication for percutaneous or surgical intervention in mitral valve disease. Recommendations for anticoagulation are presented in Table 43 and Figure 43. DOAC may be used in aortic or tricuspid valve disease and MR, but not in mitral stensosis.[612] Successful catheter ablation may reduce functional MR with restoration of SR.[113] See also Part II on valve diseases.

Hypertrophic cardiomyopathy

Patients with hypertrophic cardiomyopathy (HCM) are at greater risk of developing AF compared with the general population, and around 20-40% develop AF with an annual incidence of 2-4%. AF is associated with increased risk for mortality, stroke, and severe functional disability, particularly in patients with outflow obstruction, ≤50 years of age, or those developing chronic AF.[613] Stroke risk scoring systems (such as CHA2DS2-VASc score) are not informative in HCM given the substantial potential for stroke events in patients with low scores, and therefore should not be used for anticoagulation decisions in this disease.[614] A rhythm control strategy with catheter ablation seems preferable.[615] Fast AF may also predispose to hemodynamic collapse and VF, and electrical or pharmacological cardioversion is indicated in the absence of atrial thrombus in patients presenting with acute onset AF. When myectomy is considered, addition of maze-III procedure may also eliminate AF without increased peri-operative mortality.[614] A detailed discussion and

recommendations for HOCM as well as other cardiomyopathies are provided in Chapter 39.

Diabetes mellitus

Opportunistic screening for AF is recommended even asymptomatic patients with diabetes. Following catheter ablation for AF, semaglutide may reduce arrhythmia recurrence and improve metabolic outcomes in patients with atrial fibrillation, overweight, and type 2 diabetes.[616] Recommendations are provided in Figure 44 and Table 44.

Hyperthyroidism

AF occurs in 10–25% of patients, with hyperthyoidism especially in men and the elderly. Treatment is aimed primarily at restoring a euthyroid state, which may be associated with a spontaneous reversion to sinus rhythm. If a rhythm control strategy is selected, thyroid function should be normalized prior to cardioversion to reduce the risk of recurrence. Beta blockers are the drug of choice. Amiodarone may cause both hyper and hypothyroidism. Hypothyroidism typically occurs within the first 1-24 months and the prevalence is as high as 22% especially in patients with anti-thyroid antibodies.[617] There are two types of amiodarone-induced hyperthyroidism: type I, where there is an excess iodide-induced production of T4 and T3; and type II, where there is a destructive thyroiditis with a transient excess release of T4 and T3, and, later, reduced thyroid function. Although amiodarone may be continued when hypothyroidism has been successfully treated with replacement therapy, it is necessary to discontinue amiodarone if hyperthyroidism develops. Thyrotoxicosis may also occur after cessation of amiodarone therapy.Anticoagulation is recommended until thyroid function has returned to normal and sinus rhythm can be maintained (Table 45).

Chronic Kidney Disease and dialysis

In patients with chronic kidney disease the predictive ability of all tests is lower, and the Modified $CHADS_2$ score might be preferable.[184] In patients with concomitant diabetes, ***finerenone*** reduced the risk of new-onset AF or flutter.[197] In an extensive, retrospective cohort study on dialysis patients with AF, warfarin did not reduce stroke risk, and was associated with a higher bleeding risk.[618] Warfarin may have an unfavorable risk/benefit ratio in patients with end-stage chromic kidney disease as opposed to those with non-end-stage disease. [619] In addition, the risk of stroke may be only modestly higher in patients undergoing hemodialysis with new-onset AF,[620] and clinically relevant bleeding events are10-fold more frequent than stroke or systemic embolism among this population on anticoagulation.[621] Thus, the use of anticoagulation is highly controversial.[337, 348] However warfarin with a careful INR monitoring or apixaban (5 mg bd) that is an FDA-approved option should be used in patients with high CHA_2DS_2VAsc scores. [621-623] Recommendations are provided in Table 46 and Figure 45.

Liver disease

Patients with liver disease are not “auto-anticoagulated” and thus protected from thrombotic events. However, patients with liver disease have largely been excluded from trials of oral anticoagulants. Because all currently approved anticoagulants undergo metabolism in the liver, hepatic dysfunction may cause increased bleeding. Thus, the optimal anticoagulation strategy for patients with AF or VTE who have liver disease remains unclear.[335] Recommendations are presented in Table 47.

Wolff-Parkinson-White syndrome

AF may predispose patients with WPW syndrome to sudden cardiac death, and AV nodal blocking agents are contraindicated. A detailed discussion, and recommendations are provided the Chapter on AVRT.

Chronic obstructive pulmonary disease

AF is common in patients with chronic lung disease and has adverse prognostic implications in the context of acute exacerbations associated with hypoxia. Treatment of the underlying pulmonary disease and correction of metabolic imbalance are the primary considerations, as antiarrhythmic therapy and electrical cardioversion are likely to be ineffective until respiratory decompensation has been corrected. Multifocal atrial tachycardia is common in severe COPD and may be mistaken for AF. Agents used to relieve bronchospasm such as theophylline and b-adrenergic agonists, may precipitate AF, and controlling the rate of ventricular response may be difficult in this situation. Non-selective b-blockers, propafenone, and adenosine are generally contraindicated in patients with bronchospasm, and nondihydropyridine calcium channel antagonists are the preferred alternative (Table 48). b-1 selective blockers (e.g. nebivolol, bisoprolol, and metoprolol) in small doses are also tolerated and effective.[624]

Elderly

AF occurs with increasing incidence in the elderly, and increasing age is a potent risk factor for stroke. Although most AF trials have enrolled patients without an upper age limit, the mean age of study cohorts is 5 to 10 years younger than the average age of patients with AF in the general population. Therefore, it is unknown whether the findings of studies guiding management can be generalized to patients >=75 years of age, and especially those >=85 years of age.[625] DOAC are preferred to warfarin in the elderly, especially patients >=90 years old (see previous discussion of DOAC).

