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# Dynamics of Atrial Fibrillation Mechanisms and Comorbidities

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## Keywords

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## Abstract

Atrial fibrillation (AF) contributes to morbidity and mortality of millions of individuals. Its molecular, cellular, neurohumoral, and hemodynamic pathophysiological mechanisms are complex, and there is increasing awareness that a wide range of comorbidities can contribute to AF-promoting atrial remodeling. Moreover, recent research has highlighted that AF risk is not constant and that the temporal variation in concomitant conditions contributes to the complexity of AF dynamics. In this review, we provide an overview of fundamental AF mechanisms related to established and emerging comorbidities or risk factors and their role in the AF-promoting effects. We focus on the accumulating evidence for the relevance of temporally dynamic changes in these risk factors and the consequence for AF initiation and maintenance. Finally, we highlight the important implications for future research and clinical practice resulting from the dynamic interaction between AF risk factors and mechanisms.

## INTRODUCTION

Atrial fibrillation (AF) is a major global health burden and contributes to the mortality, morbidity, and reduced quality of life of millions of affected individuals (1). More than 20% of strokes and a twofold increase in cardiovascular morbidity and mortality are attributed to AF (2). In many cases, AF is a chronic disease starting with sporadic short-lasting episodes that spontaneously convert back to normal sinus rhythm (paroxysmal AF). However, continuous rhythm monitoring has shown that there is significant variability in the frequency, duration, and timing of paroxysmal AF episodes (3). The most common self-reported triggers in symptomatic AF patients are alcohol, caffeine, exercise, and lack of sleep, with vagal triggers tending to cluster together within individuals (4). Paroxysmal AF episodes become progressively longer and more stable, requiring electrical or pharmacological cardioversion to restore normal sinus rhythm (persistent AF). As AF progresses, attempts to restore and maintain normal sinus rhythm (rhythm-control therapy) become less successful, eventually resulting in therapy-resistant, permanent AF. However, AF progression is variable and can be low (5), with some patients even regressing (6) over time.

In most patients, AF is a manifestation of atrial remodeling [sometimes referred to as atrial cardiomyopathy (7)] produced by a wide range of comorbidities and risk factors, many of which can also be subclinical. Established AF-promoting risk factors include advancing age, heart failure (HF), hypertension, and valvular heart disease, notably mitral valve dysfunction (8). There is increasing awareness about male/female differences in AF mechanisms and management (9). In addition, obesity and metabolic syndrome, alcohol consumption, sleep apnea, and endurance exercise have emerged as potential risk factors for AF (8). Consistent with the growing list of AF risk factors, fewer and fewer patients can be considered to have lone AF (10). Indeed, previous work has shown that idiopathic AF patients develop cardiovascular disease more often, at a younger age, and with a more severe disease profile compared with healthy sinus rhythm-control patients, suggesting the presence of subclinical comorbidities (11). Similarly, in a recent retrospective study of young AF patients (mean age 46 years), only 11% of patients were free of AF risk factors or comorbidities, whereas 44% had hypertension and 25% had a family history of AF (12).

The prevalence of AF is expected to increase significantly in the upcoming years due to the ageing of the population and increased prevalence of risk factors. Current AF therapy remains suboptimal, not just because of suboptimal interventional and pharmacological treatment approaches, but also due to an incomplete understanding of the local atrial and systemic AF-promoting mechanisms resulting from different risk factors. Moreover, the presence of AF risk factors is generally only considered a binary variable even though AF risk factors (with the exception of the genetic component) are in fact highly dynamic, resulting in a temporally variable exposure of the organism to arrhythmogenic conditions that may contribute to the variability in the frequency, duration, and timing of paroxysmal AF episodes (3). Here, we provide an overview of AF mechanisms and their molecular basis, highlight the systemic regulators modulating these mechanisms, and summarize the AF-promoting mechanisms of different risk factors. We discuss the relevance of temporal variation in these risk factors for AF dynamics and its implications for AF research and management.

## OVERVIEW AND MOLECULAR BASIS OF ATRIAL FIBRILLATION MECHANISMS

### Conceptual Overview

The cellular and molecular mechanisms of AF have been described in detail in several recent reviews (13–16). Here, we provide a short summary of the major pathophysiological mechanisms underlying AF-promoting ectopic/triggered activity and reentry (**Figure 1**).

