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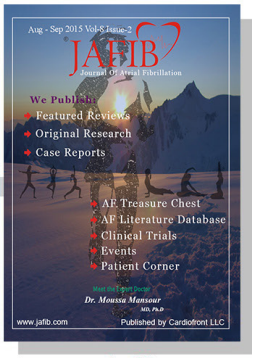

Optimization Of Stroke Prophylaxis Strategies In Nonvalvular AF – Drugs, Devices Or Both?

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia with the prevalence increasing over time. AF probably afflicts ≥2% of worldwide adult population and increases with age.[1-3] In the Framingham Heart Study, the lifetime risk of having at least one episode of AF for 40-year-old men and women was 26% and 23% respectively.[4]

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with the prevalence increasing over time. AF probably afflicts ≥2% of worldwide adult population and increases with age.1-3 In the Framingham Heart Study, the lifetime risk of having at least one episode of AF for 40-year-old men and women was 26% and 23% respectively.[4]

AF is associated with increased morbidity and mortality due to risk of systemic thromboembolism, specifically stroke. In the Framingham cohort, AF was responsible for 14.7% of all strokes, ranging 6.7% in the 50-59 year age-group to 36.2% in the 80-89 year age-group.5 Strokes related to AF are associated with higher mortality and morbidity than strokes in patients without AF.[6-8] Further, among AF related strokes, increasing age and CHADS2 score (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, 2 points for history of Stroke/transient ischemic attack) predict worse outcomes.[7, 8] Annual stroke risk in patients with AF across all risk strata is 5%.4 Additionally, subclinical cerebral ischemic events occur in around 15% of patients with AF and are correlated with cognitive dysfunction.[9, 10]

In patients with non-valvular AF, the risk of stroke increases with clinical risk factors. Risk stratification systems include CHADS2 score and its modification CHA2DS2-VASc score (2 points for age ≥75 years, and incorporating additional risk factors of vascular disease [prior myocardial infarction, peripheral artery disease or aortic plaque], age 65-74 years and female sex in conjunction with other predictors).[11, 12]

Mitigation of AF related strokes could have a profound public health impact, but there are many challenges. More than a third of AF patients might be asymptomatic and difficult to identify. The initial presentation of AF might be stroke itself. Stroke can occur even prior to the first episode of AF detected by an implanted pacemaker.[13, 14] On the other hand, in absence of extended cardiac rhythm monitoring the diagnosis of AF can sometimes remain elusive even after a stroke.[15] Even for patients in whom AF is identified upfront and who have adequate access to health care there, is no optimal way of preventing strokes. Anticoagulation is difficult to adhere to and is limited by risk of bleeding complications. An economic analysis in the USA in 2004 estimated that approximately 1.265 million patients with AF not on anticoagulation (55% of all AF patients) suffered 58,382 strokes every year, with $4.8 billion in direct costs to Medicare.16 Non-pharmacologic options like left atrial appendage (LAA) closure are expensive, require operator expertise, have an upfront risk of complications, and have an equivocal evidence base for efficacy and cost-effectiveness in preventing strokes.[17-20]

Mechanisms Of Stroke In Atrial Fibrillation

Over two-thirds of strokes in patients with non-valvular AF who are not on anticoagulation are related to cardioembolic causes.21 In a transesophageal echocardiogram (TEE) study on patients without anticoagulation, an LAA thrombus was identified in 14% acute AF and 27% chronic AF patients.22 When an AF related thrombus is identified within the left atrium, it is in the LAA in 57% of patients with rheumatic mitral valve disease and 91% of

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patients without valvular heart disease.[23] The postulated mechanisms for development of left atrial thrombus in patients with AF include left atrial enlargement, endothelial damage, inflammation, fibrosis, stasis and prothrombotic changes.[19] In addition, stroke risk factors in AF are also correlated with other mechanisms of stroke especially atherosclerotic disease of the aortic arch and carotid arteries.[19, 21]

Anatomic And Mechanical Considerations – Left Atrium And Appendage

AF causes stasis in the LAA (seen as spontaneous echo contrast on TEE) due to loss of atrial systole, dilatation, and fibrosis. The LAA in general is a long, hooked, and narrow-based extension of the left atrium, suitable for stasis and thrombosis.[22, 23] Spontaneous echo contrast and reduced LAA emptying velocity on TEE, left atrial enlargement, and te complex multi-lobulated LAA shape are factors associated with a higher risk of stroke.[17, 24-26] AF leads to structural changes in the LAA characterized by edema, myocyte hypertrophy and necrosis, mononuclear infiltrate, and fibrosis, as well as endothelial denudation and thrombotic aggregation. These changes probably underlie the delay in recovery of mechanical function of the atria despite restoration of sinus rhythm.[17]

