Thromboembolism in the Absence of Atrial Fibrillation

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Atrial fibrillation (AF) is associated with thrombus formation in the left atrial appendage and systemic embolic events including ischemic stroke. Cardiogenic thromboembolism can also occur in the absence of clinical AF as a result of various pathological conditions affecting the endocardium. The inconsistent temporal relation between AF and ischemic events has stimulated exploration for factors other than clinical AF that contribute to thromboembolism. These include subclinical AF, a thrombogenic atrial cardiomyopathy, and left atrial appendage dysfunction and embolism from other sources. In conclusion, thromboembolism during normal sinus rhythm is likely multifactorial, involving intertwined pathologic processes. Patients at risk, if accurately identified, could theoretically benefit from anticoagulation. **(Am J Cardiol 2019;124:303−311)**

Patients with atrial fibrillation (AF) face a risk of thromboembolism and ischemic stroke, as well as other causes of morbidity and mortality. Current concepts of pathogenesis hold that stasis during AF predisposes to thrombus formation in the left atrium (LA) or left atrial appendage (LAA) and that migration of thrombus into the systemic circulation is responsible for most cases of ischemic AF-related stroke. Counterintuitively, in those with paroxysmal AF, thromboembolism can occur during periods of normal sinus rhythm (NSR) and, similarly, seemingly embolic ischemic events can occur in patients with no documented history of AF.[1] In this review, we explore potential mechanisms underlying these events, offer approaches to management, and propose directions for future research.

AF and Thromboembolism

The risk of stroke associated with AF varies in relation to comorbidities associated with the thrombogenic substrate. Several risk stratification schemes are used to guide selection of patients for chronic anticoagulation therapy, since this strategy increases the risk of bleeding. The CHA_2DS_2-VASc schema, currently the most widely adopted in clinical practice guidelines, recognizes risk factors for stroke that also apply to patients without AF, particularly hypertension, heart failure, diabetes, and advanced age, as well as the higher risk of stroke faced by women and the risk of ischemia associated with concomitant atherosclerosis.

For those at intermediate or higher risk (event rate ≥2% to 3%/year), anticoagulation is recommended regardless of whether AF is paroxysmal, persistent, or permanent. Numerous large scale randomized trials have demonstrated the benefit of anticoagulation for stroke prevention in patients with AF. The 2019 AHA/ACC/HRS focused update of the 2014 guidelines[2] for management of patients with AF recommend anticoagulation for those with AF and a CHA_2DS_2VASc score ≥2. Recommendations favor one of the target-specific oral anticoagulants, dabigatran, rivaroxaban, apixaban, or edoxaban for nonvalvular AF rather than warfarin or another vitamin K antagonist (INR goal 2 to 3).

Thromboembolism During NSR

Thromboembolism can occur in the absence of AF, during NSR, and the etiologies and mechanisms responsible for these events are the focus of this review. A simple explanation is that in cases of cardiogenic embolism of atrial origin AF may have gone undetected. Alternatively, an atrial cardiomyopathy without clinical AF promotes clot formation and is both a cause and consequence of AF. Seen from this perspective, AF is a marker of this substrate, the severity of which varies with etiology, duration, and associated risk factors. Less certain is whether stasis in the LAA related to its configuration or mechanical dysfunction can result in thrombus generation and embolism in the absence of AF. And since it may be difficult or impossible to identify the actual source, an embolic event that occurs during NSR may arise from other sources altogether. Hence, we distinguish 4 interrelated aspects of thromboembolism during NSR—subclinical AF, atrial cardiomyopathy, LAA dysfunction, and alternative sources—and discuss how these may be considered individually and in combination as a foundation for selection of antithrombotic therapy (Figure 1).