Young Patients

Supraventricular reentrant arrhythmias are seen in approximately 8% of AF patients referred for catheter ablation.[626] Especially in patients with an onset of unexplained AF before 30 years of age, electrophysiological study to evaluate and treat reentrant supraventricular tachyarrhythmias is

indicated. In patents with an onset of AF before 45 years of age without obvious risk factors for AF, referral for genetic counseling, genetic testing for rare pathogenic variants, and surveillance for cardiomyopathy or arrhythmia syndromes may be also reasonable.

Physical activity and athletes

The intensity of physical activity displays a U-shaped relationship with incident AF, which may indicate that the positive antiarrhythmic effects of physical activity are partially negated when exercise is too strenuous.[69, 627] Professional athletes should be counselled that long-lasting intense sports participation may promote AF, while moderate physical activity is recommended to prevent AF (Table 49). However, it is unknown whether prescribed reduction of endurance sports leads to lower rates of AF. They should undergo standard evaluation and treatment as other adults.[628] For practical purposes only the pill in the pocket approach and catheter ablation are acceptable treatment options.

Cancer

AF may occur in patients with cancer in different settings, and it may be a marker of cancer type or occult cancer, or it may develop in patients undergoing surgery, chemotherapy, or radiotherapy.[629] Specific recommendations are provided in Table 50, and Figure 46. For a detailed discussion on Cardio-oncology see relevant Chapters.

Non-cardiac surgery

Patients with AF undergoing NCS have higher risks of all-cause mortality, HF, and ischemic stroke within 30 days of surgery than patients without preexisting AF.[630] Specific recommendatiosn are provided in Tables 51 and 52.

Other conditions

Recommendations for patients with AF and class III **obesity** (BMI ≥ 40 kg/m2) recommendations are provided in Table 53. AF in **genetic channelopathies** is discussed in the relevant chapters.

AF in Pregnancy

AF is increasingly becoming the most common newly diagnosed sustained arrhythmia during pregnancy, especially in patients with previously detected AF and without pre-existing heart disease.[631] AF or atrial flutter occurs in 1.3% of patients with structural heart disease with a peak at the end of the second trimester and is associated with unfavorable maternal outcome and lower fetal birth weight.[632] In patients with previously diagnosed AF, 52% experience new episodes during pregnancy. AF during pregnancy is well tolerated in most patients without congenital or valvular disease, but more foetal complications occur in those women who develop arrhythmias during pregnancy.

Drug therapy IV ibutilide or flecainide are usually effective for acute cardioversion and may be considered, although the experience during pregnancy is limited (Figure 48). Amiodarone may cause neonatal hypothyroidism (9% of newborns), hyperthyroidism, goiter and growth retardation. All drugs

should, if possible, be avoided during the period of organogenesis in the first trimester of pregnancy. For long-term therapy beta-1 selective beta blockers may be used as discussed in the Chapter on Cardiovascular Disease in Pregnancy, and Appendix 5.

Direct current cardioversion Several case reports have demonstrated successful cardioversion of maternal AF, without harm to the foetus.[633] General anaesthesia with intraprocedural monitoring of the foetus is preferred, and beyond 26 weeks of gestation the left lateral tilt position is recommended to minimize aortocaval compression.[631] Prior anticoagulation or TOE exclusion of left atrial thrombus is mandatory when AF is >48h, and anticoagulation is maintained for 4 weeks. In AF <48h one IV UH or LMWH is given pericardioversion. Energy requirements in pregnant and non-pregnant women are similar.

Anticoagulation is recommended in patients with ≥2 risk points of the $CHADS_2$ score or 2 risk points of the CHA_2DS_2VASC score. Vitamin K antagonists can be teratogenic in up to 7% of fetuses and in many cases should be substituted with UFH or LMWH for the first trimester. However, the risk is very low when doses <=5mg/day are adequate.[634] Warfarin crosses the placenta freely, and the foetus may be overdosed even when the mother is in the therapeutic INR range. LMWH do not cross the placenta barrier, and has been used for treatment and prophylaxis of venous thrombo-embolism during pregnancy, without adverse foetal effects. Perhaps, the most practical policy is to recommend subcutaneous administration of weight-adjusted therapeutic doses of LMWH during the first trimester and during the last month of pregnancy. The new oral thrombin antagonists such as dabigatran have shown fetotoxicity with high doses and should not be used.[635]

Anticoagulation protocols and dosing for pregnant patients with atrial fibrillation deemed at high risk of thromboembolic events are similar to those employed for mechanical valve. Thus warfarin is used for up to 36 h before delivery when UFH is started. Low-dose warfarin (<5 mg daily) use has a significantly lower risk for foetal embryopathy than higher-dose warfarin. When higher-dose warfarin (>5 mg daily) is needed to achieve goal INR, one may consider transitioning to heparin (UFH or LMWH) during the first trimester (6-12 weeks) vs continuation of warfarin.[631]

For a detailed list on the use of drugs in pregnancy see the Chapter on Cardiovascular Disease in Pregnancy, and Appendix 5. Recommendations in general are provided in Table 54 and Figures 47 and 48.

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