Atrial Fibrillation – A Common Ground for Neurology and Cardiology

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Abstract

Atrial fibrillation (AF) has a huge impact on clinical stroke because it is the primary cause of cardio-embolism, which constitutes ~20% of all strokes. As a result, there is a great need to explore safer and more effective primary and secondary prophylactic agents. In this article, we discuss the overlapping issues pertaining to AF from both a neurology and cardiology standpoint. We focus on the dynamic interplay of neurovascular and cardiovascular diseases in relation to AF, traditional and novel risk factors for AF leading to stroke, impact of AF on cognitive decline, and current upstream medical and surgical options for embolism prophylaxis.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and affects over 2.5 million Americans at a cost of over 7 billion dollars per year to Medicare alone.[1,2] The occurrence of AF is associated with a substantial increase in the risk of death, heart failure, and stroke.[3-6] It is considered to be a disease of the elderly, since half of all patients with AF are over the age of 75.

Risk factors for AF are diverse[7] and include advancing age, male sex, diabetes mellitus, hypertension, valvular disease, myocardial infarction, heart failure, obesity, elevated inflammatory marker concentrations, and PR-interval prolongation, as recently reviewed elsewhere.[8] Risk prediction models are important in order to define an individual's risk for AF, to identify novel risk factors for AF, to identify and assess potential targets of therapy, and to enhance the cost-effective implementation of therapies for both primary and secondary prevention of AF.

Embolic stroke in AF results from blood adhering to static atrial walls as rapid atrial electrical activity (400-600/minute) prevents normal mechanical activity of the atria. The risk of stroke in AF rises from 1.5% for persons aged 50-59 years to 23.5% for those aged 80-89 years.[5] It presents a 5 to6-fold increased stroke risk and accounts for at least one in every seven ischemic strokes. Importantly, 15% of all strokes are attributed to atrial fibrillation with the atrial appendage implicated as the likely source of emboli in these patients.[9] In addition to stroke , atrial fibrillation has been associated with abnormalities in the white matter (leukoaraiosis), which in turn has been associated with a higher incidence of cognitive decline and dementia.[10]

Optimal medical therapy for patients with AF include either rhythm control or rate control along with adequate anticoagulation; oral anticoagulation (OA) has proven to reduce the risk of ischemic stroke by 60% when compared to placebo and 52% fewer strokes when compared to aspirin; however both strategies are not ideal and still carry a stroke risk of 1% per year.[11] Furthermore, management of anticoagulation with Coumadin can be difficult. Even in monitored clinical trials, the therapeutic range for Coumadin is maintained only 44-83% of the time, and there is a 1-5% annual risk for major bleeding. Also, traditional OA therapy has some general misconceptions leading to underutilization in clinical practice. Recent FDA-approved OA and advancements in novel surgical therapeutics are undoubtedly shifting the paradigm of the management of AF

In recent years, there has been an explosion in interventional strategies to treat AF after the discovery by Haisaguerre that intermittent bouts of AF ("paroxysmal") are due to repetitive firing of ectopic foci located at the junction between the atria and smooth muscle of the pulmonary veins. A myriad of both catheter-based and minimally invasive surgical approaches have been introduced to isolate these pulmonary vein "triggers".[12] Minimally Invasive Surgical Pulmonary Vein Isolation (MISPVI) and atrial appendage ligation

Disclosures:
No disclosures relevant to this article were made by the authors.

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offer several advantages over medical therapy for patients in AF including: restoration of normal sinus rhythm for stroke prophylaxis, abolishment of the hot zones implicated in clot formation, and possible avoidance of anti-coagulation.

Cerebrovascular Risk Stratification in Atrial Fibrillation

Risk stratification using popular scoring systems to prevent future cerebrovascular events remains an important consideration in AF patients. These scoring systems are designed to predict clinical outcome and provide a framework to assess the appropriateness of intervention. $CHADS_2$ is the most commonly used scoring system and was recently modified as the CHA_2DS_2-VASc score for better risk stratification in low risk individuals. See Tables (1, 2, 3).[13] The $CHADS_2$, or the newer $CHADS_2$-VASc, scores are useful clinical tools in determining the appropriateness of initiating anticoagulation therapy.

Novel Risk Factors for AF and their Outcomes (Table 5)

Recent studies reveal a whole new set of emerging risk factors for AF that have received much less attention but may provide additional leverage to decrease the incidence of AF.

Genetic Basis of Familial Atrial Fibrillation: (Figure1)

Familial AF is an inherited condition that disrupts the heart's normal rhythm. The incidence of the familial form of atrial fibrillation is unknown; however, recent studies suggest that up to 30 percent of all people with atrial fibrillation may have a history of the condition in their family.[14] Several single nucleotide polymorphisms (SNPs) close to the PITX2 gene located on chromosome 4q25 strongly associate with AF,[15] especially with early-onset AF. As a follow-up to genome-wide association studies, Lubitz and colleagues did fine mapping of the 4q25 locus near PITX2 and genotyped 34 haplotype-tagging single-nucleotide polymorphisms in 790 case and 1177 control subjects from Massachusetts General Hospital and tested for association with AF[16] (Figure1). The PITX2 locus encodes a homeobox transcription factor of the paired type, previously identified to be of importance for the formation of embryonic pulmonary myocardial cells, the development of pulmonary myocardial sleeves, and the formation of a sinus node in the left atrium.[17,18]

Recent studies also show a familial predisposition for atrial fibrillation mainly due to the changes in the KCNE2, KCNJ2 and KCNQ1 genes.