Subclinical AF and Device-Detected Atrial Tachyarrhythmias

Diagnosis of AF has critical implications for stroke prevention, but detection can be problematic when the arrhythmia is paroxysmal and asymptomatic. In patients who have experienced cryptogenic ischemic stroke, detection of subclinical AF increases with extended cardiac rhythm monitoring. The 30-Day Cardiac Event Monitor Belt for Recording AF After a Cerebral Ischemic Event study demonstrated a 5-fold increase in AF detection with 30 days of continuous monitoring compared with 24-hour Holter monitoring.[3] Longer term implantable monitoring devices yielded AF detection rates of 8.9% at 6 months, 12.4% at

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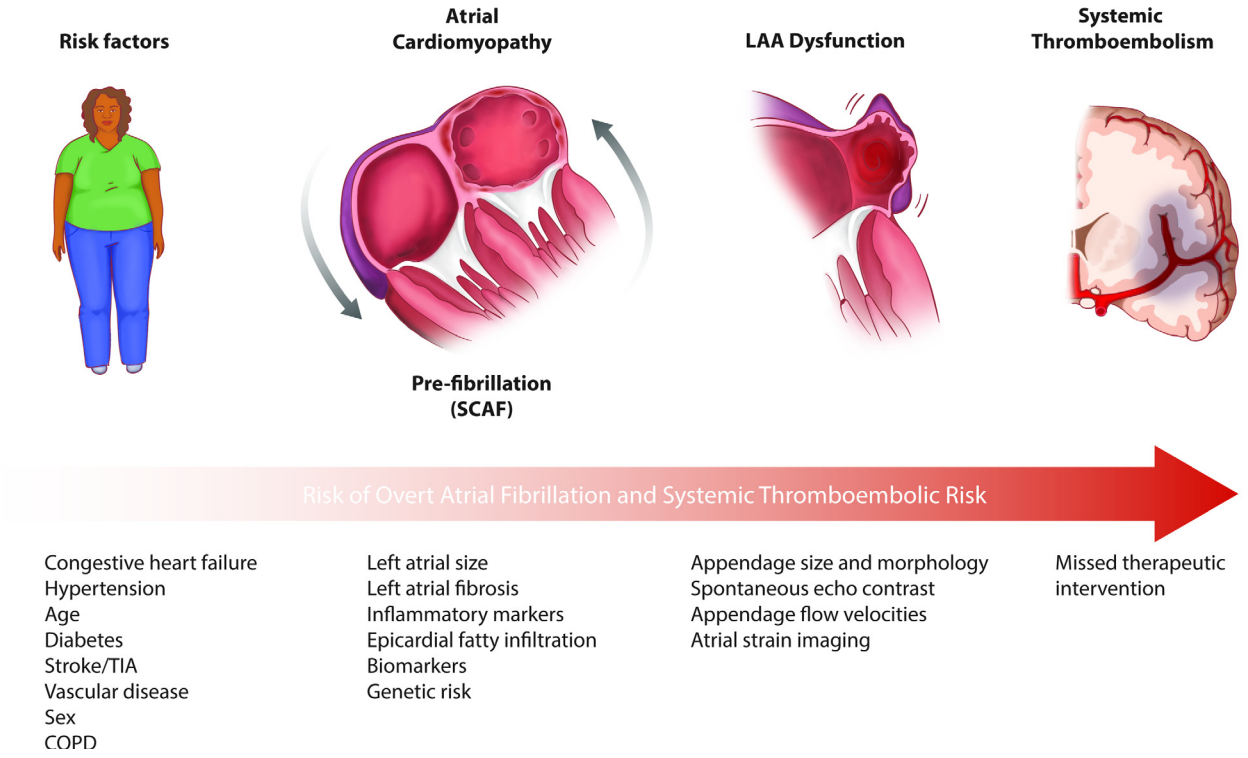