Prothrombotic State And Inflammation

AF is associated with an increased expression of prothrombotic markers of endothelial injury including the von Willebrand factor (vWF) and tissue factor, and elevation in the plasma levels of D-dimer.[17, 18, 27] Tissue-plasminogen activator (t-PA) antigen and plasminogen activator inhibitor-1 (PAI-1) are increased and plasmin-antiplasmin complex levels are reduced due to increased thrombolytic activity subsequent to thrombogenesis.[27] Moreover, AF has been described as an inflammatory disorder. Systemic levels of inflammatory markers including interleukin-6 (IL-6) and C-reactive protein (CRP) are increased. Inflammation can mechanistically lead to endothelial dysfunction and expression of tissue factors related to thrombogenesis.[17, 18, 27]

Stroke Unrelated To Left Atrial Thrombus

In a study on TEE evaluation of 72 non-valvular AF patients with ischemic stroke, one-third of patients without spontaneous echo contrast were over twice more likely to have causes of stroke other than AF including proximal aortic arch atherosclerosis, patent foramen ovale, and atrial septal aneurysm (78% versus 36%), suggesting occurrence of strokes unrelated to thrombosis in the left atrium.[28] In the Stroke Prevention in Atrial Fibrillation (SPAF) I–III trials, 32% of classifiable ischemic stroke events were due to non-cardioembolic causes.[21] In SPAF-III, 57% of AF patients had evidence for thoracic aortic atherosclerosis,[29] and absence of atherosclerosis was associated with a lower risk of stroke.[18, 30]

Left Atrial Appendage – Structure And Function

LAA is often thought of as a vestigial remnant.[19, 26, 31] However, LAA has stretch receptors and functions in fluid and electrolyte homeostasis through thirst reflex and production of natriuretic peptides. It contributes to hemodynamic efficiency by functioning as an atrial reservoir and booster.[19, 32] The regional anatomy of the LAA and variability in its shape is relevant when considering mechanical closure of LAA to reduce risk of stroke. LAA lies in the pericardial sac as a superior extension of the left atrial free wall, and is related to the left phrenic nerve. The left aortic sinus and the left main coronary artery are related to the medial aspect of the LAA ostium while the circumflex artery is related to the inferior margin. In some patients the sinus node artery arising from the left circumflex courses adjacent to the LAA ostium. The left superior pulmonary vein is related to the posterosuperior aspect of the LAA ostium and is separated by the ligament of Marshall within the left atrial ridge.[31, 33] Extremely eccentric LAA ostia can be difficult to occlude with an endovascular circular plug, and a multilobar complex LAA may be challenging to fully incorporate within an epicardially placed suture or clip.[19]

Strategies For Stroke Prevention In Atrial Fibrillation

Warfarin anticoagulation has been the mainstay of preventing strokes for over 2 decades. Patients on warfarin therapy have a preferential reduction in cardioembolic strokes, and as a result, two-thirds of the strokes in patients on warfarin are due to non-cardioembolic causes. As reduction in AF-related strokes with anticoagulation is largely due to inhibition of formation of LAA thrombi, it stands to reason that mechanical LAA exclusion would reduce strokes as well.[19, 21]

Chronic Oral Anticoagulation

Warfarin has been available for 6 decades. In a metaanalysis of 29 trials and 28,044 patients with non-valvular AF, warfarin compared to placebo decreased strokes by 64% (95% confidence interval [CI] 49–74%) and mortality by 26% (6% to 35%). Compared to antiplatelet therapy with aspirin, warfarin reduced strokes by 37% (23% to 48%).34 In recent times, drugs with a predictable dose-dependent anticoagulant effect have been developed. Direct thrombin (factor IIa) inhibitor dabigatran was the first such drug approved by the US Food and Drug Administration (FDA) followed by activated factor X (factor Xa) inhibitors rivaroxaban and apixaban.[35-38] Another factor Xa inhibitor edoxaban is awaiting marketing approval.[39] These newer agents have respectively demonstrated non-inferiority to warfarin for stroke prevention in head-to-head randomized controlled trials (RCTs) each enrolling in excess of 14,000 patients. Although overall bleeding rates with the newer oral anticoagulants are similar to warfarin, intracranial and life-threatening bleeding is lower. On the other hand, dabigatran, rivaroxaban, and edoxaban have a higher risk of gastrointestinal bleeding compared to warfarin.[35-39] Apixaban has bleeding rates comparable to aspirin alone and is superior in preventing strokes.[40] Therefore, therapy with warfarin (target INR 2.0-3.0) or the newer anticoagulants is the standard for stroke prevention in non-valvular AF and CHA2DS2-VASc score ≥2. The newer anticoagulants are, however, not recommended in patients with severe renal or hepatic dysfunction nor in those with prosthetic heart valves.[38]

Left Atrial Appendage Exclusion

LAA can be occluded with catheter-based devices implanted using venous access and transseptal puncture, or with epicardial techniques to ligate or clip the LAA. Epicardial exclusion can be done using (i) a mini-thoracoscopic or open surgical approach, (ii) using novel techniques with completely percutaneous pericardial access, or (iii) a hybrid procedure for epicardial closure from percutaneous pericardial access with navigation and deployment facilitated by a transseptal catheter in the LAA.

