TẠP CHÍ KHOA HỌC
TRƯỜNG ĐẠI HỌC TÂN TẠO

TAN TAO UNIVERSITY
From knowledge to the stars

BIOMEDICAL SCIENCE

Atrial Fibrillation: Clinical Update and Review, Paradigm Shift of Rhythm Control

Ngoc Quang Anh Nguyen*,[1], Truong Thanh Phuong Ha[1], Sanad Ahmad[1], Thi Anh Thao Chu[1] and Thach Nguyen[1,2]

[1]Cardiovascular Research, Methodist Hospital, Merrillville, Indiana, USA
[2]Tan Tao University, School of Medicine, Tay Ninh Province, Vietnam

*Corresponding author:
Ngoc Quang Anh Nguyen - Cardiovascular Research, Methodist Hospital, Merrillville, Indiana, USA.
Email: nnqa97@gmail.com

Received: 05/04/2026. **Revised:** 26/04/2026. **Accepted:** 07/05/2026. **DOI:** 10.53901/tjs.2026.v01.issue02.art03

Abstract

Background: Atrial fibrillation is a worldwide burden to clinical healthcare, characterized by loss of normal sinus node pacemaker activity due to rapid electrical impulses from multiple atrial foci, resulting in ineffective atrial contraction and impaired blood pumping. Although no single etiology exists, atrial fibrillation is associated with cardiovascular risk factors such as hypertension and diabetes mellitus. atrial fibrillation increases the risk of stroke, myocardial infarction, heart failure and mortality. This review discusses the definition, classification, pathophysiology, diagnosis, and contemporary management strategies.

Main: Atrial fibrillation is commonly classified according European Society of Cardiology to its temporal pattern into first-diagnosed, paroxysmal, persistent, long-standing persistent, and permanent atrial fibrillation. The American Heart Association further recognizes its progression through stages ranging from at-risk and pre- atrial fibrillation states to permanent atrial fibrillation. The American Heart Association's framework and European Society of Cardiology pathway share a unified principle of management: optimizing cardiovascular risk factors, preventing stroke, and controlling symptoms. Both emphasize integrated care, where comorbidity management and anticoagulation underpin therapy, while symptom control is tailored to individual patient needs.

Finding: Emerging evidence supports catheter ablation in newly diagnosed atrial fibrillation, including patients with mild heart failure, due to improved long-term cardiovascular outcomes and reduced hospitalizations. AP30663, a novel atrial-selective KCa2 inhibitor, has shown promising antiarrhythmic effects in preclinical studies and was conducted in phase II evaluation. Lifestyle and risk-factor modification, including weight reduction, exercise, smoking cessation, alcohol moderation, and control of hypertension and diabetes, are essential in slowing atrial fibrillation's progression.

Conclusion: Contemporary management increasingly emphasizes early rhythm control, particularly catheter ablation, while novel agents such as AP30663 show promising potential. Long-term management also depends heavily on lifestyle and cardiovascular risk-factor modification.

Keywords: Atrial fibrillation; Rhythm control; Rate control; Catheter ablation; Cardiovascular risk factors; Anticoagulation; AP30663.

Introduction

Atrial fibrillation (AF) represents the most frequently encountered sustained cardiac arrhythmia worldwide, with its global prevalence and healthcare burden increasing substantially over recent decades. An estimated 52.55 million individuals worldwide were affected by atrial fibrillation and atrial flutter (AFL) in 2021, representing a 137% increase compared with 19901. Similarly, data from the Framingham Heart Study demonstrated a nearly threefold increase in AF prevalence over the past 50 years [1, 2]. Aging populations, improved survival from cardiovascular diseases, and the increasing prevalence of hypertension, obesity, diabetes mellitus, and heart failure are believed to contribute substantially to this growing epidemic.

Clinically, AF carries significant consequences due to its strong association with major adverse cardiovascular events, particularly ischemic stroke, heart failure, myocardial infarction, systemic thromboembolism, and increased mortality. Although substantial advances have been made in rhythm control strategies, catheter ablation, anticoagulation, and risk-factor modification, AF management continues to evolve alongside a deeper understanding of atrial remodeling and disease progression. This review discusses the current understanding of AF classification, pathophysiology, risk factors, diagnostic approaches, and emerging management strategies in contemporary clinical practice.

Definition and Classification, Stages

Atrial fibrillation (AF) is defined as a supraventricular arrhythmia characterized by uncoordinated atrial activation, which results in the loss of effective atrial contraction4,5. The European Society of Cardiology continues to classify AF according to the duration and termination pattern of observed episodes. This temporal classification includes first-diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF, and remains widely used in both clinical practice and major therapeutic trials [3]. The American Heart Association introduced a stage-based classification framework. This model conceptualizes AF as a continuum ranging from individuals at risk of developing AF (Stage 1), to pre-AF states characterized by structural, electrical, or comorbid predisposition (Stage 2), followed by established AF with varying temporal patterns and treatment responses (Stage 3), and finally permanent AF (Stage 4) [4].

Table 1: European Society of Cardiology Temporal Classification of Atrial Fibrillation [3].

Classification	Definition
First-diagnosed AF	AF that has not been previously diagnosed, regardless of symptoms or duration
Paroxysmal AF	AF that terminates spontaneously or with intervention within 7 days
Persistent AF	AF lasting longer than 7 days without spontaneous termination
Long-standing persistent AF	Continuous AF lasting $\geq$ 12 months where rhythm control remains a therapeutic option
Permanent AF	AF in which both patient and physician decide to no longer pursue restoration of sinus rhythm

Table 2: American Heart Association Stage-Based Classification of Atrial Fibrillation [4].

Stage	Definition / Key Features
Stage 1: At Risk for AF	Presence of AF risk factors such as advanced age, male sex, genetic predisposition, obesity, hypertension, diabetes mellitus, obstructive sleep apnea, alcohol use, and physical inactivity
Stage 2: Pre-AF	Presence of structural, electrical, or clinical conditions predisposing to AF, including atrial enlargement, atrial ectopy, atrial flutter, heart failure, coronary artery disease, hypertrophic cardiomyopathy, thyroid disease, or neuromuscular disorders
Stage 3a: Paroxysmal AF	AF episodes resolving within 7 days spontaneously or following intervention
Stage 3b: Persistent AF	Continuous AF lasting $>$ 7 days
Stage 3c: Long-standing Persistent AF	Continuous AF lasting $>$ 1 year
Stage 3d: Successful AF Ablation	AF successfully controlled following catheter-based or surgical ablation
Stage 4: Permanent AF	AF where attempts to restore or maintain sinus rhythm are no longer pursued unless reconsidered jointly by patient and physician

Etiologies

AF is a multifactorial arrhythmia arising from the interaction of structural heart diseases, conduction abnormalities, systemic conditions, and genetic predisposition. The underlying etiologies can be broadly categorized into cardiac and non-cardiac causes.

Pathogenesis

The development of AF is a highly complex, multipathway co-operative process. The initiation and maintenance of AF involve dynamic interactions among electrical, structural, autonomic, inflammatory, and genetic mechanisms.

Electrical remodeling

The SCN5A-H558R loss-of-function mutation has been associated with reduced sodium current density, shortened refractory periods, and delayed atrial conduction velocity, all of which contribute to the initiation of AF [5]. L-type calcium channels are responsible for the prolonged effective refractory period in cardiomyocytes compared with skeletal muscle and neuronal cells. In patients with AF, increased expression of miR-155 in atrial cardiomyocytes may reduce the density of L-type calcium channels, thereby shortening the effective refractory period [6]. In addition, two-pore-domain K+ channels, which are predominantly expressed in the atria, play an important role in regulating atrial action potential duration. Upregulation of these channels has been associated with the development of AF [7]. Fibroblasts play a major role in the development of atrial fibrosis, which is a central pathophysiologic mechanism of AF. Transient receptor potential (TRP) channels found on the surface of fibroblasts are permeable to a wide range of cations, including Na+, Ca2+, and Mg2+, thereby contributing to intracellular cation homeostasis [8]. Increased expression of TRPM7 [9] and TRPC3 [10] has been demonstrated in patients with AF and may contribute to fibroblast Ca2+ overload, promoting fibroblast proliferation and atrial remodeling.

Structural heart disease

Congenital heart disease (CHD) contributes to the development of AF through chronic atrial volume overload, cyanosis, and hemodynamic stress, all of which promote atrial fibrosis and electrical remodeling. Patients with CHD commonly exhibit

prolonged atrial conduction times, atrial enlargement, and extensive scarring, creating a substrate for both focal and reentrant arrhythmias [11].

Several mechanisms have been proposed to explain AF-associated cardiomyopathy. In hypertrophic cardiomyopathy (HCM), which is caused by various genetic mutations, altered atrial loading conditions and myocardial fibrosis are the most likely contributors [12]. Furthermore, the CAMERA-MRI [13] (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction) trial and CASTLE-AF [14] (Catheter Ablation versus Standard conventional Treatment inpatients with Left ventricular dysfunction and Atrial Fibrillation) trial demonstrated that restoration of sinus rhythm in patients with AF significantly improved cardiac function, highlighting the bidirectional relationship between AF and cardiomyopathy.

Valvular heart disease, particularly involving mitral and tricuspid valve dysfunction, is also a well-recognized contributor to AF. Rheumatic mitral stenosis, mitral regurgitation, and tricuspid regurgitation are among the strongest valvular risk factors associated with the development of AF [15].

Autonomic nervous system

The autonomic nervous system plays an important role in the pathogenesis of AF. Studies have demonstrated that autonomic nerve fibers are unevenly distributed throughout the left atrium, with the posterior left atrial wall containing the largest nerve bundles and a predominance of parasympathetic fibers [16, 17]. In canine models of chronic AF induced by rapid atrial stimulation, increased nerve bundle volume, enhanced sympathetic and parasympathetic innervation, and heterogeneous parasympathetic distribution were observed, all of which may increase susceptibility to AF [16, 18, 19]. Furthermore, human studies have shown increased atrial autonomic nerve fiber density and elevated expression of muscarinic receptors in patients with permanent AF, suggesting that autonomic imbalance contributes to atrial electrical remodeling and arrhythmogenesis [20].

Inflammation

Inflammation plays a critical role in the initiation and progression of AF through activation of multiple inflammatory signaling pathways. The NLRP3 inflammasome has been identified as an important mediator of AF pathogenesis, promoting the release of proinflammatory cytokines such as IL-1β and IL-18, which contribute to atrial fibrosis and tissue remodeling [21, 22]. Obesity-related activation of the NLRP3 inflammasome and increased epicardial adipose tissue have been associated with a higher risk of AF through enhanced inflammation and fibrosis [22–24]. Patients with AF exhibit elevated levels of inflammatory biomarkers, including hs-CRP, IL-6, and TNF-α, which are linked to calcium dysregulation, atrial remodeling, thrombus formation, and adverse cardiovascular outcomes [25–30]. Furthermore, inflammation and AF appear to have a bidirectional relationship, as AF itself can further amplify inflammatory responses, particularly within the left atrium [30].

Genetics

Genetic factors play a significant role in the pathogenesis of AF, with genome-wide association studies identifying multiple susceptibility loci, particularly near the PITX2 gene on chromosome 4q25 [31]. Altered PITX2 expression has been linked to atrial electrical remodeling, impaired mitochondrial function, and increased AF susceptibility [32, 33]. Several additional genes involved in ion channel regulation, cardiomyocyte structure, and electrophysiology—including SCN5A, TTN, TBX5, SYNPO2L, KLF15, and TNNT2 - have also been associated with AF development and arrhythmogenesis [34–42]. Upregulation of NCX1 through FKBP5 deficiency may further promote delayed afterdepolarizations and AF triggering. Overall, both common and rare genetic variants contribute to the heterogeneous and multifactorial nature of AF, highlighting the potential role of genomics in individualized risk assessment and targeted therapy.

Clinical Presentations

The clinical presentation of AF is highly variable, ranging from asymptomatic disease to severe hemodynamic instability and thromboembolic complications. Symptom severity depends on ventricular rate, duration of arrhythmia, underlying cardiac disease, and individual patient characteristics.