Figure 1. Thromboembolism during sinus rhythm. Proposed disease progression for increased thromboembolic risk in patients with normal sinus rhythm. COPD = chronic obstructive pulmonary disease; LAA = left atrial appendage; SCAF = subclinical atrial fibrillation; TIA = transient ischemic attack.
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12 months, and 30% at 3 years in the Continuous Cardiac Monitoring to Assess AF After Cryptogenic Stroke (CRYSTAL-AF) study.[4] In a prospective study of previously undiagnosed AF documented by an insertable cardiac monitor in high-risk patients, the REVEAL AF: incidence of AF in high-risk patients (REVEAL AF) study, 385 patients with $CHADS_2$ scores >3 or >2 (with >1 additional risk factor) but without previous stroke episodes of AF lasting >6 minutes were detected in 29.3% of patients over a period of 18 months by inserted continuous rhythm monitors. The incidence of AF was independent of $CHADS_2$ score. Hence, the incidence of previously undiagnosed AF may be substantial in patients with risk factors for AF and stroke. It seems intuitive that longer periods of monitoring will increase detection of AF, and episodes of AF, atrial flutter, or other atrial tachyarrhythmias detected by implanted devices, collectively termed device-detected atrial tachyarrhythmias, is a subset of subclinical, asymptomatic AF. The improved diagnostic capabilities of implanted cardiac electrical devices can be used to guide therapy, but create the clinical conundrum of determining the minimum burden of AF, in terms of frequency and duration, that is associated with a risk of stroke warranting anticoagulant therapy.

The Mode Selection Trial in Sinus Node Dysfunction (MOST) study, which compared VVIR and DDIR pacing modes in patients with sinus node dysfunction, included a prospectively defined subgroup analysis in which device-detected AT at atrial rates ≥220 beats per minute lasting >5 minutes were associated with stroke and mortality over 27 months. Patients with at least one AT episode were 6 times more likely to develop clinical AF and twice as likely to experience stroke or death compared with those without AT.[5] In the Prospect Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics (TRENDS) study[6] of 2,486 patients with at least 1 stroke risk factor and cardiac electronic implantable devices (CEID), AT lasting ≥5.5 hours in a 30-day period doubled the risk of stroke, whereas the risk in those with lower burdens of atrial high rate episodes did not differ from that in patients without device-detected AT. Conclusions were limited by the relatively low overall stroke rate in the enrolled population. In another trial of 560 patients with heart failure and cardiac resynchronization (CRT) devices, those with AT lasting >3.8 hours were 9 times more likely to develop thromboembolism than patients with lower burdens of AT.[7] The Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial (ASSERT) of 2,580 patients demonstrated a 2.5-fold increased risk of stroke in those with just 6 minutes of AT.[8]

Temporal Relation of AF and Thromboembolism

Despite the evidence of increased stroke risk in patients with subclinical AT, no prospective trial has demonstrated benefit from treatment guided by arrhythmia detection. The Multicenter Randomized Trial of Anticoagulation Guided by Remote Rhythm Monitoring in Patients with Implantable Cardioverter Defibrillator and CRT-D Devices (IMPACT)[9] investigators evaluated 2,718 patients with implanted dual-chamber cardiac defibrillators or CRT devices that imposed a specific anticoagulation plan based upon the $CHADS_2$ score and device-detected AT assessed by

remote monitoring. Anticoagulation in the control group was based on routine office visits and physician discretion without consideration of AT identified by device-based remote monitoring. Rates of thromboembolism, bleeding, and mortality did not differ between the intervention and control groups but the results were potentially confounded by protocol nonadherence and the trial was stopped for statistical futility. Even so, these observations emphasize that anticoagulation should not be discontinued based solely upon restoration of NSR. As in TRENDS and ASSERT, the IMPACT study found no temporal relation between episodes of AT and most of the clinical thromboembolic events that occurred. A subgroup analysis of TRENDS highlights the temporal discordance between AF and embolic events. Looking at only the 40 enrolled patients (1.6%) who experienced cerebral or systemic embolic events, half had no previous detection of AT. Of the 20 with AT episodes prior to events, 14 (70%) were not in AT at the time of the ischemic event and 9 had AT >30 days earlier.[10]

The 2019 AHA/ACC/HRS focused update of the 2014 guidelines for management of patients with AF recommend device-detected atrial tachyarrhythmia prompt further exploration to document clinically relevant AF but give no specific recommendations regarding a diagnostic duration or threshold for anticoagulation.[11] Expert clinicians have recommended risk stratification using the CHA_2DS_2VASc score to guide antithrombotic therapy in patients with AT burdens >5 minutes and further risk stratification for those with lower burdens.[12] Two ongoing trials, Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected SubClinical AF (ARTESiA) trial and Nonvitamin K antagonist Oral Anticoagulants (NOACs) in Patient With Atrial High Rate Episodes (NOAH) trial may provide more information about this.