Endovascular Occlusion Of Left Atrial Appendage

Many observational studies have evaluated percutaneous LAA occlusion in patients with non-valvular AF. In a meta-analysis of 17 retrospective studies and 1052 device implantations, the pooled incidence for stroke at follow-up was 0.7 per 100 patient-years,

and transient ischemic attack (TIA) was 0.5 per 100 patient-years. Access site complications occurred in 8.6% (95% CI 6.3–11.7%) and pericardial effusion in 4.3% (3.1–5.9%).41 Several devices for endovascular implantation have been developed.

• **Plaato** (Percutaneous LAA Transcatheter Occlusion; ev3, Plymouth, Minnesota) was the first device specifically designed for LAA occlusion, but has been abandoned due to lack of financial sponsorship. Plaato sealed the LAA with a polytetrafluoroethylene (PTFE) covered self-expanding nitinol cage (diameter range 15-32 mm).19, 42, 43 A study in CHADS2 ≥1 patients demonstrated successful implantation in 108 of 111 patients and 2.2% annual stroke rate over 9.8 month follow-up. Adverse events included 4 deaths, 2 strokes, 3 pericardiocentesis, and one case each of emergency cardiac surgery, hemothorax, brachial plexus palsy, and deep venous thrombosis.43 Another study in CHADS2 ≥2 patients had successful implantation in 162 of 180 patients, LAA occlusion was confirmed in 126 of 140 patients with 2-month TEE and stroke rate was 2.3% per year. Major adverse events occurred in 12 patients including 2 periprocedural deaths, 6 pericardial tamponades (2 required emergent surgery), and one device embolism.[44]

• **Watchman** (Boston Scientific, St. Paul, Minnesota) is a permeable, polyester covered, self-expanding nitinol frame (diameter range 21-33 mm) with fixation barbs and is positioned in the LAA using transseptal access with a 12-Fr sheath. The entire device sits within the LAA without projecting out of the ostium.[19, 45] Design changes in the fourth generation Watchman include more spines for better radial strength, increased stability, and ability to recapture-redeploy the device.

In the ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology (ASAP), 150 non-valvular AF patients with CHADS2 score ≥1 and a contraindication to warfarin underwent Watchman implantation and received dual antiplatelet therapy for 6 months and aspirin thereafter. There were 13 (8.7%) serious adverse events and, during the mean 14.4-month follow-up, there were 3 ischemic and 1 hemorrhagic strokes, while 6 (4%) had device related thrombi.[46] In another study, 59 patients were treated with Watchman (device was oversized by 15% to 30%) and received dual antiplatelet therapy for 45 days followed by aspirin alone – there were 2 pericardial effusions, 3 device thrombi, and 1 thromboembolic event.[47] Two RCTs have evaluated clinical outcomes with the Watchman device

*o **Protect-AF:*** Non-valvular AF patients with CHADS2 ≥1 (mean 2.2)[48] were randomized to Watchman LAA closure (n=463) or long-term warfarin (target INR 2.0-3.0; n=244). Watchman patients were treated with warfarin for 45 days, followed by aspirin and clopidogrel for 6 months and subsequently aspirin alone. The Watchman strategy had 99.9% probability of being non-inferior to warfarin for primary composite outcome of stroke, cardiovascular death, or systemic embolism (3.0 versus 4.9 per 100 patient-years respectively at 18 months; 3.0 versus 4.3 per 100 patient-years on extended mean 2.3 year followup). However, the serious adverse events were higher with Watchman (7.4 versus 4.4 per 100 patient-years) including major bleeding (3.5%), pericardial effusion (4.8%), and device embolization (0.6%).48, 49 Device related thrombus occurred in 20 of 478 (4.2%) Watchman patients.50 Following PROTECT-AF, a non-randomized continued access registry with 460 Watchman implantations showed improved outcomes with increase in operator experience – higher implantation success (from 89.5% to 95.0%) and fewer procedural complications (from 7.7% to 3.7%, including serious pericardial effusions from 5.0% to 2.2% and procedural strokes from 0.9% to 0%).50

*o **Prevail:*** Non-valvular AF patients with CHADS2 score 2.6±1.0 were randomized to Watchman (n=269) and warfarin (n=138). Watchman patients received short-term warfarin followed by dual antiplatelet and then aspirin alone similar to PROTECT-AF. At 18 months, the composite of stroke, systemic embolism, and cardiovascular/ unexplained death was 6.4% in the Watchman group versus 6.3% in the warfarin group (relative risk 1.07, 95% CI 0.57–1.89), though not reaching the non-inferiority criterion. The rate of stroke or systemic embolism >7 days after randomization was 2.5% versus 2.0% (RR 1.6, 95% CI 0.5–4.2). For Watchman implantations, the periprocedural composite safety endpoint of all-cause death, ischemic stroke, systemic embolism, or need for cardiovascular surgery or major endovascular intervention occurred in 6 of 269 (2.2%; 2 device embolizations, 1 cardiac peroration, 1 pericardial tamponade).[51]

