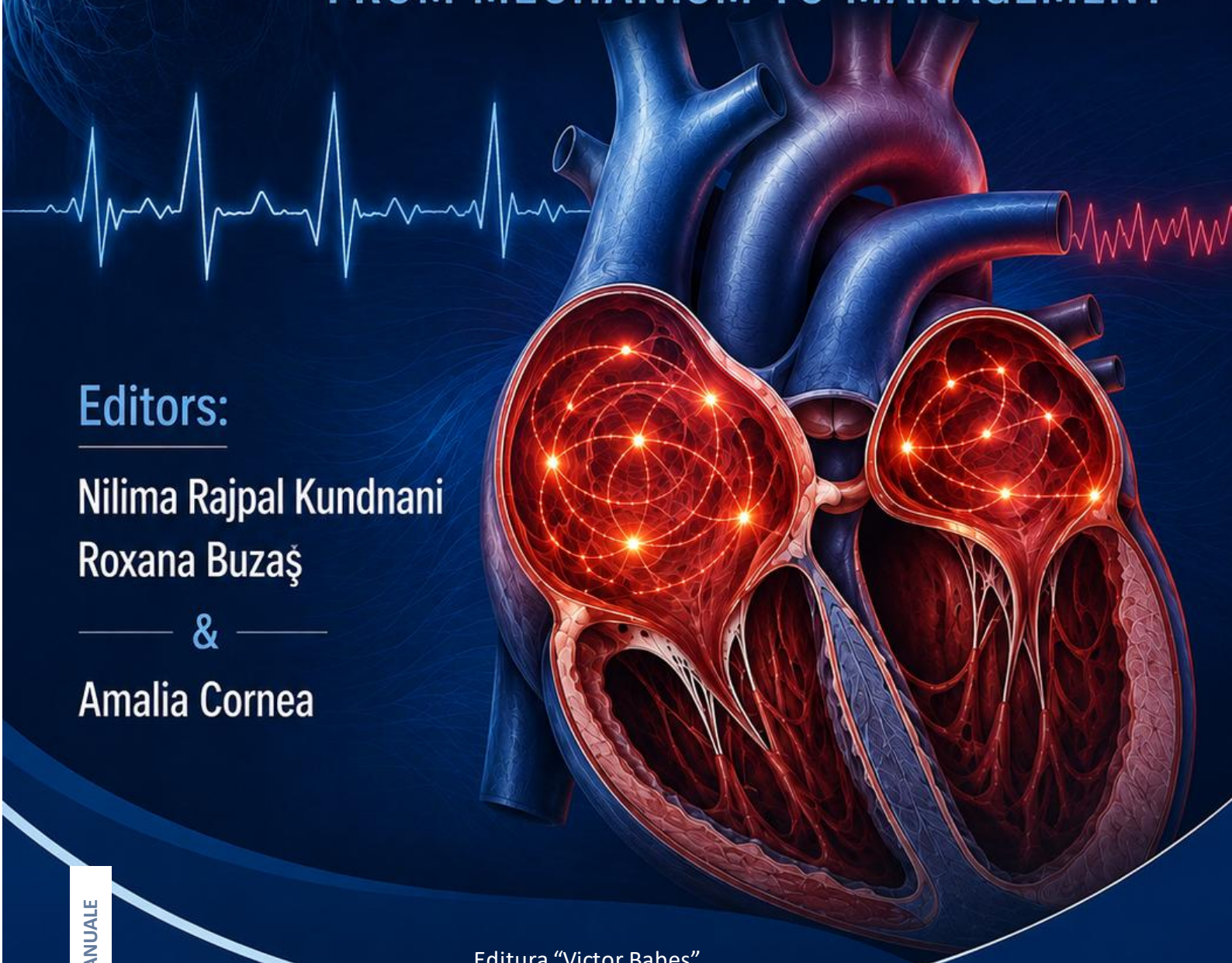
UNIVERSITATEA
DE MEDICINĂ ŞI FARMACIE
„VICTOR BABEŞ“ DIN TIMIŞOARA

ATRIAL FIBRILLATION

FROM MECHANISM TO MANAGEMENT



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Preface

Atrial fibrillation is one of the most widespread and complicated types of arrhythmias, which requires immediate assessment, appropriate diagnosis, and multidisciplinary management. The sustained and paroxysmal forms of this pathology are still considerable problems for the medical community, resulting in morbidity, mortality, and healthcare costs. Over the past decades, the incidence of atrial fibrillation has dramatically increased due to the growing number of elderly people with metabolic syndrome, hypertension, and heart diseases. Nowadays, enhanced management of chronic conditions contributes to the increased survival rate of patients with atrial fibrillation; however, it is complicated by the complex mechanisms of pathogenesis, presentation, and management of thromboembolic prevention and rhythm control. The book aims to focus on the pathophysiological and clinical features of atrial fibrillation from mechanism to management, which can help in understanding this disease better and improving the quality of healthcare. By observing the range of cases with different presentations and therapies, clinicians can identify the wide variety of outcomes and perform more accurate management of their patients. The book highlights the role of pharmacological and interventional treatment factors in the pathophysiology of atrial fibrillation, which may be useful for medical workers in making choices in accordance with the current recommendations. It includes the clinical and electrophysiological characteristics of atrial fibrillation, allowing one to estimate the risk of mortality and make proper therapeutic decisions. Particular attention is paid to the mechanisms of structural remodeling, electrical triggers, anticoagulation pathways, and the clinical consequences in everyday practice. The book can serve as a source of information for medical students, junior doctors, or researchers willing to improve their knowledge. Moreover, the book's considerations can be helpful for medical workers who are interested in the latest achievements in the study of arrhythmia and seek to improve their practice and patient health outcomes. Since the number of patients with arrhythmias and poor health outcomes increases every year, understanding their impact on systemic health and stroke prevention becomes increasingly critical.

Through this book, we aspire to contribute meaningfully to that understanding and to support the ongoing effort to balance therapeutic benefit with patient safety.

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1.1. Definition and Important Historical Milestones

1.1.1. Definition of atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac rhythm disorder encountered in clinical practice, characterized by rapid, chaotic, and disorganized atrial electrical activity, which results in an irregular and often accelerated ventricular rhythm (1,3). From a pathophysiological perspective, this arrhythmia is associated with the loss of effective atrial contraction and impaired synchronization between atrial and ventricular activity (4).

According to current guidelines from the European Society of Cardiology (ESC) and the American Heart Association (AHA), atrial fibrillation is defined as a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation, leading to impaired atrial mechanical function (1–3). Electrocardiographically, it is characterized by the absence of organized P waves, replaced by rapid and irregular oscillations ("f waves"), associated with a completely irregular ventricular rhythm.

Defining features of atrial fibrillation:

- disorganized atrial electrical activity, with a frequency of approximately 350–600 beats per minute (4);
- absence of distinct P waves, replaced by fibrillatory (f) waves, with completely irregular R–R intervals (1);
- loss of atrial contribution to ventricular filling, with decreased cardiac pump efficiency (4,39);
- increased risk of major complications, particularly stroke and heart failure (19,25);
- the diagnosis requires electrocardiographic confirmation via a standard 12-lead recording or a trace of at least 30 seconds showing the fibrillatory rhythm (1).

Atrial fibrillation is associated with significant morbidity, particularly due to thromboembolic complications and heart failure, and is also correlated with a significant increase in mortality, approximately doubling the risk of premature death (14,56).

1.1.2. Historical Milestones in the Discovery and Definition of Atrial Fibrillation

The history of atrial fibrillation reflects the evolution of medical knowledge, from empirical clinical observations to the modern understanding of electrophysiological mechanisms.

The first descriptions of an irregular pulse date back to antiquity. In the early modern period, William Harvey (1578–1657) described the relationship between cardiac contractions and blood circulation, observing irregular movements of the atria in his experiments, suggesting the atrial origin of certain rhythm disorders (4,5). Later, Jean-Baptiste de Senac (1693–1770) made one of the first clinical correlations, linking left atrial dilation in the context of mitral stenosis with the onset of arrhythmias (5).

In the 19th century, Alfred Vulpian introduced the term “fibrillation”, describing the chaotic movements of the myocardium observed experimentally (9).

A major breakthrough occurred with the invention of the electrocardiograph by Willem Einthoven in 1901, which enabled the recording of the heart’s electrical activity (7,8). Subsequently, the first electrocardiographic recordings of atrial fibrillation were obtained, highlighting the absence of P waves and the irregular nature of the ventricular rhythm (7). For his contributions, Einthoven was awarded the Nobel Prize in 1924 (7).

Figure 1. The first electrocardiograph based on the string galvanometer used by Willem Einthoven in the early 20th century (6,7,53).

In 1909, Thomas Lewis demonstrated that “pulsus irregularis perpetuus” is caused by disorganized electrical activity in the atria, thereby consolidating the modern concept of atrial fibrillation (9).

A decisive step in understanding the mechanisms of this arrhythmia was reached in the 1990s, when Haïssaguerre and colleagues identified the role of the pulmonary veins as the primary source of atrial fibrillation (27). This discovery laid the foundation for the development of modern ablation techniques.

In recent decades, technological advances have profoundly transformed the diagnosis of arrhythmias. Electrocardiography has evolved into advanced digital systems, including extended ambulatory monitoring and wearable devices, facilitating the detection of paroxysmal forms of atrial fibrillation (11). Modern Holter monitoring systems allow for continuous recording over extended periods (7–14 days), significantly improving the diagnosis rate of paroxysmal atrial fibrillation and contributing to the optimization of therapeutic management. Moreover, the integration of artificial intelligence enables the early identification of arrhythmic risk, even before obvious clinical manifestation.

1.2. Epidemiology of atrial fibrillation

1.2.1. Global prevalence of atrial fibrillation

The global prevalence of atrial fibrillation (AF) is estimated at approximately 2% of the general population, making it the most common sustained arrhythmia (13,28). The incidence of the disease is steadily increasing, a trend significantly influenced by population aging, the rising prevalence of risk factors, and improvements in diagnostic methods and early detection (13,30).

In Europe, atrial fibrillation is the most common heart rhythm disorder, with a major impact on health and quality of life, particularly among middle-aged and older adults. It is estimated that over 11 million Europeans are affected, corresponding to approximately 2% of the population (28,30). Epidemiological projections indicate a possible doubling of prevalence over the next 50 years, in the context of an aging population (30).

In North America, the prevalence of atrial fibrillation is comparable to that in Europe, with particularly high rates in the United States and Canada. The trend is upward, driven by increased life expectancy and the prevalence of cardiovascular risk factors, such as hypertension, diabetes, and obesity (13,30). In the United States, it is estimated that approximately 4–5% of the adult population is affected (13).

Atrial fibrillation is also a public health issue in Australia, where prevalence is estimated at approximately 1.5–2% in the general population (13).

In Asia, the prevalence of atrial fibrillation is generally lower compared to Western countries, but it is on the rise. South Korea and Taiwan have some of the highest rates, and in Japan, prevalence is particularly high among the elderly (15,16). In China, approximately 10–12 million people are affected, representing about 1.6–1.8% of the adult population (16). In India, the reported prevalence is lower but likely underestimated due to underdiagnosis (15).

In South and Central America, epidemiological data are limited; however, available studies highlight an increase in the incidence of atrial fibrillation and associated complications (20,68).

On the African continent, the prevalence of atrial fibrillation is reported to be lower compared to other regions, though this may reflect limitations in reporting systems and access to diagnosis. Nevertheless, an upward trend similar to that in other regions of the world is observed (21,22).

In conclusion, the global prevalence of atrial fibrillation is steadily increasing, and this condition is considered a “silent pandemic” with a significant impact on quality of life and on healthcare systems (13,28).

Below (Figure 2), the global distribution of atrial fibrillation is illustrated, highlighting significant variations between regions, with a higher incidence in Europe and North America and lower rates in Africa (13,29,63).

Figure 2. Global distribution of atrial fibrillation incidence by continent, showing higher rates in Europe and North America and lower rates in Africa (13,28,63).

1.2.2. Prevalence of atrial fibrillation by age

Atrial fibrillation (AF) is characterized by a progressive increase in prevalence with advancing age, reflecting both the accumulation of new cases and the chronic and recurrent nature of the arrhythmia (23,25,28,67). Age is one of the most important independent risk factors for the development of this arrhythmia. In the general young population, the prevalence of atrial fibrillation is low, typically below 0.5% in people under 50 years of age. After age 60, the prevalence increases significantly, frequently exceeding 3–4%, and in the elderly it can reach values above 10% (25,28,67). In the very elderly, particularly those over 85–90 years of age, the prevalence may exceed 12–15%, highlighting the major impact of the aging process on the development of atrial fibrillation (67).

Data from the *Cardiovascular Health Study* showed a prevalence of atrial fibrillation of 6.2% in men and 4.8% in women among the population aged over 65 (25). In very advanced age subgroups, the prevalence increases further, reflecting the cumulative nature of the disease and its persistence over time.

Similarly, data from the *Framingham Heart Study* demonstrated that the prevalence of atrial fibrillation nearly doubles with each decade of life, highlighting a directly proportional relationship between age and the burden of the disease (23,24,28). This trend is explained by progressive structural and electrical changes in the atria, including fibrosis, dilation, and alterations in electrical conduction.

A particularly important aspect is the cumulative lifetime risk of developing atrial fibrillation. Population-based studies have shown that approximately one in four people (≈25%) will develop atrial fibrillation after the age of 40, underscoring the major impact of this condition at the population level (23,66). (Table 1, Figure 3).

Table 1. Prevalence of atrial fibrillation by age (indicative data) (23,25,28,67)

Age group	Prevalence (%)
<50 years	<0.5%
50–59 years	1–2%
60–69 years	3–4%
70–79 years	5–7%
80–89 years	8–12%
90 years and older	12–15%

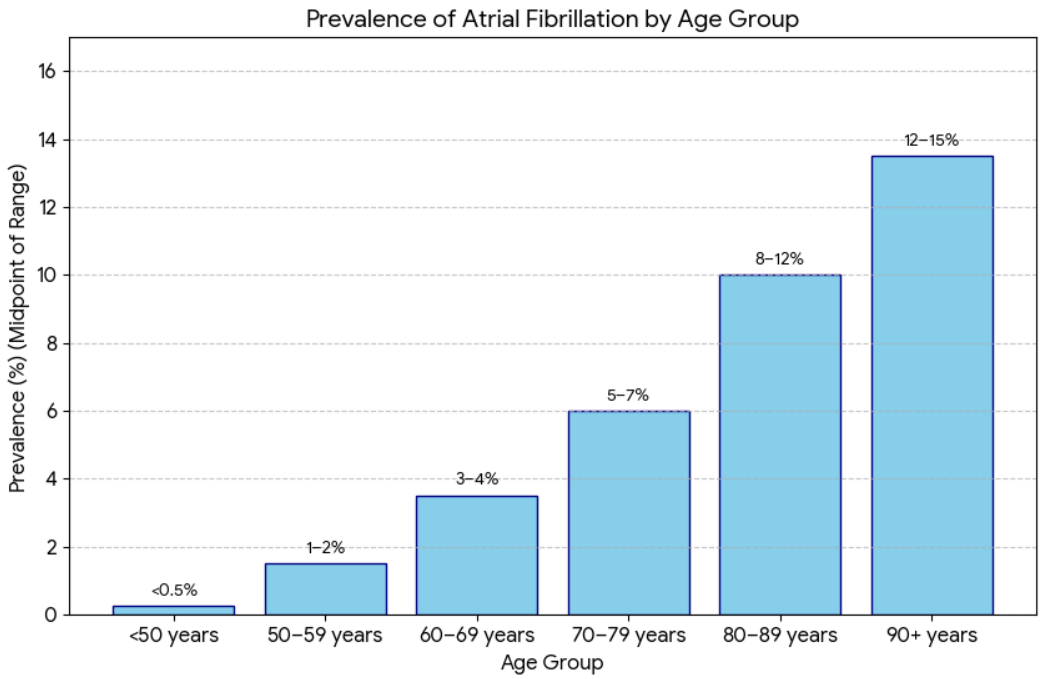

Figure 3. Prevalence (%) by age group

Interpretation and clinical implications

The increase in the prevalence of atrial fibrillation with advancing age reflects the complex interaction between the biological processes of aging and cardiovascular risk factors. Atrial structural remodeling, chronic inflammation, and the accumulation of comorbidities—such as hypertension, diabetes mellitus, and heart failure—create a substrate conducive to the onset and maintenance of arrhythmia (26,35,42).

From a clinical perspective, this distribution has major implications, as older patients not only have a higher prevalence of atrial fibrillation but also a significantly increased risk of complications, particularly stroke and heart failure. Consequently, screening, prevention, and treatment strategies must be specifically tailored to this patient population.

1.2.3. The Impact of Atrial Fibrillation on Public Health

Atrial fibrillation is a major public health problem, having a significant impact on quality of life and placing a substantial burden on healthcare systems (13,28). The increase in prevalence is accompanied by a higher incidence of complications and significant mortality. Across Europe, mortality associated with atrial fibrillation has risen in recent decades (32). The main complications are heart failure and stroke, which significantly influence patient prognosis (31,32,38). In the United States, approximately 10–12 million adults are affected, representing a significant burden on the healthcare system (13,31). In Asia, the impact is amplified by the increased frequency of cardioembolic strokes and the suboptimal use of anticoagulant therapy (16,18,60). Globally, approximately one-third of strokes are attributed to atrial fibrillation (18).

Atrial fibrillation is associated with:

- an approximately 5-fold increase in the risk of stroke (57);
- an increased risk of heart failure (60);
- increased overall mortality (62);
- reduced functional capacity and quality of life (37).

The economic impact is considerable, including significant direct and indirect costs related to hospitalizations, chronic treatment, interventional procedures, and long-term monitoring (35,36).

In conclusion, atrial fibrillation represents a major global public health problem, requiring effective strategies for prevention, early diagnosis, and appropriate management.

1.3. Cardiac Electrophysiology and Cardiac Electrical Activity

1.3.1. General Concept

Cardiac electrophysiology refers to the set of mechanisms by which electrical activity is generated, propagated, and coordinated within the myocardium, ensuring the rhythmic and efficient contraction of the heart. Under physiological conditions, this activity is strictly organized and dependent on the integrated functioning of the conduction system, cellular electrical properties, and transmembrane ionic fluxes (70,71).

1.3.2. The Normal Cardiac Conduction System (Figure 4)

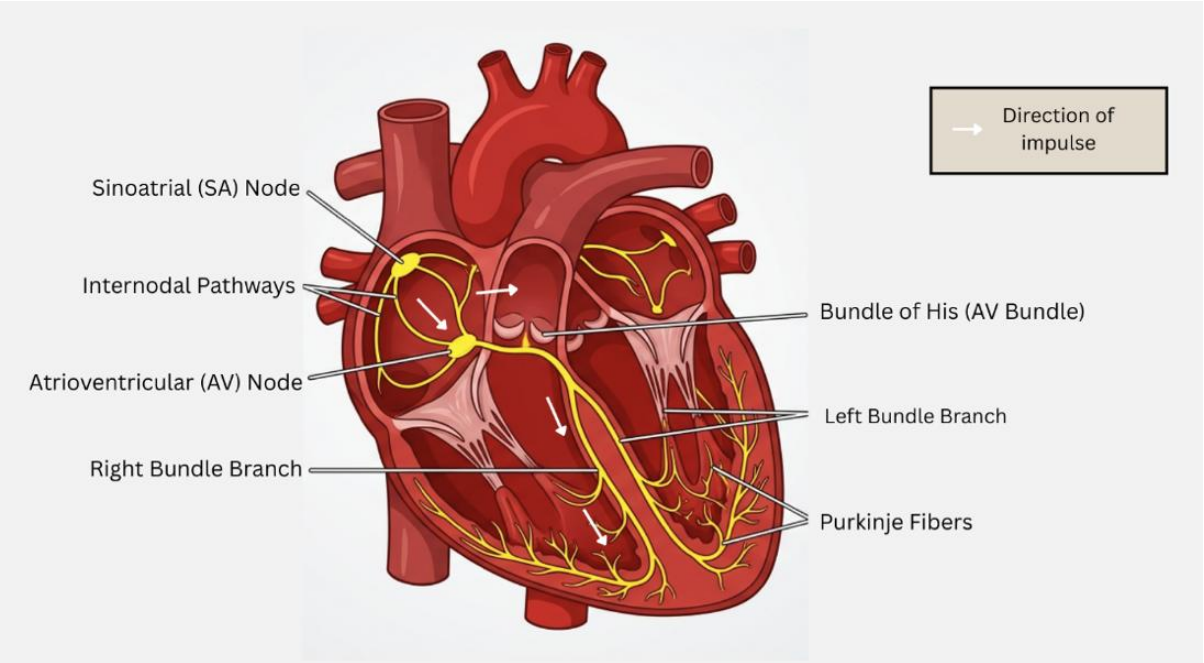

Figure 4. Heart rhythm conduction system

1. Sinus node – the generator of the heart rhythm

Cardiac electrical activity is initiated at the sinoatrial node due to the automaticity determined by spontaneous diastolic depolarization, generated by the influx of Na^+ (If), Ca^{2+}, and the reduction of K^+ efflux (70).

2. Atrial and atrioventricular conduction pathways

The electrical impulse propagates through:

- the internodal pathways (anterior, middle, posterior)
- the Bachmann bundle (toward the left atrium)

This propagation causes synchronous depolarization of the atria, reflected by the P wave (70,71).

3. Atrioventricular node – modulation of conduction

At the AV node, conduction is slowed due to Ca^{2+} dependence and tissue structure, resulting in:

- physiological delay
- atrioventricular synchronization

This corresponds to the PR interval on the ECG (70).

4. The His–Purkinje system – ventricular conduction

The impulse is rapidly transmitted through the His bundle, its branches, and the Purkinje network, causing synchronous depolarization of the ventricles, as evidenced by the QRS complex (70,71).

1.3.3. Electrophysiological properties of cardiac cells

- automaticity
- excitability
- conductivity
- refractoriness

These are regulated by Na^+, Ca^{2+}, and K^+ ionic currents (70,71).

1.3.4. Action Potential and Cardiac Excitability (Figure 5)

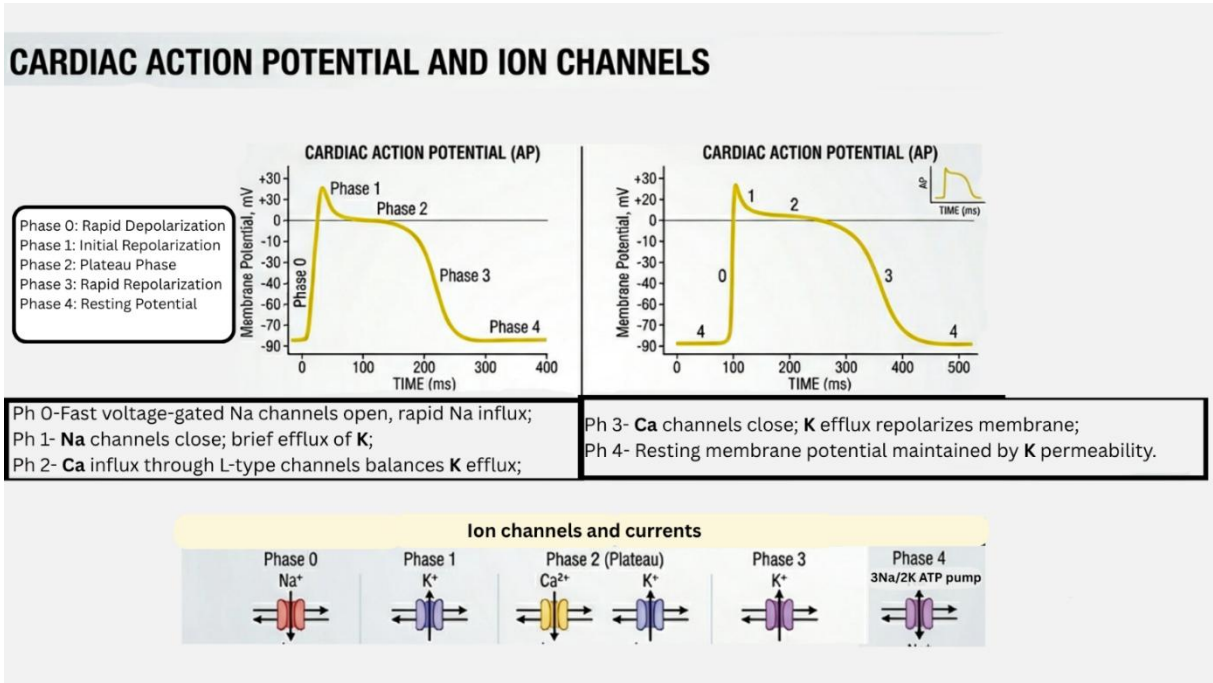

Figure 5. *Atrial and ventricular action potential*

Membrane potential changes are determined by transmembrane ion movements across the different phases of the action potential:

- **Phase 0 (depolarization)**: Na^+ influx → positive → **non-excitable**
- **Phase 1 (initial repolarization)**: brief K^+ influx + closure of Na^+ channels
- **Phase 2 (plateau)**: Ca^{2+} influx + K^+ ATPase → contraction → **non-excitable**
- **Phase 3 (repolarization)**: K^+ efflux → negative → returning excitability
- **Phase 4 (rest)**: Na^+ efflux, K^+ influx, ATPase, Ca^2 efflux, ATPase → negative → **excitability**

Principle: a negative membrane potential corresponds to an excitable state, whereas a positive membrane potential corresponds to a non-excitable state (70).

1.3.5. Cardiac electrical activity

1. Atrial electrical activity

Atrial depolarization begins in the sinoatrial node and propagates to the left atrium via the Bachmann bundle, causing synchronous contraction of the atria ("atrial kick"). This is reflected by the P wave (70,71). Atrial conduction is rapid and uniform, and refractoriness prevents premature re-excitation.

2. Ventricular electrical activity

Ventricular electrical activity is responsible for the efficient contraction of the heart and the ejection of blood.

a. Ventricular depolarization

The impulse travels through the His–Purkinje system and causes: a rapid influx of Na^+

- positive interior cells are non-excitable
- the QRS complex appears (70,71)

b. Plateau phase (contraction)

- Ca^{2+} influx
- K^+ efflux
- depolarization is maintained
- ventricular contraction is allowed
- corresponds to the ST segment

c. Ventricular repolarization

- K^+ efflux
- return to negative—excitability returns
- corresponds to the T wave (70,71)

d. Return to rest

- phase 4 → the cell becomes excitable again

- ready for a new cardiac cycle

1.3.6. Integration of electrophysiological mechanisms

Cardiac electrical activity results from:

- the initiation of the impulse in the SA node
- atrial propagation → P wave
- AV delay → PR interval
- ventricular depolarization → QRS
- plateau → ST
- repolarization → T wave

This sequence reflects the relationship between ionic currents, action potential, and excitability.

1.3.7. Conclusion

The heart's electrical activity results from the interaction between ionic flows and cellular properties, causing the alternation between the excitable and non-excitable states. The integration of atrial and ventricular activity ensures the heart's efficient functioning, and the expression of these processes on the ECG allows for the assessment of cardiac physiology and pathology (70,71).

1.4. Pathophysiology of atrial fibrillation

1.4.1. General Concept

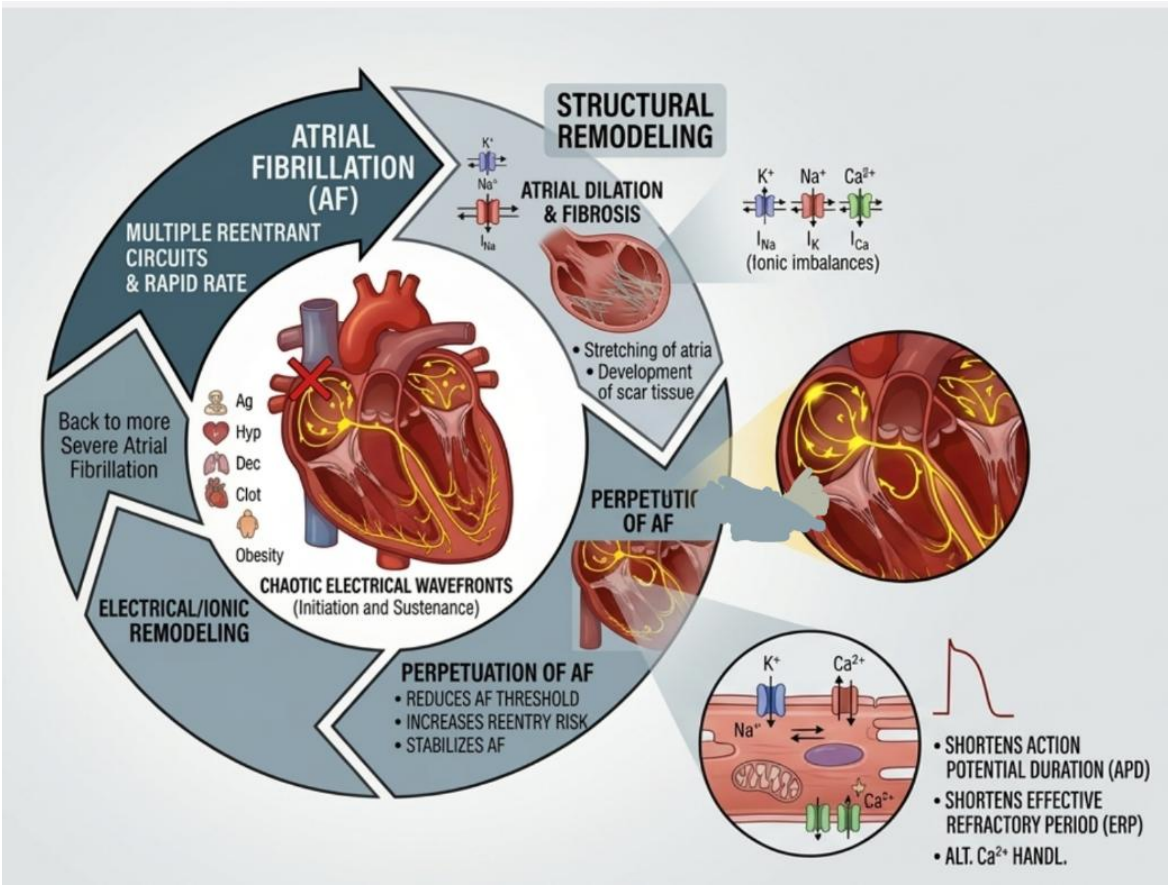

Figure 6. Pathophysiology of atrial fibrillation

Atrial fibrillation (AF) is a supraventricular arrhythmia characterized by rapid, disorganized, and asynchronous electrical activity in the atria, associated with a loss of effective contractile function. From a pathophysiological perspective, this arrhythmia results from the interaction between ectopic trigger foci and a vulnerable atrial substrate, which allows the emergence and maintenance of multiple re-entry mechanisms (70,72,75).

1.4.2. Initiation of atrial fibrillation, ectopic foci, and their role as triggers

In most cases, atrial fibrillation is initiated in the pulmonary veins, which contain myocardial fibers with unique electrophysiological properties (72). Thus, at this level, instability in intracellular calcium homeostasis leads to the occurrence of late post-depolarization, which, in turn, result in the development of abnormal automaticity. Consequently, rapid and premature electrical impulses are generated, which bypass the control exerted by the sinoatrial node and penetrate the atrial myocardium. Therefore, these ectopic foci act as triggers, initiating atrial fibrillation (72).

1.4.3. Propagation of Atrial Electrical Activity

Under physiological conditions, the atrial electrical impulse propagates uniformly, allowing for the synchronous activation of the atria. In atrial fibrillation, however, conduction becomes irregular due to the presence of areas of slow conduction and functional blocks. In this context, the initial electrical impulse progressively fragments, generating multiple electrical waves that propagate in different directions. As a result, atrial electrical activity becomes chaotic and uncoordinated (73).

1.4.4. The central mechanism—multiple reentry (Figure 7)

The fundamental mechanism that sustains atrial fibrillation is multiple reentry. This occurs when an electrical impulse circulates repeatedly in a closed circuit instead of dying out. For this mechanism to occur, several conditions are necessary: first, a shortened refractory period; second, the presence of slow conduction; and third, the presence of anatomical or functional obstacles. Thus, the electrical impulse encounters heterogeneous zones, splits, and subsequently, some waves find circular pathways, returning to the point of origin before the tissue becomes refractory. Consequently, re-entry circuits form, multiply, and self-sustain, maintaining atrial fibrillation (73).

1.4.5. Atrial Remodeling

A key aspect of the pathophysiology of AF is that this arrhythmia induces structural and functional changes that promote its persistence, a phenomenon described by the concept "atrial fibrillation generates atrial fibrillation" (75).

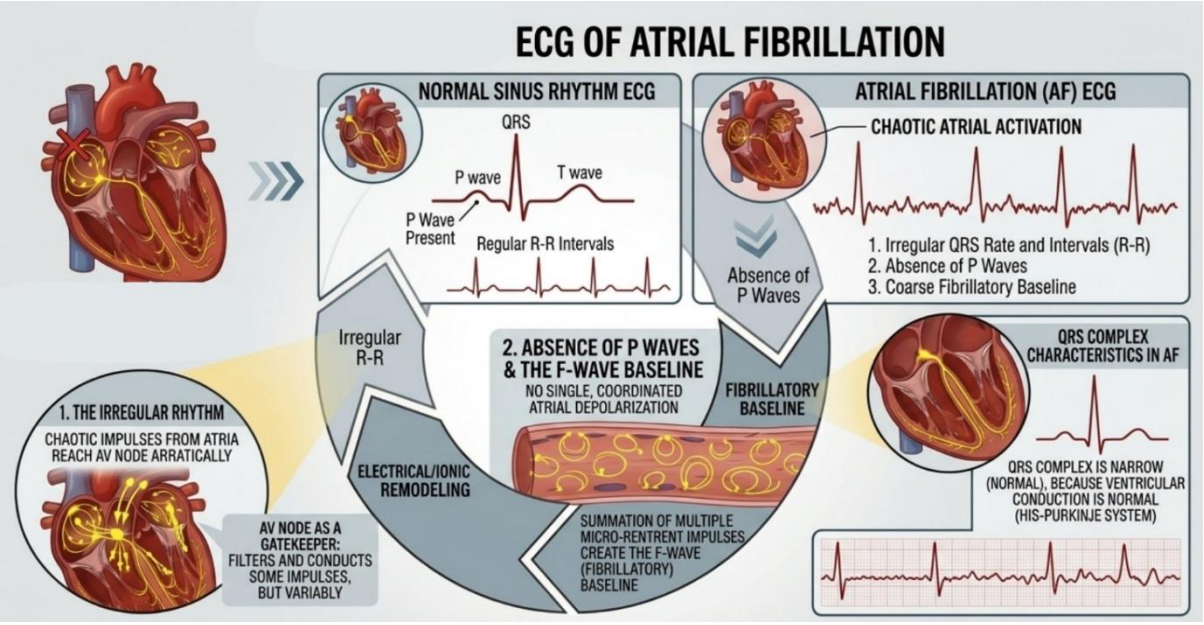

Figure 7. Atrial fibrillation ECG

1. Electrical remodeling

First, atrial fibrillation causes changes in ionic currents, characterized by a decrease in calcium current and an increase in potassium currents. As a result, the action potential shortens, and the refractory period is reduced. Consequently, myocardial cells can be depolarized more rapidly, which promotes the onset and maintenance of reentry circuits (70).

2. Structural Remodeling

Second, chronic exposure to hemodynamic and inflammatory factors leads to the development of atrial fibrosis and dilation of the atrial chambers. These changes result in discontinuities in the myocardial structure and the formation of conduction blocks. Therefore, the atrial substrate becomes heterogeneous, facilitating abnormal impulse propagation and promoting reentry (70).

3. Contractile Remodeling

Thirdly, disorganized electrical activity causes a loss of effective atrial contraction, leading to blood stasis, particularly in the left atrial appendage. This leads to an increased risk of thrombus formation and thromboembolic events.

1.4.6. The Role of the Autonomic Nervous System

The autonomic nervous system influences both the initiation and maintenance of atrial fibrillation. Thus, sympathetic activation increases myocardial excitability and promotes the emergence of ectopic foci, while parasympathetic activation shortens the atrial refractory period, facilitating reentry mechanisms. As a result, the imbalance between these two components contributes to atrial electrical instability.

1.4.7. Inflammation and Oxidative Stress

In addition, systemic inflammation plays an important role in the pathophysiology of AF. Elevated levels of proinflammatory cytokines cause oxidative stress, which activates fibroblasts and contributes to the development of atrial fibrosis. Consequently, these processes alter the electrical and structural properties of the myocardium, promoting the onset and maintenance of atrial fibrillation (76).

In conclusion, atrial fibrillation arises as a result of a complex process in which ectopic foci generate rapid impulses, which, in the presence of an altered atrial substrate, cause uneven conduction and promote multiple reentrant circuits. Subsequently, the persistence of the arrhythmia leads to progressive atrial remodeling, which stabilizes the arrhythmic mechanism and contributes to the chronicity of atrial fibrillation (70,73,75).

In Figure 8, we present the main differences in the initiation and propagation of the electrical impulse under normal conditions and in the case of atrial fibrillation, along with the corresponding electrocardiographic findings.

1.4.8. Integration of mechanisms

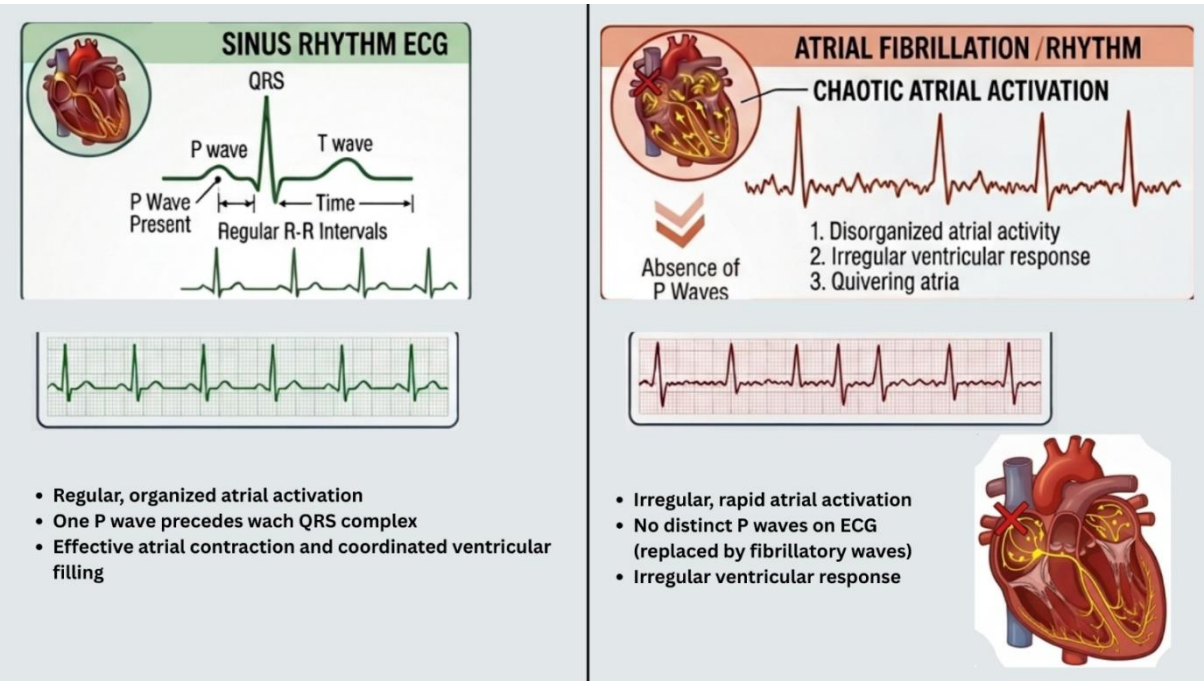

Figure 8. Atrial fibrillation: abnormal conduction in the atria comparison with normal rhythm

1.5. Classification of AF

Atrial fibrillation is classified using multiple systems based on temporal, etiological, and clinical- al parameters that reflect the complexity of this arrhythmia.

The most widely used classification today is derived from the guidelines of European and American cardiology societies, which categorize forms of AF based on the duration and behavior of the arrhythmia. Thus, based on the aforementioned parameters, AF can be:

- paroxysmal
- persistent
- long-standing persistent
- permanent

Below we present the main characteristics of the forms mentioned above.

1.5.1. Paroxysmal atrial fibrillation

Introduction

Atrial fibrillation is a complex cardiac rhythm disorder characterized by disorganized electrical activity in the atria and the loss of effective atrial contraction (1,4). In this context, the paroxysmal form constitutes, in most cases, the initial stage of this arrhythmia, marked by transient episodes that appear and disappear spontaneously (1–3). Thus, this phase reflects an early stage of the disease, in which triggering mechanisms predominate in the absence of significant structural changes (27). (Figure 9)

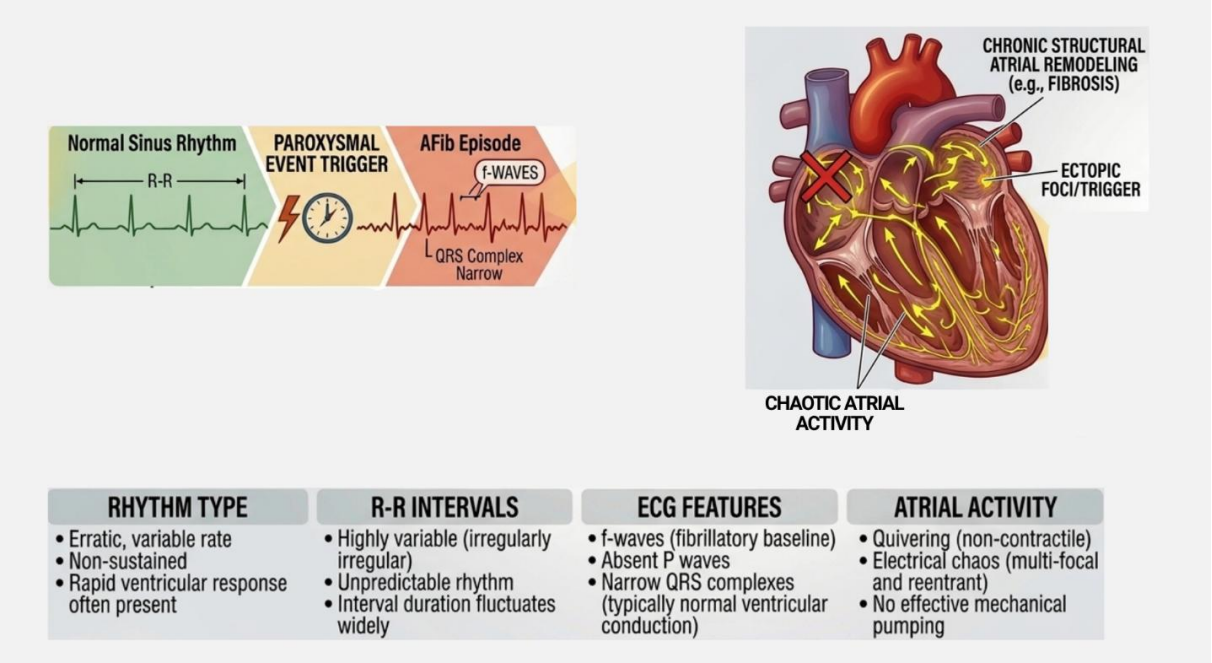

Figure 9. The main characteristics of paroxysmal atrial fibrillation

Definition and Classification

Paroxysmal atrial fibrillation is characterized by episodes that begin suddenly, resolve spontaneously, and do not exceed 7 days in duration, typically stopping within the first 24–48 hours, often without pharmacological treatment (1–3). In this sense, it is part of an evolutionary continuum of atrial fibrillation, alongside the persistent and permanent forms (1,3). Unlike these, in the paroxysmal stage, triggering mechanisms predominate, and the atrial substrate is still relatively preserved (27).

Epidemiological data

Paroxysmal atrial fibrillation accounts for a significant proportion of all cases of atrial fibrillation, estimated at approximately one-third (28,33). However, the prevalence of this form is likely underestimated, as many episodes are short-lived or asymptomatic and go undetected clinically (13). Furthermore, this form is commonly seen in middle-aged patients, but it can also occur in younger individuals, particularly in the absence of structural heart disease (33). With advancing age, the likelihood of progression to persistent forms increases (33).

Pathophysiology of Paroxysmal Atrial Fibrillation

a. General principles

The onset of paroxysmal atrial fibrillation involves two essential components: the presence of active trigger foci and a susceptible but incompletely remodeled atrial substrate (27). Therefore, at this stage, the arrhythmia is more dependent on acute events than on stable structural changes.

b. Sources of ectopic activity (triggers)

The most important trigger foci are located in the pulmonary veins, which contain extensions of myocardial tissue capable of generating rapid and repetitive electrical impulses (27). Thus, these discharges can disrupt the normal electrical activity of the atria and initiate atrial fibrillation.

c. Characteristics of the atrial substrate

In paroxysmal atrial fibrillation, the atria do not yet exhibit extensive structural changes. However, there may be local discrepancies in electrical conduction and a shortening of the refractory period (27). Consequently, these changes are largely reversible, which explains the tendency of episodes to stop spontaneously.

d. Maintenance mechanisms

Once triggered, fibrillation is sustained by multiple circuits of disorganized electrical activation and complex interactions between activation waves (27). However, in the early stages, these mechanisms are not stable enough to sustain the arrhythmia in the long term.

Etiological factors and associated conditions

Paroxysmal atrial fibrillation (AF) occurs in a broad range of clinical contexts and is frequently associated with both cardiovascular and extracardiac conditions. From a cardiovascular perspective, the most commonly implicated conditions include hypertension (41), coronary artery disease, heart failure (43), and valvular heart disease (48). *Extracardiac factors* also contribute

significantly to AF pathogenesis, including hyperthyroidism (53), alcohol consumption (49,50), obstructive sleep apnea (46,47), and obesity (44). Furthermore, acute triggers such as physical or emotional stress, infections, and surgical procedures may precipitate AF episodes. In certain situations, particularly in young people, atrial fibrillation may occur in the absence of identifiable heart disease, suggesting a role for genetic factors or autonomic regulation (54–56).

Electrocardiographic characteristics

The diagnosis is based on typical changes in cardiac electrical activity, namely the absence of organized P waves, the presence of rapid and irregular atrial electrical activity, completely variable R–R intervals, and an irregular ventricular rhythm (1). In addition, the ventricular rate is often elevated during episodes, and between episodes the electrocardiographic pattern may return to normal.

Clinical Manifestations

Clinical presentation is variable and includes palpitations, dyspnea, fatigue, decreased exercise tolerance, and dizziness, and is sometimes asymptomatic (13). Furthermore, there are situations in which episodes are completely asymptomatic and are discovered incidentally.

Course

Paroxysmal atrial fibrillation is not a static condition. Thus, over time, episodes may become more frequent, prolonged, and difficult to terminate. This phenomenon reflects the progressive remodeling of atrial tissue and the self-sustaining nature of the arrhythmia (27).

Complications

Even in its paroxysmal form, atrial fibrillation can lead to the formation of atrial thrombi and emboli, stroke (57), heart failure (60), and impaired quality of life (37). Therefore, the risk of thromboembolism is present and must be assessed on an individual basis.

Conclusions

In conclusion, paroxysmal atrial fibrillation represents an initial stage of a dynamic disease, characterized by transient episodes generated by ectopic foci on a substrate that is still reversible. Therefore, understanding this form is essential, as early intervention can influence the subsequent course and prevent severe complications.