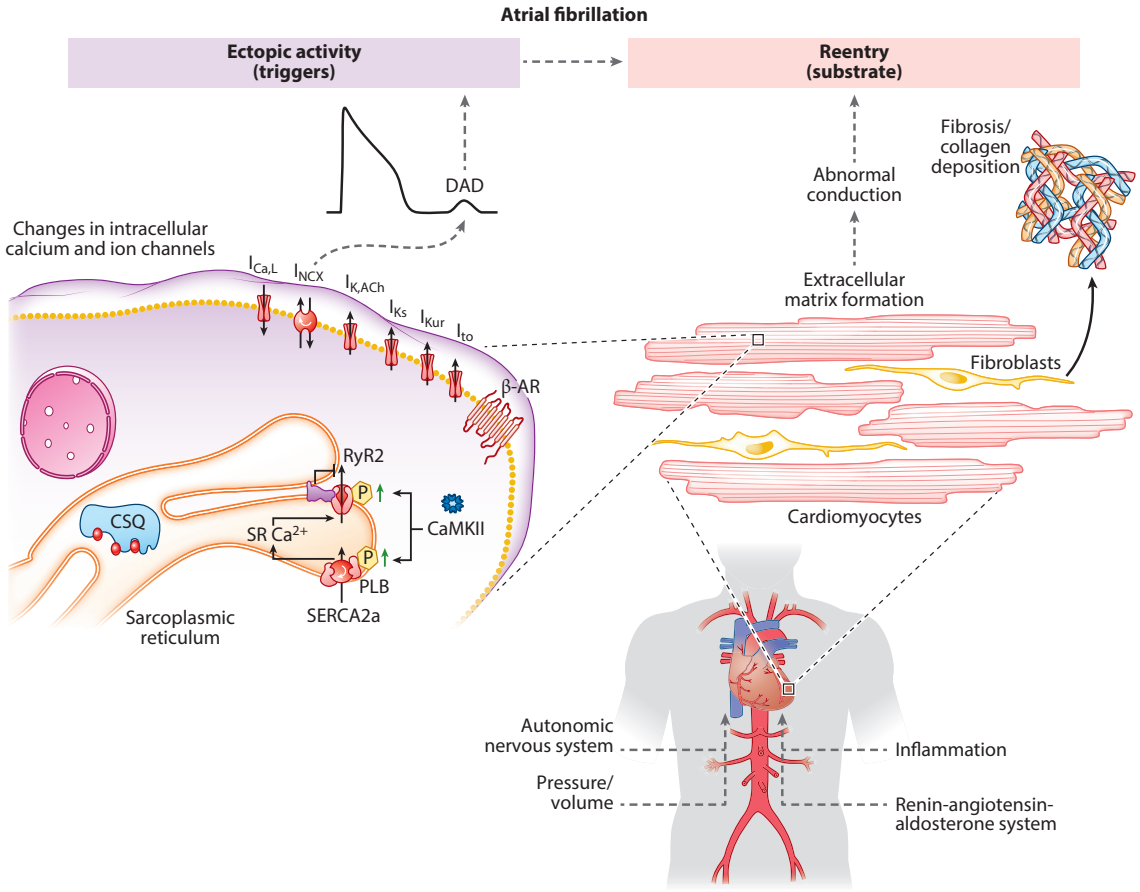



**Figure 1**

Major pathophysiological mechanisms underlying atrial fibrillation (AF)-promoting ectopic activity and reentry. Intracellular calcium changes in the sarcoplasmic reticulum (SR) occur due to phosphorylation [by calcium-/calmodulin-dependent protein kinase II (CaMKII)] of important calcium-handling proteins, such as the SR calcium-ATPase 2a (SERCA2a) and the ryanodine receptor (RyR2), which are regulated by numerous proteins, including calsequestrin (CSQ) and phospholamban (PLB). Together with mechanisms involving several ion currents, including the acetylcholine-activated inward-rectifier potassium current ($I_{K,ACh}$), the transient-outward potassium current ($I_{to}$), the ultrarapid delayed rectified potassium current ($I_{Kur}$), the slow delayed rectifier potassium current ($I_{Ks}$), the L-type calcium current ($I_{Ca,L}$), and the sodium-calcium-exchanger type 1 current ($I_{NCX}$), these intracellular calcium changes contribute to delayed afterdepolarizations (DADs), ectopic activity, and reentry. During stimulation of the autonomic nervous system (ANS), norepinephrine activates beta-adrenoceptors (beta-AR), which regulate several cellular mechanisms. Fibroblasts contribute to extracellular matrix formation by fibrosis and collagen deposition creating a substrate for reentry. Both mechanisms are modulated by ANS dysfunction, inflammation, pressure/volume changes, and activation of the renin/angiotensin/aldosterone system.

Ectopic/triggered activity refers to additional impulse formation outside of the sinoatrial node. Repeated ectopic/triggered activity occurring at high frequency, for example from the pulmonary vein sleeves, in combination with fibrillatory conduction can itself maintain AF. Ectopic activity can be due to abnormal automaticity and early or delayed afterdepolarizations (EADs and DADs, respectively). DADs are associated with calcium-handling abnormalities and are discussed in detail below. EADs are promoted by excessive prolongation of repolarization duration, providing time

for L-type calcium channels to recover from their initial inactivation and produce a secondary depolarization during the action potential (AP). Ectopic activity occurs when this depolarization is sufficiently strong to activate neighboring cardiomyocytes. Ectopic/triggered activity can result in unidirectional block and initiate reentry. Reentry is considered the predominant AF-maintaining mechanism and refers to the continuous self-excitation of cardiac tissue. Many forms of reentry have been described, including anatomical reentry around a fixed substrate and functional reentry, which can be stable or meander through the tissue. In general, most forms of reentry are promoted by a short and/or heterogeneous effective refractory period (ERP) (17) and slow, heterogeneous conduction. Progressive electrical and structural remodeling, partly due to AF itself, increases the complexity of electrical activity in more advanced forms of AF (18). Furthermore, recent work has highlighted the complex three-dimensional nature of reentry in AF, with epicardial fibrosis resulting in increased epi-/endocardial dissociation, epicardial breakthroughs, and AF complexity (19).

## Electrical Remodeling

Reentry-promoting ERP shortening is a hallmark of AF and is primarily determined by a reduction in the L-type calcium current ($I_{Ca,L}$) and an increase in potassium currents, including the basal inward-rectifier potassium current ($I_{K1}$), slow delayed rectifier potassium current ($I_{Ks}$), and two-pore domain potassium current ($I_{K2P}$) (13, 15, 20). Although electrical remodeling due to mutations in cardiac ion channels can promote the occurrence of AF, electrical remodeling is predominantly a consequence of AF. For example, electrical remodeling develops rapidly (within days) in animal models of rapid atrial pacing simulating the presence of AF and is reversible upon restoration of sinus rhythm (21, 22). In agreement, repolarization duration is unchanged in patients with paroxysmal AF who were in sinus rhythm at the time of atrial tissue collection (23), as well as in HF patients without a history of AF who are at an increased risk of developing AF (24). Shortened ERP in patients with (long-standing) persistent AF is reversible upon cardioversion (25).

## Structural and Gap-Junction Remodeling

Atrial structural remodeling is a major component of the vulnerable substrate for AF and is promoted by a wide range of signaling molecules (26). Atrial dilatation results in a larger substrate that can more easily maintain reentry. Moreover, atrial dilatation results in increased atrial stretch, which further promotes structural remodeling (26). Different types of fibrosis (replacement, interstitial, endomysial) are present in AF animal models and patients with AF (27). Replacement and endomysial fibrosis have been associated with reentry-promoting alterations in impulse conduction (27, 28). Fibrosis is due to proliferation and differentiation of cardiac fibroblasts into procollagen-secreting myofibroblasts in response to a wide range of stimuli. Finally, loss of electrical cell-to-cell coupling via gap junctions formed by connexin proteins can also produce reentry-promoting slow heterogeneous conduction (29). In agreement, mutations in *GJA5* (encoding connexin 40) that are associated with familial AF reduce gap-junctional coupling (30), although a role for connexin hemichannels has also been reported (31).

## Calcium-Handling Remodeling

During every heartbeat, calcium-influx through L-type calcium channels triggers a much larger release of calcium from the intracellular stores of the sarcoplasmic reticulum (SR) through type-2 ryanodine receptor (RyR2) channels, leading to a systolic calcium transient that initiates cardiomyocyte contraction. During diastole, calcium is transported back into the SR by the SR

calcium-ATPase (SERCA2a) and extruded from the cardiomyocyte by the sodium-calcium-exchanger type 1 (NCX1). For every calcium ion extruded by NCX1, three sodium ions enter the cell, resulting in a depolarizing inward current. Under pathological conditions, RyR2 may open in the absence of a trigger L-type calcium current, leading to spontaneous SR calcium-release events, which will also activate NCX1. If this occurs during diastole, the resulting transient inward current may depolarize the membrane potential, resulting in a DAD (32). Sufficiently large DADs may produce a voltage-dependent activation of the fast sodium current, resulting in triggered activity. An increased incidence of spontaneous SR calcium-release events and DADs has been documented in patients with paroxysmal (23) and long-standing persistent AF (24, 33, 34), although the relevance for atrial arrhythmogenesis in the latter group remains uncertain, and other studies have reported silencing of atrial cardiomyocyte calcium handling as a consequence of AF (35, 36). This suggests a role for additional modulating factors, including atrial rate and systemic regulators (discussed below) (37). Spontaneous SR calcium-release events are promoted by RyR2 dysfunction, e.g., due to abnormal posttranslational regulation, notably hyperphosphorylation by the calcium-/calmodulin-dependent protein kinase II (CaMKII) (34), or alterations in the RyR2 macromolecular complex. For example, a relative paucity of the stabilizing RyR2-interacting protein junctophilin-2 may contribute to RyR2 dysfunction in paroxysmal AF (38). Clinical evidence for a role of RyR2 dysfunction in AF comes from patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) due to RyR2 mutations, who also frequently develop atrial arrhythmias (39). Besides RyR2 dysfunction, spontaneous calcium-release events are promoted by SR calcium overload, e.g., due to increased activity of the SERCA2a in atria from HF patients (24).