• **Amplatzer Cardiac Plug** (St. Jude Medical, St. Paul, Minnesota) is not cleared for use in the USA. It is a nitinol device that comprises a lobe with barbs (shallower than the body of Watchman or Plaato) that lodges in the body of the LAA to prevent migration. This connects across a waist to an interconnecting disk that occludes the LAA ostium (diameter range 16–30 mm). The device can be recaptured and redeployed. Following implantation, dual antiplatelet therapy for 1 month and subsequently aspirin alone is recommended.19 A second generation of the Amplatzer Cardiac Plug called the Amplatzer Amulet (St. Jude Medical, St. Paul, Minnesota) has been designed with the intention to facilitate the implantation process and reduce complications.

There have been multiple retrospective reports showing a 95% to 99% implantations success with Amplatzer Cardiac Plug in patients not suitable for anticoagulation. Procedural complications include stroke (0–2.3%), device embolism (0–2.3%), and cardiac tamponade (0–3.5%). Strokes have been reported in 0–2.8% patients in follow-ups ranging 6-21 months.[19, 45, 52] There was a 16% rate of mild peri-device leak on TEE evaluations among 52 patients from 7 Canadian centers,53 whereas high rates of device-related thrombus were reported from Brazil (6 of 85, 7%)54 and Spain (5 of 35, 14%).55

As opposed to Watchman there are no RCT data available for the Amplatzer Cardiac Plug. The ACP trial (Amplatzer Cardiac Plug clinical trial; NCT01118299) comparing LAA closure versus anticoagulation with warfarin or dabigatran has been withheld after failure to procure the investigational device exemption.[20]

• **Transcatheter Patch** (Custom Medical Devices, Athens, Greece) is used for occlusion of heart defects and comprises a frameless bioabsorbable device. Balloon inflation is used to appose the device within the LAA, which then adheres to cardiac tissues by formation of fibrin over 48 hours. Innovations are being made to accelerate the adhesion process and optimize percutaneous catheter delivery. In the initial report on 17 patients undergoing LAA closure, the patch did not adhere in 3 patients, was placed beyond the ostium of the LAA in one, and led to sheath thrombosis in one although no strokes were reported at follow-up of one year.[56]

• **Lambre** (Lifetech Scientific, Shenzhen, China) device in placed in the LAA and articulates at the waist with a component that can self-orient itself flush with the LAA ostium. The device has been

engineered to be retrievable, and enable repositioning, and it has been tested in canines.[57]

Epicardial Closure Of Left Atrial Appendage

Epicardial LAA closure obviates some of the risks associated with endovascular closure of LAA related to transseptal puncture, thromboembolism (due to exposure of tissue factor from transseptal puncture and foreign material of the catheters and implanted device to systemic circulation), need for intraprocedural and post implantation anticoagulation, and risk of device dislodgement, erosion and infection. Epicardial LAA closure can be performed during open surgery, for example in combination with valve surgery and atrial maze. Dedicated epicardial LAA closure was initially accomplished with video-assisted thoracoscopic access with selective collapse of the left lung and surgical pericardiotomy.[58] Novel approaches using only subxiphoid pericardial access have also been developed.[59]

Surgical Epicardial Left Atrial Appendage Occlusion

AF patients undergoing cardiac surgery can have their LAA ligated. In a series of 205 surgical mitral valve replacements,[58] also had LAA ligation with a reduction in embolic complications independent of other predictors.[60] In a propensity-score matched cohort of patients operated by a cardiac surgeon, LAA ligation was associated with fewer post-operative strokes [0 of 145 (0%) versus 7 of 115 (6.1%) without LAA ligation].[61]

It is not uncommon to have incomplete LAA occlusion with surgical closure. A TEE evaluation published in 2000 showed incomplete LAA occlusion in 18 of 50 (36%) surgical closures. Further, 9 of these (50%) had LAA thrombus, and 4 (22%) sustained a clinical embolic event.58 In another study 94 patients with surgical LAA closure who underwent TEE prior to electrical cardioversion for post-operative AF, left atrial thrombus was much more likely with incomplete LAA occlusion (16 of 34, 47%) versus complete LAA occlusion (7 of 60, 12%). Suture closure as opposed to oversowing and amputation of LAA was more likely to have residual flow in the LAA (51% versus 17%) and have left atrial thrombus (33% versus 14%).[62] The pilot Left Atrial Appendage Occlusion Study (LAAOS) showed suture ligation having a residual leak on TEE in 6 of 11 (55%) cases and staple closure having a residual stump of LAA in 9 of 33 (27%) cases.63 Another study on[137] surgical LAA exclusions similarly showed 77% of suture ligations having residual flow and 27% of LAA excisions having a residual stump.[64]