1.5.2. Persistent atrial fibrillation

Introduction

Persistent atrial fibrillation represents an advanced stage of atrial arrhythmia, characterized by prolonged maintenance of disorganized electrical activity and the inability to spontaneously return to sinus rhythm (1,3). Thus, this form reflects the existence of an altered atrial substrate capable of sustaining the arrhythmia continuously (27). (Figure 10)

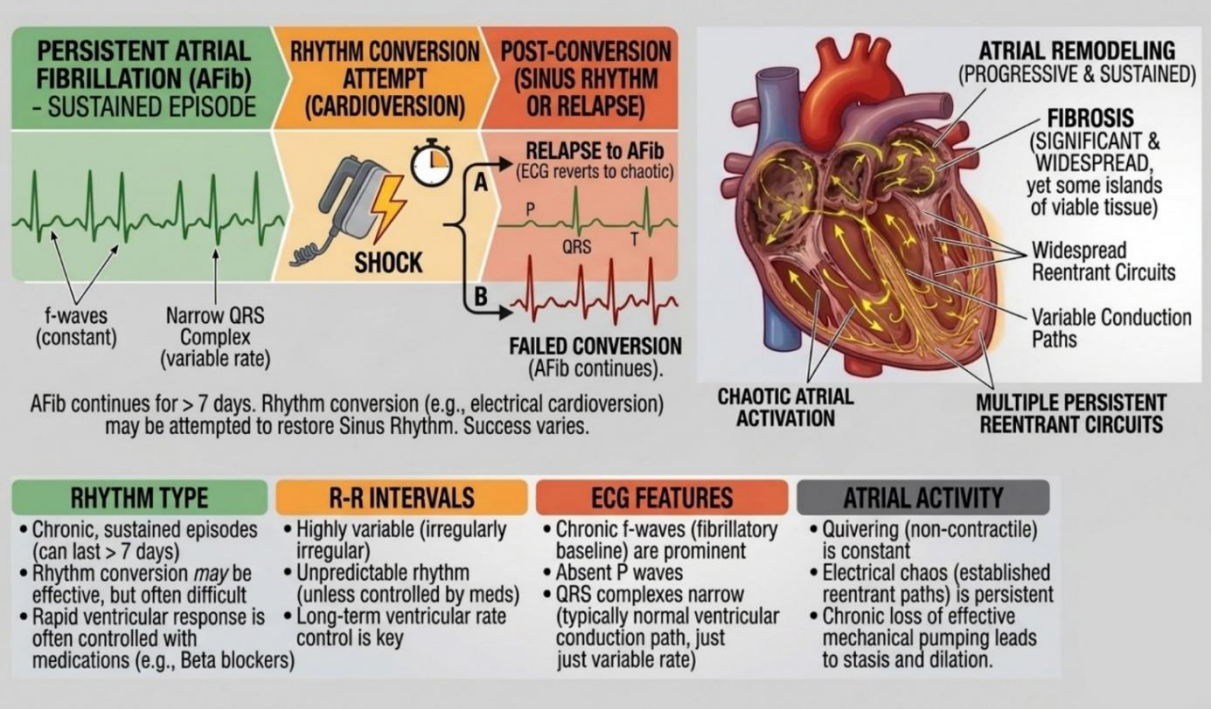

Figure 10. The main characteristics of persistent atrial fibrillation

Definition and Classification

Persistent atrial fibrillation is characterized by episodes lasting more than 7 days, which do not resolve spontaneously and require therapeutic intervention to restore sinus rhythm (1–3). Therefore, this form marks the transition from a trigger-dependent arrhythmia to a self-sustaining one (27).

Epidemiology

Persistent atrial fibrillation is more common in elderly patients and in those with structural cardiovascular disease (28,33). Furthermore, its prevalence increases with disease progression and the accumulation of cardiovascular risk factors (13,28).

Pathophysiology

a. General Mechanisms

From a pathophysiological perspective, the arrhythmia is sustained by a remodeled atrial substrate, characterized by electrical and structural changes (27,92).

b. Triggers

Although triggers can initiate arrhythmia, their role becomes secondary to the altered atrial substrate (27).

c. Atrial Substrate

Structural changes include atrial fibrosis, atrial dilation, and conduction heterogeneity (26,27). Thus, these changes promote the perpetuation of arrhythmia.

d. Maintenance mechanisms

In this context, re-entry circuits become stable, allowing for the continuous maintenance of atrial fibrillation (92).

Etiology and risk factors

Persistent atrial fibrillation is associated with chronic hypertension (41), heart failure (43), valvular heart disease (48), cardiomyopathies (64,65), and advanced age (23,25). Thus, these factors contribute significantly to the onset and maintenance of the arrhythmia.

Electrocardiographic Characteristics

Persistent atrial fibrillation is characterized by the absence of organized P waves, disorganized atrial activity, completely irregular R–R intervals, and an irregular ventricular rhythm (1). Unlike the paroxysmal form, these changes are persistent over time, and the ventricular rate is frequently controlled therapeutically.

Clinical manifestations

Clinical manifestations are generally more persistent and include palpitations, dyspnea, fatigue, and decreased exercise tolerance (13). Additionally, there is an increased risk of cardiac decompensation, particularly in patients with comorbidities.

Course

Persistent atrial fibrillation may progress to the permanent form, in the context of progressive atrial remodeling and the stabilization of mechanisms maintaining the arrhythmia (92,93).

Complications

Complications include an increased risk of thromboembolism, including stroke (57), heart failure (60), as well as impaired ventricular function and increased mortality (62).

Conclusion

In conclusion, persistent atrial fibrillation reflects an advanced stage of the disease, characterized by an altered atrial substrate and an increased tendency for arrhythmia maintenance. Therefore, it requires a comprehensive therapeutic approach, aimed at both rhythm control and the prevention of complications.

1.5.3. Long-standing persistent atrial fibrillation

Introduction

Long-standing persistent atrial fibrillation represents an advanced stage in the progression of atrial fibrillation, characterized by the continuous maintenance of arrhythmia over extended periods (1,3). In this context, this form reflects the consolidation of a profoundly remodeled atrial substrate, in which structural and electrical changes favor the stabilization and perpetuation of the arrhythmia (27,33). (Figure 11)

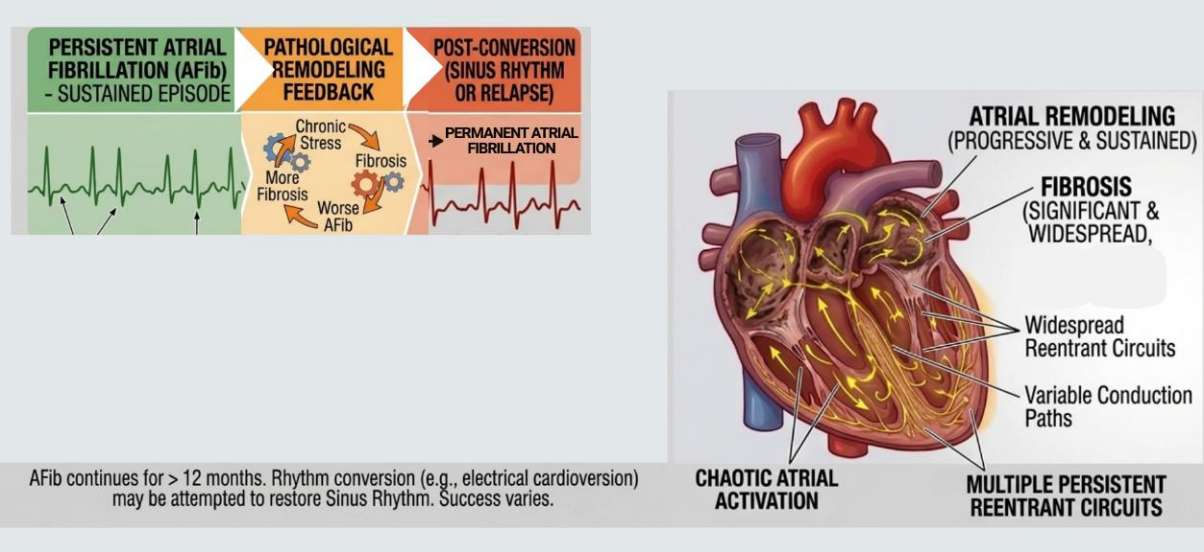

Figure 11. The main characteristics of long-standing persistent atrial fibrillation

Definition and Classification

Long-standing persistent atrial fibrillation is defined as continuous atrial fibrillation lasting >12 months, in the context of maintaining the therapeutic intent to restore sinus rhythm (1–3). Thus, this form falls between persistent and permanent atrial fibrillation, representing a phase in which the arrhythmia is stable but still susceptible to conversion (1,3).

Epidemiology

This form is more common in elderly patients, in those with multiple cardiovascular comorbidities, and in patients with a long history of atrial fibrillation (28,33). Furthermore, the prevalence of s increases with disease duration and the severity of atrial remodeling (13,28).

Pathophysiology

a. General Mechanisms

The arrhythmia is sustained by a complex, stable, and extensive atrial substrate (27,33).

b. Triggers

The role of triggers becomes minimal, as the arrhythmia is predominantly self-sustaining (27).

c. Atrial Substrate

Changes include extensive atrial fibrosis, significant atrial dilation, and alterations in electrical conduction (26,27). Consequently, these changes reduce the likelihood of spontaneous return to sinus rhythm.

d. Maintenance mechanisms

Reentry circuits are stable and well-organized, facilitating the continuous maintenance of the arrhythmia (27,33).

Etiology and risk factors

Factors involved include long-standing hypertension (41), chronic heart failure (43), advanced valvular heart disease (48), cardiomyopathies (64,65), advanced age (23,25), as well as obesity and obstructive sleep apnea (44,46).

Electrocardiographic characteristics

Long-standing persistent atrial fibrillation is characterized by the absence of P waves, persistent fibrillatory waves, chronically irregular ventricular rhythm, and variable ventricular rate, which is frequently controlled by therapy (1).

Clinical manifestations

Clinical manifestations are usually chronic and include dyspnea, fatigue, and reduced exercise tolerance (13). Episodes of cardiac decompensation may also occur.

Course

This form tends to progress to permanent atrial fibrillation, in the context of progressive atrial remodeling and the stabilization of arrhythmia mechanisms (27,33).

Complications

Complications include significant thromboembolic risk (57), progressive heart failure (60), and increased mortality (62).

Conclusions

In conclusion, long-standing persistent atrial fibrillation reflects an advanced stage of the disease, characterized by stabilization of the arrhythmogenic substrate and a reduced likelihood of conversion to sinus rhythm. Therefore, it requires complex and individualized therapeutic strategies.

1.5.4. Permanent atrial fibrillation

Introduction

Permanent atrial fibrillation represents the final stage of atrial fibrillation progression, in which the arrhythmia is accepted as the definitive heart rhythm (1,3). In this context, this stage reflects both irreversible structural changes in the atria and a therapeutic decision to no longer pursue restoration of sinus rhythm, as shown in Figure 12. (1).

Definition and Classification

Permanent atrial fibrillation is characterized by the continuous presence of atrial fibrillation, the absence of attempts to convert to sinus rhythm, and the acceptance of the arrhythmia as the definitive rhythm (1–3). Therefore, this classification is predominantly clinical and decision-based, rather than exclusively biological.

Epidemiology

Permanent atrial fibrillation is commonly seen in elderly patients, in individuals with advanced cardiovascular disease, and in patients with a long history of atrial fibrillation (28,33). Furthermore, the prevalence of this form increases progressively with age and the accumulation of comorbidities (13,28).

Pathophysiology

From a pathophysiological perspective, the arrhythmia is completely self-sustaining and independent of triggers, being maintained by a profoundly remodeled atrial substrate (27,33). Consequently, at this stage, triggers no longer play a relevant role in maintaining the arrhythmia (27).

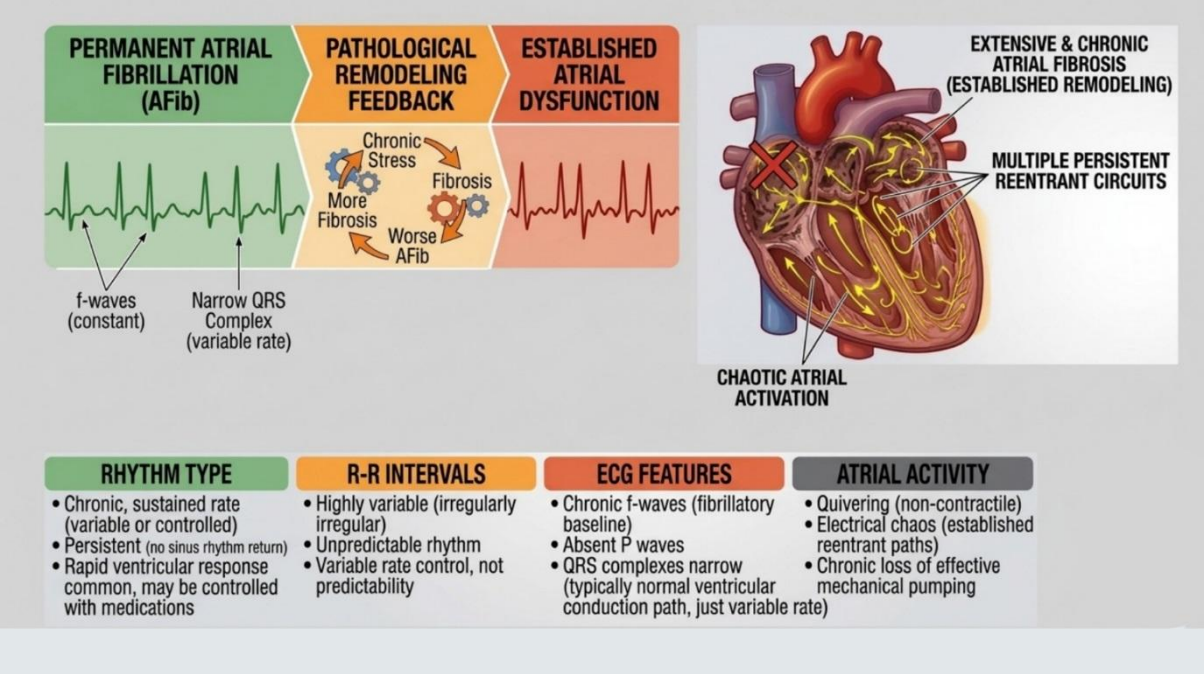

Figure 12. The main characteristics of permanent atrial fibrillation

Regarding the atrial substrate, changes include extensive fibrosis, severe structural remodeling, and loss of normal electrical properties (26,27). At the same time, the maintenance mechanisms consist of stable and permanent re-entry circuits with no tendency to terminate (27,33).

Etiology and Risk Factors

Permanent atrial fibrillation is primarily associated with advanced structural heart disease, severe heart failure, and chronic valvular heart disease (43,48). Additionally, advanced age and the presence of multiple comorbidities significantly contribute to the onset and maintenance of this form (23,25,28).

Electrocardiographic characteristics

From an electrocardiographic perspective, permanent atrial fibrillation is characterized by the absence of P waves, the presence of persistent fibrillatory waves, and a permanently irregular

ventricular rhythm. At the same time, the ventricular rate is variable and may be controlled or uncontrolled (1).

Clinical manifestations

Clinical manifestations are variable, sometimes including well-tolerated forms; however, in other situations, patients experience functional limitation or frequent episodes of cardiac decompensation (13).

Course

Permanent atrial fibrillation represents the final stage of the disease and is characterized by the absence of a tendency to return to sinus rhythm, in the context of irreversible atrial remodeling (27,33).

Complications

In terms of complications, this form is associated with an increased risk of stroke, the onset of heart failure, and a significant decline in quality of life (37,57,60).

Conclusions

In conclusion, permanent atrial fibrillation represents the final stage of atrial remodeling, in which the arrhythmia becomes stable and permanent. Thus, therapeutic management focuses primarily on controlling ventricular rate and preventing thromboembolic complications (1,3).

1.6. Main Risk Factors for Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice, resulting from a complex interaction between the atrial structural substrate, electrical remodeling, and various systemic risk factors. In particular, obesity, hypertension, coronary artery disease, valvular heart disease, sleep apnea syndrome, and alcohol consumption play a key role in both the onset and persistence of this arrhythmia, as illustrated in Figure 13.

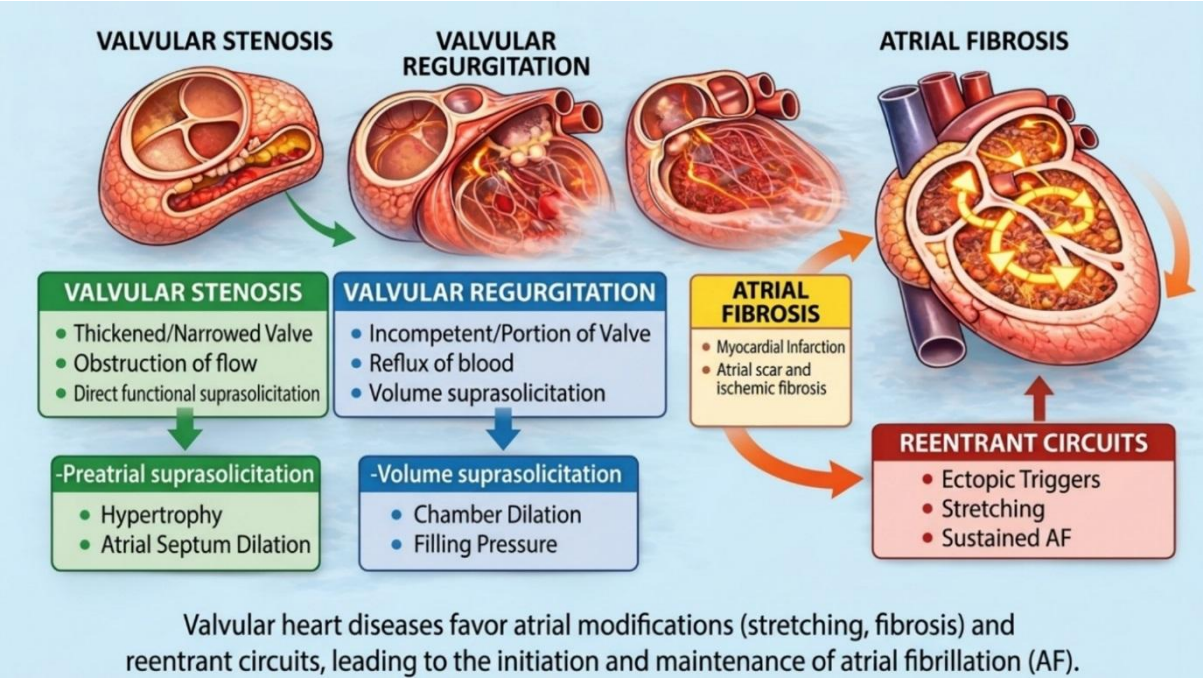

Figure 13. The main risk factors for atrial fibrillation

1.6.1. Hypertension (HTN)

Hypertension is the most common risk factor associated with atrial fibrillation, playing a central role in structural cardiac remodeling (41,42).

Prevalence and relative risk

It is estimated that between 50% and 70% of patients with AF have HTN, and the risk of developing arrhythmia is approximately 1.5–2 times higher than in normotensive individuals (41).

Pathophysiological mechanisms

HTN causes left ventricular hypertrophy and diastolic dysfunction, which leads to increased atrial pressure and left atrial dilation. These changes promote electrical remodeling and the development of re-entry circuits (26,41).

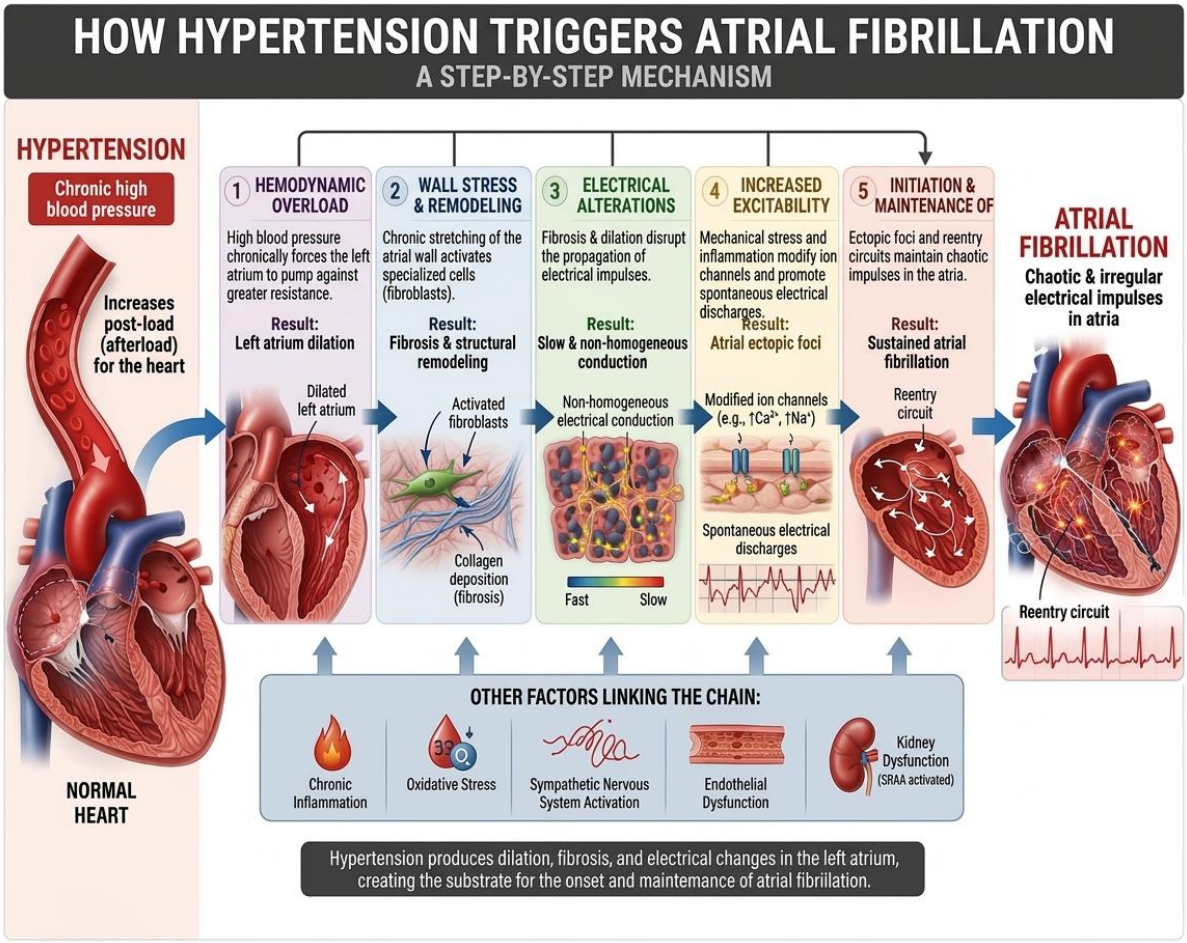

Figure 14. HPB and atrial fibrillation

Course and clinical implications

In this context, AF tends to become persistent, and the risk of recurrence is increased. Furthermore, hypertension contributes significantly to thromboembolic risk, being an important component in risk stratification scores (57).

Prognosis

The prognosis is poor in the absence of adequate blood pressure control, with an increased incidence of stroke and heart failure (41,57).

1.6.2. Coronary artery disease

Coronary artery disease (CAD) is a major risk factor for atrial fibrillation; its involvement being determined both by the effects of myocardial ischemia on the atrial substrate and by interaction with other cardiovascular factors (42,45).

Prevalence and relative risk

From an epidemiological perspective, atrial fibrillation is found in approximately 20–30% of patients with documented ischemic heart disease. At the same time, the presence of coronary artery disease increases the risk of developing AF by approximately 1.4–1.7 times compared to the population without cardiovascular disease (42).

Pathophysiological mechanisms

The mechanisms involved are complex and multifactorial. First, myocardial ischemia causes alterations in cellular metabolism and promotes the development of atrial fibrosis, leading to electrical heterogeneity. Second, impaired atrial perfusion contributes to changes in electrophysiological properties, including a shortened refractory period and the formation of re-entry circuits (26,42). Furthermore, post-infarction ventricular remodeling, associated with increased filling pressures, causes left atrial dilation, reinforcing the arrhythmogenic substrate (42).

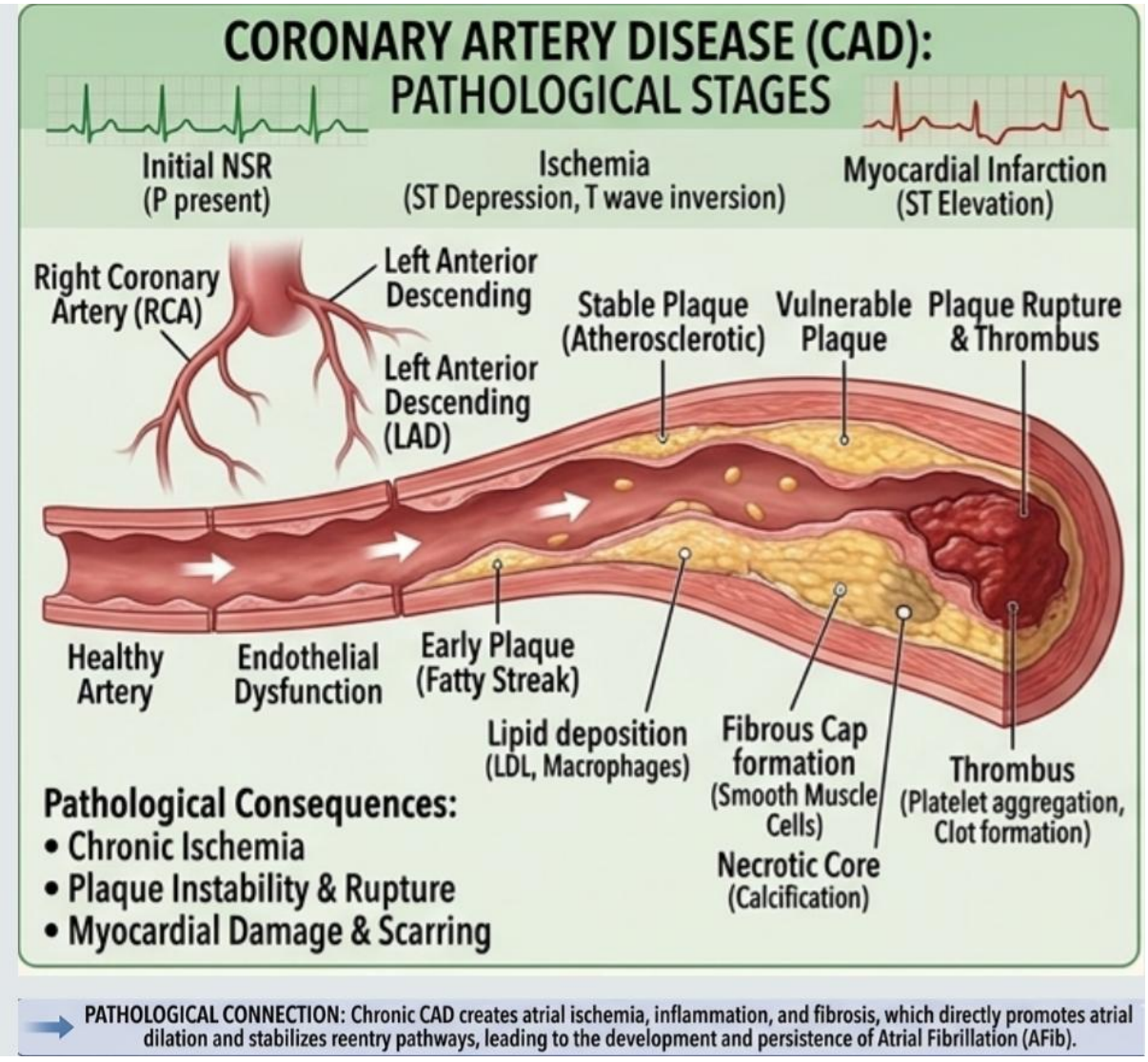

Figure 15. Coronary artery disease and atrial fibrillation

Influence on the progression of atrial fibrillation

The interaction between AF and coronary artery disease is bidirectional. Thus, AF exacerbates myocardial ischemia by increasing heart rate and shortening diastolic duration, while persistent ischemia promotes the maintenance of the arrhythmia (42,45).

Clinical manifestations

Clinically, the presentation is often dominated by the combination of arrhythmic symptoms palpitations, irregular rhythm) with ischemic manifestations (angina pectoris, dyspnea).

Prognosis

The prognosis for these patients is guarded. In the short term, there is an increased risk of acute complications, including heart failure and recurrent ischemic events. In the long term, the AF–CAD association is correlated with increased cardiovascular mortality, as well as a higher incidence of thromboembolic events (45,62).

1.6.3. Valvular heart disease

Valvular diseases, particularly those affecting the mitral valve, constitute a classic and strong substrate for the development of atrial fibrillation, through predominantly hemodynamic and structural mechanisms (48)

Prevalence and relative risk

Atrial fibrillation is present in 30–60% of patients with significant mitral valve disease, particularly in rheumatic mitral stenosis (48). Compared to the general population, the risk of AF is several times higher, depending on the severity of the valvular lesion.

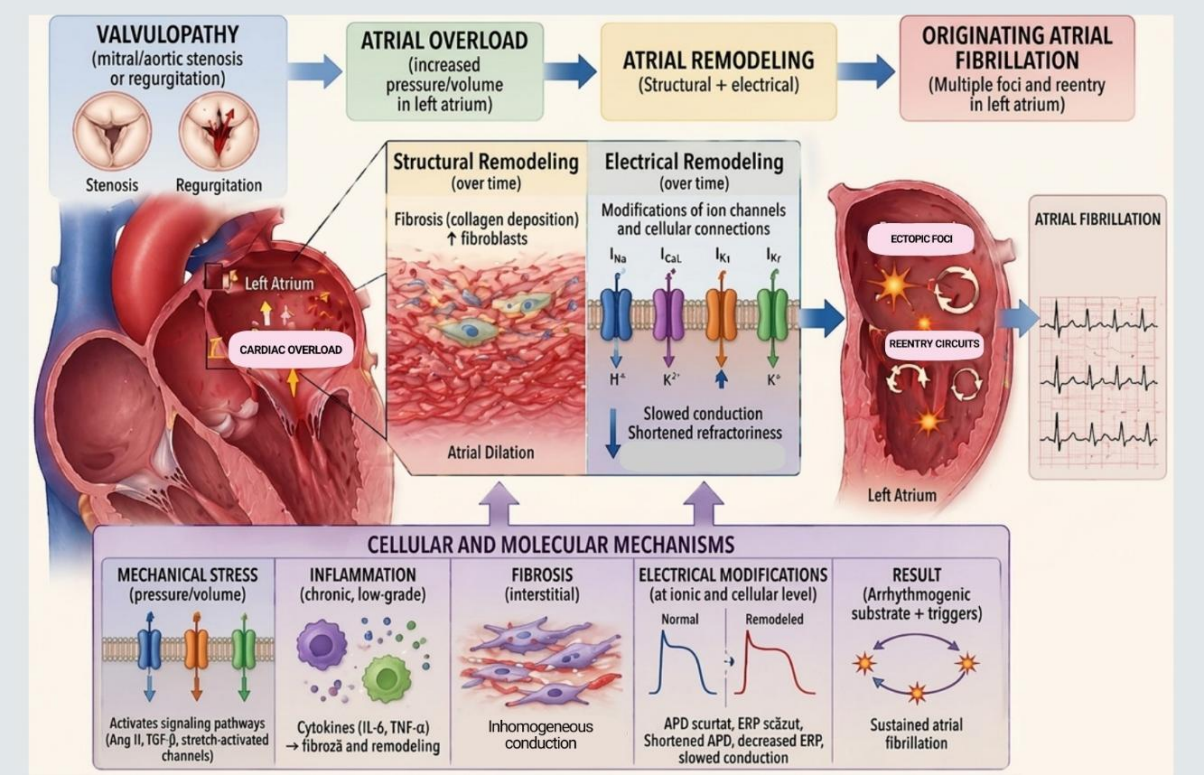

Figure 16. Valvular disease substrate of atrial fibrillation

Pathophysiological mechanisms

The central mechanism is increased pressure in the left atrium, caused by an obstruction to ventricular filling (in mitral stenosis) or volume overload (in mitral regurgitation).

This overload leads to progressive dilation of the left atrium, which becomes the substrate for structural remodeling, characterized by extensive fibrosis.(26,48). Concurrently, changes in electrical conduction occur, including fragmentation of the depolarization wave and shortening of the refractory period.

Over time, these changes promote the stabilization of re-entry circuits and the maintenance of AF.

Influence on the Progression of Atrial Fibrillation

In this context, atrial fibrillation tends to rapidly become persistent or permanent. Furthermore, the loss of atrial contraction has significant hemodynamic consequences, particularly in mitral stenosis, where the atrial contribution to ventricular filling is essential.

Furthermore, blood stasis in the left atrium, particularly in the auricle, significantly increases the risk of thrombosis and systemic embolism (57).

Clinical Manifestations

Clinically, patients present with a combination of symptoms specific to valvular heart disease (dyspnea, orthopnea, exercise intolerance) and arrhythmia (palpitations, fatigue). The onset of AF may signal a sudden deterioration in hemodynamic status.

Prognosis

The prognosis is poor in the absence of adequate treatment, with an increased risk of heart failure and stroke (57,60).

1.6.4. Obesity

Obesity should be considered not only a metabolic risk factor but also a major determinant of cardiac remodeling, with direct implications for the onset and progression of atrial fibrillation as shown in Figure 17 (49,50).

Prevalence and epidemiological impact

From an epidemiological perspective, numerous studies have demonstrated that obesity is associated with a significant increase in the risk of atrial fibrillation, estimated at approximately 1.5–2 times that of the normal-weight population (49). Furthermore, there is a linear relationship between body mass index and the incidence of atrial fibrillation, such that each 5 kg/m^2 increase is associated with an approximately 30% increase in the risk of developing the arrhythmia.

Pathophysiological Mechanisms

From a pathophysiological perspective, obesity causes a series of complex changes, both structural and functional. First, it promotes left atrial dilation as a result of increased circulating volume and intracardiac pressures. Second, infiltration of the myocardium with epicardial adipose tissue contributes to the development of a local pro-inflammatory environment.
Furthermore, obesity is associated with low-grade chronic inflammation and oxidative stress, factors that promote the development of atrial fibrosis. These changes lead to electrical

heterogeneity and impaired electrical conduction, thereby facilitating the initiation and maintenance of atrial fibrillation (49,50).

Influence on the progression of atrial fibrillation

In addition to its role in the onset of the disease, obesity also negatively influences the progression of atrial fibrillation. Thus, it promotes the transition from paroxysmal to persistent or permanent forms. At the same time, it has been demonstrated that obese patients exhibit reduced efficacy of therapeutic strategies, including electrical cardioversion and catheter ablation, as well as an increased rate of arrhythmia recurrence (50).

Clinical Manifestations and Prognosis

Clinically, obese patients frequently present with exertional dyspnea, fatigue, and palpitations, symptoms that can be attributed to both atrial fibrillation and the associated metabolic status. As for the prognosis, it is generally unfavorable. In the short term, there are difficulties in controlling heart rhythm or heart rate, and in the long term, the risk of heart failure and thromboembolic events is significantly increased. In this context, weight loss and lifestyle interventions play an essential role in the management of atrial fibrillation.

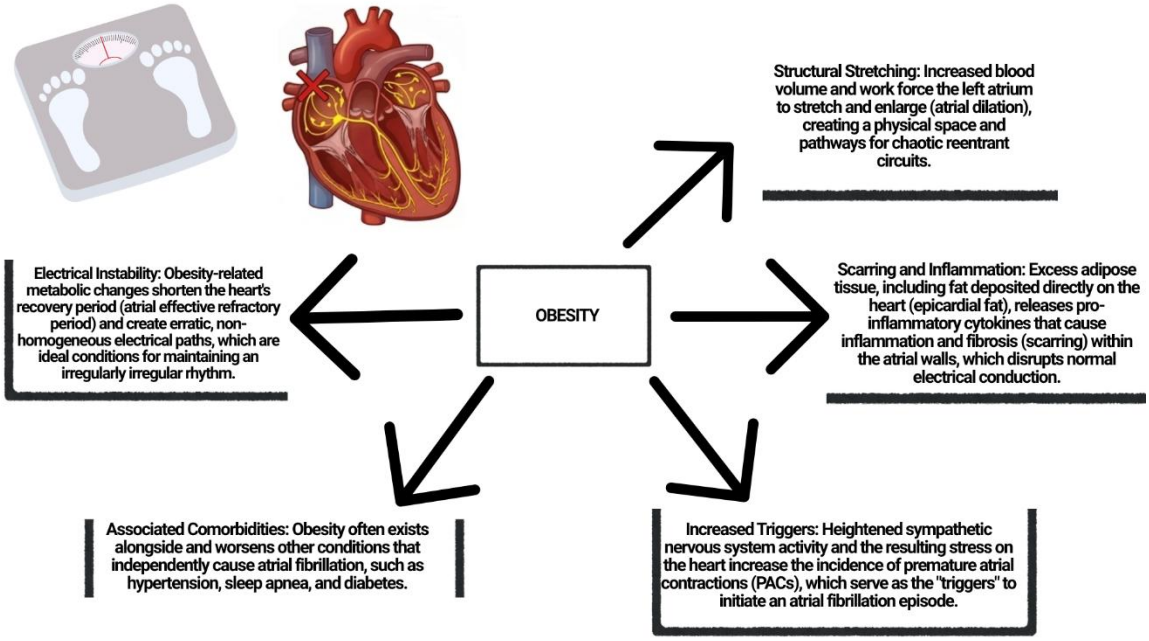

Figure 17. Obesity and atrial fibrillation

1.6.5 Sleep Apnea Syndrome

Obstructive sleep apnea syndrome (OSAS) is currently recognized as an independent and important risk factor for atrial fibrillation, having a significant impact on both the onset and recurrence of the arrhythmia, as depicted in Figure 18 (51–53).

Prevalence and Relative Risk

From an epidemiological perspective, OSA is present in approximately 30–50% of patients with atrial fibrillation. At the same time, the risk of developing atrial fibrillation is 2–4 times higher in patients with sleep apnea compared to those without this condition. Furthermore, the severity of apnea correlates directly with the risk of arrhythmogenesis (51).

Pathophysiological Mechanisms

The mechanisms involved are multiple and interdependent. First, repeated episodes of intermittent hypoxia cause oxidative stress and systemic inflammation. Second, variations in intrathoracic pressure during apnea episodes lead to atrial overload and progressive structural changes. Another key mechanism is the activation of the sympathetic nervous system, which causes increased heart rate and electrical instability. Furthermore, all these processes contribute to the electrical and structural remodeling of the atria, facilitating the onset and maintenance of atrial fibrillation(51,52).

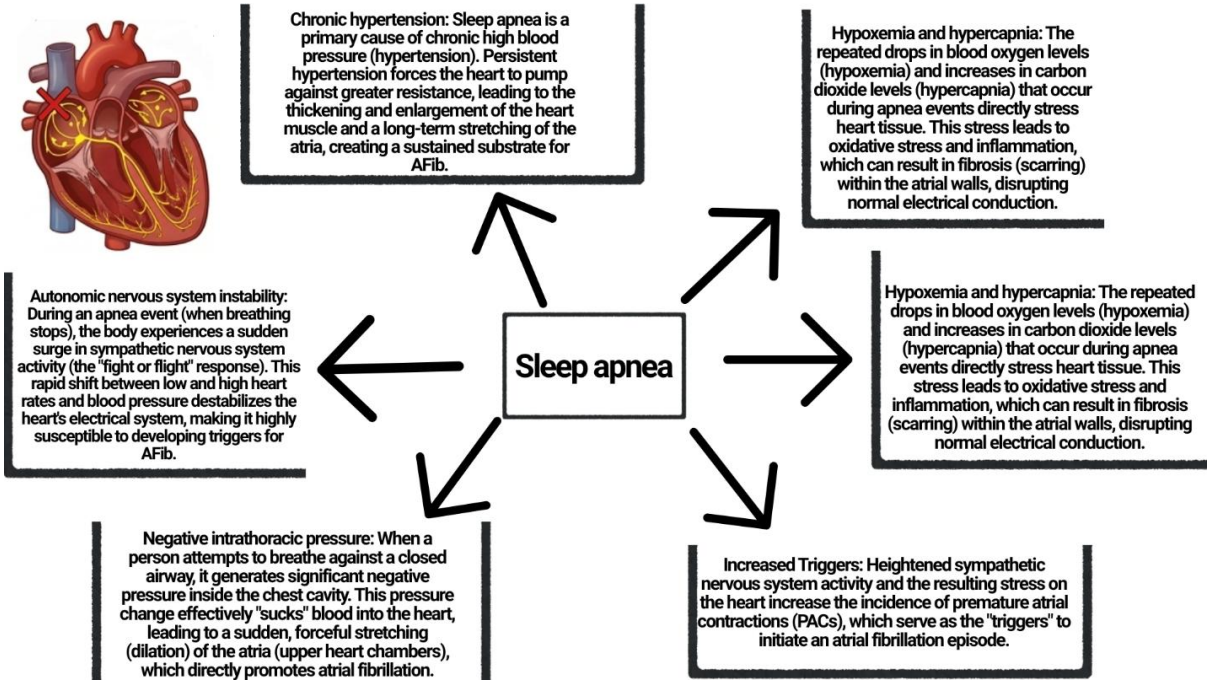

Figure 18. Sleep apnea and atrial fibrillation

Influence on the progression of atrial fibrillation

Furthermore, OSA has a major impact on the progression of atrial fibrillation. Thus, patients with sleep apnea have significantly higher recurrence rates following electrical cardioversion or catheter ablation. Furthermore, the absence of specific treatment, particularly continuous positive airway pressure (CPAP) therapy, reduces the effectiveness of therapeutic strategies. In the long term, OSA contributes to the progression of atrial fibrillation to persistent and permanent forms (53).

Clinical Manifestations

Clinically, patients with OSA frequently present with loud snoring, episodes of apnea observed by a partner, excessive daytime sleepiness, and fatigue. Furthermore, this condition is frequently associated with obesity and hypertension, which increases overall cardiovascular risk.

Prognosis

The prognosis for patients is significantly influenced by the recognition and treatment of this condition. In the short term, OSA is associated with an increased risk of atrial fibrillation recurrence. In the long term, in the absence of treatment, it contributes to the progression of arrhythmia and an increased overall cardiovascular risk.

1.6.6. Alcohol Consumption

Alcohol consumption is an important and frequently underestimated risk factor in the pathogenesis of atrial fibrillation, playing a role both in triggering acute episodes and in maintaining and progressing the arrhythmia in cases of chronic exposure as presented in Figure 19 (54,55).

Frequency and relative risk

First, numerous epidemiological studies have demonstrated that alcohol consumption is associated with an approximately 1.4–2-fold increased risk of atrial fibrillation compared to abstinent individuals (54). The relationship is dose-dependent, with the risk increasing progressively with the amount consumed. It is also important to note the phenomenon known as "holiday heart syndrome," characterized by the acute onset of AF in apparently healthy individuals following episodic excessive alcohol consumption (54).

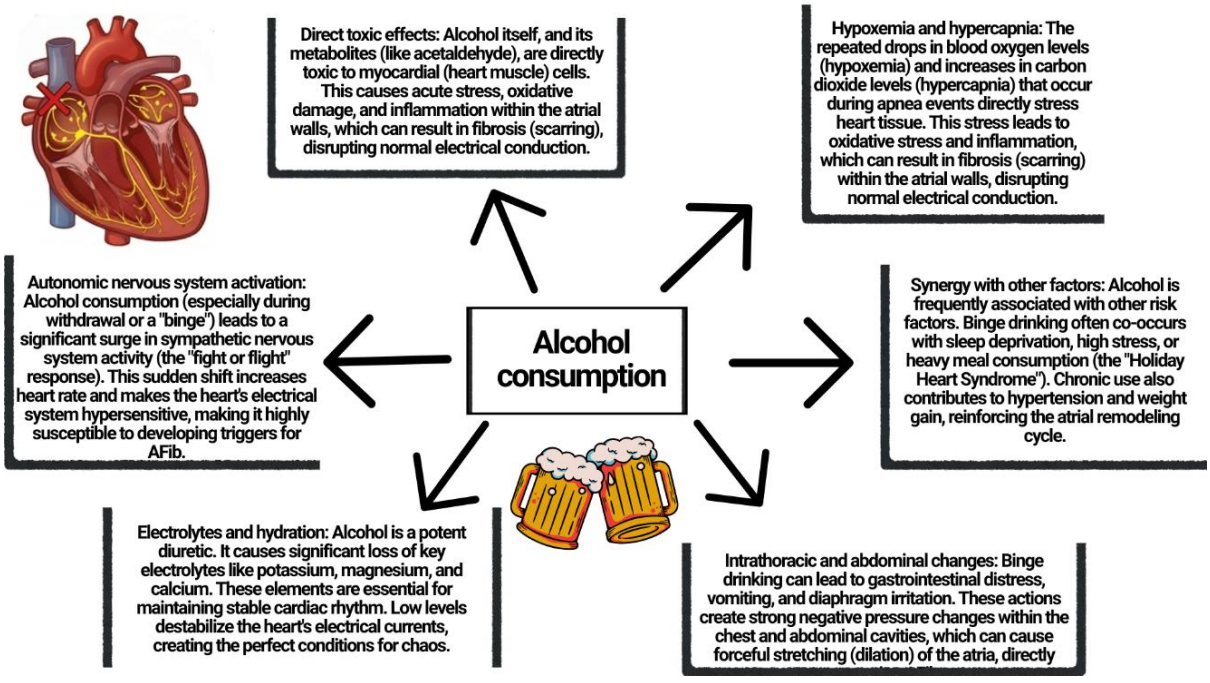

Figure 19. Alcohol consumption—a substrate for atrial fibrillation

Pathophysiological Mechanisms

From a pathophysiological perspective, alcohol exerts multiple effects on the cardiovascular system. First, it has a direct toxic effect on the myocardium, causing structural and electrical alterations (54). Second, alcohol influences atrial electrophysiological properties by shortening the refractory period and increasing automaticity (54,55). In addition, alcohol consumption

causes imbalances in the autonomic nervous system, with a predominantly sympathetic, as well as electrolyte changes (particularly hypokalemia and hypomagnesemia), which promote the onset of arrhythmias (55). Last but not least, chronic alcohol consumption is associated with the development of alcoholic cardiomyopathy, which further contributes to atrial remodeling (54).

Influence on the Course of Atrial Fibrillation

Alcohol has a significant impact on the progression of AF. Acute consumption can act as a trigger for paroxysmal episodes, while chronic consumption promotes recurrence and progression to persistent or permanent forms (54,55). Furthermore, it has been demonstrated that reducing alcohol consumption or abstaining from alcohol can lead to a significant decrease in the frequency of AF episodes and an improved response to treatment (55).

Clinical Manifestations

Clinically, the onset of alcohol-associated atrial fibrillation is often sudden, occurring a few hours after ingesting a large amount of alcohol. Patients experience palpitations, anxiety, dyspnea, and sometimes dizziness or fainting. In chronic forms, symptoms may become persistent, in the context of structural cardiac damage.

Prognosis

The prognosis depends largely on the type and duration of alcohol exposure. In the short term, acute episodes are often reversible, particularly in the absence of structural heart disease. In the long term, chronic alcohol consumption is associated with an increased risk of recurrence, progression of AF, development of cardiomyopathy, and increased cardiovascular mortality (54,55).