Conventional mechanistic concepts linking AF to thromboembolism suggest that both the burden of AF and the timing of episodes would correlate with stroke risk, but a considerable body of evidence does not support a temporal relation. In the AF Follow-up Investigation of Rhythm Management (AFFIRM) study, which compared rate control vs rhythm control strategies in patients with AF, NSR was almost twice as prevalent in the rhythm control group at 5 years, yet there was no significant difference in rates of ischemic stroke or mortality between the 2 treatment strategies.[13]

Despite trials demonstrating a lack of temporal relation between AF and stroke, there is also evidence to the contrary. A retrospective analysis of 6,563 low-risk patients with paroxysmal, persistent, or permanent AF treated with aspirin found the pattern of AF predictive of stroke, with a 2-fold increase in annual stroke rate between patients with paroxysmal versus permanent AF.[14] A large prospective study from the US Veterans Administration evaluated this relation with cardiac implantable electronic devices in patients with ischemic stroke. Over a 10-year period, AF burden ≥5.5 hours in a single day raised the short-term risk of stroke 4- to 5-fold. Risk was highest during the first 5 to 10 days after an episode of AF and diminished thereafter.[15] Perhaps a temporal relation exists in low-risk patient populations but this time dependent relation is less or not significant with increasing stroke risk.

Atrial Cardiomyopathy

The underlying substrate of the LA is critical to the pathophysiology of cardioembolic disease. It is evident that AF is not the sole cause of thrombus formation and stroke, as patients lacking traditional risk factors face stroke risk similar to those without AF, and the lack of a temporal relation between AF and embolic phenomena is now widely acknowledged. The concept of a diseased atrium, involving atrial myocardial fibrosis and LA dilation is fundamental to the pathogenesis of thrombus formation and ischemic stroke.

A fibrotic atrial cardiomyopathy occurs secondary to collagen deposition resulting in fibrosis and structural and electrical remodeling of the atrium.[16] Atrial fibrosis slows electrical conduction and increases heterogeneity of repolarization promoting electrical signal-blocking and formation of atrial re-entrant circuits.[17] The Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of AF (DECAAF) study showed that AF leads to atrial fibrosis, and the extent of fibrosis correlates with the risk of recurrent AF after catheter ablation.[18] The cause of these fibrotic changes is multifactorial, involving traditional cardiac risk factors, genetic predisposition, inflammation, fat deposition, cellular signaling pathways, and AF.

The size of the LA has prognostic implications for a variety of adverse cardiovascular outcomes. Enlargement is the result of pressure and/or volume disturbances and a marker of diastolic ventricular dysfunction,[19] and numerous studies have demonstrated links between LA size and ischemic stroke. A trial of 1,191 elderly patients with treated hypertension found LA enlargement a predictor of ischemic stroke, independent of other factors, including AF. The absence of LA size from most stroke risk stratification schemes for patients with AF reflects the importance of mitral regurgitation as a cause of LA enlargement.[20] A systematic review of 9 cohort studies evaluating LA size in patients with NSR and encompassing 67,875 patients with 3,093 stroke events found an increased risk of stroke with increased LA size, although the relation was sometimes apparent only in women.[21]

In a retrospective case-control study of atrial function in patients without AF using speckle-tracking echocardiography to compare LA reservoir function in 371 patients with cryptogenic stroke and 361 controls, greater LA strain was independently associated with cryptogenic stroke. Another analysis of 40 patients with cryptogenic stroke found a correlation with elevated biomarkers, indicative of an abnormal underlying substrate, including elevated N-terminal probrain natriuretic peptide (NT-proBNP) levels, increased P-wave terminal force velocity in lead V1 (PTFV1) of the ECG, and severe LA enlargement.[22] Increased PTFV1 correlates with left ventricular hypertrophy and elevated filling pressures,[22] and even in the absence of AF is associated with an elevated risk of ischemic stroke.[23]

LAA Dysfunction

The varied appearance of the LAA has recently been classified based on shape. Four principal morphologies

have been identified by CT and MR imaging, designated cactus, chicken wing, windsock, and cauliflower.[24] The cactus-shaped LAA has secondary lobes extending from a dominant central lobe; the chicken wing type is characterized by a bend in the dominant lobe; the windsock variety has a dominant lobe with secondary and tertiary lobes; and the cauliflower LAA lacks a dominant lobe and is characterized by irregularity.