## SYSTEMIC NEUROHUMORAL AND HEMODYNAMIC REGULATORS OF ATRIAL FIBRILLATION

Atrial cardiomyocyte electrophysiology, calcium handling, and atrial fibroblast function and downstream structural remodeling are tightly controlled by an interconnected set of neurohumoral systemic regulators, including the autonomic nervous system and the renin-angiotensin-aldosterone system (RAAS) (**Figure 1**). Additionally, hemodynamic changes involving atrial volume and/or pressure overload contribute to AF-promoting remodeling processes.

### Autonomic Nervous System

During sympathetic stimulation, postganglionic neurons release norepinephrine and activate beta-adrenoceptors (beta-ARs). The beta-adrenergic response is mediated via stimulatory G proteins, the activation of which leads to stimulation of adenylyl cyclases with subsequent protein kinase A (PKA)-mediated phosphorylation of the L-type calcium channel macromolecular complex via the inhibitory accessory protein Rad (increasing calcium influx), troponin I (enhancing myofilament relaxation), and phospholamban (disinhibiting SERCA2a and increasing SR calcium uptake) (40–42). RyR2 hyperphosphorylation during beta-AR stimulation promotes spontaneous SR calcium releases and related ectopic firing (39). Changes in ion channel activation during adrenergic stimulation also contribute to enhanced automaticity. Beta-AR stimulation inhibits the cardiac transient-outward potassium current ($I_{to}$) and increases the ultrarapid delayed rectified potassium current ($I_{Kur}$), $I_{Ks}$, and acetylcholine-activated inward-rectifier potassium current ($I_{K,ACh}$) (13). Macroscopically, the total atrial repolarization duration is either unaffected or slightly abbreviated (43).

Cholinergic muscarinergic receptors ($M_2$Rs) mediate parasympathetic control of cardiac function (41). Their stimulation has opposite effects to those of beta-AR stimulation. $M_2$R-stimulated

pertussis toxin-sensitive inhibitory G proteins ($G_i$) directly activate $I_{K,ACh}$ and inhibit $I_{Ca,L}$ by reducing cyclic adenosine monophosphate and PKA activity, leading to atrial ERP shortening. This ERP shortening is heterogeneous because of the spatial distribution of parasympathetic nerve endings and $M_2$Rs.

AF patients with structurally normal hearts primarily show a vagal AF pattern (nocturnal, postprandial, or postexercise AF), whereas patients with structural heart disease often have a sympathetic AF pattern, with AF occurring during daytime or exercise (40). Experimental and clinical studies have shown that AF onset typically requires combined sympatho-vagal activation rather than alterations in vagal or sympathetic drive alone (40, 44). In agreement, both $M_2$R and beta-AR agonists can each induce AF individually, but sequential combined sympathetic and vagal activation results in significantly increased AF inducibility (43, 44). Adrenergic, cholinergic, or combined sympatho-vagal activation can cause triggered activity-promoting EADs and DADs, contributing to the initiation of AF. However, in animal models cholinergic stimulation is primarily responsible for spontaneous AF initiation, with adrenergic tone modulating the initiation and maintenance of cholinergically mediated AF (44).

## Renin-Angiotensin-Aldosterone System

Binding of angiotensin II to angiotensin type 1 receptors leads to tyrosine phosphorylation of receptor tyrosine kinases, activating extracellular signal-regulated kinases (ERK1 and ERK2) and transcription factors, such as Elk-1 and c-fos, which are responsible for the effects on gene transcription of profibrotic pathways (27). Another tyrosine kinase that is activated by angiotensin II is Janus kinase 2 (JAK2). JAK2 initiates activation of transcription factors STAT1 and STAT3 (27). Importantly, proliferation of atrial fibroblasts was consistently more pronounced than that of ventricular fibroblasts when stimulated with a range of growth factors including angiotensin II (45). Some studies also suggest intracrine angiotensin II signaling contributing to G protein–coupled receptor signaling in the cardiac nuclear membrane (46, 47).

## Inflammation

Inflammation is essential to remove causes of cell injury and clear out damage, but it has increasingly been implicated in AF (48). Increased inflammatory markers in cardiac tissue or the systemic circulation have been associated with the onset and recurrence of AF in the general population. Although immune cells are critical mediators of systemic inflammation, inflammatory signaling through the NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) inflammasome has recently also been implicated in AF (49). Acute inflammation modulates cardiomyocyte calcium handling, thereby creating a trigger for inflammation-induced AF. In agreement, mice with constitutively active NLRP3 develop spontaneous atrial premature contractions (49). On the other hand, long-term exposure to mediators of the inflammatory response promotes reentry-promoting structural remodeling (48). Activation of the coagulation system, traditionally considered a consequence of AF, has pronounced proinflammatory effects in atrial myocardium (50), which may actually promote atrial fibrosis and AF (51).

## Volume/Pressure Changes

Atrial stretch produces electrophysiological changes via mechanoelectrical feedback that may promote AF initiation. At the same time, AF promotes atrial dilatation, thereby creating a positive feedback loop promoting AF perpetuation (52). While acute atrial stretch may result in transient

electrophysiological changes, pathophysiological conditions associated with chronic atrial stretch are characterized by atrial structural alterations (26, 52).

Acute stretch is associated with transient changes in conduction slowing and atrial refractoriness. Increased atrial pressure in the isolated rabbit heart produced a reversible increase in AF vulnerability that was closely correlated to shortening of the atrial ERP (53). Differences in atrial wall thickness result in a heterogeneous regional stretch distribution and may influence local conduction disturbances and atrial refractoriness (54). Additionally, stretching the atrium has been shown to activate the autonomic nervous system by afferents mainly carried by the vagal nerve (41). Despite long-standing evidence for a role of stretch in AF at the organ level, the underlying cellular and molecular mechanisms remain incompletely understood, particularly in humans. A wide range of inward and outward stretch-activated ion channels (SACs) can potentially modulate atrial repolarization and refractoriness (reviewed in 52), and recent work has implicated stretch-induced calcium-handling abnormalities (55). In a multiscale computational model of atrial electromechanics and mechanoelectrical feedback implementing atrial membrane behavior and atrial wall thickness heterogeneity, acute atrial stretch resulted in a heterogeneous activation of SACs that affected AF perpetuation (56).

