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Review

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Advances in basic and translational research in atrial fibrillation

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Atrial fibrillation (AF) is a very common cardiac arrhythmia with an estimated prevalence of 33.5 million patients globally. It is associated with an increased risk of death, stroke and peripheral embolism. Although genetic studies have identified a growing number of genes associated with AF, the definitive impact of these genetic findings is yet to be established. Several mechanisms, including electrical, structural and neural remodelling of atrial tissue, have been proposed to contribute to the development of AF. Despite over a century of exploration, the molecular and cellular mechanisms underlying AF have not been fully established. Current antiarrhythmic drugs are associated with a significant rate of adverse events and management of AF using ablation is not optimal, especially in cases of persistent AF. This review discusses recent advances in our understanding and management of AF, including new concepts of epidemiology, genetics and pathophysiological mechanisms. We review the current status of antiarrhythmic drug therapy for AF, new potential agents, as well as mechanism-based AF ablation.

This article is part of the theme issue 'The heartbeat: its molecular basis and physiological mechanisms'.

1. Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias worldwide. Its prevalence is estimated at 0.4% in the general population (33.5 million people), increasing to approximately 6% in older individuals over 65 years as age is an independent risk factor [1,2]. The number of patients afflicted with AF is projected to increase to 50 million worldwide by 2030 [1,3,4]. The prevalence of AF varies among geographical regions, socioeconomic status, ethnicity, age and sex. It is the number one cause of hospitalization for arrhythmias and is also associated with an unfavourable prognosis [5–7]. AF is characterized by uncoordinated electrical activity in the atria without discrete P waves and an irregular ventricular response on the surface electrocardiogram. This causes the heart beat to become fast and irregular and increases the risk of stroke and sudden death [8].

The pathophysiology of AF is complex, involving dynamic interactions among several factors, including substrates, triggers, modulators and perpetuators. The therapeutic approaches/strategies are informed by the disease

progression from initiation of the abnormal electrical rhythm to its maintenance. Owing to the potential side effects of antiarrhythmic drugs and recurrence following ablation of persistent AF, the current therapies for AF are suboptimal. This article is focused on recent advances in the epidemiology, genetics and pathophysiological mechanisms of AF. We discuss the status of antiarrhythmic drug therapy for AF today, review molecular mechanisms and the possible clinical use of some new agents, as well as mechanism-based ablation of AF.

2. Definitions of atrial fibrillation

According to the recent expert consensus documents, paroxysmal AF is defined as recurrent AF episodes that terminate spontaneously or with intervention within 7 days of onset; persistent AF is defined as continuous AF that is sustained beyond 7 days; long-standing persistent AF is defined as continuous AF of greater than 12-month duration. The first diagnosed AF refers to AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms [9–12]. From a clinical point of view, the latter is important as more than 50% of patients with a first diagnosed AF episode will not experience recurrences over long-time follow up in the absence of antiarrhythmic drugs, cardiac structural abnormalities and significant comorbidities [13]. The term permanent AF is defined as AF in which the presence of the AF is accepted by the patient and physician, and no further attempts will be made either to restore or maintain sinus rhythm [10].

Atrial myopathy is characterized by atrial fibrotic, electrical and autonomic remodelling, facilitates the development of both AF and stroke through the mechanism of inflammation and oxidative stress, which in turn leads to a worsening myopathy. Emerging evidence suggests that targeting this myopathy might shed light on the best therapy to decrease the occurrence and burden of AF [14–17]. Various animal models of atrial myopathy, such as a pacing-induced heart failure (HF) canine model with massive atrial fibrosis, a transforming growth factor (TGF)-β1 overexpressed mouse model, a rat model of obesity and obstructive apnea, proliferator-activated receptor-γ coactivator-1β deficient aged mouse model, and a crossbred mouse model expressing NaV1.5-F1759A and mitochondrial catalase, have helped decipher the complex interplay between atrial myopathy and AF [18–23]. Also, human clinical data show that individuals with markers of atrial myopathy have an elevated risk of developing both AF and stroke [24].

3. Genetics of atrial fibrillation

(a) Familial atrial fibrillation and linkage analysis

Approximately 15% of patients with AF are familial. The incidence of AF increases together with the numbers of affected individuals with early onset AF in the family [7]. A family history of AF is associated with a 40% increased risk for new-onset AF, suggesting a genetic predisposition [25,26]. AF is commonly associated with other inherited syndromes including dilated or hypertrophic cardiomyopathies, long-QT syndromes, short QT syndromes, Brugada syndrome, familial amyloidosis, congenital cardiac abnormalities and preexcitation syndromes [27–35]. Genetic variants contributing to ion channel function, cell–cell coupling, fibrosis, nuclear structure and transcript factor, have been linked to the development and maintenance of AF over the last decade. Chen and colleagues discovered the first genetic variant, *KCNQ1*-S140G, linked to familial AF in the Chinese population. This variant generates a gain-of-function in the slowly activating delayed rectifier potassium current (I_{Ks}) leading to abbreviation of the effective refractory period (ERP), thus increasing susceptibility for development of AF [36]. *NPPA* encodes the atrial natriuretic peptide, which is highly expressed in heart. A frameshift variant in this gene, c.456–457delAA, has been identified in a distinct AF family, which leads to abbreviation of ERP in an isolated heart model facilitating the occurrence of AF [37]. Somatic variants in the *GJA5* gene, encoding the connexin40 protein, have been associated with AF as well [38]. Causative variants in genes including *KCNQ1*, *SCN5A*, *KCNH2*, *GJA5*, *GJA1*, *NPPA*, *TTN*, *TBX5*, *KCN5A*, *LMNA* and *MYL4*, have been implicated in AF (table 1). Whereas, the causative association of AF with variants in other genes remains to be proved [2]. For example, research has recently illustrated that a variant in the *RYR2* gene (*RYR2*-P238S) is involved in the pathogenesis of AF through interrupting the Ca^{2+} homeostasis [39–42].

