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RECENT UPDATES REGARDING ATRIAL FIBRILLATION AND THROMBOEMBOLISM DIAGNOSIS AND MANAGEMENT APPROACH: A SIMPLE LITERATURE REVIEW

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ABSTRACT.

Background: Atrial Fibrillation is a dysregulation of a cardiac rhythm resulting in the irregularity of the atrial contraction. This dysregulation causes an increase in atrial rate between 300 to 600 bpm. Atrial Fibrillation (AF) accounts for an increasing healthcare system burden worldwide in regards to disability and economic status. AF-related morbidities include stroke, heart failure, cardiovascular death, and a profound decrease in life quality. Objective: In this review paper we aimed to give an overview of AF, predisposing factors, and the potential consequences. Additionally, the management options in treating and preventing AF-related complications, particularly ischemic stroke. Methodology: We used the PubMed database and searched for 18 relative articles, using two Mesh terms: "Atrial Fibrillation" and "Thromboembolism." Conclusion: Ischemic stroke and thromboembolism account for a significant burden to the healthcare system globally. Treating AF, and more importantly, preventing thromboembolic events can markedly reduce this burden and improve the life quality of patients. Management includes pharmacological and non-pharmacological, and choosing one of them is based on the patient eligibility and risk of bleeding.

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Introduction

Overview and Epidemiology:

Atrial Fibrillation is a dysregulation of a cardiac rhythm that results in the irregularity of the baseline electrocardiogram (ECG) of certain amplitude, contour, and spacing "Known as fibrillation waves" [1]. This dysregulation results in an increase in the atrial rate between 350 to 600 beats per minute [1]. These fibrillation waves are best seen in leads V1, II, III, and aVF [1]. Atrial Fibrillation (AF) severely affects more than 30 million people in the world [2]. AF is associated with an increased risk of mortality and morbidity, and mortality related to AF accounts for increasing disease burden globally regarding disability and economics [2, 3]. An estimated cost of individuals with AF was $8075 in the United States [3]. Morbidities related to AF include heart failure, stroke, hospitalization, cardiovascular death, sudden death, non-cardiovascular death, and a profound decrease in quality of life, functional status, and cognition [3-5]. Atrial Fibrillation (AF) is the most common type of cardiac dysrhythmias, and its prevalence increases with each decade of age [1, 3]. Individuals of 50-59 years of age have a 1% risk of developing AF, while 10% of 80-84 years of age and 11-18% of more than 85 years of age are at risk of AF [3]. Overall, black people have a lower incidence of AF despite having a high

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prevalence of AF risk factors, such as obesity, diabetes mellitus, hypertension, and heart failure [3]. The ARIC study concluded that the cumulative risk of AF at the age of 80 reached 21% in white men and 17% in white women, while it was only11% in black men and women [3].

Pathophysiology, Clinical Features, and Classifications:

In normal physiology of the heart, the sinus node originates impulses that are followed by regular atrial and ventricular activation and contraction [4]. Atrial Fibrillation (AF) has a complex pathophysiology, which can occur due to different mechanisms [5]. Atrial Fibrillation (AF) commonly results in multiple, small reentrant depolarization circuits in the atria causing rapid atrial rate reaching 300-600 beats per minute, and it is most frequently triggered by abnormal rapid discharges from pulmonary veins [1, 4, 5]. The AV node refractory period is responsible for ventricular rate irregularity [4]. These irregular beats can lead to uncontrolled rapid ventricular activity, followed by decreased myocardial blood flow, decreased cardiac output, and long-term damage to the myocardium [4]. Atrial Fibrillation (AF) might present with regular rhythm if concomitant completes heart block with atrioventricular junctional or idiopathic escaped rhythm [1, 4]. Familial AF may be developed following polymorphisms in specific genes related to sodium/potassium channels, renin-angiotensin system, sarcolipin, endothelial nitric oxide synthase, connexin-40, and interleukin-40 [3, 5]. These genetic polymorphisms lead to abnormalities in calcium handling, fibrosis, conduction, and inflammation [5]. Brugada et al. described the first genetic locus for AF in 1997 [3].

