Atrial fibrillation

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Abstract | Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and increases in prevalence with increasing age and the number of cardiovascular comorbidities. AF is characterized by a rapid and irregular heartbeat that can be asymptomatic or lead to symptoms such as palpitations, dyspnoea and dizziness. The condition can also be associated with serious complications, including an increased risk of stroke. Important recent developments in the clinical epidemiology and management of AF have informed our approach to this arrhythmia. This Primer provides a comprehensive overview of AF, including its epidemiology, mechanisms and pathophysiology, diagnosis, screening, prevention and management. Management strategies, including stroke prevention, rate control and rhythm control, are considered. We also address quality of life issues and provide an outlook on future developments and ongoing clinical trials in managing this common arrhythmia.

Atrial fibrillation (AF) is a disorder of the heart's electrical conduction system that leads to a fast and irregular heart rhythm. The condition is a growing epidemic and a major public health problem; in addition to being the most common cardiac rhythm disorder, AF has an increasing global prevalence and incidence[1]. As older age is a strong risk factor for developing AF, the cause of this global increase in AF rates might be related to an ageing population. Indeed, adults >40 years of age have a one in four lifetime risk of developing AF and, even in the absence of a heart attack or heart failure (two key risk factors for AF), this lifetime risk is still one in six[2,3]. Improvements in how we manage conditions associated with AF, such as myocardial infarction, might also have contributed to the observed increase in AF rates because the improved survival of these patients results in sequelae related to cardiac damage, including heart failure, which predispose individuals to AF.

The causes of AF are broadly cardiovascular and non-cardiovascular. The common cardiovascular risk factors for AF include hypertension, heart failure and ischaemic heart disease. Rheumatic heart disease, which is caused by rheumatic fever induced by streptococcal infection and involves irreversible damage to the heart valves, can also contribute to AF. In addition, AF commonly presents in association with non-cardiovascular conditions, including sepsis, chest infection and obstructive sleep apnoea. Although the precise pathobiological mechanisms of AF remain under investigation, they are thought to involve cardiac fibrosis and remodelling, which alter the way electrical impulses are propagated through the heart. This disordered propagation, in turn, leads to disorganized stimulation of the myocardium and subsequent arrhythmic contractions.

We are not dealing with an esoteric medical condition; AF can be present in 3–6% of patients admitted to hospital with acute conditions. AF contributes to increased mortality and morbidity, especially from stroke, systemic thromboembolism and heart failure, as well as impaired quality of life (QOL). Importantly, AF is commonly asymptomatic and the first presentation with AF is often in association with a devastating AF-related complication.

In this Primer, we provide an overview of the epidemiology, mechanisms and management of AF, as well as an outlook for new developments for this common arrhythmia.

Epidemiology

Global disease burden

Current AF epidemiology mostly reflects data from Western Europe and North America, as data from other regions of the world are scarce[1,4]. The estimated number of individuals with AF in the world population in 2010 was 20.9 million men and 12.6 million women. In addition, there are almost five million new cases of AF annually[4] and it is projected that the number of affected individuals will increase continuously in an exponential manner[5,6]. One in four 40-year-old individuals of European descent are predicted to ultimately develop AF[2,3].

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There is marked regional variability in the reported prevalence of AF, ranging from 0.1% in India[7] to 1–2% in Europe and North America[6,8] and 4% in Australia[9], with a pooled age-adjusted and sex-adjusted prevalence estimate of 2.8% (95% CI: 2.3–3.4%)[10]. A higher prevalence and incidence of AF have been reported in individuals of European ancestry than non-Europeans[8,10–15]. In China, the prevalence of AF in men and women is similar[4]. The mean age of patients with AF is lower in regions outside Europe, North America and Australia[16,17], possibly resulting from a higher prevalence of underlying rheumatic heart disease in developing countries and rural populations[1,18]. Regional and ethnic variations in AF might also result from differences in study design (for example, the prevalence of AF is higher in hospital-based versus community-based cohorts)[1,10], genetics (variable representation of AF-associated genetic variants among populations) or environmental factors[16]. Notwithstanding the possible global underestimation of AF as a result of asymptomatic or undiagnosed cases of the condition — for example, one in six patients aged >55 years with a cryptogenic stroke might have undiagnosed AF[19] — current regional differences might also result from better AF surveillance and management of risk factors in developed countries.

AF is associated with a number of serious complications, including a four- to fivefold increased risk of stroke[20] and a two- to threefold increased risk of heart failure[21]. Patients with AF generally experience increased morbidity and more admissions to hospital than those who do not have the arrhythmia. Increasing evidence also suggests an association between AF and an increased risk of 'premature' dementia[22]. The burden of AF in 2010, as measured by age-adjusted disability-adjusted life years (calculated as years lived with disability plus years of life lost owing to death from disease), was 64.5 per 100,000 men and 45.9 per 100,000 women, which represents an overall increase of 19% since 1990 (REF. 4). Importantly, AF is associated with a nearly twofold increased risk of mortality[21,23].

The burden of AF and AF-associated mortality (coupled with the increasing prevalence and incidence of this arrhythmia) are generally higher in developed countries and contribute to the public health burden of AF. The increase in mortality for women with AF may be higher in developing countries[4].

Risk factors

Most modifiable and non-modifiable risk factors (TABLE 1) are consistently associated with an increased risk of AF across all ethnic groups[10]. Although it is occasionally seen in young and apparently healthy individuals, AF is more common in elderly individuals with cardiovascular or other comorbidities, including hypertension, coronary artery disease, heart failure, chronic kidney disease and obesity[10]. Likewise, underlying AF may cause or exacerbate many of these (and other) AF 'antecedents'. Based on common risk factors that are significantly associated with the occurrence of AF in their respective derivation cohorts, several risk scores have been proposed for predicting the development of AF[24,25] (TABLE 2).

In the near future, increasing recognition of AF using ambulatory and mobile electrocardiography might modify the global AF picture. Nonetheless, high-quality epidemiological studies are needed to improve our understanding of the global burden of AF and to inform strategies for the better identification of target populations for AF screening and early intervention.

Mechanisms/pathophysiology

The central feature of AF is very rapid and uncoordinated atrial activity. This rapid activity can be caused by rapidly discharging foci or by re-entrant activity, the details of which are discussed in the following sections. AF generally requires a 'trigger' to be initiated, which is typically a focal spontaneous firing. Triggers most commonly arise from the pulmonary veins (PVs)[26], but can also emerge from non-PV foci[27]. The mechanism maintaining the arrhythmia often arises in what is commonly referred to as a 'vulnerable substrate'. This substrate might be generated through genetic predisposition, cardiac remodelling caused by heart disease and/or altered regulation by neurohormonal factors, such as autonomic imbalance and abnormal (in particular, overactive) thyroid function.

AF is commonly classified as paroxysmal if it self-terminates within 7 days, persistent if it lasts continuously for >7 days, long-standing persistent if it is present continuously for >1 year, or as permanent (chronic) arrhythmia. The mechanisms of the different forms of AF tend to differ, as discussed in detail below.

Characteristics of the irregular heart rhythm in AF

FIGURE 1 shows the hallmarks of AF. The normal heart rhythm (sinus rhythm) originates in the sinoatrial (SA) node (FIG. 1a), which acts as the physiological pacemaker. The impulse spreads from the SA node through the atria (FIG. 1b) and then travels through the specialized conducting system formed of Purkinje fibres. These fibres transmit the impulse through

Table 1 | **Commonly reported risk factors for atrial fibrillation**

Risk factor	Risk of AF	Comments
Demographics and lifestyle		
Ageing[4,10]	OR 1.3 (95% CI: 1.2–1.4) per decade of age	• Ageing is the most consistent single independent risk factor for AF across all regions and ethnic groups • Risk increases by 2.1-fold (95% CI: 1.8–2.5) in men and 2.2-fold (95% CI: 1.9–2.6) in women per decade of age • >70% of patients with AF in Europe, North America and Australia are >65 years old • On average, patients with AF in developed countries are 10–12 years older than in other regions (Africa, India and the Middle East)
Male sex[10]	OR 1.6 (95% CI: 1.5–1.9)*	• Pooled estimate of AF prevalence in men of 3.3% (95% CI: 2.7–4.0%) and in women of 2.4% (95% CI: 1.9–2.9%) • A higher incidence and prevalence of AF in men are evident across most regions and ethnic groups, excluding China, where the prevalence is reportedly similar in the two sexes
Ethnicity[8,10–15]	HR 0.6 (95% CI: 0.4–0.9) for black compared with white ethnicity	• Compared with white individuals, black individuals have a lower incidence of AF, despite a higher prevalence of AF risk factors • Limited data for Hispanic and Asian populations show a significantly lower prevalence of AF than the white population. In a hospital-based population, compared with white patients, the HR for AF in black patients was 0.84 (95% CI: 0.82–0.85) and for Hispanic and Asian patients the HR was 0.78 (95% CI: 0.77–0.79)[12]
Cigarette smoking[10]	OR 1.5 (95% CI: 1.2–1.8)*	• Both current and former smokers have an increased risk of AF
Alcohol consumption[10]	RR 1.34 (95% CI: 1.01–1.78) for consumption of >3 drinks per day	• The risk of AF increases with increasing alcohol intake • The association of alcohol intake and AF is less clear in women
Obesity (BMI of ≥30 kg m^{-2})[10,16,251]	HR 1.2 (95% CI: 1.1–1.3)	• Obesity is currently a greater health problem than malnutrition, even in some low-income countries, and might soon become a major driving force in the global increase in the prevalence of AF[16] • BMI is linearly associated with AF risk, with a 4.7% (95% CI: 3.4–6.1%) increased risk per kg m^{-2} • In the ARIC study, being overweight or obese was the second most important risk factor for AF after hypertension, contributing 17.9% of the population-attributable risk of AF[251]
Cardiovascular disorders		
Hypertension[4,10,15,24,251]	OR 1.7 (95% CI: 1.4–2.2)*	• Hypertension is the leading global risk factor and the most common medical condition associated with AF worldwide[15,251] • Treated hypertension is associated with an increased risk of AF with a HR of 1.80 (95% CI: 1.48–2.18)[24]
LVH[10,24]	HR 1.36 (95% CI: 1.03–1.80)	• LVH is an independent risk factor for AF in both sexes, but women with AF are more likely to have electrocardiographically evident LVH than men
CAD[10,24]	HR 1.8 (95% CI: 1.4–2.2)* for those with acute coronary syndrome	• CAD is associated with an increased risk of AF across all ethnicities and global regions • Acute myocardial infarction has a RR of 3.62 (95% CI: 2.59–5.07) • Angina pectoris has a RR of 2.84 (95% CI: 1.91–4.21) • ST-T wave abnormalities have a RR of 2.21 (95% CI: 1.62–3.00)
HF[10,21,251]	HR 3.2 (95% CI: 2.0–5.2)	• There is a complex interaction between AF and HF, which might precipitate each other • The prevalence of AF increases with increasing severity of HF • Both HF with reduced left ventricular systolic function and HF with preserved left ventricular ejection fraction are associated with an increased risk of AF
Valve disease[4,10,16]	OR 1.8 (95% CI: 1.2–2.5) for men and OR 3.4 (95% CI: 2.5–4.5) for women	• Rheumatic heart disease (mostly rheumatic mitral valve stenosis) is still prevalent among patients with AF in Africa, Asia and the Middle East, even in high-income Middle Eastern countries (15–29% of AF patients). This is in contrast to its low prevalence among patients with AF in developed countries in the West
Other heart disease[10]	NA	• The risk of AF increases with any underlying cardiac disease, including cardiomyopathies, pericardial disease, congenital defects, sinus node dysfunction, conduction disturbances (such as prolonged PR interval), cor pulmonale, supraventricular arrhythmias and WPW syndrome
Other factors		
Metabolic syndrome[10,252]	HR 1.6 (95% CI: 1.2–2.2)	• The clustering of cardiovascular risk factors such as increased blood pressure, hyperglycaemia and dyslipidaemia with central obesity (metabolic syndrome) increases the risk for AF
Diabetes mellitus[10,16]	OR 1.4 (95% CI: 1.1–1.9)*	• Diabetes is present in >19% of patients with AF • OR 2.1 (95% CI: 1.5–2.8) for women • OR 1.7 (95% CI: 1.2–2.3) for men
Cerebrovascular disease[10,19]	NA	• Cerebrovascular disease is present in about 30% of patients with AF • Previously undiagnosed AF has been documented in 3–25% of patients presenting with acute stroke of unknown aetiology (cryptogenic stroke)

Table 1 (cont.) | **Commonly reported risk factors for atrial fibrillation**

Risk factor	Risk of AF	Comments
Other factors (cont.)		
CKD[10,253,254]	OR for AF increases with severity of CKD	• Data from a national health insurance database showed an increasing prevalence of incident AF with increasing severity of CKD (5.0, 7.3 and 12.7 per 1,000 patients in controls, patients with non-end-stage CKD, and patients with ESRD, respectively) • Patients with both AF and CKD have a higher risk of stroke and a higher risk of bleeding with oral anticoagulant therapy compared with those who have AF without CKD • CKD stage 1–2: OR 2.67 (95% CI: 2.04–3.48) • CKD stage 3: OR 1.68 (95% CI: 1.26–2.24) • CKD stage 4–5: OR 3.52 (95% CI: 1.73–7.15)
Obstructive sleep apnoea[255,256]	OR 2.2 (95% CI: 1.4–3.4)	• Obstructive sleep apnoea is a general cardiovascular risk factor associated with CAD, HF, hypertension, cardiac arrhythmias and stroke • Risk in patients without concomitant disease: HR 1.5 (95% CI: 1.17–2.01)
COPD[10]	NA	• COPD is present in 10–15% of patients with AF • It is a general marker of cardiovascular risk
Hyperthyroidism[10]	HR 1.7 (95% CI: 1.3–2.2)*	• Both high–normal thyroid function and overt hyperthyroidism increase the likelihood of AF
Family history and genetic factors[16]	NA	• Family history of AF is associated with an increased risk of AF in patients of European or Chinese ancestry • Both polygenic and monogenic inheritance of AF have been described
Other conditions and procedures[10,257,258]	NA	• AF occurs in 30–40% of patients in the early postoperative period after CABG, in about 50% of patients after valve surgery and in 60% of those who undergo CABG plus valve replacement • AF occurs in 1–40% of patients after non-cardiac surgery • Many inflammatory diseases (such as rheumatoid arthritis and coeliac disease), infections and increased serum uric acid levels are also associated with an increased risk of AF

AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Community; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; LVH, left ventricular hypertrophy; NA, not applicable; OR, odds ratio; RR, relative risk; WPW, Wolff–Parkinson–White. *Pooled AF risk estimate[10].

the atrioventricular (AV) node, which is interposed between the atria and the ventricular conducting system, to reach the ventricles (FIG. 1c), causing cardiac contraction. FIGURE 1d shows the last normal beat before the onset of AF (FIG. 1e). In contrast to the atrial activation in sinus rhythm, the atrial activity in AF is very rapid and irregular. There is no coordinated atrial contraction and the response of the ventricles is irregular and often rapid, depending on the filtering effect of the AV node.