Typical symptoms

Palpitations are the most commonly reported symptom and are typically described as a rapid or irregular heartbeat. Other frequent symptoms include dyspnea, fatigue, poor effort tolerance, dizziness, chest tightness, and generalized weakness. Syncope is less common but may occur in patients with rapid ventricular response, underlying structural heart disease, or concomitant conduction abnormalities [43].

Rapid and irregular ventricular response reduces diastolic filling time and impairs cardiac output, contributing to symptoms, such as dyspnea or exercise intolerance. Furthermore, patients with severe irregular ventricular response may present with symptomatic hypotension, acute heart failure, and pulmonary edema. In addition, the loss of coordinated atrial contraction (“atrial kick”) may significantly decrease ventricular filling, thereby reducing cardiac output, eventually leading to myocardial ischemia and cardiogenic shock [43].

Patients with long-standing and poorly controlled AF are at increased risk of cognitive impairment,

including embolic stroke, vascular dementia, and depressive symptoms. Epidemiologically, AF accounts for 20-30% of all ischemic strokes, and 10% of cryptogenic strokes [43]. Neuroimaging studies using magnetic resonance imaging (MRI) have demonstrated more than a twofold increase in the odds of silent cerebral ischemia in patients with AF compared with individuals in sinus rhythm [44–46].

Asymptomatic AF

A large proportion of patients with AF remain asymptomatic, with the arrhythmia often detected incidentally during routine electrocardiography or ambulatory monitoring. In fact, AF is classified as symptomatic based on whether patients are aware of palpitations during episodes and whether they experience symptomatic improvement in sinus rhythm [47]. However, this approach underestimates the broader clinical impact of AF, including its association with stroke, dementia, valvular regurgitation, ventricular dysfunction, and heart failure. Importantly, asymptomatic AF has been independently associated with an increased risk of stroke and mortality compared with symptomatic AF [48–50].

Therefore, the true clinical burden of AF in apparently asymptomatic patients requires a more comprehensive assessment beyond symptom reporting alone. The Active Monitoring for Atrial Fibrillation (AMALFI) randomized clinical trial demonstrated that remote, long-term (14-day) mail-based ECG patch screening in older patients at moderate to high risk of stroke led to a modest increase in AF detection at 2.5 years [51]. This finding supports the potential value of AF screening in improving long-term detection rates and potentially increasing appropriate anticoagulation use compared with usual care.

Quality-of-life effects

AF has a substantial impact on quality of life (QoL), often independent of ventricular rate or overall arrhythmia burden. A substantial proportion of patients with AF report impaired QoL and reduced exercise tolerance, with worse outcomes observed in women, younger individuals, and patients with significant comorbidities [52–56]. The unpredictable nature of AF episodes may contribute to psychological distress, including anxiety, depression, and reduced social and occupational functioning. In addition, recurrent hospitalizations, adverse effects of antiarrhythmic or anticoagulant therapies, and fear of stroke or sudden clinical deterioration further exacerbate impairment in overall well-being [43]. These multidimensional effects highlight AF as not only a rhythm disorder but also a chronic condition with significant psychosocial and functional consequences.

Diagnostic Criteria

Screening patients with risk factors provides a better strategy in diagnosing. According to AHA's guideline, the two major predictive models are CHARGE-AF (**Table** 3), developed predominantly in populations of European descent, and the C2HEST score (**Table** 4), which has shown particular applicability in Asian populations; both have demonstrated favorable performance in predicting incident AF. The ESC provides a Class I recommendation to use the modified EHRA (mEHRA) (**Table** 5) scale to quantify symptoms. Both guidelines recommend a similar initial evaluation for newly diagnosed AF, including ECG confirmation with absent distinct P waves, irregularly irregular RR intervals, and an episode duration $\geq$ 30 seconds. A targeted history and physical examination are advised to identify potential triggers and comorbidities. Recommended laboratory investigations include renal and liver function, electrolytes, full blood count, thyroid function, and glycemic assessment. Transthoracic echocardiography is a Class I recommendation in both guidelines to assess cardiac structure, chamber size, and LVEF for therapeutic guidance.

Table 3: CHARGE-AF: Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation. (Copyright: ACC/AHA/ACCP/HRS 2023 Guideline for the Diagnosis and Management of Atrial Fibrillation) [4].

Variable (X)	Estimated β Coefficient (SE)	HR (95% CI)
Age (per 5-y increment)	0.508 (0.022)	1.66 (1.59–1.74)
White race	0.465 (0.093)	1.59 (1.33–1.91)
Height (per 10-cm increment)	0.248 (0.036)	1.28 (1.19–1.38)
Weight (per 15-kg increment)	0.115 (0.033)	1.12 (1.05–1.20)
Systolic BP (per 20-mm Hg increment)	0.197 (0.033)	1.22 (1.14–1.30)
Diastolic BP (per 10-mm Hg increment)	−0.101 (0.032)	0.90 (0.85–0.96)
Smoking (current versus former/never)	0.359 (0.063)	1.42 (1.25–1.60)
Diabetes (yes)	0.237 (0.073)	1.27 (1.64–2.48)
Myocardial infarction (yes)	0.496 (0.089)	1.64 (1.38–1.96)

Table 3 does not encompass all complications.

$\star$ Five-year risk is given by: $1 - 0.9718412736^{\exp(\Sigma\beta X - 12.4411305)}$, where β is the regression coefficient (column 2) and X is the level of each variable risk factor.

AF indicates atrial fibrillation; BP, blood pressure; CHARGE-AF, Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation; HR, hazard ratio; and SE, standard error.

Management

The American Heart Association and European Society of Cardiology use different classification and management frameworks, but both share the same core principles of AF care. Lifestyle and cardiovascular

Table 4: C_2HEST score (Copyright: ACC/AHA/ACCP/HRS 2023 Guideline for the Diagnosis and Management of Atrial Fibrillation) [4].

Acronym	Risk Factor	Points
C_2	CAD/COPD	1–2
H	Hypertension	1
E	Elderly (age $\geq$ 75 y)	2
S	Systolic heart failure	2
T	Thyroid disease (hyperthyroidism)	1

⋆ Total points 0–8. For the C_2HEST score, the C statistic was 0.749, with 95% CI of 0.729–0.769. The incident rate of AF increased significantly with higher C_2HEST scores.

AF indicates atrial fibrillation; CAD, coronary artery disease; C_2HEST, coronary artery disease or chronic obstructive pulmonary disease [1 point each]; hypertension [1 point]; elderly [age $\geq$ 75 y, 2 points]; systolic HF [2 points]; thyroid disease [hyperthyroidism, 1 point]; and COPD, chronic obstructive pulmonary disease.

Table 5: Modified European Heart Rhythm Association (mEHRA). (Copyright: 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) | European Heart Journal | Oxford Academic) [3].

Score	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

AF, atrial fibrillation. © ESC 2024

risk-factor modification are recognized as foundational therapy, while stroke prevention with anticoagulation remains a major priority. Both guidelines also emphasize shared decision-making and multidisciplinary care. The AHA uses the HEAD2TOES and SOS models, whereas the ESC adopts the AF-CARE pathway, yet both ultimately focus on optimizing comorbidities, preventing stroke, and reducing symptoms.

Optimize cardio-vascular risk factors

Consistent with both guidelines, cardiovascular risk-factor modification remains a cornerstone of AF management. Among numerous contributing factors, several have significant impact on long-term patient outcomes. In this context, the American Heart Association (AHA) HEAD2TOES framework provides a practical approach for systematic identification and optimization of major modifiable risk factors [4].

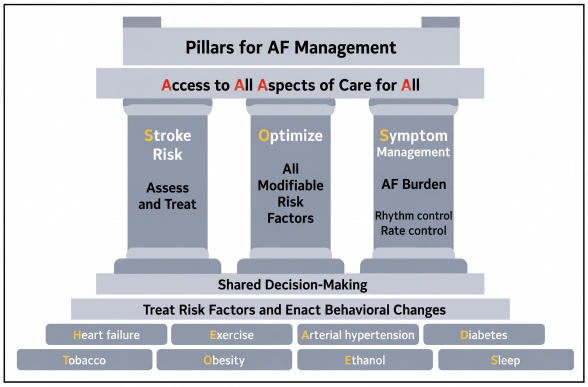

Figure 1: Pillars of AF Management: AF indicate Atrial fibrillation. Illustration from [4].

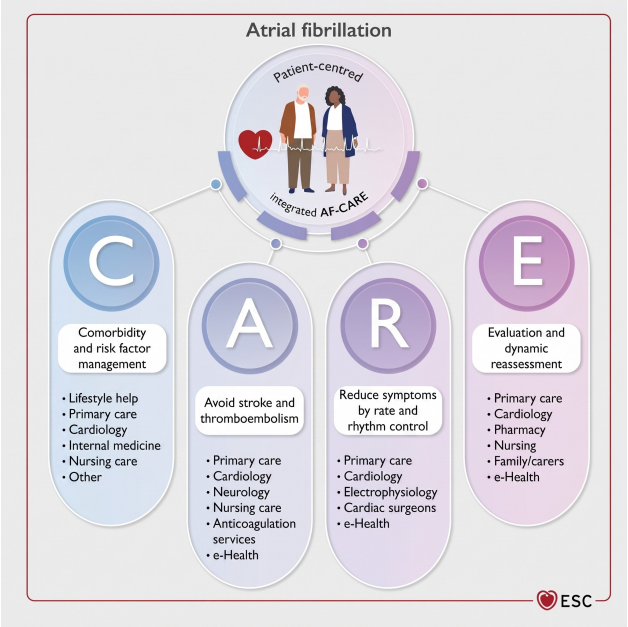

Figure 2: Multidisciplinary approach to AF management. Principal caregivers are involved in the community and hospital settings to provide optimal, patient-centred care for patients living with AF. AF-CARE, atrial fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment. Illustration from [3].

Heart failure

Heart failure is a key determinate prognosis for patients with AF, and HF is the most common cause of death for patients presenting with clinical AF. More than one-third of patients with HFpEF and no AF at baseline develop incident AF during follow-up [3, 4]. LA compliance and mechanics progressively decline with increasing AF burden in HFpEF, increasing risk for new onset AF and progressive AF [57]. SGLT2 inhibitors are recommended in patients with AF and HF to reduce HF hospitalization and cardiovascular mortality [58, 59]. For patients with HFrEF (LVEF $\leq$ 40%) ESC recommends Guideline-Directed Medical Therapy (GDMT), including ACE inhibitors/ARBs or ARNI (sacubitril-valsartan) and mineralocorticoid receptor antagonists (MRAs) [3]. In contrast, AHA

favors a more aggressive approach in rhythm control because of its greater benefit and improvement of quality of life for these patients (39). Although Sacubitril-valsartan has shown greater benefit than ACE inhibitors or ARBs in patients with symptomatic HFrEF (generally EF < 50%), there was no reduction in new-onset of AF following PARADIGM-HF trial [60]. Mineralocorticoid receptor antagonists reduce mortality regardless of AF status and decrease the risk of incident AF in HFrEF [61]. In patients with HFpEF (LVEF $\geq$ 50%) and AF, the ESC emphasizes the benefits of SGLT2 inhibitors, supported by multiple clinical trials [3, 62, 63], whereas the AHA considers catheter ablation to improve symptoms and quality of life [4]. A meta-analysis on catheter ablation in patients with HFpEF that included 7 studies has shown that ablation with these patients is associated with a similar arrhythmia-free survival and safety profile when compared to patients with HFrEF or without heart failure [64].

