Stroke Prevention in Atrial Fibrillation: The Last 20 Years

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The incidence of stroke associated with atrial fibrillation (AF) continues to be of concern. Efforts to reduce the stroke incidence over the last 20 years have focused on three primary areas: risk stratification for stroke, antithrombotic/anticoagulant therapy, and left atrial appendage (LAA) targeted procedures. The following is a rapid tour of these three areas and the practice guidelines that have helped to steer the direction of care.

Stroke Risk Assessment

One way to decrease the incidence of stroke in the AF population is to determine who is high risk and treat this population with antithrombotic drugs. The 2001 ACC/AHA/ESC guidelines for AF management[1] discussed various risk stratification schemes used in clinical settings. A discussion about determining who was low risk versus high risk was emerging. Factors that were being considered included age, history of hypertension, coronary artery disease (CAD), left ventricular (LV) dysfunction, congestive heart failure (CHF), previous stroke or TIA, diabetes, thyrotoxicosis, and gender. With the publication of the 2006 guidelines, therapy recommendations began to focus on the presence of certain risk factors such as stroke/TIA, age >75, hypertension, diabetes, and heart failure.[2] In addition, the $CHADS_2$ risk index was discussed at length (Table 1).

In 2014, the updated guidelines for management of AF[3] discussed the use of the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED risk stratification schemes. Components of the $CHADS_2$ and CHA_2DS_2-VASc are compared in Table 1. The HAS-BLED scoring system was developed to assess the risk of major bleeding in patients taking anticoagulants, and included the history of hypertension, abnormal renal/liver function, stroke, bleeding, labile INR, elderly age, and drugs/alcohol history or disposition. The guidelines recommended the use of the CHA_2DS_2-VASc score to assess stroke risk in patients with nonvalvular AF. Furthermore, the scores from CHA_2DS_2-VASc were to be used to guide specific therapy.[3] The 2019 focused update for AF management continued to promote the use of CHA_2DS_2-VASc to evaluate risk.[4] Of note, these guidelines changed from use of the term 'antithrombotic' to 'anticoagulant'.

Antithrombotic/ Anticoagulant Therapy

In the 2001 guidelines for AF, a major debate was taking place on recommending anticoagulation for all versus selective treatment for those with intermediate risk.[1] At the time, warfarin was the primary agent being used for treatment. Class 1 recommendations for anticoagulant administration included the following: administer anticoagulants to all patients with AF, except those with lone AF; individualize the selection of agent based on risk assessment; target an INR of 2-3 for those at high risk; use aspirin as an alternative in those with low risk; and use oral anticoagulation for those with AF and rheumatic mitral valve disease or prosthetic valves. The guidelines also discussed the use of transesophageal echocardiography (TEE) as a preferred mode of assessment for determining the presence of a left atrial or left atrial appendage (LAA) thrombus.

By the 2006 guidelines, antithrombotic therapy for patients with atrial flutter, equivalent to the treatment for AF, had become a Class I recommendation. Treatment recommendations specified the use of a vitamin K antagonist (warfarin) for stroke prevention. Weekly INR measurements were to be obtained until the INR was stable, and then monthly measurements were to be obtained.[2]

However, things were about to change drastically in the realm of anticoagulation. In October 2010, dabigatran, a direct thrombin inhibitor affecting factor IIa of the coagulation cascade (Figure 1), was FDA approved for use in patients with non-valvular AF. In the RE-LY study,[5] warfarin was compared to dabigatran at 2 years. The stroke rate with warfarin was 1.71% per year; the stroke rate in the dabigatran-treated group was 1.11% per year. There was a 20% reduction in major bleeding risk compared with warfarin: 2.87% vs 3.57% with the 110 mg bid dose, and 3.32% for dabigatran for the 150 mg bid dose. In 2011, a focused update of the guidelines[6] recommended dabigatran as a warfarin alternative for those without a mechanical heart valve. However, as use of dabigatran increased, there was concern that there was no specific antidote or reversal agent for its effects. This led to the search for a dabigatran reversal agent.