(b) Genome-wide association studies

Genome-wide association studies (GWAS) involve testing genetic variants across the genomes of large individuals with or without related diseases to identify genotype–phenotype associations. Although linkage analysis and genotyping are able to identify causative rare variants associated with AF, the use of GWAS has enabled identification and analysis of hundreds of thousands of genetic variants or single nucleotide polymorphisms (SNPs). A recent GWAS study demonstrates that the risk for AF conferred by genomic variation is substantial and that established AF loci only explain a moderate proportion of disease risk, suggesting that further genetic discovery with an emphasis on common variation is warranted [43]. Since the first GWAS for AF performed in 2007, GWAS have identified over 260 SNPs in 166 loci associated with pathogenesis of AF, including 4q25 near the *PITX2*, 16q22 close to the *ZFHX3*,1q21 close to the *KCNN3*, 12q24 near the *TBX5*, 6q22 near the *GJA1*, and 15q24 close to *HCN4* [1]. Variants identified by GWAS tend to locate in non-coding regions, which are presumed to alter the activity of transcriptional regulatory elements, affecting the expression of a nearby gene. *PITX2* belongs to the homeobox transcription factor family *PITX*, which is crucial for left-right asymmetry and pulmonary vein (PV) development. *PITX2c* is the major cardiac isoform [44]. Atrial-specific *PITX2*-deficient mice show a gain-of-function of I_{K1} favouring abbreviation of ERP and the development of re-entrant activity [45]. In a *PITX2c*-deficient zebrafish model, changes in sarcomere length, increased amount of fibrosis and increased expression of *HCN4* have been linked to AF [46]. *TBX5* belongs to the T-box family of transcription factors. In a murine model, conditional deletion of *TBX5* in the heart leads to spontaneous AF [47]. This research also demonstrates that *TBX5* is a direct activator of *PITX2c*, with *TBX5* and *PITX2c* antagonistically regulating the expression of ion channel genes, such as *SCN5A*, *GJA1*, *RYR2* and *ATP2A2* [48]. *TBX5* deficient

Table 1. Causative genes involved in atrial fibrillation. (AF, atrial fibrillation; BrS, Brugada syndrome; DCM, dilated cardiomyopathy; ERS, early repolarization syndrome; HCM, hypertrophic cardiomyopathy; JLNS, Jervell and Lange–Nielsen syndrome; LGMD, limb girdle muscular dystrophy; LQT, long-QT syndrome type; MEPPC, multifocal ectopic Purkinje-related premature contraction; SND, sinus node dysfunction; SQT, short QT syndrome type; TMD, tibial muscular dystrophy; VF, ventricular fibrillation.)

gene	protein	other phenotypes	effect on function
SCN5A	Na^+ channel α subunit 5 (Nav1.5)	heart block, BrS1, VF, SND, LQT3, DCM, ERS, MEPPC	loss-of-function, gain-of-function
KCNQ1	K^+ voltage-gated channel (subfamily Q1, Kv7.1)	SQT2, LQT1, JLNS	gain-of-function
KCNH2	K^+ voltage-gated channel (subfamily H2, Kv11.1)	SQT1, LQT2	gain-of-function
KCNA5	K^+ voltage-gated channel (subfamily A5) (Kv1.5)	none	loss-of-function
GJA5	connexin 40	atrial standstill, digenic (GJA5/SCN5A)	↓ electrical cell-to-cell coupling
GJC1	connexin 45	none	↓ electrical cell-to-cell coupling
TTN	titin	DCM, HCM, LGMD, TMD, Salih myopathy	disruption of sarcomeres, fibrosis
MYL4	atrial myosin alkali light chain	conduction disease	disruption of sarcomeric structure, atrial enlargement and electrical abnormalities
LMNA	lamin A/C	DCM1A, Emery-Dreifuss muscular dystrophy 2/3, Charcot-Marie-Tooth disease, type 2B1, familial lipodystrophy type 2, Hutchinson–Gilford progeria, congenital muscular dystrophy, Malouf syndrome	↓I_{Na}, impaired interaction between lamin A/C and NUP155
NPPA	atrial natriuretic peptide	atrial standstill	gain-of-function, loss of interaction with the atrial natriuretic peptide receptor
TBX5	T-box transcription factor 5	Holt–Oram syndrome	loss-of-function, reduction in the transcriptional activity of TBX5

mice show a predisposition to development of AF. Interestingly, the phenotype is rescued by *PITX2c* [48]. Furthermore, the cooperative interactions between the transcription factors TBX5, GATA4 and NKX2-5 is key for proper binding and cooperative regulation of the downstream target genes and of cardiac development linking to AF [49].

(c) Polygenic risk score

Many common variants and SNPs have been identified in large populations using GWAS, together with rare causative variants in family, pointing to AF as a complex trait. Using genetic data to identify high-risk individuals so as to provide preventative treatment or lifestyle modification is a strategy that is being developed. Khera and colleagues develop an AF polygenic risk score (PRS) containing more than 6.6 million variants. The top 6.1% individuals with a high PRS have a more than threefold increased risk for AF [50]. Weng and colleagues combine PRS with a clinical risk factor burden [51]. Individuals in the highest tertile of polygenic risk have a higher lifetime risk for AF (43.6%) compared with the individuals in the lowest tertile (22.3%). When clinical risk increases to the highest tertile, the lifetime risk of AF continues to augment irrespective of the polygenic risk. Numerous studies have recently focused on the PRS predictive value for post-operative AF, recurrence of AF in patients undergoing ablation, recurrence in patients after direct current cardioversion and after and ischaemic stroke [52–57]. Marston and colleagues show that AF PRS is a strong independent predictor of incident AF in patients with cardiovascular conditions and provides strong complementary predictive value when combined with clinical risk factors and amino-terminal pro-B-type natriuretic peptide [58].

4. Pathophysiology of atrial fibrillation

(a) Electrophysiology

The initiation and maintenance of AF involve both triggers and substrates (figure 1). PV has a smaller I_{K1}, $I_{Ca,L}$ and larger I_{Kr} and I_{Ks} reducing resting potentials and action potential duration (APD). Furthermore, PV possesses a unique anatomical structure consisting of branching fibres with limited lateral coupling and abrupt fibre-orientation transitions, which increases their ability to generate spontaneous activity. These properties facilitate the development of ectopic activity via a re-entrant mechanism, serving as a trigger of AF [59,60]. Delayed afterdepolarizations (DADs) are believed to be responsible for ectopic activity arising from other parts of the atrium. Dysfunction of the ryanodine receptor 2 (RyR2) Ca^{2+}-release channels or elevated SR Ca^{2+} load leads to increased diastolic Ca^{2+} concentration,