In this context, lifestyle interventions, particularly reducing alcohol consumption, are an essential component of AF management.

The onset of AF is facilitated by a multitude of risk factors; in addition to those described above, the following should be considered (51–53,57–60):

- *Diabetes mellitus* increases the risk of atrial fibrillation through chronic inflammation, oxidative stress, and atrial fibrosis, and is also associated with a higher risk of thromboembolism (57).
- *Smoking* contributes to the development of AF through oxidative stress and endothelial dysfunction, promoting atrial remodeling and arrhythmia recurrences (58).
- *Hyperthyroidism* increases myocardial excitability and sympathetic tone, making it a common cause of paroxysmal AF, which is often reversible after treatment (59).
- *Heart failure* promotes AF through atrial dilation and increased intracardiac pressures, with the two conditions exacerbating each other (60).
- *Male gender* is associated with a higher incidence of AF, likely due to hormonal and cardiovascular structural differences (62).
- *Advanced age* (see epidemiology)

Genetic factors play an increasingly well-defined role in the pathogenesis of atrial fibrillation, contributing to individual susceptibility to developing the arrhythmia, even in the absence of classic cardiovascular risk factors. In this context, atrial fibrillation can be considered, at least in part, a disease with complex genetic determinism, as shown in Figure 20 (64–67). First, family studies have shown that patients with first-degree relatives with atrial fibrillation have a significantly higher risk of developing this arrhythmia (66). This observation supports the existence of a hereditary predisposition, independent of environmental factors. Furthermore, "lone" forms of atrial fibrillation (occurring in young patients without structural heart disease) are frequently associated with genetic determinism (64–67). From a molecular perspective, genetic factors primarily influence the electrical and structural properties of the atrial myocardium. Thus, mutations in genes encoding ion channels can cause changes in the action potential, favoring the onset of abnormal electrical activity and re-entry circuits (64,67).In addition, other genetic variants are involved in cardiac development and the structural organization of the atria, contributing to susceptibility to atrial remodeling and fibrosis (65).

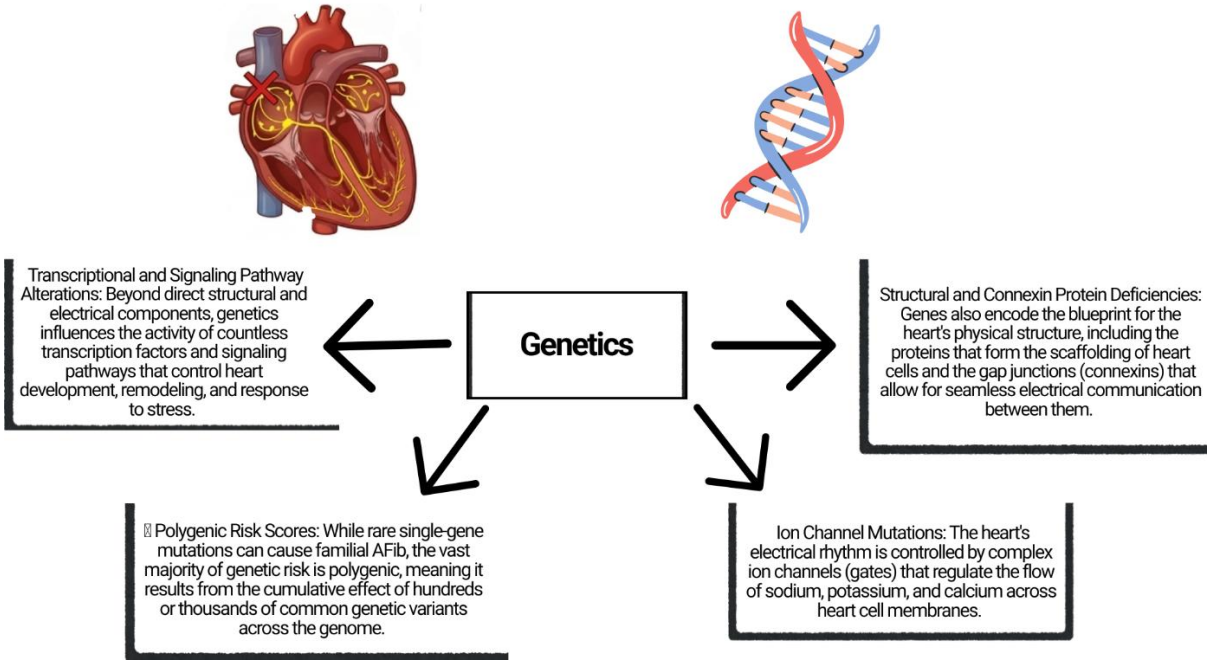

Figure 20. Genetics and atrial fibrillation

Genome-wide association studies (GWAS) have identified multiple genetic loci associated with an increased risk of atrial fibrillation, of which the 4q25 chromosomal region is one of the best known (65). These genetic variants do not directly cause the disease but increase individual susceptibility, particularly in the presence of other risk factors (64–67).

From a clinical perspective, characterizing genetic determinants can help refine risk stratification and tailor treatment strategies. However, the routine implementation of genetic testing remains limited due to its still-undetermined clinical utility.

1.7. Complications of atrial fibrillation

Introduction

This loss of atrial function has significant hemodynamic and thrombogenic consequences. From a pathophysiological perspective, AF is associated with Virchow's triad—blood stasis, endothelial dysfunction, and hypercoagulability—which explains the increased risk of thromboembolic complications. Furthermore, electrical and structural remodeling of the myocardium contributes to the perpetuation of the arrhythmia and the development of cardiac complications.

1.7.1. Stroke as a Complication of AF

Introduction

Stroke is one of the most severe and feared complications of atrial fibrillation (AF), having a major impact on prognosis, survival, quality of life, and healthcare costs (1,69). The significance of this association stems from the fact that AF promotes blood stasis in the left atrium, particularly in the left atrial appendage, which creates the conditions necessary for the formation of intracardiac thrombi. Subsequently, these thrombi can dislodge into the systemic circulation and cause cerebral embolisms, leading to cardioembolic ischemic stroke, as illustrated in Figure 21 (1,69).

From a clinical perspective, AF-associated stroke is particularly relevant because, compared to other subtypes of ischemic stroke, it tends to be more extensive, more severe, more disabling, and associated with higher mortality (69,72). Consequently, the presence of AF alters not only the risk of a major neurological event but also the patient's entire subsequent clinical course.

Pathophysiological Mechanisms

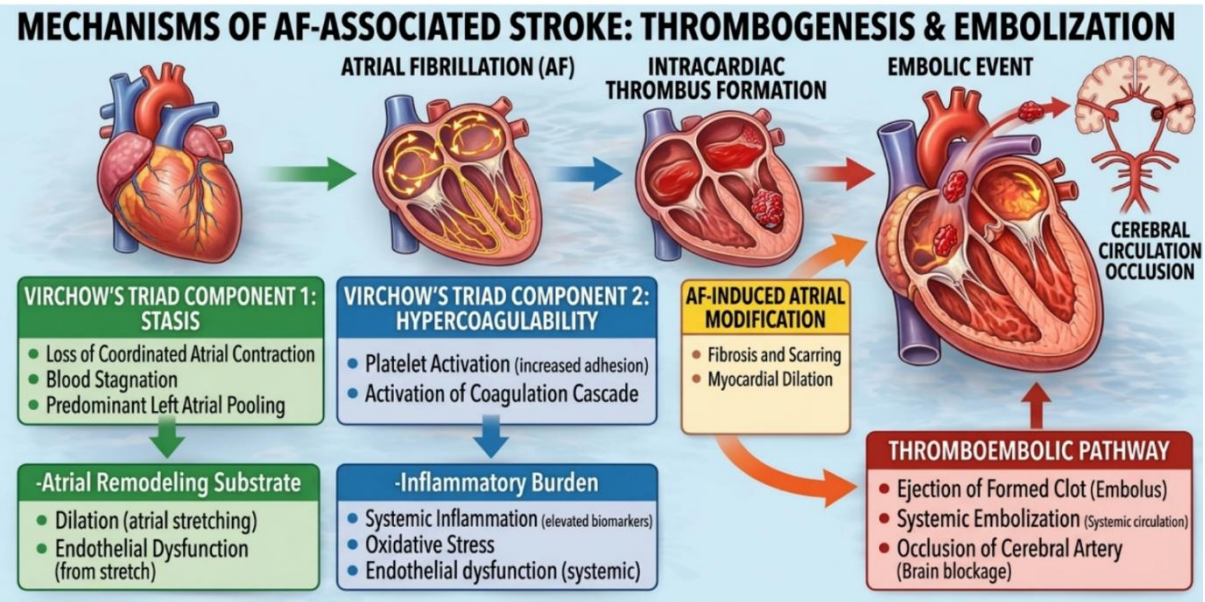

Figure 21. Atrial fibrillation complication—Stroke

Atrial fibrillation primarily causes *a loss* of *effective atrial contraction*, leading to *blood stasis*, predominantly in the left atrium. Concurrently, atrial remodeling characterized by *inflammation, fibrosis, and oxidative stress* promotes the development of *endothelial dysfunction.*

At the same time, AF induces a state of *hypercoagulability* through platelet activation and activation of the coagulation cascade. Thus, the three components of Virchow's triad are fulfilled, facilitating the formation *of intracardiac thrombi.* Subsequently, the formed thrombus can *embolize* into the systemic circulation, frequently reaching the cerebral circulation, where it causes *occlusion of a cerebral artery.* This mechanism underlies *cardioembolic ischemic stroke*, the most common form of stroke associated with atrial fibrillation (1,69).

In contrast, *thrombotic stroke* occurs through the formation of a thrombus *in situ*, usually against a background of cerebral atherosclerosis, without direct cardiac embolization. However, AF can also contribute indirectly to this type of stroke by promoting systemic inflammation and endothelial dysfunction (1,69).

In both situations, vascular occlusion leads to *decreased cerebral perfusion*, triggering the ischemic cascade, characterized by cellular energy deficit, calcium influx, excitotoxicity, and, ultimately, neuronal necrosis.

Stroke Incidence in Patients with Atrial Fibrillation

AF is a major independent risk factor for stroke, increasing the likelihood of an ischemic stroke by approximately 4–5 times compared to the population without this arrhythmia (69). In the absence of anticoagulation, the annual risk of stroke is highly variable and depends on the individual clinical profile, particularly age and comorbidities. Thus, in patients with low thromboembolic risk, the incidence may be less than 1% per year, while in those with high risk scores it may exceed 5–7% annually (1,73).

It should also be noted that approximately 15–20% of all ischemic strokes are attributed to atrial fibrillation, and this proportion increases with age (69). In geriatric practice, the contribution of AF to stroke becomes even more significant, as it represents one of the leading causes of cerebral embolism in the elderly.

Frequency by Age Group

Age is one of the strongest determinants of stroke risk in patients with AF. In young adults, in the absence of other cardiovascular risk factors, the probability of a cardioembolic stroke is relatively low . However, as age increases, the risk progressively rises, both due to the increased prevalence of AF and the accumulation of comorbidities such as hypertension, diabetes mellitus, heart failure, or vascular disease (1,73).

In patients under 65 years of age, in the absence of other major risk factors, the incidence of stroke is generally low. Between 65 and 74 years of age, the risk becomes significantly higher, and after 75 years of age it rises sharply, with this age group accounting for a significant proportion of AF-associated thromboembolic events (1,62). In practical terms, as patients move into an older age group, the likelihood of a stroke increases not only due to the simple effect of vascular aging but also due to the worsening of the pro-inflammatory, procoagulant, and atherosclerotic substrate.

Differences by Demographic Regions and Continents

The distribution of AF-associated stroke also varies by region, due to both biological factors and differences in access to diagnosis, screening, and anticoagulant therapy (69,75). In Europe and North America, where the population is older and AF is diagnosed more frequently, the absolute number of AF-associated strokes is high. However, in these regions, the wider use of modern oral anticoagulants has partially reduced the incidence of severe events (1,75). In Asia, AF-related stroke is of particular importance, as numerous cohorts have shown a significant thromboembolic burden, sometimes higher than in Western populations, particularly given suboptimal control of risk factors and variable access to treatment (75,76). In Africa and certain regions of Latin America, data are more limited, but the clinical impact is often more severe due to delayed diagnosis, insufficient monitoring, and unequal access to anticoagulation, brain imaging, and neurological rehabilitation services (69,75).

Therefore, although stroke remains a major complication of AF across all continents, its consequences tend to be more severe in regions with limited medical resources, where prevention and treatment are implemented less effectively.

Severity of Atrial Fibrillation-Associated Stroke

A defining feature of AF-associated cardioembolic stroke is its increased severity. Compared with non-cardioembolic ischemic stroke, it is more frequently associated with occlusion of large cerebral vessels, extensive infarcts, sudden neurological onset, and significant neurological deficit (69,72). This explains why patients with AF often have higher initial neurological scores, higher rates of residual disability, and an increased likelihood of institutionalization following the event. Furthermore, AF-associated stroke carries a higher risk of recurrence, especially in the absence of adequate anticoagulation (1,73). Clinical severity is also exacerbated by the fact that many of these patients are elderly and have concomitant heart failure, chronic kidney disease, or frailty.

Stroke Outcome in the Context of Atrial Fibrillation

The course of a stroke occurring in a patient with AF is generally more unfavorable than in other forms of ischemic stroke (69,72). In the acute phase, mortality is higher, and neurological and systemic complications are more common. In the medium and long term, persistent disability is common. In addition, AF increases the risk of both recurrent stroke and silent cerebral infarcts, which over time contribute to cognitive decline and loss of independence (77).

How it alters the prognosis in patients with AF

The occurrence of a stroke in a patient with AF profoundly alters the prognosis. First, it transforms a chronic arrhythmia into a disease with major neurological consequences. Second, it significantly increases the risk of death, vascular recurrence, and long-term institutionalization (1,69).

In particular, the prognosis becomes much more severe in elderly patients, those with heart failure, diabetes mellitus, chronic kidney disease, or a history of stroke/TIA. Furthermore, after a first cardioembolic stroke, the patient enters a very high-risk category, which requires rigorous secondary prevention (1,73).

Impact on Quality of Life

Quality of life is often profoundly impaired after a stroke associated with AF. Motor deficits, speech disorders, cognitive impairment, anxiety, and depression significantly reduce the patient's ability to perform daily activities and maintain social and professional independence (77,79). In many cases, patients become dependent on family or long-term care services. In addition to the patient's physical and psychological suffering, the impact extends to caregivers, who bear the burden of daily care; the life-altering changes associated with AF are not merely a medical complication but an event with profound social consequences.

Impact on life expectancy

Due to the association between increased mortality and severe disability, stroke leads to a significant reduction in life expectancy among patients with AF (69,75). The loss of life years is greater when stroke occurs at younger ages, but the absolute impact is also very significant in the elderly, where the event accelerates biological frailty and functional dependence. Furthermore, healthy life expectancy is affected even more profoundly than crude survival. Many patients survive, but with persistent neurological disability, requiring permanent care, and with severely diminished autonomy (69,77). For this reason, the assessment of stroke impact should not be limited to mortality but should be expanded to include the concept of quality-adjusted life years.

Impact on Mortality Rates

The impact on mortality is significant. AF-associated stroke is associated with a higher mortality rate than other subtypes of ischemic stroke (69). In various cohorts, 30-day mortality is significant, and 1-year mortality can reach approximately 20–30%, depending on initial severity, age, comorbidities, and access to specialized treatment (69). In the long term, mortality remains elevated not only due to the direct effect of the neurological injury but also due to secondary complications, such as aspiration pneumonia, prolonged immobilization, venous thromboembolism, decompensation of heart failure, and embolic recurrences (74). Consequently, stroke represents one of the main mechanisms through which AF increases overall mortality.

Impact on the Healthcare System and the Economy

From a healthcare system perspective, AF-associated stroke generates considerable costs through acute hospitalizations, use of emergency services, advanced imaging, thrombolysis or thrombectomy when available, care in specialized stroke units, and long-term neurological rehabilitation (69,75). Costs are further increased by readmissions, complications, chronic monitoring, and the need for medical and social services. Economically, the impact includes both direct medical costs and indirect costs related to lost productivity, early retirement, disability, and the need for informal care provided by family members (75,79). In aging societies, where the prevalence of AF is rising, the economic burden of cardioembolic stroke is becoming increasingly significant.

Prevention at a glance

Stroke prevention in patients with AF relies primarily on accurate identification of thromboembolic risk and the initiation of anticoagulant therapy in eligible patients (1,73). Oral anticoagulation reduces the risk of ischemic stroke by approximately 60–70%, representing the most effective preventive measure (73). At the same time, blood pressure control, diabetes management, smoking cessation, reduced alcohol consumption, and heart failure management contribute to lowering the overall risk (1).

Prevention must also include early diagnosis of AF, especially in the elderly, as well as improved treatment adherence and patient education. In this way, a complication with devastating consequences can be prevented to a significant extent.

1.7.2. Heart Failure as a Complication of Atrial Fibrillation

Introduction

Heart failure (HF) is one of the most common and significant complications of atrial fibrillation (AF), with a complex bidirectional relationship between these two conditions. AF can promote the onset or worsening of heart failure, and heart failure, in turn, increases the risk of developing and perpetuating AF (1,46). This interaction creates a pathophysiological vicious cycle in which hemodynamic dysfunction, structural remodeling, and neurohormonal activation mutually amplify each other, as presented in Figure 22. From a clinical perspective, the AF–HF association is highly significant because it leads to a substantial increase in morbidity, mortality, hospitalizations, and healthcare costs (46). In many modern cohorts, heart failure is even more common than stroke as a major event associated with AF.

Pathophysiological Mechanisms

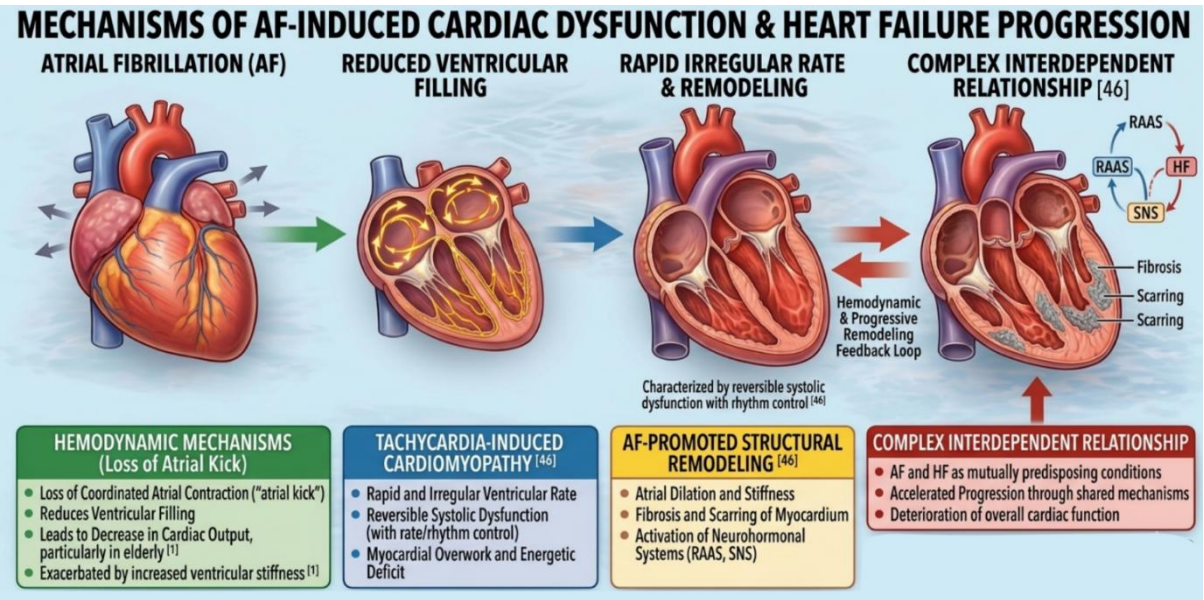

Figure 22. Atrial fibrillation and heart failure

The development of heart failure in the context of AF is driven by several mechanisms. First, the loss of atrial contraction ("atrial kick") reduces ventricular filling, which leads to a decrease in cardiac output, particularly in elderly patients or those with increased ventricular stiffness (1).

Secondly, rapid and irregular ventricular rate can cause a form of tachycardia-induced cardiomyopathy, characterized by reversible systolic dysfunction if the rhythm is controlled (46). Furthermore, AF promotes myocardial structural remodeling, atrial dilation, and activation of neurohormonal systems (the renin–angiotensin–aldosterone system and the sympathetic nervous system), contributing to the progression of heart failure (46).

Thus, AF is not merely an isolated arrhythmia but an active factor in the deterioration of overall cardiac function. Furthermore, atrial fibrillation and heart failure are in a complex interdependent relationship, in which each condition not only predisposes to the onset of the other but also accelerates its progression through hemodynamic mechanisms and progressive cardiac remodeling.

Prevalence of heart failure in patients with AF

Heart failure is extremely common in patients with AF. Recent epidemiological data show that up to 30–40% of patients with AF develop heart failure over the course of the course of the disease (46). Furthermore, population-based studies have demonstrated that the risk of developing heart failure is higher than that of stroke in patients with AF, suggesting that it represents one of the main long-term complications of the arrhythmia (46).

Prevalence by Age Group

Age is a major determinant of the development of heart failure in patients with AF. In young patients, in the absence of structural heart disease, heart failure occurs relatively rarely and is often linked to forms of tachycardia-induced cardiomyopathy, which may be reversible if AF is treated appropriately (46). Between the ages of 65 and 74, the risk increases significantly as risk factors such as hypertension, diabetes, and coronary artery disease accumulate (1,46). In patients over 75 years of age, heart failure becomes very common. In large cohorts, the 10-year absolute risk may exceed 20%, with this age group accounting for the majority of severe cases (46). Thus, advancing age increases both the incidence of AF and the myocardium's susceptibility to dysfunction.

Differences by Demographic Regions and Continents

The distribution of AF-associated heart failure varies globally. In Europe and North America, where the population is older, the prevalence of the AF–HF combination is high, but access to modern treatments (beta-blockers, RAAS inhibitors, anticoagulants, ablation) has improved the prognosis (1,46). In Asia, the burden of the disease is growing rapidly, against a backdrop of urbanization and rising prevalence of metabolic risk factors, and inadequate control of these factors contributes to more severe outcomes (46). In resource-limited regions (Africa, some areas of Latin America), heart failure associated with AF often has a poorer prognosis due to delayed diagnosis and limited access to optimal treatment (46).

The severity of heart failure associated with AF

The association of AF with heart failure leads to more severe clinical forms of the condition. Patients frequently present with more intense symptoms (dyspnea, fatigue, exercise intolerance), reduced ejection fraction, or heart failure with preserved ejection fraction but symptomatic (46). Furthermore, this association significantly increases the risk of acute decompensation, requiring repeated hospitalizations. AF contributes to hemodynamic instability, and heart rate variability worsens tissue perfusion (1).

The Course of Heart Failure in the Context of AF. Prognostic Changes in Patients with AF

The progression of heart failure in patients with AF is generally progressive and more unfavorable compared to patients without AF. Recurrent episodes of AF or inadequate heart rate control accelerate the deterioration of ventricular function (46). In the long term, patients experience an increased rate of hospitalizations, worsening symptoms, and decreased functional capacity. Additionally, AF increases the risk of complications such as thromboembolism, further worsening the clinical course (1).

Impact on Quality of Life

Heart failure associated with AF has a major impact on quality of life. Patients experience significant limitations in daily activities, chronic fatigue, and reduced exercise capacity (46).

In addition to physical symptoms, there is also a significant psychological impact, including anxiety and depression. Dependence on care and reduced autonomy affect both the patient and their family (46).

Impact on Life Expectancy

The combination of AF and heart failure leads to a significant reduction in life expectancy. Studies show that this combination is associated with higher mortality than either condition alone (46).

The impact is more pronounced in younger patients, where the loss of life years is greater, but also in the elderly, where it contributes to frailty and functional dependence (46).

Impact on Mortality Rates

Mortality in patients with AF and heart failure is significantly increased. Data show that the risk of death may be 2–3 times higher compared to the general population (46). In the long term, mortality is influenced by both the progression of heart failure and associated complications, including thromboembolic and arrhythmic events (1).

Impact on the Healthcare System and the Economy

Heart failure associated with AF generates significant costs for healthcare systems. These include frequent hospitalizations, complex chronic treatments, monitoring, and long-term care (46). Indirect costs are also significant, due to lost productivity, work disability, and the need for long-term care (46).

Prevention at a Glance

Prevention of heart failure in patients with AF is based on adequate control of heart rhythm or heart rate, treatment of comorbidities, and the use of cardioprotective therapies (1).

Additionally, managing risk factors (hypertension, obesity, diabetes) and early treatment of AF can prevent cardiac remodeling and progression to heart failure (1,46).

1.7.3. Cardiomyopathy as a complication of atrial fibrillation

Introduction

Cardiomyopathy is an important but frequently underdiagnosed complication of atrial fibrillation, occurring primarily as tachycardia-induced cardiomyopathy (46). It occurs in the context of a rapid and persistent ventricular rate, characteristic of uncontrolled atrial fibrillation, leading over time to ventricular dysfunction which, under certain conditions, may be reversible (46). The relationship between atrial fibrillation and cardiomyopathy is complex and bidirectional, as atrial fibrillation can cause deterioration of myocardial function, and pre-existing structural cardiomyopathy can promote the onset and maintenance of arrhythmia (1,46). **(Figure 23)**

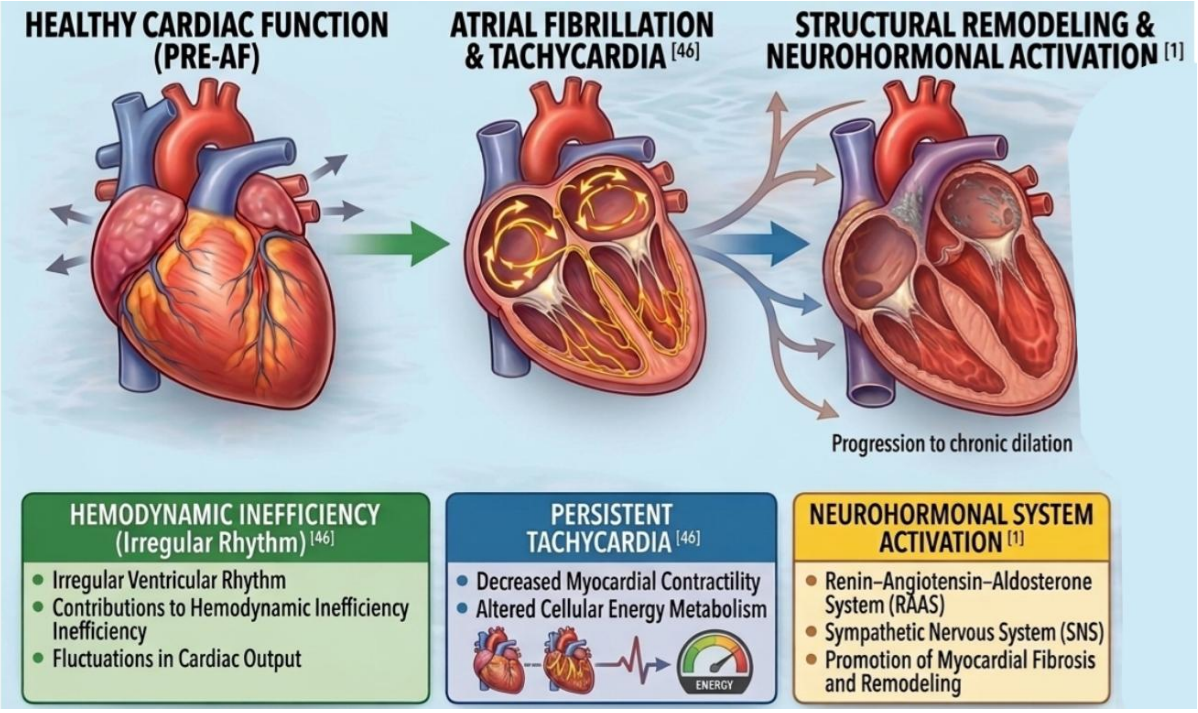

Figure 23. Mechanisms of atrial fibrillation-induced cardiomyopathy

Pathophysiological Mechanisms

The development of cardiomyopathy in the context of atrial fibrillation results from the interaction of several pathophysiological mechanisms. Persistent tachycardia plays a central role, leading to decreased myocardial contractility and altered cellular energy metabolism (46). At the same time, the irregular ventricular rhythm characteristic of atrial fibrillation contributes

to hemodynamic inefficiency and fluctuations in cardiac output (46). In addition, activation of neurohormonal systems, particularly the renin–angiotensin–aldosterone system and the sympathetic nervous system, promotes myocardial remodeling and fibrosis (1). Consequently, these changes progressively lead to left ventricular dilation, decreased ejection fraction, and the development of functional dilated cardiomyopathy (46).

Prevalence of cardiomyopathy in patients with AF

The prevalence of cardiomyopathy associated with atrial fibrillation is difficult to estimate accurately, as it is often confused with other forms of heart failure or is not recognized as a distinct entity (46). However, studies show that a significant percentage of patients with uncontrolled atrial fibrillation develop tachycardia-induced cardiomyopathy. A key point is that this form of myocardial damage is, in many cases, potentially reversible if therapeutic intervention is initiated early (46).

Prevalence by Age Group

The distribution of atrial fibrillation-associated cardiomyopathy varies by age (46). In young patients, this complication occurs relatively rarely and is usually associated with prolonged episodes of tachycardia, being reversible in most cases (46). As age advances, the risk increases, particularly between the ages of 65 and 74, when cardiovascular risk factors accumulate and structural heart disease becomes more common (46). In patients over 75 years of age, cardiomyopathy is frequently associated with chronic atrial fibrillation and often manifests in the context of already established heart failure (1).

Differences by Demographic Regions and Continents

There are significant variations in the global distribution of atrial fibrillation-associated cardiomyopathy (46). In developed countries, where access to early diagnosis and treatment is better, the incidence of severe forms is lower, due to effective control of heart rate and rhythm (46). In contrast, in resource-limited regions, atrial fibrillation is often diagnosed late, which promotes progression to severe ventricular dysfunction and irreversible cardiomyopathy (46).

Severity of Cardiomyopathy Associated with Atrial Fibrillation

The severity of cardiomyopathy in the context of atrial fibrillation ranges from mild, subclinical forms to severe forms of dilated cardiomyopathy (46). In advanced cases, patients present with a significant reduction in ejection fraction, marked ventricular dilation, and obvious symptoms of heart failure (1). An important point is that, in the early stages, the severity may be reduced or even reversible if appropriate therapeutic intervention is provided (46).

The Course of Cardiomyopathy in the Context of AF

The progression of cardiomyopathy depends largely on the control of atrial fibrillation (1). In the absence of effective treatment, cardiomyopathy progresses, and ventricular dysfunction becomes permanent (46). Conversely, if sinus rhythm is restored or heart rate is adequately controlled, ventricular function may improve significantly, and cardiac remodeling may be partially reversible (46)

Impact on Prognosis in Patients with AF

The presence of cardiomyopathy in patients with atrial fibrillation has a negative impact on prognosis (1). It increases the risk of heart failure, promotes the development of other arrhythmias, and is associated with higher cardiovascular mortality. Thus, cardiomyopathy serves as a marker of advanced cardiovascular disease and a more severe clinical course (46).

Impact on Quality of Life

Cardiomyopathy associated with atrial fibrillation significantly affects patients' quality of life (1). Symptoms such as fatigue, dyspnea, and exercise intolerance limit daily activities and reduce functional autonomy (46). In addition, the psychological impact is not negligible, as patients frequently experience anxiety and a reduced ability to adapt to the disease (1).

Impact on Life Expectancy

This complication leads to a significant reduction in life expectancy, particularly when ventricular dysfunction becomes irreversible (1). The impact is more pronounced in elderly patients and those with multiple comorbidities, where it contributes to accelerating functional and biological decline (46).

Impact on Mortality Rate

Patients with both atrial fibrillation and cardiomyopathy have higher mortality rates compared to those without ventricular involvement (1,46). The risk of death is driven by both the progression of heart failure and the occurrence of severe arrhythmias or thromboembolic complications (46).

Impact on the Healthcare System and the Economy

From the healthcare system's perspective, cardiomyopathy associated with atrial fibrillation entails significant costs, driven by repeated hospitalizations, chronic treatments, and the need for long-term monitoring (46). Added to these are indirect costs related to loss of work capacity and the need for long-term care (46).

Prevention at a Glance

Prevention of cardiomyopathy in the context of atrial fibrillation is based on adequate control of heart rate or rhythm, as well as proper treatment of comorbidities (1,46). Early intervention is essential to prevent irreversible myocardial remodeling and to improve the patient's prognosis (46).

1.7.4. Mortality as a Complication of Atrial Fibrillation

Introduction

Mortality is one of the most significant consequences of atrial fibrillation, reflecting the cumulative impact of the cardiovascular and systemic complications associated with this arrhythmia. Although atrial fibrillation is not directly a lethal condition, its presence is associated with a significant increase in the risk of death, through both direct and indirect

mechanisms (46). Thus, mortality should be understood as a global indicator of disease severity and its interaction with the patient's comorbidities.

Mechanisms Leading to Increased Mortality

The increased mortality in atrial fibrillation results from several interdependent mechanisms.

First, AF promotes the development of thromboembolic complications, particularly stroke, which is associated with high mortality (1). Second, atrial fibrillation contributes to the development and worsening of heart failure, which is a major cause of cardiovascular death (46). Furthermore, AF is associated with a pro-inflammatory and procoagulant state, which accelerates the progression of atherosclerotic disease and increases the risk of ischemic events, including myocardial infarction (46). Last but not least, the presence of arrhythmia often reflects an advanced cardiovascular condition, characterized by cardiac remodeling and biological fragility, which further contributes to increased mortality (46).

Mortality Rates and Distribution in Patients with AF

Mortality in patients with atrial fibrillation is significantly higher compared to the general population. Epidemiological studies show that AF is associated with a risk of death approximately 1.5–2 times higher (46). This increase in mortality is observed across all age groups, but the absolute impact is more pronounced in elderly patients, where the prevalence of comorbidities is higher (46).

On the other hand, in younger patients, although absolute mortality is lower, the relative risk compared to the population without AF is significantly increased, suggesting a major impact of the arrhythmia on long-term prognosis (46).

Differences by Age Group

Age plays a key role in determining mortality associated with atrial fibrillation. In patients under 65 years of age, mortality is generally lower, but it increases significantly in the presence of cardiovascular risk factors or associated complications (46).

Between the ages of 65 and 74, mortality increases progressively, reflecting the accumulation of comorbidities and the progression of cardiovascular disease (46). In patients over 75 years of age, mortality becomes very high, driven by the combination of AF, heart failure, vascular disease, and biological frailty (46).

Regional and Global Differences

Globally, mortality associated with atrial fibrillation varies significantly. In developed countries, although the prevalence of AF is higher, access to modern treatments, including anticoagulation and management of comorbidities, has contributed to a reduction in mortality (1,46).

In contrast, in resource-limited regions, mortality is higher due to delayed diagnosis, limited access to treatment, and suboptimal control of cardiovascular risk factors (46).

Causes of death in patients with AF (Figure 24)

Mortality in atrial fibrillation is not caused solely by stroke but has a multifactorial etiology. The main causes of death include heart failure, ischemic heart disease, and thromboembolic

complications (46). Recent data show that non-cardiovascular causes, including infections and neoplasms, also make a significant contribution (46). This distribution suggests that atrial fibrillation is more a marker of a complex systemic pathology than an isolated cause of mortality (46).

Mortality Trends Over Time

Mortality trends in patients with atrial fibrillation are influenced by disease control and the management of comorbidities. In the absence of adequate treatment, the risk of death increases progressively. In contrast, modern treatment, particularly oral anticoagulation and integrated management, can significantly reduce mortality (1). The presence of atrial fibrillation is an independent predictor of mortality (46). It worsens the prognosis of patients with other cardiovascular diseases and increases the risk of major adverse events (46). Although mortality is an objective indicator, the impact of atrial fibrillation must also be analyzed in the context of survival with disability. Many patients are left with significant functional impairment after acute events. Atrial fibrillation leads to a significant reduction in life expectancy, particularly when diagnosed at a young age (46).

Mortality associated with atrial fibrillation also reflects the burden on the healthcare system, due to costs generated by repeated hospitalizations and complex treatments (46).

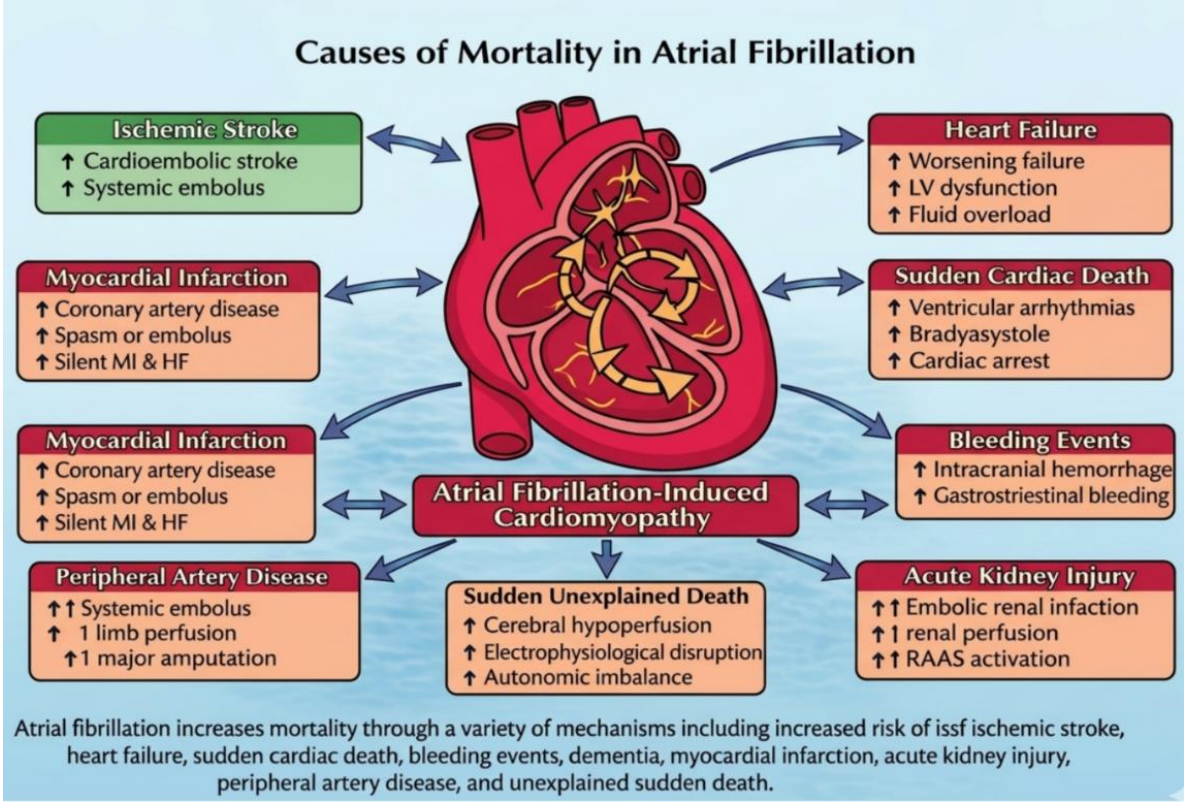

Figure 24. Causes of mortality in atrial fibrillation

Prevention and reduction of mortality

Reducing mortality in patients with atrial fibrillation relies on anticoagulation, control of heart rate or rhythm, and treatment of comorbidities. Integrated patient management— —in accordance with modern guidelines is essential for improving survival (1)

1.8. The Natural Course of Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice, constituting a major global public health problem due to its increasing prevalence and significant impact on morbidity and mortality (1,13,14). In recent decades, understanding of the natural history of this arrhythmia has deepened considerably, highlighting its progressive nature and close relationship with cardiovascular risk factors and the aging process (13,33).

From a pathophysiological perspective, AF is the result of a complex process of atrial remodeling, involving electrical, structural, and neurohormonal changes. Initially, episodes of atrial fibrillation are typically self-limiting, defining the paroxysmal form. However, in the absence of adequate control of predisposing factors, these episodes become more frequent and prolonged, progressing to persistent and subsequently permanent forms (1,3).

This progression is supported by the well-known concept that "atrial fibrillation generates atrial fibrillation," reflecting the fact that disorganized electrical activity causes further atrial remodeling, which, in turn, facilitates the maintenance of the arrhythmia (27,33). Therefore, AF should be viewed not as an isolated event, but as a dynamic condition on an evolutionary continuum, driven by both the progression of the arrhythmogenic substrate and the accumulation of comorbidities (33,46). (**Figure 25)**

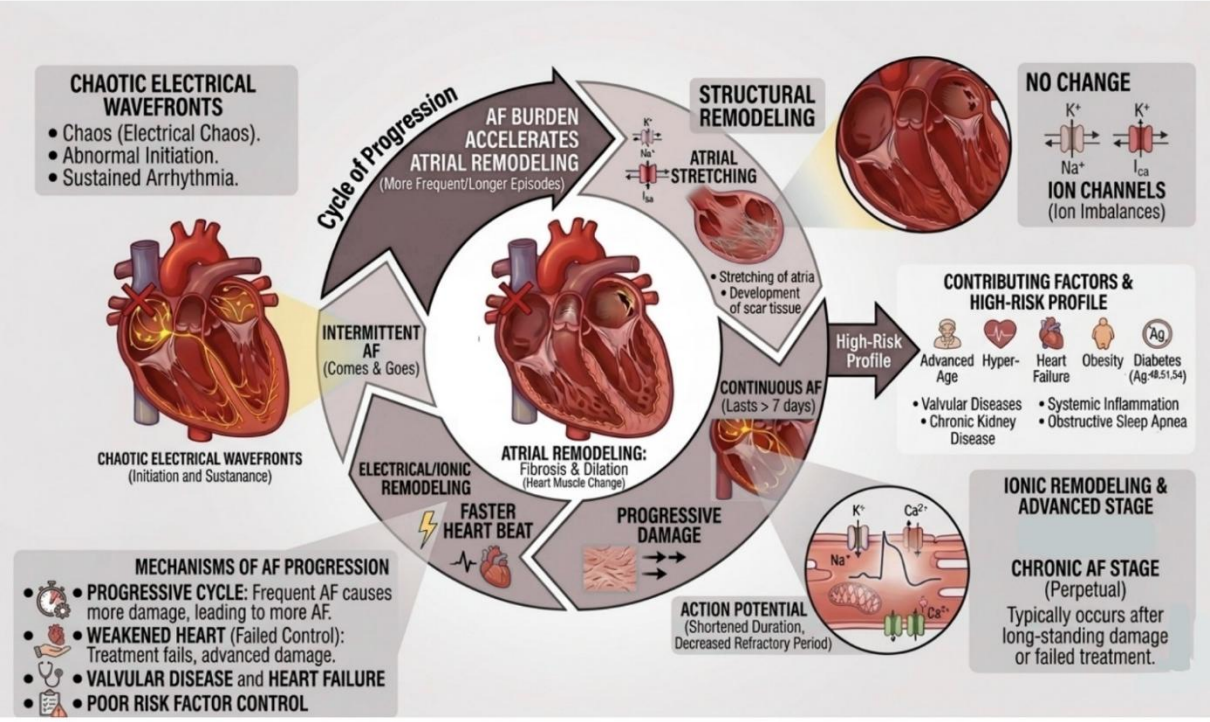

Figure 25. Natural progression of atrial fibrillation

Data from observational studies indicate that progression from paroxysmal AF to persistent or permanent forms occurs in approximately 5–15% of patients annually, and may reach up to 15–25% in the presence of a high-risk profile (26,33,41,42). This progression is not random, as it is influenced by numerous contributing factors, including advanced age, hypertension, heart failure, and obesity. Added to these are left atrial dilation, valvular diseases, systemic inflammation, chronic kidney disease, and obstructive sleep apnea (42,48,51,54). Furthermore, an increased burden of AF episodes accelerates atrial remodeling, promoting the perpetuation of the arrhythmia (27).

From a temporal perspective, cumulative estimates suggest that approximately 8–15% of patients progress within the first year, 20–35% within 3 years, and up to 25–50% within 5 years (26,33). Thus, paroxysmal AF is not a benign form, but often an initial stage in a continuous evolutionary process. When atrial fibrillation persists continuously for a period longer than 12 months, it is classified as long-standing persistent AF (1,43). This stage typically occurs when cardioversion fails to maintain sinus rhythm or when atrial remodeling is already advanced (46). Progression to this form is facilitated by the presence of heart failure, valvular heart disease, and inadequate control of risk factors (42,48). Clinical data show that approximately 20–40% of patients with persistent AF progress to the long-standing form within 1–3 years, with a higher percentage among elderly patients and those with significant atrial dilation (25,33).

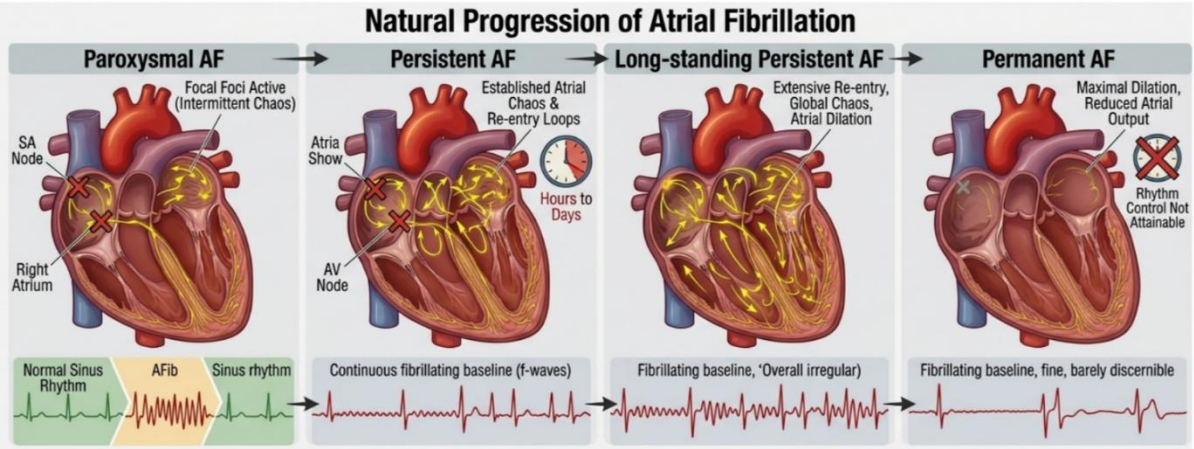

Figure 26. Progression of atrial fibrillation forms

Progression to permanent AF is influenced by both biological mechanisms and therapeutic decisions (1,3). In elderly patients with moderate symptoms and multiple comorbidities, the decision is frequently made to discontinue rhythm control strategies, which leads to AF being classified as permanent (43). In the absence of effective sinus rhythm control, approximately 30–60% of patients progress to permanent AF within a few years (33), with this transition reflecting the stabilization of the arrhythmia on a profoundly remodeled atrial substrate.

Permanent AF represents the most advanced stage of the disease, characterized by the stability of the arrhythmic rhythm and a strong association with a high burden of comorbidities (33,46). Typically, this form no longer progresses to other types of AF and is associated with advanced age, significant atrial dilation, and extensive structural cardiac damage (25,42).