Efforts to reduce the stroke incidence over the last 20 years have focused on three primary areas: risk stratification for stroke, antithrombotic/anticoagulant therapy, and left atrial appendage targeted procedures. The following is a rapid tour of these three areas and the practice guidelines that have helped to steer the direction of care.

In a 2011 focused management update,[7] the addition of clopidogrel to aspirin was considered in patients where warfarin was unsuitable due to patient preference or inability to safely sustain anticoagulation. In that same year, rivaroxaban was approved by the FDA for use in patients with nonvalvular AF. This was the first in the group of Xa inhibitors, which prevent prothrombin from being generated from thrombin and inhibit the generation of tissue factor-induced thrombin (Figure 1).[8] The ROCKET AF phase III study had shown rivaroxaban to be noninferior to warfarin for stroke or systemic embolism prevention. Major bleeding was found to be equivalent, but intracranial and fatal bleeding occurred less frequently in those on rivaroxaban.[8]

Table 1. Comparison of $CHADS_2$ and CHA_2DS_2-VASc scoring systems.

	$CHADS_2$	CHA_2DS_2-VASc
C= CHF	1 point	1 point
H= Hypertension	1 point	1 point
A= Age >75 years	1 point	2 points
D= Diabetes	1 point	1 point
S= Prior stroke/TIA	2 points	2 points
V= Vascular disease*		1 point
A= Age 65-74		1 point
S= Sex Category (ie, female sex)		1 point
TOTAL:	6 points	9 points