Cognitive Impairment and Atrial Fibrillation

The role of atrial fibrillation in cognitive impairment and dementia, independent of stroke, is uncertain. Marzona et al. suggest cognitive and functional decline as an important consequence of atrial fibrillation, even in the absence of overt stroke. However, previous epidemiologic studies evaluating atrial fibrillation's association with cognitive function have been inconsistent.[19-21] Several researchers in the late 1970s became aware of an intriguing link between a sick heart and the start of cognitive deterioration that often led to vascular dementia.[22] This link came to be known as "cardiogenic dementia".
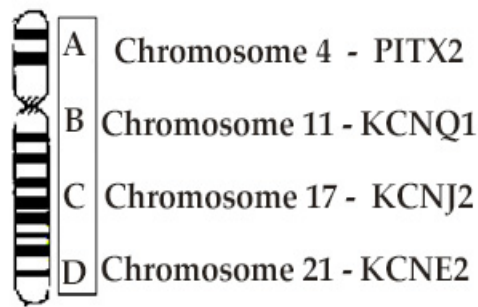
Common denominators leading to AF and cognitive decline:

1. Age and Gender: The risk of atrial fibrillation increases with age and is more common in males.

2. Diabetes: Diabetes in the elderly has been linked to cognitive impairment in cross-sectional case-control studies,[23] and impaired cognitive performance in diabetic subjects has been related to poorer metabolic control

3. Hypertension: The relationship between hypertension and cognitive impairment was strongest in men without antihypertensive treatment. High BP and impaired glucose metabolism[24] are both independent predictors of cerebrovascular disease. Recently, a large population-based study of persons 65 years and older in Cache, Utah, reported that the use of antihypertensive medication, including angiotensin-converting enzyme inhibitors, -blockers, calcium channel blockers, and diuretics, significantly lowered the risk of Alzheimer's disease (AD).[25]

4. Stroke: When stroke cases were included in the analyses previously described, the relationships between vascular risk factors and low cognitive performance remained almost identical.

5. Multivariate Analysis of different variables: In a multivariate model that included 24-hour DBP, p-glucose, p-insulin, M/I, s-triglycerides, BMI, HDL cholesterol, treatment, age, and educational and occupational levels, an increase of 24-hour DBP with 1 SD was associated with an odds ratio of 1.45 (1.20 to 1.75) of cognitive impairment. Despite higher DBP in treated men, antihypertensive treatment was associated with a decreased risk, i.e., treatment was a negative confounder.

6. BP circadian variability: Changes in BP circadian variability indicate alterations of central nervous regulatory systems, mediated by sympathetic activation. However, sympathetic over-reactivity could also be etiologically linked to the syndrome of hypertension and insulin resistance and primarily affect cognitive function by vasoconstriction and cerebral small-vessel lesions.

Table 1:	Popular Scoring Systems and their Correlation with Stroke Risk Prediction	
R i s k F a c t o r s	**S c o r i n g S y s t e m s**	
	$CHADS_2$ score	CHA_2DS_2-VASc score
Congestive heart failure	1	1
Hypertension	1	1
Age ≥ 75 years	1	2
Diabetes	1	1
TIA/stroke	2	2
Vascular Disease		1
Age 65-74 years		1
Sex: Female		1

Each risk factor is assigned points and the total score will be used to calculate the annual stroke risk incidence.

Table 2:	Popular Scoring Systems and their Correlation with Stroke Risk Prediction		
$CHADS_2$ score	**Annual Stroke Risk**	**CHA_2DS_2-VASc score**	**Annual Stroke Risk**
0	1.9	1	1.3
1	2.8	2	2.2
2	4.0	3	3.2
3	5.9	4	4
4	8.5	5	6.7
5	12.5	6	9.8
6	18.2	7	9.6
		8	6.7
		9	15.2

Figure 1: Chromosomes and their Genetic Association

The diagram depicts representative chromosomes and genetic polymorphism locations enrolled in the familial predisposition for AF. **A**: PITX2 Gene on the long (q) arm of chromosome 4 , **B**: The KCNQ1 gene is located on the short (p) arm of chromosome 11, **C**: The KCNJ2 gene is located on the long (q) arm of chromosome 17 , **D**: The KCNE2 gene is located on the long (q) arm of chromosome 21.

Novel Risk Factors Leading to AF and Cognitive Decline:

1. Genetic factor: Carriers of the ApoE4 allele may be at a higher risk for cognitive decline because, among other things, the presence of this gene predisposes an individual to an increased risk of cardiovascular pathology.[26] Aside from sharing many environmental risk factors for AD and for cardiovascular disease, there appears also to be an overlap between genetic risk factors for both conditions. For example, the ApoE4 allele, a well-studied risk factor for AD, can increase the risk of coronary heart disease by approximately 40%.

2. Ejection Fraction or Cardiac Output: There is mounting epidemiologic evidence that AD is associated with an increased risk of symptomatic left ventricular dysfunction (LVD).[27] LVD produces many changes in the structure and function of the heart through a variety of mechanisms. It can lead to reduced ejection fraction, heart failure, heart attack, and other cardiovascular complications. When ejection fraction dropped below 30%, patients older than 63 years showed a significant decline in memory performance, specifically, a delay in verbal recall and recognition. In comparison, those younger than 63 years were able to maintain stable memory function or similar ejection fraction levels.[28]

3. Valvular Heart Disease: Autopsy findings have reported significant aortic and mitral valve damage in AD subjects when compared to a non-demented control group. This association between valvular damage and AD is consistent with the presence of brain hypoperfusion at an early stage of AD pathology,[29] or even prior to AD-- an observation that supports previous findings

4. Coronary artery disease and heart failure: The risk to AD could stem primarily from atherosclerotic coronary vessels that damage endothelial cells and lower the heart's pumping ability to optimally perfuse the brain. This theory is supported by the presence of high levels of cholesterol, low density lipoprotein, and triglycerides found in the blood of probable AD subjects.