LAAOS II incorporated measures to improve efficacy of LAA closure (1) amputation or stapling of the LAA instead of simple oversowing or ligation, (2) intraoperative TEE to evaluate successful closure, and (3) goal for any residual LAA stump to be smaller than 1 cm.19, 65 Overall, surgical excision of the LAA appears to be the most successful technique.[45, 66] The inconclusive success of surgical LAA exclusion and the potential for a high risk of thromboembolism with incomplete exclusion makes it difficult to recommend it for all AF patients undergoing cardiac surgery.[38]

LAAOS III is an ongoing Canadian multicenter trial due in 2019 with 4-year follow-up on 4700 cardiac surgical AF patients randomized to LAA occlusion or no occlusion (NCT01561651).[45]

Specifically designed devices can be used to facilitate quick occlusion of the LAA during open cardiac surgery

• **AtriClip Pro** (AtriCure, West Chester, Ohio) can be used to clip the base of the LAA from the epicardial aspect. It has been reported to be effective in LAA occlusion in ≥96% cases in small series, without associated complications.[67, 68]

• **Tigerpaw System II** (Maquet, Rastatt, Germany) uses a delivery forceps to place the device, with an opposing series of barb connectors in a compliant silicone housing, at the base of the LAA. Connectors on one side have a needle that punctures through the LAA tissue and catches the receptor mechanism on the other side. In a prospective 60-patient study, the reported mean application time was 27 seconds, and two patients required adjunctive sutures. No leaks were seen on 90-day TEE among 54 patients, though residual LAA stump was ≥6 mm in 5 patients.[69]

Percutaneous Epicardial Left Atrial Appendage Occlusion

Aegis Medical (Vancouver, Canada) has developed a percutaneous subxiphoid epicardial approach with a tool to record bipolar electrograms from its jaws to identify and grab the LAA. A preloaded suture with a flexible-size loop and a support wire for fluoroscopic visualization is positioned around the LAA and is tightened and locked. Loss of LAA electrical activity on the bipolar electrograms confirms adequate occlusion of the LAA.[70, 71] The loop can be undone and repositioned, or additional loops placed over the first one if needed.[19, 59] Over time the LAA shrinks and atrophies. Epitek (Bloomington, Minnesota) created a fiber-optic endoscope for visualizing the LAA to facilitate grasping and closure, but further development has been abandoned.

Hybrid Epicardial-Endovascular Approach For Left Atrial Appendage Occlusion

Lariat (SentreHeart, Palo Alto, California) suture delivery device uses a hybrid endocardial-epicardial strategy. An endovascular sheath is placed across the interatrial septum in the LAA ostium. Following contrast angiography to define the LAA anatomy, a magnet-tipped wire is positioned in the LAA. Using percutaneous access a second magnet-tipped wire in the pericardial space attaches to this wire to form a rail across the LAA muscle. A preformed suture loop is positioned epicardially and locked down. Lariat is not feasible when the LAA diameter measures ≥40 mm or the LAA has a superiorly directed body or lobe.[19]

A retrospective series showed successful Lariat placement in 85 of 89 (96%) patients who had a favorable LAA anatomy on CT scan. Four patients had ≤3 mm residual leak. Complications occurred related to transseptal puncture in one and pericardial access in 2 patients. Two patients had severe post-procedural pericarditis, one developed late pericardial effusion, 2 had late non-embolic strokes, and there were 2 sudden deaths. Though ineligibility for anticoagulation was the criterion for Lariat, at 1-year follow-up 55% of patients were on warfarin.[72] In another retrospective study Lariat was placed successfully in 25 of 27 patients, and in 22 there was no residual LAA flow at 4-month TEE. There was one LAA perforation, 3 pericarditis, 1 periprocedural stroke, and 1 late non-embolic stroke.[73]

Anticoagulation Versus Left Atrial Appendage Exclusion

Chronic oral anticoagulation is the benchmark for stroke prevention in non-valvular AF. The role of LAA exclusion depends on the safety and effectiveness in excluding the LAA and how it compares to oral anticoagulation in stroke prevention.[18]

Factors Favoring Anticoagulation Over Left Atrial Appendage Exclusion

Contribution of LAA in stroke: Strokes in AF are not completely attributable to thrombi originating in the LAA, and the source of thrombus for embolism can originate in the left atrial chamber itself. This is particularly true for AF in context of valvular heart

disease like rheumatic mitral valve stenosis.[23] AF is also correlated with atherosclerotic causes of stroke. Only a systemic therapy as opposed to targeted LAA exclusion can diminish such non-LAA related sources of stroke. Oral anticoagulation mitigates the systemic prothrombotic milieu, though attenuation of atherosclerotic risk is better dealt with by statin and antiplatelet therapy.[18]