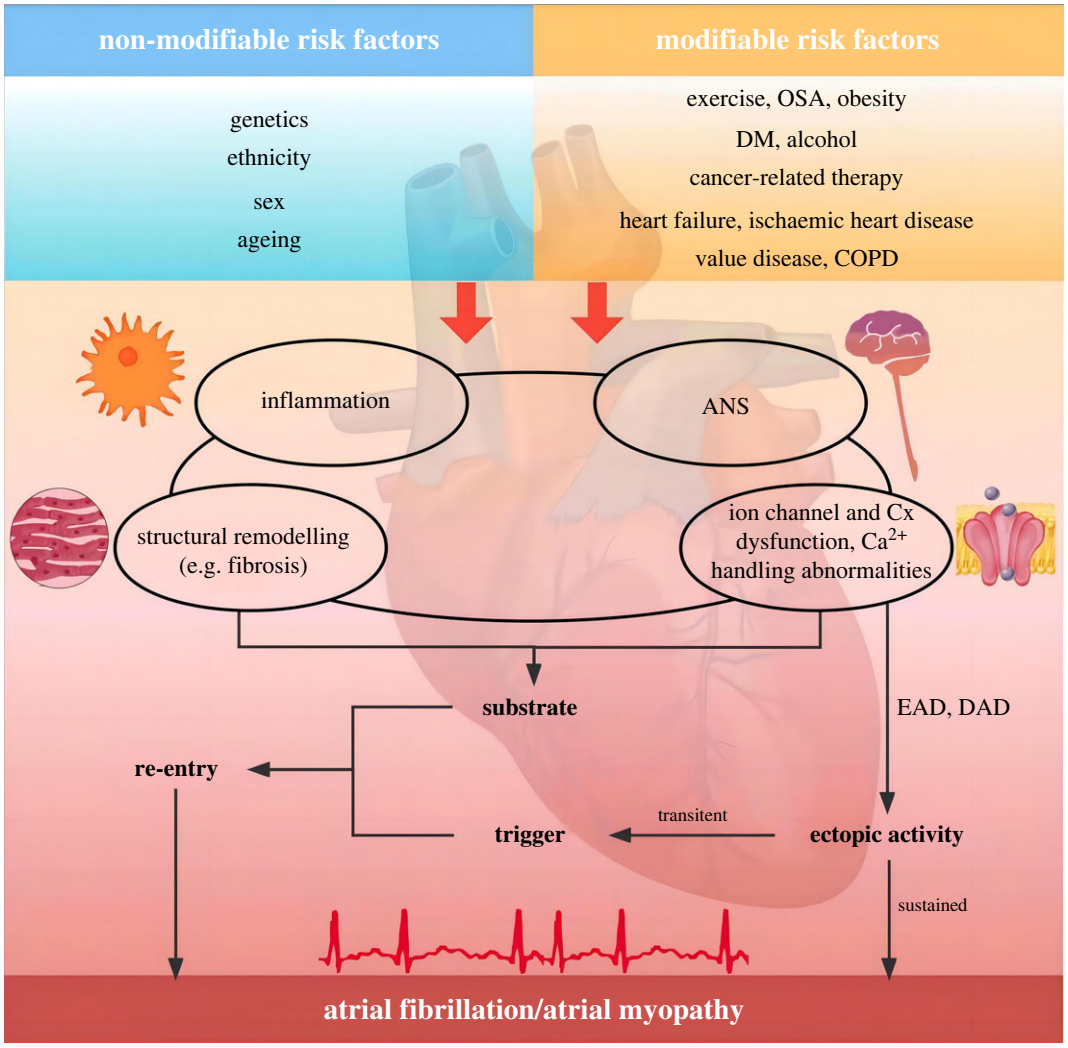

Figure 1. Summary of mechanisms underlying the initiation and maintenance of atrial fibrillation. Atrial fibrillation can be maintained by either re-entry or sustained ectopic activity. Trigger (commonly from an ectopic beat) combined with vulnerable substrate facilitate the development of re-entry. Inflammation, ANS dysfunction, structural remodelling, ion channel, connexin dysfunction and Ca^{2+} handling abnormalities underline the generation and progression of vulnerable substrate. Risk factors (modifiable and non-modifiable) are the basal component closely associated with atrial fibrillation. OSA, obstructive sleep apnea; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ANS, autonomic nerve system; Cx, connexin; EAD, early afterdepolarization; DAD, delayed afterdepolarization (Online version in colour.).

predisposing to the development of DADs [5]. Even sub-threshold DADs can be proarrhythmic by promoting dispersion of excitability with conduction block owing to heterogeneous voltage-dependent Na^+-channel inactivation [61]. An alternative mechanism generating ectopic activity is early afterdepolarization (EAD). EAD-induced triggered activity is commonly associated with prolongation of the atrial APD [62]. Mice with long-QT syndrome 3 show excessive atrial APD-prolongation and EADs [63]. Similarly, acute Calcium-calmodulin dependent protein kinase II (CaMKII) activation initiates AF through EAD-mediated triggered activity in old rats, which can be suppressed by inhibition of $I_{Na,late}$ [64].

The maintenance of AF generally requires a vulnerable substrate which may be a result of both age/disease-related remodelling as well as AF-related electrical and structural remodelling [5]. AF leads to downregulation of Ca^{2+} current *via* reduced expression of α-subunit of the Ca^{2+} channel which underlies the abbreviation of ERP [65]. Additional changes in ion channels that contribute to abbreviation of ERP include increased expression of I_{Ks}, I_{KACh} and I_{K1}. All of these changes in ion channels abbreviate ERP, stabilize the re-entry circuits and increase AF vulnerability and sustainability [66]. Meanwhile, several research articles suggest that the expression of the small-conductance Ca^{2+}-activated K^+ channel (SK) subunit and SK open probability are augmented in AF, promoting repolarization shortening [5,67]. Moreover, the decreased expression of connexins and relocalization of connexins to lateral margins, promote conduction abnormalities facilitating development of re-entry [68]. Structural remodelling includes progressive atrial dilatation at the macro level, as well as abnormalities of the atrial cardiomyocyte, fibrotic changes, and alterations in the interstitial matrix at the cellular level [69,70]. Atrial fibrosis plays a pivotal role in the maintenance of AF and the transition from paroxysmal to persistent AF. A wide range of molecular mechanism are involved in the pathogenesis of AF *via* atrial fibrosis [71]. The detailed mechanisms are elaborated below. There are four hypotheses for AF maintenance: multiple wavelet theory, focal source(s), rotor theory, and the double layer hypothesis [72–74]. Although these hypotheses can explain some phenomena, the mechanisms underlying the development of AF are diverse and still not fully understood.