5. Hypotension and Brain Hypoperfusion: Low diastolic blood pressure is associated with an increased risk of AD in the elderly population, particularly among users of antihypertensive drugs. While the reason for this finding is not clear, undetected cerebral hypoperfusion could explain the pathogenic link of hypotension to cognitive decline and AD.[30] Cerebral blood flow is known to decline with age. However, under normal circumstances, in the absence of vascular disease, it will not result in significant cognitive loss.[27] To appreciate the clinical importance of developing suboptimal brain blood flow during advanced aging, it is important to point out that within the last few years, chronic brain hypoperfusion has been reported to be a preclinical condition to mild cognitive impairment and an accurate indicator for predicting whether people will develop AD.[31,32]

6. A few risk factors of atrial fibrillation are either completely reversible (smoking, alcohol consumption, especially binge consumption, sleep apnea due to obesity, and some infections that may predispose to occurrence of atrial fibrillation), or partially modifiable (Endocrine causes such as hypothyroidism and Diabetes mellitus, hypertension).

Stroke Prophylaxis (Please See Figure 2):

Rate Versus Rhythm Control: Is Rhythm Control Sufficient as a Stroke Prevention Tool?

Rhythm control does not seem to have any additional protection against stroke.[11,33] Most antiarrhythmic drugs (AADs) only provide sinus rhythm maintenance about 25% of the time after 12 months of use. As a result, pharmacotherapy in AF is targeted at rate control. In the absence of complicating features, rate control is usually achieved with either blockade of calcium channels (dilitazem, verapamil) or beta receptors. Digoxin has a role in the treatment of AF when there is co-existent heart failure. In patients with poor left ventricular function, amiodarone may be used.

Once rate control and hemodynamic stability are achieved and secondary causes of AF have been evaluated, the clinician must address the potential need for cardioversion. Patients who are symptomatic with new onset AF warrant an attempt with pharmacological or electrical cardioversion to restore sinus rhythm. Patients with an elevated bleeding risk should not be cardioverted if anticoagulation cannot be initiated prior to or following the return to normal sinus rhythm (NSR). Additionally, risk associated with cardioversion may outweigh the benefit in many patients, especially elderly asymptomatic patients with a larger number of co-morbidities.[34]

In the management of AF, it is imperative that the clinician identify situations indicating the need for immediate cardioversion. Pharmacological or electrical cardioversion is indicated in the following scenarios: electro physiologic or clinical evidence of ischemia, any evidence of organ hypoperfusion, severe manifestations of heart failure, or presence of a pre-excitation pathway.

In these situations, the hemodynamic stability that is provided by return to NSR outweighs the thromboembolic risk. And although prompt initiation of heparin is of the upmost importance, it should not delay cardioversion. However, if new onset AF has been present for greater than 48 h, transesophageal echocardiogram (TEE) is recommended prior to cardioversion because of the increased risk of LA thrombus. In the setting of a LA thrombus or inability to perform

Table 3:	Each Risk Factor is Assigned Points and the Total Score will be used to Calculate the Annual Stroke Risk Incidence.	
CHADS$_2$/CHADS$_2$-VASc Scores	Risk	Management
Score: 0	Low Risk	Antiplatelet
Score: 1	Moderate Risk	Aspirin or OA
Score: 2 and above	High Risk	OA
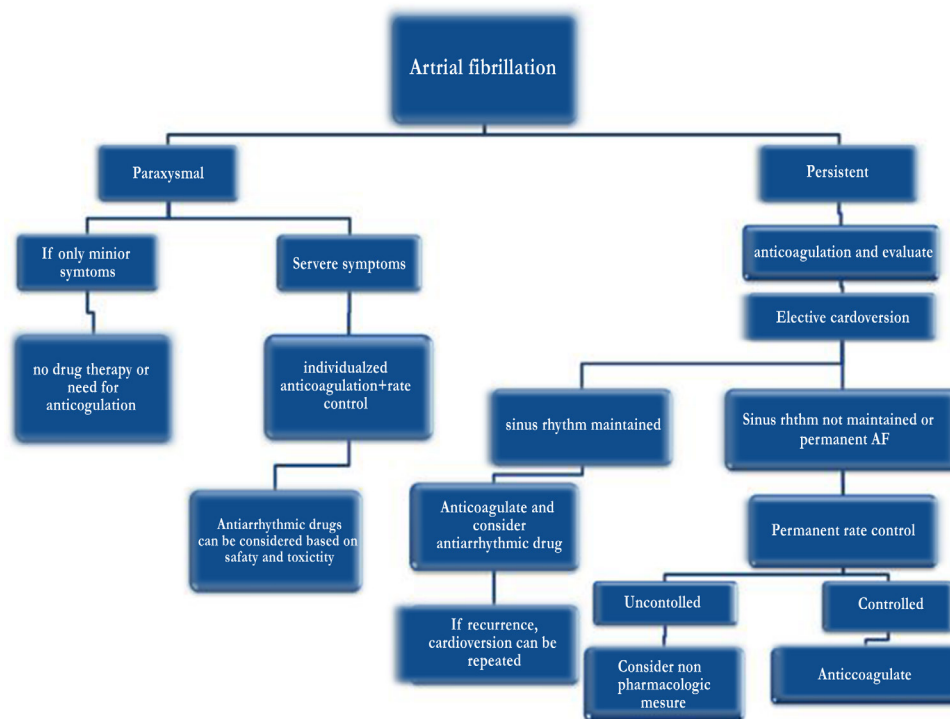
Figure 2:   Clinical Approach to Atrial Fibrillation

TEE, anticoagulation with heparin for at least three weeks prior to cardioversion is needed to allow for resolution of thrombus. The goal of anticoagulation prior to cardioversion is to prevent embolic shed from preexisting thrombus. Additionally, even if AF has been present for less than 48 h, delayed cardioversion with anticoagulation may also be indicated, especially if there is a history of thromboembolic events or if there is a significant history of heart failure, mitral valve disease, or cardiomyopathy.[34,35] Continuous oral anticoagulation is the cornerstone of stroke prevention in AF patients and relies on adequate delivery of anticoagulant therapy, such as achieving therapeutic INR values.[36] But even on optimal anticoagulant therapy in controlled trials, the residual stroke rate in AF patients remains unacceptably high at ~1.5% per year.