Chronic atrial stretch promotes extracellular matrix formation and fibrosis, increased cardiomyocyte diameters, and disorganization of connexins. These effects disrupt side-to-side electrical connections between muscle bundles, producing local conduction abnormalities and increased AF susceptibility (13). At the molecular level, the development of atrial fibrosis due to pressure and/or volume overload is mediated by both angiotensin II–dependent and –independent mechanisms (57, 58).

## ATRIAL FIBRILLATION–PROMOTING MECHANISMS OF COMORBIDITIES AND RISK FACTORS

### Advancing Age

Advancing age is the strongest independent AF risk factor, but identifying AF-promoting mechanisms resulting from aging is challenging, as many comorbidities (coronary artery disease, diabetes, valve disease, and HF) become more prevalent and severe with advancing age. Nonetheless, progressive age-dependent structural remodeling, including atrial dilatation and fibrosis and its associated reductions in conduction velocity, is a consistent finding in both animal models (that lack confounding comorbidities) and patients (59, 60). Aging is also associated with gap-junction remodeling (59), which is in part due to activation of c-Jun N-terminal kinase (JNK) and may further contribute to the reentry-promoting substrate (61).

Several studies have investigated electrical remodeling associated with advancing age. Heterogeneous ERP prolongation is often reported, and the associated dispersion could contribute to reentry formation, although results are inconsistent (see overview in 60). The molecular basis for this heterogeneous ERP prolongation also remains incompletely understood. According to recent work, Kir2.1/Kir2.3 expression levels underlying $I_{K1}$ are age independent, but an age-dependent increase in miR-328 may contribute to an AF-promoting reduction in L-type calcium channel expression (62), although this cannot explain the ERP prolongation observed in other studies. On the other hand, calcium-handling abnormalities, e.g., via JNK-mediated CaMKII activation (63), are common in aged atria (64) and may provide an increasing incidence of triggers for AF initiation. Calcium-handling abnormalities may also be due to changes in cardiomyocyte ultrastructure, including age-dependent cellular hypertrophy (65), which has been associated with increased susceptibility to spontaneous calcium releases in rat atrial cardiomyocytes (66). In agreement, altered subcellular structure, including changes in RyR2 spacing, contributes to calcium-handling

abnormalities in computer modeling studies (67). Clinical data support a role for atrial ectopy in age-related AF risk, with older individuals having a greater burden of atrial premature beats (68).

Finally, age-dependent changes in systemic regulators may contribute. For example, the balance between sympathetic and parasympathetic regulation of cardiac electrophysiology changes with age (69), and a reduction in testosterone levels with aging has been implicated in AF (60). Similarly, blood inflammatory markers increase with age and contribute to cardiac remodeling, a concept referred to as inflammaging (70), which may contribute to age-dependent AF promotion (71). Aging is an inherently time-dependent AF risk factor, although its dynamics are slow and unidirectional. Accordingly, aging will be one of the main reasons for the increased prevalence of AF in the years to come (60).

## Heart Failure

AF and HF share common risk factors (e.g., hypertension) and promote each other. Atrial electrical remodeling in HF differs depending on species and type and duration of HF (72), with prolonged, shortened, and unaltered AP duration reported in atria of HF patients with reduced left ventricular (LV) ejection fraction (HFrEF) (24, 72). On the other hand, reentry-promoting atrial structural remodeling due to activation of systemic neurohumoral signaling, as well as increased atrial stretch resulting from increased hemodynamic load, is common in HF. For example, dogs with HF induced by rapid ventricular pacing have an increased ability to maintain AF and extensive atrial fibrosis on histological examination (73, 74). Similarly, HFrEF patients have increased right-atrial expression of profibrotic markers and larger collagen-1 protein levels (24). Calcium-handling abnormalities, including an increased incidence of spontaneous transient-inward currents, likely resulting from a combination of elevated SR calcium load and RyR2 dysfunction, have been reported in HF animal models and HFrEF patients (24, 75, 76). Finally, activation of systemic regulators, including the autonomic nervous system and RAAS, plays a major AF-promoting role. For example, direct nerve recordings from the stellate ganglia and vagal nerves demonstrated increased sympathetic and vagal nerve discharges before the onset of atrial arrhythmias in dogs with pacing-induced congestive HF (77).

AF is also strikingly common in HF with preserved LV ejection fraction (HFpEF), in part due to shared risk factors (78). The mechanisms of AF in the setting of HFpEF are less well characterized than in HFrEF, in part due to a relative paucity of (large) animal models. Recent work has identified structural remodeling (atrial enlargement and fibrosis) and associated conduction abnormalities in aged rats with HFpEF, as well as increased atrial inflammation (71). Hypertensive rats with metabolic syndrome that develop HFpEF also have atrial enlargement and contractile dysfunction, as well as increased SR calcium leak (79).

Thus, chronic HF promotes both AF-initiating triggers and a structural substrate for AF maintenance. Additionally, the fast and irregular ventricular heart rate during AF often leads to a tachycardiomyopathy, which often promotes the progression of HF (78). In agreement, rhythm control of AF patients with LV systolic dysfunction through catheter ablation is associated with improvements in ventricular function (80) and outcome (81). The dynamics of this potentially bidirectional interaction between AF and HF can be further modulated by temporal alterations in volume status (e.g., during periods of decompensation) and ventricular response rate (e.g., due to variations in autonomic regulation of atrioventricular conduction).

## Hypertension

AF-promoting remodeling due to chronic hypertension primarily involves structural remodeling, including atrial enlargement and fibrosis, as well as reduced connexin expression (82–84). In

addition, electrophysiological and calcium-handling changes have been reported (see 85 for an overview of hypertension-related atrial remodeling in animal models). Together, these mechanisms result in reentry-promoting conduction abnormalities and are associated with longer, more fractionated AF episodes (83, 85). Structural remodeling in chronic hypertension is in part mediated by activation of the RAAS due to increased atrial pressure (84, 86). On the other hand, AF inducibility was also increased after short-term (5 weeks) hypertension in sheep and was associated with atrial hypertrophy and inflammation (83). Thus, hypertension-associated atrial remodeling develops rapidly, with different reentry-promoting mechanisms involved over time.

## Valvular Heart Disease

Cardiac valve disease, for which mitral regurgitation is a paradigm with extensive experimental data, also promotes AF via structural remodeling (87, 88). Atrial stretch is likely a central profibrotic stimulus in valve disease (26, 27), although the distribution of fibrosis is highly heterogeneous (88). Electrical remodeling is also present in models of mitral valve regurgitation, although ERP prolongation is more common (87, 88) than ERP shortening (89), suggesting that structural remodeling is the primary reentry-promoting mechanism. Moreover, atrial dilatation due to AF itself can produce functional mitral valve dysfunction, indirectly promoting AF progression.