The electromechanical consequences of AF have important clinical implications. The absence of effective atrial contraction increases the risk of blood coagulation and thrombosis, particularly in the left atrial appendage (FIG. 1a). The rapid and irregular ventricular rate during AF can reduce the efficiency of ventricular contraction, worsening existing heart failure or sometimes even causing *de novo* heart failure.

The rapid and irregular rhythm comprising AF can be maintained by each of three principal mechanisms[28,29] (FIG. 2). First, one or more rapidly firing atrial ectopic foci may be present (FIG. 2a), with irregular conduction towards the rest of the atria producing irregular fibrillatory activity. Alternatively, one or a small number of primary re-entry circuits (or rotors) — which occur when an action potential travels in a continuous fashion through a potential conducting circuit — may produce rapid local activation (FIG. 2b), with fibrillatory conduction causing AF. Finally, AF may be maintained by many functional re-entry waves with irregular patterns and no consistent activation pattern (FIG. 2c).

Physiological mechanisms

Afterdepolarizations and extra-systolic activity. Atrial ectopic activity may arise from a number of mechanisms, but the most important is 'triggered activity' as a result of 'delayed afterdepolarizations' (DADs)[30] (FIG. 3a). DADs are abnormal spontaneous diastolic depolarizations that occur during phase 4 in cardiomyocytes after the end of normal action potential repolarization. DADs are caused by abnormal diastolic Ca^{2+} release from the sarcoplasmic reticulum (SR) via the SR Ca^{2+} release channel, also known as ryanodine receptor 2 (RyR2). The SR is the principal cardiac Ca^{2+} storing organelle and RyR2 releases SR Ca^{2+} in response to Ca^{2+} entry during the action potential, greatly increasing the concentration of cytoplasmic free Ca^{2+} and thereby causing cellular contraction. The released Ca^{2+} is then taken back into the SR during diastole via a pump called the sarcoplasmic/endoplasmic reticulum calcium ATPase. RyR2s are normally closed throughout diastole, allowing a smooth decrease in the cytoplasmic concentration of Ca^{2+}. However, in some situations, such as when SR Ca^{2+} concentrations are increased or RyR2s are hyperphosphorylated, RyR2s release Ca^{2+} during diastole. This increases the cytoplasmic Ca^{2+} concentration and the released Ca^{2+} is exchanged for Na^{+} through the Na^{+}/Ca^{2+} exchanger (NCX) located at the plasma membrane. The NCX extrudes one Ca^{2+} ion (charge +2) for every three Na^{+} ions (charge +3) brought into the cell, bringing a net positive charge of one into the cell for each Ca^{2+} ion extruded and, therefore, moving the intracellular potential in the positive direction. This net inward movement of positive ions carried by NCX is

called the transient inward current (I_{ti}) and it is responsible for the depolarization that causes the DAD. If the DAD is large enough, it depolarizes the cell and causes a premature atrial ectopic beat. A series of DADs can cause an atrial tachycardia, which can trigger atrial re-entry or, if rapid enough, maintain AF (FIG. 2a). Direct evidence for DAD-mediated ectopic activity related to abnormal Ca^{2+} handling has been provided in animal models of AF[31] as well as in patients with AF[32,33]. Interestingly, although DADs occur in patients with both paroxysmal AF and long-standing persistent arrhythmia, the underlying molecular abnormalities differ[32,33], indicating that therapies targeting abnormal Ca^{2+} handling might need to be tailored to specific types of AF.

An alternative mechanism that can generate spontaneous extra-systolic activity is provided by an early afterdepolarization (EAD). These are particularly likely to occur in the presence of the strong simultaneous discharge of vagal and sympathetic nerves (vagosympathetic discharge)[34–36]. Vagal discharge shortens the action potential duration and consequently the refractory period (RP) — the minimum time required for reactivation following the depolarization phases of an action potential when the cell membrane becomes inexcitable — whereas sympathetic stimulation increases the magnitude of Ca^{2+} transients — the rapid increase in cytoplasmic free Ca^{2+} during the action potential. Simultaneous activation of both the vagal and sympathetic components, therefore, enhances the probability that spontaneous depolarization as a result of enhanced Ca^{2+} release will depolarize the cell, cause an EAD during phase 3 and trigger a spontaneous action potential[34–36] (FIG. 3b).

Table 2 | **Risk models for the prediction of incident atrial fibrillation in adults**

Risk model	Components	Predictive value: c-statistic
Framingham Heart Study[24]	• Age • Sex • Body mass index • Systolic blood pressure • Treatment for hypertension • PR interval • Clinically significant cardiac murmur • Heart failure	0.78 (95% CI: 0.76–0.80)
ARIC study[259]	• Age • Race (black or white) • Height • Systolic blood pressure • Treatment for hypertension • Smoking status (never, former or current) • Precordial murmur • Diabetes mellitus • Heart failure • Coronary artery disease • Left atrial enlargement • Left ventricular hypertrophy	0.77 (95% CI: 0.75–0.78)
CHARGE-AF consortium[25]	• Age • Race • Height • Weight • Systolic and diastolic blood pressure • Current smoking • Treatment for hypertension • Diabetes mellitus • History of myocardial infarction or heart failure	• 0.765 (95% CI: 0.748–0.781) in derivation cohort • 0.664 (95% CI: 0.632–0.697) in validation cohort 1 • 0.705 (95% CI: 0.664–0.747) in validation cohort 2

AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; CI, confidence interval.

Atrial re-entry. There are two main conceptual models of re-entry, which are illustrated in FIG. 4. The classic model is the 'leading circle' model (FIG. 4a), in which re-entry naturally establishes itself in the shortest zone (smallest circuit) that can support re-entry[37]. In this model, the centre of the re-entry zone is kept continuously depolarized by centripetally moving impulses. The dimension of this circuit is given by the wavelength (WL), where WL = RP × CV (CV is the conduction velocity). The stability of AF according to the leading circle concept is determined by the number of simultaneous re-entry circuits that the atria can accommodate[28]. When the WL is short (as a result of reduced RP or CV) or when the atria are enlarged, more re-entrant circuits can be accommodated and AF is more likely to maintain itself[28].

The 'spiral wave' concept (FIG. 4b) is biophysically based. This model considers re-entry to be a natural phenomenon analogous to a tropical storm, with a leading edge that maintains re-entry as long as the energy for rotation — determined by the strength of the depolarizing current at the leading edge — is sufficient to maintain activity in the excitable medium, which is governed by tissue excitability, of which the degree of refraction is a major determinant[38]. Stable spiral waves can act as continuous rotors that maintain fibrillatory activity. A reduced RP favours spiral wave re-entry by making it more likely that fully excitable tissue is encountered by the activation wavefront of the rotor.

There has been considerable debate about the relative applicability of the spiral wave versus leading circle models. Both models generally require a trigger for initiation, which is usually provided by an ectopic discharge from a DAD- or EAD-mediated mechanism. One major difference between the two models is the predicted response to drugs that block Na^+ channels. Na^+ channel blockade slows conduction (decreases the CV), which should make AF more likely according to the leading circle model; conversely, by reducing the excitatory energy of the rotor waves, Na^+ channel blockers are expected to terminate AF in the spiral wave model[38,39]. The clinical efficacy of Na^+ channel blockers in AF thus provides indirect support for the spiral wave theory. Evidence for the operation of spiral wave rotors in AF has also come from mapping studies in patients[40,41], although it remains controversial whether the underlying rotors are stable in space and time[40] or whether they are unstable but tend to arise in consistent atrial regions in individual patients[41]. Modelling work indicates that spiral wave rotors tend to localize at or near the PVs[42], largely as a result of the particular ion current properties of the cardiac cells in the sleeves surrounding PVs[43]. Thus, PVs are favoured regions for both focal activity and re-entry, accounting for their central role in many forms of AF[44].

There are two important factors that can promote re-entry. First, a shortened atrial RP, generally resulting from a reduced atrial action potential duration (FIG. 4c), promotes leading circle re-entry by allowing

re-entry to be stable in smaller circuits. This can be achieved because the shortest path length that can support re-entry, the distance the cardiac impulse travels in one RP or 'wavelength', is the product of the RP and CV. Conversely, reduced RPs also effectively increase the excitability of atrial tissue during re-entry and stabilize spiral wave rotors. Second, fibrosis (FIG. 4d) makes re-entry more likely by acting as an 'anchoring' mechanism that stabilizes re-entry circuits[45]. A recent optical mapping study in explanted human hearts succeeded in obtaining evidence that re-entry underlies AF[46] and found that transmural re-entry was stabilized by anatomical structures with important local fibrosis. The basic mechanisms underlying AF have important implications for therapy[47,48].

Atrial remodelling. An important concept in AF pathophysiology is the idea of atrial remodelling. Atrial remodelling can arise from cardiac disease, from normal ageing or from AF itself. The idea that AF alters atrial properties in a way that makes AF more likely was first elegantly demonstrated by researchers from the Allessie laboratory, who showed that AF results in rapid (within 48 hours) RP shortening and increases in AF stability, as indicated by spontaneous AF maintenance[49]. Subsequently, this RP shortening was shown to be a result of the downregulation of the Ca^{2+} current that maintains the action potential plateau, so that the excess cell Ca^{2+} resulting from the very fast atrial firing rate is attenuated, at the price of a shorter action potential and increased likelihood of re-entry[50,51]. Additional

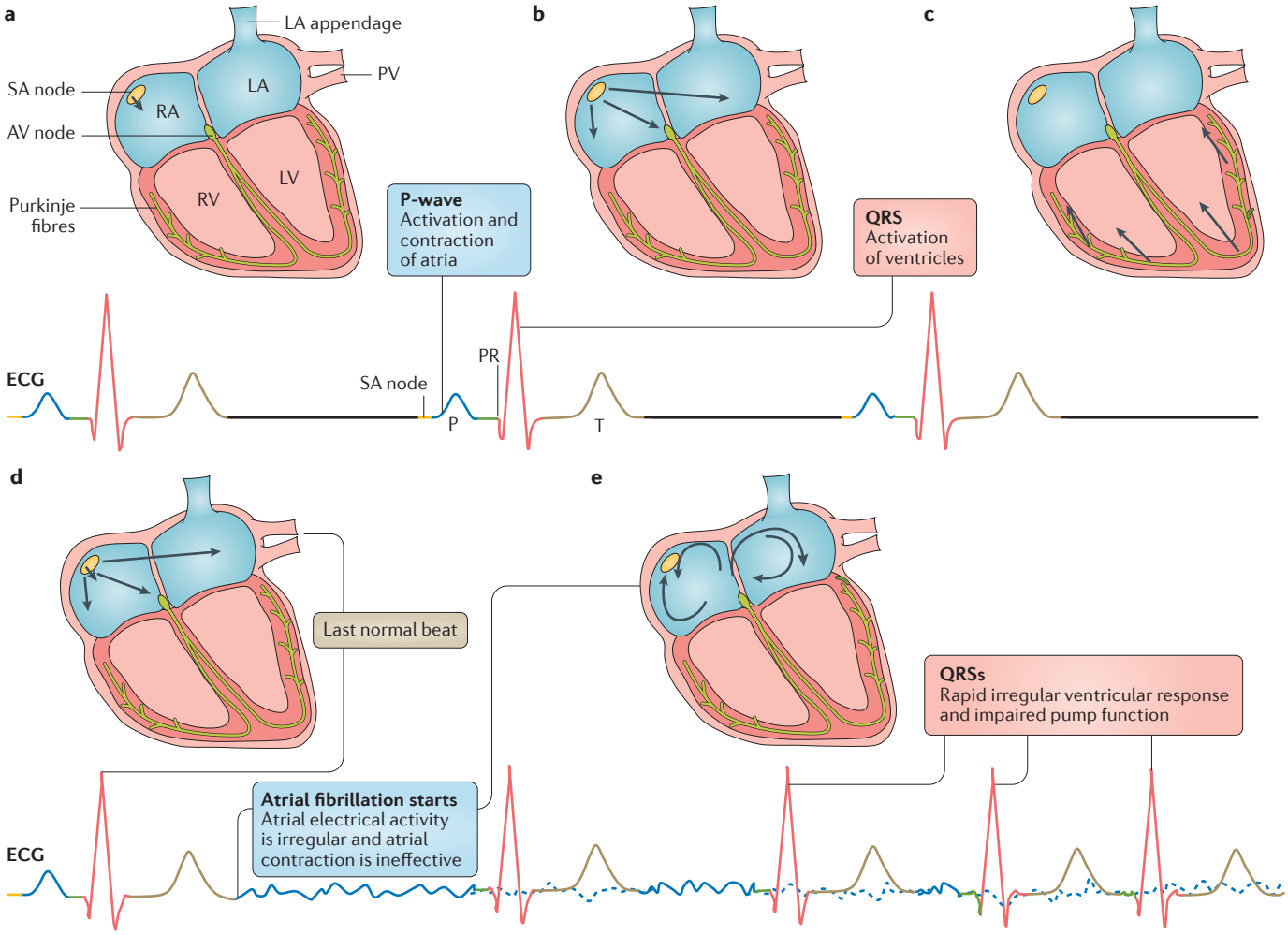

Figure 1 | **Electrical conduction during sinus rhythm and atrial fibrillation.** Schematic diagrams of cardiac mechanisms (top of each panel) and electrocardiograms (ECGs; bottom of each panel) in normal sinus rhythm (parts **a**–**c**) and atrial fibrillation (AF; parts **d**,**e**). **a** | The sinoatrial (SA) node is a cluster of cells located in the upper wall of the right atrium (RA), from which electrical impulses originate. **b** | Impulses are propagated through the heart, initially through working atrial muscle cells and then via the conduction system (in green), causing cardiomyocyte membrane depolarization and subsequent contraction. On an ECG, atrial depolarization and contraction is denoted by the P-wave. **c** | The atrioventricular (AV) node delays conduction between the atria and the ventricles, ensuring that atrial contraction and blood pumping into the ventricles precedes ventricular contraction. On an ECG, ventricular depolarization is indicated by the QRS complex, ventricular repolarization by the T wave and the time taken for the electrical impulse to travel from the SA through the AV node (measured from the start of the P-wave to the beginning of the QRS) is the PR interval. **d** | The last normal beat before the onset of AF. **e** | AF is characterized by rapid and uncoordinated atrial activity, causing ineffective atrial contraction. The ventricles respond with rapid and irregular electrical activity that produces weaker contractions than usual. LA, left atrium; LV, left ventricle; PV, pulmonary vein; RV, right ventricle.