Almost all available studies so far have investigated the effect of anticoagulant therapy in patients with established AF, which is often chronic. The long-term impact of 'transient' AF (e.g. post-operative AF) and of 'silent' AF is much less well studied even though short episodes of AF can affect stroke risk. Based on this information, it appears unlikely that rhythm control therapy alone can be sufficient to prevent AF-related strokes. Nonetheless, treatment with dronedarone is associated with reduced stroke rates in the ATHENA trial. Whether this effect was related to preventing AF is not clear. There are two surveys after ablation of AF (n= 750 and 3300 patients) that detected low stroke event rates in patients who discontinued anticoagulation. The authors of those studies propose that stopping anticoagulation may be acceptable, but the stroke risk in these populations and follow-up times was not sufficient to accrue adequate stroke numbers. This is especially important when considering the reports on very late recurrences of AF after ablation. Hence, rhythm control does not appear to be sufficient in preventing strokes in AF patients in the absence of oral anticoagulation. On the other hand, rhythm control therapy could very well contribute to reduce residual stroke rates in patients on anticoagulation.

In summary, rhythm control alone is not sufficient in reducing mortality associated with cardiac cause, but rate control does seem to reduce mortality in AF patients, especially those with congestive cardiac failure.[37]

Anticoagulation

The clinical goal in the management of AF is to reduce the risk of cardio embolic events. This can be achieved by chronic anticoagulation which prevents thrombus formation in the LAA, the most favored location of thrombi formation. Historically, chronic anticoagulation has been the mainstay in the treatment of AF among patients with moderate-to-high risk of subsequent stroke and TIA (based on aforementioned clinical risk stratification). It is recommended that low-risk patients and those with contraindications to anticoagulation be managed with 81–325 mg Aspirin daily. The warfarin related annual risk of a fatal bleed is 0.6%, risk of major bleed is 3%, and risk of combined (major or minor) bleed is 9.6%. This represents a fivefold increase risk as compared to those without anticoagulation.[38] The AFFIRM trial first reported that combined rate control with anticoagulation improved survival and reduced stroke risk when compared to rhythm control. Chronic anticoagulation is usually achieved with Coumadin while maintaining a target INR of 2-3.

With the frequency of AF expected to double by 2050, there has been a large push by the medical industry to find alternatives to warfarin that are cost-effective, clinically practical, simple for patients, and free of frequent monitoring requirements.[39] Newer oral anticoagulants have since been introduced as attractive alternatives to warfarin.

Most notably in October 2010, dabigatran (Pradaxa), a direct thrombin inhibitor, received FDA approval for the treatment of stroke prevention in AF. Its major advantage is the lack of INR monitoring that is normally required with Coumadin. Dabigatran

etexilate is a prodrug of dabigatran, independent of CYP-450 and a potent nonpeptide molecule that reversibly inhibits thrombin by binding to the active site of the thrombin molecule. The half-life of dabigatran has been estimated to be 12–14 h.[40]

Novel Anticoagulants

Dabigatran (Pradaxa): In the RE-LY study, compared to warfarin, taking dabigatran 150 mg orally twice a day was found to decrease the risk of stroke or systemic embolism. The dose provided a relative risk reduction of 34% and an absolute risk reduction of 0.58%, with no increase in the risk of major bleeding and a decrease in the risk of hemorrhagic stroke.[41] On the other hand, dabigatran 110 mg twice a day dose was noninferior to warfarin for stroke prevention. At this dose, dabigatran was associated with a decreased risk of major bleeding and hemorrhagic stroke except for major gastrointestinal bleeding, which was more common with dabigatran 150 mg twice daily than with Coumadin.[42] Dosing is adjusted as per the patient's renal function to account for decreased clearance among patients with severe renal impairment.

Rivaroxaban (Xarelto): is an oral competitive factor Xa inhibitor which targets factor Xa, a common factor in both the extrinsic and intrinsic coagulation pathway. It was recently (2011) approved for stroke prevention in nonvalvular atrial fibrillation. The landmark trial ROCKET-AF demonstrated that it was as effective as warfarin in reducing stroke while carrying a similar overall bleed risk and decreased risk of intracranial and fatal bleeds.[43] Like dabigatran, the recommended dose of Rivaroxaban is adjusted in patients with renal impairment, but dosing is once daily.

Apixaban (Eliquis): is another oral factor Xa inhibitor which got FDA approval (2012) that has been compared to both ASA and warfarin for stroke prevention in AF. In a randomized controlled trial of patients considered unsuitable for warfarin therapy, a dose of apixaban 5 mg, orally twice a day, was more effective than Aspirin for prevention of stroke or systemic embolism. The result was a 50% relative risk reduction and a 2.1% absolute risk reduction in the primary outcome and no observed increase in the risk of major bleeding.[44] A reduced dose of apixaban (2.5 mg twice a day) was used for individuals aged over 80 years or with a serum creatinine greater than 1.5 mg/dL. In another randomized controlled trial, apixaban 5

mg twice daily was more effective than warfarin in reducing the risk of stroke or systemic embolism, with a relative risk reduction of 21%, an absolute risk reduction of 0.33%, and a decrease in the risk of major bleeding and hemorrhagic stroke.[45]

Limitations for Using Novel Oral Anticoagulants

1. Inability to monitor its effect with lab tests (such as INR) and dosing concerns in the setting of renal impairment generates some uncertainty with respect to physiologic impact.