Evidence base: The anticoagulants approved for stroke prevention in AF including warfarin, dabigatran, rivaroxaban, and apixaban have been studied in rigorous large-scale RCTs in thousands of patients, to establish their efficacy and safety profiles.[34-37] These have been vetted by the regulatory agencies such as the FDA prior to marketing approvals. Warfarin has been in commercial use for 6 decades and has a robust long-term safety record.[34, 38] All LAA closure devices have been in clinical use for a limited time, and long-term efficacy and safety profile is not available. Only the Watchman device has been evaluated in prospective RCTs powered for clinical outcomes in approximately 1100 patients.49, 51 It is unclear if demonstration of clinical benefit for such a device can be extrapolated to other devices.[20] The clinical use of other endovascular and epicardial devices relies on poor quality data. Efficacy data limited to successful exclusion of LAA cannot be extrapolated to clinical benefit. Some devices in commercial use such as the Lariat do not have stroke prevention in AF as an approved indication. The largest series on LAA exclusion with Lariat for stroke prevention had only 89 patients.[72]

Procedural And Device Complications With LAA Exclusion: Interventional LAA exclusion is fraught with risk of complications, although with technological improvements and operator experience, procedural outcomes improve over time.[50] All transvenous methods require transseptal puncture and placement of catheters in the left atrium. Complications include vascular trauma, venous thromboembolism, aortic or coronary artery injury, systemic thromboembolism including stroke, pericardial effusion with cardiac tamponade, and device dislodgement, embolism, erosion or infection. The complications might require pericardiocentesis, blood transfusions, or surgical interventions and can be fatal.[44, 45, 49, 51, 54] Cases of pulmonary artery tear with resultant pericardial bleeding and tamponade have been reported from hooks of the Amplatzer Cardiac Plug.[74, 75] Transseptal puncture and catheters/device in the left atrium pose a risk for systemic thromboembolism and full therapeutic anticoagulation is required during the procedure. Disruption of preformed left atrial thrombi and embolism of debris or air confer additional risk of periprocedural strokes. Screening with TEE to exclude any left atrial thrombus prior to such procedures is obligatory. Pericardial access for percutaneous epicardial techniques requires expertise and can have complications like coronary artery injury, myocardial perforation, diaphragmatic bleeding, hemothorax, intra-abdominal bleeding, liver laceration, and right ventricle-abdominal fistula. LAA ligation leads to infarction of the LAA along with consequent pain and pericarditis. Pericardial access and manipulation in itself poses risk for pericarditis with potential for subsequent recurrences or pericardial constriction.[20] As opposed to LAA exclusion, anticoagulants do not have a substantial upfront risk at the time of initiation.

Incomplete LAA Exclusion And Risk For Device Related Thrombus: Leaks around endovascularly implanted LAA occlusion devices like Watchman and Amplatzer Cardiac Plug occur in 30% to 60% of cases due to eccentric oval shape of the ostium, and there can be a residual LAA stump with Watchman and epicardial closure devices.[19, 76] Though retrospective analyses suggest that peri-device leaks are usually small with brisk flow and are not high risk for thromboembolism, these are nonetheless a cause of concern.19, 76 Endocardially placed occlusion devices have a risk of thrombus formation on the exposed device surface, and either warfarin or dual antiplatelet therapy is recommended for 3 to 6 months till endothelialization of the exposed surface is complete. Regardless, there was a 4% rate of Watchman device-related thrombus in the PROTECT-AF trial and ASAP registry,[46, 50] and there have been numerous well-documented reports of thrombus formation on various devices and embolic complications.[47, 54, 55, 77-79] Incomplete epicardial closure of the LAA might have a subsequent higher risk of thromboembolism.[58, 62, 80] Reopening of the Lariat suture has been reported81 as has left atrial thrombus following LAA closure with Lariat.[82-84]

Large-Scale Feasibility: Anticoagulants are easy to prescribe and administer for the providers, and easy to procure and use for the patients without need for any sophisticated operator expertise or technology. LAA exclusion, on the other hand, is a technically complex endeavor that requires expensive medical care including cost of the device, equipment, advanced catheterization lab facility, backup cardiac surgical care, as well as expensive periprocedural and followup testing like CT scans, cardiac MRIs, and TEEs. Further, patients and operators are exposed to radiation with stochastic and cumulative risks.

Candidacy For Laa Exclusion: All LAA closure devices need appropriate sizing to match the LAA anatomy. Due to variability in shape and size of the LAA, some patients with unsuitable anatomy are ineligible for these devices. Percutaneous epicardial techniques might not be feasible in patients with pericardial adhesions due to pericarditis or prior surgery.