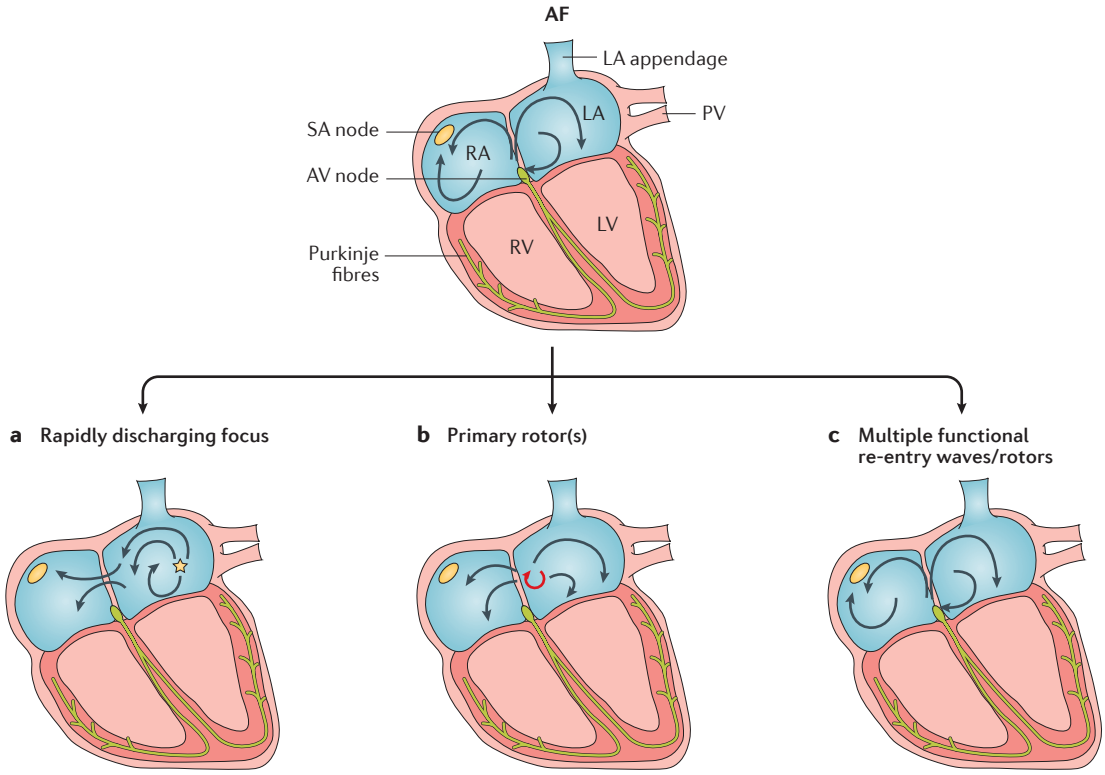

Figure 2 | **Mechanisms that can maintain atrial fibrillation.** Ectopic electrical impulses that propagate throughout the atrial myocardium in a disordered way can be maintained through a variety of mechanisms. **a** | A rapidly discharging atrial focus. **b** | A primary re-entrant rotor. **c** | Multiple functional re-entry circuits. AF, atrial fibrillation; AV, atrioventricular; LA, left atrium; LV, left ventricle; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SA, sinoatrial.

changes in ion current also occur in AF, particularly increases in outward K^+ currents that both accelerate repolarization and hyperpolarize atrial cells[30]. The background K^+ current maintains the resting potential (I_{K1}), and increases in this current are particularly important in stabilizing re-entry because they both shorten the RP and increase the current strength of the activating wavefront by enhancing the availability of the Na^+ current[52]. Interestingly, both AF-induced Ca^{2+} current downregulation and K^+ current upregulation share a common upstream mechanism: dephosphorylation of the nuclear factor of activated T cells that results from calcineurin activation by AF-induced cellular Ca^{2+} loading[51,53]. In addition to ion current changes in the cell membrane, AF decreases the expression of the connexin-based channels that connect cardiac cells and alters their distribution, causing conduction abnormalities that promote re-entry[54–56].

AF becomes increasingly persistent and resistant to therapy over time. One mechanism for this phenomenon appears to be the development of atrial fibrosis. Rapidly firing atrial cardiomyocytes generate substances that make fibroblasts differentiate into collagen-producing myofibroblasts[57]. Recent work in a sheep model of progressive AF shows that action potential shortening occurs within about 10 days and coincides with the initial spontaneous maintenance of AF, but that atrial fibrosis then occurs over a period of up to a year, coinciding with long-standing persistence[58].

Atrial remodelling that promotes AF can also result from heart disease and conditions promoting heart disease[59]. The first of these conditions to be characterized were heart failure and mitral valve disease[45,60]. Subsequent work has demonstrated how myocardial ischaemia[61,62], hypertension[63], obesity[64] and obstructive sleep apnoea[65] lead to vulnerability to AF. A common denominator of all these AF-promoting conditions is that they can all cause atrial structural remodelling — in particular, atrial fibrosis[59]. In addition, prolonged atrial ischaemia causes changes in cell Ca^{2+} handling that lead to the occurrence of spontaneous atrial ectopic extra-systoles that can initiate AF[62]. Recent work has shown that AF can be prevented by targeting the underlying risk factors[66,67]. Combined with an understanding of the progressive nature of AF itself, this work has led to a new understanding of the need for preventive therapy to forestall the factors that lead to the development of the AF substrate, rather than simply aiming to manipulate the final electrical end-product[68].

Diagnosis, screening and prevention

Diagnosis

The diagnosis of AF may be suspected on clinical grounds, but symptoms — including palpitations, fatigue, dizziness, light-headedness and dyspnoea — are non-specific and are frequently absent[69], especially in elderly patients. The diagnosis can, therefore, be made on presentation of symptoms, or incidentally when a patient's

pulse is taken or an electrocardiogram (ECG) is recorded for another reason. Because AF can be paroxysmal, the diagnosis might not be obvious between attacks. The diagnosis is often made by pulse palpation and is classically described as an 'irregularly irregular' rhythm, which may not be easily appreciated if the ventricular response is rapid. The diagnosis is usually confirmed by a 12-lead ECG, although an accurate diagnosis can be made from a single-lead rhythm strip[70]. The cardinal ECG features are complete irregularity of the RR intervals, an absence of P-waves and coarse or fine fibrillation waves in the baseline (FIG. 5). Occasionally, extremely frequent multifocal atrial ectopic beats with sinus arrhythmia (the normal variation in rhythm associated with respiration) might mimic AF. If symptoms are infrequent, confirmation of AF requires prolonged ambulatory ECG recordings or a patient-activated event recorder. In general, prolonged monitoring efforts — for example, in post-stroke patients — improve the detection rate of AF.

Once AF is documented, physical examination is required to exclude valvular heart disease, thyrotoxicosis (the presence of excess thyroid hormone) and heart failure. Understanding the history of these conditions is important, as is documenting other conditions that might predispose individuals to AF, such as excess alcohol consumption, obstructive sleep apnoea, obesity, hypertension, diabetes and pulmonary disease. A chest radiograph is recommend to exclude pulmonary disease and heart failure, and a blood level of thyroid-stimulating hormone to exclude thyrotoxicosis and a transthoracic echocardiogram should be performed to detect underlying structural heart disease, assess cardiac function and evaluate atrial size[71].

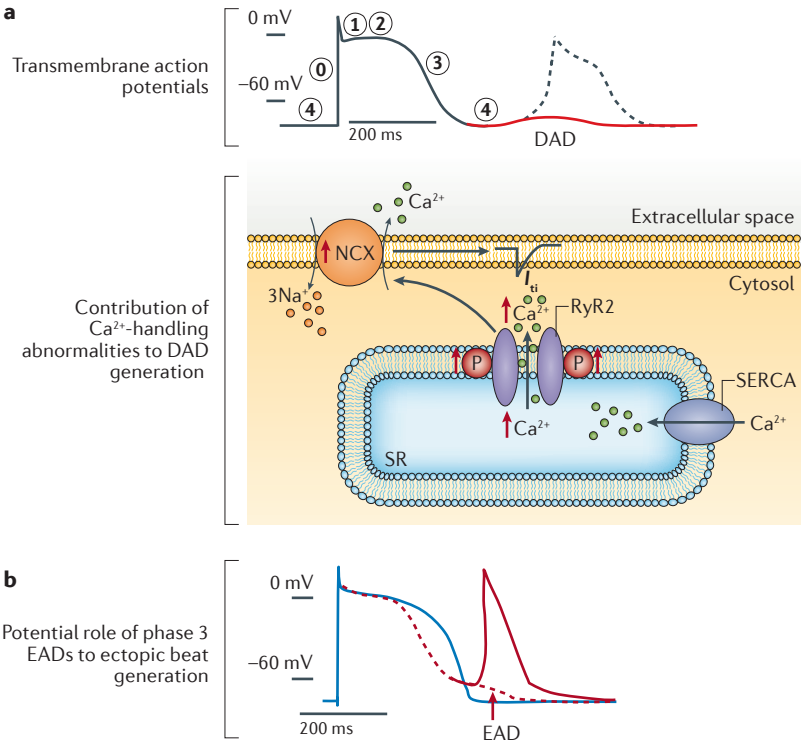

Figure 3 | **Afterdepolarization-mediated ectopic activity. a** | Mechanisms leading to delayed afterdepolarizations (DADs). The resting membrane of cardiomyocytes (phase 4) is polarized with a potential of approximately –85 to –90 mV. The phases of the action potential are circled. During an action potential, fast Na^+ influx channels in the plasma membrane open, leading to the inward movement of Na^+, which causes a net increase in the intracellular positive charge and rapid membrane depolarization (phase 0). This is followed by the closure of fast Na^+ channels (phase 1) and slower Ca^{2+} influx and K^+ efflux channel opening, leading to a plateau in the membrane potential (phase 2). Rapid repolarization (phase 3) is mediated by a net outward movement of K^+ while the Ca^{2+} influx channels close. From phase 0 to phase 3, the membrane is refractory to action potentials. Intracellular Ca^{2+} is released from storage in the sarcoplasmic reticulum (SR) through the ryanodine receptor (RyR2) in response to calcium influx from the extracellular environment, contributing to the increase in cytosolic Ca^{2+} that causes contraction. During diastole (phases 3 and 4), the RyR2 closes and Ca^{2+} is transported from the cytoplasm back into the SR through the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) pump. DADs occur when, in phase 4, the RyR2 channels reopen, leading to the release of Ca^{2+} into the cytoplasm during diastole. This excess cytoplasmic Ca^{2+} is transported out of the cell through the Na^+/Ca^{2+} exchanger (NCX), leading to a net increase in intracellular charge as a result of Na^+ influx (termed the transient inward current (I_{ti})). If this increase in positive charge is large enough, appreciable membrane depolarization can occur, causing an ectopic beat. **b** | Phase 3 early afterdepolarization (EAD)-mediated spontaneous activity. Strong vagosympathetic discharge can shorten action potential duration (and, therefore, the length of the refractory period) while causing Ca^{2+}-mediated depolarization and an EAD, which can reach threshold to cause a spontaneous extra-systolic beat. P, phosphate group.

Screening

Because stroke might be the first manifestation of silent AF[72,73], opportunistic screening for unrecognized AF has been advocated in guidelines[74]. Although systematic screening with 12-lead ECG is not cost effective[75], new, less expensive technologies to assess cardiac rhythm — by oscillometry[76], smartphone camera[77] or a hand-held ECG rhythm strip[78–80] — could facilitate population screening targeted at those ≥65 years of age, who have a higher risk of stroke if they develop AF. Screening in this age group in the clinic or community is likely to detect 1.4% of those with unrecognized AF[81]. In addition, an economic assessment has shown that this approach is likely to be cost-effective for stroke prevention[79] because of the high stroke rate and high mortality rate in patients with incidentally detected asymptomatic AF[82]. A 2015 consensus document[83] recommended more widespread screening for AF in those ≥65 years of age and contained a strong recommendation for prospective studies "to determine the most effective strategy for AF detection in populations and in patients", similar to the conclusions in a recent viewpoint article on AF screening[84].

Detection of AF in special cases

Following AF ablation procedures, there is a dissociation between symptoms and recurrence detected by ECG, with many AF recurrences unrecognized by patients and many recurrent symptoms unrelated to AF[85,86]. Accurate diagnosis of recurrence, therefore, requires the use of prolonged external recording using devices that record for longer than the conventional 24–48 hours of a Holter monitor, or the use of patient-activated intermittent hand-held recordings[87] or implanted cardiac monitoring devices.

Similarly, following ischaemic stroke in patients who did not have detectable AF during admission or on a single 24-hour Holter ECG, the use of prolonged external recording devices for 1 month[19], or implanted devices

that are capable of monitoring for even longer[88–90], showed that a considerable proportion of these patients do, in fact, have AF, and this proportion increases with increasing duration of recording. Of course, when brief episodes of AF are found many months or even years after the stroke, as in the Cryptogenic Stroke and Underlying AF (CRYSTAL-AF) study[89], it may be difficult to ascribe a causal relationship between the stroke and AF and, therefore, the requirement for anticoagulant treatment is uncertain[90].

Another special case of diagnosis occurs in pacemakers, implanted cardioverter defibrillators and cardiac resynchronization therapy devices, which have the ability to detect high-frequency atrial activity. Various studies have shown that a significant incidence of high-rate atrial episodes are due to AF[91,92]; such episodes are associated with an approximate doubling of stroke risk[92–94], although the duration and burden of episodes that should trigger thromboprophylaxis are uncertain[95,96]. Because only a small proportion of strokes that occur while a device is being worn have a close temporal relationship with recorded episodes of AF[97,98], it is also unclear whether AF detected by devices is more of a risk marker rather than a risk factor for stroke.