2. Lack of reversibility pose a clinical dilemma, particularly when patients on newer OA present with ischemic stroke and consideration is given to administer intravenous thrombolysis. The current belief, based mainly on expert opinion, is if patients are on newer anticoagulation and have been off medication for 2 days, then it might be safe to receive thrombolysis in the setting of acute ischemic stroke. However, newer OA medications provide the clinician an opportunity to initiate them in people who are reluctant to take older anticoagulants, due to the complexities discussed earlier, for primary or secondary stroke prophylaxis. This can contribute not only to greater disease control, but greater patient compliance and satisfaction.

3. Reversal of bleeding complications: In cases of dabigatran-related ICH, no specific antidote exists and activated charcoal can be used if ingested within 2 h. More likely, rVIIa 60–90 μg/kg or PCC 50 u/kg may be used in an attempt to reverse anticoagulation. In cases of Rivaroxaban associated ICH, there is no specific antidote, and the half-life of the drug is 5–9 h. PCC can be considered in the management of intractable bleeding with a recommended dose of 50u/kg.[46]

4. Higher risk of GI bleeds with newer anticoagulants.
hemorrha

Surgical Management

various surgical techniques have been developed in the last 25 years that play a complementary role in the treatment of AF.

1. The Maze procedure (or Cox-Maze III) has been established as the gold standard for surgical approaches in patients with AF.[47,48] The basic principle is to create multiple right and left atrial (LA) incisions in an organized manner to interrupt rogue reentrant circuits and simultaneously guide electrical impulses to the AV node. The Maze procedure also includes removal of LAA and isolation of the pulmonary veins.[48] Operative site exposure provided by this open approach can be used for additional interventions such as valvular repair or bypass during the same procedure. This procedure also requires the patient to be on cardiopulmonary bypass and undergo median sternotomy. The Maze procedure has been successful at long-term elimination of AF with 93% success rate after 8.5 year follow-up.[47] Thoracoscopic approaches to the Maze procedure have also been introduced to reduce the invasive nature of the procedure. While introducing higher surgical costs, this approach offers decreased length of stay and decreased post-operative recovery time, with an efficacy similar to the traditional MAZE procedure.[49] While the traditional MAZE procedure is performed with physical interruption of electrical pathways by incisions, a number of novel energy sources, such as laser, ultrasound, and radiofrequency, have since been employed to create tissue scarring more rapidly and safely than "cutting and sewing."

2. Radiofrequency ablation is now available as an additional

Table 4:	Traditional risk factors for AF and their Outcomes	
	Traditional Risk Factors	**Incidence; hazard ratio and other information**
1	Age	Age is one of the key risk factors for AF, hazard ratios range between 1.1 and 5.9 per decade of age. [14-16]
2	Gender	Males have a slightly higher preponderance for AF. [67-71]
3	Endocrine	Diabetes mellitus and hyperthyroidism have been recognized as independent risk factors for AF. Blood glucose RR is 1.08 (95% CI=1.03-1.13) .[68]
4	Hypertension	The higher the blood pressure, the greater the risk of AF with a RR of 1.11 (95% CI=1.05-1.18). [68]
5	Congestive Heart Failure (CHF)	CHF is not well defined or used in a broad sense .[72]
6	Valvular Heart Disease (VHD)	VHD is associated with the development of AF and has RR=2.42 (95% CI=1.62-3.6). [68]
7	Toxic and Environmental factors	ETOH abuse and possibly moderate alcohol consumption and smoking are well-established risk markers for AF. [17,24]

ablative technique that has been used in conjunction with the traditional Maze approach, often referred to as the modified Maze procedure, or Maze IV.[12,50] Radiofrequency is also available as a standalone procedure that can be performed through a thoracoscopic or catheter-based approach.

Catheter-based radiofrequency ablation with the intent to achieve NSR by eradicating the faulty electrical pathways in a manner that is far less invasive than sternotomy or thoracoscopy is also available. Many consider catheter-based ablation to be minimally invasive and highly efficacious, but the data suggest a low rate of success of about 30% from a single procedure and 80% with repeat procedures.[50]

3. Cryoablation can be employed through both a catheter-based approach or in conjunction with the Maze or minimally invasive Maze procedure. In cryoablation, tissue is cooled with helium or argon to low temperatures (-50 to -75°C) in order to induce targeted scarring. Compared to other ablative techniques, cryoablation prevents vascular/collagen damage and lessens peripheral tissue damage.[51]

4. High-frequency ultrasound, another ablative technique, scars cardiac tissue in a trans-mural fashion through hyperthermic lesions. This can be performed through a catheter-based approach in a quick manner that offers the potential for wall visualization given the nature of the technology. However, this approach carries the risk of delivering hyperthermic stress to adjacent tissues. Esophageal or mediastinal injury has been reported following ultrasound and radiofrequency ablation.[52]

5. Microwave ablation has been similarly used to produce thermal injury to cardiac tissue and is capable of producing a trans-mural lesion when it is applied to the epicardial surface via a thoracoscopic approach. However, both microwave- and laser-based ablations have been taken off from the market in recent years due to poor efficacy.