Atrial Fibrillation (AF) can present with various symptoms, varying from non to disability, depending on several causal mechanisms [5, 6]. At least 25% of all AF patients are asymptomatic, and history taking alone is insufficient in screening [5]. Patients with AF become symptomatic due to one or more of the following: (I) rapid ventricular response rate; (II) irregular ventricular response; (III) loss of atrial participation to ventricular filling; and (IV) systemic thromboembolism [6]. Symptoms include palpitations, shortness of breath, exercise intolerance, easy fatigability, lightheadedness, anxiety, chest pain, embolic events, and rarely, syncopal attack [5, 6]. The syncopal attack can be caused either by AF itself, especially if concomitant left ventricular outflow obstruction (as in aortic stenosis) exists, or by sudden pause following cessation of AF [6].

Atrial Fibrillation (AF) is classified under several categories, shown in Table 1 [6].

Discussion

Predisposing Factors:

For the past few decades, there has been a concerted effort to reduce the impact of atherosclerosis and cardiovascular disease on the broad population, such as statin therapy, hypertension control, and encourage smoking cessation [3]. Despite the reduction in risk of coronary artery diseases and arteriosclerosis, the incidence of AF continues to grow, indicating that reducing cardiovascular risks may be insufficient to reduce the occurrence of AF to a similar extent [3]. There are firmly established risk factors for AF that are indicated in Table 2 [3-5, 7]. However, the single most important risk factor influencing the incidence of AF is age; the older the study's sample size, the more prevalent AF will be reported during follow-up [7]. In a large cohort study involving a population between 35-74 years, 447,020 people were included and underwent investigations and assessment of cardiovascular disease (CVD) risk in primary care [8]. The study results revealed that 12,739/447,020 (2.8%) have an AF diagnosis by routine CVD risk assessment in primary care [8]. Fifty-four percent of diagnosed AF were below 65 years, and one-third were female, 78% had hypertension, 40% had a history of vascular disease, 31% had a history of heart failure, and 30% had diabetes mellitus [8].

Table 1. Classifications of Atrial Fibrillation.

Category	**Definition**
• Paroxysmal AF	Self-terminating with Recurrent Attacks
• Persistent AF	Episode Lasting >48H until Cardioversion Performed
• Mixed AF	When Paroxysmal and Persistent Exist.
• Permanent AF	When AF lasts for a Long Time and Cardioversion is not Indicated or Failed.
• Chronic AF	The episode lasts for >7 days.
• Lone AF	AF in Absence of Heart Disease, HTN, Thyroid Diseases, or Alcohol
• Adrenergic AF	Occurs Typically after Exercise
• Vagotonic AF	Occurs Typically after Meals or at Night

Abbreviations: HTN: Hypertension.

Table 2. Predisposing Factors for Atrial Fibrillation

• Age
• Male Gender*
• Familial "Mutation"
• Caucasians
• Obesity
• Hypertension
• Congestive Heart Failure (with Impaired or Preserved LVSF)
• Myocardial Infarction/CAD
• Valvular Heart Disease
• Left Atrial Enlargement
• Diabetes Mellitus
• Thyrotoxicosis**
• Alcohol Use
• Chronic Kidney Disease
• Obstructive Sleep Apnea
• High-level Endurance Training
• Cardiomyopathy
• Cardiac Tumors
• Stimulant Use

* Women with AF are commonly presenting with Stroke.
** Thyrotoxicosis is the most common correctable cause of AF.
Abbreviations: LVSF: Left Ventricular Systolic Function. CAD: Coronary Artery Disease

Atrial Fibrillation and Cryptogenic Stroke:

Annually, more than 790 thousand people experienced a new or recurrent stroke in the United States [7]. After hospitalization, the cause behind ischemic stroke remains undetermined in 10% to 40% of cases; this is often known as "Cryptogenic" stroke (CS) [7-9]. There are different definitions and diagnostic tests that participate in this variable incidence in published series [7]. To relieve this limitation, the term "embolic stroke of undetermined source" (ESUS) has recently been referred to identify cases where the causes of non-lacunar stroke remain obscure after complete diagnostic workup [7]. In a recently published series, the prevalence of ESUS was 16% to 32% [7]. Consequently, the cause of ischemic stroke remains obscure in many patients even after standardized diagnostic workup; thus, it represents a major challenge for selecting treatment. [7]. A recent study showed that patients with CS have an ischemic stroke recurrence rate of 9.1%, 24.0%, and 31.9% at 1, 5, and 10 years, respectively [7]. Recurrent strokes in these patients were again classified as CS in 63% of cases [7]. Potential causes of stroke recurrence include paroxysmal AF, arterial source of thromboembolism, patent foramen oval (PFO), structural heart diseases, and other less frequent etiologies [7-10]. Ischemic strokes caused by AF has been increased in the last few decades [9].

The Relation between AF and Stroke/Cognitive Impairment:

Ischemic stroke provoked by AF occurs following the classical sequence of atrial auricular blood stasis, coagulation cascade activation, thrombus formation, and eventually embolization [7]. Nevertheless, it is unknown that this is the only pathophysiological explanation for emboli formation, especially when an attack of stroke occurs within a few minutes of paroxysmal AF [7]. The updated pathophysiological mechanism suggests that in some cases, AF might be related to an atrial wall disease, causing dysfunction of the atrial cells, and ultimately triggering activation of platelet, coagulation cascade, and thrombus formation [7]. Moreover, AF has been linked to cognitive function impairment in patients without clinical stroke [10]. This association has been demonstrated by multiple mechanisms: micro-embolic events affecting the cerebral circulation that lead to silent cerebral ischemia (SCI), confirmed by brain imaging, such as Magnetic Resonance Imaging (MRI) [10].

Compared to the general community, AF is associated with at least a 5-folds increased risk of stroke, 2-folds increased in all mortality causes and a higher risk of congestive heart failure [5, 8]. After CS or ESUS, AF detection and treatment provide a great opportunity to decrease the risk of stroke recurrence by offering oral anticoagulation (OAC) [7]. But, AF is often asymptomatic, paroxysmal, and hard to be detected with standard tools, and is found in only a few cases even after three years of monitoring events [7-9]. Various tools for monitoring have been investigated to detect asymptomatic AF, such as Holter ECG of variable duration, loop recorders, mobile cardiac outpatient telemetry, and implantable cardiac monitors [7]. Furthermore, AF is an independent risk factor for developing dementia in up to 30% of patients regardless of cardiovascular events [10].

Biomarkers Associated with AF Events:

Evidence suggests that specific biomarkers can predict the likelihood of developing cardioembolic events or ischemic stroke [9]. Patients with normal heart function who have elevated plasma levels of the N-terminal fragment of B-type natriuretic

peptide (NT-proBNP) are 5 times more likely to develop an ischemic stroke than others with normal levels [9]. Elevated plasma BNP was strongly associated with higher post-stroke mortality rates compared to others with normal levels [9]. Additionally, patients with higher levels of troponin (I) are more likely to develop thromboembolism [9]. Inflammation is strongly associated with AF, and elevated plasma levels of C-reactive protein had a 33% high risk of developing AF events in the future [9].