Prevention

An algorithm to predict the onset of AF was developed in the Framingham cohort[24] and has subsequently been used in multiple cohorts[25]. This algorithm includes a number of factors that might be considered as causative of AF. Hypertension, diabetes and heart failure are three important conditions that predict future AF, so prevention or better treatment of these conditions might prevent the onset of new AF. Rheumatic heart disease is still common in developing countries. Rheumatic heart disease leads to mitral valve disease, which results in mitral stenosis and regurgitation, an important cause of AF[99], with high rates of thromboembolism. Early treatment of streptococcal disease and the prevention of initial and subsequent episodes of rheumatic fever with antibiotics or, potentially, a vaccine could prevent valvular disease and subsequent AF[100,101].

Various lifestyle factors that are amenable to modification are recognized causes of AF. These include obesity[102–104], high and low extremes of physical activity[105–107], excessive alcohol intake[108,109] and obstructive sleep apnoea[110,111]. Continuous positive airway pressure treatment of obstructive sleep apnoea reduces the recurrence of AF after ablation[67,112]. In addition, treatment of obesity has been shown to reduce incident AF[104], P-wave dispersion[113] and recurrent AF[114], so it is likely that attention to lifestyle factors could reduce or prevent the onset of AF.

AF occurs in approximately one-quarter to one-third of patients who have had coronary bypass surgery. This association might be attributable to various reasons, including mechanical manipulation of the heart during the operation, the use of medications and hypoxia. This is a special case where prevention has been tested using β-blockers and antiarrhythmic drugs[115], statins[116], colchicine[117] and angiotensin-converting enzyme or receptor-blocking drugs[118]. Of all these therapeutic approaches, only statins have shown some evidence for reducing incident AF in meta-analyses of population studies[116,119].

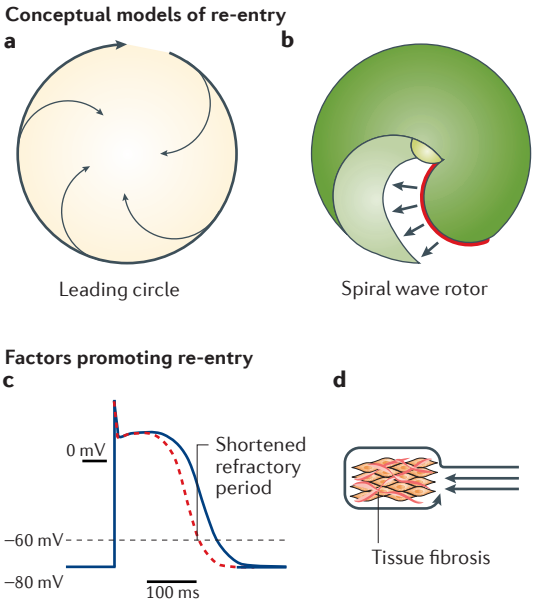

Figure 4 | **Re-entry and models of arrhythmia development. a** | Leading circle model. Re-entry establishes itself in a circuit of dimension WL, where WL = RP × CV (WL is the wavelength, RP is the refractory period, and CV is the conduction velocity). **b** | Spiral wave re-entrant rotor. The ability of the rotor to sustain itself depends on the ability of the rotor wavefront to continue to excite tissue in front of it, which will depend on the strength of the depolarizing current at the activating wavefront (shown in red) and tissue excitability. Tissue that has previously been activated by the rotor and is still depolarized is shown in dark green. If the RP is shorter, the trailing edge of refractory tissue will be far from the activating wavefront and re-entry will persist. If the RP is increased, additional tissue will be refractory (light green region) and the leading edge might fail to excite it, causing re-entry to terminate. **c** | RP is determined by the duration of the action potential from initial depolarization until excitability is restored when the cell repolarizes to –60 mV. A reduced duration of the action potential shortens the RP and promotes re-entry. **d** | Tissue fibrosis makes re-entry more likely by stabilizing the re-entry circuit. Here, fibrosis is shown to anchor re-entry by producing an inexcitable zone at the centre of a re-entry circuit. Recent evidence suggests that re-entry might be stabilized at the border between fibrotic and non-fibrotic tissue.

Management

Stroke prevention

Patients with AF are at a high risk of stroke and thromboembolism. The reasons why AF pathophysiologically predisposes to stroke are multifactorial and can be described in relation to Virchow's triad for thrombogenesis — that is, abnormal blood stasis in the atria ('abnormal blood flow'), structural heart disease ('abnormal vessel wall') and abnormalities of blood coagulation ('abnormal blood constituents')[120]. Stroke prevention is central to the management of AF[121]. The risk of stroke

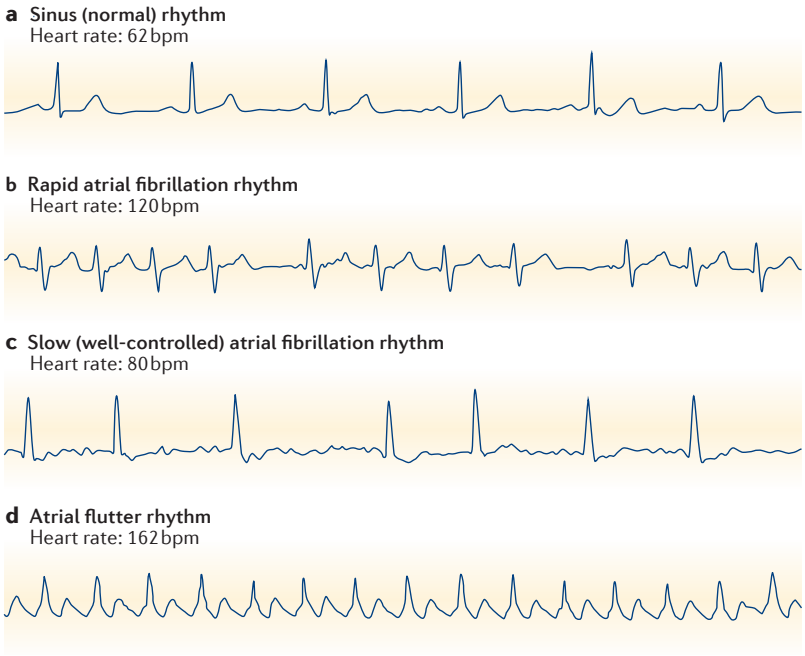

Figure 5 | **Typical electrocardiograms in normal sinus rhythm and in atrial fibrillation and flutter.** Electrocardiograms (ECGs) were recorded at 25 mm s^{-1}. Compared with sinus rhythm (part **a**), which has a regular rhythm of QRS complexes, atrial fibrillation (parts **b**,**c**) shows an irregularly irregular rhythm (spacing) of QRS complexes, an absence of P-waves before each QRS and usually a low-amplitude irregularity (fluctuation) of the baseline between QRS complexes. Atrial flutter (part **d**) is usually fairly regular with QRS complexes spaced at some multiple of the flutter wave frequency (classically 300 min^{-1}). The sawtooth-shaped flutter waves are best seen in leads 2 and 3 or the aVF (augmented vector foot), but may be hard to visualize if the QRS rate is 150 min^{-1} (half the flutter wave frequency due to 2:1 atrioventricular block of the flutter waves).

in patients with AF is increased fivefold and strokes in association with AF are associated with greater mortality and disability, with longer hospital stays and lower rates of discharge to a patient's own home compared with strokes that are not associated with AF[122].

In patients with AF, the use of oral anticoagulation (OAC) with a vitamin K antagonist (VKA) such as warfarin reduces stroke risk by 64% and all-cause mortality by 26% compared with control or placebo treatments[123]. By contrast, the use of antiplatelet therapy in patients with AF only reduces the incidence of stroke by 22%, with no significant reduction in mortality. When the antiplatelet data are confined to aspirin, there is a non-significant reduction in stroke by 19% compared with control or placebo. Even this 19% reduction is driven by the one single positive trial, the Stroke Prevention in AF (SPAF) 1 trial, which was the only trial to report a positive result with aspirin, showing a 42% reduction in stroke compared with placebo. However, this trial reported internal heterogeneity in the aspirin effect, with a significant 94% reduction in stroke compared with placebo in the anticoagulation eligible arm, compared with a more realistic non-significant 8% reduction in stroke compared with placebo in the non-anticoagulation eligible arm of the trial[124]. Finally, aspirin did not reduce stroke in those >75 years of age in this trial, nor did it prevent severe strokes.

Stroke risk assessment. The risk of stroke in AF is not homogeneous and is dependent on the presence of various stroke risk factors. These factors have been derived from patients who were not being treated with anticoagulants in selected older (now historical) clinical trial cohorts and large observational cohorts[125]. These risk factors have been used to formulate various stroke risk stratification schemes, the most common of which are the $CHADS_2$ and CHA_2DS_2-VASc scores.

The $CHADS_2$ score was originally proposed with five common stroke risk factors derived from the non-warfarin arms of the historical trial cohorts[126]. This score was used to help define low-, moderate- and high-risk patients, so that the 'high-risk' patients could be targeted for OAC with a VKA. However, the $CHADS_2$ score had several limitations and did not include many common risk factors for stroke[127]. In addition, clinical risk scores (whether for AF or other conditions) based on clinical factors have only a modest predictive value for defining patients at high risk, as reflected by a *c*-statistic of 0.6–0.7 for $CHADS_2$.

The CHA_2DS_2-VASc score refined the $CHADS_2$ score by including non-$CHADS_2$ stroke risk factors, including age 65–74 years, vascular disease (such as previous myocardial infarction, peripheral artery disease and complex aortic plaque) and female sex[128] (BOX 1). The focus has also moved towards a risk-factor-based approach to stroke prevention, rather than an artificial categorization of risk into low-, moderate- or high-risk strata. After all, stroke risk is a continuum and patients often do not fall neatly into one of these three risk strata. In addition, risk scores are designed to be simple and reductionist and to help in practical decision making (in this case, whether to use OAC for stroke prevention).

The CHA_2DS_2-VASc score is best at identifying 'low-risk' patients and is as good as — and possibly better than — the $CHADS_2$ score in identifying high-risk patients[129–131]. Furthermore, the CHA_2DS_2-VASc score has been validated in multiple independent cohorts, including those from Asian and Middle Eastern patients with AF[132,133]. Interestingly, one study even suggested that among Asian (specifically Chinese) patients the age threshold could be lowered to 50 years because the ischaemic stroke rate for patients 50–64 years of age was 1.5% per year[134].

Recent advances have led to improved management with VKAs — emphasizing the importance of good anticoagulation control with the average individual time in therapeutic range (TTR) (that is, an international normalized ratio (INR) of 2.0–3.0) of >70% — and with non-VKA oral anticoagulants (NOACs). As a result, the initial focus of stroke prevention in AF has shifted towards the initial identification of low-risk patients (a CHA_2DS_2-VASc score of 0 in men and 1 in women) who do not need any antithrombotic therapy[135]. Effective stroke prevention in the form of OAC can be offered to patients with ≥1 stroke risk factors (that is, a CHA_2DS_2-VASc score of ≥1 in men and ≥2 in women) (FIG. 6). Given that clinical trials focused on a single stroke risk factor are limited,

OAC should be considered in these patients after taking bleeding risks and patient values and preferences into consideration.

Reported stroke rates vary between different study cohorts and populations, and the actual stroke risk might vary with respect to any given CHA_2DS_2-VASc score in an individual patient — for example, a man with AF aged 65 years is likely to have a lower stroke risk than another male patient aged 74 years, although both still have a score of 1. Nonetheless, we should be less concerned with identifying the 'exact' stroke risk, especially because the clinical status of patients does not remain static. Clinical risk scores such as CHA_2DS_2-VASc are designed to be reductionist and simple to facilitate their practical and broad use in various (and busy) clinical settings. Indeed, it is not necessary for risk scores to identify the exact stroke risk per se, but to provide useful thresholds at which important dichotomous clinical decisions are made — for example, the question of when to use OAC[136]. We should not forget that OAC reduces stroke risk as well as all-cause mortality.

Even patients with AF who have only one risk factor are at increased risk of stroke. However, the actual absolute risk differs between risk factors, as it would be overly simplistic to assume that all stroke risk factors carry equal weight[137,138]. For instance, in the study by Chao *et al.*[137], the risk factors that were associated with the highest risk of ischaemic stroke in those with AF and a single risk factor were an age of 65–74 years and diabetes mellitus. Even with a single stroke risk factor, the net clinical benefit of OAC compared with aspirin, or OAC compared with no treatment, is positive in favour of OAC when the risks of thromboembolism, mortality and serious bleeding are balanced[139,140].

Echocardiography and biomarkers can refine stroke risk stratification. For example, using 2D transthoracic echocardiography, only moderate-to-severe left ventricular dysfunction is an independent predictor of stroke risk. With transoesophageal echocardiography, additional independent predictors of stroke risk include complex aortic plaque, spontaneous echocontrast and low left atrial appendage velocities. Cerebral imaging studies also indicate features associated with a higher risk of stroke, such as small vessel disease[141,142].

Vitamin K antagonists. Adjusted-dose VKAs keeping within the INR therapeutic range of 2.0–3.0 are well established as oral anticoagulants for stroke prevention in patients with AF, but they have important limitations, including significant inter- and intra-patient variability in INR as a result of diet, drug and patient factors. This imposes the requirement for regular monitoring. We now recognize that good-quality anticoagulation control with VKAs, as reflected by a high TTR, is associated with maximum efficacy and safety.

A high TTR can be related to various clinical features, and a clinical risk score (SAMe-TT_2R_2) has been proposed[143] to help to predict those patients who are likely to do well on VKA therapy and to achieve a high TTR (SAMe-TT_2R_2 score of 0–2) or those patients who are less likely to achieve a good TTR (SAMe-TT_2R_2 score >2). In those patients who are unlikely to achieve a good TTR, additional review and educational intervention is needed to help improve outcomes or to consider alternative oral anticoagulants (such as a NOAC)[144] (FIG. 7). The SAMe-TT_2R_2 score can be used to predict the likelihood of labile INRs and, consequently, an increased risk of severe bleeding, thromboembolism and death[145].

Non-VKA oral anticoagulants. The NOACs have changed the landscape for stroke prevention in AF. NOACs fall into two broad classes: the direct thrombin inhibitors, such as dabigatran; and the oral factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban. The NOACs have been tested in large Phase III trials that have confirmed their efficacy, safety and relative convenience compared with warfarin.