The clinical significance of the natural course of AF stems primarily from its association with severe complications. Atrial fibrillation increases the risk of stroke by approximately 4–5 times, and associated thromboembolic events are frequently more severe and disabling (66,67,68). At the same time, AF contributes to the onset and progression of heart failure, establishing a bidirectional relationship that worsens the patient's prognosis (60,46). Furthermore, AF is associated with an approximately 1.5–2-fold increase in all-cause mortality compared to the general population, with this increase primarily driven by cardiovascular complications and associated comorbidities (45,33). Globally, the burden of the disease is steadily increasing, particularly in the context of an aging population and the rising prevalence of metabolic risk factors (13,14).

Therefore, understanding the natural history of atrial fibrillation is essential not only for optimizing therapeutic strategies but also for developing effective preventive interventions aimed at reducing disease progression and its impact on survival and quality of life.

1.9. Summary, Keywords, and Concepts

Atrial fibrillation (AF) is a complex supraventricular arrhythmia defined by disorganized atrial electrical activity, irregular ventricular rhythm, and loss of effective atrial contraction, resulting from the interaction between the arrhythmogenic substrate, triggers, and mechanisms that maintain the arrhythmia.

History and Conceptual Development:

Understanding of AF evolved with the introduction of the electrocardiogram (ECG) by Willem Einthoven, a method that allowed for the objective characterization of arrhythmias. The term "atrial fibrillation" was coined by Sir Thomas Lewis, who demonstrated the relationship between the absence of P waves, absolute irregularity of rhythm, and chaotic atrial electrical activity, laying the foundation for modern diagnosis.

Epidemiology and health impact:

AF is the most common sustained arrhythmia, with globally increasing incidence and prevalence, strongly correlated with advancing age. Incidence increases exponentially after age 60–70, reflecting population aging and the accumulation of comorbidities. AF has a major impact on public health by increasing the risk of stroke, heart failure, recurrent hospitalizations, and mortality, generating significant costs for healthcare systems.

Electrophysiology – triggers, initiation, and maintenance mechanisms:

AF arises from the interaction between:

- triggers (initiation): rapid ectopic foci (predominantly from the pulmonary veins), triggered activity (*early and late post-depolarizations*),
- arrhythmogenic substrate: refractory heterogeneity, conduction delay,
- sustaining mechanisms: multiple re-entry circuits (multiple wavelets).

These processes are reinforced by:

- electrical remodeling (*shortening of the refractory period, ionic adaptation*),
- structural remodeling (*atrial fibrosis, dilation, tissue infiltration*),
- defining the central concept "AF begets AF" – self-sustaining arrhythmia.

Pathophysiology:
AF causes loss of atrioventricular synchronization, decreased cardiac output, and atrial blood stasis, particularly in the left atrium, promoting thromboembolism. Concurrently, systemic inflammation, oxidative stress, endothelial dysfunction, and prothrombotic cascades are activated, contributing to disease progression and its complications.

Mechanistically integrated *risk factors* (including genetics):

The factors involved act through converging mechanisms on the atria:

- structural remodeling (fibrosis, dilation) *(hypertension, valvular heart disease,*
- *, obesity, genetic predisposition – extracellular matrix damage)*,

- inflammation and oxidative stress *(obesity, diabetes, smoking, sleep apnea, genetic variations in the inflammatory response)*,
- electrophysiological alterations (ion channels, conduction) *(coronary artery disease, alcohol, genetic mutations in ion channels)*,
- atrial pressure/volume overload *(hypertension, valvular disease, heart failure)*,
- autonomic dysfunction *(alcohol, sleep apnea, stress, smoking)*.

The genetic component modulates all these processes, influencing individual susceptibility, early onset, and response to treatment.

Course and dynamics of the forms:

AF has a progressive course, characterized by a transition from rare, self-limiting episodes to recurrent, prolonged, and subsequently self-sustaining episodes, against a background of increasing electrical and structural remodeling. This progression reflects the consolidation of the arrhythmogenic substrate, a reduced likelihood of spontaneous conversion, and decreased efficacy of therapeutic interventions.

Complications:

The main consequences include ischemic stroke (embolic), heart failure, tachyarrhythmia-induced cardiomyopathy, and increased mortality, with AF being a major cause of cardiovascular disability.

Conclusion:

Atrial fibrillation is an arrhythmia caused by the interaction between triggers, the arrhythmogenic substrate, and re-entry and remodeling mechanisms, sustained by processes such as inflammation, oxidative stress, and genetic influences. Its progressive course and thromboembolic and hemodynamic complications define the major clinical impact of the disease and the need for an integrated approach.

Keywords:

- arrhythmogenic substrate, triggers, ectopic foci, pulmonary veins, multiple re-entry, electrical re , atrial fibrosis, refractory heterogeneity, atrial stasis, thromboembolism, inflammation, oxidative stress, genetics, arrhythmic progression, AF begets AF

Concepts:

- initiation and maintenance of arrhythmia, trigger–substrate interaction, progressive atrial remodeling, electrical instability, triggered activity, reentry circuits, electro-structural vicious cycle, prothrombotic dysfunction, gene–environment interaction, clinical and electrical progression of AF

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Abbreviation list

AF Atrial fibrillation
AHA American Heart Association
Ca Calcium
CAD Coronary artery disease
CPAP positive airway pressure
ECG electrocardiogram
ESC European Society of Cardiology
f fibrillatory
HF Heart failure
HTN Hypertension
K Potassium
Na Sodium
Na^+ (If) Funny current
OSA Obstructive sleep apnea
OSAS Obstructive sleep apnea syndrome
RAAS Renin–Angiotensin–Aldosterone System

CHAPTER 2 — CLINICAL PRESENTATION AND DIAGNOSIS - *Nilima Rajpal Kundnani, Roxana Buzaș, Ciprian Ilie Rosca, Stefan Bolog, Victor Buciu, Abhinav Sharma*

2.1. Clinical Symptoms

Atrial fibrillation (AF) has no single clinical face. Some patients come to the emergency department because they suddenly feel that their heart is racing or beating chaotically. Others present in a much less dramatic way. They may report only reduced exercise tolerance, unusual tiredness, poor concentration, or shortness of breath on effort. A meaningful proportion of patients have no symptoms at all, and AF is first identified during a routine consultation, a preoperative assessment, rhythm monitoring, or an evaluation for stroke [1-4]. This broad clinical spectrum is one of the reasons why AF remains both common and, at times, deceptively easy to miss.

For students and residents, the first practical lesson is that symptoms can suggest AF, but they can never establish the diagnosis on their own. The diagnosis remains electrocardiographic. Clinical symptoms are important because they trigger suspicion, guide the urgency of evaluation, influence quality of life, and often shape the way patients describe the burden of the arrhythmia. However, the symptom pattern is variable and varies by age, ventricular rate, irregularity of the response, episode duration, left ventricular function, diastolic properties, coexisting valvular disease, autonomic tone, anxiety, and the patient's own sensitivity to bodily sensations [1-5].

Another important point is that symptom burden and AF burden are not always parallel. A patient with very short paroxysms can be highly symptomatic, while another patient with longstanding AF may report very little discomfort. This weak correlation between rhythm pattern and subjective experience is well described in the literature and explains why a careful history remains essential even in an era of prolonged rhythm monitoring and digital devices [3-6]. From a teaching perspective, this is a useful place to introduce the idea that AF is not only an electrical disorder. It is also a clinical syndrome that interacts with the patient's physiology, comorbidities, and psychosocial context.

That is exactly the reason why the European Heart Rhythm Association (EHRA) symptom classification was developed.. It offers a simple clinical tool to measure how much AF-related symptoms are affecting daily activity, ranging from no symptoms to disabling symptoms [5]. Even when a formal scale is not used at the bedside, its logic remains useful. The clinician should ask not only what the patient feels, but also how much those symptoms interfere with daily life. For a patient, a few minutes of severe palpitations before every work shift may be more important than a longer episode that is barely noticed. Symptom assessment therefore belongs to the core of AF evaluation, even before management decisions are discussed in later chapters [1,2,5].

This subchapter focuses on the symptom profile of AF. The most common symptoms are palpitations, dyspnea, fatigue, dizziness or presyncope, and the absence of symptoms in so-called silent AF. These categories are practical, easy to teach, and clinically relevant. At the bedside they help the physician move from a vague complaint to a structured differential diagnosis.

They also help identify patients who need urgent evaluation, such as those with severe shortness of breath, chest discomfort, hypotension, or syncope. Table 2.1 summarizes the main symptom groups and their immediate diagnostic implications, while Figure 2.1 shows the broader clinical spectrum and the factors that modify symptom burden. At the same time, these examples remind the clinician that AF can be subtle and that a quiet presentation does not equal a low-risk disease [1-4].

Table 2.1. Main atrial fibrillation symptom groups and immediate clinical implications. Original table created for this subchapter based on references [1-7].

Symptom	**Typical patient description**	**Main diagnostic implication**	**Urgency clue**
Palpitations	Racing, pounding, fluttering, or irregular heartbeat	Raises suspicion for AF but is not specific; rhythm documentation is required	Urgent if prolonged, poorly tolerated, or accompanied by chest pain or hypotension
Dyspnea	Exertional breathlessness, reduced exercise tolerance, orthopnea	Suggests hemodynamic impact or coexisting heart failure/structural disease	Urgent if severe at rest, associated with hypoxemia, pulmonary edema, or instability
Fatigue	Low energy, poor stamina, reduced concentration, functional decline	Often underrecognized; may reflect chronic AF burden or comorbidity	Concerning if new, progressive, or associated with weight loss, anemia, or decompensation
Dizziness / presyncope	Light-headedness, near fainting, unsteadiness	Requires broader differential; may reflect poor tolerance, rapid rate, or another arrhythmic mechanism	Urgent if true syncope, trauma, neurologic deficit, or severe hypotension occurred
Silent AF	No clear symptoms or very mild non-specific symptoms	Does not imply low risk; may first appear through screening or stroke workup	High relevance in patients with stroke, embolic events, or device-detected episodes

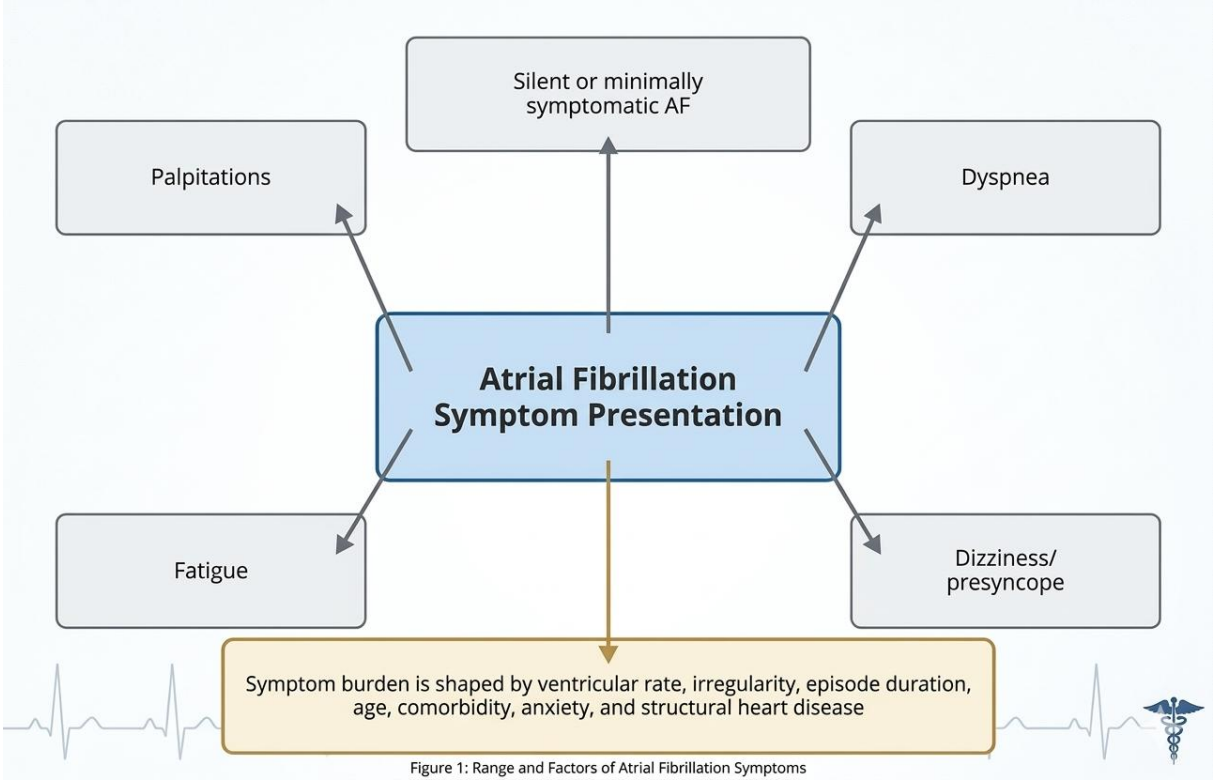

Figure 2.1. Clinical spectrum of atrial fibrillation symptoms and the main factors that shape symptom burden. Original figure created for this subchapter based on references [1-6, 8-12].

2.1.1. Palpitations

Palpitations are the symptom most typical of AF. Patients often describe such sensations in very detailed and personal terms. For instance, they may say something like “my heart was flipping”, “it was pounding in my throat”, “it started racing all of a sudden”, or “it felt irregular and chaotic”. Such descriptions are rather typical for AF, as they indicate an irregular firing of the ventricles, which makes its way to the peripheral circulation. In the case of paroxysmal AF, the start of the episode may be sudden and noticeable, so that the patient can even describe the moment when it started.They may even describe a trigger, such as alcohol intake, emotional stress, poor sleep, acute illness, or exertion, although the true mechanistic link is not always clear [1-4].

Despite their classical association with AF, palpitations are not specific to AF. They also occur in sinus tachycardia, premature atrial or ventricular beats, atrial flutter, supraventricular tachycardia, panic states, anemia, and hyperthyroidism. For that reason, palpitations should be viewed as a clinical entry point rather than a final diagnostic answer. A common teaching mistake is to equate “palpitations” with “AF.” A better approach is to regard palpitations as an invitation to define the rhythm objectively, ideally with ECG documentation or appropriate ambulatory monitoring [1-3].

Palpitations are also influenced by the speed and irregularity of the ventricular response. Some patients tolerate a regular tachycardia surprisingly well but feel intensely uncomfortable when the rhythm is irregular. Others are less bothered by irregularity itself and react mainly when the heart rate becomes rapid. The same patient may experience feelings of one episode and

barely notice the second one due to sleep deprivation, stress, fever, fluid intake, and coexisting diseases. For this reason, the history-taking process should dwell on the frequency and duration, specific features and accompanying symptoms, and the time it takes for the body to return to normal instead of asking if the patient has palpitations or not[3-6].

In younger or otherwise healthy individuals, palpitations may be the dominant and sometimes the only complaint. In older patients, especially those with structural heart disease, palpitations may be less prominent than dyspnea or fatigue. This age-related difference matters because silent or poorly perceived AF becomes more frequent in the elderly and in patients with reduced physical activity [3,4,7-10]. Thus, the absence of prominent palpitations should not reassure the clinician too early.

Palpitations also have educational value because they illustrate one of the central paradoxes of AF: the symptom can be very striking, yet the underlying hemodynamic impact may be modest in one patient and severe in another. A person with preserved ventricular function and no valvular disease may mainly feel the rhythm. Another with diastolic dysfunction may deteriorate quickly because the loss of atrial contraction and irregular ventricular filling are poorly tolerated. When teaching AF, it is therefore helpful to connect the patient's language to the physiology behind it. This makes the symptom easier to remember and clinically more meaningful.

2.1.2. Dyspnea

Dyspnea is one of the most important symptoms in AF because it often signals hemodynamic consequence rather than pure rhythm perception. It can manifest as dyspnea on exertion, decreased exercise tolerance, orthopnea, or even dyspnea without an apparent cause such as "it is difficult to breathe." Dyspnea most often results from decreased ventricular response, impaired filling of the ventricle, loss of atrial kick, and an increase in left atrial pressure.[1-4]. In practical terms, the atria stop contributing effectively to ventricular filling, diastole becomes less efficient, and patients with limited reserve start to feel it quickly.

This symptom is especially common in older patients, in those with hypertension-related diastolic dysfunction, heart failure, significant valvular disease, or underlying pulmonary disease. AF does not need to be the only mechanism for dyspnea to be clinically relevant. In fact, one of the most important bedside questions is whether AF is the main cause of the breathlessness, a trigger that worsened an underlying cardiac condition, or simply a marker of another disease that is now becoming apparent [1,2]. This distinction is diagnostic before it becomes therapeutic.

Students should learn that dyspnea in AF deserves a broader clinical mindset. If the patient is short of breath, one should not stop at the rhythm strip. The evaluation should consider heart failure, acute ischemia, pulmonary embolism, pneumonia, chronic obstructive pulmonary disease, anemia, and thyroid disease, depending on the context. AF can coexist with all of these. In some situations, AF may be secondary to the systemic illness rather than the primary event [1-3]. This is one reason why symptom-based diagnosis must always be integrated with physical examination, imaging, and laboratory testing.

Dyspnea also illustrates why symptom intensity does not always correlate with AF pattern. A patient with brief but fast episodes may report major exertional limitation. Another with persistent AF and adequate rate adaptation may remain fairly comfortable until walking tolerance is tested formally. Several studies have shown that AF-related symptoms influence quality of life substantially, and dyspnea is among the symptoms most strongly linked to limitations in daily activity [4-6,11]. For this reason, asking about stairs, walking distance, carrying groceries, and ordinary household effort often yields better clinical information than asking simply, "Are you short of breath?"

There is also a practical teaching value in separating dyspnea from anxiety. Patients with AF may become frightened by the irregular rhythm and develop a sense of air hunger even when oxygenation is normal and congestion is absent. This does not make the symptom clinically insignificant. It shows that symptom perception in AF is multidimensional and can be amplified by autonomic arousal and uncertainty [4,6,11]. Good clinical interviewing should therefore validate the symptom while still searching for its physiological correlate.

2.1.3. Fatigue

Fatigue is one of the most underrecognized yet most disabling symptoms of AF. It is often not volunteered spontaneously. Patients may instead say that they have "less energy," "do not feel like before," "cannot focus," or "get tired too fast." Because these phrases are nonspecific, fatigue is easy to misattribute to aging, stress, depression, sleep deprivation, or chronic disease. In AF, however, fatigue can be the leading manifestation, particularly in patients with persistent arrhythmia or recurrent paroxysms that do not produce dramatic palpitations [3-6].

The mechanisms are multifactorial. AF reduces the efficiency of cardiac output through loss of atrial contraction, irregular ventricular filling, and sometimes an inappropriately rapid ventricular response. The result is not always frank instability. More often it is a chronic sense of reduced reserve. Patients feel slower, less effective during exertion, and less able to sustain ordinary activities. In addition, AF frequently coexists with sleep apnea, obesity, heart failure, thyroid disease, and systemic inflammation, all of which may contribute to tiredness [1-4]. This is why fatigue in AF should be interpreted as both a symptom and a clue to possible comorbidity.

From an educational point of view, fatigue is important because it teaches diagnostic humility. Not every tired patient with AF is tired because of AF, but AF should not be dismissed either simply because the complaint sounds vague. A good history should include questioning as to whether the fatigue is intermittent or constant, whether it is associated with palpitations or exertion, whether it began with first episodes of recognized arrhythmia, and whether there are associated symptoms, such as insomnia, shortness of breath, or impaired concentration [4,6,11]. These factors can help make an otherwise vague complaint more useful.Fatigue also has a strong quality-of-life dimension. Many patients with AF do not fear the arrhythmia because of pain or dramatic hemodynamic collapse; they fear it because they stop feeling normal. They cannot perform at work, they avoid exercise, and they begin to organize daily life around unpredictability. This functional burden is one reason why symptom assessment is not a cosmetic exercise. It is central to understanding the lived impact of AF [4-6]. For medical students,

this is an excellent example of why symptom inquiry should include activity limitation and not only organ-specific language.

Another important aspect is that fatigue can persist even after AF is documented because symptom perception is not purely mechanical. Anxiety, poor sleep, chronic disease, and recurrent monitoring can keep the patient in a cycle of reduced confidence and reduced activity. This does not diminish the role of AF; it broadens it. The symptom reflects the interaction between arrhythmia burden, underlying cardiovascular status, and patient adaptation. In a textbook chapter, it is worth emphasizing this point because it helps learners move beyond a narrow ECG-centered view of disease.

2.1.4. Dizziness

Dizziness, light-headedness, and presyncope are less specific than palpitations, but they are clinically important. In AF, these symptoms usually result from transient cerebral hypoperfusion or from an abrupt drop in hemodynamic efficiency when the ventricular response is too rapid or poorly tolerated. Patients often describe feeling "unsteady," "as if they might faint," or "not fully present," especially when standing, walking quickly, or during the onset of an episode [3,4,12]. In some cases the symptom is brief and self-limited. In others it becomes a reason for urgent evaluation.

The diagnostic value of dizziness lies partly in its ambiguity. AF can cause it, but so can many other conditions. Orthostatic hypotension, medication effects, bradyarrhythmias, pauses after AF termination, ventricular arrhythmias, dehydration, anemia, and vestibular disorders must all be considered depending on the presentation. That is why dizziness in AF should never be interpreted in isolation [1-3,12]. The clinician must ask about syncope, near-syncope, chest discomfort, exertional onset, trauma, neurologic deficits, and medication changes.

True syncope is relatively uncommon in uncomplicated AF and should always raise concern for another or additional mechanism. This teaching point is worth underlining for residents. If a patient with presumed AF presents with actual loss of consciousness, one should widen the differential immediately. Severe hypotension, very rapid pre-excited AF, advanced conduction disease, post-conversion pauses, aortic stenosis, pulmonary embolism, and ventricular tachyarrhythmias are all possibilities that may carry higher short-term risk than AF itself [1,2]. In other words, dizziness can fit AF, but syncope demands a more urgent and more critical approach.

Recent literature has also drawn attention to the fact that dizziness may be more relevant in AF than clinicians sometimes assume. It can occur as part of a symptom cluster with palpitations, dyspnea, and anxiety, but it may also appear more independently, especially in older adults or in those with poorer cardiovascular reserve [11,12]. This makes it a symptom worth asking about directly, rather than waiting for the patient to report it spontaneously.

From a teaching perspective, dizziness is a useful bridge between arrhythmia physiology and bedside risk awareness. It reminds the learner that AF is not simply "an irregular pulse." In some patients it reduces cerebral perfusion enough to impair safety, confidence, and mobility.

A structured history should therefore explore timing, triggers, relationship to posture, associated palpitations, and whether the patient ever had complete loss of consciousness. These simple questions often determine whether the presentation is routine or urgent.

2.1.5. Asymptomatic (Silent) AF

Silent AF is clinically one of the most important presentations because it is common, easily overlooked, and potentially dangerous. The term refers to AF that causes no recognized symptoms or only symptoms so mild that the patient does not connect them to an arrhythmia. In many series, about a third of patients with documented AF are asymptomatic or minimally symptomatic; the precise proportion varies with the population studied and the mode of AF detection [3,7-10]. Thus, lack of symptoms should not be surprising. It is part of the AF clinical spectrum

AF may be discovered incidentally during a routine ECG, on preoperative testing, or while monitoring an implantable cardiac device; however, it may also be picked up on a Holter monitor, wearable cardiac monitors, or, most notably, after an acute stroke event. The latter scenario probably accounts for silent AF's biggest clinical significance. AF can lead to thrombus formation with increased risk of stroke, heart failure decompensation, and progressive atrial remodeling [1-3,7-9]. Thus, silent AF serves as a simple reminder that patients with AF can present with few or nonspecific symptoms and have a high risk of complications.

Several explanations have been proposed for why some patients do not perceive AF. Older age, lower activity levels, autonomic differences, gradual adaptation to persistent arrhythmia, and competing chronic symptoms may all reduce symptom awareness. It is also possible that some patients simply attribute reduced stamina or mild dyspnea to aging or other diseases and therefore do not report them as symptoms at all [4,7-10]. The distinction between "truly asymptomatic" and "poorly recognized" AF is therefore not always simple.

For medical education, silent AF is an excellent topic because it links bedside diagnosis to modern screening strategies. Opportunistic pulse checks, office ECGs, prolonged ambulatory monitoring in selected patients, and device-based detection all become relevant precisely because not all AF announces itself through symptoms [1,2]. The growth of wearables has reinforced this concept, but the core principle is older and remains unchanged: clinicians must think of AF even when the patient does not.

The prognostic implications of silent AF remain an area of active research, but existing literature consistently shows that asymptomatic AF cannot be considered benign merely because the patient feels well [7-10]. Stroke may be the first manifestation. In some patients, silent AF is discovered only after a transient ischemic attack, an embolic stroke, or unexplained deterioration in exercise capacity. This is one reason why the clinical history should include not only classic arrhythmia symptoms, but also subtle changes in function, cognition, and exercise tolerance.

In summary, the symptom profile of AF is broad, sometimes dramatic, and often surprisingly quiet. Palpitations remain the most recognizable symptom, but dyspnea, fatigue, dizziness, and silent presentation are equally important in daily practice. For students and residents, the key educational message is simple: symptoms guide suspicion, but they do not define the disease

completely. AF must be documented electrocardiographically, interpreted in clinical context, and evaluated with awareness that symptom burden may be out of proportion to rhythm burden and risk [1-5]. This patient-centered understanding of symptoms is the first step toward accurate diagnosis and evidence-based management.

2.2. Physical Examination

Physical examination still matters in atrial fibrillation, even though the formal diagnosis is electrocardiographic. At the bedside, examination does not prove AF on its own, but it often creates the first strong clinical suspicion and helps the clinician understand how urgent the situation is. Current European and American guidelines both place bedside evaluation early in the diagnostic pathway, before the arrhythmia is fully characterized with ECG, imaging, and laboratory tests [1,2]. This is important for students and residents because AF is not only an ECG pattern. It is also a clinical syndrome, and the first clues are often simple: an irregular pulse, variable heart sounds, dyspnea, signs of congestion, or an otherwise unexplained decline in exercise tolerance [1-3].

The physical examination should begin with basic hemodynamic assessment. Blood pressure, pulse rate, respiratory rate, oxygen saturation, mental status, skin perfusion, and the patient's general appearance give immediate information about tolerance of the rhythm. Some patients with AF are fully stable and discovered incidentally. Others arrive with hypotension, pulmonary edema, chest discomfort, presyncope, or overt heart failure. In such cases, the bedside examination does more than raise suspicion. It separates a stable outpatient presentation from an unstable clinical picture that requires rapid confirmation and action [1-3].

A good examination in suspected AF should also look beyond the rhythm itself. Irregular pulse palpation should be followed by cardiac auscultation, assessment for jugular venous distension, peripheral edema, lung crackles, and the presence of murmurs. These findings may suggest underlying structural heart disease, valvular disease, or heart failure, which often coexist with AF and influence the rest of the diagnostic workup [1-3]. The bedside exam may also reveal possible contributors, such as fever, dehydration, alcohol excess, or thyrotoxic appearance. In other words, physical examination is not only about recognizing irregularity. It is about placing the arrhythmia in a wider clinical context.

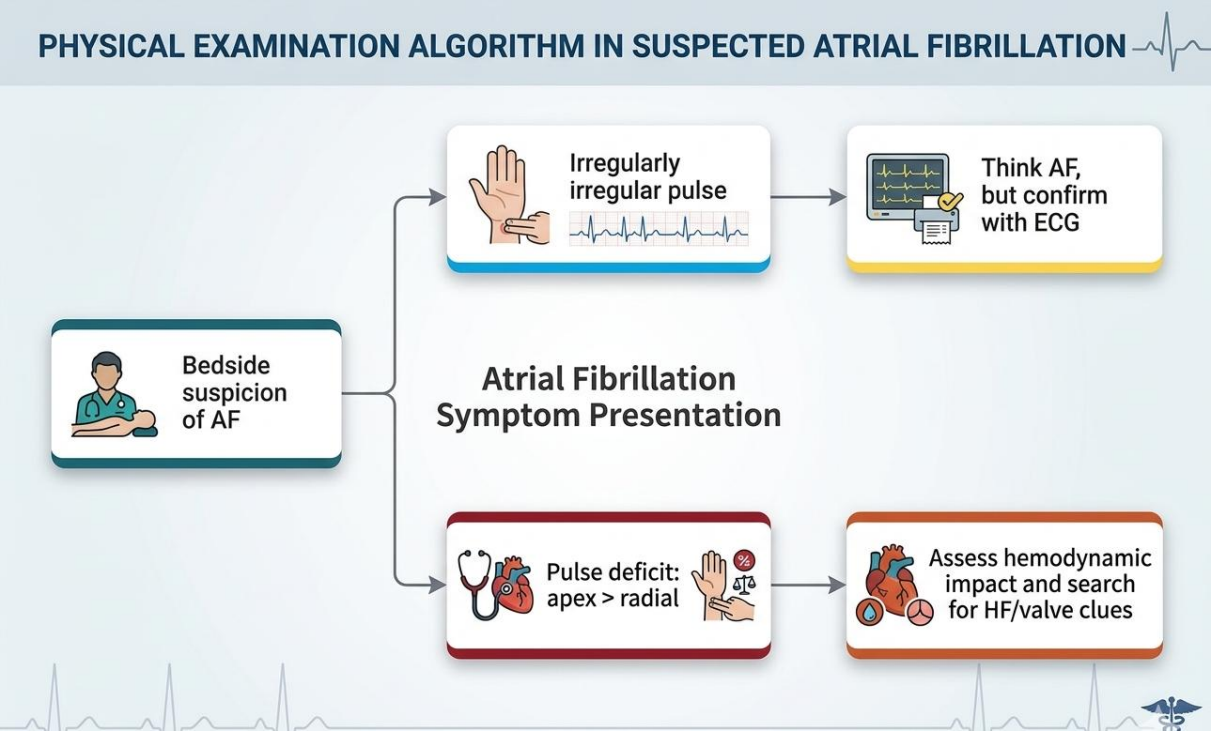

Figure 2.2. Bedside examination in suspected atrial fibrillation.

Footnote: Educational schematic created for this subchapter on the basis of references [1-3,13-16]. It summarizes the main bedside findings that raise suspicion of atrial fibrillation before ECG confirmation. AF, atrial fibrillation; ECG, electrocardiogram.

2.2.1. Irregularly irregular pulse

The classic bedside clue in AF is the irregularly irregular pulse. The interval between beats varies in a non-repeating way because atrial activation is chaotic and atrioventricular conduction becomes unpredictable. When this finding is present, the clinician should immediately think of AF, although the diagnosis still has to be confirmed on ECG [1-3]. At the bedside, the pulse may be palpated at the radial artery, but the examiner should also appreciate whether the rhythm is fast or slow, whether the pulse volume changes from beat to beat, and whether the patient becomes more symptomatic during minimal effort. These features help estimate the clinical impact of the arrhythmia before the tracing is obtained.

Pulse palpation remains useful because it is simple, rapid, and available everywhere. This is one reason why opportunistic AF case finding still begins with pulse assessment in many settings. However, pulse irregularity is not specific for AF. Frequent atrial or ventricular ectopy, sinus arrhythmia, multifocal atrial tachycardia, or atrial flutter with variable block can all produce an irregular pulse. A systematic review by Cooke and colleagues found that pulse palpation had high sensitivity but low specificity for detecting AF, making it a reasonable screening tool but not a definitive diagnostic test [13]. A subsequent meta-analysis by Taggar and colleagues found that pooled sensitivities and specificities were approximately 92% and 82%, respectively, for pulse palpation, also supporting its use as an initial diagnostic test alongside ECG as the primary diagnostic tool [14].In practice, the irregularly irregular pulse should not be interpreted in isolation. The examiner should compare pulse findings with heart sounds,

because AF often produces variable intensity of the first heart sound and an inconsistent peripheral pulse volume from one beat to the next. In some patients, the jugular venous pulse also loses any recognizable organized atrial pattern. These classical findings are less often emphasized now, but they remain educationally useful. They help students understand that AF is a disorder of atrial electrical disorganization with mechanical consequences that can be appreciated clinically, not only electronically [2,3].

There is also a practical teaching point here. Not every patient with AF feels dramatically symptomatic, and not every irregular pulse represents AF. The bedside skill lies in recognizing when irregularity deserves immediate electrocardiographic confirmation and when other clues suggest an alternative rhythm. For example, a very regular tachycardia argues against AF. A clearly patterned irregularity may suggest bigeminy rather than fibrillation. A patient with chronic lung disease and visible P-wave activity on ECG may instead have multifocal atrial tachycardia. This diagnostic caution is important because bedside examination is a tool for intelligent suspicion, not for overconfident labeling [1-3].

Table 2.2. Key physical examination findings that support suspicion of atrial fibrillation.

Bedside finding	How it is assessed	Why it matters
Irregularly irregular pulse	Radial pulse palpation over at least 30-60 seconds	It is a pathognomonic bedside finding. Raises suspicion of AF, but still requires ECG confirmation [1-5].
Variable pulse volume	Palpate whether beat strength changes from one beat to the next	Reflects irregular ventricular filling and variable stroke volume [2,3].
Irregular heart sounds	Cardiac auscultation at the apex	Supports rhythm irregularity and may reveal a higher apical rate than the radial pulse [2,6].
Signs of congestion or murmurs	Inspect and auscultate for JVP, crackles, edema, and valve lesions	Helps identify associated HF or structural heart disease, which shapes the next diagnostic steps [1-3].

Footnote: AF, atrial fibrillation; HF, heart failure. This table is intended for teaching and quick bedside review. Final diagnosis of AF still requires electrocardiographic confirmation.

2.2.2. Pulse deficit

Pulse deficit is another traditional but still meaningful bedside sign in AF. It describes the difference between the apical heart rate heard on auscultation and the peripheral pulse rate palpated at the wrist. In AF, some ventricular contractions occur after such short filling intervals that they generate little forward stroke volume and fail to produce a palpable peripheral wave. As a result, the heart may be beating faster than the radial pulse suggests [15,16].

This phenomenon matters for two reasons. First, it explains why peripheral pulse palpation can underestimate the true ventricular rate in AF. A patient may appear to have a moderate pulse at the wrist while the apical rate is clearly higher. Second, pulse deficit is a simple sign of hemodynamic inefficiency. The more irregular the ventricular filling and the weaker the resulting stroke volume, the more likely it is that some beats will be lost at the periphery. Mechanistic work has linked this finding to variations in preload and ineffective forward flow during short RR intervals [15,16]. More recent work has suggested that a larger pulse deficit may also track with worse exercise tolerance in some AF populations [15].

At the bedside, pulse deficit is assessed by simultaneously auscultating the apex and palpating the radial pulse for a full minute. This is an old-fashioned maneuver, but it remains helpful in teaching and in busy clinical environments where the peripheral rate seems inconsistent with the patient's symptoms. It also reminds trainees that radial pulse alone is not always a reliable surrogate for ventricular rate in AF [15]. In patients with very rapid and irregular rhythms, counting only the wrist pulse may falsely reassure the examiner and may underestimate the hemodynamic burden of the arrhythmia.

Pulse deficit should not be overanalyzed. It is not mandatory for the diagnosis of AF, and many modern algorithms do not explicitly require it, rapidly moving from palpation to ECG confirmation without further documentation. Nevertheless, it is a valuable sign that helps establish the relationship between clinical signs and physiological processes occurring in patients with AF. Specifically, irregular pulse is associated with reduced ventricular filling during diastole and reduced peripheral perfusion during systole. In this regard, clinicians and medical students can benefit from a simple and easily performed test that is directly related to basic physiological concepts [1-3,15,16].

Thus, the role of the physical examination in AF is to connect clinical manifestations with documented evidence of arrhythmia.

It begins with recognition of irregularity, but it should always extend to hemodynamic status, signs of heart failure, murmurs suggesting valvular disease, and bedside clues that explain symptom severity. The irregularly irregular pulse remains the most recognizable sign, while pulse deficit adds a more refined understanding of beat-to-beat hemodynamic inefficiency [1-3,15]. For trainees, this subchapter should reinforce a simple idea: the ECG confirms AF, but the physical examination explains the patient in front of you.

2.3. Electrocardiographic Diagnosis

Electrocardiographic diagnosis is the central step in confirming atrial fibrillation. Symptoms, pulse irregularity, and wearable alerts may raise suspicion, but they do not establish the diagnosis by themselves. Current major guidelines still require documentation of the rhythm on an interpretable electrocardiographic tracing. In practice, this is usually done with a standard 12-lead electrocardiogram, but a good-quality single-lead recording may also confirm AF when

the tracing is sufficiently clear and of adequate duration [1,2]. This point is important for students and residents because it separates clinical suspicion from formal diagnosis. A patient may strongly "sound like" AF, yet the final label still depends on the tracing.

2.3.1. ECG characteristics of AF

The classical ECG pattern of atrial fibrillation includes two main elements. The first is the absence of consistent, discrete P waves. The second is an irregularly irregular ventricular rhythm, meaning that the R-R intervals vary unpredictably and do not follow a repeating pattern [1,2,21]. In many tracings the baseline looks fibrillatory, with fine or coarse undulations replacing organized atrial depolarization. The QRS complexes are usually narrow, unless there is a bundle branch block, aberrant conduction, pre-excitation, or ventricular pacing [1-3].

For teaching purposes, it is useful to stress that irregularity alone is not enough. Many learners identify any irregular rhythm as AF, which leads to avoidable errors. The diagnosis becomes stronger when the reader deliberately looks for the missing P waves, the absence of an isoelectric pattern of organized atrial activity, and the beat-to-beat variability of the ventricular response. In other words, AF is not simply "fast and irregular." It is an atrial rhythm without stable atrial depolarization, coupled with an irregular ventricular consequence [1,3,21].

The tracing should also be interpreted in context. AF may present with a rapid ventricular response, but it can also be normocardic/normal ventricular rate or even slow, especially in patients using rate-limiting drugs or in those with underlying conduction disease. Therefore, rate does not define the rhythm. This is a frequent examination point for trainees. A slow irregular rhythm can still be AF, and a fast rhythm is not automatically AF just because it is symptomatic [1,2]. Figure 2.3 summarizes a practical ECG-based approach to AF and its main mimics.

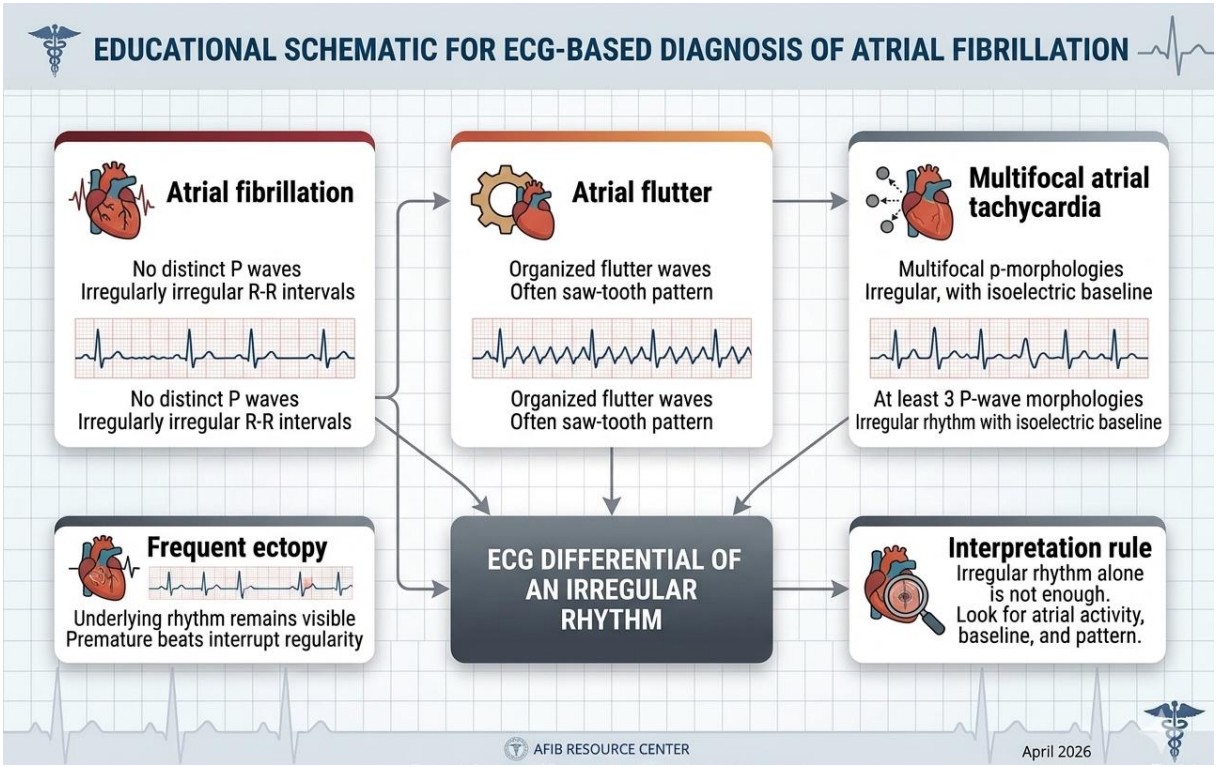

Figure 2.3. Electrocardiographic approach to atrial fibrillation and its main mimics.

Footnote: Educational schematic created for this subchapter based on references [1-3,17-21]. It highlights the main ECG clues that support the diagnosis of atrial fibrillation and the practical features that help distinguish it from common mimics.

2.3.2 Differential diagnosis

The differential diagnosis of AF on ECG mainly includes rhythms that are either irregular themselves or give the false impression of irregularity. The most relevant examples are atrial flutter with variable atrioventricular conduction, multifocal atrial tachycardia, sinus rhythm with frequent premature atrial or ventricular beats, and atrial tachycardia with variable block [2,3,17]. The diagnostic task is to decide whether the rhythm is truly disorganized at the atrial level or whether organized atrial activity is still present and simply being conducted in an uneven way.

Multifocal atrial tachycardia deserves special attention because it can look deceptively similar to AF at first glance. It is also irregular, but the ECG still shows identifiable P waves. Importantly, there are at least three different P-wave morphologies, and an isoelectric baseline can usually be seen between them. This differs from AF, where organized P waves are absent [2,3]. MAT is especially relevant in older patients with pulmonary disease or metabolic stress, so the clinical setting may offer an additional clue.

Frequent atrial or ventricular ectopy may also create an irregular pulse and an apparently chaotic strip when the tracing is short or noisy. In these situations, the underlying rhythm is usually preserved, and the irregularity comes from premature beats rather than from fibrillation. Careful inspection across several leads often reveals the basic rhythm. This is why a poor-quality single strip should not be overinterpreted when the morphology is uncertain [1,2,20]. Table 2.3 presents a compact differential diagnosis that residents can use at the bedside or during ECG teaching sessions.

Table 2.3. Practical ECG differential diagnosis in an irregular supraventricular rhythm.

Rhythm	**Atrial activity**	**Ventricular rhythm**	**Key distinguishing clue**
Atrial fibrillation	No discrete P waves; fibrillatory baseline may be present	Irregularly irregular	No repeating atrial pattern
Atrial flutter with variable AV block	Organized flutter waves, often best in II, III, aVF, V1	May be irregular	Repeating atrial activity suggests flutter, not AF
Multifocal atrial tachycardia	At least 3 P-wave morphologies with isoelectric baseline	Irregular	Visible P waves with changing shape
Sinus rhythm with frequent ectopy	Underlying sinus P waves remain identifiable	Irregular because of premature beats	Irregularity is intermittent, not continuously disorganized

Footnote: AF, atrial fibrillation; AFL, atrial flutter; AV, atrioventricular; MAT, multifocal atrial tachycardia. This table is intended for teaching and quick review. Final rhythm identification should always be based on direct ECG interpretation in the clinical context.

2.3.3. Atrial flutter vs AF

The distinction between atrial flutter and atrial fibrillation is clinically important and sometimes surprisingly difficult. Typical atrial flutter is a macro-reentrant atrial tachycardia. On the ECG it produces organized flutter waves, classically with a saw-tooth appearance in the inferior leads and often clear activity in lead V1 [17,19]. In contrast, AF has disorganized atrial activity and no repeating atrial pattern. This difference may sound simple in theory, yet in practice the two rhythms are often confused, especially when flutter has variable AV block [17,18,20].
When atrial flutter conducts variably to the ventricles, the ventricular rhythm may become irregular and can mimic AF. In these cases, the key is to search carefully for organized atrial activity. The tracing should be reviewed in several leads, not just one. Inferior leads and V1 are especially useful. If a repeating atrial pattern is identified, the diagnosis shifts toward flutter even when the ventricular response looks irregular [17-20]. The problem becomes even greater in coarse AF, where large fibrillatory waves may resemble flutter waves. Several studies have shown that even physicians misclassify these tracings with some frequency, which makes a systematic reading method essential [18-20].

A practical teaching rule is this: if the baseline appears continuously organized, think of flutter; if it appears chaotically disorganized, think of AF. The distinction is not just academic. Flutter and AF share risk factors and may coexist in the same patient, but they reflect different electrical mechanisms and may lead to different procedural strategies later on. For a diagnostic chapter, the main message is that the ECG must be read carefully enough to define the rhythm mechanism as accurately as possible before any further clinical decisions are made [1,2,17].

In daily clinical work, electrocardiographic diagnosis of AF depends on discipline rather than on complexity. The clinician must confirm the rhythm, identify its defining features, and then actively exclude the most relevant mimics. This structured method is more reliable than intuition alone. For students, it builds good habits early. For residents, it reduces misclassification in real patients. The final ECG interpretation should always be linked back to the clinical setting, but the tracing remains the decisive diagnostic document [1-3].

2.4. Ambulatory Rhythm Monitoring

Ambulatory rhythm monitoring occupies a central place in the diagnostic evaluation of atrial fibrillation when the office electrocardiogram is nondiagnostic. This is especially true in paroxysmal AF, where the arrhythmia may be absent during the consultation and appear only intermittently during daily life. Current European and American guidelines recommend extending rhythm surveillance when clinical suspicion remains high after a normal standard ECG, particularly in patients with recurrent palpitations, episodic dyspnea, unexplained dizziness, or ischemic stroke without an immediately obvious cause [1,2]. The basic rule is simple and useful for students: the less often the symptoms occur, the longer the monitoring period should be.

This subchapter should not be understood as a purely technical inventory of devices. Ambulatory monitoring is a clinical strategy. Its value lies in matching the right tool to the right patient. A short recording is appropriate when symptoms occur every day. It is much less helpful when

episodes happen once every few weeks. In the same way, monitoring after embolic stroke requires a different level of persistence than monitoring a young patient with brief, clearly symptomatic spells. Reviews on ambulatory ECG monitoring have repeatedly shown that diagnostic yield depends not only on device type, but also on episode frequency, recording duration, signal quality, and whether the patient can activate the recorder during symptoms [22,23].

There is also an important conceptual point. A negative short recording does not exclude AF. Many paroxysmal episodes are brief, asymptomatic, or both. For this reason, ambulatory monitoring is often the bridge between clinical suspicion and electrocardiographic proof. In modern practice it also helps estimate AF burden, correlate symptoms with rhythm, and uncover silent AF in selected high-risk settings such as cryptogenic stroke [1,2,22-28].