Management:

Rate Control

According to the American College of Cardiology, American Heart Association, and European Society of Cardiology guidelines, the target ventricular rate in resting-state is 60 to 80 beats per minute (bpm) and 90 to 115 bpm during moderate activity [11, 12]. The most frequent medications achieving the target heart rate include beta-blockers (BBs) (metoprolol or carvedilol), Calcium channel blockers (CCBs), and digoxin [11, 12]. These agents are working by slowing AV node conduction [11, 12]. Beta-blockers (BBs) should be used with caution in patients with hypotension of CHF [11]. Calcium Channel Blockers CCBs can be used in AF patients with preserved left ventricular systolic function, and it has the safest profile in patients with obstructive lung disease [11]. Digoxin in the acute setting is relatively slow and ineffective in controlling heart rate [12]. Compared to BBs, CCBs have weaker AV nodal blockers and improve symptoms and quality of life in patients with CHF [11]. Amiodaron is indicated when both rate control and cardioversion are considered in patients with chronic AF [12]. Amiodarone is proven to improve ventricular rate control when added to digoxin [13]. Though, the long-term toxicity makes amiodarone a less attractive alternative for long-term rate control compared with BBs and digoxin [13].

Rhythm Control

In symptomatic AF patients, the mainstay of treatment is rhythm control, whether a new-onset emerged of recurrent of a persistent type [11]. The duration of AF must be kept in mind because studies have shown low sinus rhythm maintenance in patients with long-standing arrhythmia, and stroke prevention with anticoagulant must be carefully considered in regards to AF duration [11]. Patients with AF can be cardioverted without anticoagulation for less than 48 hours, as the risk of thrombus formation is extremely low [11]. While patients presenting with AF for more than 48 hours require to wither anticoagulation for 3 to 4 weeks before cardioversion or obtaining transesophageal echocardiogram-guided cardioversion [11]. Cardioversion is frequently used in addition to antiarrhythmic medications to achieve the maintenance of sinus rhythm, particularly in long-standing persistent or recurrent episodes of atrial fibrillation [11]. When rhythm control therapy is applied early after establishing the diagnosis of AF, it could suggestively protect atrial structures and function and maintain sinus rhythm [13]. A randomized clinical trial under phase 4 is currently investigating approximately 3,000 patients with recent onset of AF at risk of stroke (CHA2DS2VASc score>2) [13]. This trial referred to the Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST) and the aim to compare AF patients with a high risk of stroke under standard care and patients under early rhythm control therapy in a prospective, randomized, open, blinded outcome assessment trial [13]. EAST will conclude whether early rhythm controls treatment after establishing an AF diagnosis that can prevent cardiovascular complications associated with AF [13]. The types of antiarrhythmic drugs are beyond the scope of this review paper.

Thromboembolism Prevention

The basis of AF therapy in preventing stroke and systemic thromboembolic events is oral anticoagulation (OAC) [10]. The 2016 European Society of Cardiology (ESC) guidelines recommends starting OAC therapy upon assessing the individual risk of stroke based on the CHA2DS2-VASc score (shown in Table 3) [10]. If the patient has no contraindications, OAC therapy is recommended when the score>1 in male patients or >2 in female patients [10]. Vitamin K antagonists are the only OAC recommended for valvular AF patients (valvular AF referred to AF in the setting of moderate to severe mitral stenosis or in the presence of mechanical heart valves) [10, 14]. Non-vitamin K oral anticoagulants (NOAC), i.e., dabigatran (direct thrombin inhibitors), apixaban, rivaroxaban, and edoxaban (factor Xa inhibitors) are generally preferred in non-valvular AF [10, 14]. A recent meta-analysis concluded that NOACs reduce stroke and systemic embolism for valvular AF compared with warfarin, but with differences in risk of bleeding [14]. Four RCTs compared NOACs with warfarin [14]. NOACs were shown to be non-inferior to warfarin in terms of stroke and thromboembolic prevention, but superior in terms of safety profile [14]. They are recommended as a first-line treatment for suitable patients [14]. Betrixaban, a fifth NOAC that has not been proven to use in AF patients by the FDA [14]. All FDA approved NOACs for AF patients need dosing consideration by renal function (creatinine clearance using the Cockcroft-Gault equation) [14]. Apixaban has additional dose consideration for the age of over 80 years or weight less than 60 Kg [14]. Edoxaban is not approved for use in patients with decreased renal function (CrCL <30mL/min) or upper-range renal function (CrCL >95 mL/min) [14]. Additionally, the liver function test should be occasionally observed for the factor Xa inhibitors [14]. Apixaban accumulates in patients with chronic kidney disease on dialysis, and 2.5mg twice a day resulted in steady-state drug concentration compared to 5mg twice a day in patients with normal kidney function [14].