Hypertension

Hypertension is one of the lead contributors to AF development according to AHA, and intensive blood pressure control has been shown in observational and randomized studies to reduce incident AF risk [4]. While the AHA highlights hypertension as a leading contributor to AF development, ESC guidelines similarly recognize hypertension as a major modifiable risk factor without explicitly ranking its relative contribution [3]. Furthermore, a large observational data demonstrated that heart failure showed the strongest association with AF compared to other comorbidities, including coronary artery disease (CAD), hypertension (HTN), hyperlipidemia (HLD), and type 2 diabetes (T2D) [65]. Regardless of whether hypertension is considered the leading determinant of AF, substantial evidence consistently identifies it as a major risk factor. A systematic review demonstrated a linear association between systolic blood pressure and AF risk, while diastolic blood pressure showed a nonlinear relationship with steeper risk increases at lower levels. AF risk increased even within normal blood pressure ranges, and individuals with blood pressure around 180/110 mmHg had a 1.8-2.3-fold greater AF risk than those with 90/60 mmHg [66]. Given the strong association between hypertension and AF, antihypertensive therapy has been investigated not only for blood pressure control but also for AF prevention such as ACEi, ARBs, MRAs. The benefit of ACE inhibitors and ARBs in AF primarily derives from inhibition of angiotensin II-mediated profibrotic and proarrhythmic signaling via the ATII type 1 receptor, thereby attenuating structural and electrical remodeling [67]. Similarly, aldosterone promotes fibrosis through mineralocorticoid and amplifies angiotensin II effects via ATII type 1 receptor activation, providing a mechanistic basis for the protective role of MRAs in AF prevention [68]. Both the AHA and ESC support the use of ACE inhibitors and ARBs in hypertensive patients with AF. Multiple studies have demonstrated favorable outcomes in reducing AF recurrence within this population [4, 69]. Notably, one comparative study evaluating telmisartan and nifedipine for AF recurrence prevention reported similar therapeutic efficacy between the two agents, but telmisartan demonstrated greater attenuation of atrial remodeling progression [70]. Mineralocorticoid receptor antagonists (MRAs): spironolactone, eplerenone, finerenone have accumulated a consistent signal in preventing AF occurrence across meta-analyses. A 2026 meta-analysis of 6 major placebo-controlled RCTs across cardiorenal metabolic populations found a 21% reduction in new-onset AF [68]. A 2025 Bayesian network meta-analysis including 22 RCTs and 66,156 patients compared antihypertensive strategies for AF prevention. Using SUCRA (Surface Under the Cumulative Ranking Curve) analysis, ACE inhibitors combined with thiazide diuretics ranked highest, followed by ARBs, MRAs, and ACE inhibitors alone for preventing AF events [71].

Obesity

Obesity is associated with the development and progression of AF, and well established in cardiovascular epidemiology. Patients with obesity can increase up to 49% of new incidence of AF [72]. Weight reduction is consistently recommended for patients with AF, but an important clinical question remains: how much weight loss is truly required to achieve meaningful benefit? A metanalysis of 5 studies (548 patients) has shown $\geq$ 10% body weight loss cuts AF recurrence by 71% compared with those who lose < 10% or gain weight — and < 10% loss was not significantly protective [73]. Physical fitness weekly also highly recommended for AF patients. Evidence indicates that 60-120 minutes moderate-to-vigorous intensity exercise weekly may provide significant clinical benefit, including improved quality of life, reduction in cardiovascular adverse events, and increased likelihood of maintaining freedom from AF [74, 75].

Diabetes

Diabetes is also a major risk factor, present in roughly 25% of AF patients, it worsens the prognosis for these patients [3]. Addressing diabetes in patients with AF is clinically relevant for reducing AF burden, with SGLT2 inhibitors demonstrating the most consistent and significant favorable AF signal. A large data with individuals with diabetes coexisting with AF reported significantly lower all-cause mortality with SGLT2 inhibitors compared to other oral antidiabetics [76, 77]. GLP-1 receptor agonists, in contrast, have shown inconsistent findings. A 2025 meta-analysis of observational studies published in the European Heart Journal found no reduction in AF incidence with GLP-1 therapy [78]. However, a subsequent 2026 meta-analysis reported an 18% reduction in AF among overweight individuals, independent of weight loss or

concomitant SGLT2 inhibitor use [79], suggesting that overweight status itself may influence the effectiveness of GLP-1 therapy in AF prevention. Metformin still remains as a background therapy with a safety profile for hospitalized and non-critical ill patients [80]. A 2025 meta-analysis of observational studies reported that metformin was associated with a 15% reduction in new-onset AF. However, this association appeared attenuated with increasing age, with weaker effects observed in older patients. The proposed benefit of metformin may relate not only to glycemic control, but also to its anti-inflammatory and antioxidative properties. Glycemic control by the ACCORD trial has shown no difference in incidence of AF between intensive control (HbA1c target < 6%) vs. standard (7–7.9%) [81]. However in the ablation context, poor glycemic control in 12 months preablation predicts 91% recurrence of AF post ablation [3, 4, 82].

Tobacco (Smoking)

Smoking is an established independent risk factor associated with increasing risk of AF. It is genuinely modifiable and rapidly beneficial, making it a priority target alongside weight management and blood pressure control. A large meta analysis of prospective studies has shown dose dependent on current smoker with relative risk was 1.32 (95% CI 1.12–1.56, I2=84%, n=11 studies), 1.09 (95% CI 1.00–1.18, I2=33%, n=9) for former smokers and 1.21 (95% CI 1.12–1.31, I2=80%, n=14) for ever smokers compared to never smokers [83]. Another separate metanalysis of prospective cohort studies also shares the same association, with relative risk of 1.38 on current smokers in men, but 1.28 in women (95% CI, 0.93–1.76; p=0.1356) with non-statistic significant result [84]. Smoking cessation has a great positive impact on reduction of recurrence AF. A longitudinal cohort study has shown risk of AF was 13% lower in former smokers and 18% lower in those who quit smoking during the study compared to current smokers [85].

Alcohol

Alcohol consumption enhances the risk of AF in a fairly linear fashion, with clear evidence that binge drinking heightens the risk [4]. Abstinence from alcohol shows reduced recurrence of AF about a 24.3% relative reduction compared with non-abstinence's group and the abstinence group had a longer period before recurrence of atrial fibrillation than the control group [86].

Sleep

Sleep disorders are recognised as one of the risk factors significantly contributing to AF. OSA among them has shown the most signal across studies. A large 2022 meta-analysis found AF incidence 88% higher in OSA patients, with age and hypertension further amplifying the association [87]. Dose-dependent effect was also observed among patients with OSA [88]. Furthermore, the risk of AF was not limited at OSA, insomnia is a condition that is worth taking attention. A 2022 Taiwan national wide cohort has shown sleep disorders increasing risk of new-onset AF, with insomnia as a major contributor following with sleep apnea [89]. Treatment for these conditions might have a positive result on preventing recurrence of AF as well as adverse outcomes. A nuance from a 2025 JAHA study (n = 466, severe OSA) is clinically important: CPAP didn't reduce early (within 1-year) recurrence but dramatically reduced very late recurrence beyond 1 year (7.6% vs. 21.6%, adjusted HR 0.30) [90]. With this in mind, CPAP long term adherence might prove its benefit in management of AF. However, most available evidence is derived from observational studies. Notably, one analysis comparing randomized controlled trial with observational data demonstrated no significant difference between CPAP and non-CPAP groups [91]. Therefore, the effect still needs to be considered.

Rate control

Rate control is a fundamental pillar of care focused on alleviating symptoms and preventing tachycardia-induced cardiomyopathy. Both guidelines adopt a lenient rate control strategy as the initial goal for most patients, based largely on the RACE II trial [3, 4]. The study has shown a lenient approach (resting HR < 110 bpm) cardiovascular morbidity and mortality at 3 years was lower, higher target attainment, and fewer clinical visits compared with strict rate control (resting HR < 80 bpm + exercise < 110 bpm). Even among patients who successfully achieved strict control, outcomes were no better than lenient. Stricter control reserve for symptomatic or who develop worsening ventricular function [92]. According to both of the guidelines, the choice of rate-control medication is primarily dictated by the patient's left ventricular ejection fraction (LVEF) with the cut-off 40%. For patients with LVEF > 40%, intravenous beta-blockers or nondihydropyridine CCBs are preferred with adequate rate control in 70% of patients for beta-blockers and 54% for CCBs [93]. CCBs perform comparably to beta-blockers for resting rate control but allow significantly higher maximum exercise heart rates [94]. For patient with LVEF < 40%, CCBs is contraindicated due to increasing complications (worsening HF [95], AKI [96], hypotension [97]. Beta-blockers remain the cornerstone therapy for this patient subgroup, whereas digoxin is generally reserved as an alternative because its vagotonic effects fail to adequately control ventricular rate during exercise and long-term use has been associated with increased mortality [98, 99]. In hemodynamically unstable patients, amiodarone was considered for acute rate control in supported clinical evidence [97, 100]. Notably, AHA uniquely considers adjunctive intravenous magnesium (Class IIa) to facilitate achievement and maintenance of acute rate control [4]. Monotherapy usually fails to control the rate or symptoms (70% patients for beta-

blockers, 54% for CCBs as mentioned above), both guidelines recommend combining agents. The first line approach should be digoxin with either a beta-blocker or calcium channel blocker. Digoxin with beta-blocker has demonstrated durable rate control and reduced mortality, with the greatest benefit observed in patients with HFrEF [101]. Digoxin + CCBs as alternative and require monitoring due to the risk of bradycardia [3]. Ivabradine represents a novel approach to rate control in AF, acting through If channel inhibition to reduce AV nodal conduction [102]. Upon that finding, BRAKE-AF project is conducted to assess ivabradine use for rate control in atrial fibrillation, which might include into AF management [103]. For patients whose symptoms remain refractory to intensive pharmacological rate and rhythm control, atrioventricular (AV) node Ablation combined with permanent pacemaker implantation are recommended [3, 4]. Furthermore, a case report of refractory HF driven by AF complicated by hypertrophic cardiomyopathy highlighted His bundle pacing as an alternative to conventional right ventricular pacing following AVNA, potentially avoiding pacing-induced dyssynchrony [104].

Rhythm control

Rhythm control, alongside rate control, contributes substantially to symptom reduction and remains a major pillar in the management of AF. Early rhythm control, initiated within 12 months of AF diagnosis with maintenance of sinus rhythm, is no longer regarded solely as symptom management, but has demonstrated significant reductions in mortality, hospitalization, and major cardiovascular adverse events [3, 4]. Multiple studies have shown catheter ablation remarkably reduce mortality compare to antiarrhythmic agents, HF patients are group which receive the most benefit [105–109]. Electrical cardioversion is recommended in hemodynamically unstable patients or when rapid rhythm restoration is required, following exclusion of atrial thrombus by imaging or at least 3 weeks of anticoagulation therapy. Its immediate success rate approaches 90%, and maintenance of sinus rhythm at 1 month strongly predicts sustained sinus rhythm at 12 months [110]. However, AF management should not rely solely on physician-directed decisions, as patient preference remains central to treatment selection. Therefore, antiarrhythmic drugs (AADs) remain essential, particularly for patients who are ineligible for, decline, or require adjunctive therapy alongside catheter ablation or electrical cardio conversion to maintain sinus rhythm. Across head-to-head comparisons and network meta-analyses, the efficacy ranking for maintenance of sinus rhythm remains consistent: amiodarone > flecainide/propafenone $\approx$ sotalol > dronedarone. Although amiodarone is the most effective antiarrhythmic agent, its substantial long-term toxicity limits use [111]. Accordingly, selection of AAD therapy is largely determined by the presence of structural heart disease. In patients with no or minimal structural heart disease, flecainide, propafenone, or dronedarone are preferred first-line agents. In patients with coronary artery disease, dronedarone or sotalol are favored, whereas flecainide and propafenone are contraindicated. For patients with HFrEF (LVEF $\leq$ 40%), amiodarone and dofetilide remain the only recommended options, while other AADs are considered potentially harmful [3, 4]. Current antiarrhythmic drugs for AF remain limited by incomplete efficacy, contraindications, and adverse effects. AP30663, a KCa2 channel inhibitor, was evaluated in a phase II trial, where patients receiving AP30663 were significantly more likely to achieve conversion to sinus rhythm compared with placebo, with greater efficacy observed at higher doses, thereby introducing a novel, more atrial-selective approach to AF management [112].