Ruff *et al.*[146] have reported a meta-analysis of the four Phase III trials comparing a NOAC (42,411 patients) with warfarin (29,272 patients). This analysis found that NOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (relative risk (RR): 0.81; 95% CI: 0.73–0.91; $P<0.0001$), a result that was particularly driven by a reduction in haemorrhagic stroke (RR: 0.49; 95% CI: 0.38–0.64; $P<0.0001$). NOACs also significantly reduced all-cause mortality (RR: 0.90; 95% CI: 0.85–0.95; $P=0.0003$) and intracranial haemorrhage (RR: 0.48; 95% CI: 0.39–0.59; $P<0.0001$), but increased gastrointestinal bleeding (RR: 1.25; 95% CI: 1.01–1.55; $P=0.04$). There was a greater relative reduction in major bleeding with NOACs than with warfarin when the centre-based TTR was <66% compared with higher TTRs (RR: 0.69; 95% CI: 0.59–0.81 compared with RR 0.93; 95% CI: 0.76–1.13; $P=0.022$ for interaction). Finally, low-dose NOACs produced overall reductions in stroke or systemic embolic events that were similar to those produced by warfarin (RR: 1.03; 95% CI: 0.84–1.27; $P=0.74$), and also showed less bleeding than warfarin (RR: 0.65; 95% CI: 0.43–1.00; $P=0.05$), but resulted in significantly more ischaemic strokes (RR: 1.28; 95% CI: 1.02–1.60; $P=0.045$).

Box 1 | **CHA_2DS_2-VASc score**

Conditions or characteristics and their contributions to the CHA_2DS_2-VASc score, which has a maximum score of 9 points:

- Congestive heart failure: 1 point
- Hypertension: 1 point
- Age ≥75 years: 2 points
- Diabetes mellitus: 1 point
- Stroke, transient ischaemic attack or thromboembolism: 2 points
- Vascular disease (prior myocardial infarction, peripheral arterial disease or aortic plaque): 1 point
- Age 65–74 years: 1 point
- Sex category (female): 1 point

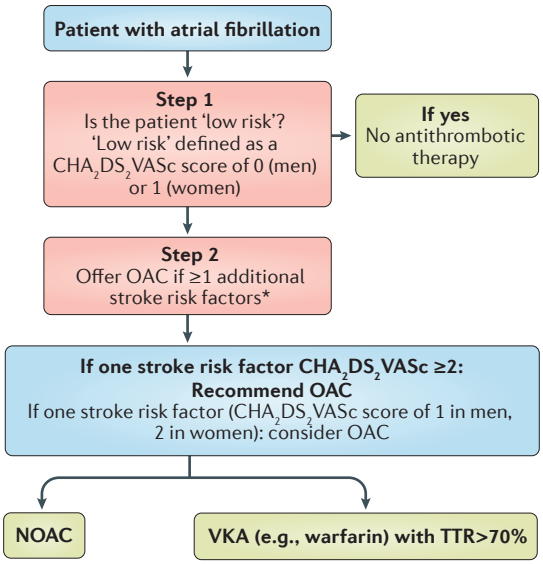

Figure 6 | **Risk stratification and decision making in thromboprophylaxis.** The flowchart shows that the first step is to identify 'low-risk' patients using the CHA_2DS_2-VASc score (0 in men, 1 in women); these patients do not need any antithrombotic therapy. The next step is to consider effective stroke prevention (oral anticoagulation (OAC)) for those patients with ≥1 additional stroke risk factors. OAC refers to a well-controlled vitamin K antagonist (VKA) (time in therapeutic range (TTR) >70%) or a non-vitamin K antagonist oral anticoagulant (NOAC). *Use the HAS-BLED score to identify patients at high risk of bleeding for more careful review and follow up, and to address reversible risk factors for bleeding. A high HAS-BLED score (≥3) does not preclude the use of OAC and might help with the selection of NOAC dose.

With the availability of various NOACs, the drug can be fitted to the patient's clinical characteristics. One suggested scheme is shown in FIG. 8. Various clinical factors to be considered when choosing a particular NOAC can be summarised by the acronym ABCDE: abnormally low weight (dose reduction may be needed with some agents); bleeding risk, particularly gastrointestinal; creatinine clearance (as a measure of renal function); drug interactions; and elderly age (dose reduction may be needed).

Antiplatelet therapy. The role of antiplatelet therapy in stroke prevention in AF is limited. In patients who are not eligible for warfarin use, aspirin–clopidogrel combination therapy resulted in a 28% reduction in ischaemic stroke compared with aspirin alone[147]. Even in elderly patients, warfarin is superior to aspirin for preventing stroke and thrombotic events, but the rate of major bleeding and intracranial haemorrhage is similar between warfarin and aspirin. With NOACs, one Phase III trial (AVERROES) showed that apixaban was superior to aspirin for stroke prevention among patients who were deemed unsuitable for warfarin or those who had refused warfarin, with a similar rate of major bleeding and intracranial haemorrhage between the two treatments[148].

Antiplatelet therapy is only used in combination with OAC in patients with AF who present with an acute coronary syndrome or who undergo percutaneous coronary intervention or stenting[149]. In this situation, we have to consider prevention of stroke (using OAC), recurrent cardiac ischaemia (which requires antiplatelet therapy) and stent thrombosis (using antiplatelet therapy), as well as balancing against the enhanced risk of bleeding that accompanies therapy (especially with a combination of OAC and antiplatelet therapy). A suggested scheme for managing these patients is shown in FIG. 9, which has been derived from the 2014 joint European consensus document and endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society.

Rate control

The majority of patients with AF need acute management of their ventricular heart rate. After initial rate control, long-term rate control management can be the treatment of choice for those with minimal symptoms of AF, predominantly elderly patients. The goals of rate control therapy are to reduce symptoms, improve QOL, minimize the development of heart failure and prevent thromboembolic complications. Intuitively, strict rate control might achieve these goals; however, important limitations of strict rate control therapy are the adverse effects of rate-controlling drugs. These drugs generally act to reduce the activity of the SA node (after conversion to sinus rhythm) and AV node, which can eventually lead to the need for pacemaker implantation.

The best evidence for a lenient optimum rate control target was provided by the Rate Control Efficacy in Permanent Atrial Fibrillation (RACE II) trial, in which lenient rate control (target resting heart rate <110 bpm) was as effective as strict rate control (target resting heart rate <80 bpm and <100 bpm during moderate exercise) regarding the development of cardiovascular morbidity and mortality, symptoms and QOL. In addition, lenient rate control was easier to achieve than strict rate control[150,151].

The choice of rate-controlling drug, including β-blockers, non-dihydropyridine calcium antagonists, digoxin and (rarely used) amiodarone, alone or in combination, depends on the symptoms, comorbidities and potential adverse effects. It is uncertain which rate control drug or combination is the most effective. Based on the available data, digoxin seems to be the least effective, and β-blockers or rate-limiting calcium channel blockers seem to be the most effective[152,153]. One analysis suggested that the use of β-blockers was associated with a lower risk of mortality than other drugs[153]. However, until data from randomized trials are available, we stress that the choice of rate-controlling drugs should be individualized depending on age, lifestyle, associated comorbidities and heart rate. It is important to institute rate-controlling drugs cautiously. Digoxin can be also be carefully instituted[154,155].

In rare situations in which heart rates cannot be controlled by a rate-controlling drug, atrioventricular node ablation (with permanent pacemaker implantation) can be considered, or a rhythm control treatment strategy can be instituted.

Rhythm control: drugs

AF frequently recurs after termination of the arrhythmia; antiarrhythmic drugs (AADs) remain the most common therapeutic approach for the restoration of sinus rhythm and/or the prevention of recurrence of the arrhythmia. AADs can be categorized into classes depending on their predominant mode of action. Class I agents are Na^+ channel blockers and include flecainide and propafenone; class II agents are β-blockers; class III agents are multichannel blockers, such as amiodarone; and class IV agents are calcium channel blockers.

Cardioversion of AF. In patients who present with an episode of AF, more than two-thirds have spontaneous conversion to sinus rhythm[156]. Pharmacological or electrical cardioversion (ECV) — the restoration of sinus rhythm — should be considered in patients with persistent AF, especially for those who have new-onset AF or remain symptomatic after rate control and adequate anticoagulation therapy. In general, pharmacological cardioversion using AADs should be attempted initially as it can avoid the cost and potential risk of ECV and reduce the risk of recurrence after successful cardioversion. For recent-onset, persistent AF (duration of <7 days), the administration of class IC and class III or atrial-selective AADs can restore sinus rhythm in 34–95% of patients within 24 hours. For persistent AF of >7 days duration, the use of class IC and class III AADs can achieve cardioversion in only 15–40% of patients and, therefore, ECV is more likely to be required for these patients[157].

Flecainide and propaferone are the most commonly prescribed class IC AADs for cardioversion of AF in patients without significant dilated or hypertrophic cardiomyopathy[157]. They are associated with an increased risk of proarrhythmias (new or more frequent arrhythmias) in patients with left ventricular dysfunction after myocardial infarction[158]. Both drugs can be administrated intravenously or orally as a 'pill in the pocket' approach for conversion of AF within 1–2 hours. Nevertheless, they can convert AF into atrial flutter with a rapid ventricular rate as a result of 1:1 conduction (where the atrial and ventricular rates are the same because of the conduction of each atrial impulse to the ventricle), and the concomitant use of AV nodal blocking agents should be considered to reduce the risk of this outcome. Intravenous or oral amiodarone is the most commonly used class III AAD for pharmacological conversion. Amiodarone can be used in patients with dilated or hypertrophic cardiomyopathy, but conversion usually occurs several hours later than with other AADs[159]. Other class III agents, including intravenous ibutilide and oral dofetilide, are also effective for pharmacological conversion of AF, but they are not widely available and require in-patient monitoring for QT interval prolongation during administration. Intravenous ibutilide is more effective in converting atrial flutter and recent-onset AF than other arrhythmias. Intravenous vernakalant is an atrial-selective AAD with multichannel action and is more effective than intravenous amiodarone for the conversion of recent AF, but it has limited efficacy for the conversion of atrial flutter and AF with a duration of >7 days[160]. Intravenous vernakalant is currently only approved in Europe for cardioversion of recent AF (duration of <7 days).

The safety and efficacy of these AADs for the cardioversion of AF are summarized in TABLE 3. Although these agents are more effective than placebo, there is limited evidence to suggest any major clinical differences between them for the cardioversion of AF. Similarly, there is clear evidence to support the routine adjunctive use of class IC and class III AADs to facilitate ECV. However, pharmacological pretreatment can be used for patients in whom initial ECV is unsuccessful and in those with AF re-initiation (within minutes) or recurrence (days or weeks) after cardioversion. For instance, pretreatment and maintenance with oral amiodarone before and after ECV significantly increased the rate of cardioversion in patients in whom previous ECV and the maintenance of sinus rhythm was unsuccessful[158]. Similarly, the use of ibutilide can also potentiate ECV and prevent the recurrence of AF.

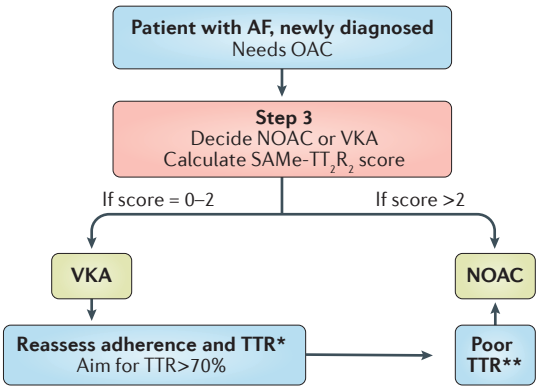

Figure 7 | **Using the SAMe-TT_2R_2 score to aid decision making between a non-vitamin K antagonist oral anticoagulant and a vitamin K antagonist.** In a newly diagnosed anticoagulation-naive patient with atrial fibrillation (AF), some clinical features can be associated with a good likelihood of a high time in therapeutic range (TTR). These features have been incorporated into the SAMe-TT_2R_2 score, in which a score of 0–2 suggests that the patient may do well on a vitamin K antagonist (VKA) with a high TTR, whereas a SAMe-TT_2R_2 score of >2 suggests that a good TTR may be difficult to achieve. Thus, better education and/or counselling, more careful review and follow up is needed for a patient treated with a VKA oral anticoagulant (OAC), or a non-VKA oral anticoagulant (NOAC) should be used rather than a VKA. *When calculating the TTR, use a validated method, such as the Rosendaal method for computer-assisted dosing, or a proportion of tests in the range for manual dosing. Exclude measurements taken during the first 6 weeks of treatment and calculate the TTR over a maintenance period of ≥6 months. **Reassess if poor anticoagulation is shown by any of the following: two international normalized ratio (INR) values of >5 or one INR value of >8 within the past 6 months; two INR values of <2 within the past 6 months; and TTR of <65%. Consider diet and drug interactions, as well as patient adherence, as contributors to poor TTR.

