Emerging Strategies for Stroke Prevention in Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is a common cause of stroke. In the US nearly 800,000 people suffer stroke each year and about 130,000 die as a result. Stroke care accounts for an estimated US$34 billion in health care expenditures in the US each year. Among all strokes, AF is the cause in 15–20 % of cases. The incidence of AF in the US has grown steadily over time to a current estimate of 6.1 million with the condition. With the anticipated growth in the worldwide AF population, the need for effective new therapeutic strategies for stroke prevention is clear.

Keywords

Atrial fibrillation, stroke prevention, left atrial appendage occlusion, rhythm control

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It is presumed that the pathogenesis of stroke in atrial fibrillation (AF) patients is due to embolization of thrombus from the left atrium. Within the left atrium, the left atrial appendage is the predominant site of thrombus formation. In a study of 233 patients with new onset AF of greater than 48 hours in duration who were not anticoagulated, left atrial appendage thrombus was present in 15 % of patients.[1] Among patients with a recent embolic stroke, the association of atrial fibrillation and left atrial appendage thrombus is present in more than 20 % of patients.[2] In patients with documented left atrial appendage thrombus and AF discovered during transesophogeal echochardiograhy (TEE), the subsequent incidence of transient ischaemic attack (TIA) is nearly 10-fold higher than those without thrombus.[3]

Systemic anticoagulation with warfarin has been shown to reduce the incidence of stroke in AF patients by about two thirds.[4] In spite of the proven efficacy of warfarin therapy for stroke prevention, the effective and safe use of this agent has proved challenging. In particular, frequent blood tests, dietary effects, and pharmacologic interactions with other therapeutic agents limits effective use of this agent. The requirement for tight control of the intensity of anticoagulant effect of warfarin has resulted in frequent occurrences of under- and overdosing. Despite intention-to-treat with warfarin, 50 % of patients who experience a stroke are found to have subtherapeutic anticoagulation.[4] Supratherapeutic anticoagulation raises the risk of severe bleeding episodes including intracranial hemorrhage.[5] Among patients prescribed warfarin, one in four discontinue the medication within the first year of use.[6]

Recently, the introduction of a series of novel oral anticoagulants (NOACs) has provided therapeutic alternatives to warfarin in patients with preserved renal function. In a meta-analysis of the major clinical trials of these agents including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixoban, rivaroxaban and edoxaban, the incidence of stroke or systemic embolic events was reduced by 19 % relative to patients treated with warfarin.[7] Although the risk reduction for ischemic stroke was similar to warfarin in the meta-analysis, the incidence of intracranial hemorrhage (a separate cause of stroke) was reduced by 52 %. In spite of the enhanced stroke prevention efficacy associated with the NOACs, a 25 % increase in gastrointestinal bleeding was observed with these agents.

A new standard risk calculation has now been widely adopted because of bleeding risks inherent in systemic oral anticoagulation. This has helped guide the decision based on quantification of the risk of thromboembolic events in patients with non-rheumatic AF. Known by the acronym $CHADS_2$-VASc (C = congestive heart failure; H = hypertension; A = age; D = diabetes mellitus; S2 = Stroke and female sex; Vasc = vascular disease), this risk calculation assigns points for the known stroke risk factors in non-rheumatic AF made up by female sex, a history of congestive heart failure, hypertension, age >65 years, age >75 years, diabetes mellitus, vascular disease, and two points for a prior history of stroke. In both men or women with one additional risk factor, oral anticoagulation is recommended. The effect of this new risk calculation scheme, relative to the older $CHADS_2$ system, is to include a larger portion of patients with AF in the recommendation for oral anticoagulant. The predicted effect of these recommendations together with the new oral anticoagulants should be more comprehensive stroke protection in the AF patient population. Despite this, many patients have contraindications to oral

anticoagulation due to fall or bleeding risks and proven alternative stroke prevention strategies are needed.