Anticoagulation

Anticoagulation therapy in atrial fibrillation (AF) is a foundational component of management, primarily guided by clinical risk scores and the presence of specific comorbidities. The 2024 ESC recommends the CHA_2DS_2-VA score, excluding sex as a scoring criterion, with oral anticoagulation (OAC) recommended for scores $\geq$ 2 (Class I) and considered for scores of 1 (Class IIa) [3]. On the other hand, the 2023 AHA continues to endorse the CHA_2DS_2-VASc score, recommending OAC for high-risk patients ($\geq$ 2 in men, $\geq$ 3 in women; Class I) and considering it reasonable for intermediate-risk patients (1 in men, 2 in women; Class IIa) [4]. HAS-BLED serves as a tool for safety and risk modification rather than a gatekeeper for therapy. Both organizations emphasize that a high bleeding risk score ($\geq$ 3) should not be used as a reason to withhold necessary oral anticoagulation (OAC), more like a signal to correct modifiable bleeding risk factors (uncontrolled hypertension, labile INR if on warfarin, NSAIDs, alcohol). Overall, both guidelines favor direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs), supported by major trials including RE-LY (dabigatran), ROCKET AF (rivaroxaban), ARISTOTLE (apixaban), and ENGAGE AF (edoxaban), which demonstrated noninferiority or superiority in stroke prevention with lower rates of intracranial bleeding compared with VKAs [3, 4, 113–116]. The presence of certain conditions significantly alters which anticoagulant is used and how it is dosed. In CKD, regardless of creatinine clearance DOACs are favored over VKAs because of better mortality outcomes [117]. DOACs have variable degrees of renal clearance: dabigatran 80%, edoxaban 50%, rivaroxaban 35%, apixaban 27%, and they require dose adjustment based on different stages of CKD which are listed on **Table** 6 of AHA guideline [4, 118]. In advanced CKD, current evidence favors apixaban because of its lower renal excretion (27%) and lower thromboembolic risk compared with dabigatran [119]. Furthermore, in CKD stages 3-5, apixaban has been associated with lower bleeding risk compared with VKAs [120]. HF in AF patients does not change

Table 6: DOACs dose adjustment in CKD patients (Copyright: ACC/AHA/ACCP/HRS 2023 Guideline for the Diagnosis and Management of Atrial Fibrillation) [4].

	CrCl (mL/min)				
DOAC	> 95	**51–95**	**31–50**	**15–30**	< 15 **or on dialysis**
Apixaban	5 or 2.5 mg twice daily*	5 or 2.5 mg twice daily*	5 or 2.5 mg twice daily*	5 or 2.5 mg twice daily*	5 or 2.5 mg twice daily*
Dabigatran	150 mg twice daily	150 mg twice daily	150 mg twice daily	75 mg twice daily	Contraindicated
Edoxaban	Contraindicated	60 mg once daily	30 mg once daily	30 mg once daily	Contraindicated
Rivaroxaban	20 mg once daily	20 mg once daily	15 mg once daily	15 mg once daily	15 mg once daily†

Note that other, nonrenal considerations such as drug interactions may also apply. The gray area indicates doses not studied in the pivotal clinical trials of these agents.

* If at least 2 of the following are present: serum creatinine $\geq$ 1.5 mg/dL, age $\geq$ 80 y, or body weight $\leq$ 60 kg, the recommended dose is 2.5 mg twice daily. The ARISTOTLE trial excluded patients with either a creatinine of > 2.5 mg/dL or a calculated CrCl < 25 mL/min.

† Rivaroxaban is not recommended for other indications in patients with a CrCl < 15 mL/min, but such a recommendation is not made for the AF indication. However, pharmacokinetic data are limited.

AF indicates atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CrCl, creatinine clearance; and DOAC, direct oral anticoagulant.

the choice of anticoagulation therapy (DOACs still preferred), but one key interaction needs to be noted: Amiodarone increases DOAC plasma concentrations, which may elevate bleeding risk, although no significant difference in mortality has been observed [121]. This is believed to be the mechanism of amiodarone as CYP3A4 inhibitors and DOACs as substrates of p-glycoprotein, which heavily rely on CYP3A4 to metabolize [118]. In valvular heart disease, particularly mechanical prosthetic valves and rheumatic mitral stenosis, evidence suggests that DOACs are associated with a higher risk of thromboembolic events compared with VKAs; therefore, VKAs remain the recommended therapy [122, 123]. For all other valvular diseases, DOACs are still preferred. In patients with coexisting CAD and AF, antithrombotic management is particularly complex due to the need to balance between stroke prevention with oral anticoagulation and dual antiplatelet therapy required after PCI. In patient with recent PCI (within 12 months), triple therapy (DOAC + aspirin + P2Y12) is necessary short-term (1-4 weeks), then aspirin should be omitted and DOAC with P2Y12 (preferably clopidogrel) be continued in 6-12 months. Multiple studies have shown the dual therapy reduces 40% bleeding risk compared to triple therapy without meaningfully increasing ischemic events, with apixaban has shown least bleeding events [124]. In patients with chronic CAD (> 12 months from the last event, no recent stenting), combination therapy with OAC and antiplatelet agents has been associated with higher mortality outcomes compared with OAC alone [125]. Therefore, OAC monotherapy, preferably with a DOAC, is the standard approach beyond 12 months after the index event [3, 4].

Differential Diagnosis

Atrial fibrillation must be differentiated from other arrhythmias and conduction abnormalities that can present with similar presentation of irregular or rapid heart rhythms. Accurate distinction requires careful history, thorough physical examination and electrocardiographic evaluation. The primary mimickers of atrial fibrillation (AF) and their major differentiating features include:

Atrial Flutter

Atrial Flutter: Atrial flutter is driven by an organized macroreentrant circuit unlike the chaotic, irregular signals seen in atrial fibrillation. The surface ECG reveals classic "sawtooth" flutter waves (F waves) with a consistent morphology that are best visualized in the inferior leads (II, III, aVF). True F waves will consistently maintain a constant rate and amplitude [4].

Multifocal Atrial Tachycardia (MAT)

MAT is an irregular rapid supraventricular tachycardia originating from multiple ectopic foci within the atria. The diagnosis is established electrocardiographically by identifying three or more distinct P-wave morphologies in a single lead, heart rate greater than 100 beats/min, irregular P-P intervals, and a clearly preserved isoelectric baseline between P waves. MAT most commonly present in elderly patients with significant pulmonary disease-particularly chronic obstructive pulmonary disease (COPD) [126].

Sinus Tachycardia

Sinus tachycardia is a supraventricular tachycardia originating from the Sinoatrial node. It usually occurs as a physiologic response to conditions such as fever, pain, anemia, hypovolemia or hyperthyroidism. On electrocardiogram, it is defined by a heart rate > 100 bpm, with a normal P wave preceding every QRS

complex, a constant PR interval, and a regular R–R interval. It also has a gradual onset and off-set [127].

Premature atrial complexes (PACs)

Clinically, frequent Premature Atrial Contractions (PACs) can mimic the irregular pulse of atrial fibrillation, though a standard ECG easily differentiates the two: PACs present as early, ectopic P waves that interrupt an underlying sinus rhythm, whereas AFib is characterized by a chaotic, P-wave-less baseline. These premature beats are a strong, independent risk marker for the future development of incident AFib [128]. Accurately quantifying this ectopic risk requires careful monitoring. Because a patient's daily PAC burden fluctuates significantly, securing a reliable estimate usually demands at least seven days of ambulatory monitoring; however, a single-day finding of $\geq$ 10,000 PACs is highly specific and confirms severe ectopy without the need for prolonged testing [129].

Other Supraventricular Tachycardias (AVNRT and AVRT)

Atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular reentrant tachycardia (AVRT) typically present as rapid, narrow-complex tachycardias with highly regular R-R intervals and abrupt, paroxysmal onsets. On ECG, AVNRT is classically characterized by P waves that are either buried within the QRS complex or appear as retrograde deflections. In addition some patients with multiple slow retrograde pathways can resemble irregular RR on ECG, that makes the reason why it can be confused with AF. A case report of 3 patients has demonstrated this well, a mislead into AF which led into initiation of amiodarone and DOACs can cause major consequences if the correct diagnosis has not been made [130].

Wide-Complex Tachycardias (Polymorphic VT and Pre-excited AF)

Wide-complex irregular tachycardias commonly arise when atrial fibrillation (AF) is accompanied by aberrant intraventricular conduction (e.g., a rate-related bundle branch block) or anterograde conduction over an accessory pathway (e.g., Wolff-Parkinson-White syndrome). Clinically, these rhythms must be urgently differentiated from polymorphic ventricular tachycardia (VT). Electrocardiographically, pre-excited AF is distinguished by extreme R-R irregularity, exceptionally rapid ventricular rates, and highly variable QRS morphologies that reflect shifting degrees of fusion between the accessory pathway and the atrioventricular node. Accurate diagnostic differentiation is critical; the inadvertent administration of standard AV-nodal blocking agents in pre-excited AF can paradoxically accelerate accessory pathway conduction, precipitating rapid hemodynamic collapse and degeneration into ventricular fibrillation [131].

Prognosis

AF is a progressive disease that significantly worsens a patient's long-term health trajectory, particularly regarding mortality and hospitalization. AF is associated with a 2-fold increased risk of all-cause mortality, with heart failure being the most frequent cause, and 5 fold risk for stroke [3, 4, 132]. The prognosis of AF is highly variable and strongly influenced by the time of diagnosis [133], adherence to management [134], and appropriate risk assessment strategies such as the CHA2DS2-VASc score [135]. As AF tends to progress from paroxysmal to persistent forms which have worse prognosis, early intervention is critical. The EAST-AFNET 4 trial found that the earlier initiation of rhythm-control therapy following AF diagnosis the lower the cardiovascular mortality, stroke, and hospital admission rates due to heart failure compared to standard care [136]. In addition, catheter-based and surgical ablation procedures have shown long-term efficacy in maintaining normal sinus rhythm, reducing AF recurrence in patients by 50% for up to five years post ablation, significantly improving long-term clinical outcomes [137]. Overall, early diagnosis along with timely initiation of rhythm-control therapies and using validated risk assessment scores are essential to improve long clinical outcomes and to reduce atrial fibrillation related complications.

Complications

Stroke and Systemic Thromboembolism

Atrial fibrillation is a well-established predictor of stroke, increasing risk by nearly five-fold, primarily due to blood stasis and subsequent thrombus formation within the left atrial appendage. Compared with non-AF strokes, AF-related strokes more frequently result in fatal outcomes or significant long-term disability [132]. Thromboembolic risk must be routinely stratified using clinical tools such as the CHA2DS2-VASc score. For patients at elevated risk, anticoagulation with a vitamin K antagonist or a direct oral anticoagulant reduces stroke risk by 60% to 80% [138].

Heart Failure and Cardiomyopathy

Atrial fibrillation and heart failure (HF) share a highly complex, bidirectional pathophysiological relationship. The loss of coordinated atrial systole, combined with rapid, irregular ventricular rates, severely impairs cardiac output and directly promotes progressive left-ventricular dysfunction, frequently precipitating tachycardia-induced cardiomyopathy [139]. The coexistence of HF and AF is associated with increased mortality compared to either condition alone, although early rhythm control via ablation in patients with HF with reduced ejection fraction (HFrEF) has been shown to improve systolic function [138].

Myocardial Infarction and Ischemia

Independent of common atherosclerotic risk factors, patients with AF remain at nearly twice the risk of developing MI [140]. An AF-induced increase in peripheral prothrombotic risk mediated through systemic platelet activation, thrombin generation, endothelial dysfunction, and inflammation—offers a highly plausible mechanistic explanation for this increased risk. Additionally, episodes of poorly controlled, rapid AF with an uncontrolled ventricular response can result in demand ischemia, leading to type 2 MI, which typically occurs without ST elevation. This excess risk of MI and related cardiovascular events is notably higher in women than in men [141]. Furthermore, the co-occurrence of AF and MI significantly elevates the risk of HF, ischemic stroke, and all-cause mortality compared to either condition alone [142].