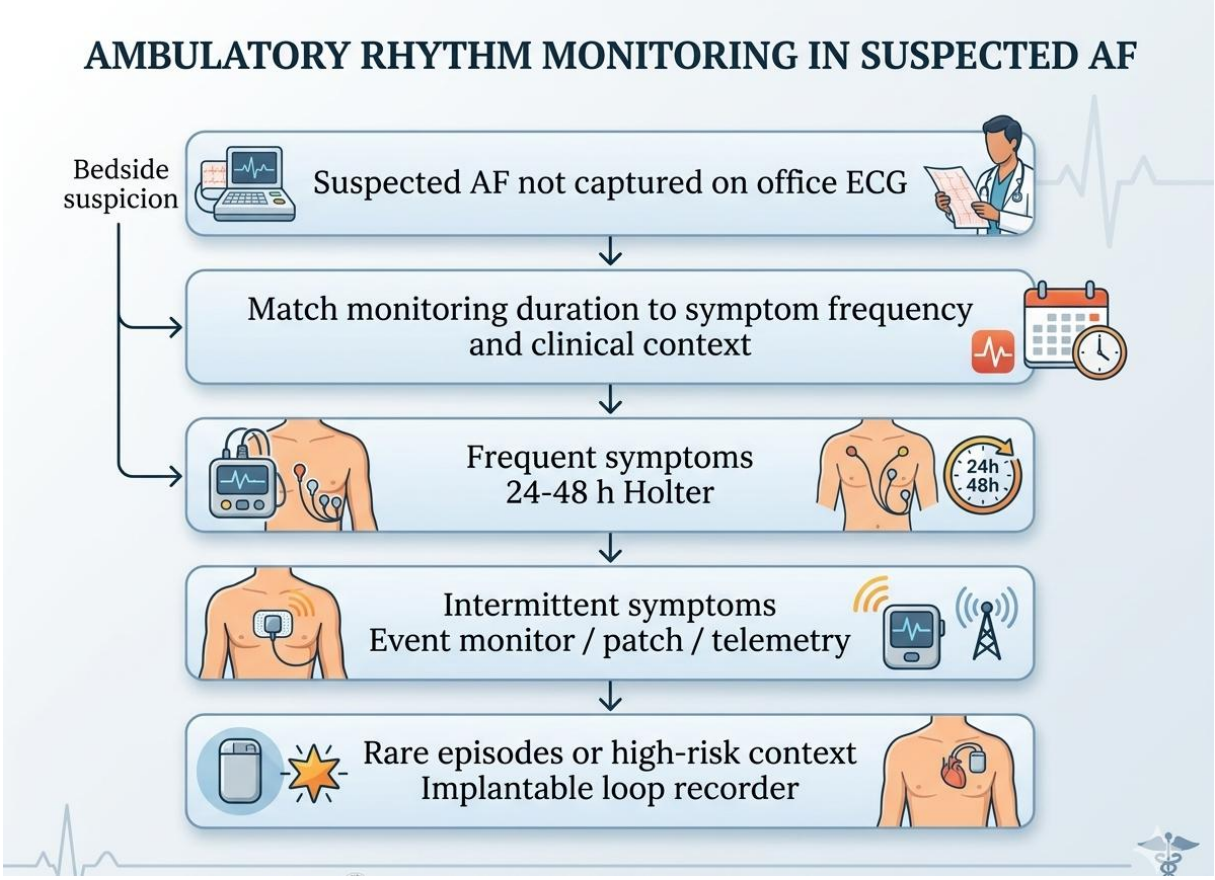

Figure 2.4. Choice of ambulatory rhythm monitoring according to symptom frequency and clinical suspicion.

Footnote: Educational schematic created for this subchapter on the basis of references [1,2,22-28]. A negative short recording does not exclude AF when suspicion remains high. AF, atrial fibrillation; ECG, electrocardiogram.

2.4.1. Holter monitoring

Holter monitoring is the traditional starting point for ambulatory rhythm assessment. It records the ECG continuously, most often for 24 or 48 hours, although longer patch-based Holter systems are now widely available. Its main strength is that it captures every beat during the mon-

itoring window, which makes it useful for frequent symptoms, rate assessment, and initial correlation between symptoms and rhythm [1,2,22,23]. In a patient who reports daily palpitations or repeated episodes over several days, Holter monitoring is often the most practical first step. The limitation of Holter monitoring is not quality but time. If suspected AF occurs only once every few weeks, a 24-hour study can easily miss it. This does not make the Holter "negative" in an absolute sense. It only means that no event was captured during that short window. For trainees, this is a very important distinction. Many false reassurances in clinical work come from overinterpreting a nondiagnostic short recording as if it ruled out intermittent arrhythmia [22,23].

Holter monitoring still has several advantages despite this limitation. It is widely available, familiar to clinicians, and useful not only for diagnosing AF but also for identifying other rhythm disturbances, pauses, ectopy, or rate-related symptoms. It can also quantify ventricular rate variability in patients with already documented AF. In diagnostic pathways, however, its real value is highest when symptom frequency is relatively high. When symptoms are rare, the clinician should quickly move to a longer strategy rather than simply repeating short recordings without a clear rationale [1,2,22,23].

2.4.2. Event monitors

Event monitors extend surveillance beyond the limits of the standard Holter. Some are patient-triggered and store the rhythm when the patient activates the recorder during symptoms. Others are auto-triggered and can capture asymptomatic episodes as well. In current practice, this category also includes external loop recorders, adhesive patch monitors used for 1 to 4 weeks, and some mobile cardiac telemetry systems. Their main role is in patients whose symptoms are intermittent rather than daily [22,23].

The advantage of event monitoring is a higher chance of matching symptoms with rhythm over a longer period. This becomes especially relevant in paroxysmal AF, where the arrhythmia may be brief and infrequent. In the EMBRACE trial, noninvasive monitoring for 30 days revealed a significantly higher number of AF cases compared to the standard 24-hour monitoring in patients with cryptogenic stroke, which underlines the importance of prolonged recording in selected populations [24]. Similar results were found in several meta-analyses including patients with stroke, where increased monitoring duration was associated with higher detection rates beyond 24 hours, though the yield was highly dependent on the population studied and monitoring duration [28].

Furthermore, implantable loop recorders require patient initiation and thus are indicated only in patients with typical symptoms, making them ineffective in recognizing silent AF episodes. Adhesive patches appear to be better tolerated than older methods using wires, but similar limitations regarding skin irritation, adherence issues, and missed recording time apply.

. Mobile telemetry increases yield further in some settings, but it also produces more incidental findings and may require more intensive review. For students, the take-home message is that event monitors are not "better than Holter" in every situation. They are simply better when the suspected episode frequency justifies a longer external recording period [22,23,28].

2.4.3. Implantable loop recorders

Implantable loop recorders, now often called insertable cardiac monitors, provide the longest surveillance window. They are placed subcutaneously and can record rhythm information for months to years. Their greatest value appears when AF is strongly suspected but remains undocumented after noninvasive monitoring, or when the clinical consequence of missing AF would be important, as in cryptogenic stroke [1,2,22,23].

The best-known evidence to date comes from the CRYSTAL AF trial. In which, long-term monitoring using an insertable monitor detected more cases of AF after cryptogenic stroke than conventional follow-up, and the difference grew over time [25,26]. This is clinically intuitive. A device that remains in place for months has a much better chance of detecting rare and silent episodes than a monitor worn for only a few days. For this reason, implantable monitoring should be seen as a high-yield diagnostic option for carefully selected patients rather than as a last resort used only after repeated low-yield short tests.

Implantable monitoring also changed how clinicians think about subclinical AF. In ASSERT, device-detected atrial tachyarrhythmias were common in patients without previously known clinical AF and were associated with future clinical AF and thromboembolic events [27]. This does not mean that every short device-detected episode has the same immediate clinical significance, but it does confirm that prolonged monitoring can uncover relevant atrial arrhythmia that would otherwise remain invisible.

The disadvantages of implantable monitors are equally worth teaching. They require a minor invasive procedure, generate large amounts of rhythm data, and may detect episodes whose interpretation is not always straightforward. They are therefore not the first test for every patient with palpitations. Their use makes the most sense when the pre-test probability is meaningful and when a documented diagnosis would clearly influence the next step in care. From a diagnostic perspective, implantable loop recorders are the most sensitive tools for infrequent AF, but they should be deployed selectively and purposefully [1,2,22-27].

Table 2.4. Comparison of ambulatory monitoring strategies used in suspected atrial fibrillation.

Modality	Typical duration	Best clinical use	Main points
Holter monitor	24-48 h	Frequent symptoms or initial rate/rhythm assessment	Continuous recording and broad availability, but low yield for rare episodes.
Event monitor / external loop / patch	1-30 days	Intermittent symptoms or suspicion of paroxysmal AF not captured on Holter	Longer external monitoring increases diagnostic yield and can correlate symptoms with rhythm.
Implantable loop recorder	Months to years	Rare episodes, cryptogenic stroke, or high suspicion after nondiagnostic external monitoring	Highest yield for infrequent or silent AF, but invasive and data-intensive.

Footnote: AF, atrial fibrillation. The table synthesizes practical teaching points from references [1,2,22-28]. Device selection should always be adapted to symptom frequency, pre-test probability, and the clinical consequence of missing paroxysmal AF.

In summary, ambulatory rhythm monitoring is not a secondary diagnostic step but an extension of electrocardiographic diagnosis into the patient's real life. Holter monitoring is appropriate for frequent events. Event monitors and patch systems are more useful when symptoms are intermittent. Implantable loop recorders are most helpful when episodes are rare, silent, or clinically high-stakes. The choice of device should therefore be guided by symptom frequency, clinical context, and the likelihood that longer surveillance will change diagnostic certainty [1,2,22-28].

2.5. Imaging in Atrial Fibrillation

Imaging does not establish the electrocardiographic diagnosis of atrial fibrillation, but it is a core part of the diagnostic work-up once the rhythm has been documented. In practice, imaging explains the clinical context in which AF appears. It helps identify structural heart disease, quantifies chamber size, evaluates ventricular function, detects valve lesions, and clarifies whether thrombus is likely to be present before rhythm-control procedures [1,2,12,13,29]. For students and residents, this is an important transition point in reasoning. The clinician moves from the question "Is this AF?" to the more useful question "What kind of heart is this AF occurring in?"

The first imaging test in most patients is transthoracic echocardiography. It is a noninvasive, easily repeated, and highly informative examination. The standard echocardiographic study allows the assessment of the left atrial size, left ventricular systolic function, wall thickness, right ventricular function, valvular involvement, pericardial condition, and indirectly the filling pressure [1,2,12,13]. These parameters are essential to evaluate since isolated atrial fibrillation (AF) is rare, while hypertensive heart disease, heart failure, valvular pathology, myocardial scar, and cardiomyopathy significantly impact AF management.

2.5.1. Echocardiography

Transthoracic echocardiography is the routine imaging modality in newly recognized AF. The main value of the test is not simply descriptive. It changes diagnostic interpretation. Left atrial enlargement supports the presence of chronic atrial remodeling, while reduced left ventricular ejection fraction suggests that the arrhythmia may coexist with or worsen heart failure [1,2,12,13,29]. Concentric wall thickening and left ventricular hypertrophy point toward long-standing hypertension. Regional wall motion abnormalities may indicate prior myocardial ischemia or infarction. Significant mitral or aortic valve disease may account for both the symptoms and the arrhythmia.

In addition, evaluation by echocardiography can also help relate the patient's symptoms to his hemodynamics. For example, in a patient with dyspnea on exertion, absence of abnormal ventricular size or reduced ejection fraction does not rule out clinically significant disease, because increased filling pressures due to abnormal diastolic function, left atrial dilation and pulmonary venous congestion can cause dyspnea [1,12,29].

In contrast, marked ventricular dysfunction or severe valve disease immediately changes how the entire AF episode is interpreted. The imaging study therefore supports the history and the physical examination rather than standing apart from them.

Another practical role of transthoracic echocardiography is risk framing. Larger left atrial size has been associated with AF persistence and recurrence after cardioversion or ablation, although imaging findings should never be interpreted in isolation [1,2,29]. Residents should understand that echocardiography is not used to "confirm AF," but to characterize substrate, severity, and associated disease. That distinction prevents the common mistake of treating imaging as secondary, when in fact it is often central to understanding the patient.

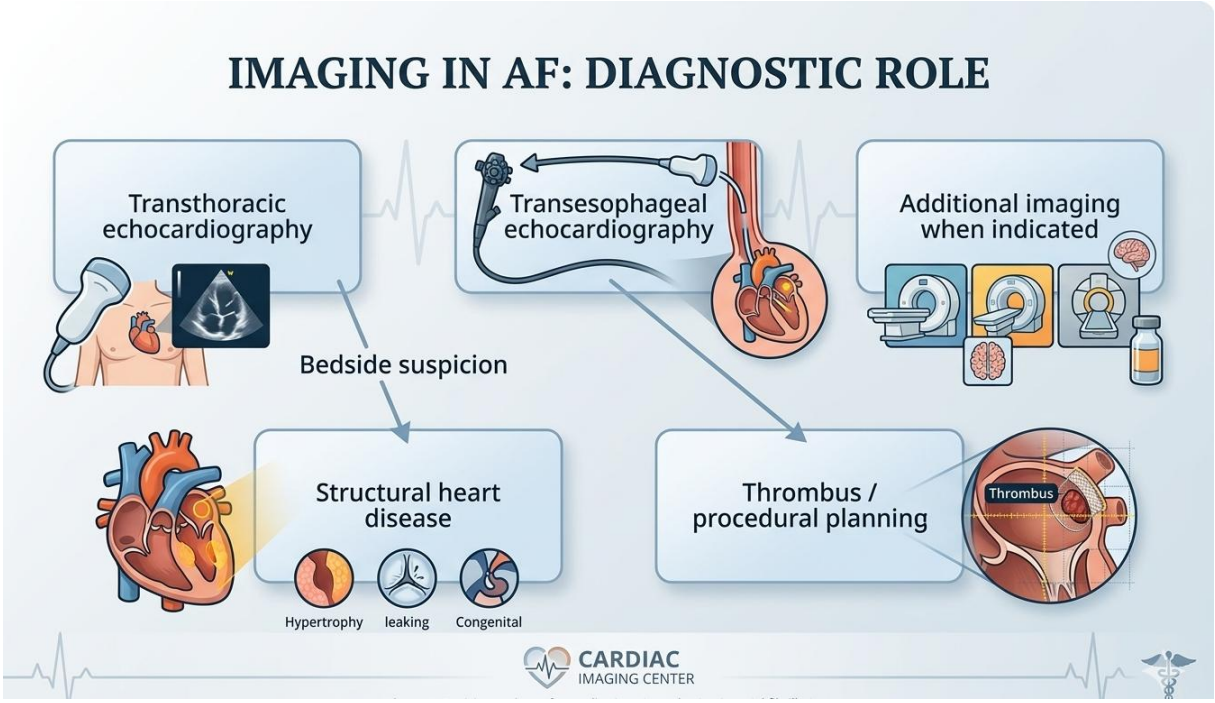

Figure 2.5. Imaging in AF: practical diagnostic roles of TTE and TEE.

Footnote: TTE is the first-line imaging study in most patients with documented AF. TEE is used selectively, mainly for left atrial appendage thrombus exclusion, more detailed left atrial assessment, and procedural planning. AF = atrial fibrillation; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

2.5.2. Transesophageal echocardiography

Transesophageal echocardiography has a narrower but very important diagnostic role. Its main strength is visualization of the left atrium and, especially, the left atrial appendage. This is the location where thrombus most commonly forms in nonvalvular AF. TEE is therefore particularly useful when cardioversion is being considered and the duration of AF is uncertain or prior anticoagulation has been absent, incomplete, or difficult to verify [1,2,14,30].

Compared with transthoracic imaging, TEE provides better spatial resolution for posterior structures and can define spontaneous echo contrast, appendage emptying velocity, thrombus, and complex atrial anatomy. These details matter before cardioversion and in procedural settings such as left atrial appendage occlusion or some ablation strategies [1,2,30]. The technique is semi-invasive, however, and it should not be presented as a routine test for every AF patient. It is best taught as a targeted extension of the diagnostic pathway.

A useful teaching point comes from the classic TEE-guided cardioversion strategy. When no left atrial thrombus is seen, rhythm control can be initiated more quickly in selected patients if general guidelines regarding anticoagulation are followed [14,30]. This highlights the theme that AF imaging should consider not only anatomical information but also implications for timing, safety, and procedural sequencing.

Table 2.5. Main echocardiographic options used during the AF diagnostic work-up.

Imaging modality	**Main diagnostic contribution**	**Typical clinical use**
Transthoracic echocardiography (TTE)	Structural assessment: chamber size, ventricular function, valves, pericardium	Baseline imaging in most patients with newly documented AF
Transesophageal echocardiography (TEE)	Left atrial and left atrial appendage visualization; thrombus exclusion	Before cardioversion when anticoagulation history is uncertain or for procedure planning
Additional imaging when indicated	Selected anatomical clarification beyond echo	Complex structural disease or pre-procedural assessment

Footnote: This table summarizes the usual diagnostic roles of echocardiographic imaging in AF. The exact choice depends on clinical context, symptom profile, anticipated intervention, and the need to exclude left atrial appendage thrombus. AF = atrial fibrillation; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

In summary, imaging in AF is less about proving the arrhythmia and more about understanding its setting. Transthoracic echocardiography gives the broad structural overview and should be regarded as the routine first-line study. Transesophageal echocardiography is used more selectively, mainly when appendage thrombus exclusion or more detailed atrial assessment is needed [1,2,12,14,29,30]. If students remember that ECG documents AF and imaging explains AF, they will already have a sound diagnostic framework.

2.6. Laboratory Evaluation

Laboratory testing does not diagnose atrial fibrillation by itself, but it often explains why the arrhythmia appeared, how unstable the patient may be, and which associated conditions should be looked for next. Once AF has been documented on electrocardiography, the laboratory work-up becomes part of clinical interpretation In contrast, the new cases allow the identification of some triggers that can be easily reversed, such as thyrotoxicosis or electrolyte imbalances. Besides, in the context of dyspnea, fatigue, or decompensation present in the patient, the differential diagnosis of isolated arrhythmia from a more comprehensive cardiac or systemic problem is achieved [1,2,31-36].

A pragmatic approach to teaching laboratory evaluation is to divide the interpretation process into three key questions. First, is there a metabolic or endocrine trigger that might have contributed to the arrhythmia development? Second, are there any internal disturbances, especially those related to potassium or magnesium levels, that might promote arrhythmias or interfere

with the therapy? Third, do the biomarkers reflect myocardial tension, heart failure, ischemia, or the presence of a high-risk phenotype? This approach helps the trainee think about test results in the context of patient care [1,2,35,36].

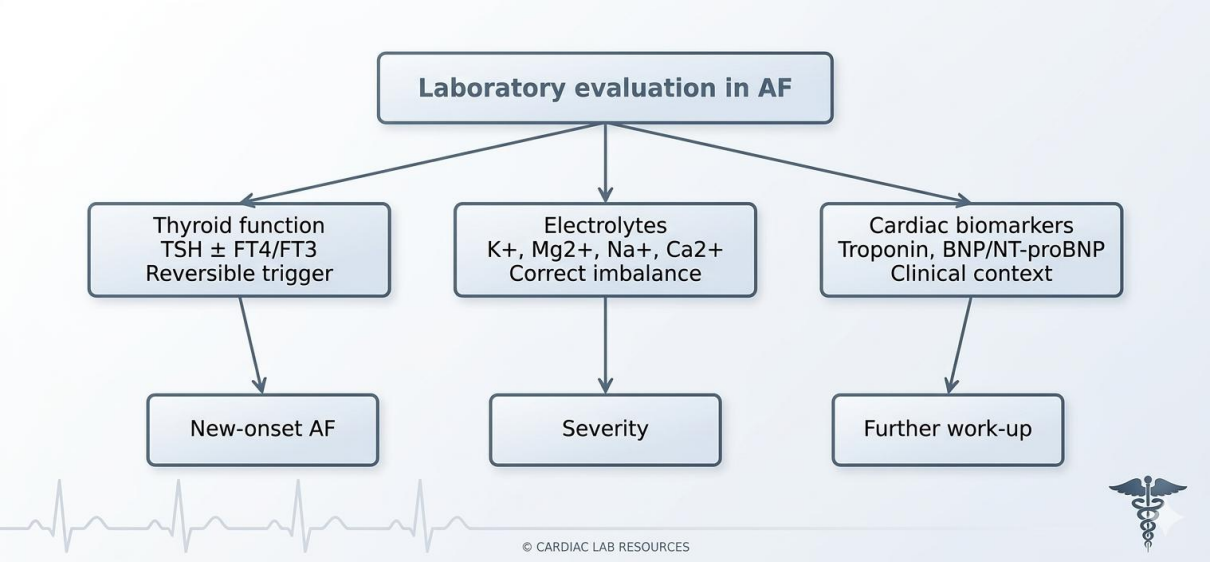

Figure 2.6. Main roles of laboratory evaluation after atrial fibrillation has been documented on ECG.

Footnote: AF, atrial fibrillation; BNP, B-type natriuretic peptide; ECG, electrocardiogram; FT3, free triiodothyronine; FT4, free thyroxine; K+, potassium; Mg2+, magnesium; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TSH, thyroid-stimulating hormone. Educational schematic created for this subchapter on the basis of references [1,2,31-36].

2.6.1. Thyroid Function

Thyroid function tests are an integral part of the work-up in AF. Hyperthyroidism is a common cause of atrial fibrillation that may be reversed by anti-thyroid agents. Increased sympathetic activity, shortening of the refractory period of the atrium, and triggered activity are possible mechanisms by which hyperthyroidism may induce AF. New-onset AF may be the first clinical manifestation of underlying thyroid dysfunction.. This is why most guidelines still recommend thyroid function testing, usually with TSH as the first-line assay, in patients with newly documented AF [1,2,31,32].

From a bedside point of view, thyroid testing is especially relevant when AF appears without an obvious structural explanation, when the ventricular response is unexpectedly rapid, or when the history includes weight loss, tremor, heat intolerance, diarrhea, anxiety, or goiter. It is equally important in older adults, because thyrotoxicosis can present subtly and still drive arrhythmia. Current literature also suggests that even subclinical thyroid dysfunction, particularly subclinical hyperthyroidism, is associated with a higher risk of incident AF, which supports a low threshold for testing in unexplained cases [31,32].

Thyroid results should be interpreted carefully. A suppressed TSH with elevated FT4 or FT3 supports overt hyperthyroidism and makes endocrine treatment part of AF management. A mildly abnormal TSH may need confirmation, correlation with medication history, or repeat testing after acute illness, because non-thyroidal illness and over-replacement with levothyroxine can distort the picture. For students and residents, the key lesson is simple: thyroid testing in AF is not a box-ticking exercise. It is a search for a potentially modifiable driver of the arrhythmia [1,2,31,32].

2.6.2. Electrolytes

Electrolyte testing is another practical cornerstone of AF evaluation. Potassium and magnesium deserve particular attention because both influence cardiac excitability and conduction. Hypokalemia and hypomagnesemia may increase atrial ectopy, facilitate arrhythmia maintenance, and make other rhythm disturbances more likely. This becomes especially relevant in acutely ill patients, in those receiving diuretics, and in patients with vomiting, diarrhea, renal dysfunction, or recent medication changes [1,2,33,34].

Electrolytes matter not only because they can contribute to the onset of AF, but also because they influence how safely the patient can be managed afterward. A patient with AF and significant hypokalemia may be more vulnerable to additional arrhythmias. A patient with renal dysfunction and abnormal magnesium handling may need more careful interpretation of both laboratory values and subsequent therapies. Recent observational data have reinforced the longstanding clinical view that low potassium and low magnesium states are associated with a higher likelihood of AF, although the relationship is complex and not purely causal [33,34].

In teaching, it is important to reinforce that laboratory evaluation should be clinically oriented. Not every patient with AF will have precipitating electrolyte abnormalities, and not every patient with abnormal electrolytes will have them as the underlying cause of AF. Nevertheless, restoring normal electrolyte concentrations is indicated because it reduces the number of possible contributing factors to AF and improves general physiological function. Electrolyte review is therefore best framed as both diagnostic and preventive: it helps explain the episode and reduces the chance that a correctable substrate will be missed [1,2,33,34].

Table 2.6. Core laboratory domains that should be considered during the diagnostic work-up of atrial fibrillation.

Test domain	Main examples	Why it matters in AF	Typical clinical caveat
Thyroid function	TSH ± FT4/FT3	Looks for overt or subclinical thyroid dysfunction that may trigger or sustain AF	Acute illness and thyroid replacement therapy can distort interpretation
Electrolytes	K+, Mg2+, Na+, Ca2+	Identifies correctable internal imbalance that may favor arrhythmia or instability	Borderline values may still matter in diuretic use or renal dysfunction
Cardiac biomarkers	Troponin, BNP, NT-proBNP	Provides context for myocardial stress, ischemia, HF, and prognostic risk	Elevation is not specific for acute coronary syndrome or for AF itself

Footnote: AF, atrial fibrillation; BNP, B-type natriuretic peptide; FT3, free triiodothyronine; FT4, free thyroxine; HF, heart failure; K+, potassium; Mg2+, magnesium; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TSH, thyroid-stimulating hormone. This table is intended for teaching and quick clinical review. It summarizes the practical contribution of laboratory testing in AF on the basis of references [1,2,31-36].

2.6.3. Cardiac Biomarkers

Cardiac biomarkers do not confirm AF, but they are helpful in understanding the diagnosis. Troponin may be elevated in AF because of tachycardia-related myocardial stress, supply-demand mismatch, concomitant coronary disease, or another acute cardiac process. On the other hand, natriuretic peptides such as BNP or NT-proBNP are often elevated when AF is associated with atrial stretch, ventricular dysfunction, or overt heart failure. For that reason, biomarkers are most likely to reflect context rather than rhythm [1,2,35,36].

Context is essential in interpreting these findings and determining the underlying mechanism. Thus, an increased troponin level does not necessarily rule out acute coronary syndrome, nor does an increased level of natriuretic peptides indicate that AF is the sole reason for symptoms, especially in the presence of heart failure.In other words, biomarkers are not shortcuts; they are amplifiers of clinical reasoning [35,36].

Recent literature has also emphasized the prognostic role of biomarkers in AF. High-sensitivity troponin, natriuretic peptides, and markers such as GDF-15 have been incorporated into biomarker-based risk models and may improve prediction of stroke, bleeding, heart failure events, and death in selected settings. For undergraduate teaching, however, the most useful message is more modest: when cardiac biomarkers are abnormal in AF, they should prompt the clinician to look harder for structural disease, myocardial injury, or decompensation rather than to label the finding as nonspecific and move on [1,2,35,36].

In summary, laboratory evaluation in AF is not a mechanical list of blood tests. It is part of the diagnostic narrative. Thyroid testing looks for a reversible endocrine trigger. Electrolyte testing looks for correctable internal instability. Cardiac biomarkers help frame severity, comorbidity, and prognosis. When these results are interpreted alongside the history, examination, ECG, and imaging, they make the diagnosis of AF more clinically meaningful and more useful for subsequent decision-making [1,2,31-36].

2.7. Risk Stratification

Risk stratification completes the diagnostic reasoning in atrial fibrillation. Once the arrhythmia has been documented, the clinician still has to answer two practical questions. First, how high is the patient's risk of thromboembolism, especially ischemic stroke? Second, how high is the patient's risk of clinically relevant bleeding if anticoagulation is prescribed? These two questions are linked, but they are not the same. Good clinical practice requires that both are assessed explicitly, rather than relying on impression alone [1,2,37,38].

For students and residents, this is an important turning point. Up to this stage of the work-up, the focus is mainly descriptive. The physician has recognized symptoms, confirmed the arrhythmia on ECG, and searched for underlying structural or systemic contributors. Risk stratification shifts the discussion from diagnosis to consequences. In other words, the clinician asks not only "Does this patient have AF?" but also "What does this AF mean for future stroke and bleeding risk?" [1,2].

The two most familiar bedside tools remain the CHA_2DS_2-VASc score for thromboembolic risk and the HAS-BLED score for bleeding risk. Neither score is perfect, and neither should replace clinical judgement. Their value lies in standardizing bedside reasoning, identifying patients at truly low risk, highlighting patients who need closer review, and making treatment discussions more objective and reproducible [1,2,37-40].

Table 2.7. Main clinical risk scores used in atrial fibrillation.

Score	Components	Teaching point
CHA_2DS_2-VASc	Congestive heart failure/LV dysfunction (1), Hypertension (1), Age ≥75 years (2), Diabetes mellitus (1), Prior stroke/TIA/systemic embolism (2), Vascular disease (1), Age 65-74 years (1), Sex category female (1).	Best known score for bedside estimation of stroke risk in AF. Particularly useful for identifying truly low-risk patients. Many current teaching materials still use this score.
HAS-BLED	Hypertension (1), Abnormal renal function (1), Abnormal liver function (1), Stroke history (1), Bleeding history or predisposition (1), Labile INR (1), Elderly age >65 years (1), Drugs predisposing to bleeding (1), Alcohol excess (1).	Used to flag bleeding vulnerability and, above all, to uncover modifiable factors. It should not be used as an automatic reason to withhold anticoagulation.

Footnote: LV = left ventricular; TIA = transient ischemic attack; INR = international normalized ratio.

2.7.1. Stroke Risk (CHA_2DS_2-VASc)

The CHA_2DS_2-VASc score is still the most widely recognized clinical tool for stroke risk estimation in atrial fibrillation. It evolved from the older $CHADS_2$ model by adding vascular disease, age 65-74 years, and female sex, while keeping age ≥75 years and prior stroke or TIA weighted more heavily. Its practical strength is not that it predicts every event with perfect precision, but that it performs well in identifying patients who are truly at low risk and therefore may not gain meaningful net benefit from anticoagulation [37,39,41].

The score is intentionally simple. It uses variables that are already available from the history and basic chart review. That simplicity explains its wide adoption in daily practice and in education. A student can calculate it at the bedside within seconds. More importantly, the score creates a common language. When a clinician says that a patient has a CHA_2DS_2-VASc score of 4, most readers immediately understand that the patient carries a clearly non-trivial thromboembolic risk [1,2,37].

At the same time, this score should not be used in a rigid mechanical way. It does not include all relevant sources of stroke risk. It also does not capture the intensity of each comorbidity. A well-controlled hypertensive patient and a patient with severe uncontrolled hypertension both receive one point. The same simplification applies to diabetes, vascular disease, and heart failure. This is why the score is best understood as a structured clinical shortcut rather than a complete biological model [1,2,39].

A point of current interest is the role of female sex. The 2024 ESC guideline simplified thromboembolic risk assessment by moving from CHA_2DS_2-VASc to CHA_2DS_2-VA in formal decision support, reflecting evidence that female sex behaves more as a risk modifier than as a stand-alone risk factor in many contemporary cohorts [1,42]. Even so, CHA_2DS_2-VASc remains extremely important in textbooks, previous studies, and many educational settings. For that reason, students should be comfortable with both concepts. In practice, they should understand why the traditional score remains widely quoted and why newer guidance may frame the sex category differently [1,2,39,42].

Another practical lesson is that stroke risk is not static. A patient who is low risk today may no longer be low risk one or two years later after aging into a new category or developing hypertension, diabetes, vascular disease, or heart failure. Periodic reassessment is therefore part of good AF care. Risk stratification is not a one-time administrative act performed at diagnosis and then forgotten. It should be revisited whenever the clinical picture changes [1,2,41].

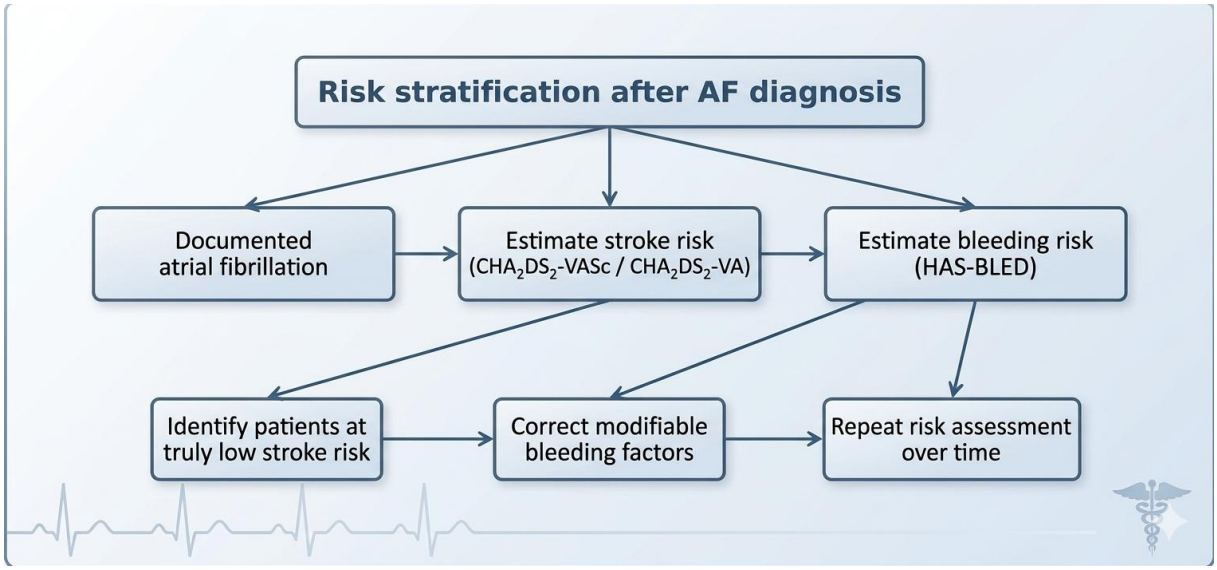

Figure 2.7. Practical sequence for stroke and bleeding risk assessment after AF has been documented.
Footnote: The figure is schematic and meant for teaching. In current ESC guidance, thromboembolic risk may be discussed using CHA_2DS_2-VA, while many educational resources still present CHA_2DS_2-VASc.

2.7.2. Bleeding Risk (HAS-BLED)

The HAS-BLED score was developed to estimate the risk of major bleeding in patients with atrial fibrillation, particularly in those being considered for anticoagulation. Like CHA_2DS_2-VASc, it is practical because it is quick, bedside-friendly, and built from variables that are usually already known. The score reminds the clinician that risk assessment in AF has two sides. Preventing stroke matters greatly, but the patient's vulnerability to bleeding also deserves structured attention [38,40].

The most important teaching point is that HAS-BLED is not a "do not anticoagulate" score. That misunderstanding is common and should be actively corrected in training. The real purpose of HAS-BLED is to identify modifiable bleeding risk factors and to prompt closer follow-up in patients who are more fragile. Uncontrolled blood pressure, excess alcohol intake, concomitant non-steroidal anti-inflammatory drugs, poorly managed vitamin K antagonist therapy,

and untreated renal or liver disease all deserve attention because they may change the balance of risk in a way that is actionable [1,2,38].

Like all clinical scores, HAS-BLED has limitations. Its predictive accuracy is moderate rather than perfect, and some of its items are broad. It also performs differently across populations and treatment strategies. Still, systematic reviews have generally supported its continued clinical usefulness, especially because it is simple and because its components are easy to understand and often modifiable [38,40]. In educational terms, it works well not because it predicts every bleed, but because it forces the clinician to think carefully about bleeding vulnerability in a structured way.

The most useful bedside approach is to read HAS-BLED as a checklist. A higher score should trigger a deeper look, not therapeutic paralysis. The clinician should ask whether blood pressure is controlled, whether drug interactions can be reduced, whether alcohol is excessive, whether renal and hepatic function are acceptable, and whether follow-up can be improved. This is exactly why stroke and bleeding scores should be interpreted together. Stroke risk helps identify the need for protection from thromboembolism, while bleeding risk guides how carefully and under what conditions that protection should be delivered [1,2,38,40].

In summary, risk stratification in AF should be deliberate, dynamic, and clinically contextual. The student should leave this topic with three simple ideas. First, the presence of AF alone does not define future stroke risk. Second, bleeding risk assessment is essential but should not be misused as a reason to deny effective stroke prevention without careful thought. Third, both forms of risk evolve over time and should be reassessed rather than treated as fixed labels [1,2,37-42].

2.8. Diagnostic Algorithm

A diagnostic algorithm in atrial fibrillation is useful because it organizes a common but sometimes messy clinical presentation into a reproducible sequence. In real practice, AF may present with clear palpitations, vague exercise intolerance, an incidental irregular pulse, a smartwatch notification, or an embolic event in a patient who never felt any arrhythmia at all [1,2,3]. Students often learn the separate pieces of the work-up but have difficulty connecting them in the right order. The value of an algorithm is not that it replaces judgement. Its value is that it shows which questions should be asked first, which tests truly establish the diagnosis, and which findings must be documented before the case can be considered complete [1,2,41].

The first step is clinical suspicion. AF should be considered when a patient reports episodic palpitations, exertional dyspnea, fatigue, dizziness, reduced exercise tolerance, or a history suggestive of embolic stroke without another obvious cause. It should also be suspected when examination reveals an irregularly irregular pulse or a pulse deficit, even when the patient feels relatively well [1,2,12,15]. The purpose of this first step is simple. It identifies the patients who need rhythm documentation and prevents the clinician from dismissing nonspecific symptoms too early. In teaching, it is worth emphasizing that symptoms guide suspicion, but they do not prove the rhythm diagnosis [1,2].

The second step is electrocardiographic confirmation. Current guidelines still require documentation of atrial fibrillation on a 12-lead electrocardiogram or, if unavailable, on a rhythm strip of adequate duration, usually > 30 s, to capture the irregularly irregular pattern of AF [1,2]. This is the essential step in the algorithm. An irregular pulse, smartwatch alert, or emergency department monitor can suggest AF, but none replaces the value of a documented rhythm strip. At this step, the physician should confirm that distinct P waves are absent, that the ventricular response is irregularly irregular, and that conditions that simulate AF (e. g., atrial flutter with variable block, multifocal atrial tachycardia) have been excluded [1,2,17,18,19,20,21].

The next step in the algorithm consists of ambulatory rhythm monitoring. This modality is no longer an option but a necessity when the initial tests are normal but clinical suspicion is high. The general principle is to match the duration of monitoring with the frequency of symptoms. If daily or almost daily, then 24- or 48-h Holter monitoring is appropriate. If the events are less frequent, patch-type or event recorders are better options. Implantable loop recorders should be considered in patients with intermittent cryptogenic stroke or with highly suspicious episodes of AF occurring rarely [1,2,22,23,24,25,26,27,28].

At this point in the algorithm, it is critical to emphasize that short-term recordings (e. g., < 24 h) should not be used to rule out AF.

The fourth step in the algorithm is the characterization of AF as paroxysmal, persistent, or longstanding. Even though the subsequent section deals mainly with treatment, a brief description of paroxysmal AF is needed here. It is important to distinguish between paroxysmal AF and persistent forms of the arrhythmia since the management differs [1,2]. In addition, it is helpful to note whether AF was associated with significant symptoms or with changes in the heart rate, the tolerance for the arrhythmia, and possible triggers (infection, surgery, excessive alcohol use, thyrotoxicosis).

At this stage, the clinician is no longer asking only “Is this AF?” but also “In what setting did it occur, and how unstable is the patient right now?” That distinction is clinically important because diagnostic urgency increases when AF is accompanied by hypotension, pulmonary edema, ischemic chest pain, or syncope [1,2,31-36].

The fifth step is structural evaluation of the heart. Transthoracic echocardiography is the standard imaging test after the rhythm has been confirmed. It identifies chamber enlargement, ventricular dysfunction, hypertensive remodeling, valve disease, and indirect signs of elevated filling pressures [1,2,12,13,29]. This is important because AF is often the presenting manifestation of an underlying substrate rather than an isolated electrical event. A structurally normal heart does not exclude AF, but significant structural abnormalities change the way the arrhythmia is interpreted and later managed. In particular, in selected cases where cardioversion is being considered and the patient’s anticoagulation history is unavailable, transesophageal echocardiography is indicated as a part of the algorithm to assess the left atrium and left atrial appendage for thrombus[1,2,14,30].

The sixth step is laboratory evaluation. Laboratory tests are not included to “diagnose AF,” but to explain it and to identify reversible contributors or associated systemic disease. Thus, thyroid-stimulating hormone is included in the battery due to the possibility of hyperthyroidism as a reversible proarrhythmic factor. Potassium and magnesium should be reviewed because electrolyte abnormalities may facilitate arrhythmia and complicate later treatment. Renal function tests

are another routine component of workup that contribute to the management of patients with AF. On the one hand, they help estimate the overall prognosis and guide the choice of therapy, including anticoagulation, which is invariably nephrotoxic to some degree. On the other hand, cardiac biomarkers, including troponins and natriuretic peptides, may stage acute myocardial infarction or decompensated heart failure as an underlying cause of AF, thereby influencing the management [1,2,31-36]. In terms of the algorithm, laboratory tests come after establishing the diagnosis of AF and before proceeding to the final risk stratification. The final step is formal risk stratification. In clinical teaching, this is where diagnosis becomes prognosis. In many ways, this is where the diagnostic process converges into the determination of prognosis. After AF has been diagnosed and characterized, the clinician must estimate the thromboembolic and bleeding risks using established tools, such as the CHA_2DS_2-VASc score and HAS-BLED score, respectively [1,2,37-40]. These scores do not replace judgement, but they complete the diagnostic picture. A patient with documented AF has not been fully evaluated until the clinician can also describe what the rhythm implies for future stroke risk, what modifiable bleeding risk factors exist, and whether further preventive planning will be required [1,2,37-40].

Seen as a whole, the algorithm follows a simple logic: suspect, confirm, extend monitoring if needed, characterize the episode, evaluate cardiac structure, search for systemic contributors, and stratify risk. This sequence is easy to remember and clinically practical. It also helps students avoid two frequent mistakes. The first is stopping too early after detecting an irregular pulse. The second is stopping too early after documenting AF on one ECG. A good diagnostic work-up does more than name the arrhythmia. It explains the context in which it appeared and defines the risks attached to it [1,2,41-44].

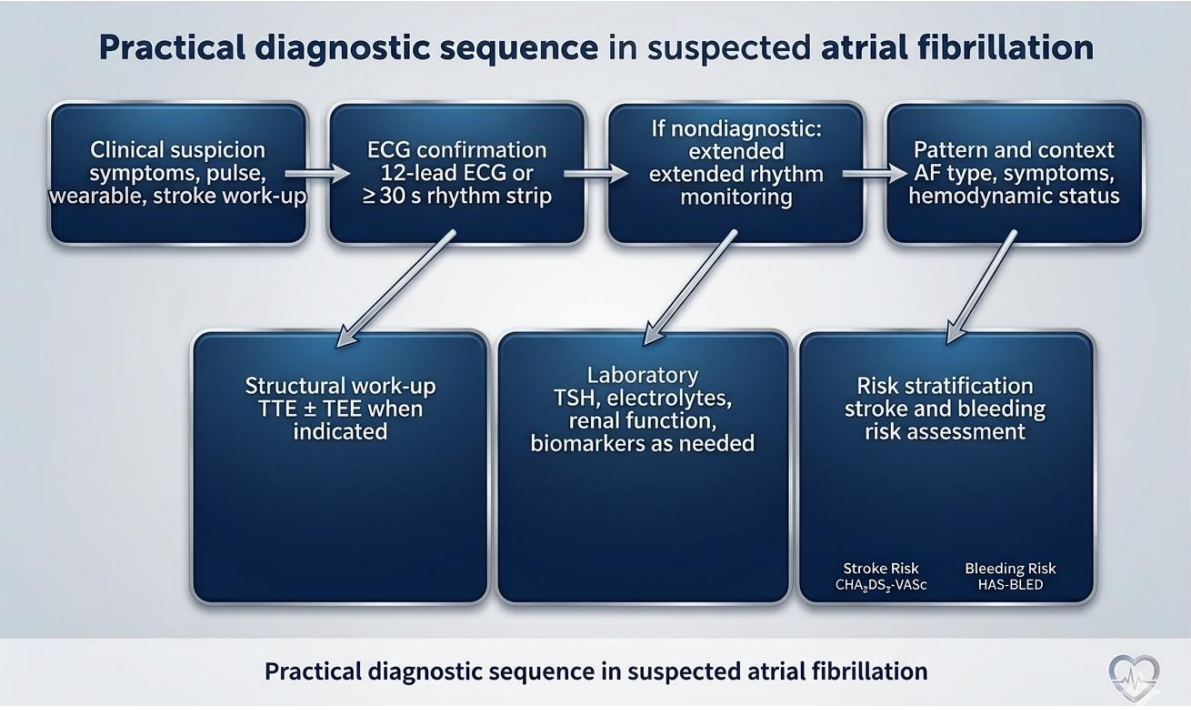

Figure 2.8. Practical diagnostic pathway in suspected atrial fibrillation.

Footnote: AF, atrial fibrillation; ECG, electrocardiogram; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. Educational schematic created for this subchapter on the basis of references [1,2,12-15,17-21,22-30,31-40,41-44].

Table 2.8. Core steps of the diagnostic algorithm in atrial fibrillation.

Step	Question	Core action	Main output
1	Why suspect AF?	Assess symptoms, pulse findings, incidental alerts, stroke context	Clinical suspicion
2	Is AF documented?	Obtain 12-lead ECG or diagnostic rhythm strip	Electrocardiographic confirmation
3	Could paroxysmal AF be missed?	Choose Holter, event monitor, patch monitor, or loop recorder	Rhythm capture over time
4	How is the episode behaving?	Define pattern, rate, symptom burden, tolerance, triggers	Clinical characterization
5	What is the cardiac substrate?	Perform TTE; add TEE when indicated	Structural and thrombus assessment
6	Are there reversible or associated systemic factors?	Check thyroid status, electrolytes, renal function, biomarkers	Laboratory context
7	What are the future risks?	Estimate stroke and bleeding risk	Risk stratification

Footnote: AF, atrial fibrillation; ECG, electrocardiogram; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. The table summarizes the practical sequence described in the text and is intended for educational use by medical students and residents.

2.9. Clinical Cases

A case-based section is useful at the end of a diagnostic chapter because it forces the reader to connect symptoms, examination, electrocardiography, ambulatory monitoring, imaging, laboratory testing, and risk assessment in the order in which they appear in real practice. Students often learn these elements separately. The difficulty appears when they must move from one clue to the next without losing the clinical thread. A good case discussion makes that transition easier. It shows that atrial fibrillation is not recognized from one isolated sign, but from a pattern that becomes clearer as data accumulate [1-3].

Another advantage of clinical cases is that they illustrate how variable AF can be. One patient presents with obvious palpitations and an irregular pulse. Another presents only with dyspnea or fatigue. A third patient has no rhythm-related complaint at all and first enters the AF pathway after an embolic event or during prolonged rhythm monitoring. The diagnostic principles remain the same, but the entry point differs. This is exactly why students need to practice the reasoning process repeatedly and not memorize only one classic presentation [1-3,24,25].

The cases below are deliberately simple and educational. They are not intended to cover every therapeutic decision in detail, because treatment strategy belongs to the management chapter. Their purpose is narrower and more practical: to show how suspicion is raised, how AF is confirmed, which accompanying tests are useful, and how the initial clinical meaning of the diagnosis is framed [1,2,40-44].

2.9.1. Case 1. Palpitations and abrupt-onset paroxysmal atrial fibrillation

A 67-year-old man presents to the emergency department because he felt his heart "flip into an irregular fast rhythm" about two hours earlier while climbing stairs. He reports palpitations, mild breathlessness, and anxiety, but no syncope and no chest pain. On examination he is hemodynamically stable. The pulse is rapid and irregularly irregular. Cardiac auscultation shows variable first heart sound intensity, and the radial pulse is more difficult to count than the apical rate. This first contact already gives the examiner a strong bedside suspicion of AF [1,2,13-15].

A 12-lead ECG confirms the diagnosis. There are no discrete P waves, the baseline is fibrillatory, and the RR intervals are irregular. This is the clearest and most efficient example of how AF is diagnosed in practice. Symptoms suggested the rhythm disorder, the examination supported it, and the ECG established it. Once the rhythm has been documented, the diagnostic task moves from confirmation to characterization. The clinician now needs to ask whether this is likely to be a first-detected episode, whether structural heart disease is present, and what the patient's thromboembolic and bleeding profile may be [1-3,17-21,37,38].