*Defined as previous MI, peripheral arterial disease, or aortic plaque

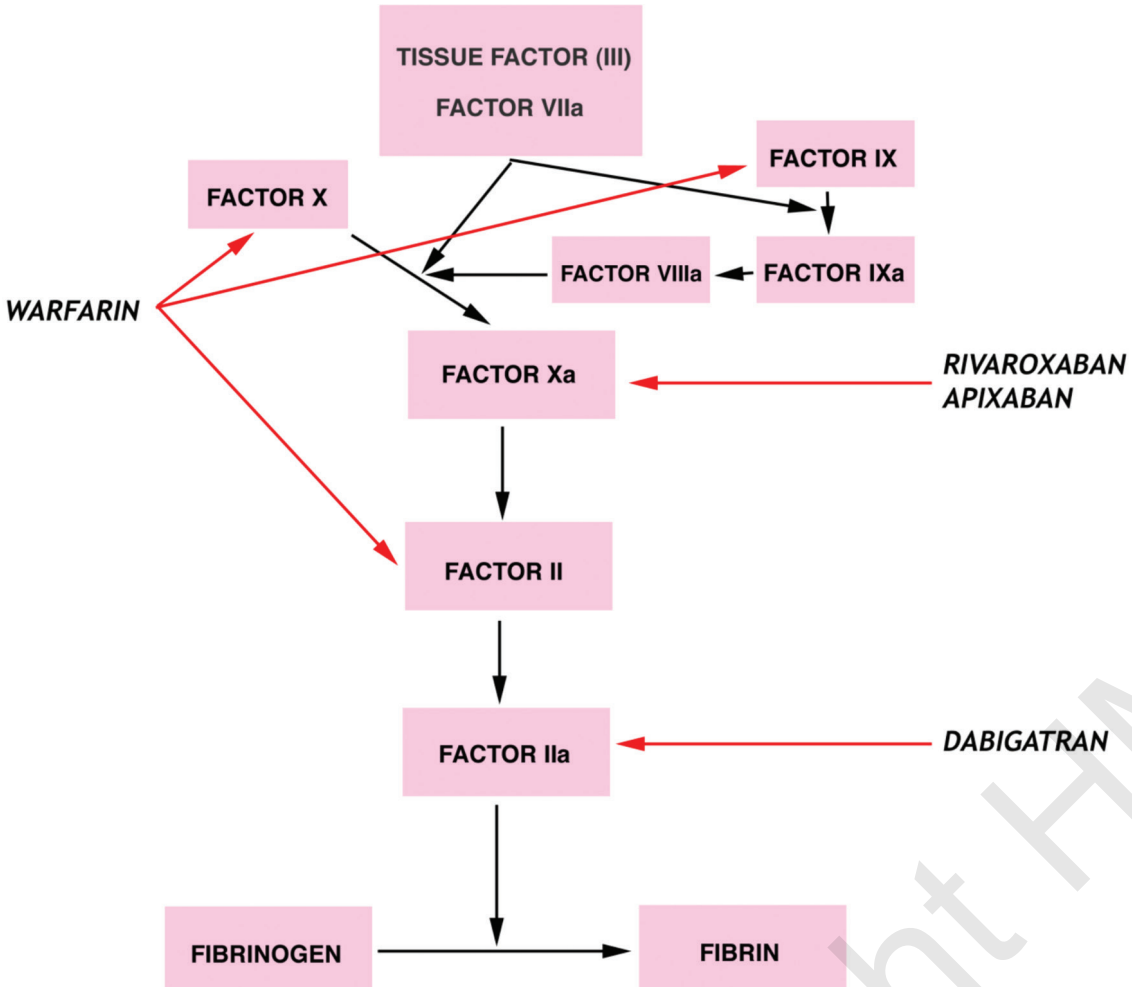

Figure 1. **Action of anticoagulants within the coagulation cascade. Red arrows indicate portion of the coagulation cascade affected by drug actions.** ***(Used with permission from the Order and Disorder EP Training Program, 2012.)***

A comparison of the Xa inhibitors and dabigatran can be found in Table 2. Note the frequency of dosing and excretion of each; compliance can be an issue with dosing frequency as well as renal function with drug excretion.

Table 2. Summary of novel oral anticoagulants (NOACs).

Generic Name	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Trade Name	Pradaxa	Xarelto	Eliquis	Savaysa
Year of FDA Approval	2010	2011	2012	2015
Cascade Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Dosing	Twice a day	Daily	Twice a day	Daily
Maximum Concentration	1 hour	2-4 hours	3 hours	1-2 hours
Half-Life	12-17 hours	Healthy patients: 5-9 hours; Elderly patients: 9-13 hours	About 12 hours	10-14 hours
Mode of Excretion	80% renal 20% fecal	66% renal 34% fecal	75% fecal 25% renal	50% renal 50% fecal

Quickly on the heels of the rivaroxaban approval, apixaban, another Xa inhibitor, was approved in December 2012. Apixaban was studied in the ARISTOTLE[9,10] and AVERROES trial.[11,12] For the ARISTOTLE study, superior efficacy and safety were shown with apixaban compared with warfarin, as well as an improvement in all-cause mortality. For the primary outcome of ischemia, hemorrhagic stroke, or systemic embolism at one year, results were 1.27% for apixaban and 1.60% for warfarin. Incidence of major bleeding was 2.13% for apixaban and 3.09% for warfarin. The AVERROES trial compared apixaban to aspirin (in patients unable to take warfarin). For the apixaban group, there was a reduced risk of stroke and systemic embolism, and a slight increase in major bleeding or intracranial hemorrhage. The apixaban group experienced a 1.6% rate of stroke or systemic embolism versus 3.7% for the aspirin group. The major bleeding rate for apixaban was 1.4% vs 1.2%, and death rate was 3.5% vs 4.4%.

In January 2015, another Xa inhibitor, edoxaban, received FDA approval. In the ENGAGE AF-TIMI 48 trial, edoxaban was noninferior to warfarin in the prevention of stroke or systemic embolization, and rates of bleeding were significantly lower.[13] The 2019 guidelines recommended dabigatran, rivaroxaban, apixaban, and edoxaban over warfarin in all except those with moderate-to-severe mitral stenosis or a mechanical valve.[4] This is because of the lower risk of bleeding and non-inferiority in stroke or thromboembolism prevention when compared to warfarin. Atrial flutter anticoagulation guidelines were the same.