Cognitive Impairment and Dementia

Atrial fibrillation acts as a chronic driver of cognitive decline; patients with AF are subject to accelerated deterioration in memory and executive function, exhibiting an approximately 1.4-2.2-fold higher risk of developing incident dementia compared to those in normal sinus rhythm. Mechanistically, cognitive impairment in AF may result from cerebral hypoperfusion, thromboembolic events, systemic inflammation, neurohormonal activation, and brain atrophy. Consequently, oral anticoagulation (OAC) in AF is associated with lower rates of incident dementia compared with no anticoagulation or warfarin, but randomized trials such as BRAIN-AF and GIRAF have not demonstrated a clear cognitive benefit, underlining the low-to-moderate certainty of this evidence [143–145].

Conclusion

Atrial fibrillation, one of the most common arrhythmias worldwide, remains a major burden to global healthcare. Its association with multiple cardiovascular risk factors contributes to severe adverse outcomes, including stroke, heart failure, myocardial infarction, and increased mortality. With extensive studies, the understanding of AF has evolved from electrical disorder to a progressive systemic disease, which was driven by integration among arrhythmogenic triggers, atrial substrate remodeling, autonomic dysfunction, genetic, and cardiometabolic abnormalities. This impacts on diagnosis and management significantly. Both guidelines despite using different classification and framework, they emphasize cardiovascular risk factors modification, stroke prevention, and symptom control. Emerging evidence highly supports early rhythm-control (within 12 months of diagnosis), especially catheter ablation, remarkably reduced cardiovascular events and mortality. Rate control alongside rhythm control with the aim to reduce patient's symptoms and improve exercise capacity. Despite modern diagnostic and management measures, challenges still remain, recurrence of AF, antiarrhythmic agent's adverse effect, residual cardiovascular risk. With novel promising atria-selective therapy, metabolic management, outcomes will improve.

Successful AF management requires a patient's center approach not just focus only on arrhythmia suppression, reduction of cardiometabolic risk factors, but also the quality of life.

List of Abbreviations

AADs: Antiarrhythmic drugs
ACEi: Angiotensin-converting enzyme inhibitors
AF: Atrial fibrillation
AFL: Atrial flutter
AHA: American Heart Association
AMALFI: Active Monitoring for Atrial Fibrillation
ARB: Angiotensin receptor blocker
ARNI: Angiotensin receptor-neprilysin inhibitor
AVNRT: Atrioventricular nodal reentrant tachycardia
AVRT: Atrioventricular reentrant tachycardia
CCB: Calcium channel blocker
CAD: Coronary artery disease
CKD: Chronic kidney disease
COPD: Chronic obstructive pulmonary disease
CPAP: Continuous positive airway pressure
DOAC: Direct oral anticoagulant
OAC: Oral anticoagulant
ECG: Electrocardiogram
ESC: European Society of Cardiology
GDMT: Guideline-directed medical therapy
GLP-1: Glucagon-like peptide-1
HbA1c: Hemoglobin A1c
HCM: Hypertrophic cardiomyopathy
HEAD2TOES: Heart failure, Exercise, Arterial hypertension, Diabetes/type 2 diabetes, Tobacco smoking, Obesity, Ethanol/alcohol, Sleep disorders
HF: Heart failure
HFpEF: Heart failure with preserved ejection fraction
HFrEF: Heart failure with reduced ejection fraction
HR: Heart rate
hs-CRP: High-sensitivity C-reactive protein
HTN: Hypertension
IL: Interleukin
INR: International normalized ratio
KCa2: Small-conductance calcium-activated potassium channel 2
LVEF: Left ventricular ejection fraction
MAT: Multifocal atrial tachycardia
MI: Myocardial infarction
MRI: Magnetic resonance imaging
MRA: Mineralocorticoid receptor antagonist
mEHRA: Modified European Heart Rhythm Association
NSAID: Nonsteroidal anti-inflammatory drug
OSA: Obstructive sleep apnea
PAC: Premature atrial contraction

PCI: Percutaneous coronary intervention
QoL: Quality of life
RACE II: Rate Control Efficacy in Permanent Atrial Fibrillation II
RCT: Randomized controlled trial
SCN5A: Sodium voltage-gated channel alpha subunit 5
SGLT2: Sodium-glucose cotransporter-2
SOS: Stroke risk, Optimize symptoms, Shared decision-making
SUCRA: Surface Under the Cumulative Ranking Curve
TNF-α: Tumor necrosis factor alpha
TRP: Transient receptor potential
TRPC3: Transient receptor potential canonical 3
TRPM7: Transient receptor potential melastatin 7
VKA: Vitamin K antagonist
VT: Ventricular tachycardia
WPW: Wolff-Parkinson-White syndrome

Acknowledgments

None

Ethics Approval and Consent to Participate

Not applicable

Funding

None to declare

Competing interests

None of the authors has conflicts of interest to declare

References

[1] M. F. Karatela and H. Calkins, "The global impact of atrial fibrillation," *Arrhythmia Electrophysiol. Rev.*, vol. 14, p. e28, Nov. 2025, doi: 10.15420/aer.2025.33.

[2] D. M. Lloyd-Jones *et al.*, "Lifetime risk for development of atrial fibrillation: the framingham heart study," *Circulation*, vol. 110, no. 9, Aug. 2004, doi: 10.1161/01.CIR.0000140263.20897.42.

[3] "2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) | European Heart Journal | Oxford Academic," 2026, accessed: March 13, 2026. [Online]. Available: https://academic.oup.com/eurheartj/article/45/36/3314/7738779.

[4] J. A. Joglar *et al.*, "2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines," *Circulation*, vol. 149, no. 1, Jan. 2024, doi: 10.1161/CIR.0000000000001193.

[5] R. An *et al.*, "Risk factors and SCN5A-H558R polymorphism for atrial fibrillation in Tibetans living at different altitudes," *Medicine (Baltimore)*, vol. 101, no. 46, p. e31778, Nov. 2022, doi: 10.1097/MD.0000000000031778.

[6] J. Wang *et al.*, "Inhibiting microrna-155 attenuates atrial fibrillation by targeting CACNA1C," *J. Mol. Cell. Cardiol.*, vol. 155, pp. 58–65, Jun. 2021, doi: 10.1016/j.yjmcc.2021.02.008.

[7] F. Wiedmann *et al.*, "Treatment of atrial fibrillation with doxapram: TASK-1 potassium channel inhibition as a novel pharmacological strategy," *Cardiovasc. Res.*, vol. 118, no. 7, pp. 1728–1741, Jun. 2022, doi: 10.1093/cvr/cvab177.

[8] A. Gwanyanya and K. Mubagwa, "Emerging role of transient receptor potential (TRP) ion channels in cardiac fibroblast pathophysiology," *Front. Physiol.*, vol. 13, p. 968393, Oct. 2022, doi: 10.3389/fphys.2022.968393.

[9] I. Andriulė, D. Pangonytė, A. Gwanyanya, D. Karčiauskas, K. Mubagwa, and R. Mačianskienė, "Detection of TRPM6 and TRPM7 proteins in normal and diseased cardiac atrial tissue and isolated cardiomyocytes," *Int. J. Mol. Sci.*, vol. 23, no. 23, p. 14860, Nov. 2022, doi: 10.3390/ijms232314860.

[10] M. Harada *et al.*, "Transient receptor potential canonical-3 channel–dependent fibroblast regulation in atrial fibrillation," *Circulation*, vol. 126, no. 17, pp. 2051–2064, Oct. 2012, doi: 10.1161/CIRCULATIONAHA.112.121830.

[11] V. Waldmann, M. Laredo, S. Abadir, B. Mondésert, and P. Khairy, "Atrial fibrillation in adults with congenital heart disease," *Int. J. Cardiol.*, vol. 287, pp. 148–154, Jul. 2019, doi: 10.1016/j.ijcard.2019.01.079.

[12] N. W. D'Elia, P. M. Kistler, and A. Voskoboinik, "Atrial fibrillation in the young," *JACC Clin. Electrophysiol.*, vol. 11, no. 5, pp. 1051–1066, May. 2025, doi: 10.1016/j.jacep.2025.04.001.

[13] S. Prabhu *et al.*, "Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction," *J. Am. Coll. Cardiol.*, vol. 70, no. 16, pp. 1949–1961, Oct. 2017, doi: 10.1016/j.jacc.2017.08.041.

[14] N. F. Marrouche *et al.*, "Catheter ablation for atrial fibrillation with heart failure," *N. Engl. J. Med.*, vol. 378, no. 5, pp. 417–427, Feb. 2018, doi: 10.1056/NEJMoa1707855.

[15] E. Diker *et al.*, "Prevalence and predictors of atrial fibrillation in rheumatic valvular heart disease," *Am. J. Cardiol.*, vol. 77, no. 1, pp. 96–98, Jan. 1996, doi: 10.1016/S0002-9149(97)89145-X.

[16] G. Gussak *et al.*, "Region-specific parasym-

pathetic nerve remodeling in the left atrium contributes to creation of a vulnerable substrate for atrial fibrillation," *JCI Insight*, vol. 4, no. 20, p. e130532, Oct. 2019, doi: 10.1172/jci.insight.130532.

[17] R. Arora *et al.*, "Neural substrate for atrial fibrillation: implications for targeted parasympathetic blockade in the posterior left atrium," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 294, no. 1, pp. H134–H144, Jan. 2008, doi: 10.1152/ajpheart.00732.2007.

[18] S. Yoo *et al.*, "Regions of highly recurrent electrogram morphology with low cycle length reflect substrate for atrial fibrillation," *JACC Basic Transl. Sci.*, vol. 8, no. 1, pp. 68–84, Jan. 2023, doi: 10.1016/j.jacbts.2022.07.011.

[19] P.-S. Chen, L. S. Chen, M. C. Fishbein, S.-F. Lin, and S. Nattel, "Role of the autonomic nervous system in atrial fibrillation: Pathophysiology and therapy," *Circ. Res.*, vol. 114, no. 9, pp. 1500–1515, Apr. 2014, doi: 10.1161/CIRCRESAHA.114.303772.

[20] I. M. Oliveira *et al.*, "Cardiac autonomic nervous system remodeling may play a role in atrial fibrillation: A study of the autonomic nervous system and myocardial receptors," *Arq. Bras. Cardiol.*, vol. 117, no. 5, pp. 999–1007, Nov. 2021, doi: 10.36660/abc.20200725.

[21] Y. Xing *et al.*, "The relationship between atrial fibrillation and NLRP3 inflammasome: a gut microbiota perspective," *Front. Immunol.*, vol. 14, p. 1273524, Nov. 2023, doi: 10.3389/fimmu.2023.1273524.

[22] L. Scott Jr *et al.*, "NLRP3 inflammasome is a key driver of obesity-induced atrial arrhythmias," *Cardiovasc. Res.*, vol. 117, no. 7, pp. 1746–1759, Jun. 2021, doi: 10.1093/cvr/cvab024.

[23] M. Ma, H. Zhi, S. Yang, E. Y.-W. Yu, and L. Wang, "Body mass index and the risk of atrial fibrillation: A mendelian randomization study," *Nutrients*, vol. 14, no. 9, p. 1878, Apr. 2022, doi: 10.3390/nu14091878.

[24] B. Ahmed and T. J. Bunch, "Editorial commentary: Adiposity, altered inflammatory pathways, and atrial fibrillation: Mechanistic links or an epiphenomenon?" *Trends Cardiovasc. Med.*, vol. 34, no. 3, pp. 159–160, Apr. 2024, doi: 10.1016/j.tcm.2023.01.001.

[25] L. Hazarapetyan, P. Zelveian, and S. Grigoryan, "Inflammation and coagulation are two interconnected pathophysiological pathways in atrial fibrillation pathogenesis," *J. Inflamm. Res.*, vol. 16, pp. 4967–4975, Oct. 2023, doi: 10.2147/JIR.S429892.