(b) Inflammation

Accumulating evidence indicates that inflammation is implicated in various AF-related pathological processes including structural and electrophysiological remoulding [75,76].

Recent investigations have shown that the tumour necrosis factor (TNF)-α, macrophage migration inhibitory factor, interleukin (IL)-1β and IL-6 facilitate the progression of AF [77–79]. TNF-α administration to PV cardiomyocytes produces a variety of ionic changes including a smaller $I_{Ca,L}$, larger transient outward K^+ current (I_{to}), elevated systolic Ca^{2+} transients (larger diastolic intracellular calcium), enhanced inward sodium-calcium exchange, and decreased sarcoplasmic reticulum (SR) ATPase expression, facilitating the development of DADs-induced triggered activity in PV [80]. In addition, TNF-α has the ability to alter the expression and distribution of connexin43 and connexin40 [81]. Moreover, TNF-α is also involved in the pathogenesis of atrial fibrosis *via* activation of the TGF-β signalling pathway and increased secretion of matrix metalloproteinases [81]. Clinical research suggests that macrophages are increased in AF patients. Moreover, pro-inflammatory macrophages (M1) participate the generation of AF in mouse and canine models through secreting IL-1β [82]. Our research further demonstrate that Ang-II-treated human cardiac myocyte-derived exosomal plasmacytoma variant translocation 1 facilitates extracellular-matrix remodelling of atrial fibroblasts by inducing macrophage to M1 polarization *via* upregulation of the expression of IL-16 [83]. In turn, activated macrophages enhance atrial fibroblast proliferation and differentiation. JUN N-terminal kinases (JNKs) orchestrate cellular stress responses and regulate cell differentiation, survival and migration, involved in the development of AF in humans and animal models, especially JNK2 [84–86]. JNK2 increases diastolic Ca^{2+} leak from the SR through stimulating activity of sarco/endoplasmic reticulum ATPase type 2 and activating CaMKII [87,88]. Moreover, JNK2 is implicated in both impaired cell-to-cell communication and slowed atrial conduction velocity *via* reduced expression of connexin43 [88]. Activation of NACHT, LRR and PYD domains-containing protein-3 (NLRP3) releases IL-1β and IL-18 through active caspase-1, mediating inflammatory response. NLRP3-inflammasome enhances aberrant RyR2-mediated SR Ca^{2+} release during diastole owing to increased RyR2 protein expression or CaMKII-dependent hyperphosphorylation of RyR2. Yao *et al*. show that activation of NLRP3 signalling enhances the protein expression of RyR2, leading to increased RyR2-mediated arrhythmic SR Ca^{2+} release events, which ultimately cause ectopic firing *via* the generation of DADs [89]. Furthermore, NLRP3-inflammasome augments I_{Kur} and I_{KACh} current and increases atrial hypertrophy and fibrosis, participating in the electrical and structural remodelling of atrium [1,90].

(c) Fibrosis

Atrial fibrosis is a common feature in AF patients, yet how and if atrial fibrosis is involved in AF generation is poorly understood [91]. Ramos *et al*. reported recently that the amount of atrial fibrosis is not different in patients with various stages of AF and controls [92]. It is atrial structural remodelling rather than atrial fibrosis that can be causal for AF [92]. Interestingly, mild and moderate atrial fibrosis has been reported to be associated with an increase of AF burden and advanced atrial fibrosis (encountered in patients with severe HF) is associated with a reduction of AF burden [93,94]. Advanced atrial fibrosis is accompanied by a rate-dependent depression of atrial excitability, reducing the occurrence of rapid activation (i.e. AF). Mild and moderate rather than severe atrial fibrosis may be causative for AF. In addition to structural remodelling in AF itself, atrial fibrosis also results from a broad range of factors, including mechanical stretch, inflammation, neurohumoral activation, oxidative stress, ageing and so on. Fibroblasts play a pivotal role in the pathogenesis of fibrosis. Ca^{2+} entry is important for fibroblast responsiveness and fibrosis generation. Owing to lacking of voltage-gated Ca^{2+} channels, transient receptor potential (TRP) channels are mediators of Ca^{2+} signalling in cardiac fibroblasts [95]. TRP channels, both TRPC3 in canine, goat and human models and TRPM7 in human AF, are significantly upregulated in AF-fibroblasts and enhance fibroblast Ca^{2+} entry [96–98]. Moreover, I_{K1} in fibroblast is upregulated, which hyperpolarizes the resting potential, increases the driving force for Ca^{2+} entry, and promotes fibroblast proliferation [99]. Pro-fibrotic cell membrane receptors including connective tissue growth factor, angiotensin-II (particularly type 1 receptors), platelet derived growth factor and TGF-β through down-stream signalling, such as mitogen-activated protein kinases (MAPK), Janus kinase (JAK) and NLRP3, modify the messenger RNA-transcription of proteins like procollagen, fibronectin, matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases that govern extracellular-matrix remodelling and lead to fibrosis [100]. Reactive oxygen species coupled to type-1 Ang-II receptors and TGF-β *via* down-stream systems like MAPK and NLRP3-inflammasome formation and pro-fibrotic inflammatory signalling play a prominent role in AF [101–103]. M1 macrophages participate in the pathogenesis of AF through a pro-inflammatory effect, whereas non-classical M2 macrophages promote AF *via* pro-fibrotic effect [104]. In the animal models of acute ischaemic injury, hypertension and chronic HF, M2 macrophages facilitate the development of fibrosis [105–107]. Accordingly, compared to non-AF individuals, patients with AF show significantly higher pro-fibrotic M2 macrophage level in atrial tissue [108]. The increased extracellular-matrix disrupts myocardial bundle continuity and disorganizes gap-junction formation. These effects lead to slowed conduction velocity and increased heterogeneous conduction [109], which promotes re-entrant substrates for the maintenance and perpetuation of AF [109,110]. Also, cardiomyocyte–fibroblast electrical interactions have particular significance for the electrical remodelling in AF. Fibroblasts are essentially non-excitable cells. However, they have a typical resting potential of about −30 mV and couple with cardiomyocytes and transfer current between cardiomyocytes through connexins. Therefore, cardiomyocyte–fibroblast coupling has been suggested to slow conduction, abbreviate APD, alter myocyte excitability by depolarizing cardiomyocyte resting membrane potential (RMP) and induce spontaneous phase 4 depolarization [95,99,111,112].