## (Cardiac) Surgery

Approximately one-third of patients undergoing cardiac surgery subsequently develop postoperative AF (90, 91). The time course of postoperative AF generally follows that of systemic inflammatory markers, peaking around day 2–3 post surgery, although late occurrences of postoperative AF are increasingly recognized (92). Animal models of sterile pericarditis, mimicking the postoperative inflammatory state, have increased AF inducibility (91). These data suggest a major role for an inflammation-induced vulnerable substrate promoting ectopy and reentry in AF following (cardiac) surgery. In agreement, meta-analyses suggest a protective effect of anti-inflammatory therapy with colchicine against postoperative AF (93) and early recurrences of AF after pulmonary vein isolation (94).

## Sex

There are significant sex differences in the prevalence, clinical presentation, patient profile, associated comorbidities, and therapy outcomes of AF (95, 96). Although AF is more common in men, with an age-adjusted incidence 1.5–2.0-fold that of women, the lifetime risk of AF is similar for both sexes owing to a longer life expectancy of women (97). Women are more often symptomatic, with a relative risk of asymptomatic AF of 0.57 compared to men and have worse quality of life (97). Women also have a consistently higher risk for stroke (hazard ratio between 1.1 and 2.0), and an increased risk of death associated with AF has been reported in some studies (e.g., a 1.9-fold versus 1.5-fold increase in the risk of death in women versus men in the Framingham Heart Study) (97).

Electrophysiological and structural properties of male and female atria may contribute to sex-related differences in AF (97). Expression of several potassium channel subunits (e.g., HERG, minK, Kir2.3, Kv1.4, KChIP2, SUR2, and Kir6.2), as well as connexin 43 and phospholamban, is lower in female compared to male ventricular samples (98). By contrast, women undergoing AV-nodal reentry tachycardia ablation have shorter atrial ERP than men (9). Atrial electrophysiology is strongly regulated by sex hormones, with estrogen prolonging action potential duration (9). Estrogen also increases the propensity for triggered activity by altered calcium handling. Autonomic nervous system activation can be impacted by the menstrual cycle. Low levels of estrogen

and elevated levels of progesterone increase catecholamine levels, and there is higher sympathetic activity in the luteal phase of the menstrual cycle. These hormonal changes during the menstrual cycles may contribute to a monthly variability in exposure and AF risk, which may be more pronounced in younger women than in older women. Similarly, in postmenopausal women an increased predominant sympathetic tone is associated with reduced estrogen levels. In agreement, AF incidence is low in premenopausal women but increases after menopause. A higher incidence of AF in patients undergoing antiestrogen treatment and a lower risk of AF with estrogen-based hormonal replacement therapy have also been suggested (9). Finally, the lack of female sex hormones in postmenopausal women is associated with changes in comorbidities, thereby indirectly impacting on AF risk. A summary of sex-related AF mechanisms is provided elsewhere (9).

## Obesity and Metabolic Syndrome

Increasing evidence indicates that obesity may contribute to the AF substrate through a number of pathways, including epicardial adipose tissue (EAT) biology, inflammatory pathways, structural cardiac remodeling, and atrial fibrosis (99–101). Genetic, epigenetic, and environmental factors may drive a shift toward a dysfunctional EAT, characterized by a proinflammatory and profibrotic phenotype. Owing to the close anatomic proximity to coronary arteries, a thicker and dysfunctional EAT actively contributes to regional atrial remodeling processes. Besides classical paracrine transmission EAT may directly release mediators into the vasa vasorum of the coronary arterial wall, a mechanism referred to as vasocrine. Additionally, infiltration of adipocytes into the atrial myocardium could also disorganize the depolarization wave front, favoring microreentry circuits and a local conduction block. In agreement, atrial epicardial mapping in patients undergoing cardiac surgery revealed a higher incidence of conduction disorders in obese compared to non-obese patients (102). While weight-loss management prevents or even reverses the type and natural progression of AF (6), weight fluctuations offset this benefit by reducing energy expenditure and increasing appetite, adipocytokines, and metabolic dysfunction, including increased body fat composition and reduced glucose tolerance (103).

## Alcohol Consumption

There is increasing awareness about the AF-promoting effects of alcohol consumption (104). Both the amount and duration of alcohol consumption influence AF risk. An ∼8% increase in risk with each 10 g per day alcohol intake (105) and a ∼20% decrease in incident AF for every decade abstinent from alcohol have been reported (106), but exact quantification of the impact of alcohol on AF is challenging. Alcohol has both short- and long-term AF-promoting effects. Chronic alcohol consumption promotes the development of a cardiomyopathy, including atrial hypertrophy and fibrosis, which provide a substrate for AF (104). Furthermore, it stimulates other AF-promoting risk factors such as hypertension and obesity. Acute binge alcohol exposure (holiday heart syndrome), often defined as >5 standard drinks or a blood-alcohol content of 0.8%, also has direct and indirect AF-promoting effects. Binge drinking promotes episodes of sleep disordered breathing and autonomic nervous system dysfunction. On the other hand, alcohol has complex direct effects on atrial electrophysiology and calcium handling, acutely affecting numerous ion channels in a dose-dependent manner. Owing to the complex interactions between these ion channel effects [e.g., involving both augmenting and inhibiting effects on $I_{K1}$ depending on the concentration (107)], it is challenging to predict the pro- or antiarrhythmic consequences of alcohol-induced electrophysiological alterations. Finally, recent work has identified ectopic activity-promoting calcium-handling abnormalities in response to acute alcohol exposure (108), in part via activation of JNK and its downstream effects on CaMKII (109).

## Sleep Apnea

Obstructive sleep apnea is characterized by repetitive obstructive respiratory events during sleep, which results in intermittent hypoxia and negative intrathoracic pressure swings due to ineffective inspiration against the obstructive upper airways (110). Intermittent hypoxia in rats, induced by repetitive interruptions of ventilation during daily intubation, shows atrial conduction abnormalities related to connexin dysregulation and increased atrial fibrosis after four weeks of simulated sleep apnea (111). In atrial myocardium of patients with sleep apnea, increased CaMKII-dependent phosphorylation of $Na_V1.5$ results in dysregulation of sodium currents with proarrhythmic activity that is independent from preexisting comorbidities (112). Chronic hypoxemia promotes remodeling by modulating the expression of hypoxia-inducible factors (HIF) 1 and 2, which act as key regulators in the adaptive response to hypoxia and regulate hypoxemia-induced endoplasmic reticulum stresses.