In 2014, the practice guidelines recommended that therapy should be individualized based on shared decision making, bringing patients into the language of the decision-making process.[3] The selection of therapy type was to be based on the risk of thromboembolism. Warfarin was to be used if the patient had valvular AF. If there was a history of prior stroke or TIA, or if the CHA_2DS_2-VASc score was ≥2, options included warfarin, dabigatran, rivaroxaban, or apixaban. Direct thrombin or factor Xa inhibitors were to be used if a therapeutic INR could not be maintained with warfarin. The same anticoagulant recommendations were put forth for atrial flutter cases. A comparison of the Xa inhibitors and dabigatran can be found in Table 2. Note the frequency of dosing and excretion of each; compliance can be an issue with dosing frequency as well as renal function with drug excretion.

In 2015, the FDA approved idarucizumab, a humanized monoclonal antibody fragment from mice, for patients treated with dabigatran, when reversal of the anticoagulant effects of dabigatran is needed in an emergency. Its mechanism of action is to bind with dabigatran to counteract its anticoagulant effects. Andexanet alfa, a recombinant modified version of human activated factor X, was approved by the FDA in 2018 as an antidote for rivaroxaban and apixaban.[14] The drug acts as a decoy receptor and sequesters factor Xa inhibitors. The protocols for reversal of anticoagulants continue to evolve.

Table 3. Historical review of left atrial appendage closure devices. (Adapted from Asmarata and Rodés-Cabau[25])

ENDOCARDIAL DEVICE	MANUFACTURER	APPROVAL STATUS
PLAATO	Appriva Medical	Discontinued 2006
WATCHMAN	Boston Scientific	FDA 2015; CE Mark 2005
WATCHMAN FLX	Boston Scientific	FDA 2020; CE Mark 2015 and withdrawn 2016, approved 2019
ACP	Abbott	CE Mark 2008
Amulet	Abbott	FDA 2021; CE Mark 2013
WaveCrest	Biosense Webster	CE Mark 2013
Occlutech	Occlutech	CE Mark 2016
LAmbre LAA closure system	Lifetech Scientific	CE Mark 2016
Ultraseal	Cardia	Clinical Evaluation
EPICARDIAL DEVICES	**MANUFACTURER**	**APPROVAL STATUS**
LARIAT	SentreHEART	CE Mark 2015; FDA 510(k) 2006 for surgical use only
Sierra Ligation System	Aegis Medical Innovations	Clinical Evaluation

LAA-Targeted Procedures

The embolism responsible for stroke in the setting of AF is often traced back to the LAA. The LAA anatomy makes it a prime location for clot formation when atrial flow is decreased from AF. Over the past 20 years, there have been many approaches to physically altering the LAA. LAA interventions may offer an alternative for some patients who would benefit from anticoagulants and direct thrombin inhibitors, but may have contraindications to taking them or would be unable or unwilling to adhere to anticoagulation long term.

The surgical exclusion of the LAA dates back to 1946. The 2006 ACC/AHA guidelines for valvular heart disease recommended that LAA amputation be conducted routinely in the setting of mitral valve surgery.[15] Techniques for amputation or exclusion have included a row of running or purse-string sutures, use of a stapler, or excision. Success rates were not especially consistent: 73% for excision, 23% for suture exclusion, and 0% for use of stapler, due to high rates of residual stump formation. [16-19] Another surgical approach is the Cox maze procedure, which involves isolation of the pulmonary veins and surgical excision of both right and left atrial appendages.[20] However, those with advancing age or comorbidities may not qualify.

The Minimaze procedure was being reported in the literature by 2005.[21] This is a minimally invasive, video-assisted, off-pump surgical procedure in which a bipolar RF clamp is placed around the pulmonary veins to isolate them. Ganglionic plexi are ablated, linear lesions are created, and the LAA may be excluded via excision or, more recently, the use of a clip. This procedure continues to evolve.