(d) Neural mechanisms

The heart is richly innervated by the autonomic nervous system (ANS), including extrinsic and intrinsic nervous systems, which plays a significant role in the occurrence and maintenance of AF [113,114]. Activation of sympathetic nerves enhances automaticity via reducing I_{K1} and increasing I_f current. Meanwhile, diastolic RyR2 Ca^{2+} leak and increased RyR2 open probability, owing to protein kinase A (PKA)/CaMKII phosphorylation, induced by β-adrenergic enhancement result in

DADs. Furthermore, β-adrenergic activation can augment $I_{Ca,L}$ through PKA/CaMKII phosphorylation, increasing EAD likelihood, particularly when I_{Ks} is dysfunctional, such as long-QT syndrome type 1 [115,116]. Additionally, β-adrenergic activation increases I_{kur}, I_{Ks} and I_{KACh}, and facilitates ERP shortening, while, α-adrenoceptor stimulation displays the opposite effect through inhibiting I_{to} [66,117]. Proximal renal sympathetic activation induces shortening of ERP, significantly increasing ERP dispersion and AF inducibility in dogs [118]. Renal sympathetic denervation in canines could suppress AF and reduce the increasing trend of TNF-α and IL-6 induced by rapid atrial pacing [119]. Acute middle cerebral artery occlusion in canines leads to an increase in left stellate ganglion activity, atrial β1-AR expression, atrial macrophage infiltration and AF vulnerability, while ablation of the left stellate ganglion reverses these changes [120]. Although the definitive mechanism is not very clear, it is possible that the effect is related to sympathetic nerve-regulated immune remodelling [114,121].

In general, vagal nerve activation can trigger the release of the neurotransmitter ACh, leading to the repression of TNF-α, IL-1β and IL-6 in macrophages by *α7*nAChR and then producing a cascade effect to reduce systemic inflammation via the cholinergic anti-inflammatory pathway. This pathway has been identified through myriad research on AF. Previous research of canines with rapid atrial pacing uncovers low-level vagus nerve stimulation significantly suppresses atrial electrical remodelling and AF inducibility, accompanied by low levels of TNF-α and IL-6 in the left atria [122–124]. Spinal cord stimulation facilitates the effect of vagus nerve stimulation and reduces the induction of AF via increasing nerve growth factor and repressing SK2 [125]. We further demonstrate that median nerve stimulation can heighten cardiac vagal tone and atrial ACh levels, and reverse the enhanced inflammation and AF inducibility by short-term rapid atrial pacing [126]. It cannot be ignored that vagal stimulation strongly abbreviates atrial refractoriness by augmenting I_{KACh} [117]. Moreover, vagal stimulation increases the AF inducibility and duration in a dog model via abbreviating atrial refractoriness and increasing spatial dispersion of APD restitution [127].

Extensive studies involving both AF patients and animal models indicate that onset of AF is associated with combined sympatho-vagal activation rather than alterations in vagal or sympathetic drive alone [128,129]. Cholinergic stimulation is commonly the main factor for AF initiation in animal models, but adrenergic tone regulates the initiation and maintenance of cholinergically mediated AF [117]. Atrial sympathetic hyperinnervation and extracardiac nerve remolding have been reported in experimental animals and humans [130–133]. Sympathetic hyperinnervation may lead to spatial heterogeneity through heterogeneous β-adrenoceptor activation, increasing the risk of focal triggers and creating gradients of repolarization and increasing the susceptibility to re-entry [66]. This suggests a bidirectional relationship between the ANS and AF.

5. Special conditions and atrial fibrillation

(a) Sleep apnea

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete upper airway obstruction and results in hypoxia, hypercapnia, oxidative stress, inflammation, intrathoracic pressure changes and hyperactivity of the ANS [134]. Patients with OSA are two to four times more likely to develop AF. Acute apneic episodes result in sympatho-vagal co-activation, shortening atrial ERP and promoting the initiation of AF [135]. Repetitive OSA may lead to atrial structural and electrical remodelling characterized by atrial dilation, fibrosis, connexin remodelling, and dysfunction of NaV1.5, all of which may predispose to AF [136,137].

(b) Obesity

Obesity has been increasing globally over the past 40 years and is an independent risk factor for AF as every 1 kg m^{-2} increment in body mass index is associated with a 4% increase in the incidence of new-onset AF [136,138]. Left atrial enlargement and diastolic dysfunction are known consequences of obesity. Furthermore, recent studies have confirmed the correlation between increased epicardial adipose tissue and onset, severity and recurrence of AF [139,140]. Epicardial adipose tissue promotes atrial fibrosis and its associated electrical substrate through the effect of adipokines, inflammatory cytokines, reactive oxygen species and ANS dysfunction [135]. In addition, hypertension and sleep apnea which are considered to be associated with obesity, are deemed indirect mechanisms for obesity-induced AF. Weight loss through lifestyle changes or bariatric surgery could reverse atrial remodelling and result in a significant reduction of AF burden [141]. Weight fluctuations may offset this benefit by reducing energy expenditure and increasing appetite, adipocytokines and metabolic dysfunction [142].

(c) Ageing

Age is the most important risk factor for the development of AF. Older age is associated with increased AF burden, with a sharp incline after the age of 65 years. Ageing-related atrial remodelling shares common mechanisms with AF, including atrial fibrosis, inflammation, oxidative stress, gap-junction remodelling and changes in Ca^{2+} homeostasis [136]. Increased fibrosis can disrupt the coupling between individual myocytes and result in conduction abnormalities, which can lead to re-entry. Age-related calcium handling abnormalities are characterized by increasing spontaneous diastolic Ca^{2+} leak, which promotes afterdepolarizations and spontaneous atrial ectopic activity [143]. In addition, ageing carries other AF risk factors including HF, hypertension, and obesity. These indirect ageing effects may increase AF occurrence through atrial remodelling. Furthermore, age-dependent changes in systemic regulators may contribute to AF, such as the imbalance between sympathetic and parasympathetic, reduction in testosterone levels and elevation of blood inflammatory markers [110,144].