Flow in the LAA during NSR is quadriphasic.[24] Emptying begins during transmitral flow. Dilation of the left ventricle in diastole causes compression of the inferomedial wall of the LAA, contributing to diastolic emptying of the appendage. During mid-diastole, the LA fills from pulmonary venous inflow and subsequent emptying of the LAA at end-diastole reflects LAA function. How electrical-mechanical activation and flow patterns vary in relation to appendage morphology and the relation of these factors to thromboembolic risk have been incompletely defined.

Once thought of as vestigial, the main apparent function of the LAA is regulation of intravascular volume. When LA pressure rises in response to increased blood volume, the LAA expands,[24] producing 30% of the atrial natriuretic peptide of cardiac origin. When stimulated by myocyte distension, low oxygen tension or oxytocin, it modulates diuresis,[25] plays a role in the thirst response, and contributes to regulation of heart rate and blood pressure through sympathetic and parasympathetic pathways. These factors may bear upon the severity of stasis and local thrombogenicity that also influence embolic risk.

The mechanistic links between the LAA and ischemic stroke have been studied almost exclusively in patients with AF, and there is a paucity of data for patients in NSR. We will explore the risk factors associated with LAA morphology and function in patients with AF before discussing circumstances applicable to NSR.

In patients with AF, the LAA has both physiologic and morphologic attributes that correlate with ischemic stroke. The LAA is the most frequent location of intracardiac thrombus formation. Thrombi can be identified in about 15% of patients with AF unrelated to rheumatic mitral stenosis or prosthetic heart valves, and 90% are located in the LAA.[26] Thrombus formation in the LAA has been attributed to stasis of blood in the long, blinded pouch[27] and, as noted, the size, mobility and morphology of thrombus predict embolic risk. Thrombi that are >1.5 cm in diameter and have pedunculated forms are associated with the greatest risk.[28]

Aside from thrombus discovery, the echocardiographic features of the LAA that correlate most strongly with stroke risk in patients with AF are dense spontaneous echo-contrast and low LAA emptying velocity.[29] The velocities of flow into and out of the LAA correlate with thromboembolic risk. Emptying velocities up to 100 m/s are followed by a negative diastolic wave reflecting LAA recoil. During AF, the appendage loses contractility, leading to distension and low flow velocities,[30] which increase the risk of thromboembolism.[31] The risk of thrombus developing in the LAA rises with velocities ≤55 cm/s.[32] A low LAA ejection fraction has been associated with a risk of thromboembolism during both AF and NSR.[33]

The morphologic features associated with stroke include LAA shape, number of lobes, orifice size, and fibrosis. In a retrospective review of 932 patients with $CHADS_2$ scores of 0 to 1, the chicken wing morphology was associated with the lowest risk of embolism.[34] This shape also correlates with a lower risk of subclinical infarcts on brain MRI[35] and increased flow velocities measured by TEE.[36] The number of lobes has been linked to ischemic risk.[37] with ≥3 conferring elevated risk. Larger LAA orifice areas have also been implicated in stroke risk.[38]

Transesophageal echocardiography is the standard method for detection and characterization of LAA thrombus with a sensitivity and specificity of 100% and 99%, respectively, when compared with intraoperative observations.[39] The function of the LAA is generally assessed by recording pulse wave Doppler flow velocity in the proximal segment of the LAA. Reduced flow velocity is associated with cardioembolic stroke. Assessment of the LAA by TTE is challenging because of its posterior location, size, and variable anatomy, but novel methods are under investigation. Investigators measured left atrial wall motion velocity using pulse-wave tissue Doppler imaging in the parasternal long axis view in patients in NSR 2 weeks after an ischemic event. The initial downward spike, labeled La', occurred immediately following the P wave, representing atrial contraction. Decreased La' velocity was independently predictive of LAA dysfunction as assessed by TEE and correlated with TEE LAA exit velocity and LAA fractional area change.[40] Among patients in NSR with suspected cardioembolic stroke undergoing 2-dimensional speckle-tracking echocardiography, the peak LA strain and precontraction LA strain correlated positively with LAA emptying velocity and thrombus as assessed by TEE.[41] Whereas methods to assess LAA function are advancing, LAA assessment is not routinely incorporated in clinical management decisions.