Chronic obstructive sleep apnea produces a vulnerable substrate for AF maintenance. In addition, acute transient arrhythmogenic changes depending on the severity of individual apnea may further contribute to AF development (113). In a pig model of obstructive sleep apnea, application of negative tracheal pressure during tracheal occlusion, but not apnea-associated changes in blood gases alone, reproducibly and reversibly shortened atrial ERP and enhanced AF inducibility (114). In rats, obstructive respiratory events resulted in acute left-atrial dilation and increased AF inducibility (111). The transition from hypercapnia back to normal blood gases, rather than longer hypoxic or hypercapnic episodes per se, resulted in increased atrial vulnerability in a sheep model with continuous ventilation under autonomic blockade. This effect was due to a differential recovery of atrial refractoriness and atrial conduction properties (115). Besides transient apnea-associated changes in conduction and atrial ERP, acute apneas may also increase trigger formation. During the arousal reaction at the end of an obstructive episode, pronounced sympathetic activation is accompanied by activation of the diving reflex, resulting in vagal activity and bradycardia (110). This sympatho-vagal activation promotes premature atrial contractions with the potential to initiate AF in a vulnerable substrate.

## Exercise

Emerging clinical evidence suggests that the undeniable benefit of physical activity and exercise, which have been shown to reduce cardiovascular disease incidence, morbidity, and mortality, may not hold for AF patients, particularly with greater and more intense lifetime training histories (116, 117). Ongoing endurance exercise training brings about a shift in autonomic balance, with a transition toward greater parasympathetic activation and blunted sympathetic tone (118, 119). Additionally, abrupt shifts in sympatho-vagal balance, as may be observed frequently at the start of exercise and during recovery, often precede the onset of AF. Furthermore, the large hemodynamic load during high-intensity exercise likely contributes to increases in atrial size (120). The changes in autonomic nervous system activation and the development of fibrosis with endurance exercise were elegantly demonstrated in a rat model of training, whereby 16 weeks of training resulted in a significant increase in atrial fibrosis (118). Increased fibrosis was associated with activation of profibrotic pathways, and expression of transforming growth factor-β, a known stimulant of collagen-producing cardiac myofibroblasts, and increased inflammation mediated by the inflammatory protein tumor necrosis factor-alpha (121). Intriguingly, during detraining AF inducibility was diminished, which was associated with a reversal of the increased vagal activation, but not with a full reversal of atrial fibrosis, suggesting a relevant role of autonomic nervous system activation for AF associated with intense exercise (118).

**Table 1 Overview of atrial fibrillation (AF) risk factors, their predominant AF-promoting mechanism, systemic regulators, and prominent dynamic components**

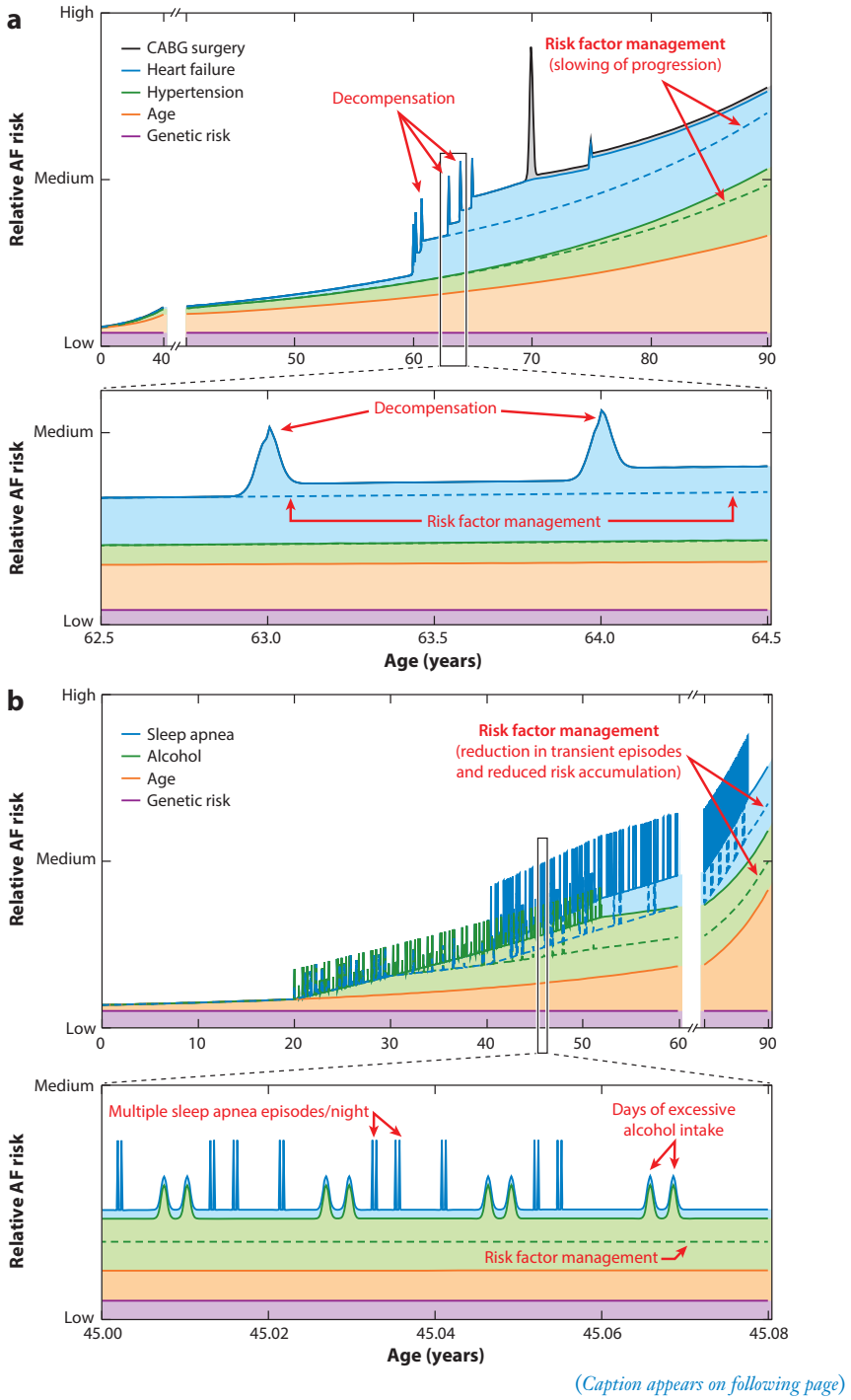
| Comorbidity/ risk factor | Predominant AF-promoting mechanism | Systemic regulators involved | Prominent dynamic component(s) (timescale) | References |
|---|---|---|---|---|
| Age | Structural remodeling | NA | Advancing age (years) | 60 |
| Alcohol | Structural remodeling (chronic)/ ERP changes + calcium-handling abnormalities (acute) | ANS, inflammation | Blood alcohol level changes (minutes to hours) | 104, 108, 109 |
| Exercise | Structural remodeling (chronic)/ ERP changes + calcium-handling abnormalities (acute) | ANS | Periods of exercise and recovery (minutes to hours) | 118, 121 |
| Heart failure | Structural remodeling + calcium-handling abnormalities | ANS, RAAS, hemodynamics | Volume changes during periods of decompen-sation (days), electrolyte changes, e.g., hypokalemia (hours to days) | 24, 57, 72–74, 76, 134 |
| Hypertension | Structural remodeling | RAAS, hemodynamics | Blood pressure variability (hours to days) | 85 |
| Metabolic syndrome | Structural remodeling | Inflammation | Fluctuations in body weight (weeks) | 99–101, 103 |
| Sex | Electrophysiological changes + calcium-handling abnormalities | ANS | Hormonal fluctuations (weeks and years) | 9 |
| Sleep apnea | Structural remodeling (chronic)/ ERP changes + calcium-handling abnormalities (acute) | ANS, hemodynamics | Variable occurrence and intensity of apneas (days) | 111, 112, 114, 115 |
| Surgery | Connexin remodeling + calcium-handling abnormalities | ANS, inflammation | Resolution of postoperative inflammation (days) | 90, 91 |
| Valve disease | Structural remodeling | Hemodynamics | NA | 87–89 |