(d) Exercise and diabetes mellitus

Moderate physical exercise is beneficial for cardiovascular health and to decrease AF risk. However, long-term vigorous exercise increases the risk of AF [145]. Potential underlying mechanisms may include atrial dilation, fibrosis, hypertrophy, excessive ANS stimulation, and chronic inflammation, occurring as a response to increased cardiac output and atrial wall stretch during exercise [136]. Lately, Aschar-Sobbi *et al.* and colleagues illustrated that intense exercise induces TNF-α dependent activation of the signalling pathway, prompts atrial structural remodelling and AF vulnerability [146].

Diabetes mellitus (DM) is associated with about a 40% increase in risk for AF. This association has not yet been comprehensively elucidated. There seems to be a multifactorial, complex relationship comprising mechanisms such as oxidative stress, inflammation, insulin resistance, endothelium dysfunction, atrial fibrosis and connexin remodelling, which leads to mechanical and electrical left atrial remodelling [143]. Recent researche demonstrate that glycemic fluctuations, rather than hyperglycaemia alone, contribute to the development of AF in diabetes [147]. Glucose fluctuations are associated with increased atrial fibrosis, oxidative stress and susceptibility to AF in a rat model of DM. Therefore, management of diabetes should be focused on not only reducing blood glucose levels, but also preventing glycaemic fluctuations [148].

(e) Alcohol

Alcohol consumption is prevalent worldwide and excessive binge drinking has been closely associated with the development of cardiac arrhythmia, often known as 'holiday heart syndrome'. AF is the most frequently diagnosed arrhythmia in patients with 'holiday heart syndrome' [88,136]. In a recent clinical trial on secondary prevention of AF, alcohol abstinence reduces AF recurrence [149]. The mechanisms by which alcohol excess increases the risk of AF are multifactorial [150]. First, alcohol could directly affect atrial electrophysiological properties. Both binge and frequent drinking decrease atrial conduction velocity and atrial ERP. Second, alcohol could cause the hyperactivation of the ANS and exaggerate cardiac arrhythmia. Furthermore, chronic alcohol consumption is associated with larger left atrial size and impairments in atrial mechanical and reservoir function. Additionally, alcohol is also associated with inflammation, hypertension, sleep apnea and left ventricular dysfunction, which all increase the risk of AF.

(f) Cancer and related therapy

Cancer increases the risk of AF. The incidence of AF in cancer patients is up to 20%, peaking in the first three months after diagnosis [136]. In a Danish nationwide study, an increase in AF occurrence in cancer patients is observed for all major types of cancer, with lung cancer patients having the highest AF incidence [151]. The potential mechanisms underlying the association between cancer and increased AF risk remain unclear [152]. Shared risk factors (e.g. advanced age, obesity, diabetes and inflammation) may explain this association. In addition, cancer treatments, including surgery, radiation, chemotherapy, targeted therapies and high-dose corticosteroids, increase the risk of AF [153]. The most notable chemotherapeutics associated with AF are alkylating agents. For example, the incidence of AF with cisplatin is 15–32% [154]. Recent research reports that AF incidence rates may reach 38% in patients treated with ibrutinib [155]. Proposed mechanisms for treatment-associated AF include the exacerbated inflammatory response, atrial fibrosis, oxidative stress, neurohormonal dysregulation and calcium homeostasis disorder.

6. Drug and ablation development of atrial fibrillation

(a) Status of antiarrhythmic drugs

The key mechanisms for initiation and maintenance of AF are combined with triggers and substrates. Therefore, removal of ectopic triggers, prevention of the formation and progression of vulnerable substrates and disruption of re-entry are the key strategies for terminating AF [156]. RyR2 channels play a major role in the Ca^{2+}-handling abnormalities which underlie DADs. Targeting abnormal RyR2 channels either by using direct RyR2-channel blockers or RyR2 function modulators would be an alternative. Because of the RyR2-Ca^{2+} channel blocking effect, flecainide, a classic Ic Na^+ channel blocker, can also been viewed as a IVb antiarrhythmic drug according to the new classification criteria of antiarrhythmic drugs [157]. According to the leading circle concept, re-entry circuits can be destabilized when conduction velocity is slowing and/or refractoriness is prolonged, so that the re-entrant wavefront will reach tissue that is still in the refractory state [158]. K^+ blockers and multichannel blockers destabilize re-entry through prolonging ERP, while, Na^+ channel blockers reduce excitability and delay conduction leading to collapse of the re-entry wavelet [159]. According to updated classification of current antiarrhythmic drugs, molecular mechanisms influencing longer-term changes upstream of the electrophysiological processes and tissue structure remodelling also constitute novel potential therapeutic antiarrhythmic targets. As for AF, inflammatory signalling (JNK2, NLRP3), pro-fibrotic signalling (renin–angiotensin–aldosterone system, TGF-β, JAK-STAT), mitochondrial dysfunction (NAD^+/NADH level) and sarcomeric cytoskeleton damage (HDAC) are involved in the structural and electrical remodelling of atrium. Moreover, clinical studies have provided supportive data for the potential value of such 'upstream therapy' with the renin–angiotensin–aldosterone system targetted, for primary prevention of AF [160,161].

Antiarrhythmic drugs are widely used for cardioversion and prevention of AF. The current clinically approved anti-AF agents are: (i) the rapidly activating delayed rectifier potassium current (I_{Kr}) inhibitors (dofetilide, ibutilide, etc.); (ii) sodium channel current (I_{Na}) blockers (flecainide, propafenone, etc.); and (iii) potent multiple channel blockers (amiodarone, quinidine, etc.). Anti-AF efficacy of these agents is relatively high against paroxysmal AF and relatively low against persistent AF.

A major limitation of anti-AF agents is their safety. The use of I_{Na} blockers having slowly unbinding kinetics (flecainide and propafenone) is associated with an increased risk of developing ventricular arrhythmias in patients with significant structural heart diseases. The risk of I_{Kr} inhibitors is a potential induction of long-QT-mediated Torsade-de-Pointe arrhythmias. The use of amiodarone is rarely associated with ventricular arrhythmias. However, there is a relatively high risk of extracardiac side effects with long-term application (such as pulmonary toxicity), significantly limiting long-term use of amiodarone. The annual AF recurrence rate is still high, ranging from 40% to 70% under the use of antiarrhythmic drugs, therefore new drugs with improved efficacy, safety and tolerability are urgently needed [162].