Periods of LAA dysfunction have been documented in the absence of AF. Following cardioversion, LAA and LA mechanical contractile dysfunction or "stunning" develop in 38% to 80% of cases as assessed by the appearance in the LA of spontaneous echo-contrast, a marker of stasis that predisposes to thrombus formation.[42] The risk of stunning may be related to the short mitral E-wave deceleration time, reflecting reduced atrioventricular compliance. While the mechanisms responsible for stunning are not fully understood, transient atrial mechanical dysfunction may be related to elevated LV filling pressure, dispersion of electrical quiescence, and/or ion-channel recovery phenomena that follow restoration of NSR. A state of intracellular hypocalcemia may exist during the transition to NSR that leads to atrial hypocontractility[43] and electromechanical dissociation may vary depending on duration of AF.[44]

Catheter ablation based on electrical isolation of the pulmonary veins is commonly employed for management of patients with symptomatic AF, and AF triggers have also been identified in the LAA. In a study of 987 patients undergoing repeated catheter ablation for AF, 27% demonstrated firing from the LAA, and electrical isolation of the LAA resulted in freedom from AF in a number of these cases.[45] In The Effect of Empirical LAA Isolation on Long-term Procedure Outcome in Patients With Persistent or Long-standing Persistent AF Undergoing Catheter Ablation (BELIEF) trial, patients with longstanding persistent AF

undergoing repeated catheter ablation with electrical isolation of the LAA exhibited improved freedom from AF.[46] Of the 62 patients who remained in NSR at 6-months follow-up, 56.5% had impaired LAA function on TEE, based on peak flow velocity <0.4m/s (80%), inconsistent A waves (11.4%), or both (8.6%). This highlights the potential discordance between the electrical and mechanical properties of the LAA.

A similar phenomenon could explain how patients with paroxysmal AF face stroke risks similar to those with persistent AF. An evaluation of 201 patients with paroxysmal AF found that 25% demonstrated abnormal LAA flow velocities in NSR.[47] Mechanical dysfunction may also occur prior to onset of the arrhythmia. One study of patients with acute ischemic stroke in NSR found reduced LAA function a modest predictor of paroxysmal AF.[48]

The pathophysiology, timing, and clinical implications of LAA dysfunction during NSR are uncertain. Among the most pressing questions are whether phenomenon exists before the onset of arrhythmia or develops concurrently with AF and persists after spontaneous cardioversion. LAA dysfunction may evolve gradually, reflecting a diseased substrate, or more rapidly as a consequence of intermittent arrhythmia. Whether AF is mandatory for LAA dysfunction or if prefibrillators are also at risk are among the many difficult but clinically relevant issues that remain.

Alternative Sources of Thromboembolism

The occurrence of clinical thromboembolism appropriately prompts a search for AF, but a number of other conditions are established causes of thromboembolism during NSR. Because these directly involve neither AF nor LAA dysfunction, we address them only briefly.