The next differential diagnostic steps are relatively straightforward. The baseline lab work is requested, which includes renal function tests, electrolytes, CBC, and thyroid function. Transthoracic echocardiography is also indicated due to the possibility of the atrial enlargement and valvular pathology. Even though the patient is stable now, it is important to rule out any acute processes that may contribute to the observed irregular heartbeat pattern. [1,2,29-36].

The teaching point from this case is simple. Paroxysmal AF often enters practice through symptoms. When the episode is ongoing during the consultation, the diagnosis can be rapid. Students should remember that the work-up does not end with the ECG. Once AF is captured, the clinician still has to define the context in which it occurred and the risk profile that follows from it [1,2,40-44].

2.9.2. Case 2. Silent atrial fibrillation discovered after ischemic stroke

A 79-year-old woman is admitted with an ischemic stroke. She has no history of palpitations and denies previous episodes of rapid heartbeat. Early telemetry during admission does not immediately show AF. The first impression might therefore be that the stroke has no rhythm-related explanation. However, the patient's age and embolic presentation keep the suspicion of occult AF alive. This is a classic setting in which intermittent, clinically silent AF must still be considered [1-3,24,25].

In this case the key diagnostic lesson is persistence. A normal admission ECG and a short period of telemetry do not exclude paroxysmal AF. When episodes are infrequent, longer monitoring increases the diagnostic yield. External prolonged monitoring or an implantable loop recorder may reveal episodes that are never captured during a brief hospital observation window. This is exactly why ambulatory monitoring is part of the diagnostic chapter and not an optional extra [1,2,24-28].

When AF is eventually documented, the significance is immediate even though the patient never felt the arrhythmia. Symptom burden and risk burden are not the same. Silent AF can still carry substantial thromboembolic relevance, especially in older patients with vascular

comorbidity. For students, this case is important because it breaks the common but incorrect assumption that the diagnosis of AF depends on palpitations. Sometimes the first meaningful clue is the complication, not the symptom [1-3,37,38].

The practical message is that a negative short tracing should be interpreted in light of pretest probability. If suspicion remains high, the monitoring strategy must be extended rather than abandoned. This case also reinforces a broader teaching point from Chapter 2: the diagnosis of AF is often a process, not a single moment [1,2,24-28,40-44].

2.9.3. Case 3. Newly diagnosed AF in a patient with hyperthyroid features

A 58-year-old woman is referred for fatigue, heat intolerance, weight loss, hand tremor, and recent awareness of an irregular heartbeat. Her pulse is fast and irregular. The ECG confirms AF with a rapid ventricular response. At first glance the arrhythmia seems to explain the symptoms, but the examination suggests that the rhythm disturbance may be part of a broader systemic disorder [1,2,31-33].

This is a useful case because it teaches students not to stop at rhythm documentation. AF has been established, but the next question is why it appeared. Thyroid function testing is part of the standard evaluation precisely because overt hyperthyroidism is a well-recognized reversible or contributing factor. In this patient, a suppressed TSH and elevated thyroid hormones would not replace the AF diagnosis, but they would explain the clinical context and shape further management decisions [1,2,31-33].

A second lesson from this vignette is that not all AF symptoms are generated by the arrhythmia alone. Fatigue, tremor, weight loss, and intolerance to heat come from the endocrine disease. The rhythm is important, but the diagnostic work-up must integrate all clues rather than treating AF as an isolated event. In educational terms, this is the difference between naming the rhythm and understanding the patient [1-3].

The broader principle is easy to remember. Whenever AF is confirmed, look for correctable contributors. Thyroid disease, electrolyte abnormalities, acute infection, alcohol excess, and decompensated cardiac disease can all modify how AF presents and how severe it becomes. A good diagnostic habit is therefore to ask not only “what rhythm is this?” but also “what is pushing the atria into this rhythm?” [1,2,31-36].

2.9.4. Case 4. Dyspnea, edema, and persistent AF in structural heart disease

A 75-year-old man presents with progressive exertional dyspnea, ankle swelling, reduced walking distance, and a sense of declining stamina over several weeks. The pulse is irregularly irregular and moderately fast. There are bibasal crackles and mild peripheral edema. The ECG confirms AF, but the bedside picture strongly suggests that the arrhythmia is occurring in the setting of structural heart disease rather than as an isolated electrical event [1-3,13-15].

In this situation echocardiography becomes central. The rhythm has already been documented, so imaging is used to determine what kind of heart the AF is occurring in. Transthoracic echocardiography may show left atrial enlargement, left ventricular systolic dysfunction, diastolic impairment, hypertensive remodeling, or relevant valvular disease. Each of these findings

changes the clinical meaning of the arrhythmia. The symptom complex in this case is probably not explained by AF alone, but by AF plus impaired cardiac substrate [1,2,29,30].

This case is educational because it highlights the limits of a rhythm-only mindset. Students sometimes assume that once the ECG says AF, the case is solved. In reality, AF is often a marker of broader cardiovascular disease. Dyspnea, edema, and exercise intolerance should prompt the physician to search for heart failure or other structural pathology rather than attributing everything to irregularity and rate alone [1-3,29,30].

The diagnostic lesson is therefore one of layering. First confirm AF. Then ask whether the symptoms reflect the rhythm itself, the underlying heart, or both. This stepwise interpretation is what turns an ECG finding into clinically useful diagnosis [1,2,40-44].

2.9.5. Case 5. Irregular tachycardia: AF or atrial flutter with variable block?

A 70-year-old patient presents with palpitations and an irregular pulse. The initial rhythm strip appears chaotic at first sight, and AF is suspected immediately. However, closer inspection of the ECG shows organized atrial activity in the inferior leads, raising the possibility of atrial flutter with variable AV conduction. This is an excellent teaching case because it demonstrates why not every irregular tachycardia is AF [1,2,17-21].

The clinical symptoms in flutter and AF can overlap considerably. What separates them diagnostically is the tracing. AF lacks discrete P waves and shows disorganized atrial activity. Typical flutter, in contrast, produces organized macro-reentrant atrial depolarization and often a sawtooth pattern, especially in leads II, III, and aVF. When AV block varies, the ventricular rhythm can become irregular enough to mimic AF. This is exactly where careful ECG reading matters most [1,2,17-21].

For a student, the main lesson is caution. A quick glance at an irregular rhythm strip is sometimes enough to raise suspicion, but not enough to assign the final label. When the diagnosis is uncertain, the examiner should slow down, inspect multiple leads, and actively search for organized atrial activity. Good diagnosis is often less about speed and more about disciplined pattern recognition [1-3].

This final case closes the chapter well because it brings the reader back to fundamentals. Symptoms open the diagnostic pathway, but the ECG defines the rhythm. Once the tracing is interpreted correctly, the rest of the diagnostic algorithm can be applied with more confidence [1,2,40-44].

Table 2.9 condenses the same cases into a quick-review format that students can use for revision before rounds, seminars, or examinations.

Table 2.9. Summary of representative clinical cases in atrial fibrillation.

Case	Typical entry clue	Key diagnostic test	Main learning point
1	Abrupt palpitations and irregular pulse	12-lead ECG	AF can be confirmed immediately when the episode is active
2	Ischemic stroke without symptom history	Extended rhythm monitoring	Silent AF may require prolonged monitoring for documentation
3	AF plus tremor, weight loss, heat intolerance	Thyroid function testing	Confirmed AF still requires a search for reversible contributors
4	Dyspnea, edema, reduced effort tolerance	Transthoracic echocardiography	Symptoms may reflect AF plus structural heart disease
5	Irregular tachycardia with uncertain atrial activity	Careful multi-lead ECG analysis	Not every irregular tachycardia is AF; flutter may mimic it

Footnote: The cases are educational examples designed to reinforce the diagnostic sequence presented in this chapter. AF = atrial fibrillation; AV = atrioventricular; ECG = electrocardiogram.

Taken together, these cases show that the diagnosis of AF is rarely difficult for one single reason and usually easier because several clues converge. Sometimes the entry point is the symptom. Sometimes it is the pulse, the ECG, the laboratory profile, the echocardiogram, or a later monitoring result. The clinician's task is to put this information in the context of a reasonable differential diagnosis (Table 1). For the learner, the safest concluding statement is that AF should be suspected and documented electrocardiographically and interpreted in context. It avoids both excessive testing and treatment while leading naturally into the next topic - rate control, rhythm control, and stroke prevention.

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Abbreviations

ABC - age, biomarkers, clinical history

ACC - American College of Cardiology

AF - atrial fibrillation

AFL - atrial flutter

AHA - American Heart Association

AV - atrioventricular

BNP - B-type natriuretic peptide

BP - blood pressure

CHA_2DS_2-VA - Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke/TIA/thromboembolism, Vascular disease, Age 65-74 years

CHA_2DS_2-VASc - Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke/TIA/thromboembolism, Vascular disease, Age 65-74 years, Sex category

ECG - electrocardiogram

EHRA - European Heart Rhythm Association

ESC - European Society of Cardiology
FT3 - free triiodothyronine
FT4 - free thyroxine
GDF-15 - growth differentiation factor 15
HAS-BLED - Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol
HF - heart failure
ICM - insertable cardiac monitor
ILR - implantable loop recorder
INR - international normalized ratio
K+ - potassium
LAA - left atrial appendage
LV - left ventricle
LVEF - left ventricular ejection fraction
MAT - multifocal atrial tachycardia
Mg2+ - magnesium
NT-proBNP - N-terminal pro-B-type natriuretic peptide
R-R interval - interval between consecutive ventricular depolarizations
TEE - transesophageal echocardiography
TIA - transient ischemic attack
TSH - thyroid-stimulating hormone
TTE - transthoracic echocardiography

CHAPTER 3 — MANAGEMENT STRATEGIES - *Amalia Cornea, Stefan Bolog, Abhinav Sharma, Lucretia Marin-Bancila*

3.1. Principles of AF Management

Atrial fibrillation (AF) is a frequently under-recognized and undertreated challenging clinical syndrome that represents a significant burden to patients and healthcare systems. AF is associated with substantial morbidity, mortality, and with increased risk of disabling stroke, heart failure, dementia and hospitalization (1).

Atrial fibrillation is a multi-factorial disease with environmental and genetic components.

An integrated approach to chronic illness is therefore appropriate, with management being largely patient-centered and with a multidisciplinary team (MDT) as well as the community as key players in decision-making (2).

An integrated approach was found to improve survival and reduce cardiovascular-related admission to hospital in patients with atrial fibrillation in a meta-analysis published in 2017 by Gallagher et al. (2).

The analysis informed the development of the ABC holistic, structured and patient-centered approach to AF management.

The MDT involves an AF specialist, cardiologist, general practitioner, sleep and endocrine specialists, an exercise physiologist, dietitian, and psychologist to engage in shared decision-making with the patient to achieve intensive risk-factor control and reduction.

AF is a progressive disease whose evolution is influenced by various risk factors that require aggressive intervention: obesity, pericardial fat, obstructive sleep apnea, aortic stiffness, pre-hypertension, excessive endurance exercise, and genetic variants, including clustering of common variants (polygenic risk) and rarer structural variants (monogenic/oligogenic risk) (3–5).

3.2. Guideline-Based Management

Atrial fibrillation is the most common sustained cardiac arrhythmia and is associated with substantial morbidity and mortality.

Care of patients with atrial fibrillation according to guidelines is based on a solid body of evidence aiming to optimize care and ensure consistent management in different settings.

The ABC ("Atrial fibrillation Better Care") pathway is an effective way back into today's guidelines, providing integrated management according to 3 simple pillars, an approach that has been demonstrated to be effective for patients and efficient in terms of costs:

1.A – Avoid stroke (anticoagulation if appropriate)

1. B – Better symptom control (rate/rhythm control with the appropriate medication)

2. C – Comorbidity management (cardiovascular and non-cardiovascular risk factor control) (1,3).

Still, adherence to the ABC concept was low (~21%) despite the considerable benefit in terms of reduced all-cause death, cardiovascular death, stroke, and major bleeding (2).

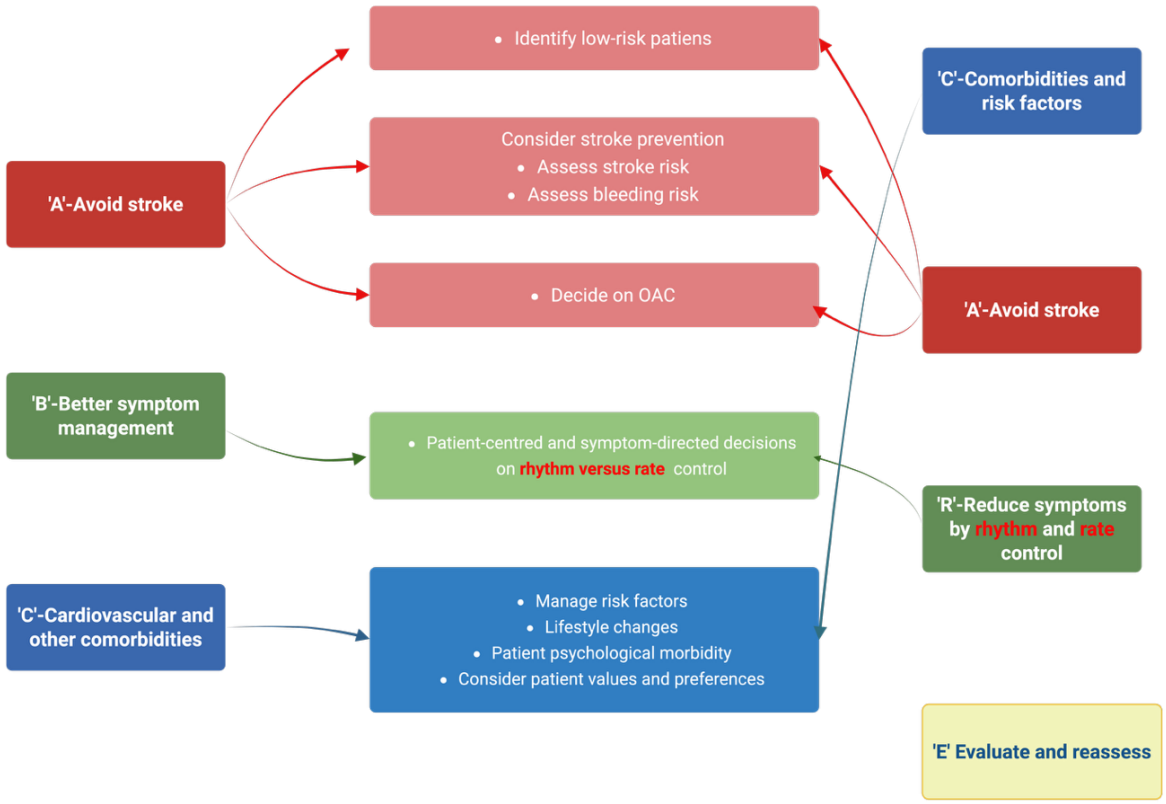

Fig. 3.2.1. Atrial fibrillation Better Care and AF-CARE pathway
. Created in BioRender. Cornea, A. (2026) https://BioRender.com/70vcm6v
(Adapted from: Potpara T, Romiti GF, Sohns C. The 2024 European Society of Cardiology Guidelines for Diagnosis and Management of Atrial Fibrillation: A Viewpoint from a Practicing Clinician's Perspective. Thromb Haemost. 2024;124(12):1087–1094. doi:10.1055/a-2434-9244.)

The European Society of Cardiology 2024 guidelines highlight integrated management of patients with atrial fibrillation going beyond rhythm or rate control by considering a broader multidisciplinary perspective that includes the management of comorbidities, thromboembolic risk, and symptoms.

An integrated, multidisciplinary approach is embodied in the AF-CARE pathway (Fig 3.2.1) and should be used to guide the management of patients with atrial fibrillation, focusing on personalized care and continuous reassessment according to the natural history of the disease and patients' needs (6).

The 2024 ESC/EACTS Guidelines on AF introduced a patient-centered approach based on four pillars of AF-CARE:
This framework is structured around four interconnected pillars.

- [C] Comorbidity and risk factor management underscores the importance of early identification and management of underlying conditions and modifiable risk factors contributing to disease progression.
- [A] Avoid stroke and thromboembolism emphasises the necessity of appropriate anticoagulation tailored to each patient's individual risk profile.

- [R] Reduce symptoms highlights the value of individualized rate and rhythm control strategies to minimize symptom burden and enhance quality of life.
- [E] Evaluation and reassessment reflect the dynamic nature of atrial fibrillation, necessitating ongoing follow-up and adaptation of therapeutic strategies over time.

This approach aims to guide treatment and care decisions, considering that associated comorbidities and risk factors can evolve over time. AF – CARE emphasises the importance of educating patients about the diseases and involving them in decision-making, and recognizes that all AF therapies are more effective when comorbidities are treated (3).

AF CARE relies on three main goals: preventing thromboembolic events, controlling heart rate and/or restoring sinus rhythm, and optimising associated cardiovascular risk factors and comorbidities. All of these must be continually monitored, as the mechanisms that cause AF change over time.

The best approach depends on the timing of AF, patient symptoms, comorbidities, and available techniques, and needs to determine whether urgent therapy is required (presence of hemodynamic instability with hypotension or severe tachycardia, whether pre-excitation is present, or whether suspected or confirmed myocardial ischemia/infarction or suspected or confirmed acute severe illness).

The initial evaluation of a patient presenting with AF determines whether emergency therapy is needed, regardless of whether AF is newly diagnosed or recurrent paroxysmal or persistent AF with a rapid ventricular rate (4).

Together, these components represent a transition toward integrated, multidisciplinary care, with the goal of improving guideline implementation in routine practice and optimising patient outcomes (5).

Risk stratification is a critical element in atrial fibrillation management, as it informs decisions regarding anticoagulation and overall therapeutic strategy.

The use of validated clinical tools promotes individualized care, leading to better outcomes.

The clinical tool used to determine the risk of thrombus formation is the CHA_2DS_2-VA (formerly known as CHA_2DS_2-VASc) score. Points are assigned to patients based on their age, sex, history of heart failure, high blood pressure, diabetes, previous stroke, and vascular disease. The score helps estimate the risk of stroke in patients with atrial fibrillation, which plays a major role in determining the need for oral anticoagulation. The higher the score, the greater the risk of thromboembolism .

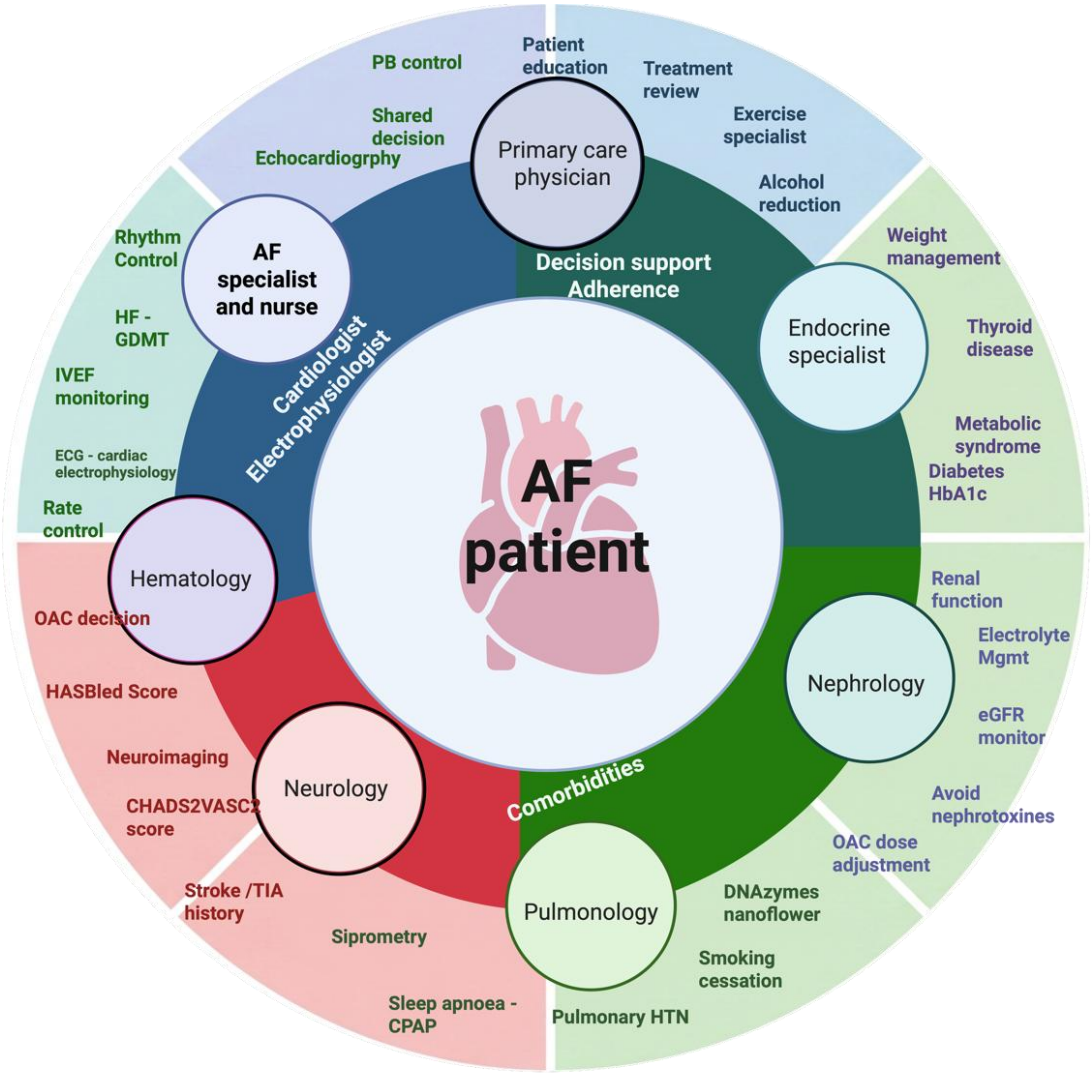

Fig. 3.2.3. Multidisciplinary approach of patients with AF.
Created in BioRender. Cornea, A. (2026)
(Adapted from:Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2021;42:373–498. Figure 11.Created in BioRender. Cornea, A. (2026))

This clinical prediction model is popular among clinicians because it is simple and has good predictive ability. It is critical to assess the risk of bleeding using the HAS-BLED score. It considers the history of hypertension, impaired renal or liver function, bleeding, unstable INR, age, and the use of drugs and alcohol. The HAS-BLED score aims to identify the risk factors that can be modified and pay special attention to them. A patient with a high HAS-BLED score may require more extensive monitoring. Overall, the HAS-BLED and CHA_2DS_2-VASc scores are essential in individualizing the treatment of patients with atrial fibrillation. They allow the doctor to weigh the risks and benefits of anticoagulation therapy.Risk stratification should be regarded as a dynamic process that necessitates periodic reassessment as patient characteristics change over time (7). The management of atrial fibrillation (AF) can be broadly divided into rate control and rhythm control approaches. Rate control strategies aim to reduce ventricular response by administering beta-blockers, which helps in minimizing the signs and symptoms of rapid heart rate.

On the other hand, rhythm control is achieved by using antiarrhythmic drugs, electrical cardioversion, or radiofrequency ablation to restore and maintain normal heart rhythm.
Clinical studies have demonstrated the superiority of rhythm control over rate control in terms of enhanced symptoms and quality of life, especially when initiated early after diagnosis. However, there is no conclusive evidence that rhythm control therapies lead to reduced mortality compared to rate control strategies.

Therefore, it is essential to make individualized treatment decisions while considering patient-specific factors such as baseline characteristics, comorbidities, and patient preferences (5,8,9).

Catheter ablation has become a central component of rhythm control, especially for patients who remain symptomatic despite pharmacological therapy. Recent advances have also improved the efficacy and safety of this procedure, making it an attractive option for restoring and maintaining normal heart rhythm.
Several studies have reported the superiority of catheter ablation over antiarrhythmic drug therapy in achieving durable sinus rhythm and reducing arrhythmia recurrence. Moreover, studies suggest that early intervention with catheter ablation may provide optimal benefits, especially for patients presenting with persistent or long-standing AF (10,11).

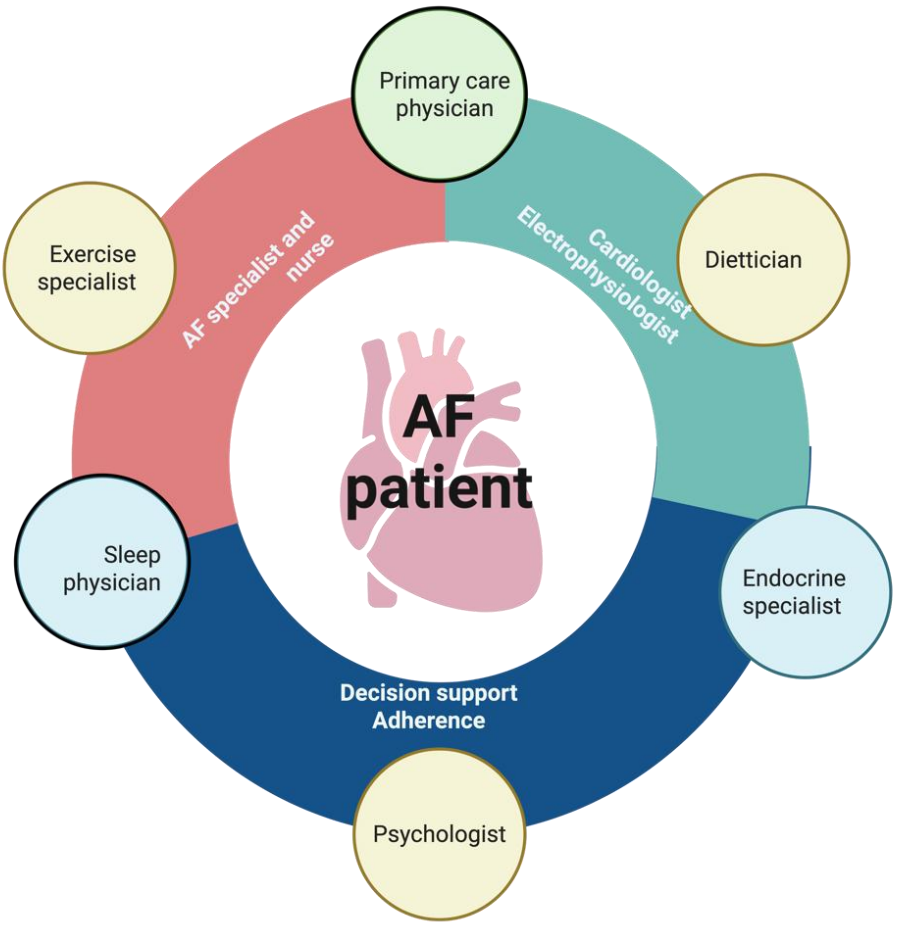

Fig. 3.2.2. Steps toward holistic approach of patients with AF
Created in BioRender. Cornea, A. (2026)
(Adapted from: Brandes A, et al. A call for action to include psychosocial management into holistic, integrated care for patients with atrial fibrillation. Europace. 2024;26(4):euae078. doi:10.1093/europace/euae078.Created in BioRender. Cornea, A. (2026))

In summary, the management of atrial fibrillation is changing towards multidisciplinary and holistic approaches (Figure 3.2.2, Figure 3.2.3) that focus on rate/rhythm control, management of concomitant conditions, and prevention of stroke. The importance of using clinical prediction models to estimate the risk of stroke and bleeding to guide oral anticoagulant treatment cannot be overstressed. Furthermore, modern treatment strategies allow for restoration of normal sinus rhythm that improve patients' symptoms and quality of life. Overall, the comprehensive control of atrial fibrillation that takes into account the complexity of this condition reduces morbidity and mortality and helps in managing the disease efficiently.

3.3. Treatment Algorithms

The 2024 ESC guidelines recommend a patient-centered treatment algorithm for atrial fibrillation, focusing on individualized therapy to achieve optimal long-term outcomes, while reducing disease progression and limiting symptomatic exacerbations (6).

Within the treatment algorithm, the first step is the accurate diagnosis and classification of the atrial fibrillation phenotype. This begins with a thorough ECG assessment to evaluate characteristic electrophysiological changes, followed by classification of the condition as paroxysmal, persistent, or permanent based on its clinical course and treatment response.

The next step following diagnosis is to identify the underlying cause and any existing comorbidities that may influence the patient's response to therapy.

Conditions such as hypertension, diabetes mellitus, and heart failure, the patient's nutritional status, and any history of chronic alcohol consumption or smoking require optimization of treatment, aiming to maximize therapeutic efficacy while minimizing the risk of adverse effects.(12).

Atrial fibrillation is characterized by rapid, chaotic, disorganized atrial electrical activity, leading to an irregular, accelerated ventricular response.

The absence of synchronized atrial depolarization leads to a decline in effective atrial mechanical function, resulting in inadequate atrial emptying and blood stasis, particularly in the left atrial appendage.

Consequently, it significantly increases the risk of thrombus formation and subsequent thromboembolic events, most frequently ischemic stroke.

Stroke prevention represents the next step in the management algorithm. Direct oral anticoagulants (DOACs) are used for their favorable efficacy and safety profiles. Individualized risk stratification is crucial to guide therapeutic decision-making.

Clinical prediction rules such as the CHA_2DS_2-VA score help estimate the risk of stroke/systemic embolism in AF patients. The HAS-BLED score is useful to evaluate the possibility of bleeding and the potential to modify risk factors; it is esential to note that the HAS-BLED score was not designed to determine eligibility for anticoagulation but rather to allow for an individualized risk assessment in order to optimize the therapeutic strategy (7).

In order to improve the quality of life and prevent possible complications, the majority of AF patients require pharmacologic or procedural intervention in order to normalize the heart rhythm or reduce the resting heart rate effectively, allowing them to resume normal activities without developing serious consequences.

Rhythm control procedures generally aim to restore and maintain sinus rhythm, which would improve the patients' functional capacity and quality of life and reduce AF-related symptoms.

There are several methods to achieve this goal, including pharmacologic cardioversion, electrical cardioversion, long-term antiarrhythmic drug therapy, and catheter or surgical ablation. It is essential to choose the optimal strategy based on patients' symptoms, comorbidities, and anatomical features through collaborative discussion with the patient.

Furthermore, restoring sinus rhythm as early as possible may prevent remodeling and further progression of AF.

The rate control procedures normally involve reducing the resting ventricular response in order to minimize tachycardia-induced cardiomyopathy and symptoms in patients with rapid and irregular heartbeats. The main objective is to reduce the resting heart rate and prevent excessively rapid responses during episodes of increased activity. The most common drugs used to control the heart rate in AF patients include beta-blockers, non-dihydropyridine calcium channel blockers, and in certain instances, digoxin.

The target heart rate should be individualized for each patient, depending on their general well-being and level of activity tolerance; in some cases, a more aggressive rate control strategy may be required in patients with reduced left ventricular functions or those who continue to have symptoms at higher heart rates, but it should also be regularly reassessed to avoid excessive bradycardia and ensure adequate patient comfort (7).

In general, the treatment algorithm for AF involves a stepwise strategy aimed at continuous evaluation of the condition, maintaining a healthy lifestyle, drug administration and regular follow-ups to ensure optimal quality of life and prevent risks such as thrombus formation and pulmonary edema. It is crucial to emphasize the importance of patient compliance and physician-patient relationships in order to achieve the best outcome.

The AF treatment algorithm includes individualized assessments followed by the introduction of appropriate treatment strategies, including rhythm or rate control measures, and continuous patient evaluation. Individualized approaches are vital to ensure the best outcome. Lifestyle changes are significant in AF management, as they can reduce the likelihood of possible triggers and associated conditions such as hypertension and obesity. The implementation of novel advancements such as artificial intelligence can assist in the individualized risk assessment and management strategies for patients with AF.

3.3.1. Acute AF Pathway

Atrial fibrillation management should begin with assessment of hemodynamic stability, prioritizing immediate cardioversion in the presence of inadequate organ perfusion or imminent cardiovascular collapse.

Hemodynamic instability → immediate electrical cardioversion

Stable patient → rate vs rhythm decision

3.3.2. Long-Term Strategy Pathway

- Stroke risk assessment → anticoagulation decision
- Symptom/substrate → rate vs rhythm selection
- Escalation ladder:
- Rate control → rhythm control → ablation → surgery

In hemodynamically stable patients, a rate-control strategy might be an appropriate initial approach when rapid restoration of sinus rhythm is not imperative or is unlikely to confer clear clinical benefit.

For most patients, a relatively mild rate-control strategy is appropriate as an initial approach, and the target resting heart rate should be below 110 beats per minute.

A more aggressive rate-control strategy should be considered if symptoms or heart failure persist, or if tachycardia-induced cardiomyopathy develops.

Management should be individualized, and consideration should be given to more aggressive intervention if symptoms or objective measures of cardiac function do not improve with lenient rate control. Upgrading therapy may include rhythm control or consideration of atrioventricular nodal ablation with permanent pacing.

3.4. Stroke Prevention

Anticoagulation for stroke prevention in atrial fibrillation represents a major challenge for global health systems, with a shift from vitamin K antagonists (VKAs) such as warfarin to direct oral anticoagulants (DOACs). The main challenge remains to balance thromboembolic protection against bleeding across different, often high-risk AF populations (4,13–16).

AF is a leading cause of cardioembolic stroke, largely due to embolization of left atrial thrombi, which causes ischemic stroke and carries a high risk of recurrence without treatment (4,15,17).

Stroke prevention is the foundation of AF management, and oral anticoagulation is indicated for patients with CHA_2DS_2-VASc scores of ≥2 in men and ≥3 in women, reflecting higher risk and supporting the recommendation for oral anticoagulation (7,13,14,18).

CHA_2DS_2-VASc and HAS-BLED remain the main tools for stroke and bleeding risk stratification, guiding initiation and optimization of anticoagulation (7,14,17,18).

3.4.1. Warfarin (VKA) in Stroke Prevention

VKAs are effective for stroke prevention and have historically served as the standard of care (18,19).

Moreover, they possess a narrow therapeutic window, require frequent INR assessments, interact with numerous meals and medications, and demonstrate inconsistent anticoagulation effects (18-20). In addition, the utilization of Warfarin is suggested in particular scenarios, including mechanical valves or moderate-to-severe mitral stenosis (7,13).

3.4.2. DOACs vs Warfarin

Several randomized trials plus meta-analyses established the superiority of DOACs over warfarin in terms of decreased risk of stroke/systemic embolism and all-cause mortality with significantly reduced risk of intracranial hemorrhage (21,22).

Standard reduced DOAC doses showed protection from stroke or systemic embolism and significantly decreased the risk of intracranial bleeding with no significant increase in major bleeding (20,21).

Because of these advantages, DOACs are preferred over VKAs in most patients with non-valvular AF (4,13,18). The meta-analyses showed differences between the DOACs with apixaban and dabigatran proving more effective for reducing the risk of stroke, while apixaban had the best risk-benefit profile for bleeding events (17,20,22).

Using higher-dose regimens of dabigatran and rivaroxaban is associated with an increased risk of gastrointestinal bleeding compared with corresponding doses of apixaban or warfarin (19,20).

Selection of DOAC and dose should be individualized based on renal function, age, body weight, and bleeding risk (17,21).

3.4.3. Special Populations and Secondary Prevention

In patients with a history of stroke, the use of DOACs showed similar efficacy and safety profiles when compared to warfarin (17,23).

Initiating DOACs as an early continuation forms a safe and effective option in patients with atrial fibrillation and ischemic stroke to reduce the risk of early recurrent embolism, with no significant increase in the risk of hemorrhagic transformation (17,24).

In patients with large infarcts and uncontrolled hypertension, anticoagulation was postponed due to the fear of hemorrhagic transformation of these infarcts.

Nevertheless, based on randomized trials and observational studies, DOACs seem to be an option for early anticoagulation, with the timing depending on the size and severity of the infarct (24).

One of the practical approaches used in the clinic is the "1 – 3 – 6 – 12-day rule". According to this rule, anticoagulation could be initiated on the 1st day after TIA, 3 days after minor stroke, 6 days after moderate stroke, and at least 12 days after severe stroke due to a high risk of hemorrhagic transformation in large infarcts.

Early treatment did not significantly increase the risk of symptomatic intracranial hemorrhage, supporting the safety of this strategy with appropriate patient selection, as demonstrated by recent randomized trials that have supported a shift toward earlier DOAC initiation after AF-related ischemic stroke in selected patients.

In the ELAN study, early treatment was defined as initiation within 48 hours after a minor or moderate stroke and on days 6–7 after a major stroke. It did not lead to excess hemorrhagic complications and showed a favorable signal for reducing recurrent ischemic events (25).

The TIMING study demonstrated that early NOAC initiation was noninferior to delayed treatment, and the OPTIMAS study further supported the safety of starting DOAC therapy within 4 days in many patients after ischemic stroke associated with atrial fibrillation (26,27)

The treatment must remain individualized, as patients with large infarcts, hemorrhagic transformation, uncontrolled hypertension, or high bleeding risk may still benefit from delayed initiation (21,28).

In advanced chronic kidney disease or on dialysis, there is a possibility that apixaban is a reasonable alternative to warfarin in carefully selected patients (28).

Current guideline recommendations are for direct oral anticoagulants as a preferred therapy for patients with non-valvular atrial fibrillation with VKA's being used in situations where the DOACs are contraindicated or unavailable (1,13). It is easy to see how the convenience of direct oral anticoagulants would be preferred in most situations over VKA's given the elimination of regular INR checks and dose adjustments (19).

Factor XI inhibitors are emerging therapies designed to reduce bleeding risk while maintaining antithrombotic efficacy, although further evidence is required (13).

Anticoagulation remains the basis of stroke prevention in AF. DOACs are preferred for most patients due to superior safety, particularly lower risk of intracranial hemorrhage, and comparable or improved efficacy compared with warfarin (8,18,20,21).

Warfarin continues to have a role in certain clinical situations, but its use should be tailored to the individual. DOAC-based therapy within an integrated care framework currently provides the best-supported strategy for reducing stroke risk in AF.

3.5. Rate control vs Rhythm control

Rate control, which involves slowing the heart rate, and rhythm control, aimed at restoring or maintaining sinus rhythm, are both available options to alleviate atrial fibrillation symptoms and reduce morbidity (6).

Rate control was historically the first-choice strategy in the management of AF, while rhythm control was reserved for patients with persistent symptoms (11).

The rate-control strategy (Figure 3.5.1) was grounded in the concept that AF is primarily an electrical disorder triggered by abnormal ectopic beats arising from the pulmonary veins, reflecting ion-channel dysregulation and yielding an initial electrical remodeling (29,30).

At the same time, the strategy of obtaining and maintaining sinus rhythm through electrical conversion followed by anti-arrhythmic drug therapy was associated with frequent AF rebounds and medication side effects (which might have a pro-arrhythmic effect and organ toxicity) (30).

The AFFIRM trial was the first comparative study of rhythm versus rate control strategies in patients with AF, with a follow-up period of over five years. It demonstrated no significant difference in either the ischemic stroke rate (7.1% vs. 5.5%; p = .79) or mortality (23.8% vs. 21.3%; p = .08) (31).

The RACE I trial added to the evidence by showing no significant advantage of rhythm control over rate control, with the composite cardiovascular endpoint (which consisted of: death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for implantation of a pacemaker, or severe adverse effects of antiarrhythmic medication) occurring in 22.6% vs. 17.2% (rhythm vs. rate control, respectively) over a mean follow-up of 2.3 years (32).

AF phenotypes varied across the trials. AFFIRM included approximately 30% with paroxysmal AF and 70% with persistent AF (about 1,230 vs 2,830 patients). RACE I consisted solely of persistent AF (100%, n=522), while RACE II included only permanent AF (100%, n=614). This offers a shifted perspective on the progressive spectrum of atrial disease, characterized by pre-existing structural remodeling with limited reversibility of atrial changes and a lesser response to rhythm-control strategies (30,33,34).

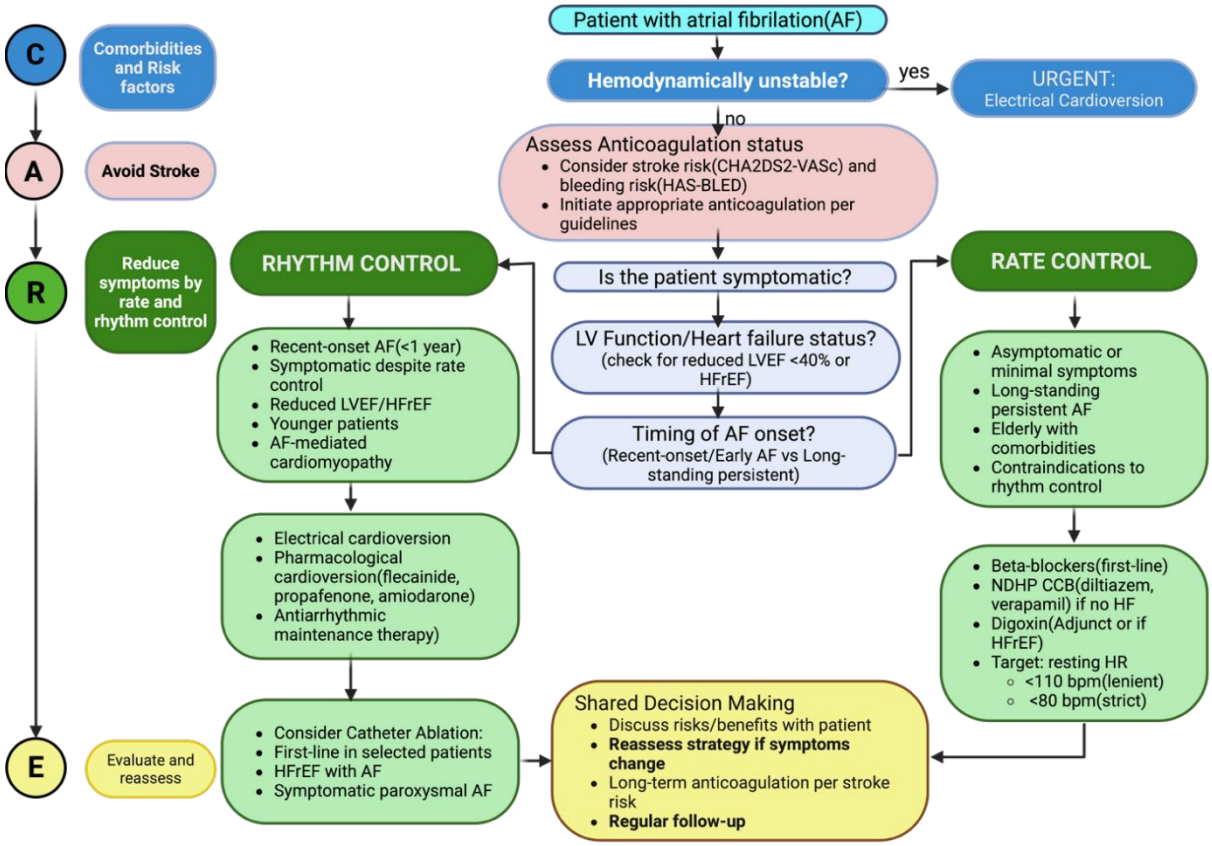

Fig. 3.5.1 Rhythm vs Rate control decision chart *(Adapted and modified from: Van Gelder IC, Rienstra M, Bunting KV, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2024;45(36):3314–3414. doi:10.1093/eurheartj/ehae176. --Figure adapted using SciSpace Research Agent (SciSpace, 2026). Created in BioRender. Cornea, A. (2026)*

3.5.1. Rate Control Strategy

Rate control in AF (beta-blockers, calcium channel blockers, digoxin, and ± AV nodal ablation) remains a valid therapeutic option to maintain hemodynamic stability and reduce symptom burden.

The main objectives of rate control in patients with acute or chronic atrial fibrillation and a rapid ventricular response are to alleviate symptoms and to reduce the risk of developing left ventricular systolic dysfunction (12).

Rate control remains the preferred initial strategy in elderly (>65 – 70 years) patients with long-standing persistent or permanent AF without a history of heart failure (HF) and association of multiple comorbidities or in patients with contraindication to anti-arrhythmic drugs.

A rate-control strategy might be used for patients who cannot tolerate rhythm control or for whom it has proven ineffective.

By reducing the ventricular rate, this approach restores cardiac efficiency and alleviates common symptoms, including palpitations, fatigue, dyspnea, and impaired exercise capacity.

In advanced cases, effective rate control prevents ischemic manifestations such as angina, episodes of presyncope, or syncope.

Ventricular rate control is a key factor in preventing tachycardia-induced cardiomyopathy, which is linked to sustained rapid ventricular rates (30).

Ventricular rate reduction can help facilitate spontaneous return to sinus rhythm, particularly in patients with recent-onset AF (<48 hours) or with paroxysmal, self-terminating episodes (3).

By reducing atrioventricular nodal conduction and atrial stretch, rate control may indirectly promote electrical stabilization and increase the likelihood of spontaneous cardioversion (3,35).

Findings from the RACE II trial suggest that a lenient rate-control approach—aiming for a resting ventricular rate below 110 bpm- helps reduce this risk in stable patients without interfering with clinical outcomes (13,34).

Evaluation of ventricular rate should be assessed at rest and during physiological stress, as rate control adequacy may differ substantially with exertion.

In most of the patients, the evaluation can be performed using either one of the following: ECG monitoring (e.g., 24–48 h Holter), the six-minute walk test, or the submaximal or maximal exercise electrocardiogram (ECG) testing (3).

Wearables and consumer-grade monitoring devices may provide additional long-term information on heart rate trends but need ECG confirmation for clinical decisions (3).

Maintaining the mean ventricular rate below <80 bpm (strict target) or <110 bpm (lenient target) is the most informative clinical parameter for guiding rate-control therapy (15).

Peak exertion rates can reveal insufficient rate control under stress. Monitoring is essential when starting and adjusting rate-control therapy, and ongoing follow-up is necessary to maintain therapeutic targets and manage symptom control (3,32).

3.5.2. AF rate control with beta blockers, calcium channel blockers, and digoxin

Rate control in atrial fibrillation is usually achieved with beta blockers (BBs), non-dihydropyridine calcium channel blockers NDCCBs (diltiazem/verapamil), and digoxin, often in combination. Choice depends on age, activity level, comorbidities (heart failure, HF, chronic obstructive pulmonary disease, COPD), blood pressure, and patient tolerance.

Beta blockers (BB)

The main mechanism by which BB controls ventricular rate in AF is its negative dromotropic effects at the AV node, which prolongs refractoriness and reduces conduction of atrial impulses (36).

They also lower myocardial oxygen demand and prevent tachycardia-induced cardiomyopathy, exerting negative chronotropic and inotropic effects, which is particularly useful in persistent AF with rapid ventricular response (RVR) (36).

They represent the first-line therapy in patients with preserved or reduced ejection fraction and sympathetic activation and can be used as monotherapy or in combination with digoxin (35).

In AFFIRM, beta blockers (use alone or with digoxin) achieved adequate rate control in ~70%, more than CCBs (54%) or digoxin alone (58%) (37).

Guidelines recommend BBs as first-line therapy in most patients, especially in those with prior myocardial infarction (MI) or left ventricular (LV) dysfunction/heart failure with reduced ejection fraction (HFrEF) (38–41).

In a small cohort of 45 patients with recent-onset atrial arrhythmias, sinus rhythm conversion occurred more often with esmolol (≈50%) than with verapamil (≈12%). These results may reflect secondary effects rather than intended treatment outcomes, as these agents are primarily indicated for rate control rather than rhythm control (42).