Abbreviations: ANS, autonomic nervous system; ERP, effective refractory period; NA, not applicable; RAAS, renin-angiotensin-aldosterone system.

## STATIC VERSUS DYNAMIC SUBSTRATES

Different components of the AF-promoting substrate have distinct dynamics. For example, although structural remodeling is a common end point of most AF-promoting risk factors (**Table 1**), it develops and progresses slowly. This suggests that the variability in individual AF episodes (3) is due to fluctuations in triggers and/or components of the substrate that occur transiently and can be rapidly modified (e.g., posttranslational modifications of ion channels altering the electrical substrate due to autonomic nervous system activation). Furthermore, slow progressive structural remodeling due to advancing age and comorbidities likely contributes strongly to AF maintenance and progression.

Each AF risk factor has different dynamic components with distinct time courses, and their combination creates a strong temporal variability in AF risk. AF risk factors can primarily cause a progressive AF-promoting substrate (**Figure 2*a***), can transiently elevate AF risk, potentially with incomplete recovery resulting in an accumulation of AF risk in the presence of multiple transient events (**Figure 2*b***), or a combination of both. Advancing age is a prime example of a slow, progressive AF risk factor. Similarly, hypertension has a strong progressive component with limited transient variability. Indeed, although blood pressure can fluctuate significantly, no significant




(*Caption appears on following page*)

**Figure 2** (*Figure appears on preceding page*)

Temporal dynamics of atrial fibrillation (AF) risk factors. (*a*) Relative AF risk during a hypothetical individual's lifetime with fixed genetic (*purple*) and progressive risk factors: advancing age (*orange*), hypertension (*green*), and heart failure (HF, *blue*, e.g., in the setting of ischemia) and transient components caused by decompensation-induced increases in HF-related AF risk (shown on an expanded scale in panel *b*). Coronary artery bypass grafting (CABG) surgery (*gray area*) produces a transient inflammation-related increase in AF risk but slows the progression of HF-related risk. The effects of risk-factor management, resulting in slowing of HF- and hypertension-related progressive remodeling and reduced incidence of transient decompensation-related increases in AF risk, initiated at 62-years of age, are shown using dashed lines. (*b*) Similar to panel *a* for a hypothetical individual with major transient risk factors that produce a cumulative increase in AF risk from a young age: (excessive) alcohol intake multiple days a week (*green*) and sleep apnea multiple times a night vary throughout the month (*blue*). The bottom panel shows the transient increases within a month, leading to slow progressive structural remodeling and accumulation of AF risk over time.

link between visit-to-visit blood pressure variability and risk of new-onset AF was identified in a systematic review of 14 large randomized controlled trials (122). HF also has a strong progressive structural-remodeling component that has been characterized in animal models (57), but HF-related changes in hemodynamics and electrolytes can additionally create dynamic changes in AF risk (**Figure 2*a***). In particular, AF is common in the setting of acute decompensated HF, occurring in more than 30% of cases, can worsen pre-existing HF, and is associated with a worse outcome (123, 124). Similarly, hypokalemia resulting from diuretic therapy is common in HF patients and is associated with increased AF risk (125). Hypokalemia promotes triggered activity in atrial and pulmonary vein cardiomyocytes via DADs and EADs (126, 127), with the exact mechanism likely depending on subcellular structure (127), providing one potential mechanistic explanation for transient changes in AF risk in HF patients. For these progressive risk factors, risk factor management or upstream therapy targeting key remodeling processes has the potential to slow down progressive remodeling and reduce the incidence of events acutely increasing AF risk (e.g., reducing the likelihood of decompensation) (see dashed lines in **Figure 2*a***). However, clinical studies of upstream therapy in AF patients have thus far produced mixed results, potentially due to initiation too late in the disease process or due to a need for targeting multiple upstream pathways (12, 128).

Risk factors such as exercise, sleep apnea, surgery, and alcohol consumption have major transient AF-promoting components (**Figure 2*b***) that are due to the modulation of systemic regulators such as activation of the autonomic nervous system in the case of exercise (118), pressure changes in sleep apnea (110), or inflammation following cardiac surgery (90, 91). In addition, direct ion channel modulation may contribute in the case of binge alcohol intake (108). These transient effects are partially or fully reversible [e.g., following detraining (118)] and are modulated by variability in risk factor severity (129). For example, the VARIOSA-AF Study showed that there is considerable night-to-night variability in sleep apnea severity and that AF risk is associated with sleep apnea severity during the preceding night (113). Simultaneously, over time these risk factors promote slow progressive structural remodeling (111), which may outweigh transient increases in AF risk. For example, frequent alcohol intake is a more important risk factor for new-onset AF than binge drinking (130). Risk-factor management can reduce the incidence of transient events and their cumulative impact on progression of the AF-promoting substrate (see dashed lines in **Figure 2*b***).

Of note, AF risk is not just determined by risk factors with clinical manifestation but also by the variability of subclinical risk factors. For example, in AF patients without overt risk factors, the inter-visit variability of metabolic parameters showed a close association with the risk of AF (131). The interaction between temporally varying risk factors can be highly nonlinear, so that

the total AF risk is more than the sum of its parts. For example, rats with spontaneous hypertension and obesity show more pronounced structural remodeling and AF susceptibility than lean hypertensive rats, with selective upregulation of the profibrotic extracellular matrix protein osteopontin in hypertensive obese animals (82). Finally, when AF has been initiated, AF itself produces transient (reversible) electrical remodeling as well as progressive structural remodeling, further contributing to the complex dynamic changes in AF risk (15).