Aortic arch atherosclerosis has a strong association with ischemic stroke and has been implicated both as a source of thromboembolism and a marker of more generalized atherosclerosis.[49] It may represent as high as a 4-fold increase in the risk of ischemic stroke. In patients with aortic atherosclerosis, antithrombotic therapy with warfarin has never shown a net clinical benefit. Only high-intensity statin therapy has been shown to reduce the risk of recurrent ischemic events in patients with NSR and complex aortic arch atheroma,[50] and the 2014 AHA/ASA guidelines for secondary stroke prevention recommend statin and antiplatelet therapy rather than anticoagulation.[51]

Abnormalities of the interatrial septum, including a patent foramen ovale (PFO) can predispose to paradoxical embolism. Characteristics such as PFO size and atrial septal aneurysm are associated with increased risk of cryptogenic stroke or TIA.[52] Patients with PFO also have a higher incidence of AF.[53]

Myocardial infarction is a risk factor for ischemic stroke both as a marker of atherosclerosis and because ventricular akinesia or dyskinesia can be associated with formation of left ventricular mural thrombus, a potential source of embolism.[54] Patients with heart failure (HF) and reduced left ventricular ejection fraction are 3 times more likely to develop ischemic stroke than those without HF,[55] yet no trial has demonstrated a benefit of anticoagulation in the HF population outside of AF.[56]

Other causes of thromboembolism include mechanical prosthetic heart valves, infective endocarditis, mitral and aortic valve calcification, aortic stenosis, myxomatous valvulopathy, cardiac myxoma, papillary fibroelastoma, atrial septal aneurysm, nonbacterial endocarditis, Chiari network, tumor emboli, and pulmonary AV fistula, among other etiologies. These topics are less pertinent to this review.

Implications for Therapy

Anticoagulation is recommended for patients with AF regardless of pattern,[11] effectively resulting in treatment of a large proportion of the population in NSR. Given that NOACs have a more rapid onset and offset of action than vitamin K antagonists, the concept of a "pill-in-the-pocket" approach to anticoagulation has been investigated. The Rhythm Evaluation for AntiCoagulaTion With COntinuous Monitoring (REACT COM) study uses a leadless implanted cardiac rhythm monitor to guide anticoagulation with a NOAC. In a pilot phase, the investigators achieved 94% reduction in time on anticoagulation, but efficacy for stroke prevention has not been assessed.[57]

The Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease (COMPASS) trial identified an advantage to low-dose rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg daily) over aspirin alone for prevention of cardiovascular events in patients in NSR with stable coronary or peripheral artery disease; risk reduction was greatest for ischemic stroke (hazard ratio 0.51; 95% confidence interval 0.38 to 0.69, p <0.001).[58] The risk of bleeding was high with combination therapy, and this difference would likely expand with more intensive anticoagulation necessary to prevent cardiogenic embolism. The results align with outcomes in the Prevention of Cardiovascular Events in Patient with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial,[59] where ticagrelor plus aspirin in patients in NSR with previous myocardial infarction reduced ischemic stroke (HR 0.76; 95% confidence interval 0.56 to 1.02). There was increased major bleeding but no difference in hemorrhagic stroke.

The LAA can be excluded from the circulation with device closure or surgical plication.[60] The Watchman device is approved for stroke prevention in patients with AF. The Lariat device is approved for suturing but not stroke prevention in AF. Other approaches, including the AtriClip device, Amplatzer plug, and second generation Amulet LAA Occluder represent additional options for LAA occlusion. In the WATCHMAN LAA System for Embolic PROTECTion in Patients With AF (PROTECT AF) study,[61] the device was noninferior to long-term warfarin anticoagulation for the primary endpoint of stroke and all-cause death, but the noninferiority criterion was not satisfied for prevention of ischemic stroke. The Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With AF Versus Long Term Warfarin Therapy (PREVAIL) trial[62] met this noninferiority endpoint with the device for prevention of ischemic stroke or systemic embolism >7 days postprocedure, allowing for periprocedural ischemic events. The longer term results

(mean follow-up 3.8 years) of PROTECT AF for percutaneous LAA closure met criteria for both noninferiority and superiority compared with warfarin for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death, and superiority for cardiovascular and all-cause mortality.[63] Surgical closure or excision of the LAA has been associated with conflicting results.[64]

Future Directions

Clear and concise evidence-based guidelines for anticoagulation of patients with AF are based upon balancing the risks of stroke and bleeding. However, approximately 1 in 4 strokes are cryptogenic, and a majority have neuroimaging profiles suggestive of embolic mechanisms.[65] In an uncertain proportion, an atrial myopathic substrate could lead to thromboembolism through appendage dysfunction with or without AF. A synergistic interplay between the myopathic substrate and arrhythmia likely allow one to propagate the other. A critical challenge is to identify patients with NSR who benefit from earlier anticoagulation. Whereas several risk schemes have been proposed to identify patients at risk of developing AF, none have yet been validated as a basis for early initiation of anticoagulation in the absence of documented AF. Further studies are needed to evaluate these tools as guides to anticoagulation of patients at risk, including but not limited to those with embolic stroke of undetermined source.