Rate control with BB is associated with lower mortality than no rate control therapy in observational data, but no robust randomized trials demonstrate a mortality reduction attributable specifically to β-blockers in AF alone. In a meta-analysis (Ma et al., 2020), BB were found to reduce all-cause mortality in AF patients with concomitant heart failure (RR ≈ 0.78 in pooled analyses), but this effect was not sustained in randomized controlled trial (RCT) sub-analyses (43).

Xu et al.'s 2019 meta-analyses included 38133 patients from 12 studies and showed that in patients with AF and HF, β-blocker treatment was associated with an overall significant decrease in all-cause mortality (RR = 0.73; 95% CI 0.65–0.82, P < 0.001) in observational studies, but failed to indicate a clear benefit of BB treatment for AF without HF, suggesting a phenotype-specific effect (44).

Non-dihydropyridine calcium channel blockers (NDCCBs)

NDCCBs slow the ventricular response in AF via the atrioventricular (AV) node and produce both negative chronotropic and negative inotropic effects. They inhibit L-type calcium channels in the AV node, prolonging the AV nodal refractory period and reducing conduction of atrial impulses to the ventricles; hence, they function as AV nodal blockers, not rhythm-control drugs. Their importance lies in ventricular rate control in the absence of pre-excitation.

In patients with AF and LVEF above 40%, diltiazem or verapamil are the primary options for rate control, used together with beta-blockers. For hemodynamically stable AF with a rapid ventricular response and preserved ejection fraction, IV verapamil or diltiazem is recommended for immediate rate control (12).

Siu et al. demonstrated in a 2009 open-label randomized controlled trial of 150 patients that ventricular rate (VR) control was achieved more rapidly with diltiazem, with a median time of 3 hours (range: 1–21 hours), which was significantly shorter than with digoxin (6 hours, range: 3–15 hours) or amiodarone (7 hours, range: 1–18 hours), as demonstrated by log-rank analysis ($p < 0.0001$) (45). Moreover, the proportion of patients achieving adequate rate control was higher in the diltiazem group (90%) than in the digoxin and amiodarone groups (74% each). In patients with acute AF with a rapid ventricular response and preserved ejection fraction, IV verapamil or diltiazem is recommended for immediate rate control (45).

At the same time, due to their negative inotropic effect, they should not be used in patients with moderate to severe LV dysfunction (12).

For chronic rate control, NDCCBs are effective, and in preserved EF (LVEF above 40%), they may be particularly attractive when symptoms are exercise-related (1).

In this regard, NDCCB preserved exercise capacity and improved the neurohormonal profile compared with β-blockers in patients with AF and preserved EF (12,46).

In a small, randomized study of 60 patients (Ulimoen et al., 2013), diltiazem and verapamil preserved peak VO2 at baseline, whereas metoprolol and carvedilol significantly reduced it ($P < 0.001$) (46). In parallel, diltiazem and verapamil significantly reduced NT-proBNP levels at rest and during peak exercise, whereas β-blockers were associated with an increase in NT-proBNP ($P < 0.05$) (22).

NDCCBs attain a comparable level of lenient control (<110 bpm) as BBs (approximately 92–93%) but result in less sinus bradycardia in non-permanent AF (47).

In chronic AF without HFrEF, NDCCBs have a clinical effect and safety profile similar to those of BBs in both acute and chronic settings (48).

They might be the preferred choice in patients with bronchospasm/ COPD but are avoided in AV associated with HFrEF (49).

Digoxin

Digoxin slows the ventricular rate in AF by prolonging the AV nodal refractory period and reducing AV nodal conduction. Because it acts via vagal mediation, it better controls the resting ventricular rate than the exertional rate (12).

This explains why digoxin, as a first-line monotherapy for rate control, is less effective in active patients and more suitable for sedentary individuals. It is also used as an add-on when beta-blockers (BB) or calcium channel blockers (CCB) are insufficient, regardless of ejection fraction levels, or when other agents are not preferred, tolerated, or contraindicated (5,6).

Digoxin is a better choice, particularly when hypotension limits the use of BB or NDCCB, or in concomitant HF with or without preserved EF.

In chronic rate control, low-dose digoxin resulted in similar quality of life (QoL) and resting HR, greater symptom improvement, and fewer adverse events than bisoprolol at 6 months in older patients with permanent AF and documented heart failure symptoms, as shown in the RATE-AF randomized trial. It is also associated with lower NT-proBNP levels. The report of fewer adverse events is clinically relevant for older symptomatic patients, in whom drug tolerability is linked to long-term compliance (50).

Contrary evidence came from a large Taiwanese cohort, in which digoxin was associated with higher mortality vs no rate control (HR 1.12), while BBs and CCBs lowered mortality (38).

Digoxin might be the preferred option, particularly in AF with heart failure, because it slows the ventricular rate without the negative inotropic effect of verapamil or diltiazem, but it does not necessarily improve survival in this setting (12,50).

The main contradiction is related to mortality as indicated by the observational studies in the article by Chao et al.(45) and the AFFIRM studies. In most cases, digoxin was prescribed to the sicker older adults with heart failure, renal issues, or intolerance to other medications resulting in conflicting and confounded outcomes (39).

The data are suggestive, but not definitive, of a prognostic benefit from rate-control therapies. Observational analyses suggest that agents such as BB and NDCCB may improve survival, particularly among patients with concomitant cardiovascular disease (38,39).

However, randomized trials, such as the AFFIRM trial, did not demonstrate a clear mortality advantage for rate control over rhythm control, and these findings should therefore be interpreted cautiously (5,48).

For a cardiologist, the essential difference is that beta-adrenoreceptor blockers are equally recommended as first-line treatment for AF, but non-catecholamine cardioactive drugs may be preferable in patients with preserved EF due to their more favorable "hemodynamic profile" if the primary complaint includes symptoms limiting physical activity or associated pulmonary comorbidities (6).

3.6. Cardiac Resynchronization Therapy

HF has an age-dependent prevalence in the developed world, ranging from 2% of the adult population to 10% among those aged 70 years or older (40). The prevalence tends to increase with population aging, but age-specific incidence decreases (41).

HF can be classified into three phenotypes according to LVEF:

- HF with reduced EF (HFrEF) with LVEF <40%
- HF with mildly reduced EF (HFmrEF) with LVEF ranging 40–49%,
- HF with preserved EF (HFpEF) with LVEF ≥50% (37).

Cardiac conduction system disease is common in patients with HFrEF, with 25%-36% exhibiting left bundle branch block (LBBB) (51). this could result in loss of atrioventricular coordination, asynchronous contraction of the right and left ventricles, and delayed activation of different regions of the left ventricle, leading to impaired myocardial contraction and decreased cardiac output (52).

The 2021 ESC and 2022 AHA/ACC/HFSA guidelines indicate cardiac resynchronization therapy (CRT) as a Class 1/2a recommendations for patients in sinus rhythm at the time of implant, with symptomatic heart failure (HF), reduced LVEF < 35% (HFrEF), and QRS delay on electrocardiogram (ECG) >= 120 ms (especially associated with LBBB) who remain symptomatic on optimal medical treatment (53).

AF diagnosed by the device at the time of implantation and new-onset AF were reported among patients undergoing CRT, with device-based diagnostics accounting for up to 40% of cases,

and new AF in nearly 25% (54). Both were associated with worse outcomes and higher mortality rates due to loss of AV synchrony and reduced biventricular (BiV) pacing percentage (12,45).

The evolution of patients with AF during follow-up reflected the advanced heart failure substrate rather than a direct effect of CRT itself (54).

Several randomized (55,55)ed and post hoc analyses, including those based on the CARE-HF framework, indicate that CRT does not significantly prevent the development of AF. However, it still provides benefits in reducing morbidity and mortality regardless of rhythm status (55,56).

Atrial fibrillation association reduces the benefits and requires a different interventional strategy to achieve efficient biventricular pacing.

AF is now recognized as both a marker of more advanced disease and a modifiable determinant of CRT response, supporting adjunctive strategies such as atrioventricular node ablation to optimize effective resynchronization (56).

In patients with AF and HFrEF who meet CRT criteria, the presence of AF alone should not preclude CRT implantation, given that a high percentage of effective biventricular (BiV) pacing can be achieved. CRT can be used in patients with atrial fibrillation when pharmacological rate control fails, and the patient remains symptomatic, as part of a rate-control strategy, with atrioventricular node ablation as an adjunctive therapy to secure 100% BiV pacing (57).

Randomized data show CRT is superior to RV pacing after atrioventricular junction (AVJ) ablation for HF events, irrespective of classical CRT criteria (58).

CRT upgrade should be considered for patients with AF, heart failure, and significant right ventricular pacing from an existing pacemaker or ICD. This can improve clinical outcomes, such as lowering heart failure hospitalizations and promoting reverse remodeling, especially when 100% biventricular pacing is achievable (59,60).

3.7. Rhythm Control Strategy

Rhythm control aims to restore and maintain normal sinus rhythm in AF, primarily with antiarrhythmic drugs (AADs) and/or catheter ablation, which have proved relatively effective but can cause adverse drug reactions (12).

Rhythm control is linked to better symptoms and quality of life, particularly in patients with symptomatic AF and heart failure, and less frequent complications such as rates of stroke/TIA and health-related QoL(61–64).

Rate-control strategies are preferred in the management of older patients, although rhythm-control strategies are associated with lower stroke risk and are mostly used to reduce AF-related clinical symptoms (65).

Kim et al. investigated, in a national cohort study comprising 22635 adults with AF, whether the efficacy of a rhythm-control strategy varies with the interval between atrial fibrillation diagnosis and treatment initiation. The results showed that early rhythm management therapy was associated with a reduced risk of ischemic stroke (HR 0.74, 95% CI 0.60–0.91) and heart failure-related hospitalization (HR 0.79, 95% CI 0.65–0.96) (66).

When rhythm control therapy is initiated more than 1 year after AF onset (chronic AF), the advantage over rate control disappears, indicating no difference in the risk of death from all cardiovascular causes between early rhythm control and late rate control (weighted incidence rates 8.67 v 8.99 events per 100 person-years; hazard ratio 0.97, 95% confidence interval 0.78 to 1.20; P=0.76) (13).

Newer meta-analyses, including modern ablation and earlier treatment, show that rhythm control reduces cardiovascular death, stroke, and heart failure hospitalization, though not always all-cause mortality (66).

Antiarrhythmic drugs (AADs) are a key component of rhythm control, but their benefits must be weighed against limited efficacy and important safety concerns identified by older trials, which found no survival benefit over rate control and relied on older AADs (39,67).

Cardioversion

Cardioversion restores sinus rhythm in atrial fibrillation using either a synchronized shock (electrical cardioversion, ECV) or drugs (pharmacological cardioversion, PCV). The choice depends on hemodynamic stability, AF duration, comorbidities, and available expertise (3).

The main indication for cardioversion is the relief of symptoms and the prevention of further deterioration of clinical conditions such as heart failure, cardiomyopathy, and the development of embolism, including stroke or pulmonary embolism (30,68).Prior to cardioversion, the patient must be evaluated to ascertain the appropriate approach, whether electrical or pharmaceutical (3).

Electrical cardioversion is indicated in patients who have clinical signs of severe cardiac malfunction requiring emergency intervention, such as decompensated heart failure, hypotension, or unstable angina, or when drugs fail to restore sinus rhythm (2,69).The thromboembolic risk is particularly pronounced around the time of cardioversion(17,69).

Pharmacological cardioversion represents the treatment of choice in hemodynamically stable patients or in those who cannot tolerate sedation.

3.7.1. Electrical Cardioversion

Emergency vs elective use

Electrical cardioversion is preferred in patients with a first episode of atrial fibrillation, in those presenting with severe or life-threatening manifestations (such as acute decompensated heart

failure, hypotension, ongoing ischemia, or angina) requiring immediate rhythm restoration, or when pharmacological cardioversion has failed (6,68).

Anticoagulation requirements

This procedure carries a clinically significant thromboembolic risk, which is particularly pronounced around the time of cardioversion (70).

In the absence of appropriate anticoagulation, the risk of thromboembolic events associated with cardioversion ranges from 5% to 7%, whereas adequate anticoagulation reduces this risk to <1% (64,70). If a thrombus is already present prior to cardioversion, the restoration of atrial contraction can dislodge or fragment the thrombus, potentially leading to embolization. This is why peri-cardioversion anticoagulation is mandatory and should be selected primarily based on the duration of AF (64,70).

Peri-cardioversion **anticoagulation is mandatory**, and the strategy is primarily determined by the duration of atrial fibrillation. Patients with atrial fibrillation lasting less than 48 hours and low risk factors (CHA_2DS_2-VASc score of 0 or 1) have a low risk of thrombus formation in the atrial cavity; the risk of embolization is lower but not negligible, and anticoagulation should still be considered based on the individual thromboembolic risk profile (71).

For atrial fibrillation lasting 48 hours or longer, or when the duration is uncertain, patients should receive anticoagulation for a minimum of three weeks prior to cardioversion unless a transesophageal echocardiogram (TEE) demonstrates no left atrial thrombus (71).

Following cardioversion, anticoagulation should be continued for at least four weeks irrespective of baseline stroke risk, due to the potential persistence of atrial mechanical dysfunction (6,68).

Technique and energy protocols

Electrical cardioversion for atrial fibrillation (AF) has a high acute success rate, ranging from 85 to 95% depending on the population, AF duration, and substrate (72). These success rates are primarily determined by patient selection, with higher rates observed in patients with shorter AF duration (< 48 hours), smaller left atrial size, and absence of structural heart disease, whereas long-standing persistent AF or significant atrial remodeling is associated with lower rates (73).

The use of biphasic waveforms, higher initial energies (150-200 J), and anterior-posterior electrode placement have also been associated with improved cardioversion success, which may explain the overall high acute success rates of ECV in contemporary practice (72).

In a large series of consecutive patients presenting to the emergency department with AF, ECV was successful in 88% of patients with a low risk of complications (0.3%) (74).

The majority of patients were safely discharged home following the procedure (74).

These results are consistent with other studies reporting acute success rates of ECV ranging from 85 to 95% for AF cardioversion (73,74).

Thus, ECV is generally considered a safe and effective procedure for acute AF cardioversion when performed in patients under adequate anticoagulation and surveillance.

However, despite the high acute success rates, recurrence of AF within days or weeks following ECV is common, occurring in up to 30-50% of patients (60,62).

Therefore, ECV should be considered as a part of a broader treatment strategy that also includes antiarrhythmic drugs, lifestyle modifications, and anticoagulation to improve long-term rhythm control and reduce AF burden.

Predictors of success

The use of biphasic waveforms was associated with higher first-shock success rates (up to 90–95%) and lower cumulative delivered energy, thereby reducing myocardial injury and skin burns (3,75).

Progressive high-energy protocols can be used to achieve >99% success even after failure, with acceptable minor discomfort to the patient's skin. In the same study, Darrat et al. also found that high body mass index predicted the need for multiple cardioversions, whereas high transthoracic impedance was a predictor of failure (76).

Adjunctive technical approaches that may be used to improve outcome if the patient is properly sedated which decreases movement and improves electrode contact, thus allowing synchronization to avoid R-on-T phenomenon; repositioning pads or changing polarity if first shocks fail; and shocks at end-expiration because of decreased impedance (76).

3.7.2. Pharmacological Cardioversion

Rhythm control strategy adopted early after AF diagnosis reduces not only symptoms by decreasing the frequency and duration of AF episodes but also cardiovascular complications (77).

Even though they are not primarily curative, they improve cardiovascular outcomes in selected, early treated patients as part of a broader rhythm-control strategy.

Antiarrhythmic drugs

Antiarrhythmic drugs AADs have a central role in sinus rhythm (SR) strategies, not for a curative effect, but to restore SR and reduce AF burden over the long term, primarily to improve symptoms and reduce recurrence. The AF-CARE framework focuses on the need for early rhythm control in all patients to improve the outcomes during the first year after diagnosis through the use of substrate-based choice of AADs (2,18).

The EAST-AFNET 4 trial randomized 1323 patients who underwent either AAD or AF ablation, changing the paradigm of AF management, showing that early rhythm control was beneficial.

Notably, most rhythm-control patients in EAST-AFNET 4 were treated with antiarrhythmic drugs rather than ablation. Results from EAST-AFNET 4 demonstrated that early rhythm control plays an important role in improving cardiovascular outcomes, largely achieved with antiarrhythmic drugs (11).

From a pharmacological standpoint, Class I and Class III agents form the backbone of rhythm control, while Class II (BB) and Class IV (NDCCB**)** remain primarily rate-control agents but often support rhythm strategies (78).

Class IA

Quinidine, disopyramide, and procainamide act by modifying the sodium channel and inhibiting the outward potassium current, thereby prolonging the QT interval and producing significant vagolytic effects (79).

Class IA drugs are effective at SR maintenance but are associated with increased mortality and pro-arrhythmia vs control; they are largely abandoned for chronic AF rhythm control (82).

Currently, ESC and ACC guidelines no longer recommend Class IA agents for maintaining chronic rhythm, marking a significant change in the historical approach (12).

Procainamide might still be use in acute pharmacologic cardioversion, although it is inferior to newer agents such as ibutilide or Class IC drugs and is not used for long-term therapy (3).

Class IC AAD

The Class IC agents, **flecainide and propafenone**, brought a major advance in AF pharmacotherapy, as potent sodium channel blockers with strong effects on atrial conduction and relatively little extracardiac toxicity compared with amiodarone (83).

These drugs emerged as the preferred antiarrhythmics for rhythm control in patients without structural heart disease due to their efficacy in both pharmacological cardioversion of recent-onset AF and long-term preservation of sinus rhythm (3,12,80).

Randomized placebo-controlled trials of flecainide by Anderson et al. (1989) and of propafenone by Conolly et al.(1989), Pritchett et al. (1991) and UK Propafenone Study Group (199) confirm the efficacy of class IC drugs in reducing the time to recurrence of atrial fibrillation (AF) and decreasing symptomatic recurrences compared to placebo. This underpins their established role in paroxysmal AF (81-84).

Furthermore, the efficacy of class IC drugs in the acute setting is well-established, with high rates of conversion to sinus rhythm that are significantly better than placebo and among the highest reported for any oral or intravenous agent in the acute management of recent onset AF (3,12).

The findings also support the use of the “pill-in-the-pocket” approach for patients with infrequent symptomatic episodes of AF who are fit enough to undergo inpatient safety testing for flecainide or propafenone (3,12,85).

This approach, although effective and practical, must be accompanied by AV nodal blocking therapy to reduce the risk of rapid 1:1 atrial flutter conduction (12,85).

The use of Class IC drugs is strictly limited by the presence of structural heart disease, because sodium channel blockade in diseased myocardium can facilitate malignant ventricular pro-arrhythmia (3,86).

The pivotal CAST trial included 1498 patients, of whom 755 received encainide or flecainide. It showed an excess of deaths from arrhythmia and shock after acute recurrent myocardial infarction in patients treated with encainide or flecainide. The study, although not conducted in AF, transformed antiarrhythmic prescribing by demonstrating increased mortality with Class IC drugs in patients with prior myocardial infarction and ventricular ectopy (87).

Therefore, flecainide and propafenone are now contraindicated or strongly discouraged in patients with prior myocardial infarction, significant coronary artery disease, ventricular scar, or major structural heart disease (3,86). Their role is directed toward younger or otherwise selected patients with a structurally normal or near-normal heart (88).

Class III

Class III antiarrhythmic drugs prolong action potential duration and refractoriness primarily by blocking potassium channels and have gained increased importance as the limitations of Class I therapy became evident (89,90).

Trials such as the Canadian Trial of Atrial Fibrillation (CTAF) and the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) have proved that amiodarone is the most effective medication for maintaining sinus rhythm over the long term in patients with AF. The results indicate that both amiodarone and sotalol are comparatively effective in the treatment of acute episodes of AF conversion. Additionally, the study highlights the difference between the drugs' ability to maintain sinus rhythm in the long run. Indeed, the treatment with amiodarone proved to be more effective than sotalol and propafenone with significantly longer times to recurrence of AF. (80,91). This superior efficacy has made amiodarone the benchmark against which other antiarrhythmic drugs are often judged (85,89). Despite its efficacy, its long-term use is limited by pulmonary, thyroid, hepatic, neurologic, dermatologic, and ocular adverse effects, as well as numerous drug interactions. Current guidelines recommend amiodarone for patients for whom other treatments are unsuitable or contraindicated, especially those with heart failure with reduced EF or notable structural heart disease (3,86).

Sotalol combines potassium channel blockade with nonselective beta-adrenergic blockade (83,89). While it can maintain sinus rhythm in selected patients, its efficacy is lower than that of amiodarone, and its use is limited by QT prolongation and the risk of torsade's de pointes (86,91).

Both the reviews by Lafuente – Lafuente et al. (2012) and Valente et al. (2019) showed that AAD reduces AF occurrence, but at the cost of higher mortality rates, particularly associated with sotalol treatment (80,92). Recent guidelines recommend caution regarding routine sotalol use, which is indicated as a second-line option in carefully selected patients with preserved ventricular function, normal renal function, and low proarrhythmic risk (3,12).

In Danish Investigations of Arrhythmia and Mortality ON Dofetilide – CHF (DIAMOND-CHF) and related studies, dofetilide was shown to facilitate conversion to sinus rhythm, reduce recurrent AF, and lower heart failure hospitalizations without worsening overall mortality (93). Its efficacy in maintaining sinus rhythm is substantial, but the drug requires inpatient initiation with electrocardiographic monitoring due to dose-dependent QT prolongation and the risk of torsades de pointes. For this reason, dofetilide remains principally a specialist drug, most relevant in North American practice and particularly useful in selected patients with HFrEF (12).

Ibutilide is also a Class III agent, but its role is primarily limited to acute pharmacologic cardioversion rather than chronic maintenance of sinus rhythm (89). Intravenous ibutilide is effective for rapid conversion of recent-onset AF and atrial flutter, and comparative evidence suggests it can outperform procainamide in monitored emergency settings (94).

The risk of QT prolongation and torsades de pointes limits its use to closely supervised environments with immediate rhythm monitoring and resuscitation capabilities (3,86).

The development of dronedarone reflected an effort to retain some of amiodarone's antiarrhythmic efficacy while reducing its organ toxicity through structural modification and removal of iodine moieties (95,96).

Early trials such as European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and the American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) demonstrated that dronedarone prolongs time to AF recurrence compared with placebo, confirming good rhythm-maintenance efficacy, although with a weaker antiarrhythmic effect than amiodarone (10,12).

The Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA) trial showed a reduction in cardiovascular hospitalization or death in patients with paroxysmal or persistent AF or atrial flutter (96). This finding was later contradicted by the Anti-arrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) and Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trials, which demonstrated harm in patients with severe heart failure and in those with permanent AF, respectively (97,98).

As a result, dronedarone is now indicated for patients without recent decompensated heart failure, without advanced left ventricular dysfunction, and not for those with permanent AF (3,12)

Rhythm-control pharmacology has also been evaluated in specific procedural contexts, and particularly in comparison with electrical cardioversion and catheter ablation. Meta-analysis evidence suggests that pretreatment with antiarrhythmic drugs, especially Class III agents and amiodarone, improves the success of elective electrical cardioversion and may reduce early AF recurrence after restoration of sinus rhythm (99).

Short-term administration of Class I or Class III agents after AF ablation reduced early recurrences during the blanking period, although sustained long-term benefit is less certain (77). These observations reinforce the concept that antiarrhythmic drugs remain useful not only as stand-alone rhythm-control treatments but also as adjuncts to interventional strategies (3,12).

Taken together, the history of antiarrhythmic drug development in AF shows a progressive refinement from broad class-based empiricism to individualized, substrate-guided therapy (3,12,89).

The current use of antiarrhythmic drugs in AF is less driven by Vaughan-William's classification in isolation and more by the interplay among efficacy, safety, structural heart disease, and the clinical objective of therapy, whether acute cardioversion, chronic maintenance, or adjunctive post-procedural treatment (3,12).

Invasive procedures for rhythm control include catheter and surgical ablation.

3.7.3. Catheter Ablation (CA)

Catheter ablation and antiarrhythmic drug therapy are both used to rhythm control strategies in atrial fibrillation, particularly in patients with symptomatic paroxysmal AF. CA may be considered an initial therapeutic option alongside antiarrhythmic therapy, as both are effective for symptom control and maintenance of sinus rhythm (30,100).

CA is an option for patients in whom an arrhythmia control strategy is chosen and, despite appropriate antiarrhythmic treatment, episodes of AF persist, and for a selected subset of patients with a high likelihood of success who prefer to avoid long-term antiarrhythmic drug therapy (101).

Catheter ablation is a minimally invasive electrophysiological technique that involves the introduction into the heart of catheters via peripheral veins, most often the femoral veins, to eliminate the focus of arrhythmia (13,17).

Three types of energy sources can be used during catheter ablation for the treatment of AF: cryoablation (cryotherapy), radiofrequency ablation, and pulsed-field ablation.

The application of *radiofrequency* current allows for raising the temperature of the cardiac tissue to 50-60 ° C, thereby creating a lesion by resistive and conductive heating of the local myocardium. Thus, radiofrequency ablation (RFA) allows for the generation of relatively large (compared to cryoablation) punctate lesions with a high degree of shape variability at the operator's discretion, making this method suitable for complex electro-anatomical substrate ablation in patients with AF. However, RFA is associated with a risk of thermal damage to the walls of the esophagus and the development of steam pops (3).

Cryoablation with a cryoballoon or a laser balloon) is a type of cryotherapy that reduces the temperature of the tissue being ablated to – 40 to – 80 ° C, allowing for the formation of an ice ball inside the heart by freezing the interstitial fluid, which deforms the cell membranes and damages the microcirculation (97). The cryoballoon allows for single-stage pulmonary vein isolation and has a good learning curve, a relatively short procedural duration, and a reduced risk of thrombus formation and thermal complications compared to RFA, with a significant risk of phrenic nerve injury (3).

Pulsed-field ablation is a new method of non-thermal ablation that inactivates the targeted cardiomyocytes by applying a voltage to the electrodes in the form of a burst of nanosecond pulses, disrupts the integrity of cell membranes, and causes irreversible electroporation of cell membranes. In this method, the lesion geometry is created similar to conventional cryothermal and radiofrequency techniques, but without thermal destruction of the surrounding tissues, thus minimizing the risk of complications due to excessive heating or freezing of the myocardium (7).

. PFA is characterised by tissue selectivity (myocardium > esophagus, phrenic nerve, pulmonary veins) and ultra-rapid lesion delivery, with potentially improved safety profile due to reduced risk of collateral injury, though long-term safety data are still evolving (98).

An important target of catheter ablation is pulmonary vein isolation (PVI), which electrically disconnects the pulmonary veins from the left atrium. This prevents the initiation and persistence of AF driven by ectopic triggers, as demonstrated by Haïssaguerre et al. (3,102).

Periprocedural preparation includes interrupting any other antiarrhythmic drugs except amiodarone to help identify the presence of triggers of AF at the time of the procedure.

Catheter ablation is contraindicated in patients who are too frail to undergo the procedure safely, those with left atrial thrombi, and individuals with bleeding diathesis that prevents adequate peri-procedural anticoagulation (101).

The higher risk of a left atrial appendage thrombus is associated with hypertrophic cardiomyopathy, EF < 30%, persistent or longstanding AF, and an elevated CHA2DS2-VASc score (64).

CA for AF in patients with HF showed a significantly lower rate of reaching a combined endpoint of death from any cause or hospitalization for worsening heart failure compared to medical therapy.

CA reduced arrhythmia burden, promoted reverse left ventricular remodeling, and improved survival, thereby modifying the clinical course, even in advanced stages of HF, in patients with AF (3,103).

Furthermore, in CASTLE-AF study sub-analyses, a CA-associated AF burden of <50% at 6 months post-ablation was associated with a lower risk of adverse outcomes, including avoidance of the primary composite endpoint (HR 0.33; 95% CI 0.15–0.71; p = 0.014) and all-cause mortality (HR 0.23; 95% CI 0.07–0.71; p = 0.031), compared with the antiarrhythmic drugs group, which may reduce the arrhythmia burden but did not improve clinical outcomes (97,104).

3.7.4. Surgical ablation (SA)

Surgical intervention for patients with AF is usually performed during cardiac surgery for another indication (valvular disease, bypass) and aims to: create a conduction block to disrupt all micro- and macro-reentrant circuits, re-establish or maintain electrical atrioventricular synchrony, and restore atrial mechanical function to improve diastolic filling (12,47). Performance rates for surgical ablation range from 22% to 48%, depending on the procedure type (105).

Maze procedure

The Maze procedure consists of a series of strategically placed atrial incisions or ablation lines designed to interrupt macro–reentrant circuits, typically encircling the left atrial appendage orifice and the ostia of the four pulmonary veins. Thus, sinus impulses could be directed through a controlled conduction pathway from the sinoatrial node to the atrioventricular node.

The Maze procedure has evolved from the original "cut-and-sew" methods (Maze I–III), which created surgical scars that interrupted atrial re-entry circuits but were technically complex and led to chronotropic incompetence (106).

The Cox-Maze (CM) IV procedure involves the creation of linear lesions extending from the superior vena cava to the inferior vena cava on the right atrium in which they are connected to the tricuspid annulus by applying cryo-thermal energy to the tissue so that the lesion sets produced are comparable to those created by earlier Maze procedures but require a lesser duration and involve fewer risks.

The utilization of bi-atrial lesion sets together with pulmonary vein isolation, atrial lines, and left atrial appendage exclusion offers the most effective treatment while still maintaining the transport function of the atria (107).

An alternative approach, such as the radial lesion set, aims to preserve physiological atrial activation and improve atrial function, but it is still less widely adopted given comparable rhythm outcomes (108).

When performed concomitantly with cardiac surgery, the Maze procedure does not increase major morbidity or mortality, although it may prolong cardiopulmonary bypass time and increase pacemaker implantation rates (109).

The CM procedure, even with a high degree of complexity, did not increase operative risk in the context of mitral valve procedures. In the long term, the procedure demonstrated acceptable rhythm success, reduced AF burden, and a remarkably low stroke rate (72).

Newer energy-based and minimally invasive techniques (radiofrequency, cryoablation) simplify the procedure and shorten recovery, although long-term durability is still being evaluated (108).

Perioperative complications: The Maze procedure has a low (0–3%) operative mortality even when combined with other cardiac surgeries (105).

Among major complications are bleeding requiring reoperation, renal failure, mediastinitis, stroke, pneumonia, acute kidney injury, and need for intra-aortic balloon pump (110,111).

An important limitation is atrial myocardial injury, which impairs atrial transport function and may reduce the hemodynamic benefit despite restoration of sinus rhythm. The recovery of atrial

mechanical function is variable, with improvement in ~70% of patients, whereas persistent dysfunction is associated with increased thromboembolic risk (112).

The reduction in the functions of the left and right atrium may be permanent compared to the control group, signifying that they are not fully restored after ablation (106).

Complications associated with rhythm include the requirement for a permanent pacemaker insertion in 5-15% of cases, which is even more common in patients undergoing concomitant procedures.

This may be associated with sinus node dysfunction, related to pre-existing disease, surgical injury, or autonomic denervation (109).

Several analyses indicate a greater need for pacemaker rate increases than with no Maze, but the findings are inconsistent. Atrial tachyarrhythmias may occur in 8 – 12% of patients, often associated with incomplete lesion sets (109).

3.8. Lifestyle Modification

Adjusting lifestyle and modifiable risk factors, alongside arrhythmia therapy and early detection and treatment of comorbidities, constitute holistic management of atrial fibrillation within the AF-CARE framework, highlighting the importance of early detection and treatment of comorbidities to optimize patient outcomes (3,5,113).

Current evidence and clinical perceptions identify a wide range of risk factors influencing the development and progression of atrial fibrillation. Some of these factors can be modified through intervention, while others are intrinsic to the patient's underlying condition (3). Modifiable elements such as physical inactivity, obesity, hypertension, diabetes, excessive alcohol consumption, and obstructive sleep apnea are key contributors to atrial fibrillation risk that may benefit from targeted lifestyle and therapeutic strategies. Non-modifiable characteristics, including advanced age, genetic predisposition, and sex, remain essential determinants of disease susceptibility and severity and are important for risk stratification, even when they cannot be changed (5).

The current AF–CARE approach that recognizes and acts on the modifiable factors while also considering the nonmodifiable mechanisms is critical to improve long–term outcomes in patients with atrial fibrillation (3).

High blood pressure and diabetes mellitus are two frequent comorbidities that play a major role in the pathophysiology of the disease. Hypertension contributes to higher risks of stroke, heart failure, bleeding, and mortality. It is crucial to control blood pressure to reduce the negative impact on the development of AF. Furthermore, a significant number of AF patients also have diabetes, which relates to higher rates of adverse outcomes and healthcare utilization and decreased effectiveness of treatment, such as catheter ablation, and higher recurrence rates (12).

Therefore, in AF patients, it is essential to closely control blood pressure and glucose levels to ensure the best outcomes and quality of life (114).

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Abbreviations:

AADs antiarrhythmic drugs

AF Atrial fibrillation

AV atrioventricular

AVJ atrioventricular junction

BBs beta blockers

CA Catheter Ablation

COPD chronic obstructive pulmonary disease

CRT cardiac resynchronization therapy

ECG electrocardiogram

ECV electrical cardioversion

HF Heart failure

HFpEF heart failure with preserved ejection fraction

HFrEF heart failure with reduced ejection fraction

LBBB left branch bundle block

LV Left ventricle

MI Myocardial infarction

NDCCB non-dihydropyridine calcium channel blockers

PCV pharmacological cardioversion

QoL quality of life

RCT randomized controlled trial

RVR rapid ventricular response

SR sinus rhythm

VR ventricular rate

RFA Radiofrequency ablation

PVI pulmonary vein isolation

SA Surgical ablation

Chapter 4: ATRIAL FIBRILLATION IN SPECIAL SCENARIOS - *Vlad Sabin, Roxana Buzaș, Abhinav Sharma, Nilima Rajpal Kundnani, Amalia Cornea*

4.1. Atrial Fibrillation in heart failure

Atrial fibrillation is the most common arrhythmia in patients with heart failure, the incidence of atrial fibrillation being directly proportional to age and severity of heart failure. The development of atrial fibrillation is directly associated with a worsening prognosis in these patients, the causes being both mechanical-structural and neurohormonal changes. [1,2]

Prevention of embolic events, identification of the etiological substrate of atrial fibrillation, rate and rhythm control are constitutive elements of the treatment of this complication [65]. In the absence of contraindications, long-term anticoagulation is indicated, with direct oral anticoagulants being preferred, and left atrial occlusion may be considered in those with contraindications to anticoagulation.

Rate control has not shown significant differences between a strict approach with a HR < 80 bpm and a more lax approach with a target HR < 110 bpm, but observational studies suggest a higher risk in patients with higher HR. Both beta-blockers and digoxin can be used for rate control, and if rate control is ineffective or contraindicated, nodal ablation can be used [3].

Rate control can be achieved both medically and electrically. Electrical conversion should follow anticoagulation guidelines, with an optimal period of at least 3 weeks of effective anticoagulation. Electrical cardioversion can be performed if there are signs of hemodynamic deterioration or if there is rapid worsening of HF. Medical cardioversion with amiodarone is the drug of choice, as propafenone, flecainide, or dronedarone are all associated with a higher risk of HF-FEV [4].

Ventricular arrhythmias can be treated with amiodarone, but it should be noted that this does not reduce the risk of sudden cardiac death or mortality. Bradyarrhythmias are evaluated and managed according to recommendations for the respective pathologies. Patients with HF-FEV benefit from resynchronization therapy if there is atrioventricular block or slow-conducting atrial fibrillation [5,6].

Heart failure strongly influences prognosis in patients with atrial fibrillation and is a major contributor to atrial fibrillation recurrence and progression. Over 30 years of follow-up in the Framingham cohort, 57% of individuals with new heart failure also had atrial fibrillation and 37% of those with new atrial fibrillation had heart failure [7].

Many cardiovascular and noncardiovascular conditions predispose to both atrial fibrillation and heart failure, converging on atrial cardiomyopathy. In the emergency setting for acute heart failure, atrial fibrillation is a frequent precipitant. The onset of heart failure in people with atrial fibrillation doubles the risk of stroke and thromboembolism, even with anticoagulation, and is associated with a 25% increase in all-cause mortality [8].

Prognosis depends on the level of left ventricular ejection fraction (LVEF): mortality was highest for patients with atrial fibrillation and heart failure with reduced ejection fraction (HFrEF; LVEF $\leq 40\%$) compared with atrial fibrillation and HF with preserved EF (HFpEF; LVEF $\geq 50\%$). However, the incidence of stroke and heart failure hospitalization did not differ significantly between the left ventricular ejection fraction categories. Because atrial fibrillation and heart failure often coexist, strategies to optimize outcomes are integrated into the AF-CARE pathway, and heart failure should be managed intensively in patients with atrial fibrillation to prevent avoidable morbidity and mortality[9].

Recent additions to HFrEF therapy—eplerenone, sacubitril–valsartan, and SGLT2 inhibitors—included substantial numbers of patients with atrial fibrillation in randomised controlled trials, and atrial fibrillation did not appear to modify their effects on reducing cardiovascular mortality or heart failure hospitalization [10].

Cardiac resynchronization therapy for patients with HFrEF and atrial fibrillation emphasizes achieving effective biventricular pacing and often recommends a low threshold for atrioventricular node ablation. Patients with HFmrEF (LVEF 41%–49%) and atrial fibrillation are generally managed following HFrEF recommendations, though direct evidence in atrial fibrillation is limited. For HFpEF with atrial fibrillation, prespecified subgroup analyses from large trials indicate that SGLT2 inhibitors (dapagliflozin, empagliflozin, sotagliflozin) improve prognosis [11].

Effective heart failure management may lower AF recurrence by limiting adverse atrial and ventricular remodeling, though evidence for specific therapies is limited. In relation to the RACE 3 trial, it has been concluded that a comprehensive strategy to address mild-to-moderate heart failure, including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoid receptor antagonists, statins, and cardiac rehabilitation, can improve the maintenance of sinus rhythm on ambulatory monitoring at 12 months. However, this benefit was not observed at the 5-year follow-up, potentially due to the cessation of the intervention after the first year [12].

The 2023 Focused Update of the 2021 ESC Guidelines for acute and chronic heart failure focuses on the importance of achieving euvolemia with diuretics not only to optimize the management of heart failure but also to facilitate rate control of atrial fibrillation.

For HFrEF, many older guideline-recommended therapies have limited specific evidence of benefit in patients with concomitant AF. Trial data are lacking for ACE inhibitors in this subgroup, ARB data are inconsistent, and individual patient–level meta-analysis of RCTs showed no benefit of beta-blockers versus placebo [13].

4.2. Atrial fibrillation and valvular heart disease

Atrial fibrillation and valvular heart disease interact closely, influencing prognosis and the course of valvular heart disease over time. Valvular heart disease independently predisposes to atrial fibrillation, and nearly one-third of people with atrial fibrillation have a history of valvular heart disease. Conversely, atrial fibrillation commonly precipitates secondary atrial

mitral and tricuspid regurgitation: in one cohort, 8% of people with atrial fibrillation developed moderate to severe tricuspid regurgitation within three years compared with 2% of those in sinus rhythm. Although altered annular dynamics have been suggested, the mechanisms causing secondary atrioventricular valvular disease in some people with atrial fibrillation but not others remain incompletely understood [14].

Patients with both valvular heart disease and atrial fibrillation face high rates of thromboembolic and bleeding events. Direct oral anticoagulant drugs have largely replaced vitamin K antagonist drugs for most valvular scenarios and are recommended for patients with valvular heart disease presenting with atrial fibrillation, except for those with a mechanical heart valve or rheumatic mitral stenosis with valve area ≤2.0 cm2. Subgroup analyses support the use of apixaban, dabigatran, edoxaban, and rivaroxaban in these populations [15].

Connolly et al. evaluated how oral anticoagulation use influenced outcomes after surgical left atrial appendage occlusion among participants in the Left Atrial Appendage Occlusion Study III. The investigators performed a prespecified analysis comparing stroke, systemic embolism, and bleeding outcomes according to perioperative and follow-up oral anticoagulant strategies. Among patients with atrial fibrillation undergoing cardiac surgery who received concomitant surgical left atrial appendage occlusion, the procedure reduced risk of stroke or systemic embolism versus no occlusion. Benefit was consistent across subgroups defined by prescription of vitamin K antagonist therapy, direct oral anticoagulant therapy, or no oral anticoagulation at hospital discharge. Absolute risk reductions were similar irrespective of anticoagulant class, and the relative effect of appendage occlusion did not differ significantly by anticoagulation status. Major bleeding rates were not increased by appendage occlusion. The analysis supports that surgical left atrial appendage occlusion provides incremental stroke prevention beyond contemporary anticoagulant strategies in patients with elevated thromboembolic risk undergoing cardiac surgery. Findings reinforce consideration of routine appendage occlusion at the time of cardiac surgery in patients with atrial fibrillation and a sufficient stroke risk score, while acknowledging that anticoagulation decisions should remain individualized. Further randomized data could clarify optimal integration with long-term anticoagulation strategies.[16].

In a randomized trial of patients with severe aortic stenosis and atrial fibrillation undergoing transcatheter aortic valve implantation, concomitant transcatheter left atrial appendage closure was non-inferior to medical therapy for a composite endpoint of all-cause mortality, stroke, and major bleeding at two years. However, similar rates of major or life-threatening bleeding and a higher rate of arterial or venous thromboembolism in the combined procedure group leave uncertainty about the value of performing both procedures together [17].

Atrial cardiomyopathy is a broad, multifactorial process that links structural, functional, electrophysiological, and biochemical alterations of the atria, with valvular heart disease being one of the most common clinical contexts in which accelerated atrial remodeling occurs.

The authors [16] present basic, translational, and clinical evidence to formulate a conceptual framework in which atrial disease forms part of the substrate for stroke, heart failure, and arrhythmia progression. Atrial fibrosis, inflammation, microvascular dysfunction, meta-

bolic and neurohormonal abnormalities, and genetic and ageing-related factors, amongst others, play an important role in atrial remodelling and contribute differently to the mechanisms underlying various atrial cardiomyopathies. The combined use of imaging tools such as echocardiography and cardiac magnetic resonance to assess fibrosis and atrial strain, electrocardiographic methods and advanced electrophysiological signal analysis to study conduction disturbances, and biomarkers to determine inflammatory status and myocardial injury in such patients is therefore recommended. According to the authors, cardiomyopathy may develop within an atrium in association with most cardiovascular conditions, including hypertension, valvular heart disease, diabetes, and heart failure, which calls for the need to manage these comorbid factors to prevent the development of atrial cardiomyopathy. Effective therapeutic interventions for atrial cardiomyopathy range from rhythm and rate control, upstream treatments to reduce the burden of atrial arrhythmia, and stroke prevention strategies to manage the substrate of atrial cardiomyopathy beyond rhythm control. The authors conclude by advocating for future research on biomarkers and atrial imaging as well as therapies targeted at modifying atrial myocardial substrates and recommend employing a multidisciplinary team to address the diverse aspects of atrial cardiomyopathy.

Molnár et al. review the pathogenesis, clinical significance, and treatment of atrial cardiomyopathy, with emphasis on its role in valvular heart disease. The authors discuss various molecular mechanisms and pathological processes underlying cardiomyopathy resulting from valve disorders. In this review, cardiac fibrosis, inflammation, oxidative stress, apoptosis, extracellular matrix remodelling, and changes in ion channels, transporters, and calcium homeostasis in the atrium are associated with pressure and volume overload resulting from valvular heart disease. These alterations contribute to atrial dilation, dysfunction, arrhythmias, and thrombus formation that promote atrial arrhythmia, stroke, and worsening of regurgitant disease. The authors also elaborate on therapeutic interventions for valvular heart disease and atrial cardiomyopathy, including the need to control arrhythmia and rate, prevent and treat stroke, as well as intervene to reverse the effects of volume overload and pressure on the atrium. The latter also involves the need to manage upstream factors such as neurohormonal activation and inflammation since preliminary evidence suggests that these may be beneficial in targeting the mechanisms of cardiomyopathy [18].

For example, some inflammatory molecules such as nuclear transcription factor kappa B or miRNA targeting might influence the atrial fibrillation remodelling beneficially, but there are studies that show for example, that IL-6 targeting might negatively affect these processes.[19-21]

4.3. Postoperative atrial fibrillation

Postoperative atrial fibrillation is a common complication after cardiac and noncardiac surgery, peaking within the first week and associated with longer hospital stay, stroke, and mortality.

Pathogenesis is multifactorial: acute inflammation, oxidative stress and possible atrial ischemia. Stretch, autonomic imbalance, and pre-existing atrial cardiomyopathy are also possible mechanisms involved. Clinical and biomarker based risk models improve prediction but ack universal callibration. Prevention strategies with the strongest evidence include perioperative beta-blockers and amiodarone; colchicine and statins are new candidates that have shown promise in new and ongoing studies [22].

The optimal fluid intake and electrolyte management, minimization of atrial trauma, and anesthetic techniques can decrease the risk of POAF. The management of rate or rhythm should be individualized depending on hemodynamics and symptoms; the use of short-term anticoagulation should be determined based on the balance between the risk of thromboembolism and hemorrhage. In addition to the immediate consequences, POAF is associated with a higher incidence of subsequent atrial fibrillation(AF) and cardiovascular events, underscoring the need for standardized protocols for secondary prevention and randomized clinical trials investigating the role of novel anti-inflammatory and upstream therapies and the integration of wearable cardiac monitors into the perioperative care pathway [23].In table 1 are summarised the main factors that contribute to postoperative atrial fibrilation [adapted from 24].

Table 4.3.1- Perioperative atrial fibrilation causes.

Preoperative	Intra-procedural	Postoperative
Age, gender, ethnicity	Volume overload	Infection
Genetic factors	By-pass time	Bleeding
obesity	Cannulation site	Electrolytes imbalance
Medical history including hypertension, diabetes mellitus , COPD, heart failure		Prolonged ventilation
Drug abuse		Oedema
Echocardiographic parameters		Ischemia
Abnormal ECG		

There are different definitions of postoperative atrial fibrillation ranging from an episode requiring treatment to episodes lasting over 30 seconds or any new episode or even episodes lasting > 10 minutes [25,26].

Incidence of postoperative atrial fibrilllation is summarized in table 2 (adapted from [26,27]).

Table 4.3.1-Incidence of postoperative atrial fibrillation by different types of surgery

After cardiac surgery	After thorcic surgery	After other surgery
General 30%	General 15%	General: 0.4-15%
Coronary bypass graft 20%	Pneumectomy 30%	Colorectal 5-15%
Aortic procedures 30%	Lobectomy 4.5%	
Transplant 4%		
Valve procedures 50%		

Treatment of postoperative atrial fibrillation (POAF) depends on hemodynamic status. Hemodynamically unstable patients need immediate electrical cardioversion to restore sinus rhythm. In hemodynamically stable patients, rate control using beta-blockers, calcium-channel blockers, or digoxin (if left ventricular ejection fraction (LVEF) is normal), or rhythm control using antiarrhythmic drugs (AADs) can be used. However, beta-blockers or digoxin alone are recommended for patients with reduced LVEF. Pharmacological cardioversion with either class IC or III AADs is preferred for normal LVEF or amiodarone for reduced LVEF.

There is no clear evidence that either strategy (rate vs. rhythm control) is superior after cardiac surgery. The randomized trial demonstrated that both strategies had comparable length of hospitalization, survival, and adverse events. Additionally, most patients converted to sinus rhythm by the time of discharge in both groups [28]. Therefore, the choice of pharmacological interventions mainly depends on efficacy, safety, and recurrence risk.