6. Appendage closure devices: The left atrial appendage (LAA) is a remnant of the left atrium (LA). Embryologically, the LAA arises from the pulmonary veins and normally consists of a trabeculated, 2–4 cm long, tubular structure that is in direct continuity with the LA cavity.[9] Its unique anatomy allows predisposition for in-situ thrombus formation. Failure of the fibrillating atrium to contract is believed to lead to atrial stretch and dilatation, thus promoting stasis and thrombus formation inside the LAA.[53] The LAA is the site of the majority (up to 91%) of thrombi in patients with non-rheumatic AF. In fact, 98% of arterial thrombi were found in the LAA through TEE trials involving 1181 patients.[54] This led to the technique of LAA occlusion as a means of reducing the risk of stroke in AF. Surgical ligation or excision of the LAA is considered the standard procedure of care in patients who undergo mitral valve surgery or as an adjunct to a surgical Maze procedure for treatment of AF. In addition, in selected patients with AF and an elevated risk of thromboembolic events, particularly in those with contraindication to oral anticoagulation (OA) therapy, it is reasonable to consider LAA exclusion to offer protection against ischemic stroke and other embolic complications. Although results from several recent percutaneous LAA closure and ligation studies are promising, the

	Novel Risk Factors	Important Characteristics
	Table 5:	**Newer Modifiable and Non-Modifiable Risk Factors: Description of the Novel Risk Factors and their Implications in AF.**
1	Genetic	Details are discussed below in section "Genetic Basis of Familial AF".
2	Ethnicity	African Americans appear to be at lower risk of AF than Caucasians. Risk of AF was 25% lower in blacks than Caucasians (HR 0.75, 95% CI=0.64-0.87) .[73]
3	Sleep apnea syndrome	Sleep Apnea Syndrome is associated with obesity, which in turn increases AF risk .[70]
4	Pericardial Fat	Increased epicardial fat is linked with increased AF persistence independent of other risk factors .[74]
5	Blood Pressure in Non-hypertensive Range.	Data regarding the risk of AF at lower blood pressure levels are sparse. An analysis of 34,221 women participating in the Women's Health Study showed that blood pressure was strongly associated with incident AF, and systolic blood pressure was more strongly related to AF incidence than diastolic blood pressure.[75]
6	Subclinical Coronary Artery Disease	Nucifora et al. [76], however, used multislice computed tomography to detect asymptomatic coronary artery disease. Eighteen percent of patients with AF were classified as having no coronary artery disease, whereas 41% showed non-obstructive coronary artery disease, and the remaining 41% had obstructive coronary artery disease compared with patients without AF (P=0.01).[76]
7	Physical Activity	Physical activity is associated with a 3 to 5 mm Hg reduction in systolic blood pressure .[77] a reduction in body weight and body mass index [78], and the prevention of coronary heart disease, suggesting that exercise may reduce the incidence of AF.
8	Chronic Kidney Disease	Patients with chronic kidney disease are at higher risk for coronary heart disease and heart failure.[79] Alonso et al. [80] sought to examine the risk between chronic kidney disease and AF in 10,328 men and women from the Atherosclerosis Risk in Communities study. They found that impaired kidney function and presence of albuminuria were strongly associated with the incidence of AF.
9	EKG-base parameters	EKG-based parameters such as long (within the normal range) or prolonged PR interval clearly relate to AF in the population, and possibly relate to atrial structural remodeling and delayed intra-atrial conduction[81]
10	Left Ventricular Diastolic Dysfunction	Atrial fibrillation and left ventricular diastolic dysfunction share multiple risk factors, including aging and hypertension [82]. Because diastolic dysfunction causes atrial pressure and volume overload, atrial structural remodeling is common among patients with abnormal diastolic parameters. More recently, investigators of the Cardiovascular Health Study examined echocardiographic parameters of diastolic function in 4,480 older adults and reported that Doppler peak E-wave velocity and left atrial diameter were positively and nonlinearly associated. Doppler A-wave velocity time integral displayed a U-shaped relationship with the risk of AF. [83]
11	Biochemical and structural association	A. Serum biomarkers: Biomarkers can be potentially used as novel instruments to enhance AF risk prediction and to provide insights into the pathophysiology of the disease, and may help to identify novel targets for therapy. B-type natriuretic peptide (BNP) Even though BNP is traditionally investigated as a biomarker for heart failure, elevated levels have been reported in patients with incident AF [84,85]. In the Cardiovascular Health Study, a community-based population of 5,445 older adults, N-terminal proBNP was a strong predictor of incident AF, adjusting for other risk factors (adjusted HR, 4.0; 95% CI, 3.2–5.0; P<0.001) [86]. Blood lipids: are established risk factors for coronary artery disease, which may precede incident AF. B. Functional imaging: Echocardiographic estimators of left atrial size is 'integral' to measure the degree of left atrial structural changes over time, and thereby relate to incident AF or to AF-related complications, including death. Left atrial size or volume and left ventricular mass may predict AF and AF-related mortality.

evidence for long-term efficacy and safety is insufficient to presently recommend this approach to all patients other than those in whom long-term OAC is contraindicated.

Prevention of AF-Related Stroke: OAC versus LAA Devices?

Pharmacologic therapy, even when greatly effective in reducing the AF burden, has consistently failed to demonstrate a reduction in the stroke risk in patients with AF.[11] Thus, OAC therapy with agents such as warfarin and recently, newer agents, remains the mainstay of therapy in treating these patients. Nonetheless, OAC does not come without significant risk. Recipients of OAC, with either warfarin or any of the newer OAC agents, remain at risk for hemorrhagic stroke and life-threatening bleeding (i.e., gastrointestinal, etc). In addition, those treated with warfarin generally require close outpatient monitoring as well as significant lifestyle modifications largely due to the drug's narrow therapeutic window, requirement for dietary restrictions, and potential for drug-drug interactions.