(b) New drug uses and new molecular mechanisms

Numerous novel pharmacological targets and approaches for rhythm control of AF have been suggested over the past 30 years [163]. Most prominent have been atrial-specific or selective inhibition of the I_{Kur}, SK, I_{KACh} and I_{Na}, intending to cause atrial-specific or selective prolongation of the ERP

Table 2. Experimental drugs for the management of atrial fibrillation. (AF, atrial fibrillation; SK, small-conductance Ca^{2+}-activated K^+ channel; SAC, stretch-activated nonselective cation channel; JNK, JUN N-terminal kinase.)

agent	mechanism of action	description
MK-0448	I_{Kur} inhibition	effective in preclinical studies, well tolerated in phase 1 clinical trials
XEN-D0101	I_{Kur} inhibition	suppresses AF in preclinical studies, does not prolong QT interval in phase1 clinical trials
xention-D0103/ S66913	I_{Kur} inhibition	effective in preclinical studies, no effect in phase 2 clinical trials, but safe and well tolerated
acacetin	multi K^+ current blocker: Ito, I_{Kur} and I_{KACh}	effective in preclinical studies
AP14145	SK inhibition	effective in preclinical studies and does not prolong QT interval, no clinical trial
AP30663	SK inhibition	effective in preclinical studies, safe and well tolerated in phase 2 clinical trials
gadolinium	SAC blocker	effective in preclinical studies
ranolazine	multichannel blocker: I_{Na}, I_{Kr}	atrial selective I_{Na} inhibition, significantly reduces clinical AF burden in combination with dronedarone
WenXin KeLi	multichannel blocker: I_{Na}, I_{to}, $I_{Ca,L}$	effective in preclinical and clinical studies
BMS914392	I_{KACh} inhibition	ineffective in phase 2 clinical trials, well tolerated and does not affect QTc
budiodarone	multichannel blocker: I_{Kur}, I_{Na}, I_{KACh},I_{Kr}, I_{Ks}	effective in preclinical and phase 2 clinical trials, few adverse events
ShenSong YangXin capsule	prolongs the atrial effective refractory period, inhibits atrial fibrosis, decreases intracellular iron overload	effective in preclinical and clinical studies
vanoxerine	multichannel blocker: I_{Na}, I_{Kr}, $I_{Ca,L}$	effective in preclinical and phase 2 clinical trials, QT prolongation but no effect on transmural dispersion of repolarization, increased risk of ventricular proarrhythmia in patients with structural heart disease, needs additional studies
moxonidine	centrally acting sympathoinhibitory agent	reduces AF burden in hypertensive patients and postablation AF recurrences in hypertensive patients in phase 2 clinical trials, needs additional studies
rotigaptide	connexin modulator, prevents the uncoupling of connexin 43-mediated gap-junction communication and normalizes cell-to-cell communication	improvement of conduction velocity does not correlate with AF vulnerability in preclinical studies
SP600125	JNK inhibitor	under preclinical studies
dantrolene	RyR2 stabilizer	effective in preclinical studies, no clinical study
JTV-519	multi-ion channel blocker: I_{Na}, I_{Ca}, I_{KACh}, I_{Kr}, I_{Ks}; promotes RyR2-FKBP12.6 (calstabin2) binding	effective in preclinical studies, undergoing phase 2 trials for restoration and maintenance of sinus rhythm, and terminates, no data available

(table 2). Li *et al*. report acacetin, a natural flavone, inhibits I_{to}, I_{Kur} and I_{KACh}, without significantly influencing other major cardiac ion channel currents in atria. It prevents AF without prolonging the corrected QT interval in an *in vivo* canine model [164]. Later on, they further synthesize highly water-soluble acacetin prodrug effectively terminating acute AF in the canine model [165]. Although inhibition of I_{Kur} and SK channels is shown to promote AF termination in animal models, these agents were not effective in terminating AF in humans [166]. This failure is predicted on the basis of studies conducted in coronary-perfused canine atria exposed to a low concentration (50 µM) of 4-aminopyridine, which is selective for inhibition of I_{Kur}. Inhibition of I_{Kur} abbreviates the atrial action potential owing to recruitment of I_{Kr} secondary to a positive shift of the action potential plateau. The abbreviation of atrial APD permits induction of AF with premature stimulation [167]. I_{KACh} is constitutively upregulated during AF. Activation of I_{KACh} by vagal stimulation decreases

ERP, and contributes to maintenance of AF. Selective block of I_{KACh} seems a potential target for AF treatment. It is important to note that selective I_{KACh} blockers for AF must avoid significant vagolytic adverse effects at therapeutic doses [166]. BMS914392, a potent and selective oral inhibitor of I_{KACh}, fails to maintain sinus rhythm in patients with paroxysmal AF when it is administered at the doses required to avoid neurologic adverse effects [168]. Although new drugs blocking I_{KACh} have not emerged for clinical use, inhibition of I_{KACh} remains a promising therapeutic target for the management of AF. Atrial-selective inhibition of I_{Na} is shown by us and others to be valid in terms of anti-AF efficacy and safety in both experimental and clinical studies [169–174]. Atrial-selective prolongation of ERP and anti-AF efficacy of I_{Kur} and SK channel blockers have turned out to be largely or exclusively owing to concomitant atrial-selective inhibition of I_{Na} [171,175]. Ranolazine effectively terminate AF owing to an atrial-selective sodium channel blocking effect combined with I_{kr} blocking in various AF models [169,176–178]. De Ferrari *et al.* show higher doses of ranolazine (500 and 750 mg) are associated with an approximately 35% reduction of recurrence in persistent AF patients. Furthermore, Reiffel *et al.* demonstrate that ranolazine combined with dronedarone significantly decrease the AF burden in paroxysmal AF patients. Ranolazine displays tolerance and safety well in both trials [166,170,179]. It appears that atrial-selective inhibition of I_{Na} is a reasonable and practical approach in the search for novel anti-AF agents so far. WenXin KeLi is a Chinese herb extract capable of atrial-selective inhibition of I_{Na} owing to more negative voltage for steady-state inactivation, less negative RMP, and shorter diastolic intervals in atria. Besides, it has more complex effects prompting the management of AF, including inhibition of $I_{Ca,L}$ and I_{to}, regulating the CaMKII signal pathway, suppressing the atrial substrate remodelling and anticholinergic action [173,180]. The Shensong Yangxin (SSYX) capsule is another traditional Chinese herbal medicine potentially a drug for AF. SSYX reduces AF susceptibility and prevents the progression of AF, *via* extending the atrial ERP and reducing the dispersion of the atrial ERP, partially through regulating the imbalance of autonomic nerve activity, reactive oxygen species production and the cholinergic anti-inflammatory pathway in various animal models including metabolic syndrome-induced AF mouse models, long-term intermittent pacing-induced AF mouse models and post-myocardial infarction HF mouse models [181–183].