The oral anticoagulation for the prevention of stroke related to POAF is controversial. According to the guidelines, patients should be considered for oral anticoagulation, and the decision should be made on an individual basis. Thus, continued anticoagulation with vitamin K antagonists may be considered for patients after noncardiac surgery (ESC IIa), whereas the decision should be made on a case-by-case basis after cardiac surgery, pending further randomised trials [29].

In the study of Riad et al. [29], it was found that there was a significant incidence of new-onset postoperative atrial fibrillation (POAF) in patients undergoing cardiac surgery, including those from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. The analysis reveals that a substantial number of patients received anticoagulation therapy during their hospitalization, yet there was considerable variability in treatment protocols across different institutions.

The findings show a correlation between anticoagulation use and reduced rates of thromboembolic events in patients with POAF. However, several studies also highlight an increase in bleeding complications associated with anticoagulant administration [30].

Importantly, there was no definitive consensus on the ideal anticoagulation strategy, reflecting a need for standardized treatment guidelines. Overall, the results underscore the necessity for further investigation into optimal anticoagulation approaches to enhance patient safety and outcomes in the context of new-onset POAF after cardiac surgery.

4.4 Atrial fibrillation in athletes

Atrial fibrillation (AF) is becoming more prevalent among athletes, especially those involved in endurance activities such as marathon running and cycling. It often occurs due to a combination of structural and electrical remodeling (Pelliccia & Maron, 2015). The most common risk factors for AF among athletes include age, sex, family history, and the presence of other cardiac conditions and the strenuous physical activity involved in sports (31). Some of the symptoms of AF include having a feeling of fluttering in the chest, experiencing weakness or fatigue, dizziness, and shortness of breath. These signs may affect an athlete's performance if they are not managed appropriately. The diagnostic procedures used for AF include ECG and

Holter monitoring. An echocardiogram may also be used to determine structural abnormalities in the heart. AF treatment options include making lifestyle changes, drugs to control heart rate and rhythm, and ablation as a treatment for patients whose AF recurs, despite treatment with medications (Pelliccia & Maron, 2015). Athletes who are diagnosed with AF should consult with their cardiologists about the best drug regimen to allow them to participate in sporting activities. It is essential for an athlete to understand the clinical implications of AF on their performance and health because it will help them maintain an appropriate training regime. As such, further research on AF among athletes will be vital in helping athletes to understand how to deal with the condition better

Newman et al [32] performed a study whose objective was to estimate the strength of association between athletic participation and atrial fibrillation.

They searched studies for a period of 30 years, from 1990 to 2020, and included cohort case-contsol studies reporting atrial fibrillation in athletes versus non-athletes. Thirteen studies were pooled using the data from over 6800 athletes and over 63000 controls, and random effects meta-analysis found that athletes had higher odds of atrial fibrillation than non-athletes. (OR 2.46, 95% CI 1.73–3.51; $p<0.001$). Interestingly, meta-regression showed age and sport type modified risk, younger athletes had a greater relative risk and mixed-sport participation conferred higher risk than endurance-only activities. In the article, the authors discussed possible mechanisms, such as enlargement of the atria that can occur with exercise, increased vagal tone, and excessive exposure over a prolonged period to adrenergic shifts, leading to inflammation and atrial fibrosis. The meta-analysis had several limitations, including heterogeneity, a lack of female participants, and an inability to establish an exercise dose-response relationship. The paper concluded that although regular physical activity is generally beneficial for health, high levels of athletic performance are linked to higher risks of AF and that further prospective studies were needed to understand the mechanisms and develop methods for prevention and management.

Table 4.4.1- Common risk factors for atrial fibrillation in athletes (adapted from [30-33]

General risk factors	Specific risk factors for athletes
Age	Intensity and duration of traininh
Hypertension	Type of sport (endurance vs mixed)
Obesity	Previous history of arrhythmias
Diabetes	Atrial enlargement due to training
Heart disease	Vagal tone influence
Family history of arrhythmias	Chronic inflammation
Alcohol and smoking	Certain drugs, including hormones (approved or non-approved)

Moderate and regular physical activity is essential for preventing atrial fibrillation by altering several of its risk factors. Therefore, it is necessary to encourage patients who are prone to developing AF to exercise in order to prevent this disease. Nevertheless, AF was more prevalent in active and former male master athletes, participating in high-level endurance sports, supporting the U-shaped association between physical activity and AF, which was not observed in females.

Before recommending sports to patients with recognized AF, the exclusion of structural heart disease and pre-excitation should be verified. In addition, hyperthyroidism, alcohol abuse, and illicit drug use should also be evaluated. Strenuous sports should be suspended until the provoking factor is identified. Atrial fibrillation can cause accelerated atrioventricular conduction during exercise, resulting in weakness, dizziness, exercise intolerance, and poor exercise capacity. Patients should stop physical activity if they experience any of these symptoms. Moreover, rate control should be optimized [34].

If AFL is diagnosed, it is advisable to perform a prophylactic cavo-tricuspid isthmus ablation. Rate control medication alone may not be sufficient, although it is often the first-line treatment for AFL during exercise. Beta-blockers are the most common drugs, but they decrease performance; calcium channel blockers combined with digitalis are less effective or ineffective in most cases. A combination of negative chronotropic agents is needed, which reduces the risk of sinus bradycardia and chronotropic incompetence [35].

Furthermore, the management of rhythm is challenging in patients with AFL due to the potential inadequate efficacy and safety of class III agents in younger population. While class I drugs can prevent AF recurrences, they should not be used alone due to the risk of atrial flutter. Prophylactic ablation should be considered if class I monotherapy is employed. Sporadic AF patients should avoid sports until AF resolves [36].

Anticoagulant prescriptions depend on risk profiles, and contact sports should be avoided by patients on these medications. Catheter ablation should be considered if drug therapy fails or is not preferred. Studies suggest that outcomes of pulmonary vein isolation in athletes with paroxysmal AF are comparable to those in non-athletic patients [37].

Table 2.4.2- Drug classes that can be used in athletes with atrial fibrillation

Medication / Class	Drug class	Effect on exercise performance	Typical indication / notes
Beta-blockers	Beta-adrenergic blockers	Often impair peak exercise capacity; can cause fatigue, reduce tolerance	Common rate control option; used cautiously in athletes due to negative performance effects
Verapamil	Non-dihydropyridine Ca2+ channel blocker	Less impact on exercise capacity than beta-blockers; slows AV nodal conduction	Viable alternative for rate control in symptomatic athletes sensitive to beta-blocker effects
Digoxin	Cardiac glycoside	Minimal effect on exertional heart rate control; little impact on exercise performance	More useful for resting rate control or when HF with reduced EF coexists; limited use in athletes
Sotalol	Class III antiarrhythmic (also beta-blocking effects)	May have negative exercise effects; proarrhythmic risk	Rhythm control option; may be insufficient or carry risks in young athletes
Amiodarone	Class III antiarrhythmic	Significant extracardiac effects; can affect performance indirectly via side effects	Effective rhythm control but relatively contraindicated/used cautiously in young athletes due to toxicity

Class I antiarrhythmics (e.g., flecainide)	Class I sodium-channel blockers	Variable; can have limitations in highly active patients	Used with caution due to atrial flutter risk; may be used as pill-in-the-pocket for sporadic AF
Flecainide (example)	Class Ic antiarrhythmic	May be limited in highly active patients	Often pushes consideration of ablation when symptoms persist despite meds

4.5. Atrial fibrillation in the elderly

The prevalence of atrial fibrillation (AF) rises with age, making it the most prevalent arrhythmia among individuals over 65 years old. AF is common in the elderly population affecting approximately 10% of the population that is aged 80 years or older. In addition, about 70% of cases occur in patients aged 65-85 years. AF incidence increases with age, and this condition is becoming more prevalent because of the aging population. Although AF is not life-threatening, it considerably increases the mortality risk. According to the Framingham study, the odds ratio for total mortality was 1.5 and 1.9 for men and women with AF, respectively, after adjusting for age and other potential confounders [38].

In addition, older adults with AF experience many health problems that often require prolonged hospitalization, such as heart failure, stroke, pacemaker implantation, and response to antiarrhythmic drugs. Moreover, recent improvements in pharmacologic and invasive therapies make AF an attractive area of research and innovation. Nowadays, older patients with AF who were previously excluded from clinical trials are being enrolled in clinical studies, which leads to new discoveries in AF treatment and better understanding of this disease.

This review focuses on the management of AF in very elderly patients.[38]

Key characteristics of elderly patients are summarized in Table 5 based on [38,39].

Table 4.3.1 -Chracteristics of aged patients with atrial fibrillation

Characteristic	Details
Prevalence in Age Groups	- 10% for patients over 80 years
	- 70% of AF patients aged 65-85 years
Mortality Odds Ratio	- 1.5 for males
	- 1.9 for females
Common Morbidities	- Heart failure
	- Stroke
	- Need for pacemaker implantation
	- Adverse effects from antiarrhythmic therapy
Historical Context	- Recognized since ancient civilizations (China, Egypt, Greece)
Recent Advances	- New drug therapies and invasive techniques
	- Increased participation of elderly patients in clinical trials

Graph 1 illustrates the key clinical characteristics of atrial fibrillation in older adults, emphasizing its complexity and management challenges. Approximately 80% of patients with atrial fibrillation are 65 years of age or older; thus, the condition is strongly associated with the aging population. The main concern related to atrial fibrillation is a stroke, which is a serious and potentially debilitating complication, and oral anticoagulants have been proven to reduce the risk of stroke significantly. However, it is crucial to note that anticoagulants also pose a substantial risk of hemorrhagic events that can be even more dangerous than a stroke, especially in the elderly population and those with reduced physical function. Moreover, most of these patients often present with multiple morbidities, and a significant proportion of them typically take several medications to manage their conditions. Therefore, it is essential to consider each patient's specific circumstances and provide individualized care rather than a uniform approach.Clinical decisions should integrate risk comorbidities, functional status, and patient preferences to optimise outcomes in this heterogeneous and vulnerable population.

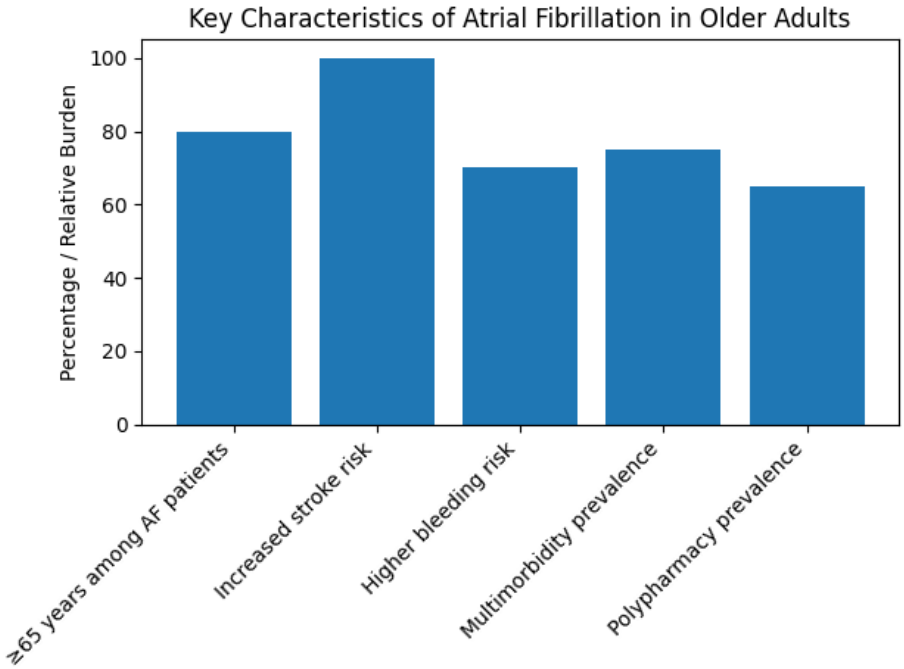

Figure 4.5.1 {adapted from [39]

A study by Elbadawi et al [40] showed that systematic atrial fibrillation screening utilizing non-invasive tools resulted in a higher rate of new atrial fibrillation detections and the initiation of oral anticoagulation . In contrast, opportunistic screening did not yield increased detection rates. There were no notable differences among the various atrial fibrillation screening methods regarding all-cause mortality or cerebrovascular accident events. One limitation the authors found, was that these analyses may be underpowered, indicating the necessity for future randomized controlled trials to investigate the effects of systematic atrial fibrillation screening on mortality and cardiovascular outcomes.

Atrial fibrillation (AF) is one of the most common arrhythmias that occur in most of the elderly population and can be accompanied by a variety of comorbidities that significantly affect the

course of the disease and the choice of treatment options. Chronic kidney disease and hyperuricemia are two common conditions associated with AF that usually occur in the elderly population.

Chronic kidney disease (CKD) significantly affects the mechanisms of AF and increases the risk of developing this type of arrhythmia. The accumulation of electrolytes and fluid retention that occur as a result of impaired kidney function can damage the heart muscle and cause irregular heartbeats. In addition, patients with CKD often require drug treatments that can aggravate AF or interfere with antiarrhythmic therapy and anticoagulant use [41].

Hyperuricemia often occurs in older people and is characterized by high levels of uric acid in the blood. This condition is also a significant risk factor for AF since uric acid can increase oxidative stress and inflammatory processes in the body, affecting the function of the heart muscle.

In patients with both hyperuricemia and chronic kidney disease, the combination could have a synergistic effect, heightening the risk of atrial fibrillation and poor cardiovascular outcomes.

An analysis of the data by Buzas et all [42] based on SEPHAR III [43] study showed that hyperuricemia is associated with arterial hypertension and with suboptimal BP control in treated hypertensive subjects. Adult patients had significantly lower serum uric acid levels than elderly patients, irrespective of glomerular filtration rate. They also differed significantly from the elderly group in terms of lower intima-media thickness. In line with earlier studies, age was found to be a predictor of increased serum uric acid levels. The study further revealed that arterial hypertension became more prevalent with advancing age, while blood pressure control deteriorated. Since comorbidities are common in the elderly population, it is essential to implement comprehensive management approaches. For instance, consideration should be given to functions of the kidneys, uric acid levels, and anticoagulant therapy for the effective management of atrial fibrillation. In addition, the elucidation of the mechanism linking atrial fibrillation, chronic kidney disease, and hyperuricemia may contribute to the development of new therapeutic strategies for the targeted treatment of the illness. Overall, the findings on these associations are significant for the improvement of care and lifestyle of older people with atrial fibrillation.

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4.6. Atrial fibrillation in pregnancy

Atrial fibrillation (AF) occurs rarely during pregnancy, with the incidence of 27 cases per 100,000 pregnancies and increases when cardiac pathology is present.[44]

The cause of AF during pregnancy depends to a considerable extent on whether there was a pre-existing cardiac disease or not, and pregnancy can act as a provocative factor. Structural heart disease is the most common cause of atrial fibrillation during pregnancy. Congenital heart disease, valve abnormalities (most commonly mitral valve prolapse), and cardiomyopathy are more prevalent among pregnant women for the development of AF than in the general female population.[45]

Furthermore, a history of atrial arrhythmia in the current pregnancy or a previous episode of AF also contributes to the development of AFL during pregnancy. Moreover, some women may experience atrial fibrillation related to the pregnancy for the first time, even without a history of heart disease or heart failure. In addition to cardiac causes, there are several other non-cardiac causes of AF during pregnancy, including electrolyte imbalance, thyroid dysfunction, pulmonary embolism, and the presence of pro-arrhythmic agents in the body. Increased demands on the cardiovascular system during pregnancy can also be a reason for AF. A significant increase in blood volume during pregnancy places additional stress on the heart muscle.

Concurrent hormonal changes, including rising estrogen and progesterone levels, alter autonomic tone and myocardial excitability [46].

Importantly, AF in pregnancy is often not an isolated phenomenon but a marker of underlying cardiovascular vulnerability. In structurally normal hearts, it is typically transient and benign; however, in the presence of cardiac disease, it may lead to significant maternal and fetal complications. Thus, the aetiology of AF in pregnancy is best understood as a combination of substrate, trigger, and modulating physiological changes. A complex interaction of hemodynamic, hormonal, and autonomic adaptations drives the pathophysiology of atrial fibrillation during pregnancy. Pregnancy induces profound cardiovascular changes that collectively create a pro-arrhythmic environment [47].

One of the earliest changes is systemic vasodilation, leading to a marked reduction in peripheral vascular resistance—up to 40% below baseline by mid-pregnancy. This is accompanied by a compensatory increase in cardiac output, which may rise by as much as 50%. These adaptations are mediated by neurohormonal activation and increased sympathetic nervous system activity. Simultaneously, total blood volume expands significantly due to increased plasma volume and red cell mass. While this supports uteroplacental perfusion, it also results in atrial and ventricular dilation. The stretching of atrial myocardial fibers alters electrophysiological properties, including shortening of the atrial effective refractory period and slowing of conduction velocity. These changes facilitate re-entry circuits and ectopic activity, which are key mechanisms in AF initiation and maintenance [48,49].

Hormonal influences further contribute to arrhythmogenesis. Elevated levels of estrogen and progesterone increase adrenergic receptor sensitivity and myocardial responsiveness to catecholamines. This enhances sympathetic tone and predisposes to tachyarrhythmias. Additionally, increased circulating catecholamines and heightened autonomic reactivity amplify electrical instability [50].

Pregnancy is also associated with an increase in resting heart rate and a higher frequency of premature atrial and ventricular contractions, both recognized triggers for AF. The presence of these ectopic beats in a structurally remodeled atrium increases the likelihood of arrhythmia onset. Another contributing factor is the hypercoagulable state of pregnancy, which, while not directly causing AF, exacerbates its clinical consequences. Overall, the pathophysiology of AF in pregnancy reflects a convergence of mechanical stretch, autonomic imbalance,

and hormonal modulation. These factors act synergistically on a susceptible substrate, explaining why AF is more likely to occur in women with pre-existing cardiac abnormalities but can also arise in otherwise healthy individuals [51,52].

The management of atrial fibrillation during pregnancy is complex and requires balancing maternal benefit with fetal safety. Treatment strategies are guided primarily by hemodynamic stability and the presence of underlying cardiac disease.In general, rhythm control is preferred over rate control in pregnant patients. Restoration and maintenance of sinus rhythm help preserve atrial contribution to ventricular filling and optimize cardiac output, which is critical for uteroplacental perfusion.[53]

Electrical cardioversion (ECV) is considered safe throughout pregnancy and is recommended in cases of hemodynamic instability or when there is a risk to maternal or fetal well-being. Prompt intervention is essential, as rapid ventricular response and loss of atrial contraction can lead to reduced cardiac output and compromised fetal circulation, but due to a lack of clinical studies, it should remain a tool of last resort. Also in need of electrical cardioversion, fetal heart monitoring is required, and a cesarean facility should be immediately available. [54]

For pharmacological management, beta-blockers (labetalol, metoprolol and bisoprolol) are the first-line agents for rate control. Calcium channel blockers and digoxin may be used as alternatives in selected cases, but digoxin can cause fetal heart disturbances. However, antiarrhythmic drugs must be used cautiously due to potential teratogenic effects and limited evidence from randomized trials [55], while amiodarone is labeled as class D toxicity, and has a class III recommendation (should not be used in pregnacy).[56]

Anticoagulation is a critical component of management due to the hypercoagulable state of pregnancy. Low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) are preferred because they do not cross the placenta. Vitamin K antagonists may be used in specific situations but carry risks of embryopathy, particularly in the first trimester, with limb defects, nasal hypoplasia or central nervous abnormalities being the most common side effects reported. Direct oral anticoagulants are not recommended due to insufficient safety data and potential fetal toxicity [57,58].

Management should be individualized and conducted by a multidisciplinary cardio-obstetric team. Regular monitoring and adjustment of the therapy are needed in connection with the gestational age and potential risks for the fetus. In other words, the main point is to ensure maternal hemodynamic stability while reducing fetal intervention as much as possible. Atrial fibrillation during pregnancy is a condition characterized by a complex interaction of maternal and fetal factors. Although rare, this type of arrhythmia often occurs in pregnant women with underlying heart disease or experiencing some pathological conditions. The main cause of atrial fibrillation during pregnancy is considered to be hemodynamic changes associated with structural and functional cardiovascular changes during pregnancy, as well as the impact of various factors on the autonomic nervous system and hormone levels [59]. In addition, the development of this pathology is facilitated by several predisposing factors, including heart disease, pregnancy itself, and some accompanying syndromes. Atrial fibrillation during pregnancy is considered to be a self-limited condition associated with increased intracardiac pressure and postpartum regression of remodeling [60].

As a rule, the management of this type of arrhythmia is based on the principle of rhythm control. In addition, cardioversion is used as an essential method for treating atrial fibrillation during pregnancy. Particular attention is paid to anticoagulant therapy, which is conditionally recommended in all patients. At the same time, there is a need for careful selection of drugs in order to reduce the risks for the fetus. The lack of clinical studies on the use of antiarrhythmic drugs during pregnancy requires an individual approach to each case of atrial fibrillation. In addition, it is important to consider the associated risks for the fetus and mother, which are different for each patient. Thus, the presence of heart disease increases the risk of morbidity and mortality for both the mother and the fetus, while isolated atrial fibrillation is generally considered to be a safe diagnosis [61]. However, further research is needed to develop and optimize treatment strategies and understand the risks and benefits of various therapeutic interventions.

In conclusion, it is possible to note that atrial fibrillation during pregnancy is a complex disease requiring a comprehensive approach. The main aspects of this condition include the leading causes and pathology mechanisms, as well as the principles of treatment.

Table 4.4.1- Atrial fibrillation characteristics in pregnancy (adapted from [44], [57] ,[59]

Category	Risk Factor	Mechanism / Explanation
Demographic	Advanced maternal age (>40–41 years)	Strongest predictor; risk increases ~4–5× vs younger women
	African-American ancestry	Higher observed prevalence (possible genetic/environmental factors)
	Low socioeconomic status	Associated with increased AF incidence
Cardiac disease	Congenital heart disease	Structural substrate for arrhythmia
	Valvular heart disease (especially mitral)	Atrial dilation and pressure overload
	Cardiomyopathies	Structural/electrical remodeling
	Prior history of AF	Strong predictor of recurrence during pregnancy
Cardiovascular risk factors	Hypertension (chronic)	Atrial stretch and remodeling
	Diabetes mellitus	Metabolic and inflammatory effects
	Obesity	Increased atrial size and inflammation
Pregnancy-related physiology	Increased blood volume	Atrial stretch → arrhythmogenesis
	Increased heart rate	Promotes electrical instability
	Neurohormonal changes	Sympathetic activation → arrhythmia trigger (
	Hypercoagulable state	Indirectly worsens AF complications
Other triggers	Hyperthyroidism	Increased sympathetic tone
	Electrolyte imbalance	Alters cardiac conduction
	Pulmonary embolism	Acute right heart strain
	Drug toxicity	Pro-arrhythmic effects
	Accessory pathways / re-entry circuits	Electrical substrate for AF

4.7. Atrial fibrillation and stroke

Atrial fibrillation is an independent risk factor for stroke. Atrial fibrillation-associated strokes are more severe (Figure 3) and frequently related to higher mortality and disability; therefore, their prevention plays a central role in the management of patients with atrial fibrillation.

The pathogenesis of stroke in atrial fibrillation is mainly cardioembolic, with thrombus formation, most common in the left atrial appendage, leading to embolization in different sites [62].

The key method for the primary prevention of stroke in patients with atrial fibrillation is the timely detection of individuals at risk and the initiation of anticoagulant therapy. The assessment of the stroke risk in patients with atrial fibrillation is performed using a CHA2DS2-VA score. The choice of the anticoagulant drug and the indication for its use are determined based on this score. It is well documented that the use of oral anticoagulants reduces the risk of thromboembolic events, especially in patients with a high stroke risk [62,63].

Direct oral anticoagulants are replacing vitamin K antagonists in the majority of patients with nonvalvular atrial fibrillation due to their better safety profiles and proven efficacy.

Large meta-analyses demonstrate reductions in stroke, mortality and intracranial hemorrhage with direct oral anticoagulants compared to warfarin[64]

In addition to pharmacological therapy, modern management emphasizes a holistic approach. The acronym „ABC pathway" (avoid stroke with anticoagulants, better symptom control and cardiovascular risk management) has been associated with improved outcomes. Modifiable risk factors such as hypertension and diabetes should be optimally controlled, and alcohol consumption and smoking should be vigorously contested and cessation should be encouraged. Also, screening in high risk populations is an emerging component of a healthy medical system.[65]

Secondary prevention targets patients who have already experienced a stroke or transient ischemic attack (TIA) in the setting of AF. In this population, the risk of recurrence is particularly high, and long-term anticoagulation is strongly recommended regardless of AF pattern. Oral anticoagulation remains the cornerstone of therapy, with DOACs preferred in most non-valvular cases. These agents have proven efficacy in secondary prevention of recurrent stroke with a favorable risk profile in terms of bleeding. Discontinuation of anticoagulation has been associated with higher risks of recurrent ischemic stroke, highlighting the importance of persistence in treatment and management of associated conditions such as atrial fibrillation [66].

In patients with contraindications to anticoagulation, consideration may be given to other options for reducing stroke risk, including surgical or procedural interventions to eliminate or reduce atrial appendage. Clinical studies suggested that these interventions may have similar efficacy to oral anticoagulants such as warfarin in appropriately selected patients. Antiplatelet agents should not be used in addition to anticoagulant therapy, except in patients with known coronary artery disease, because of an increased risk of bleeding complications [67].

Prevention measures are similar to those used in primary prevention, but achieve greater emphasis on the management of associated conditions. The management of patients with atrial fibrillation and stroke requires a comprehensive, individualized approach that includes consideration of both primary and secondary prevention strategies.

Anticoagulation remains the most effective intervention, with DOACs now preferred for most patients. Risk stratification, adherence to therapy, and control of comorbid conditions are essential components of care. [68]

Across four large randomized trials comparing direct oral anticoagulants with warfarin in nonvalvular atrial fibrillation, RE-LY found dabigatran 150 mg twice daily reduced stroke or systemic embolism to 1.11% per year versus warfarin 1.69% per year (hazard ratio 0.66) with similar major bleeding (3.1% versus 3.4% per year) and markedly lower intracranial hemorrhage (0.23% versus 0.74% per year). The ROCKET-AF trial established that rivaroxaban 20 mg once daily is non-inferior to standard oral anticoagulation, with a rate of stroke or systemic embolism of 2.1% per year (hazard ratio [HR], 0.88) versus 2.4% per year with warfarin, and rivaroxaban had a similar incidence of major bleeding. In turn, according to the results of the ARISTOTLE trial, apixaban 5 mg twice a day can reduce the risk of stroke or systemic embolism by 1.27% versus 1.60% per year (HR, 0.79) and major bleeding by 2.13% versus 3.09% per year (HR, 0.69) compared to warfarin and have lower overall mortality. Finally, the ENGAGE AFTIMI 48 trial demonstrated edoxaban's (60/30 mg) non-inferiority to warfarin in terms of the risk of stroke or systemic embolism (1.18% versus 1.50% per year) with significantly fewer major bleeds, which implies that direct oral anticoagulants (DOACs) are better in reducing the risk of intracranial hemorrhage [69-72].

Ultimately, a holistic model such as the ABC pathway offers the best framework for reducing stroke burden in AF patients, improving both survival and quality of life.

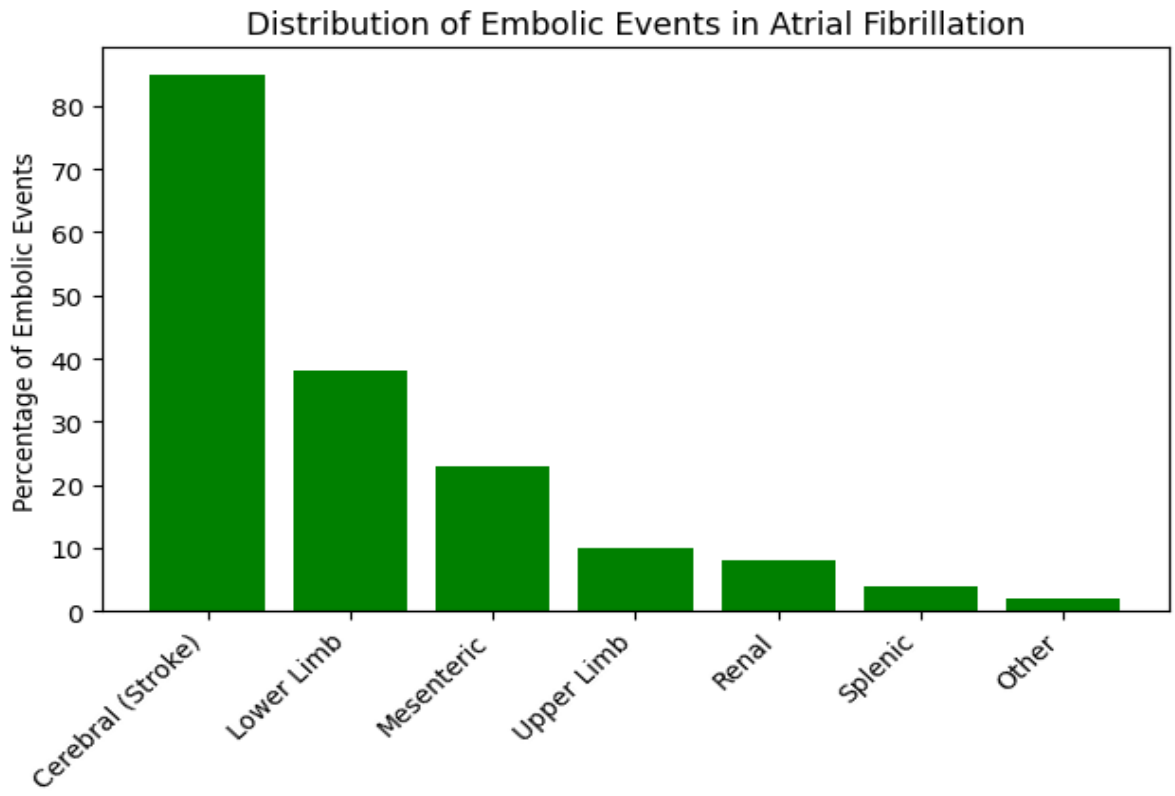

Figure 4.7.1 adapted from [62]- Figure 1. Distribution of systemic embolic events in patients with atrial fibrillation. Cerebral embolism represents the predominant manifestation, accounting for the majority of events. Peripheral embolism, particularly involving the lower extremities, constitutes the largest extracranial events.proportion of Visceral embolism (mesenteric, renal, splenic) is less common but associated with higher morbidity and mortality. Rare embolic sites include the coronary and retinal arteries.

4.8. Left atrial appendage occlusion

Atrial fibrillation is often accompanied by a risk of cardioembolic stroke. The left atrial appendage is the most common source of cardioembolic infarcts in patients with AF. Left atrial appendage occlusion, either surgical or percutaneous, has been considered as an option for reducing the risk of thrombus formation and consequent cardioembolic strokes. The concept of left atrial occlusion for the prevention of stroke is considered in the management of two clinical scenarios. First, as an alternative to oral anticoagulants in patients with a history of intracranial hemorrhage or increased bleeding risk. Second, as an adjunct to oral anticoagulant treatment in patients who have suffered from a stroke while on anticoagulant therapy [73].

The study by Landmesser et al. included 912 adult participants who underwent left atrial appendage occlusion and were compared to those who received standard medical treatment. Thus, the analysis involved 446 patients who received left atrial appendage closure as treatment (device group) and 442 patients who were treated with physician-directed optimal medical therapy (medical-therapy group). The mean age of the sample was 77.9±7.1 years, with 38.6% women. Patients had a mean CHA2DS2-VASc score of 5.2±1.5 (range 0–9) and a mean HAS-BLED score of 3.0±0.9 (range 0–9).

The results showed that in patients with atrial fibrillation at high risk for both stroke and bleeding, left atrial appendage closure was noninferior compared with physician-directed optimal medical therapy for the composite outcome of stroke, systemic embolism, major bleeding, or cardiovascular or unexplained death. Numerically, outcomes were somewhat worse (16.8 vs 13.3 events per 100 patient-years), which contributed to failing noninferiority.

Table 4.8.1- Left Atrial Appendage Occlusion (LAAO): Pros vs Cons (adapted from [73-75])

Pros (Advantages)	Cons (Limitations / Risks)
Alternative to long-term anticoagulation – useful in patients with contraindications (e.g., prior intracranial hemorrhage)	Did not meet noninferiority vs modern medical therapy in high-risk patients (CLOSURE-AF)
Targets main source of thrombus – >90% of AF-related clots originate in the left atrial appendage	Higher or similar event rates vs medical therapy in recent trial (no clear superiority)
Reduces stroke risk without lifelong anticoagulation (shown in earlier trials vs warfarin)	Procedural risks – pericardial effusion, device embolization, vascular complications (invasive procedure)
May reduce long-term bleeding risk compared with anticoagulation (especially relevant in high bleeding risk patients)	Serious adverse events relatively frequent (e.g., >80% in device arm in CLOSURE-AF, though many not device-related)
One-time intervention (no adherence issues like missed anticoagulant doses)	Requires short-term anticoagulation or antiplatelet therapy post-procedure
Useful in "real-world" patients unsuitable for anticoagulants (registry data supports feasibility and broad adoption)	Device-related complications – thrombus on device, peri-device leak
Comparable efficacy to warfarin in earlier trials (PROTECT-AF, PREVAIL)	Benefit less clear vs DOACs (modern standard therapy is highly effective and safer than warfarin)
May be combined with other procedures (e.g., AF ablation) with acceptable outcomes	Loss of appendage physiological function (minor but theoretically relevant)
Eliminates need for INR monitoring (vs warfarin)	Operator and center experience dependent (learning curve affects outcomes)

4.9. Future Therapies

4.9.1. AI based detection

Artificial intelligence (AI) has made tremendous strides in the diagnosis of atrial fibrillation (AF). Advanced learning algorithms can recognize characteristic patterns of AF in an ECG, even when the heart is in normal sinus rhythm. A groundbreaking study by Zachi Attia and colleagues used a convolutional neural network to analyze standard ECGs and detect concealed AF. Additionally, analysis of wearable devices in large populations has revealed that

photoplethysmography from commercial fitness watches can be used to identify irregular heartbeats indicative of AF [81,82].AI-enabled tools improve sensitivity compared with conventional methods and allow continuous, non-invasive monitoring. However, challenges remain, including false positives, data bias, and integration into clinical workflows. Overall, AI holds strong potential for scalable, early AF detection and prevention of stroke.

4.9.2. New anticoagulants

Modern anticoagulant therapy has been revolutionized by DOACs, yet these agents still carry a clinically significant bleeding risk, especially in elderly patients, those with renal impairment, or those with cancer. This unmet need has stimulated the search for safer anticoagulants that can dissociate thrombosis prevention from impairment of physiological hemostasis.[76]

A central focus of current research is inhibition of factor XI (FXI) and its activated form FXIa, components of the intrinsic coagulation pathway. Unlike thrombin or factor Xa, FXI appears to play a larger role in pathological thrombosis than in normal hemostasis. Observational and genetic data show that individuals with FXI deficiency have reduced rates of thromboembolic events with relatively mild bleeding tendencies. [77]

This biological property makes FXI an appealing target for therapeutic intervention. Several approaches to pharmacological modulation of FXI activity are currently under investigation [78–80]:

1. Small-molecule FXIa inhibitors (oral agents).

Compounds such as asundexian and milvexian inhibit FXIa activity. They are expected to have similar convenient oral administration to DOACs and appear to be associated with favorable results from phase II trials, including reduction of bleeding compared to standard of care.

2. Monoclonal antibodies.

FXI/XIa binding monoclonal antibodies such as abelacimab interfere with FXI activation and possess long serum half-lives, enabling subcutaneous dosing once monthly in some cases. Inhibition of FXI with these agents also appeared to reduce bleedings, compared to rivaroxaban in early trials.

3. Antisense oligonucleotides (ASOs).

These agents reduce FXI production in the liver, decreasing its plasma concentrations, among them is fesomersen (IONIS-FXI-LRx). Such an approach may be beneficial for long-term prevention of blood clots.

4. Other biologics and peptides.

Aptamers and inhibitory peptides to FXI/XIa are also under development; however, most of the studies are at early stages.

Several clinical trials of these agents were carried out in patients with AF, venous thromboembolism (VTE) or after total knee replacement (TKR), including PACIFIC-AF, AXIOMATIC-TKR, OCEANIC-AF, etc. In general, all these studies demonstrated reduced rates of bleeding; however, the efficacy of these drugs was inconsistent. The OCEANIC-AF trial of asundexian was terminated prematurely due to its inferiority to apixaban. Thus, in attempts to reduce the risk of bleedings, researchers should not ignore the possibility of increased rates of thrombosis, and the benefits of the new agents must be demonstrated in large-scale phase III trials.

Besides, other approaches to reduce thrombosis risk are under investigation, including inhibition of FXII, which plays a minor role in normal hemostasis, compared to FXI, and the development of polyphosphate pathway inhibitors, new antithrombin or protein C pathway modulators, etc. In total, the current landscape of anticoagulant drug development is quite wide, and more than 8 different FXI-targeting agents are under investigation in numerous clinical trials. The main advantage of such drugs is the possibility of "decoupling" of thrombosis and bleeding, which will allow their use in more patients, including those at high risk of both complications. However, the challenges of demonstrating non-inferiority or superiority over existing treatments, selecting the right indications, as well as cost-effectiveness, remain relevant.

Table 4.9.2- new drugs targeting different pathways in developement (adapted from [76-80]

Drug	Class / Type	Molecular Target	Mechanism of Action	Route	Development Stage
Asundexian	Small molecule	FXIa	Direct enzymatic inhibition	Oral	Phase III - ended (mixed results)
Milvexian	Small molecule	FXIa	Direct enzymatic inhibition	Oral	Phase II–III
Abelacimab	Monoclonal antibody	FXI/FXIa	Prevents activation and activity	SC / IV	Phase II–III
Fesomersen	Antisense oligonucleotide	FXI synthesis	Reduces hepatic FXI production	SC	Phase II
Osocimab	IgG1 monoclonal antibody	inhibits factor XIa	Direct inhibition	IV	Phase II
EP-7041	Small molecule	Inhibition of coagulation factor XI/activated factor XI	Intravenous inhibition	IV	Early clinical
FXII inhibitors (various)	Biologics / small molecules	FXII	Block contact pathway activation	Various	Preclinical–early clinical

4.10. Prevention strategies

A key concept is that atrial fibrillation is often the final manifestation of cumulative cardiovascular stress. Therefore, prevention begins with the aggressive control of all modifiable risk factors. Hypertension is considered the most significant risk factor, and strict control of blood pressure reduces AF incidence. Obesity is also strongly associated with AF development, and weight loss interventions can reduce AF burden and progression. The ESC guidelines suggest a body mass index (BMI) target of <27 kg/m 2 and maintaining a healthy weight [83]. Physical activity is protective against AF, but extremely strenuous activity can be a risk factor. Therefore, the ESC guidelines recommend moderate-intensity physical activity while avoiding high-intensity endurance exercise. Alcohol consumption should also be limited as it increases AF risk in a dose-dependent manner, and smoking cessation is recommended as a risk reduction measure.

In addition, the management of comorbidities is also an essential part of AF prevention. The ESC guidelines highlight the importance of screening and treating conditions associated with AF, including diabetes, heart failure, chronic kidney disease, and obstructive sleep apnea. In particular, the guidelines recommend screening for sleep apnea and treating it with continuous positive airway pressure to reduce AF risk. Similarly, optimal control of glucose levels in diabetic patients and treatment of heart failure are essential in AF prevention [83].

The guidelines also recommend opportunistic screening for AF in high-risk populations, such as those aged ≥65 years, using pulse palpation or single-lead electrocardiography. In addition, systematic screening with wearable devices or prolonged ECG monitoring may be considered in patients at high risk of AF, including those with a history of stroke or multiple risk factors. Early detection of AF enables the implementation of appropriate treatment and stroke prevention strategies. However, the ESC guidelines do not recommend the routine use of antiarrhythmic drugs for AF prevention. On the other hand, RAAS inhibitors may prevent AF in patients with hypertension, left ventricular dysfunction, or structural heart disease. Similarly, statins may reduce AF risk by targeting inflammation, but they are not recommended for AF prevention alone [83,84].

The AF-CARE framework proposed by the ESC guidelines is an innovative approach to AF management. The guidelines suggest that prevention is part of a continuum of care that requires ongoing reassessments and adjustments to patient care plans. Therefore, AF prevention involves patient education, counseling, and shared decision-making to encourage long-term lifestyle changes. The guidelines also highlight the importance of managing inflammation and metabolic syndrome in AF prevention, as these factors contribute to the development and progression of AF.

Genetic risk factors play a significant role in AF development; however, the ESC guidelines do not recommend genetic screening for AF prevention. The guidelines emphasize the importance of counseling patients with a family history of AF and those at high genetic risk. Finally, the guidelines note that cardiovascular prevention and AF prevention are closely intertwined. Therefore, the ESC guidelines recommend following cardiovascular prevention principles, such as a healthy diet, physical activity, and regular health assessments, to reduce AF risk and improve overall health outcomes.

In summary, the primary prevention of AF is the focus of the 2024 ESC guidelines. The guidelines recommend early and sustained intervention to reduce AF risk factors, manage comorbidities, and implement screening and early detection measures. These strategies will help reduce AF incidence and morbidity, including stroke prevention.

A key innovation in the ACC/AHA 2023 guidelines [84] is the conceptualization of AF as a progressive disease that involves multiple stages, ranging from "at risk" and "pre-AF" through to established and permanent AF. This approach highlights the importance of early intervention and the need to individualize care based on a patient's risk factors and clinical presentation. In addition, the guidelines recommend a more aggressive approach to the management of AF, including early rhythm control and catheter ablation.

The prevention of stroke is a critical component of AF management, and the guidelines recommend using the CHA 2 DS 2 -VASc score to assess stroke risk. In addition, DOACs are preferred over warfarin in most patients, and anticoagulation decisions should be made based on an individual patient's risk-benefit profile. The guidelines also emphasize the importance of regular follow-up visits to monitor the patient's response to treatment and adjust therapy as needed.

Another critical innovation in the ACC/AHA guidelines is the emphasis on early rhythm control of AF. The guidelines recommend early intervention to reduce the risk of AF progression and its associated morbidity and mortality. The guidelines suggest that catheter ablation is an appropriate treatment option for patients with symptomatic paroxysmal AF.

4.11. Clinical case discussions

4.11.1 Case presentation

The patient aged 81, former smoker with about 30 packs/year, non-smoker for about 15 years, with known history of essential hypertension and dyslipidemia, and with intermittent episodes of stable angina pectoris at high exertion and prostatic hyperplasia, around 04:00 a.m. started presenting sub intensive angina episodes that partially succumbed to sublingual nitroglycerin. Therefore, he showed up to the emergency room about 2 hours after onset. Objective examination on admission revealed a BMI of 29.5 kg/m2 SC, BP 170/75 mmHg, with no other significant pathological features detectable at the time of presentation.

The EKG showed a atrial fibrillation with left bundle branch block (age undetermined); troponin I at presentation was normal with a CK-MB above normal, while 1 hour later, troponin-HS I showed an increase of more than 10 times the normal value. The echocardiography revealed altered global and segmental function with a LVEF of 44% with mild mitral regurgitation. Speckle tracking indicated severe hypokinesis to akinesis in the inferior and posterior segments of the left ventricle.

A coronary angiogram was performed which revealed the trunk of the left coronary artery, circumflex artery, and atheromatous anterior descending artery, but without occlusions (Figure 2 – top left). However, an occlusion on the right coronary artery was identified (Figure

2 – top right image), and a PTCA was performed on this artery (Figure 2 – bottom left image), with angiographic result TIMI 3

The immediate post-stenting evolution was favorable, under anticoagulant treatment and double antiplatelet therapy. At 12 hours post-procedure the patient presented with hematochezia and massive hematuria, hemoglobin decreasing by 2.5g/dl; clopidogrel de-escalation was performed. On rectal exam, a tumor was identified approximately 3-5 cm from the external anal opening, and a recto sigmoidoscopy with biopsy sampling was performed. Imaging suggested the presence of both a rectal tumor formation and the presence of an intravesical formation.

Under de-escalation therapy and conservative therapy, the evolution was towards remission of the bleeding episode.

Three months after PCI, surgery was performed with an intention of radicality, with left iliac colostomy, the final histopathological result being a pT3N1Mx rectal adenocarcinoma. The described tumor was also approached intravesical by TUR-V with endoscopic resection during the 2nd part of surgery, one month after rectal resection, also resulting in pT2NxMx urothelial adenocarcinoma.

4.11.2. Discussion

One of the major challenges is that most cancer patients are excluded from prospective trials testing the effects of medications, which limits the evidence and leads to reliance upon expert consensus. Consequently, treatment strategies often lack firm, evidence-based recommendations and tend to be individualized.

In addition, many oncology patients do not receive optimal cardiovascular therapy, with only about one-third treated according to guideline standards. Data from Salim Yusuf et al. [85] demonstrated that aspirin use after myocardial infarction was associated with a doubling of survival in cancer patients (36% vs 18%). Despite this, only 46% of such patients received aspirin, including just 15% of those with ST-elevation myocardial infarction. These findings highlight a substantial gap between general treatment guidelines and their application in complex populations such as patients with neoplastic disease.

A study [86] on a population-based analysis including 2.5 million patients with an average follow-up rate of 7.3 years showed that the use of at least one antiplatelet in combination or not with an anticoagulant suggested that the occurrence of hematuria within the first 6 months of institution was associated with urothelial neoplasia, the incidence being almost double that of those who did not take an antiplatelet or were diagnosed at more than 6 months.

The peculiarity of this case is the concomitant existence of two different neoplasia, this being rather uncommon. There are few studies that evaluate such cases. In a cohort of more than 2 million cancer patients, 8.1% of survivors developed a second malignancy [87]

4.12. Key take home messages

- Atrial fibrillation is often silent. Oportunistic screening in patient >65 years or at high risk enables earlier detection
- A definitive diagnosis requires evidence on the ECG . Wearables can aid in supportingdiagnosis, but confirmation is still mandatory
- Estimate the thromboembolism risk using validated scores such as CHA_2DS_2-VA and use the results to guide anticoagulation decision. Oral anticoagulation is the basis of stroke prevention. Vitamin K antagonists are not preferred over direct oral anticoagulants. Avoid under-dosing anticoagulants because of stroke, combination with antiplatelets increases risk
- Rate control improves symptoms; rhythm control improves outcomes
- Early rhythm control, including catheter ablation may reduce atrial fibrillation progression in selected candidates
- Control comorbidities such as hypertension, obesity, diabetes, sleep apnea and alcohol intake
- Frequent reassessment of stroke risk, bleeding risk, and atrial enlargement

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Abbreviations:

AADs antiarrhythmic Drugs)

AF atrial fibrillation

AFL - atrial flutter

AI artificial intelligence

ASOs Antisense oligonucleotides

CHA_2DS_2-VA congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke/TIA/thromboembolism, Vascular disease, Age 65-74 years

CKD chronic kidney disease

COPD chronic obstructive pulmonary disease

ECG -electrocardiogram

ECV electrical cardioversion

HFpEF heart failure with preserved ejection fraction

HFrEF heart failure with reduced ejection fraction
LMWH low-molecular-weight heparin
LVEF left ventricular ejection fraction
POAF postoperative atrial fibrillation
SGLT2 sodium Glucose Cotransporter 2
TIA transient ischemic attack
TKR after total knee replacement
UFH unfractionated heparin
VTE thromboembolism