Rhythm Control

There have been several randomized trials comparing rate versus rhythm control in patients with AF. These trials have demonstrated similar rates of death or embolism regardless of the strategy.[9–13] Of these, the A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation (AFFIRM) trial was the largest, randomizing 4,060 patients with recurrent AF to rate control (using beta blockers, calcium channel blockers or digoxin) and anticoagulation with warfarin compared to the most effective antiarrhythmic drug. All patients were initially anticoagulated, but those in the rhythm control group who maintained sinus rhythm for at least four, but preferably 12, consecutive weeks could be withdrawn from warfarin. In the rhythm control arm the most frequently used antiarrhythmics were amiodarone (38 %) and sotalol (31 %).

By the end of the 3.5 years of follow-up, 63 % had been prescribed amiodarone at least once. Patients initially assigned to rhythm control crossed over to the rate control group in 17 % of patients at one year and 38 % of patients at 5 years. This was mainly due to a failure to maintain sinus rhythm or intolerance to the antiarrhythmic medications. After the 3.5 years of follow-up the rate control arm had a trend toward a significant decrease in all-cause mortality (21.3 % versus 23.8 %; HR 0.87; 95 % CI [0.75–1.01]). There was no statistical difference between the groups in cardiac death, arrhythmic death or deaths due to ischemic or hemorrhagic stroke.[9] However, groups without a history of heart failure and those aged >65 years or older had a significant reduction in mortality with rate control.[14] There was a higher rate of stroke among those patients who had discontinued warfarin, suggesting that anticoagulation should be continued even if a rhythm control strategy is pursued. This is in part due to a high rate of recurrence of AF, even if asymptomatic.[9]

Restoration of sinus rhythm can be a valuable goal for many patients with symptoms or hemodynamic consequences from AF. Antiarrhythmic medications have potential side effects, can be proarrhythmic and can increase mortality.[15] The 2014 AHA/ACC/HRS guidelines regarding the management of patients with AF suggest that catheter ablation is reasonable for patients who have failed at least one antiarrhythmic medication.[16] Potential procedural risks of ablation, however, must be weighed carefully against risks of long-term use of antiarrhythmic drugs.

In a multicenter Italian registry, major complications occurred in 4 % of patients (2.2 % vascular access, 0.5 % cardiac tamponade, 0.6 % pericarditis, 0.2 % transient ischemic attacks, 0.2 % stroke and 0.1 % had phrenic nerve paralysis).[17] Complications such as pulmonary vein stenosis or atrial-esophageal fistulae happened rarely but were probably under recognised if they occurred late. Despite the evolution of AF ablation over the past several years, recurrence rates are still high enough to warrant continuation of long-term anticoagulation. A systematic review of six trials suggested recurrence of AF after one year occurred in 20–40 % of patients after catheter ablation and in greater than 70 % of patients on antiarrhythmic drugs.[18] Hence, rhythm control with antiarrhythmic medications or catheter ablation is useful for reducing symptoms or hemodynamic consequences of AF but should not be used as a means of reducing thromboembolic risk.

Left Atrial Appendage Occlusion

The left atrial appendage (LAA) has been shown to be the location of thrombus formation 91 % of the time in patients with non-valvular AF.[19] The structure of the LAA varies and consists of two lobes in 54 % of the population and three lobes in 23 % of the population.[20] There have also been several studies to show the LAA has important functions in the release of atrial and brain natriuretic peptides, and loss of this may have adverse consequences on volume status after LAA occlusion.[21,22] Up to one-third of patients who would benefit from anticoagulation based on their $CHADS_2$ score cannot take warfarin due to various contraindications.[23] Hence, there has been increasing interest in physically occluding the LAA to decrease risk of thromboembolic events associated with AF.

Occlusion of the LAA was first achieved surgically in 1949 in patients with rheumatic AF. The surgical procedure has evolved over the past several decades in its methods and efficacy, and there has been increasing interest recently in devising less invasive methods to occlude the LAA. One of the first percutaneous methods to occlude the LAA was the Thorascopic Extracadiac Obliteration of the Left Atrial Appendage for Stroke Risk Reduction in Atrial Fibrillation (LAPTONI) procedure, which used a left lateral thoracotomy approach to ensnare the LAA to the base from the epicardial aspect.[24] Since then, there have been several percutaneous methods developed to occlude the LAA from either the epicardial on endocardial approaches.