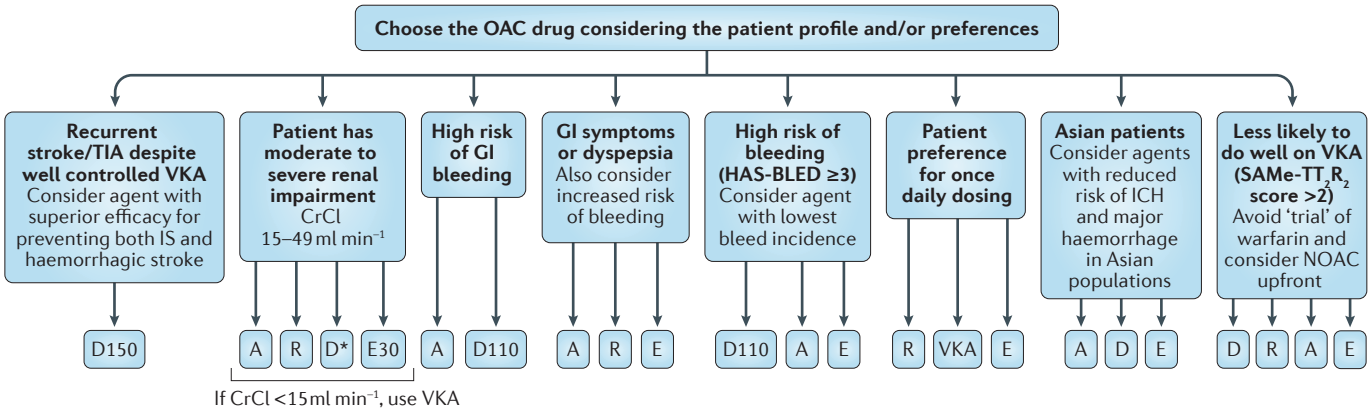

Figure 8 | **Selection of oral anticoagulant drugs.** A schematic representation of decision making in the selection of an oral anticoagulant (OAC) drug based on patient and drug characteristics using illustrative examples. A, apixaban; CrCl, creatinine clearance; D, dabigatran (D75, dabigatran 75 mg two times per day, available in the United States only; D110, dabigatran 110 mg, not available in the United States for AF; D150, dabigatran 150 mg); E, edoxaban (E30, edoxaban 30 mg); GI, gastrointestinal; ICH, intracranial haemorrhage; IS, ischaemic stroke; NOAC, non-vitamin K antagonist oral anticoagulant; R, rivaroxaban; TIA, transient ischaemic attack; VKA, vitamin K antagonist. *D110 for patients with a CrCl 30–49 ml min^{-1} (most countries); in the United States only, D75 for patients with CrCl 15–29 ml min^{-1} (and only 150 mg b.i.d. dose available in the United States, for CrCl >30 ml min^{-1}). Figure adapted with permission from REF. 250, Wiley.

Maintenance of sinus rhythm. Chronic use of AADs can be used to prevent the recurrence of AF in patients with paroxysmal AF and to maintain sinus rhythm after successful cardioversion or relapse after non-pharmacological therapies (catheter or surgical ablation). Recent pooled analyses have shown that treatment with several class IA AADs (disopyramide and quinidine), class IC AADs (flecainide and propaferone), class III AADs (amiodarone, dofetilide, dronedarone and sotalol) and a β-blocker (metoprolol) significantly reduce the recurrence of AF compared with placebo[161]. As class IA AADs are poorly tolerated, less efficacious than other AADs and associated with increased mortality, they have a limited role in the maintenance of sinus rhythm in patients with AF[162]. Although amiodarone is more effective than flecainide, propafenone, sotalol and dronedarone for the maintenance of sinus rhythm, the long-term extra-cardiac toxicities of amiodarone preclude it as a first-line agent for the majority of patients with AF. As a result, current clinical guidelines[74] recommend that flecainide, propafenone, sotalol and dronedarone are first-line agents in patients with lone AF or minimal structural heart disease. Similar to the cardioversion of AF, class IC agents (flecainide and propafenone) should be avoided in patients with ischaemic or structural heart disease — for example, left ventricular dysfunction, left ventricular hypertrophy and cardiomyopathy. In patients with coronary artery disease, dronedarone, sotalol and dofetilide are appropriate first-line agents, but dronedarone and sotalol are contraindicated in patients with heart failure. Dronedarone should not be used in patients with permanent AF or in combination with digoxin[163,164]. Sotalol should be used cautiously in patients at risk of proarrhythmias, such as women, and patients who use diuretics, have electrolyte abnormalities and a prolonged QT interval. Amiodarone is reserved as a first-line agent in patients with congestive heart failure or significant left ventricular hypertrophy, and is used as a second-line agent after the failure of other AADs. Similarly, dofetilide is the first-line agent in patients with heart failure or is used as a second-line therapy after the failure of other AADs, but it is only available in the United States. The safety and efficacy of these AADs for the maintenance of sinus rhythm in patients with AF are summarized in TABLE 4.

Pooled analyses and studies reveal that all these AADs are associated with an increased risk of withdrawal owing to adverse effects, and all except amiodarone and dronedarone increase the incidence of proarrhythmias[165]. Moreover, the use of sotalol is associated with increased all-cause mortality, but other AADs have a neutral effect. Recent results from the ROCKET AF and ARISTOTLE trials have confirmed that the use of amiodarone or other AADs does not increase mortality, although amiodarone is associated with poorer anticoagulation control in patients treated with warfarin and, therefore, increases their risk of stroke and systemic embolism compared with the non-use of amiodarone[166,167]. The periprocedural use of amiodarone in patients with persistent AF who receive catheter ablation reduced their admission to hospital for atrial tachyarrhythmias during the blanking period, but did not prevent the recurrence of AF[168,169].

Several new classes of AADs, including different derivatives of amiodarone (such as budiodarone and celivarone)[170,171], atrial-selective agents (including an oral preparation of vernakalant, XEN-D0101 and AVE0118)[171,172] and other multichannel blockers (ranolazine and vanoxerine)[173,174], are under development[171–174]. The safety and clinical efficacy of these new AADs for the treatment of AF will emerge as clinical trials progress.

Rhythm control: ablation

AF ablation has emerged as an alternative to AADs for rhythm control in patients with AF. Catheter ablation is indicated in patients with paroxysmal, persistent or long-standing persistent AF that is refractory or intolerant to antiarrhythmic drugs. In addition, catheter ablation may be considered as a first-line therapy for patients with symptomatic paroxysmal AF[71]. The main objective of this procedure is to create a series of lesions that prevent AF by eliminating the triggers that initiate it or modifying the substrate that maintains it.

The most common and first-recognized triggers are ectopic beats that originate from the PVs[26] (FIG. 10). The electrophysiological disconnection of the PVs from the atria is called PV isolation and is the cornerstone of every AF ablation procedure. PV antrum isolation involves the creation of lesions within the left atrium cavity (antrum) in close proximity to the PV. Inclusion of the antrum is important because it reduces the risk of PV stenosis and increases the success rate of the procedure[175]. Indeed, the PV antrum shares the same embryological origin as the PVs and harbours trigger sources[176]. The contribution of different trigger sources to AF varies depending on whether the AF is paroxysmal, persistent or long-standing persistent (FIG. 10). PV antrum isolation by itself is effective only in patients with paroxysmal AF[177]. When AF persists, electrophysiological and structural changes predispose patients to the development of other triggers and make the atria the perfect substrate for sustained AF. Thus, in persistent and long-persistent AF it is important to use an extensive approach, including the ablation of non-PV triggers or the substrate. Non-PV triggers are usually found in other thoracic veins such as the superior vena cava, coronary sinus and vein of Marshall, and other locations such as the crista terminalis and the left atrial appendage[177]. In particular, left atrial appendage triggers are common in patients with non-paroxysmal AF, and left atrial appendage isolation has been shown to reduce the post-ablation recurrence of AF in this population[178].

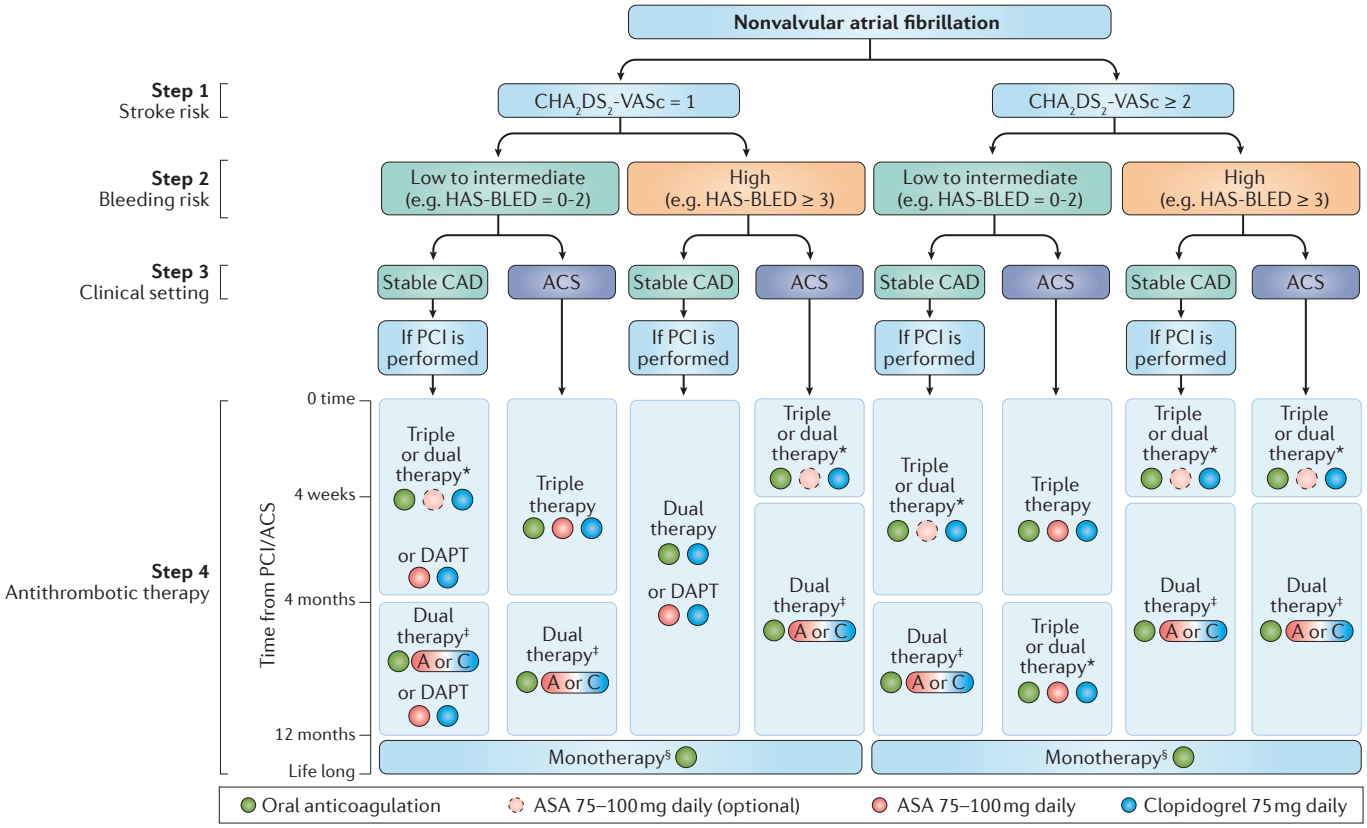

Figure 9 | **Management of atrial fibrillation.** A suggested scheme for the management of patients with atrial fibrillation presenting with an acute coronary syndrome (ACS) and/or undergoing percutaneous cardiovascular interventions, derived from the recent joint European consensus document and endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society. CAD, coronary artery disease; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention. *Dual therapy with oral anticoagulation and clopidogrel may be considered in selected patients. A and C indicate acetylsalicylic acid (ASA) and clopidogrel, respectively. ‡Aspirin as an alternative to clopidogrel may be considered in patients on dual therapy (that is, oral anticoagulation plus a single antiplatelet agent). §Dual therapy with oral anticoagulation and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at very high risk of coronary events. Figure adapted with permission from REF. 149. Lip, G. Y. H. *et al.*, Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur. Heart J.*, 2014, **35** (45), 3155–3179, by permission of Oxford University Press.

Table 3 | **Antiarrhythmic agents for cardioversion of atrial fibrillation**

Drug	Indication	Efficacy	Adverse effects	Contraindications
Class IC				
Flecainide	Atrial fibrillation for <7 days	67–92% (1–6 h, usually 0.5 h)	Hypotension, atrial flutter with 1:1 conduction, unmasking of Brugada syndrome and type ST elevation Torsades de pointes	Heart failure, coronary artery disease, ventricular tachycardia and prolonged QT interval
Propaferone	Atrial fibrillation for <7 days	41–91% (2–6 h, usually 0.5–2 h)	Hypotension, atrial flutter with 1:1 conduction, unmasking of Brugada syndrome and type ST elevation Torsades de pointes	Heart failure, coronary artery disease, ventricular tachycardia and prolonged QT interval
Class III				
Amiodarone	Atrial fibrillation or atrial flutter	• <7 days: 34–95% of patients (>24 h) • >7 days: 15–40% of patients	Hypotension, phlebitis, Torsades de pointes and bradycardia	Bradycardia
Dofetilide	Atrial fibrillation or atrial flutter	• <7 days: 44–85% of patients (24–36 h) • >7 days: 30–40% of patients	Torsades de pointes and bradycardia	Prolonged QT interval
Ibutilide	Atrial fibrillation or atrial flutter for <7 days	50–71% (~90 min, usually 30 min)	Torsades de pointes and bradycardia	Prolonged QT interval
Vernakalant	AF or atrial flutter for <7 days	45–62% conversion rate	Torsades de pointes, bradycardia, nausea, sneezing and dysgeusia	Heart failure, severe valvular disease, hypotension and prolonged QT interval

Substrate modification to prevent the perpetuation of AF can be achieved with linear lesions to compartmentalize the left atrium; these lesions are usually performed along the atrial roof and mitral isthmus. In addition, substrate modification can involve the ablation of complex fractionated electrograms, rotors or autonomic ganglionated plexi[40,41,177,179]. Substrate modification is challenging and potentially pro-arrhythmic, and the benefit of targeting these structures remains controversial[180,181].

Catheter ablation. Catheter ablation of AF is mainly performed in the left atrium, which is accessed from the right atrium by trans-septal puncture. Trans-venous catheters are positioned with the use of fluoroscopy, intracardiac echocardiography and 3D mapping systems that can recreate cardiac anatomy with real-time catheter tip localization. Ablation is usually obtained through the application of radiofrequency energy. Radiofrequency ablation achieves myocardial necrosis through tissue heating by delivering a low-voltage alternating electrical current from the tip of the ablation catheter. The most commonly used ablation catheter has an irrigated tip that reduces excessive heating at the electrode–tissue interface, allowing the use of more power to achieve deeper lesions with less risk of char or thrombus formation. The size of ablation lesions is also determined by the degree of electrode–tissue contact; new ablation catheters with real-time feedback of the contact force have been shown to improve success in paroxysmal AF ablation when catheter stability and good tissue contact are achieved[182].

Cryoablation or laser ablation are used as alternative ablation techniques applied through balloon-tipped catheters that are inflated at the opening of the PVs. This allows the creation of circumferential lesions to electrophysiologically isolate the PVs from the left atrium, reducing the relevance of the skill of the operator. This approach is only effective in patients with paroxysmal AF, in which AF is mainly triggered by the PVs[183,184]. In addition, robotic navigation systems that allow remote ablation have been developed and multiple electrode radiofrequency ablation catheters to shorten procedural times are under clinical investigation[185–187].