Loss of physiologic functions of LAA: LAA exclusion causes a loss of physiologic functions of the LAA including regulation of fluid and electrolyte homeostasis and functions as a reservoir and booster of left atrial function, though in most patients with AF these might already be dysfunctional.[32]

Factors Favoring Left Atrial Appendage Exclusion Over Anticoagulation

Long-Term Convenience And Dependability: Despite its benefit, a fifth of the AF patients with CHADS2 score ≥2 in the USA are not on anticoagulation.[85] There are many barriers to anticoagulation in high-risk AF patients, foremost being concern for bleeding complications.18 Patients with higher bleeding risk scores are less likely to be anticoagulated.85 Additionally, many patients are non-compliant with anticoagulants due to lack of adequate patient education, no overt clinical benefit, logistical challenges in INR monitoring with warfarin, adverse effects like bruising and other psychosocioeconomic reasons.10, 86 Over long term, adherence to anticoagulation might drop as low as 20% to 30% range.[87] On the other hand, LAA exclusion is a one-time procedure, and although with endovascularly placed devices, anticoagulation or dual antiplatelet therapy might be warranted for up to 6 months, over the long term there is little scope for interruption in benefit due to non-compliance.

Bleeding Complications With Anticoagulants: Risk of bleeding with anticoagulation is the primary reason for development of LAA closure techniques. Warfarin increases intracranial bleeding

by an absolute 0.2% per year compared to aspirin.34 Despite less intracranial bleeding, newer oral anticoagulants still pose a substantial bleeding risk for many patients. Gastrointestinal bleeding occurs in 2.1% to 3.6% per year, and patients with highest bleeding risk were not included in the landmark RCTs.35-40 Some patients might have absolute contraindications to anticoagulation like recurrent falls, history of intracranial hemorrhage, or bleeding diathesis. LAA closure is an attractive alternate to anticoagulation in patients at risk of bleeding. It needs to be noted that for endovascularly implanted devices like Watchman and hybrid procedures like Lariat still require intraprocedural full therapeutic anticoagulation with heparin. Endovascular devices additionally require warfarin or dual antiplatelet therapy at least for 6 weeks post-implantation.

Cost-Effectiveness: A cost-effectiveness analysis on percutaneous LAA occlusion for non-valvular AF as compared to warfarin and dabigatran was performed from the perspective of the Ontario Ministry of Health and Long Term Care, the third-party payer for insured health services in Ontario, Canada. The average discounted lifetime cost was $21,429 for a patient taking warfarin, $25,760 for a patient taking dabigatran, and $27,003 for LAA occlusion. Compared with warfarin, the incremental cost-effectiveness ratio for LAA occlusion was $41,565 per quality-adjusted life year while dabigatran was extendedly dominated.[88]

Combination Of Left Atrial Appendage Exclusion With Antithrombotic Drugs

Certain patients with AF remain at high risk of thromboembolism despite therapeutic anticoagulation. Predictors of cardioembolic strokes despite anticoagulation include dense spontaneous LAA echo contrast, reduced LAA emptying velocities on TEE,89 and systemically elevated levels of D-dimer90 or von Willebrand factor.[91] These predictors need further validation, and whether supplementing anticoagulation with LAA closure in such patients at persistently elevated risk will lead to better outcomes is not known. Such a two-pronged strategy might be considered on an individual case basis, especially in cases of anticoagulation failure with LAA thrombi and embolic events.

Left Atrial Appendage Exclusion Added To Catheter Ablation For Atrial Fibrillation

AFFIRM was the largest RCT evaluating rhythm-control versus rate-control strategy for AF and did not show any benefit in mortality or stroke with rhythm control.[92] However, a subanalysis suggested that mortality was reduced in patients that maintained sinus rhythm and was likely offset by adverse effects of antiarrhythmic drugs.[93] Furthermore, retrospective analyses specifically looking at patients that maintain sinus rhythm following catheter ablation of the left atrium suggest that the risk of thromboembolism is exceedingly small.[17, 94-96]

Electrical isolation of the LAA has been described as an adjunct to pulmonary vein isolation for maintaining sinus rhythm in patients undergoing catheter ablation of atrial fibrillation. Though most of the benefit is reserved for patients with AF triggers emanating from the LAA, some benefit is assumed from alteration in the substrate available to sustain AF.97 However, electrical isolation of the LAA risks loss of mechanical function of the LAA with potential for thromboembolism in the absence of anticoagulation.[98] Epicardial LAA occlusion on the other hand, in addition to excluding the LAA to minimize stoke risk, leads to electrical isolation with subsequent infarction and atrophy.[70, 71] Therefore, the possibility of using epicardial LAA exclusion to complement pulmonary vein isolation in patients with AF needs to be explored. In addition, novel technological developments are underway to use the epicardial access for autonomic modulation by targeting neural ganglia in epicardial fat or for an entirely epicardial ablation procedure to further minimize thromboembolic risks.[99] To this end, minimally invasive thoracoscopic epicardial pulmonary vein isolation with LAA excision and partial cardiac denervation has been developed.100 Sole-Therapy Treatment of Atrial Fibrillation (RESTORE SR II, NCT 00566176) is a prospective feasibility study on 25 patients evaluating minimally invasive epicardial bipolar radiofrequency ablation for pulmonary vein isolation along with LAA exclusion.