Endocardial devices were developed to offer a less invasive solution to LAA exclusion. The PLAATO device (Appriva Medical) was introduced transeptally into the LAA in order to block and seal off the chamber; a self-expanding nitinol cage was covered with a polytetrafluoroethylene membrane.[22] Device development was discontinued in 2006. The initial WATCHMAN device (Boston Scientific) had a self-expanding nitinol frame, fixation barbs, and polyester fabric.[23] At this point the device was still in clinical trials, but would be approved with modifications in 2015.

The 2006 AF guidelines included a brief discussion on the emerging technologies for obliteration of the LAA, including via direct surgical amputation, intravascular catheters, or transepicardial approaches. All of these options were considered investigational.[2]

Meanwhile, in 2012, a focused update of the ESC guidelines for the management of atrial fibrillation was published[24] and included a Class IIb recommendation for LAA closure/occlusion/excision.

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Table 3 is a review of endocardial and epicardial device development in the U.S. and Europe.[25] One such device is the Amplatzer Cardiac Plug (ACP, Abbott), which initially started with off-label use. It consists of a nitinol platform with a distal lobe and proximal disk that occluded the LAA ostium with expansion.[26]

The LARIAT (SentreHEART) represented a transpericardial approach using an epicardial snare with a pre-tied suture to lasso and occlude the LAA.[27] The LARIAT received FDA approval in 2006 for surgical applications "where soft tissues are being approximated and/or ligated with a pre-tied polyester suture" (LARIAT loop application).[28] (In 2015, none of the literature related to the LARIAT included longitudinal outcome assessments; it was not felt that the literature gave insight into its effectiveness for stroke reduction or safety relative to other approaches.[29])

The 2014 AF guidelines discussed percutaneous approaches such as WATCHMAN and the Amplatzer plug. No recommendations were offered for their use. The LARIAT procedure was also discussed. The Class IIb recommendation advised that "surgical excision of the LAA may be considered in patients undergoing cardiac surgery.[3]

In 2015, the ACC/HRS/SCAI LAA occlusion device societal overview summarized the state of LAA devices.[29] The WATCHMAN device was approved as an alternative to warfarin for stroke prevention with nonvalvular AF in those qualifying for warfarin but unable to take it. This was the only FDA-approved device. The guidelines included discussion about the WaveCrest LAA Occluder System (Coherex Medical/Biosense Webster), a polytetrafluorethylene-based platform, as well as the LAmbre LAA Closure System (Lifetech Scientific), a self-expanding nitinol and polyester device. However, no peer-reviewed reports were available for these devices at this time.

Surgical discussions from the societal review included issues with mechanical complications resulting in hemorrhage during surgical suturing or stapling. The LAAOS III study[30], a large randomized trial of LA ligation, including the use of devices, was also reviewed. The most widely used device was the AtriClip (AtriCure), which consists of a parallel titanium crossbar clip covered with woven polyester fabric.[31] It was approved for LAA closure with direct visualization during open heart surgery. Trials of minimally invasive thoracoscopic procedures using the AtriClip were being conducted.

In the 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation, the Class IIb recommendation was LAA occlusion may be considered for those with AF at increased risk of stroke and with contraindications to long-term anticoagulants.[4] (Outside the U.S., there were trials of LAA closure and antiplatelet regimes for oral anticoagulant-ineligible patients.) In addition, surgical occlusion of the LAA may be considered in patients with AF undergoing cardiac surgery (Class IIb). Surgical LAA occlusion was also compared to no LAA occlusion; occlusion was associated with lower unadjusted rates of readmission for thromboembolism, all-cause mortality, and composite endpoint, but there was no significant difference in the rate of hemorrhagic stroke.[32]

Efforts aimed at stroke prevention in atrial fibrillation over the last 20 years have been exciting and ever changing. The next 20 years are sure to bring changes just as radical as these. Hold on tight!

In 2021, the FDA approved the Amplatzer Amulet LAA Occluder (Abbott) to treat patients with AF who are at risk of ischemic stroke.

Summary

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