Success rates for the catheter ablation of AF are variable and mainly depend on the type of AF, the presence of comorbidities, the experience of the electrophysiologist performing the procedure and the duration and intensity of follow up. Ablation is more effective in patients with paroxysmal AF and a relatively normal heart (single procedure success rate: 60–75%) than in those with persistent and long-standing persistent AF (single procedure success rate: 45–60%). Performing a second or third ablation increases the effectiveness of this procedure[188].

Catheter ablation is not without risk, with an overall incidence of major complications of 4.5%[189]. Complications can result from direct injury to cardiac structures, such as myocardial perforation with subsequent cardiac tamponade and PV stenosis. Thermal injury to adjacent non-cardiac structures can also cause complications, such as phrenic nerve and vagal plexus injury, resulting in diaphragmatic paresis and gastro-esophageal hypomobility or atrioesophageal fistula. Finally, catheter ablation can also cause thromboembolic

Table 4 | **Antiarrhythmic drugs for maintenance of sinus rhythm**

Drug	Drug interaction	Cardiac adverse effects	Non-cardiac adverse effects	Contraindications
Class IA				
Quinidine	• Inhibits CYPs: ↑ digoxin levels • Inhibits CYP2D6: ↑ levels of TCAs and metropolol	QRS prolongation and Tdp (non-dose-related)	Rash, thrombocytopenia, cinchonism and pruritus	Heart failure, CAD and prolonged QT interval
Disopyramide	• Caution with CYP3A4 inhibitors (verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors and grapefruit juice) and inducers (rifampicin, phenobarbital and phenytoin)	Tdp and heart failure	Narrow angle glaucoma, dry mouth, constipation, urinary retention and visual blurring	Heart failure, CAD and prolonged QT interval
Class IC				
Flecainide	• Caution with CYP2D6 inhibitors (quinidine, fluoxetine and TCAs)	Hypotension, atrial flutter with 1:1 conduction, unmasking of Brugada syndrome and type ST elevation Tdp	Dizziness, headache and visual blurring	Heart failure, CAD and prolonged QT interval
Propaferone	• Caution with CYP2D6 inhibitors (quinidine, fluoxetine and TCAs) • Inhibits *P*-glycoprotein: ↑ digoxin level • Inhibits CYP2C9: ↑ warfarin level	Hypotension, atrial flutter with 1:1 conduction, unmasking of Brugada syndrome and type ST elevation Tdp	Metallic taste and dizziness	Heart failure, CAD and prolonged QT interval
Class III				
Amiodarone	• Inhibits most CYPs to cause drug interaction: ↑ concentrations of warfarin, statins and many other drugs • Inhibits *P*-glycoprotein: ↑ digoxin level	Bradycardia	Acute or chronic interstitial lung disease, hepatitis, thyroid disorders (hypothyroidism or hyperthyroidism), blurring of vision, photosensitivity, skin discoloration, nausea, ataxia, tremor and alopecia	Bradycardia
Dofetilide	• CYP3A inhibitors (verapamil, hydrochlorothiazide, cimetidine, ketoconazole, trimethoprim, prochlorperazine and megestrol)	Tdp and bradycardia	None	Prolonged QT interval and CYP3A inhibitors
Sotalol	• None	Tdp and bradycardia	Bronchospasm	Prolonged QT interval
Dronedarone	• CYP3A inhibitors (verapamil, hydrochlorothiazide, cimetidine, ketoconazole, trimethoprim, prochlorperazine and megestrol)	Tdp and bradycardia	Anorexia, nausea and liver failure	Heart failure, permanent AF, bradycardia and CYP3A inhibitors

AF, atrial fibrillation; CAD, coronary artery disease; CYP, cytochrome P450; TCA, tricyclic antidepressant; Tdp, Torsades de pointes.

complications as a result of clot or char formation on the sheaths and catheters. Strategies can be adopted to minimize these complications, such as using intracardiac echocardiography, titrating power and contact force during ablation, monitoring the oesophageal temperature and performing procedures with uninterrupted OAC[190]. Moreover, operator experience and hospital volume are associated with a lower rate of adverse outcomes[191].

Surgical ablation. An alternative to catheter ablation is surgical ablation, which is usually performed in patients undergoing cardiac surgery[192]. The mainstay of surgical ablation is the Maze procedure, which is a form of substrate modification that involves producing a bi-atrial set of transmural linear lesions designed to interrupt all possible re-entrant circuits. These lines, which used to be created by cut-and-sew via a median sternotomy, are now obtained through ablation using a variety of techniques (most commonly radiofrequency ablation or cryoablation) during minimally invasive procedures that can be performed on a beating heart.

Quality of life

The main issues related to QOL for patients with AF are: their symptoms (including palpitations, chest pain, dyspnoea, fatigue and reduced exercise tolerance); the unpredictability of disease onset, frequency and duration; anxiety and depression; the adverse effects of treatment (and/or worries about potential side effects); and other comorbidities. Patients with AF often have a poorer QOL than the general population and age- and sex-matched healthy controls[193–195]. This discrepancy might be particularly pronounced among elderly patients (≥65 years of age)[196].

Health-related QOL (HRQOL) is one of the main patient-reported outcomes described in health care. Changes to HRQOL as a result of treatment are increasingly being recognized as important metrics for health care, particularly in chronic conditions such as AF, because the available treatment options do not prolong life, but can substantially affect symptoms and comorbidities. Thus, improving HRQOL should be a fundamental treatment objective in the management of patients

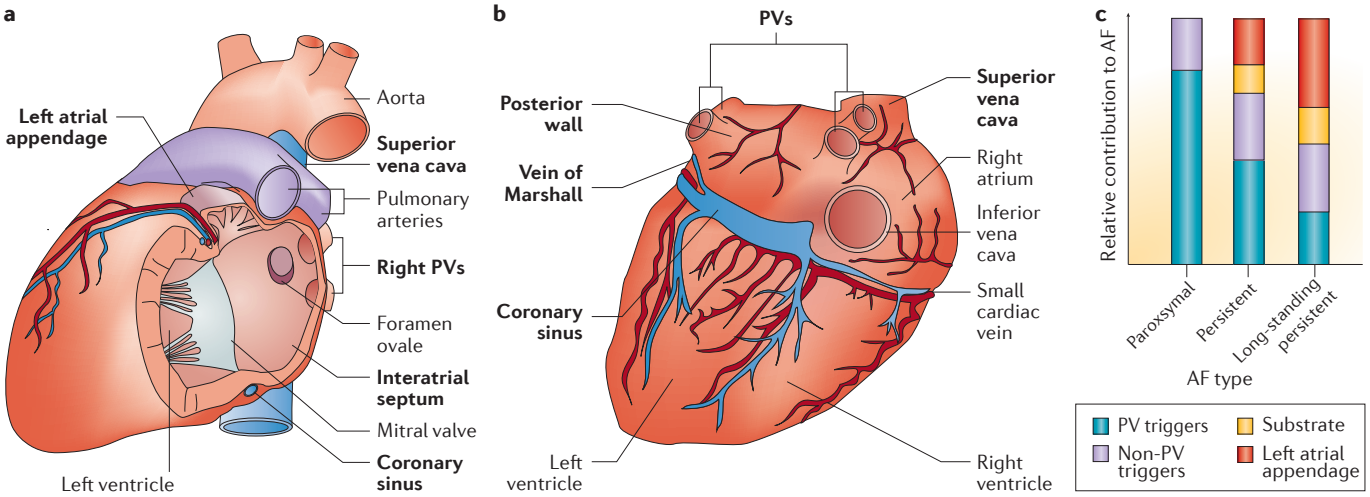

Figure 10 | **Atrial fibrillation ablation. a**,**b** | Anatomical location of the structures commonly targeted in ablation of atrial fibrillation (AF) (in bold, see text). **c** | Relative contribution of different ablation targets in the AF disease continuum. PV, pulmonary vein.

with AF. The assessment of HRQOL is recommended in every patient with AF[196–198], and the European Society of Cardiology has advocated the inclusion of patient-reported outcomes in cardiovascular trials to improve the quality of patient care[199]. A variety of generic and disease-specific tools exist to measure QOL[193] (BOX 2).

Effects of interventions for AF

Most studies assessing QOL in patients with AF have examined their QOL before and after interventions, predominantly in highly symptomatic patients[195,200].

Non-pharmacological rate control approaches ('ablate and pace' procedures), most of which were conducted in non-randomized studies, have demonstrated significant improvements in QOL[195,201]. Rhythm control strategies with pharmacological therapy and/or electrical cardioversion have demonstrated that the restoration and maintenance of sinus rhythm improves QOL[195,202,203]. Randomized controlled trials[196,204] and an observational study[205] of rate control compared with rhythm control have demonstrated improvements in HRQOL after treatment, but generally with little[205] or no[196,204] significant differences between the treatment strategies in terms of HRQOL. The improvements in HRQOL that are evident with rate control and/or rhythm control strategies are probably primarily due to symptomatic relief and cessation of AAD use (and their associated adverse effects).

Achievement of rhythm control using catheter or surgical ablation[195,200,206] is effective in improving QOL. In studies comparing catheter ablation with AADs, PV isolation significantly improved symptoms and QOL compared with pharmacological therapy alone[207–210]. However, the demographics and symptom burden of the patients offered catheter ablation or AAD therapy is likely to differ, which makes direct comparison of the two treatments problematic.

Assessment of QOL in patients with AF has tended to concentrate on global QOL rather than specifically assessing the effect of OAC per se. Among patients with AF receiving VKAs, lifestyle restrictions (such as diet, alcohol and certain activities), the necessity of regular blood tests, concerns regarding bleeding and drug–drug interactions, and effects on social life, work and family have all been cited as negative treatment effects, particularly among younger patients[211]. The limited data available suggest that after incorporating the warfarin regimen into their lifestyle, most patients reported only minor inconveniences associated with regular blood tests, dose adjustments, and diet and alcohol restrictions, rather than any significant effect on QOL, suggesting that there is a period of adjustment and adaptation that might initially affect their QOL[212–214]. There is a paucity of research examining the effect of NOACs, and NOACs compared with VKAs, on the HRQOL in patients with AF.

Future directions

The majority of the AF-specific QOL assessment tools have been developed by clinicians with little (if any) patient input. Future research using disease-specific measures is needed to assess and improve their validity, reliability, reproducibility and generalizability, in addition to testing them in different languages, ethnicities, ages and socioeconomic groups. Future research should focus on the HRQOL of the general AF population and other patient-reported outcomes to assess treatment efficacy.

Outlook

AF is a disease for which there is much ongoing research. TABLE 5 lists some of the ongoing studies and developments in this condition.

Mechanisms

It is likely that we would be able to prevent AF-related complications more effectively if we had a better understanding of its causes and mechanisms. We need to improve our knowledge of how genetic factors, subtle ultrastructural changes, alterations in ion channel handling, electrical atrial function and/or interactions

between the heart and the autonomic nervous system contribute to the initiation or persistence of AF[215,216]. Understanding the relationships among such pathways, which might have different kinetics, might help to identify novel, effective targets for the treatment of AF[217]. Early treatment might improve the prevention of AF in patients who are predisposed to the condition if clinical tools become available to reliably identify this group.

Rhythm management

Approaches to early rhythm control include measures that prevent development of the AF substrate, earlier catheter ablation and novel AADs[218]. Potential novel therapeutic options under development include the modulation of microRNAs, heat shock protein inducers, agents that influence calcium handling, vagal stimulators and more aggressive ablation strategies[216]. Catheter ablation is most effective in paroxysmal AF and is more effective than medical therapy in relatively young and otherwise healthy patients, but it may cause more severe adverse effects than other therapeutic approaches[219,220]. These outcomes support the current use of ablation in symptomatic patients who understand the benefits and risks of the procedure. The most common AF ablation technique still involves the isolation of PVs from the left atrium. Many techniques are being developed to make patients with persistent arrhythmia more eligible for this procedure. Recently, atrial substrate analysis of high-frequency and fractionated electrograms and the identification of driver domains have afforded an improvement in the outcome of more complex arrhythmias in terms of maintaining sinus rhythm[41,221]. However, the relevance of these new concepts and possible targets has not yet been established in large trials with hard clinical outcomes. Many novel techniques have been developed over recent years, such as balloon cryoablation, circular catheter ablation, laser ablation and robotic navigation. These advances might further improve the efficacy of AF ablation and possibly make intervention easier, which would facilitate efforts to make the technique more widely available or as a first-line option. The technological aid obtained from 3D electroanatomic mapping systems has further improved the safety and long-term efficacy of ablation and minimized the procedural difficulty. Some other imaging techniques are being developed and we will learn in the future whether they are more appropriate as research instruments or clinical tools, and whether the AF ablation procedure becomes simpler overall[222,223].

The Catheter Ablation versus Anti-Arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial[224] is currently running and compares ablation with antiarrhythmic drug treatment. Also ongoing is the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST), which evaluates rhythm control with ablation and antiarrhythmic drugs against guideline-mandated initial rate control in patients presenting with their first episode of AF[225]. Both trials are investigating whether early and active rhythm control of AF with a strategy involving catheter ablation can improve hard outcomes compared with standard therapies. The concept that patients who spend more time in AF are at higher risk of complications than patients who spend less time in AF, and that a different management approach might significantly affect prognosis, are still open questions. The results of these studies might considerably affect our perspective on which targets in AF management are the most relevant. Consequently, these trials might have major consequences in terms of research and in widening (or perhaps limiting) the access to invasive management for rhythm control in patients with AF in our health-care systems.

Antithrombotic management

Risk assessment and early treatment. The CHA_2DS_2VASc score is valuable and accepted for identifying patients at a high risk of stroke and patients with a truly low risk. OAC clearly prevents ischaemic strokes in patients with AF, and most patients with AF are likely to benefit from treatment with anticoagulant drugs[74]. Stroke events in AF populations have been declining recently[215], which might be a consequence of the improved use of OAC. We now need to recognize the effect of asymptomatic AF on thromboembolism. It is not clear whether short atrial high-rate episodes and longer but fully asymptomatic episodes recorded by an implanted device have the same clinical implications and prognostic effect in patients with and those without ECG-documented AF. The available data suggest that any strategy with a longer recording time will diagnose more patients with AF and that these patients are at an increased risk of stroke[19,89,92]. Earlier management of patients with 'silent' AF episodes might be beneficial, but there is a need for trials investigating the value of ECG screening or monitoring tools in populations with a high cardiovascular risk, with antithrombotic therapy initiated based on the diagnosis of silent AF and an evaluation of the subsequent prognosis. Another, more simple strategy for the prevention of AF would consist of early treatment with OAC for patients with no known AF, but who have been identified as being at risk of developing AF in the future[226]. The CHA_2DS_2VASc score, developed to gauge stroke risk in patients with AF, might help in this context because it can also predict episodes of AF in several populations with sinus rhythm[227–230].