[26] Y.-F. Hu, Y.-J. Chen, Y.-J. Lin, and S.-A. Chen, "Inflammation and the pathogenesis of atrial fibrillation," *Nat. Rev. Cardiol.*, vol. 12, no. 4, pp. 230–243, Apr. 2015, doi: 10.1038/nrcardio.2015.2.

[27] O. Gedikli *et al.*, "Inflammatory markers according to types of atrial fibrillation," *Int. J. Cardiol.*, vol. 120, no. 2, pp. 193–197, Aug. 2007, doi: 10.1016/j.ijcard.2006.09.015.

[28] S. Zhang, W. Xu, J. Xu, Y. Qiu, Y. Wan, and Y. Fan, "Association of C-reactive protein level with adverse outcomes in patients with atrial fibrillation: A meta-analysis," *Am. J. Med. Sci.*, vol. 367, no. 1, pp. 41–48, Jan. 2023, doi: 10.1016/j.amjms.2023.11.009.

[29] R. Duangrat, W. Parichatikanond, and S. Mangmool, "Dual blockade of TGF-β Receptor and Endothelin Receptor synergistically inhibits Angiotensin II-Induced myofibroblast differentiation: Role of AT1R/Gαq-Mediated TGF-β1 and ET-1 Signaling," *Int. J. Mol. Sci.*, vol. 24, no. 8, p. 6972, Apr. 2023, doi: 10.3390/ijms24086972.

[30] H. S. Lim *et al.*, "Effect of atrial fibrillation on atrial thrombogenesis in humans: Impact of rate and rhythm," *J. Am. Coll. Cardiol.*, vol. 61, no. 8, pp. 852–860, Feb. 2013, doi: 10.1016/j.jacc.2012.11.046.

[31] D. F. Gudbjartsson *et al.*, "Variants conferring risk of atrial fibrillation on chromosome 4q25," *Nature*, vol. 448, no. 7151, pp. 353–357, Jul. 2007, doi: 10.1038/nature06007.

[32] C. Schulz *et al.*, "PITX2 knockout induces key findings of electrical remodeling as seen in persistent atrial fibrillation," *Circ. Arrhythm. Electrophysiol.*, vol. 16, no. 3, p. e011602, Mar. 2023, doi: 10.1161/CIRCEP.122.011602.

[33] P. Benzoni *et al.*, "PITX2 gain-of-function mutation associated with atrial fibrillation alters mitochondrial activity in human ipsc atrial-like cardiomyocytes," *Front. Physiol.*, vol. 14, p. 1250951, Nov. 2023, doi: 10.3389/fphys.2023.1250951.

[34] Y. Lin *et al.*, "Identification of rare heterozygous linkage R965C-R1309H mutations in the pore-forming region of SCN5A gene associated with complex arrhythmia," *Mol. Genet. Genomic Med.*, vol. 9, no. 5, p. e1613, May 2021, doi: 10.1002/mgg3.1613.

[35] X. Wang *et al.*, "Downregulation of FKBP5 promotes atrial arrhythmogenesis," *Circ. Res.*, vol. 133, no. 1, Jun. 2023, doi: 10.1161/CIRCRESAHA.122.322213.

[36] A. Ullah, M. T. Hoang-Trong, W. J. Lederer, R. L. Winslow, and M. S. Jafri, "Critical requirements for the initiation of a cardiac arrhythmia in rat ventricle: How many myocytes?" *Cells*, vol. 11, no. 12, p. 1878, Jun. 2022, doi: 10.3390/cells11121878.

[37] S. Y. Wass *et al.*, "Novel functional atrial fibrillation risk genes and pathways identified from coexpression analyses in human left atria," *Heart Rhythm*, vol. 20, no. 9, pp. 1219–1226, Sep. 2023, doi: 10.1016/j.hrthm.2023.05.035.

[38] A. F. Van Ouwerkerk *et al.*, "Patient-specific

TBX5-G125R variant induces profound transcriptional deregulation and atrial dysfunction," *Circulation*, vol. 145, no. 8, pp. 606–619, Feb. 2022, doi: 10.1161/CIRCULATIONAHA.121.054347.

[39] A. G. Clausen, O. B. Vad, J. H. Andersen, and M. S. Olesen, "Loss-of-function variants in the SYNPO2L gene are associated with atrial fibrillation," *Front. Cardiovasc. Med.*, vol. 8, p. 650667, Mar. 2021, doi: 10.3389/fcvm.2021.650667.

[40] Z. T. Yoneda *et al.*, "Early-onset atrial fibrillation and the prevalence of rare variants in cardiomyopathy and arrhythmia genes," *JAMA Cardiol.*, vol. 6, no. 12, pp. 1371–1379, Dec. 2021, doi: 10.1001/jamacardio.2021.3370.

[41] N. Li *et al.*, "KLF15 loss-of-function mutation underlying atrial fibrillation as well as ventricular arrhythmias and cardiomyopathy," *Genes*, vol. 12, no. 3, p. 408, Mar. 2021, doi: 10.3390/genes12030408.

[42] J. M. Pioner *et al.*, "Genotype-driven pathogenesis of atrial fibrillation in hypertrophic cardiomyopathy: The case of different TNNT2 mutations," *Front. Physiol.*, vol. 13, p. 864547, Apr. 2022, doi: 10.3389/fphys.2022.864547.

[43] G. Hindricks *et al.*, "2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)," *Eur. Heart J.*, vol. 42, no. 5, pp. 373–498, Feb. 2021, doi: 10.1093/eurheartj/ehaa612.

[44] F. Gaita *et al.*, "Prevalance of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function," *J. Am. Coll. Cardiol.*, vol. 62, no. 21, pp. 1990–1997, Nov. 2013, doi: 10.1016/j.jacc.2013.05.074.

[45] L. Rivard and P. Khairy, "Mechanisms, clinical significance, and prevention of cognitive impairment in patients with atrial fibrillation," *Can. J. Cardiol.*, vol. 33, no. 12, pp. 1556–1564, Dec. 2017, doi: 10.1016/j.cjca.2017.09.024.

[46] D. Conen *et al.*, "Relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation," *J. Am. Coll. Cardiol.*, vol. 73, no. 9, pp. 989–999, Mar. 2019, doi: 10.1016/j.jacc.2018.12.039.

[47] H. A. Carneiro and B. Knight, "Does asymptomatic atrial fibrillation exist?" *J. Cardiovasc. Electrophysiol.*, vol. 35, no. 3, pp. 522–529, Mar. 2024, doi: 10.1111/jce.16108.

[48] G. Boriani *et al.*, "Asymptomatic atrial fibrillation: clinical correlates, management, and outcomes in the EORP-AF pilot general registry," *Am. J. Med.*, vol. 128, no. 5, pp. 509–518, May 2015, doi: 10.1016/j.amjmed.2014.11.026.

[49] T. S. Potpara, M. M. Polovina, J. M. Marinkovic, and G. Y. Lip, "A comparison of clinical characteristics and long-term prognosis in asymptomatic and symptomatic patients with first-diagnosed atrial fibrillation: the Belgrade Atrial Fibrillation Study," *Int. J. Cardiol.*, vol. 168, no. 5, pp. 4744–4749, Oct. 2013, doi: 10.1016/j.ijcard.2013.07.234.

[50] K. C. Siontis, B. J. Gersh, J. M. Killian, P. A. Noseworthy, P. McCabe, and S. A. Weston, "Typical, atypical, and asymptomatic presentations of new-onset atrial fibrillation in the community: Characteristics and prognostic implications," *Heart Rhythm*, vol. 13, no. 7, pp. 1418–1424, Jul. 2016, doi: 10.1016/j.hrthm.2016.03.003.

[51] R. Wijesurendra *et al.*, "Remote screening for asymptomatic atrial fibrillation: The AMALFI randomized clinical trial," *JAMA*, vol. 334, no. 15, pp. 1349–1357, Oct. 2025, doi: 10.1001/jama.2025.15440.

[52] S. Blum *et al.*, "Prospective assessment of sex-related differences in symptom status and health perception among patients with atrial fibrillation," *J. Am. Heart Assoc.*, vol. 6, no. 7, p. e005401, Jun. 2017, doi: 10.1161/JAHA.116.005401.

[53] J. V. Freeman *et al.*, "Association between atrial fibrillation symptoms, quality of life, and patient outcomes: Results from the outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF)," *Circ. Cardiovasc. Qual. Outcomes*, vol. 8, no. 4, pp. 393–402, Jul. 2015, doi: 10.1161/CIRCOUTCOMES.114.001303.

[54] T. E. Walters, K. Wick, G. Tan *et al.*, "Symptom severity and quality of life in patients with atrial fibrillation: Psychological function outweighs clinical predictors," *Int. J. Cardiol.*, vol. 279, pp. 84–89, Mar. 2019, doi: 10.1016/j.ijcard.2018.10.101.

[55] R. B. Schnabel, L. Pecen, F. M. Ojeda *et al.*, "Gender differences in clinical presentation and 1-year outcomes in atrial fibrillation," *Heart*, vol. 103, no. 13, pp. 1024–1030, Jul. 2017, doi: 10.1136/heartjnl-2016-310406.

[56] T. C. Randolph, D. N. Simon, L. Thomas *et al.*, "Patient factors associated with quality of life in atrial fibrillation," *Am. Heart J.*, vol. 182, pp. 135–143, Dec. 2016, doi: 10.1016/j.ahj.2016.08.003.

[57] R. Ynv, O. M, V. Fh, L. G, and B. Ba, "Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation," *J. Am. Coll. Cardiol.*, vol. 76, no. 9, Sep. 2020, doi: 10.1016/j.jacc.2020.07.009.

[58] T. Fretz, O. Ilonze, T. Tanawuttiwat, and M. Das, "Abstract 4140617: SGLT-2 inhibitors and atrial fibrillation incidence following heart failure hospitalization in a diabetic population," *Circulation*, vol. 150, no. Suppl_1, pp. A4 140 617–A4 140 617, Nov. 2024, doi: 10.1161/circ.150.suppl_1.4140617.

[59] D. L. Bhatt *et al.*, "Sotagliflozin in patients with diabetes and recent worsening heart failure," *N. Engl. J. Med.*, vol. 384, no. 2, pp. 117–128, Jan.

2021, doi: 10.1056/NEJMoa2030183.

[60] M. J. ParadigmMHF *et al.*, "Angiotensin-neprilysin inhibition versus enalapril in heart failure," *N. Engl. J. Med.*, vol. 371, no. 11, pp. 993–1004, Sep. 2014, doi: 10.1056/NEJMoa1409077.

[61] K. Swedberg *et al.*, "Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study," *J. Am. Coll. Cardiol.*, vol. 59, no. 18, pp. 1598–1603, May 2012, doi: 10.1016/j.jacc.2011.11.063.

[62] S. D. Anker *et al.*, "Empagliflozin in heart failure with a preserved ejection fraction," *N. Engl. J. Med.*, vol. 385, no. 16, pp. 1451–1461, Oct. 2021, doi: 10.1056/NEJMoa2107038.

[63] S. D. Solomon *et al.*, "Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction," *N. Engl. J. Med.*, vol. 387, no. 12, pp. 1089–1098, Sep. 2022, doi: 10.1056/NEJMoa2206286.

[64] M. U. Siddiqui *et al.*, "Catheter ablation in patients with atrial fibrillation and heart failure with preserved ejection fraction: A systematic review and meta-analysis," *J. Arrhythmia*, vol. 38, no. 6, pp. 981–990, 2022, doi: 10.1002/joa3.12794.

[65] N. Jones, T. Aviles, V. Patel, A. Feldiorean, L. Judy, and D. Saxon, "Associations between cardiac comorbidity burden and atrial fibrillation prevalence: A real-world-evidence based approach," *Proc. IMPRS*, vol. 8, no. 1, 2025, doi: 10.18060/29637.

[66] D. Aune, Y. Mahamat-Saleh, E. Kobeissi, T. Feng, A. K. Heath, and I. Janszky, "Blood pressure, hypertension and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies," *Eur. J. Epidemiol.*, vol. 38, no. 2, pp. 145–178, Feb. 2023, doi: 10.1007/s10654-022-00914-0.