As opposed to electrical isolation of the LAA with catheter ablation, epicardial exclusion affords better efficacy and efficiency in electrically isolating the LAA and obviates the thromboembolic risk from electrical standstill in the LAA.[98, 99] However, prior to clinical adoption, the combining epicardial LAA exclusion with ablation for AF needs proof of benefit on both accounts – reduction in AF recurrence and acceptably low stroke risk without long-term anticoagulation. Preliminary observational data suggests that combination of Lariat ligation of LAA in addition to catheter ablation for persistent AF improves reduces AF recurrence and need for repeat catheter ablation.[101]

Current Guideline Recommendations For Stroke Prophylaxis In Atrial Fibrillation

The current AHA/ACC/HRS Guideline for AF focuses on antithrombotic drug therapy for prevention of cardioembolic events. It recommends risk-stratification based on CHA2DS2-VASc score and informed discussion with patients regarding use of anticoagulation for stroke prevention especially in context of bleeding risk. In patients with non-valvular AF and CHA2DS2-VASc score ≥2 oral anticoagulant therapy with warfarin, dabigatran, rivaroxaban or apixaban is recommended (Class I recommendation). For those with CHA2DS2-VASc score 0, omission of antithrombotic therapy is reasonable (Class IIa). In patients with CHA2DS2-VASc score 1, no antithrombotic, aspirin or oral anticoagulation may be considered (Class IIb). For patients undergoing cardiac surgery, they specify that LAA occlusion may be considered (Class IIb). The Guideline makes a note of the percutaneously placed devices, Watchman, Amplatzer Cardiac Plug and Lariat, but do not give any indications for their use.[38] On the other hand, the European (ESC) guideline states that interventional percutaneous LAA closure may be considered in patients at high stroke risk and contraindications to chronic oral anticoagulation (Class IIb).[102]

Future Directions

Several Studies Of Percutaneous Laa Exclusion Are In Progress. The Canadian Left Atrial Appendage Occlusion Study Iii (Laaos Iii, Nct01561651) Is Randomizing 4700 Af Patients With Cha2ds2-Vasc ≥2 Undergoing Cardiac Surgery To Laa Excision Versus No Excision. Eligible (Nct01628068) Is Spanish Multicenter Rct Enrolling 120 Patients To Evaluate Amplatzer Laa Closure With 3-Month Dual Antiplatelet Therapy Versus Standard Anticoagulation For Af Patients With Cha2ds2-Vasc ≥3 And Gastrointestinal Bleeding. Left Atrial Appendage Occlusion Versus Usual Care In Patients With Atrial Fibrillation And Severe Chronic Kidney Disease (Watchafib, Nct02039167) Is Randomizing 300 Patients With Cha2ds2-Vasc ≥2

And Estimated Glomerular Filtration Rate (Egfr) <30 Ml/Min To Warfarin Anticoagulation Versus Watchman Laa Closure With 6 Months Of Dual Antiplatelet Therapy. A Prospective Observational Study Enrolling 150 Patients Is Evaluating Watchman Versus Lariat For Laa Exclusion (Nct01695564). Feasibility Studies Are Evaluating Newer Laa Exclusion Devices Like The Fourth Generation Of Watchman Device (Evolve, Nct01196897), Lambre (Nct02029014), And Open Surgical Tigerpaw System Ii (Nct00962702). There Is A Need For Head-To-Head Comparisons Of Laa Closure Devices With The Newer Oral Anticoagulants And Of Various Techniques For Laa Closure With Each Other. Additionally, Novel Techniques Like Completely Percutaneous Laa Exclusion And Pulmonary Vein Isolation Through Pericardial Access Need To Be Developed And Evaluated.

Conclusions

Stroke is the most dreadful clinical outcome of AF. There have been tremendous scientific and technological advances in mitigating the risk of stroke. Chronic oral anticoagulation remains the backbone for reducing the public health burden of stroke in the general AF population. Newer oral anticoagulants, with simple dosing schemes without need for therapeutic level monitoring and with potentially lower risk of life-threatening bleeding when compared to warfarin, have been a major advance. However, oral anticoagulation has limitations related to non-adherence with treatment and increased risk of bleeding complications. Various validated and emerging techniques to exclude the LAA from the systemic circulation offer an alternate option for stroke prevention, especially appealing for patients at high risk of bleeding complications or absolute contraindications to anticoagulants. In this milieu of increasing options for stroke prevention, in the context of other advances in management of AF like innovations in interventions to maintain sinus rhythm, the physician needs to critically evaluate the scientific evidence to determine pros and cons of various options. Keeping the patients' best interest utmost, the treatment for each patient needs to be individualized and based on the clinical, physiologic, anatomic, and socioeconomic considerations.

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