Box 2 | **Measures of health-related quality of life**

Generic measures:

- Short Form health survey (SF)-36 (REF. 238)
- SF-12 (REF. 239)
- SF-6 (REF. 240)
- EuroQoL[241]
- Nottingham Health Profile[242]
- Dartmouth Care Cooperative Information Project (CO-OP) charts[243]

Atrial fibrillation-specific measures:

- Atrial Fibrillation Effect on Quality-of-Life (AFEQT)[244]
- Health-related Quality of Life Assessment in Atrial Fibrillation (AFQoL)[245,246]
- Quality of Life in AF patients (QLAF)[247]
- Quality of Life of Atrial Fibrillation (AFQLQ)[248,249]

Table 5 | **Key ongoing trials in patients with atrial fibrillation**

Trial	Patient population	Treatment arms	Design	Target enrolment (*n*)	Follow up	Primary outcome(s)	Estimated completion
Rhythm management							
EAST	Patients with AF	Early, structured rhythm control treatment based on antiarrhythmic drugs and catheter ablation to prevent AF-related complications compared with usual care	Randomized, multicentre, open label	2,745	6 years	Composite of death, stroke and admission to hospital as a result of heart failure or acute coronary syndrome	2019
Catheter ablation							
Cryo-FIRST	Patients with paroxysmal AF	Pulmonary vein isolation performed with cryoablation as first-line therapy compared with antiarrhythmic drugs	Randomized, multicentre, open label	218	1 year	Freedom from any recurrence of atrial arrhythmia	2017
CRIOBLAF	Patients with typical atrial flutter with a history of AF (atrial flutter being the predominant arrhythmia)	Ablation procedure of typical atrial flutter compared with a combined procedure of typical atrial flutter ablation and pulmonary vein cryoballoon isolation	Randomized, multicentre, open label	170	2 years	Recurrence of AF documented by a 12-lead ECG or a remote ECG monitor	2018
CABANA	Patients with untreated or incompletely treated AF	Left atrial catheter ablation compared with current state-of-the-art therapy with either rate control or rhythm control drugs	Randomized, multicentre, open label	2,200	5 years	Composite of total mortality, stroke, serious bleeding or cardiac arrest	2018
Anticoagulation							
PIONEER AF-PCI	Patients with non-valvular AF and percutaneous coronary intervention with stent placement	Two different rivaroxaban treatment strategies and one VKA treatment strategy with various combinations of dual antiplatelet therapy or low-dose aspirin or clopidogrel (or prasugrel or ticagrelor)	Randomized, multicentre, open label	2,125	1 year	Clinically significant bleeding	2016
REDUAL-PCI	Patients with AF undergoing PCI with stenting	Dual therapy with dabigatran (110 or 150 mg two times per day) plus clopidogrel or ticagrelor compared with a triple therapy of warfarin plus clopidogrel or ticagrelor plus low-dose aspirin	Randomized, multicentre, open label	8,520	2.5 years	Death, first thrombotic event or major bleeding event	2017
MUSICA-2	Patients with AF and $CHADS_2$ score ≤2 treated with PCI and stenting	Dual therapy with aspirin (300 mg) plus clopidogrel (75 mg), compared with triple therapy with acenocoumarol, aspirin (100 mg) and clopidogrel (75 mg)	Randomized, multicentre, single-blinded	304	1 year	Composite of stroke, MI, systemic TE events, stent thrombosis and death	2015
ENSURE-AF	Patients with AF who have had an electrical cardioversion	Edoxaban compared with warfarin and enoxaparin	Randomized, multicentre, open label (PROBE)	2,200	61 days	• Composite of stroke, embolic event, MI and mortality • Major bleeding	2015
RE-CIRCUIT	Patients with NVAF undergoing AF ablation	An uninterrupted dabigatran periprocedural anticoagulant regimen compared with an uninterrupted warfarin regimen	Randomized, multicentre, open label (PROBE, exploratory study)	724	2 months	Major bleeding events (ISTH definition)	2016
AFAXA	Patients undergoing catheter ablation for NVAF	Apixaban twice daily for a minimum of 30 days compared with a VKA (INR 2–3) for a minimum of 30 days	Randomized, multicentre, open label (safety/efficacy study)	650	4 months	Composite of all-cause death, stroke and major bleeding events	2017

Table 5 (cont.) | **Key ongoing trials in patients with atrial fibrillation**

Trial	Patient population	Treatment arms	Design	Target enrolment (*n*)	Follow up	Primary outcome(s)	Estimated completion
AF screening combined with subsequent anticoagulation							
STROKESTOP	All patients aged 75 and 76 years with no history of AF	Two weeks of twice-daily ECG screening or routine care; patients with AF duration >30 s offered treatment with an OAC	Randomized, multicentre, open label	6,500	5 years	Incidence of stroke	2019
ARTESiA	Patients with a CHA_2DS_2-VASc score ≥4 with device-detected subclinical AF and no history of clinical AF	Aspirin (81 mg) compared with apixaban (5 mg) twice daily	Randomized, multicentre, double-blinded	4,000	3 years	Composite of ischaemic stroke and systemic embolism	2019
TACTIC AF	Patients with a history of non-permanent (paroxysmal or persistent) AF taking a NOAC with an intracardiac device	Withdrawal or re-initiation of factor Xa inhibitor based on remote monitoring of AF	Randomized, multicentre, double-blinded	200	1 year	Composite of stroke, death and cardiovascular complications	2016

AF, atrial fibrillation; AFAXA, Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy; ARTESiA, Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; CABANA, Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation; CRIOBLAF, Cryoballoon Pulmonary Venous Isolation in Patients Referred for Typical Atrial Flutter Ablation; Cryo-FIRST, Catheter Ablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation; EAST, Early Treatment of Atrial Fibrillation for Stroke Prevention Trial; ENSURE-AF, Edoxaban versus Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation; ECG, electrocardiogram; INR, international normalized ratio; ISTH, International Society of Thrombosis and Haemostasis; MUSICA-2, Anticoagulation in Stent Intervention; MI, myocardial infarction; NOAC, non-VKA oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PIONEER AF-PCI, a study exploring two strategies of rivaroxaban and one of oral vitamin K antagonist in patients with atrial fibrillation who undergo percutaneous coronary intervention; PROBE, Prospective Randomized Open Blinded End-Point; RE-CIRCUIT, Uninterrupted Dabigatran Etexilate in Comparison to Uninterrupted Warfarin in Pulmonary Vein Ablation; REDUAL-PCI, Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With NVAF That Undergo a PCI With Stenting; STROKESTOP, Population screening of 75- and 76-year-old men and women for silent atrial fibrillation; TACTIT AF, Safety Study on Stopping Anticoagulation Medication in Patients With a History of Atrial Fibrillation; TE, thromboembolic; VKA, vitamin K antagonist.

Comorbidities. For those patients with a clear diagnosis of AF and other conditions associated with highly competitive risks for cardiovascular and bleeding events, the optimum strategy for OAC remains to be established. The management of these patients currently involves complex decisions that can only be addressed with expert opinion rather than evidence-based medicine as a result of a lack of robust trial data. Some ongoing studies are evaluating several antithrombotic strategies in patients with AF who also have acute coronary syndrome and/or stent implantation to identify the best combination option for antiplatelet therapy–OAC[149]. Additional studies are needed in patients with co-occurring AF and stable coronary artery disease.

NOACs are indicated for patients with non-valvular AF, the definition of which is sometimes debated. Non-valvular AF usually refers to cases of AF that are not associated with pre-existing haemodynamically significant (that is, moderate to severe) native valve disease (for example, rheumatic mitral stenosis) or prosthetic mechanical heart valves. The eligibility criteria for NOACs can be questioned simply as a consequence of adopting a more or less restrictive definition of non-valvular AF[231]. A Phase II dose validation study demonstrated a higher thromboembolic and bleeding risk and no additional benefit from using a NOAC (dabigatran) compared with a VKA (warfarin) in patients with mechanical heart valves[232]. Nonetheless, future trials comparing NOACs with VKAs in patients with AF and bioprosthetic valves seem to be both ethical and relevant. NOACs are currently contraindicated in patients with kidney disease with a glomerular filtration rate <30 ml/min/1.73 m^2 (REF. 74). However, VKA treatment for AF in patients with severe chronic kidney disease has a poor safety and efficacy profile[233]. New oral anticoagulant drugs are at least as effective as VKAs, with reduced risks of major bleeding and thrombosis in patients with an estimated glomerular filtration rate <50 ml/min/1.73 m^2 (REF. 234). Lower doses of NOACs should be evaluated in patients with more severe renal failure, who might represent a substantial proportion of elderly patients with AF. More data on the relationship between drug levels, coagulation test results and clinical outcomes might be needed to guide management decisions for these patients.

Overall and integrated management of AF

In view of the high morbidity and mortality still assigned to AF and its increasing burden, it is reasonable to consider the current treatment of patients with AF as inadequate. Many aspects of the current care scenario for patients with AF set apart treatment 'strategies', whereas their combination might, in many patients, achieve better outcomes. Rhythm and rate control therapy should generally be added to the treatment of conditions that predispose to AF and contribute to cardiovascular complications, including antithrombotic therapy to prevent strokes and the prevention of heart failure and acute coronary

syndromes — in other words, 'comprehensive or holistic AF management' (REFS 215,216,218). Some findings support therapy directed at weight and risk factors in the management of AF. Weight reduction with intensive risk factor management might reduce the symptom burden and severity of AF with beneficial cardiac remodelling and might also improve the long-term success of AF ablation[114,235]. Obstructive sleep apnoea might also be an independent (and treatable) risk factor for the development and progression of AF[236]. Disease-specific management is a possible strategy to improve health outcomes in patients with AF[237]. Additional research is needed to assess the effect of intervention and home-based strategies on outcomes, such as self-care behaviours, symptom management, clinical status and/or the receipt of guideline-directed care in patients with AF. Overall, adequate therapy for AF will need to simultaneously address the management of underlying and concomitant conditions, optimum antithrombotic therapy, early and comprehensive rhythm control therapy, adequate control of ventricular rate and cardiac function, and continuous therapy to prevent AF-associated complications.

We have seen substantial improvements during the past decade in the understanding of mechanisms of AF, the implementation of ablation methods for maintaining sinus rhythm and new drugs for stroke prevention. Further studies are needed to better inform care-givers and the public about the risks and benefits of therapeutic options for patients with AF. Although considerable hope lies in prevention, future strategies for reversing the growing epidemic of AF will come from basic scientific, epidemiological and clinical studies.

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Author contributions

Introduction (G.Y.H.L.); Epidemiology (T.P.); Mechanisms/pathophysiology (S.N.); Diagnosis, screening and prevention (S.B.F.); Management (A.N., C.G., G.Y.H.L., H.-F.T., I.V.G. and M.R.); Quality of life (D.A.L.); Outlook (L.F.); Overview of Primer (G.Y.H.L.).

Competing interests

G.Y.H.L. has had guideline membership or has been involved in reviewing the European Society of Cardiology (ESC) Guidelines on Atrial Fibrillation (2010) and Focused Update (2012), the ESC Guidelines on Heart Failure (2012), the American College of Chest Physicians Antithrombotic Therapy Guidelines for Atrial Fibrillation (2012), the National Institute for Health and Care Excellence (NICE) Guidelines on Atrial Fibrillation (2006 and 2014), the NICE Quality Standards on Atrial Fibrillation (2015), the ESC Cardio-oncology Task Force (2015) and the ESC Working Group on Thrombosis position documents (2011–present). He is the chairman of the Scientific Documents Committee for the European Heart Rhythm Association (EHRA) and a reviewer for various guidelines and position statements from the ESC, EHRA, NICE and other organizations. He has been a member of steering committees for various Phase II and III studies, Health Economics and Outcomes Research and other studies, and has been an investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome and lipids. He has been or is currently a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo, and a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. L.F. has served as a consultant for Bayer HealthCare, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Medtronic and Novartis and has been on the speakers' bureau for Bayer HealthCare, Bristol-Myers Squibb/Pfizer, Boehringher Ingelheim, Boston Scientific and Medtronic. S.B.F. receives investigator-initiated research grants, personal fees and non-financial support from Bayer Pharma AG, investigator-initiated research grants and non-financial support from Boehringer Ingelheim, investigator-initiated research grants and personal fees from Bristol-Myers Squibb/Pfizer and personal fees from Servier, AstraZeneca and Gilead Sciences. These associations are not related to the submitted work. I.V.G. has had guideline membership of and been involved in reviewing the ESC Guidelines on Atrial Fibrillation (2010). She has received research grants that have been paid to the University Medical Center Groningen from Medtronic, Biotronik and St Jude Medical. A.N. has received consulting fees or honoraria from Janssen Pharmaceuticals, Biosense Webster, St Jude Medical, Medtronic and Boston Scientific. C.G. declares no competing interests. S.N. declares no competing interests. T.P. has received consultant and speaker fees from Bayer HealthCare, Pfizer and Boehringer Ingelheim. M.R. is supported by a grant from the Netherlands Organization for Scientific Research (Veni grant number 016.136.055). He declares no relationship with industry. H.-F.T. is chairman of the Clinical Trial Committee for the Asia Pacific Heart Rhythm Society. He has been or is currently a steering committee member and investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome and lipids. He has been or is currently a consultant for BayerHealthcare/Jensen J&J, MSD, Bristol-Myers Squibb/Pfizer, Boston Scientific, St Jude Medical, Medtronic, Boehringer Ingelheim and Daiichi-Sankyo, and a speaker for Bayer HealthCare/Jensen J&J, MSD, Bristol-Myers Squibb/Pfizer, Boston Scientific, St Jude Medical, Medtronic, Boehringer Ingelheim and Merck. D.A.L. has received investigator-initiated educational grants from Bayer HealthCare, Bristol-Myers Squibb and Boehringer Ingelheim and has been on the speaker bureau for Boehringer Ingelheim, Bayer HealthCare and Bristol-Myers Squibb/Pfizer. She is a steering committee member of a Bristol-Myers Squibb Phase IV trial.