[67] B. Williams, "Angiotensin II and the pathophysiology of cardiovascular remodeling," *Am. J. Cardiol.*, vol. 87, no. 8, pp. 10–17, Apr. 2001, doi: 10.1016/S0002-9149(01)01507-7.

[68] J. Neefs *et al.*, "Aldosterone pathway blockade to prevent atrial fibrillation: A systematic review and meta-analysis," *Int. J. Cardiol.*, vol. 231, pp. 155–161, Mar. 2017, doi: 10.1016/j.ijcard.2016.12.029.

[69] D. Galzerano *et al.*, "A multicentre, randomized study of telmisartan versus carvedilol for prevention of atrial fibrillation recurrence in hypertensive patients," *J. Renin Angiotensin Aldosterone Syst.*, vol. 13, no. 4, pp. 496–503, Dec. 2012, doi: 10.1177/1470320312443909.

[70] H. Du *et al.*, "Effect of nifedipine versus telmisartan on prevention of atrial fibrillation recurrence in hypertensive patients," *Hypertension*, vol. 61, no. 4, pp. 786–792, Apr. 2013, doi: 10.1161/HYPERTENSIONAHA.111.202309.

[71] D. M. Gewehr *et al.*, "Effect of antihypertensive agents on the risk of new-onset and recurrent atrial fibrillation: a Bayesian network meta-analysis of randomized controlled trials," *Eur. J. Prev. Cardiol.*, p. zwaf335, Jul. 2025, doi: 10.1093/eurjpc/zwaf335.

[72] N. Wanahita, F. H. Messerli, S. Bangalore, A. S. Gami, V. K. Somers, and J. S. Steinberg, "Atrial fibrillation and obesity—results of a meta-analysis," *Am. Heart J.*, vol. 155, no. 2, pp. 310–315, Feb. 2008, doi: 10.1016/j.ahj.2007.10.004.

[73] O. M. Aldaas *et al.*, "Meta-analysis of effect of modest (≥10%) weight loss in management of overweight and obese patients with atrial fibrillation," *Am. J. Cardiol.*, vol. 124, no. 10, pp. 1568–1574, Nov. 2019, doi: 10.1016/j.amjcard.2019.08.009.

[74] A. D. Elliott *et al.*, "An exercise and physical activity program in patients with atrial fibrillation," *JACC Clin. Electrophysiol.*, vol. 9, no. 4, pp. 455–465, Apr. 2023, doi: 10.1016/j.jacep.2022.12.002.

[75] B. J. R. Buckley, S. S. Risom, M. Boidin, G. Y. H. Lip, and D. H. J. Thijssen, "Atrial fibrillation specific exercise rehabilitation: Are we there yet?" *J. Pers. Med.*, vol. 12, no. 4, p. 610, Apr. 2022, doi: 3390/jpm12040610.

[76] G. Y. Heo *et al.*, "Comparative effects of second-line oral antidiabetic medications on atrial fibrillation risk in patients with type 2 diabetes: a nationwide retrospective cohort study," *Cardiovasc. Diabetol.*, vol. 25, no. 1, p. 65, Jan. 2026, doi: 10.1186/s12933-025-03024-9.

[77] M. Z. Ameer *et al.*, "Cardiovascular outcomes with SGLT-2 inhibitors in individuals with diabetes and co-existing atrial fibrillation: A systematic review and meta-analysis," *Int. J. Cardiol.*, vol. 426, p. 133083, May 2025, doi: 10.1016/j.ijcard.2025.133083.

[78] K. Banerjee, "Effect of glucagon-like peptide-1 receptor agonists on atrial fibrillation incidence: a systematic review and meta-analysis," *Eur. Heart J.*, vol. 46, no. Supplement_1, p. ehaf784.409, Nov. 2025, doi: 10.1093/eurheartj/ehaf784.409.

[79] P. Karakasis *et al.*, "Effect of GLP-1 receptor agonists and co-agonists on atrial fibrillation risk in overweight or obesity: systematic review and meta-analysis of randomized controlled trials," *Metabolism*, vol. 175, p. 156463, Feb. 2026, doi: 10.1016/j.metabol.2025.156463.

[80] T. Alauddin and S. E. Petite, "Evaluation of the safety and efficacy of metformin use in hospitalized, non–critically ill patients," *J. Pharm. Technol.*, vol. 36, no. 3, pp. 102–109, Jun. 2020, doi: 10.1177/8755122520911689.

[81] O. Fatemi, E. Yuriditsky, C. Tsioufis *et al.*, "Impact of intensive glycemic control on the

incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study)," *Am. J. Cardiol.*, vol. 114, no. 8, pp. 1217–1222, Oct. 2014, doi: 10.1016/j.amjcard.2014.07.045.

[82] E. Donnellan *et al.*, "Association between pre-ablation glycemic control and outcomes among patients with diabetes undergoing atrial fibrillation ablation," *JACC Clin. Electrophysiol.*, vol. 5, no. 8, pp. 897–903, Aug. 2019, doi: 10.1016/j.jacep.2019.05.018.

[83] D. Aune, S. Schlesinger, T. Norat, and E. Riboli, "Tobacco smoking and the risk of atrial fibrillation: A systematic review and meta-analysis of prospective studies," *Eur. J. Prev. Cardiol.*, vol. 25, no. 13, pp. 1437–1451, Sep. 2018, doi: 10.1177/2047487318780435.

[84] Q. Wang *et al.*, "Smoking as a risk factor for the occurrence of atrial fibrillation in men versus women: A meta-analysis of prospective cohort studies," *Heart Lung Circ.*, vol. 27, no. 1, pp. 58–65, Jan. 2018, doi: 10.1016/j.hlc.2017.01.021.

[85] J. T. Teraoka, J. J. Tang, F. N. Delling, E. Vittinghoff, and G. M. Marcus, "Smoking cessation and incident atrial fibrillation in a longitudinal cohort," *JACC Clin. Electrophysiol.*, vol. 10, no. 10, pp. 2198–2206, Oct. 2024, doi: 10.1016/j.jacep.2024.06.019.

[86] V. A *et al.*, "Alcohol abstinence in drinkers with atrial fibrillation," *N. Engl. J. Med.*, vol. 382, no. 1, pp. 20–28, Jan. 2020, doi: 10.1056/NEJMoa1817591.

[87] A. I. Moula *et al.*, "Obstructive sleep apnea and atrial fibrillation," *J. Clin. Med.*, vol. 11, no. 5, p. 1242, Jan. 2022, doi: 10.3390/jcm11051242.

[88] E. Zhao, S. Chen, Y. Du, and Y. Zhang, "Association between sleep apnea hypopnea syndrome and the risk of atrial fibrillation: A meta-analysis of cohort study," *BioMed Res. Int.*, vol. 2018, p. 5215868, 2018, doi: 10.1155/2018/5215868.

[89] C.-C. Chen *et al.*, "Association between sleep disorder and atrial fibrillation: A nationwide population-based cohort study," *Sleep Med.*, vol. 96, pp. 50–56, Aug. 2022, doi: 10.1016/j.sleep.2022.05.002.

[90] N. Tanaka *et al.*, "Impact of long-term CPAP adherence on recurrence after atrial fibrillation ablation in patients with severe sleep apnea," *J. Am. Heart Assoc.*, vol. 14, no. 10, p. e038742, May 2025, doi: 10.1161/JAHA.124.038742.

[91] E. D. Itaya *et al.*, "Efficacy of continuous positive airway pressure on atrial fibrillation recurrence after catheter ablation in patients with obstructive sleep apnea: a systematic review and meta-analysis," *J. Interv. Card. Electrophysiol.*, vol. 68, no. 8, pp. 1749–1759, Nov. 2025, doi: 10.1007/s10840-025-02063-2.

[92] H. F. Groenveld *et al.*, "Rate control efficacy in permanent atrial fibrillation: Successful and failed strict rate control against a background of lenient rate control," *J. Am. Coll. Cardiol.*, vol. 61, no. 7, pp. 741–748, Feb. 2013, doi: 10.1016/j.jacc.2012.11.038.

[93] B. Olshansky *et al.*, "The atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study," *J. Am. Coll. Cardiol.*, vol. 43, no. 7, pp. 1201–1208, Apr. 2004, doi: 10.1016/j.jacc.2003.11.032.

[94] T. Koldenhof, B. Gareb, M. D. Smit, T. S. A. Bergwerff, M. Rienstra, and R. G. Tieleman, "Rate control treatment with calcium channel blockers and beta blockers for patients with atrial fibrillation: a systematic review and meta-analysis," *Eur. Heart J. Open*, vol. 6, no. 2, p. oeag062, Mar. 2026, doi: 10.1093/ehjopen/oeag062.

[95] M. Hasbrouck and T. T. Nguyen, "Acute management of atrial fibrillation in congestive heart failure with reduced ejection fraction in the emergency department," *Am. J. Emerg. Med.*, vol. 58, pp. 39–42, Aug. 2022, doi: 10.1016/j.ajem.2022.03.058.

[96] M. B. Jandali, "Safety of intravenous diltiazem in reduced ejection fraction heart failure with rapid atrial fibrillation," *Clin. Drug Investig.*, vol. 38, no. 6, pp. 503–508, Jun. 2018, doi: 10.1007/s40261-018-0631-7.

[97] G. Delle Karth *et al.*, "Amiodarone versus diltiazem for rate control in critically ill patients with atrial tachyarrhythmias," *Crit. Care Med.*, vol. 29, no. 6, pp. 1149–1153, Jun. 2001, doi: 10.1097/00003246-200106000-00011.

[98] G. Gazzaniga, D. Menichelli, F. Scaglione, A. Farcomeni, A. Pani, and D. Pastori, "Effect of digoxin on all-cause and cardiovascular mortality in patients with atrial fibrillation with and without heart failure: an umbrella review of systematic reviews and 12 meta-analyses," *Eur. J. Clin. Pharmacol.*, vol. 79, no. 4, pp. 473–483, 2023, doi: 10.1007/s00228-023-03470-y.

[99] J. B. Segal *et al.*, "The evidence regarding the drugs used for ventricular rate control," *J. Fam. Pract.*, vol. 49, no. 1, pp. 47–59, Jan. 2000.

[100] H. F. Clemo, M. A. Wood, D. M. Gilligan, and K. A. Ellenbogen, "Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias," *Am. J. Cardiol.*, vol. 81, no. 5, pp. 594–598, Mar. 1998, doi: 10.1016/s0002-9149(97)00962-4.

[101] L. Fauchier *et al.*, "Comparison of beta blocker and digoxin alone and in combination for management of patients with atrial fibrillation and heart failure," *Am. J. Cardiol.*, vol. 103, no. 2, pp. 248–254, Jan. 2009, doi: 10.1016/j.amjcard.2008.09.064.

[102] R. L. Verrier *et al.*, "If inhibition in the atri-

oventricular node by ivabradine causes rate-dependent slowing of conduction and reduces ventricular rate during atrial fibrillation," *Heart Rhythm*, vol. 11, no. 12, pp. 2288–2296, Dec. 2014, doi: 10.1016/j.hrthm.2014.08.007.

[103] A. Fontenla *et al.*, "Ivabradine for chronic heart rate control in persistent atrial fibrillation. Design of the BRAKE-AF project," *Rev. Esp. Cardiol. (Engl. Ed.)*, vol. 73, no. 5, pp. 368–375, May 2020, doi: 10.1016/j.rec.2019.09.004.

[104] S. Chu *et al.*, "His bundle pacing combined with atrioventricular nodal ablation: a novel strategy for refractory heart failure led by atrial fibrillation complicated with hypertrophic cardiomyopathy," *J. Am. Coll. Cardiol.*, vol. 75, no. 11_Supplement_1, p. 3232, Mar. 2020, doi: 10.1016/S0735-1097(20)33859-6.