The LARIAT® device (SentreHeart) was created as a catheter-based method to ensnare the LAA from the epicardial aspect. An endorcardial balloon catheter with a magnetic tip is placed via transseptal access into the LAA. With pericardial access, a separate magnetic tipped catheter is advanced to the epicardial aspect of the LAA to meet at the appendiceal tip with the endocardial magnetic balloon. The LAA ostium is identified with balloon inflation of the endocardial catheter, and a pre-tied suture is advanced from the epicardial aspect over the magnetic guidewire rail to the base of the LAA. The suture is tightened and the endocardial balloon is deflated and removed. Through this technique there is no permanent endocardial structure, which limits risk of infection or device embolization.

Procedural complications can occur with access of the dry pericardium, transseptal access and perforation or laceration of the LAA. Miller et al. published a cohort of 41 patients who had undergone LARIAT. The acute success of the procedure, defined as complete occlusion of the LAA with <1 mm LAA leak on intraprocedural TEE, is approximately 93 %.[25] Limitations to successful closure included large LAA size, numerous lobes, unfavorable LAA anatomy or pericardial adhesions. Long-term success has been variable and residual LAA leak seen on a CT scan or TEE at 3 months was seen in 24 % of patients.[25]

A larger multicenter study from the US Transcatheter LAA Consortium showed successful suture deployment in 94 % of patients.[26] Major complications including death, myocardial infarction, stroke, or cardiac surgery occurred in 9.7 % of patients. Other complications included significant pericardial effusion (10.4 %) and major bleeding (9.1 %). At follow-up TEE 1–3 months post-procedure, there was a high incidence of residual leak (20 %).[26] The major advantage of LARIAT is that anticoagulation

is not required after complete occlusion of the LAA. However, due to the high incidence of residual leak afterwards, many centres will continue anticoagulation for at least 1–3 months post-procedure if there is no residual leak seen on follow-up TEE.[27,28] Randomized, controlled trials are required to further evaluate the long-term safety and efficacy of the LARIAT device as an alternative to anticoagulation.

Several endocardial LAA occlusion devices have also been developed. The most notable of these is the WATCHMAN™ device (Boston Scientific). This parachute-shaped device is a self-expanding nitinol cage with fixation anchors and a membrane made of polytetrafluoroethylene. It is available in various sizes (20 mm, 21 mm, 24 mm, 27 mm and 33 mm) and should be sized 10–20 % larger than the LAA. A sheath is placed via transseptal access into the LAA over a pigtail catheter. The device is then advanced through this sheath and sized and placed in the LAA ostium under TEE and fluoroscopic guidance. This device requires that patients are anticoagulated with warfarin for at least 45 days post-procedure.

The WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT) AF study was the first randomized, controlled trial comparing a LAA occlusion device versus warfarin.[29] This was a non-inferiority study for 707 patients with non-valvular AF who were eligible for anticoagulation with warfarin. The patients were randomized in a 2:1 ratio for WATCHMAN or anticoagulation with a follow-up of 18 months. The device was successfully deployed in 91 % of patients. If follow-up TEE demonstrated residual flow ≤3 mm around the device, warfarin was discontinued in 86 % of patients at 45 days and 92 % of patients at 6 months. The primary efficacy endpoint was a composite of stroke, cardiovascular death and systemic embolism occurred in 3.0 per 100 patient-years in the device group and 4.9 per 100 patient-years in the warfarin group (RR = 0.62; 95 % CI [0.35–1.25]). The probability for non-inferiority of the intervention group was more than 99.9 %. The primary safety endpoint included major bleeding, pericardial effusion, and device embolization, which occurred more frequently in the device group than in the control group (7.4 versus 4.4 per 100 patient-years, RR = 1.69, 95 % CI [1.01–3.19]). There were five procedural-related ischemic strokes, 22 pericardial effusions and three device embolizations.[11] Due to the higher rate of the primary safety endpoint in the WATCHMAN group and the lack of long-term follow-up data, the US Food and Drug Administration requested a second randomized trial prior to device approval.

The Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy (PREVAIL) study was designed to validate the initial results of PROTECT AF.[30] This trial randomized 407 patients with a mean $CHADS_2$ score of 2.6 in a 2:1 fashion to device versus warfarin. At 18 months, the rate of the first co-primary efficacy endpoint (composite of stroke, systemic embolism and cardiovascular/unexplained death) was 0.064 in the device group and 0.063 in the control group with a RR of 1.07 with an upper bound of 1.89, which was higher than the prespecified criterion of 1.75 for non-inferiority (CI 95 %). Although this trial did not achieve non-inferiority for this endpoint, it did achieve non-inferiority for the second co-primary efficacy endpoint (stroke or systemic embolism >7 days post-randomization) at a rate of 0.0253 in the device group compared to 0.0200 in the control group (95 % credible interval (CrI) -0.0190–0.0273). Early safety events occurred in 2.2 % of the patients in the WATCHMAN arm, significantly lower than in PROTECT AF, achieving the pre-specified performance goal. A significant improvement in implant success rate of 95.1 % was noted compared to 90.9 % in the PROTECT AF trial.

The Continued Access Protocol (CAP) registry was designed to gain further efficacy and safety data in a non-randomized fashion in patients undergoing WATCHMAN implantation.[31] Combining longer-term data from PROTECT AF and CAP, there was a significant decrease in procedure or device-related safety events. The rate of serious pericardial effusion decreased from 5.0 % in PROTECT AF to 2.2 % in CAP (p=0.019) and periprocedural stroke decreased from 0.9 % to 0 % (p=0.039).[31] There was also a reduction in safety events noted from the first half of the PROTECT AF patients compared to the second half of the study. This signifies a reduction of safety events with improved operator experience.[31] Newer data from the PROTECT AF study with a follow-up of 3.8 years was published in 2014. Non-inferiority of WATCHMAN compared to warfarin was repeatedly demonstrated. In addition, superiority for the primary efficacy endpoint (composite of stroke, cardiovascular death and systemic embolism) was seen for the first time. Also, the primary safety endpoint was similar to the warfarin group. The device group had a lower rate of hemorrhagic strokes in addition to a lower mortality rate with a 34 % relative risk reduction compared to warfarin.[32] The results of the PROTECT AF and PREVAIL trials, in combination with the CAP registry and long-term follow up data from PROTECT AF, led to FDA approval of WATCHMAN in March 2015, in higher-risk patients (CHADS-VASc score of ≥2) with non-valvular AF as an alternative to long-term anticoagulation.

One of the major limitations to WATCHMAN is the necessity for anticoagulation for at least the first 45 days post-implant. This is a crucial consideration since one of the main indications for LAA occlusion is a contraindication to chronic oral anticoagulation. This prompted the ASA Plavix Feasibility Study with WATCHMAN Left Atrial Appendage Closure Technology (ASAP) study,[33] which was a prospective, non-randomized study in patients who underwent WATCHMAN with a contraindication to oral anticoagulation. Instead of warfarin for the first 45 days, 150 patients with non-valvular AF and a mean $CHADS_2$ score of 2.8 who underwent WATCHMAN received continuous aspirin and clopidogrel for six months. The primary efficacy endpoint was a composite of ischemic stroke, hemorrhagic stroke, systemic embolism and cardiovascular/unexplained death, with a mean follow-up of 14 months. Serious procedure- or device-related safety events occurred in 8.7 % of patients.

All-cause stroke or systemic embolism occurred in four patients (2.3 % per year), ischemic stroke in three patients (1.7 % per year) and hemorrhagic stroke in one patient (0.6 % per year). The ischemic stroke rate was less than would be expected by $CHADS_2$ score.[33] This study suggested that LAA occlusion with WATCHMAN could be safely performed without a warfarin transition in patients with a contraindication to anticoagulation. These results must be interpreted with caution, however, since the study was small and observational in nature.