For cryptogenic stroke in the absence of AF, the AHA/ASA guidelines recommend antiplatelet rather than anticoagulant therapy to prevent recurrent stroke,[51] based on several randomized trials that show no benefit of VKAs over antiplatelet therapy.[66] Given their favorable efficacy and bleeding profiles, several NOACs are under investigation for this purpose[67]: the Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source (RE-SPECT ESUS), Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (NAVIGATE ESUS), and Apixaban for the Treatment of Embolic Stroke of Undetermined Source (ATTICUS) studies. The NAVIGATE ESUS trial was terminated because of futility, however rivaroxaban demonstrated efficacy similar to aspirin therapy; bleeding events were low but higher with rivaroxaban.[68] No conclusions can be reached until the full data set is published in addition to the ongoing trials RE-SPECT ESUS and ATTICUS. In addition, The AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA) is not only evaluating Apixaban in cryptogenic stroke, but in those with evidence of an atrial cardiopathy.

We have examined different markers for atrial dysfunction, representing an underlying atrial myopathy with increased risk of ischemic stroke, such as Fibrosis on DE-MRI, LA size and enlargement, NT-proBNP, in addition to evidence for LAA dysfunction, including appendage morphology, spontaneous echo-contrast, LA Fibrosis, and flow velocities. Is it time to put some of these parameters into clinical practice? LA size has been shown to correlate with $CHADS_2$ and CHA_2DS_2VASc schema[69] but it has not been studied alone or in conjunction with other parameters to predict stroke risk and guide management. For patients with AF, the ABC (Age, Biomarkers, Clinical History) stroke risk score, which incorporates biomarkers, was developed based on the highest weighted variables contributing to stroke assessed by Cox-regression analysis. Patient age, previous history of stroke or TIA, in addition to the biomarkers NT-proBNP and cardiac troponin high-sensitivity (cTn-hs) are the predictive variables. This schema was then validated in an external cohort and was associated with C-indices higher than the CHA_2DS_2VASc score (0.66 vs 0.58) at the expense of greater complexity.[70] A schema, involving biomarkers of appendage dysfunction or a myopathic substrate, to evaluate stroke risk in patients without AF has yet to be investigated.

Improved risk stratification tools that demonstrate evidence for an atrial myopathy and LAA dysfunction could prove a useful tool in several different clinical scenarios; (1) Improved risk stratification in patients with AF, (2) Further risk stratification of patients with AF and a CHADS-VASc of 0 to 1, (3) Cryptogenic stroke without evidence of AF, (4) High-risk stroke populations without evidence of AF, and (5) Prophylactic appendage closure for patients undergoing cardiac surgery.

Conclusions

Thromboembolic disease occurs during normal NSR. Cardiac implantable electronic devices have revealed the lack of a temporal relation between AF and stroke. This has called into question the over simplified mechanism for cardioembolic disease, that stasis in the LAA from a fibrillating atrium is the lone cause of thromboembolism. Sinus rhythm and embolic disease can be the result of subclinical AF, or one of many alternative sources of thromboembolism. In addition, thromboembolic disease during NSR is probably the result of an underlying thrombogenic atrial myopathy, resulting in a dysfunctional LAA leading to increased risk of embolic stroke. The myopathy is also likely responsible for electrical remodeling and eventual AF, with AF a reflection of the underlying substrate but also contributing to worsening fibrosis and cardioembolic risk. Markers for atrial myopathy and LAA dysfunction have been identified and evaluated but have not yet been integrated into clinical practice. With 25% of strokes deemed cryptogenic, earlier identification and improved risk stratification models using these markers for initiation of antithrombotic therapy need to be developed and tested.

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