These therapeutic limitations coupled with the severity of AF-related systemic embolic events have led to a great deal of interest in developing novel therapeutic strategies and the concept of LAA exclusion as a means of reducing stroke and other embolic complications in patients with AF.

•Percutaneous Endovascular LAA Occlusion

There are three devices, include the Percutaneous LAA Transcatheter Occlusion (PLAATO, EV3, Plymouth, MN, USA), the Amplatzer Cardiac Plug (AGA Medical, Plymouth, MN, USA), and the WATCHMAN LAA system (Atritech Inc., Plymouth, MN, USA). These devices are delivered via a transseptal puncture approach generally under transesophageal and/or intracardiac echocardiographic guidance.

1. The PLAATO device consists of a nitinol cage coated with an impermeable polytetrafluoroethylene that is sealed within the LAA, rendering thrombus formation obsolete, and designed to occlude the orifice of the LAA. The first human implantation of the PLAATO device was described in 15 patients with permanent AF with contraindications to OAC therapy.[55] LAA occlusion proved successful in all patients, and there were no complications or embolic events at 1 month follow-up. More recently, the long-term efficacy of the PLAATO was described by Ussia et al., who reported no embolic events at a mean follow up of 40±10 months.[56]

2. The Amplatzer device was initially developed for atrial septal defect closure. The amplatzer system was not evaluated further for LAA closure because a new system (the Amplatzer Cardiac Plug) specifically designed for occlusion of the LAA was subsequently introduced. The device is constructed from a nitinol mesh and Dacron, and consists of a lobe and a disk connected by a central waist. There are 12 stabilizing wires equally spaced about the main disc. The lobe is designed to conform to the inner wall of the LAA with a depth of 10 mm or more, and provides secure device placement and retention with the stabilizing wires. The size of the device should be at least 2 mm larger than the LAA landing zone diameter.

The WATCHMAN device consists of a nitinol frame that is coated with a permeable polytetrafluoroethylene membrane. This frame self-expands when deployed within the LAA, but unlike the PLAATO device, it remains permeable to blood, so once endothelialized the device will eliminate thrombus formation. Until that time, about 45 days following the procedure, the risk of thrombus formation and dislodgement remains and conventional prophylaxis is required. The

PROTECT AF trial was a multicenter prospective randomized study that sought to document the effectiveness of the WATCHMAN implant when compared to control patients solely based on long-term warfarin. The primary endpoint included hemorrhagic or ischemic stroke, cerebrovascular death, systemic embolism, documented TIA, and life-threatening bleeds requiring transfusion. Control patients were maintained at an INR between 2 and 3 and were re-evaluated at 45 days and 6, 12, 24, 36, 48, and 60 months. Patients that underwent the WATCHMAN implantation and had an INR below 2 were prescribed aspirin 81mg at least 1 day before procedure. These patients were back on therapeutic levels of warfarin until a 45-day post-op TEE showed LAA occlusion, suggesting lack of flow through the implant and jet flow of less than 3 mm around the device. Warfarin was then discontinued, and clopidogrel 75 mg and ASA 325 mg were then administered for the duration of the trial. An article in the Lancet (Aug 2009) reported the results of 707 eligible patients. Over 1065 patient-years follow up; primary efficacy was 3.0 per 100 patient years in the WATCHMAN group and 4.9 per 100 patient years in the warfarin control group, which was a statistically significant noninferiority of more than 99.9%. More primary safety events occurred in the WATCHMAN implant group 7.4 per 100 patient-years vs. 4.4 per 100 patient-years in the control group. Authors note that these safety events were a result of peri-procedural complications.[57] Evidence for the noninferiority of the WATCHMAN device suggests that LAA occlusion may be an alternate option to warfarin therapy. However, the FDA has not yet approved release of the WATCHMAN device.

Benefits of the Endocardial Approach of these Devices

1. Compared to the conventional surgical approach, there is a reduction in recovery time and bleeding risk, combined with the advantage of eliminating the need for long-term anticoagulation.[58]

Risks of above 3 Devicess

1. Implantation of LAA occlusion devices is associated with a learning curve that is inversely related to the complication rate of the transseptal puncture approach. Complications such as pericardial effusion, cardiac tamponade or air embolization may arise. The rate of major pericardial effusion and tamponade was 50 % higher at less-experienced centers, as noted in the PROTECT-AF study.[58]

2. Acute ischemic stroke due to air or thromboemboli, sepsis, vascular perforation, or device embolization can also occur.

3. Endovascular and device-related infection.

4. Antithrombotic therapy post-LAA occlusion.

5. Incomplete LAA Occlusion: Incomplete LAA occlusion is one of the major concerns with surgical LAA occlusion. A study by Kanderian et al. revealed that only 40% of patients had complete occlusion of the LAA.[59] Similarly, a meta-analysis of surgical LAA occlusion also revealed an occlusion rate of 55%-66% by surgical techniques. Patients with incomplete occlusion may be at an increased risk.[60] In a series of 50 patients who had mitral valve surgery and concomitant LAA ligation, 18 patients (36%) had incomplete closure by TEE. Nine of these patients (50%) had spontaneous echo contrast or thrombus in the LAA, and 4 of the 18 patients had thromboembolic events.[61]

•Novel Approach: Percutaneous Epicardial LAA Ligations

More recently, Bartus et al. reported on the first human experience of a closed-chest, percutaneous, epicardial catheter-based LAA

ligation technique using the LARIAT snare device (SentreHEART Inc., Palo Alto, CA, USA).[62] This technique involves a combined endocardial and percutaneous subxiphoid epicardial magnet-tipped wire-guided approach to 'snare' and ligate the LAA at its ostium. In the initial report, 10 of the 11 patients successfully underwent acute LAA ligation using this novel approach (nine with percutaneous epicardial access and two with simultaneous open surgical MV replacement).[62]

Follow-up data was available in six patients at 60 days, of whom four continued to demonstrate successful and complete LAA closure. Two patients had reopening of the ostial closure up to 2 mm. No data are presently available regarding whether small gaps in the ostial LAA closure are clinically relevant to long-term risk of stroke. A potential advantage of this strategy is the lack of need for OAC immediately following the procedure.