Another significant limitation to the WATCHMAN trials is that the device was compared only to warfarin. The novel oral anticoagulant

medications are non-inferior, if not superior, to warfarin in efficacy and safety. The benefit of LAA occlusion with the rising use of NOACs for stroke risk reduction of non-valvular AF is unclear.

The Amplatzer™ Cardiac Plug (ACP) (St Jude) is another potential option for LAA occlusion. It was originally used for closure of a patent foramen ovale or atrial septal defect. The device was redesigned and used for the LAA. The first generation is a self-expanding nitinol wire mesh and polyester patch with a lobe and disk connected by a central waist. The device is delivered across a transseptal puncture into the LAA, and the disk unfolds to cover the appendage. There have been several small clinical studies showing successful LAA occlusion in approximately 98 % of the patients with risks of procedural complications in approximately 9.8 % of the patients.[34] This device has been implanted under local anaesthesia as well as under general anaesthesia and post-procedure anticoagulation is not required. However, despite dual antiplatelet therapy post-procedure follow-up imaging detected thrombus formation on the device in 17 % of the patients. Other complications included stroke, major bleeding, pericardial effusion and device embolization. A second-generation device (ACP2 Amulet) has been developed that allows closure of larger LAA, improves stability, decreases the risk for embolization and is repositionable.[35] This device is not currently available in the US.

Several other LAA occlusion devices such as WaveCrest™ (Coherex Medical), LAmbre™ (Lifetech), and CellAegis Devices are in development and early stages of testing.[36] There are limited clinical safety and efficacy data on these so far but studies are ongoing. LAA occlusion represents a growing therapy for thromboembolic stroke risk reduction in patients with non-valvular AF, particularly in those who are unable to take long-term anticoagulation. More prospective trials with longer follow-up durations are needed in addition to comparisons against novel oral anticoagulants.

Transient Anticoagulation at the Time of Atrial Fibrillation Detection

In patients with whom rhythm control strategy is the preferred therapeutic option the duration of AF may play a critical role in determining the period of their most significant thromboembolic risk. Patients with AF lasting two days or more have a 5–7 % risk for clinical thromboembolism if cardioversion is not preceded by several weeks of warfarin therapy.[37–40] The risk decreases to 0–1.6 % with 2–4 weeks of warfarin prophylaxis or short term anticoagulation therapy in addition to screening with tranesophageal echocardiogram.[37,39] Hence, in patients with AF duration less than 48 hours, the benefit of thromobembolic risk reduction by anticoagulation warrants a closer examination to determine if these patients with short AF episodes require any anticoagulation therapy.

A prospective observational study attempted to estimate the thromboembolic risk of patients with AF duration less than 48 hours.[41] A cohort of 357 patients admitted to a hospital with AF duration less than 48 hours were followed. One hundred and eighty-one patients (48.3 %) had a prior history of AF, and 23 (6.1 %) had a prior history of thromboembolism. Three hundred and fifty seven patients (95.2 %) converted to sinus rhythm during the index admission. Spontaneous conversion occurred in 250 patients (66.7 %) and pharmacological or electrical cardioversion was done in one hundred and seven patients (28.5 %). Three patients (0.8 %) who had converted spontaneously had a clinical thromboembolic event. One patient had a stroke, one had a TIA and one had a peripheral thromboembolus. None of the three patients had a prior history of AF or thromboembolism and all had normal left ventricular systolic function.

It was concluded that in patients presenting with AF duration less than 48 hours, the likelihood of cardioversion-related clinical thromboembolism was low. A review of the published data,[42] mainly from emergency medical patient encounters, supports the practice of cardioversion and discharge from the emergency room as safe and adequate rhythm control management for patients presenting with recent onset AF of less than 48 hours. The 2014 AHA/ACC/HRS AF guidelines[16] assigns a Class IIb indication for cardioversion of patients with AF or atrial flutter of less than 48 hours duration, who are at low thromboembolic risk without the need for post cardioversion oral anticoagulation.