A combination of atrial-selective inhibition of I_{Na} with potassium channel blockers may enhance the safety and efficacy of anti-AF drugs. Among the potential combinations are agents that atrial-selectively inhibit I_{Na} and I_{Kr}. Such a combination may cause synergistic atrial-predominant prolongation of ERP with little or no risk of ventricular arrhythmias [184]. Atrial selectivity of I_{Na} blockers essentially eliminates the risk of conduction-related ventricular arrhythmias, and concomitant inhibition of late I_{Na} reduces the risk of long-QT-mediated arrhythmias. A combined inhibition of I_{K1} and I_{Na} may enhance the efficiency of I_{Na} blockers to cardiovert AF and prevent its recurrence (particularly persistent AF) [185]. I_{K1} is augmented in persistent AF, bringing the atrial RMP to more negative voltages, and, therefore, reducing I_{Na} blocking efficiency of I_{Na} blockers. Restoration of atrial RMP with reduction of I_{K1} should augment the inhibition of the sodium channel by I_{Na} blockers, which, in turn, is expected to increase anti-AF efficiency of the blockers [185]. Owing to the well-known antiarrhythmic efficacy of amiodarone, multichannel blockade drugs are being developed, which are expected to have strong antiarrhythmic effect and broad cardiac safety and less extracardiac adverse effects. Budiodarone, an analogue of amiodarone, undergoes rapid metabolism by plasma and tissue esterases [186]. In preliminary randomized trials in patients with paroxysmal AF, budiodarone significantly reduces AF burden after 12 weeks of treatment compared with placebo [187]. In addition, vanoxerine developed as a drug for Parkinson's disease is shown to potently inhibit I_{Kr}, I_{Na} and $I_{Ca,L}$ [188]. In a multicentre, phase IIb trial, involving 104 patients with recent-onset AF, vanoxerine is statistically more effective in cardioverting AF compared with placebo, with better safety [189]. Inhibition of the RyR2 and CaMKII are among the preclinical experimental pharmacological anti-AF approaches [163,190]. Flecainide reduces the open probability of RyR2 *in vitro* via an open-state blocking mechanism and eliminates the formation of Ca^{2+}-dependent DADs. Hence, it prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans caused by RYR2 mutation [191,192]. Salvage *et al.* illustrate that flecainide rescues the atrial arrhythmogenic phenotype by increasing atrial wavelength and I_{Na} in a homozygous RYR2-P2328S mouse model [191,193,194]. Dantrolene, a clinical drug to treat malignant hyperthermia, has shown to stabilize cardiac RyR2 channels by improving the interaction between the channel N-terminal and central domains. Research has shown that dantrolene could suppress the susceptibility of AF in a left atrial myocardial infarction sheep model, a CaMKIIδ_C overexpressing mouse model and an electrically maintained AF dog model [156,195]. There are also a number of factors that have been associated with AF generation, including inflammation, oxidative stress and ANS [190]. Their feasibility as targets for pharmacological rhythm control management of AF is under investigation (moxonidine, MCC950, SP600125, nicotinamide riboside, 4-phenylbutyrate, ACY-1215) [84,196,197].

(c) Mechanism-based atrial fibrillation ablation

Catheter ablation has become an important treatment for rhythm control of AF. Haissaguerre and colleagues demonstrate that local elimination of PV triggers using radiofrequency energy is highly effective in terminating AF [198]. Pulmonary vein isolation (PVI) is currently the cornerstone for ablation of AF [11,199]. While this approach is often successful in cases of paroxysmal AF, it is less so in cases of persistent and long-standing persistent AF, in which recurrence of AF is high [200]. When AF persists, electrophysiological and structural changes predispose patients to development of non-PV triggers, by creating the substrate for sustained AF. Other regions participating in AF maintenance, often need to be ablated as well, including the posterior left atrial wall, the vein of Marshall, coronary sinus and the left atrial appendage [201–203]. Many of these regions are empirically targeted for ablation without underlying mechanistic insights. The lack of target specifity can result in an extensive area of ablation [204]. The widely accepted mechanism underlying AF is that it is maintained by high-frequency drivers establishing a spatial hierarchy gradient of progressively slowing activation rates as the wavefronts propagate centrifugally from the source. Numerous studies have

emerged focused on a mechanism-based approach for mapping drivers [205–209]. In a prospective, multicentre, single-arm study, Seitz and colleagues conclude that clusters of electrograms with spatial dispersion at a minimum of three adjacent bipoles is indicative of the presence of drivers. Compared with conventional ablation approach (PVI and stepwise), patients undergoing ablation of spatio-temporal dispersion areas, have a higher arrhythmia-free survival rate as well as shorter radiofrequency times [207]. A meta-analysis shows that AF driver ablation alone or added to PVI has a freedom from AF ratio of 3 : 1, freedom from all arrhythmias ratio of 1 : 8 and predicts a favourable outcome compared with controls [210]. However, the evidence comes mainly from uncontrolled and non-randomized studies, with substantial heterogeneity in reported outcomes. Further research is needed to confirm the results. Looking to the future, new technologies, including three-dimensional mapping, a combination of high-resolution ultrasound and optical mapping, as well as advanced signal processing algorithms, are expected to significantly advance the concept of mechanism-based ablation of AF.

7. Conclusion

AF is the most common cardiac arrhythmia with a complex genetic basis. Both rare variants and common SNPs are with increased predisposition of AF. The mechanisms underlying AF are not fully understood. The initiation and maintenance of AF involve both trigger and substrate, that are accentuated by electrical and structural remodelling of atrium. Inflammation, fibrosis and ANS dysfunction form a complex network participating in the pathogenesis of AF. Environmental factors, including alcohol, ageing, obesity, exercise, DM, OSA and cancer, can significantly increase the susceptibility to development of AF. Current pharmacologic and ablation approaches to therapy of AF are suboptimal, calling for innovative new safe and effective drugs as well as mechanism-based ablation leading to higher success rates and fewer recurrences.

Data accessibility. This article has no additional data.

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