The Atriclip is one such clip that was recently evaluated with regard to safety and effectiveness. The Atriclip was approved by the FDA to be applied epicardially via a median sternotomy approach at the time of mitral valve or bypass surgery. However, surgeons have begun to use the clip off label via thoracoscopic port access procedures. The LAA Atriclip system consists of a titanium core frame with nitinol springs on each end and is covered with a polyester fabric sleeve. The device is currently available in a number of sizes to account for the variability in LAA size. When closed, the clip applies uniform pressure over the length of the two parallel branches to ensure consistent, secure occlusion of the LAA. This device can be easily deployed during other cardiac procedures that are being performed through a sternotomy. In fact, The ACC and AHA have recommended that LAA ligation be performed during the course of valvular surgery. The Atriclip provides an effective option to achieve this goal. Out of 61 patients that underwent CT imaging follow-up at 6 months,[60] (98%) were confirmed to have absence of LAA thrombus, clip stability, and successful LAA closure.[63] Another clinical study of 34 patients utilizing a LAA clip showed that none of the patient mortalities were linked to use of the surgical device.[64]

Benefits of Epicardial Devices

1. Unlike intracardiac implants that require anticoagulation to protect against thrombus formation while endothelialization occurs, the LARIAT snare device and Atriclip can offer immediate LAA closure without implantation of a foreign object inside the LA.

2. In addition, it may also overcome the potential complications related to implantable devices such as cardiac perforation, erosion, and device migration and embolization.

Risks of Epicardial Devices

1. The main procedural limitation of this approach is the requirement to obtain epicardial access in all patients – a technique that is not familiar to many operators, and one that is often not possible in patients with a prior history of cardiac surgery and those with pericardial adhesions. There are also anatomical considerations with respect to successful ligation of the LAA using the LARIAT snare device or Atriclip.

2. Also, in patients with superiorly orientated LAA lobes or posteriorly rotated hearts, there is a chance that the entire LAA may not be completely captured by the snare, once again leading to incomplete LAA closures.

3. The LARIAT snare loop is able to expand to a maximum diameter of 40 mm, which is believed to accommodate LAA sizes in about 90 % of patients. Thus, in patients with larger LAA diameters, successful ligation of the LAA may not be possible.

Indications of Percutaneous LAA Occlusion

1. Hemorrhagic complications of OAC therapy remain a significant clinical problem, especially in the elderly.[65] The high mortality of warfarin-associated Intracerebral Hemorrhage (ICH) (50% vs. 10% for ischemic stroke) strongly impacts the life expectancy of AF patients taking OAC. Usually, OAC is reversed immediately after ICH, but the decision to resume OAC after an ICH is complicated and may depend on the location of the hemorrhage and additional risk factors. So in patients with previous ICH, percutaneous LAA occlusion may be considered as an alternative to the use of novel anticoagulants.

2. Recurrent GI bleeding: Gastro-intestinal (GI) bleeding is the most common type of extracranial bleeding in AF patients receiving either warfarin or novel OAC drugs.[43] In the setting of intestinal angiodysplasia, overanticoagulation is an independent risk factor for recurrent bleeding (odds ratio: 4.1).[66] As a result, initiation of OAC in patients with an increased risk for GI bleeding or continuation after OAC-associated GI bleeding with well-controlled anticoagulation is questionable.

3. Recurrent ischemic stroke despite well-controlled therapeutic OAC: Percutaneous LAA occlusion may be considered after exclusion of other sources of embolism.

4. Coagulopathies: Low platelet counts, myelodysplastic syndrome.

5. Co-morbidities: Uncontrolled hypertension, cerebral microbleeds, cerebral amyloid angiopathy.

6. Intolerance to new OA drugs: GI intolerance, severe liver and kidney dysfunction, and vitamin K antagonists are the first signs to consider.

Conclusions:

The traditional risk factors for AF do not explain all cases of AF. Present risk stratification tools for AF are an important step forward. However, future research is needed to determine the extent to which novel risk factors are associated with AF. There is some evidence that AF may be associated with cognitive decline and dementia, but this link should be supported by more powerful, long-term longitudinal studies. AF carries a significant risk of cerebral embolism; therefore, anticoagulation plays a vital role in mitigating this risk. Although oral anticoagulation with warfarin remains the standard of care and is effective, it is limited by adverse effects like major and minor bleeding and difficulties achieving an adequate therapeutic level of anticoagulation. However, clinicians can now turn to newer options that have been well-studied for their safety and efficacy in recent clinical trials. For example, FDA-approved alternative anticoagulants, which act by direct thrombin and factor Xa inhibition, have demonstrated comparable results to warfarin. Literature in recent years has shown atrial fibrillation is often initiated by ectopic foci in the pulmonary veins. Accordingly, there have been an increased number of catheter-based and minimally invasive surgical approaches to isolate the pulmonary vein "triggers" and ablate foci in the left atrium responsible for AF. Percutaneous LAA occlusion offers an alternative for physicians who are facing a complicated risk–benefit analysis in deciding if AF patients should receive OA who are at risk for both stroke and bleeding. Increasing

the awareness of possible therapeutic options across relevant medical disciplines may improve stroke prevention strategy for patients who are currently inappropriately protected.

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