[105] L. Eckardt *et al.*, "Attaining sinus rhythm mediates improved outcome with early rhythm control therapy of atrial fibrillation: the EAST-AFNET 4 trial," *Eur. Heart J.*, vol. 43, no. 40, pp. 4127–4144, Oct. 2022, doi: 10.1093/eurheartj/ehac471.

[106] N. F. Marrouche *et al.*, "Catheter ablation for atrial fibrillation with heart failure," *N. Engl. J. Med.*, vol. 378, no. 5, pp. 417–427, Feb. 2018, doi: 10.1056/NEJMoa1707855.

[107] F. A. Simader *et al.*, "Catheter ablation improves cardiovascular outcomes in patients with atrial fibrillation and heart failure: a meta-analysis of randomized controlled trials," *EP Europace*, vol. 25, no. 2, pp. 341–350, Feb. 2023, doi: 10.1093/europace/euac173.

[108] C. Sohns *et al.*, "Catheter ablation in end-stage heart failure with atrial fibrillation," *N. Engl. J. Med.*, vol. 389, no. 15, pp. 1380–1389, Oct. 2023, doi: 10.1056/NEJMoa2306037.

[109] Z. Wang *et al.*, "Catheter ablation vs drug therapy in patients with atrial fibrillation and nonmodifiable recurrence risk factors: A secondary analysis of the CABANA randomized clinical trial," *JAMA Network Open*, vol. 8, no. 8, p. e2528124, Aug. 2025, doi: 10.1001/jamanetworkopen.2025.28124.

[110] M. Castrichini *et al.*, "Prevalence and predictors of persistent sinus rhythm after elective electrical cardioversion for atrial fibrillation," *J. Cardiovasc. Med.*, vol. 22, no. 8, pp. 626–630, Aug. 2021, doi: 10.2459/JCM.0000000000001182.

[111] N. Freemantle, C. Lafuente-Lafuente, S. Mitchell, L. Eckert, and M. Reynolds, "Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation," *EP Europace*, vol. 13, no. 3, pp. 329–345, Mar. 2011, doi: 10.1093/europace/euq450.

[112] A. G. Holst *et al.*, "Inhibition of the KCa2 potassium channel in atrial fibrillation: a randomized phase 2 trial," *Nat. Med.*, vol. 30, no. 1, pp. 106–111, Jan. 2024, doi: 10.1038/s41591-023-02679-9.

[113] C. B. Granger *et al.*, "Apixaban versus warfarin in patients with atrial fibrillation," *N. Engl. J. Med.*, vol. 365, no. 11, pp. 981–992, Sep. 2011, doi: 10.1056/NEJMoa1107039.

[114] S. J. Connolly *et al.*, "Dabigatran versus warfarin in patients with atrial fibrillation," *N. Engl. J. Med.*, vol. 361, no. 12, pp. 1139–1151, Sep. 2009, doi: 10.1056/NEJMoa0905561.

[115] R. P. Giugliano *et al.*, "Edoxaban versus warfarin in patients with atrial fibrillation," *N. Engl. J. Med.*, vol. 369, no. 22, pp. 2093–2104, Nov. 2013, doi: 10.1056/NEJMoa1310907.

[116] R. M. Patel *et al.*, "Rivaroxaban versus warfarin in nonvalvular atrial fibrillation," *N. Engl. J. Med.*, vol. 365, no. 10, pp. 883–891, Sep. 2011, doi: 10.1056/NEJMoa1009638.

[117] A. Makani *et al.*, "Safety and efficacy of direct oral anticoagulants versus warfarin in patients with chronic kidney disease and atrial fibrillation," *Am. J. Cardiol.*, vol. 125, no. 2, pp. 210–214, Jan. 2020, doi: 10.1016/j.amjcard.2019.10.033.

[118] A. Chen, E. Stecker, and B. A. Warden, "Direct oral anticoagulant use: A practical guide to common clinical challenges," *J. Am. Heart Assoc.*, vol. 9, no. 13, p. e017559, Jun. 2020, doi: 10.1161/JAHA.120.017559.

[119] S. M. Jang, K. Bahjri, and H. Tran, "Safety and efficacy of direct oral anticoagulants for atrial fibrillation in patients with renal impairment," *Pharmacy*, vol. 8, no. 1, p. 30, Mar. 2020, doi: 10.3390/pharmacy8010030.

[120] J. W. Stanifer *et al.*, "Apixaban versus warfarin in patients with atrial fibrillation and advanced chronic kidney disease," *Circulation*, vol. 141, no. 17, pp. 1384–1392, Apr. 2020, doi: 10.1161/CIRCULATIONAHA.119.044059.

[121] F. Michael *et al.*, "Risk of bleeding with the concurrent use of amiodarone and DOACs: a systematic review and meta-analysis," *Eur. Heart J. Cardiovasc. Pharmacother.*, vol. 11, no. 3, pp. 241–250, May 2025, doi: 10.1093/ehjcvp/pvae097.

[122] J. W. Eikelboom *et al.*, "Dabigatran versus warfarin in patients with mechanical heart valves," *N. Engl. J. Med.*, vol. 369, no. 13, pp. 1206–1214, Sep. 2013, doi: 10.1056/NEJMoa1300615.

[123] R. Verma and D. A. Latter, "Anticoagulation for rheumatic mitral stenosis, INVICTUS in perspective," *Curr. Opin. Cardiol.*, vol. 38, no. 2, pp. 55–60, Mar. 2023, doi: 10.1097/HCO.0000000000001013.

[124] R. D. Lopes *et al.*, "Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation," *N. Engl. J. Med.*, vol. 380, no. 16, pp. 1509–1524, Apr. 2019, doi: 10.1056/NEJMoa1817083.

[125] S. Yasuda *et al.*, "Antithrombotic therapy for atrial fibrillation with stable coronary disease,"

N. Engl. J. Med., vol. 381, no. 12, pp. 1103–1113, Sep. 2019, doi: 10.1056/NEJMoa1904143.

[126] A. M. Custer, V. S. Yelamanchili, and S. L. Lappin, "Multifocal atrial tachycardia," in *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2026, [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/29083603/.

[127] K. A. Mayuga *et al.*, "Sinus tachycardia: a multidisciplinary expert focused review," *Circ. Arrhythm. Electrophysiol.*, vol. 15, no. 9, p. e007960, Sep. 2022, doi: 10.1161/CIRCEP.121.007960.

[128] T. A. Dewland *et al.*, "Atrial ectopy as a predictor of incident atrial fibrillation," *Ann. Intern. Med.*, vol. 159, no. 11, pp. 721–728, Dec. 2013, doi: 10.7326/0003-4819-159-11-201312030-00004.

[129] A. Måneheim *et al.*, "Diagnostic reliability of monitoring for premature atrial and ventricular complexes," *EP Europace*, vol. 26, no. 8, p. euae198, Aug. 2024, doi: 10.1093/europace/euae198.

[130] V. Soorampally, Y. Lokhandwala, and V. R. Vaidya, "Typical atrioventricular nodal re-entry tachycardia masquerading as atrial fibrillation," *JACC Case Rep.*, vol. 29, no. 19, p. 102578, Oct. 2024, doi: 10.1016/j.jaccas.2024.102578.

[131] A. H. Kashou, P. A. Noseworthy, C. V. DeSimone, A. J. Deshmukh, S. J. Asirvatham, and A. M. May, "Wide complex tachycardia differentiation: A reappraisal of the state-of-the-art," *J. Am. Heart Assoc.*, vol. 9, no. 11, p. e016598, Jun. 2020, doi: 10.1161/JAHA.120.016598.

[132] S. E. Choi, D. Sagris, A. Hill, G. Y. Lip, and A. H. Abdul-Rahim, "Atrial fibrillation and stroke," *Expert Rev. Cardiovasc. Ther.*, vol. 21, no. 1, pp. 35–56, Jan. 2023, doi: 10.1080/14779072.2023.2160319.

[133] R. B. Schnabel *et al.*, "Early diagnosis and better rhythm management to improve outcomes in patients with atrial fibrillation: the 8th AFNET/EHRA consensus conference," *EP Europace*, vol. 25, no. 1, pp. 6–27, Feb. 2023, doi: 10.1093/europace/euac062.

[134] D. Qin *et al.*, "Patient outcomes according to adherence to treatment guidelines for rhythm control of atrial fibrillation," *J. Am. Heart Assoc.*, vol. 4, no. 4, p. e001793, Apr. 2015, doi: 10.1161/JAHA.115.001793.

[135] G. Y. H. Lip, R. Nieuwlaat, R. Pisters, D. A. Lane, and H. J. G. M. Crijns, "Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation," *CHEST*, vol. 137, no. 2, pp. 263–272, Feb. 2010, doi: 10.1378/chest.09-1584.

[136] P. Kirchhof *et al.*, "Early rhythm-control therapy in patients with atrial fibrillation," *N. Engl. J. Med.*, vol. 383, no. 14, pp. 1305–1316, Sep. 2020, doi: 10.1056/NEJMoa2019422.

[137] B. T. Muston, J. Bilbrough, C. Eranki, C. Wilson-Smith, and A. R. Wilson-Smith, "Mid-to-long-term recurrence of atrial fibrillation in surgical treatment vs. catheter ablation: a meta-analysis using aggregated survival data," *Ann. Cardiothorac. Surg.*, vol. 13, no. 1, pp. 18–30, Jan. 2024, doi: 10.21037/acs-2023-afm-16.

[138] D. Ko, M. K. Chung, P. T. Evans, E. J. Benjamin, and R. H. Helm, "Atrial fibrillation: A review," *JAMA*, vol. 333, no. 4, pp. 329–342, Jan. 2025, doi: 10.1001/jama.2024.22451.

[139] D. V. M. Verhaert, H.-P. Brunner-La Rocca, D. J. van Veldhuisen, and K. Vernooy, "The bidirectional interaction between atrial fibrillation and heart failure: consequences for the management of both diseases," *EP Europace*, vol. 23, no. 23 Suppl 2, pp. ii40–ii45, Apr. 2021, doi: 10.1093/europace/euaa368.

[140] E. Z. Soliman *et al.*, "Atrial fibrillation and the risk of myocardial infarction," *JAMA Intern. Med.*, vol. 174, no. 1, pp. 107–114, Jan. 2014, doi: 10.1001/jamainternmed.2013.11912.

[141] A. R. Chapman, C. Taggart, J. Boeddinghaus, N. L. Mills, and K. A. A. Fox, "Type 2 myocardial infarction: challenges in diagnosis and treatment," *Eur. Heart J.*, vol. 46, no. 6, pp. 504–517, Dec. 2024, doi: 10.1093/eurheartj/ehae803.

[142] T. C. Frederiksen, M. K. Christiansen, E. J. Benjamin, A. Olsen, H. K. Jensen, and C. C. Dahm, "Temporal order of atrial fibrillation and acute myocardial infarction and associated prognosis in the Danish Diet, Cancer and Health cohort," *Open Heart*, vol. 12, no. 1, p. e003132, Jan. 2025, doi: 10.1136/openhrt-2024-003132.

[143] A. Santamaria, C. Antón, N. Ibarra, M. Fernández, P. González, and R. Carrasco, "Atrial fibrillation and cognitive decline: A systematic review of pathophysiological mechanisms, therapeutic strategies, and digital health technologies in neuroprotection," *J. Clin. Med.*, vol. 15, no. 5, p. 1744, Feb. 2026, doi: 10.3390/jcm15051744.

[144] B. Caramelli *et al.*, "Effects of dabigatran versus warfarin on 2-year cognitive outcomes in old patients with atrial fibrillation: results from the GIRAF randomized clinical trial," *BMC Med.*, vol. 20, no. 1, p. 374, Oct. 2022, doi: 10.1186/s12916-022-02563-2.

[145] L. Rivard *et al.*, "Anticoagulation to prevent ischemic stroke and neurocognitive impairment in atrial fibrillation: the BRAIN-AF randomized clinical trial," *Nat. Med.*, vol. 32, no. 1, pp. 297–305, Jan. 2026, doi: 10.1038/s41591-025-04101-y.