Table 3. CHA2DS2VASc Score

C: Congestive Heart Failure
H: Hypertension
A: Age >75 Years “2 Points”
D: Diabetes Mellitus
S: Prior Stroke of TIA “2 Points”
V: Vascular Disease
A: Age between 65 to 74
S: Sex Category

TIA: Transient Ischemic Attack.

Non-Pharmacological Management

Catheter Ablation: Catheter ablation in AF patients aims to isolate the pulmonary veins from the left atrium body [11]. This approach came to practice after discovering that the electrical impulses that trigger AF arise at the connection of the left atrium veins [11]. Catheter ablation is an adequate procedure to restore and maintain sinus rhythm in non-valvular AF patients [15]. Accumulated data have found that catheter ablation is more effective in maintaining sinus rhythm than antiarrhythmic drug therapy [15]. It can restore the sinus rhythm in up to 70% of paroxysmal AF patients, and 50% in persistent AF [15]. Radiofrequency catheter ablation (RFCA) approved by several randomized clinical trials to be superior to antiarrhythmic drugs [16]. Recent guidelines suggest RFCA as a second-line treatment for drug-refractory paroxysmal AF as a Class I indication, and Class IIa indication in paroxysmal AF patients without prior antiarrhythmic drug use [16]. Notably, a delayed diagnosis-to-ablation times (DATs) were shown to be associated with a lower rate of success for AF treatment [16].

Hypothetically, catheter ablation should reduce the risk of thromboembolic events simultaneously [15]. However, since there are not enough data on the exact incidence of thromboembolism following catheter ablation [15], the 2016 ESC guidelines for the management of AF recommend OAC after catheter ablation, regardless of the outcome rhythm [15]. Therefore, further randomized clinical trials are needed to establish the efficacy of catheter ablation in thromboembolism prevention in AF patients.

Percutaneous Left Atrial Appendage Closure:

Is a procedure performed by implanting a device into the left atrial appendage thought trans-catheterization to exclude it from the systemic circulation [17]? It may allow for alternative stroke prevention therapy, especially in AF patients with contraindications to OAC [17]. Interestingly, it has shown non-inferiority to warfarin for stroke prevention, with a reduction in the risk of major bleeding and mortality [17].

How is the procedure performed? Left atrial appendage closure is a transvenous trans-septal procedure performed under general anesthesia with the guidance of transesophageal echocardiography [17]. Once the place is secured in the left atrial appendage, the device is released and re-endothelialized throughout one to two months [17].

Conclusion

Atrial fibrillation is the most common cardiac arrhythmia worldwide. It is characterized by dysregulation of the sinus rhythm, commonly by abnormal impulses originating from the pulmonary veins. There are several types of atrial fibrillation, one of which is asymptomatic with paroxysmal attacks. Many contributing factors found to be associated with AF, but age is the single most important factor. Ischemic stroke and thrombotic events can be presenting following paroxysmal AF, and treating AF with rate, rhythm control, and anticoagulation can markedly prevent further thromboembolic events. Cryptogenic stroke represents a significant challenge to the healthcare system in terms of adverse outcomes and cost-effectiveness. Adequate anticoagulation, according to the CHA2DS2-VASc score, can successfully prevent thromboembolism with different kinds of OAC according to patient eligibility, with caution to the bleeding risk. Catheter ablation and left atrial appendage closure are new modalities of restoring the sinus rhythm. But, it is unclear whether or not these methods can prevent future thromboembolic events compared to OAC. Therefore, further randomized clinical trials are strongly needed to evaluate these modalities in regards of thrombosis prevention. Furthermore, we suggest establishing a new screening program for AF, particularly in the elderly population who have multiple risk factors to avoid ischemic stroke leading to life-long disability and decrease in the quality of life.

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