## IMPLICATIONS FOR FUTURE RESEARCH AND CLINICAL PRACTICE

The nonlinear combination of temporally variable risk factors underlying the dynamic AF risk has important implications for future preclinical and clinical research and clinical AF management. For example, it has become clear that most comorbidities and risk factors exert their AF-promoting effects via systemic regulators (**Figure 3**; **Table 1**). These systemic effects are not adequately incorporated in in vitro studies and thus underscore the need for animal models that allow multiscale, in vivo analyses of the AF-promoting effects of systemic regulators. In agreement, animal models have been instrumental in elucidating the AF-promoting effects of exercise and sleep apnea, which are largely mediated via systemic regulators (114, 118). At the same time, there are important interspecies differences in cardiac electrophysiology and calcium handling, as well as in the impact of different systemic regulators (132, 133). Similarly, current animal models focus on individual risk factors and cannot reproduce the complex nonlinear interactions between temporally variable risk factors developing over long periods of time in patients. Therefore, studies in human atrial samples will remain essential to study the consequences of clinically

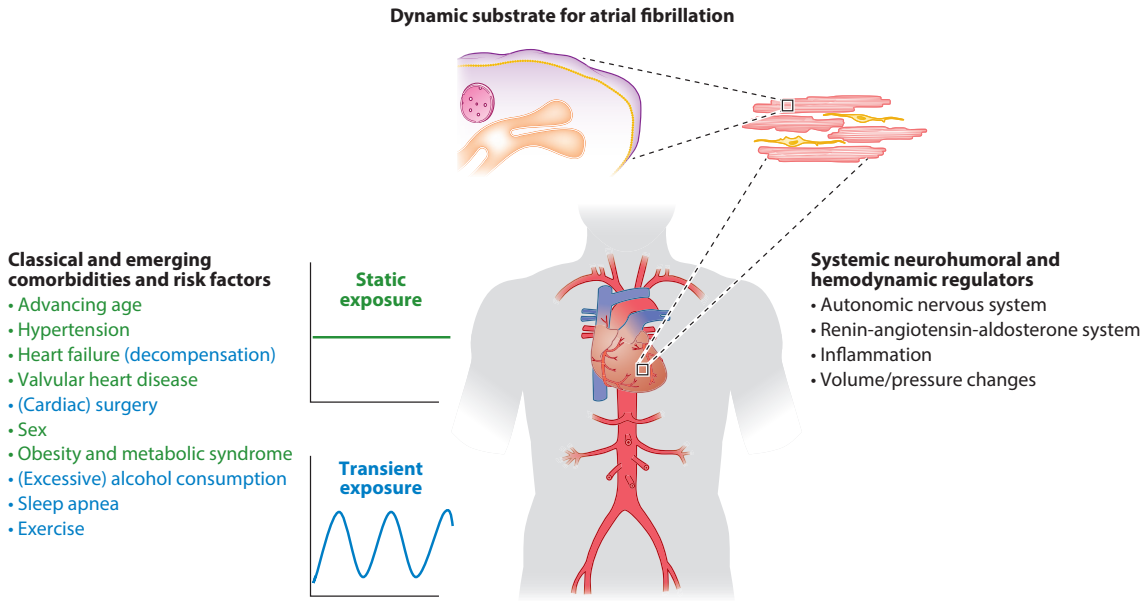



**Figure 3**

Dynamic substrate for atrial fibrillation (AF). Classical comorbidities and newly emerging risk factors are associated with static (*green*) and transient (*blue*) modulation of systemic neurohumoral and hemodynamic regulators of AF.

relevant disease-related remodeling in a human context. For example, recent work has identified the proarrhythmic molecular and cellular mechanisms contributing to AF in patients with heart failure (24, 134) or sleep apnea (112). However, human atrial samples are only available from patients undergoing cardiac surgery, which likely have a risk factor profile that is dominated by ischemic heart disease and/or valve disease and may not be representative for all AF patients. Furthermore, atrial samples are often restricted to right or left atrial appendages, which may undergo distinct remodeling from regions that are considered more relevant for AF maintenance (e.g., the pulmonary veins and left atrial free wall). Nonetheless, right atrial sources for AF are increasingly reported (135, 136). Most importantly, human atrial samples can only provide a single snapshot of the cumulative effects of all AF risk factors, ignoring their complex temporal dynamics. As such, a combination of animal models, human atrial samples, and noninvasive measurements in patients allowing longitudinal assessment of risk factors and AF mechanisms will be necessary.

A growing body of literature indicates that risk factor management can reduce AF burden and improve outcomes of rhythm-control therapy in AF patients (6, 137). However, in current clinical practice, established risk factors are assessed in a structured way only when patients present for the first time in the AF clinic. Because several AF risk factors may show a high day-to-day variability (e.g., sleep apnea) or may only occur during specific conditions (e.g., exercise-induced hypertension), clinically relevant risk factors will be missed if only one assessment is performed or the evaluation is only undertaken under resting conditions.

Recent technological advances have significantly expanded the options for noninvasive, longitudinal assessment of AF and potential underlying risk factors. Implantable loop recorders and a variety of wearables have enabled longitudinal or (near) continuous AF monitoring (138), making it possible to directly link specific clinical conditions to the occurrence of AF. Furthermore, longitudinal risk factor monitoring is becoming increasingly feasible. For example, some pacemakers can perform continuous monitoring of sleep disordered breathing (113), heart rate variability, and skin sympathetic nerve activity, which can serve as noninvasive indicators of autonomic nervous system activity (139), and implantable pulmonary arterial pressure monitors provide hemodynamic information that is used in remote monitoring of HF patients (140). Finally, some blood-based biomarkers have been associated with AF (141). Repeated biomarker collection could potentially provide information about progressive atrial remodeling, although at present there are no biomarkers that specifically reflect individual AF mechanisms.

In summary, the molecular and cellular mechanisms of AF promoted by individual risk factors, together with their systemic regulation by the autonomic nervous system, RAAS, inflammation, and hemodynamic changes, are increasingly well characterized (**Table 1**). Progressive structural remodeling is a central AF-promoting mechanism but cannot explain the complex dynamics of individual AF episodes. Although it has become clear that risk factors exhibit strong temporal variability and complex nonlinear interactions, the impact of these properties on AF mechanisms remains largely unknown. This justifies a more structured and, importantly, longitudinal risk factor assessment to capture the dynamic nature of AF risk factors and subsequent AF risk (142).

## SUMMARY POINTS

1. Atrial fibrillation (AF) is a common clinical problem and is promoted by a wide range of risk factors and comorbidities.

2. Systemic regulation by the autonomic nervous system, renin-angiotensin-aldosterone system, inflammation, and hemodynamic changes are important mediators of increased AF risk induced by risk factors and comorbidities.
3. Progressive structural remodeling is a central AF-promoting mechanism but cannot explain the complex dynamics of individual AF episodes.
4. Risk factors exhibit strong temporal variability and complex nonlinear interactions, contributing to both a progressive AF-promoting substrate and transient changes in AF risk.

## DISCLOSURE STATEMENT

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