Pacemakers and cardiac defibrillators function as implanted cardiac rhythm monitors (ICMs) that provide a unique window on the occurrence of AF episodes. A targeted approach is to anticoagulate patients with ICMs during their most vulnerable period for thromboembolic risk during AF episodes may be an alternative therapy. This could potentially reduce chronic anticoagulation use, thereby reducing cost, bleeding risks and improving quality of life. The general approach of chronic anticoagulation in AF patients may be partly due to limitations in the ability to immediately and precisely respond to AF episodes when they occur. Hence, in patients with non-valvular, paroxysmal AF with brief episodes and who may otherwise be asymptomatic, the risk of bleeding from chronic anticoagulation may not be warranted. An alternative anticoagulation strategy may be supported by evidence for a temporal relationship between subclinical AF and embolic events.

The Asymptomatic Stroke and Atrial Fibrillation Evaluation in Pacemaker Patients (ASSERT) trial[43] followed a cohort of 2,580 patients who had ICMs and no history of AF. During follow-up, 51 patients experienced stroke or systemic embolism. Of the 51 patients 51 % had subclinical AF (SCAF) recorded by their devices. In 18 patients (35 %) SCAF was detected before stroke or systemic embolism. However, only four patients (8 %) had SCAF within 30 days of the thromboembolic event. In patients with SCAF detected greater than 30 days before their thromboembolic event, the most recent AF episode to the time of the thromboembolic event had a median interval of 339 days. The authors inferred that, although there is an increased risk of thromboembolic events in patients with SCAF, very few had SCAF in the month before the events. Hence, with remote monitoring technology and real-time monitoring for the development of AF provided by ICMs, a new approach for targeted anticoagulation therapy may be considered in low-risk, low-burden and asymptomatic non-valvular AF patients.

The Rhythm Evalution for Anticoagulation with Continuous monitoring Trial (REACT.COM)[44] is a pilot study that has been recently completed. It is designed as a single-arm, prospective multicenter study to test this strategy. The primary goal of the study was to reduce the duration of chronic anticoagulation therapy in addition to reducing the risk of stroke and bleeding with the use of ICM-guided novel oral anticoagulant

(NOAC) therapy in response to specific AF episodes. Sixty-nine patients with nonpermanent AF were enrolled. Patients were initially monitored for 60 days to document that no AF episodes longer than one hour were recorded. NOACs were subsequently discontinued but reinitiated for a 30-day duration in response to an AF episode longer than one hour diagnosed through daily ICM transmissions. Over a mean follow-up of 466 ± 131 days, compliance with transmission was 98.7 %. AF episodes longer than one hour were noted in 18 (31 %) patients, resulting in a total time on NOAC of 1,472 days. The authors concluded that there was a 94 % reduction in the duration of NOAC therapy compared to chronic anticoagulation. There were three traumatic bleeding events in patients on aspirin, and three possible TIAs were observed in patients on aspirin with $CHADS_2$ score of one. No strokes or death were noted over the study duration. This study demonstrated the feasibility of a tailored anticoagulation therapy for AF patients with the use of constant monitoring and rapid initiation of treatment to limit total anticoagulation therapy time significantly. While a larger study is necessary to validate the findings of this study, it demonstrates a potential opportunity for individualised management of anticoagulation therapy while potentially decreasing bleeding risks associated with chronic anticoagulation.

Conclusion

Stroke due to thromboembolism is a primary concern for patients with AF. Stroke prevention by systemic anticoagulation with an oral anticoagulant remains the standard of care for management of this risk. The newer $CHADS_2$-VASc thromboembolic risk estimation tool has shifted the indications for chronic anticoagulation to include a significantly greater proportion of the AF patient population. The new NOAC agents appear superior to warfarin in terms of ease of use and lower risk of intracranial bleeding. Pooled data from major clinical trials of the NOACs suggest a superior protection against stroke relative to warfarin. Despite this, a significant fraction of the AF patient population has contraindications for chronic anticoagulation. In that group, the development of strategies for occlusion of the LAA has emerged as a viable therapeutic alternative. At present, data do not support rhythm control as a means for reducing thromboembolic risk. ■

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