Approaches to Left Atrial Appendage Closure: Device Design, Performance, and Limitations

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ABSTRACT: Up to 6.1 million people in the United States have atrial fibrillation (AF), which is associated with an increased risk of stroke. Oral anticoagulants are the mainstay of stroke prevention in AF. For decades, warfarin was the only available drug, fraught with compliance limitations, a narrow therapeutic window, and a high risk of hemorrhage. Pharmacologic developments have produced new anticoagulants that have improved the rates of stroke related to AF; however, they still confer a high risk of bleeding, making them unsuitable for some patients.

Studies have shown that roughly 90% of strokes in patients with AF occur in the left atrial appendage (LAA). This understanding has prompted the development and testing of novel percutaneous strategies for LAA closure as an alternative to anticoagulation therapy. The following review examines the relative merits and shortcomings of these strategies and explores future prospects in the prevention of AF-related stroke.

INTRODUCTION

Over the past decade, tremendous progress has been made towards preventing thromboembolic complications in atrial fibrillation (AF). Novel anticoagulant drugs (NOACs) have revolutionized pharmacological stroke prevention in AF, overcoming the shortcomings of warfarin.[1–4] Notwithstanding the improved outcomes afforded by NOACs—namely reduced stroke and bleeding—all anticoagulants suffer from inextricable bleeding risks, which makes them unsuitable for certain patients. Knowledge that the left atrial appendage (LAA) is the most common anatomical origin of cardioembolic strokes[5] has prompted the development of clinical and procedural strategies to exclude the LAA either surgically or percutaneously from the circulation. This review discusses the rationale behind these strategies, their relative merits, and future prospects in preventing AF-related stroke.

EXCLUSION OF THE LAA VIA SURGICAL APPROACHES

Surgical resection of the LAA to prevent arterial embolization in AF was proposed by Madden decades ago.[10] Various forms of surgical ligation or excision became routine; however, residual flow may lead to embolism recurrence. The pilot Left Atrial Appendage Occlusion Study (LAOOS) assessed closure efficacy after various LAA surgical ligation strategies and found that 34% of patients had residual flow into the LAA after surgical exclusion,[11] although it is least frequent with LAA excision.[12-14] Correlations of surgical LAA closure with stroke reduction have provided conflicting results,[15,16] and a large randomized trial (LAOOS III) is currently ongoing.[17]

The AtriClip device (AtriCure, Inc.) is a surgically implanted clamp of the LAA.[18] In the EXCLUDE study, complete LAA closure was achieved in 95%[19] of patients who completed 3-month imaging follow-up, but stroke prevention data are lacking. Further studies using a stand-alone thoracoscopic implantation of the AtriClip are ongoing in the Stroke Feasibility Study.[20]

PERCUTANEOUS LAA OCCLUSION DEVICES

PLAATO

The PLAATO device (ev3, Inc.) was the first device designed for percutaneous LAA closure.[21] It was made of a nitinol cage covered with a polytetrafluoroethylene membrane (Figure 1 A). In a multicenter registry of 64 high-risk patients with contraindications to warfarin,[22] the procedural success was high (residual flow ≤ 3 mm in 98%), and it seemed to protect against stroke; the annual incidence of stroke or transient ischemic attack was 3.8% compared with an expected rate of 6.6% based on the $CHADS_2$ score of the study population. This device was not evaluated further, but it provided proof-of-concept for device occlusion of the LAA for stroke prevention.

WATCHMAN

The WATCHMAN™ device (Boston Scientific) consists of a self-expanding nitinol frame and a fabric cap (Figure 1 B) deployed in the LAA via a trans-septal puncture (Figure 2). The WATCHMAN device has been evaluated in two randomized, controlled, clinical trials and two continued access registries.
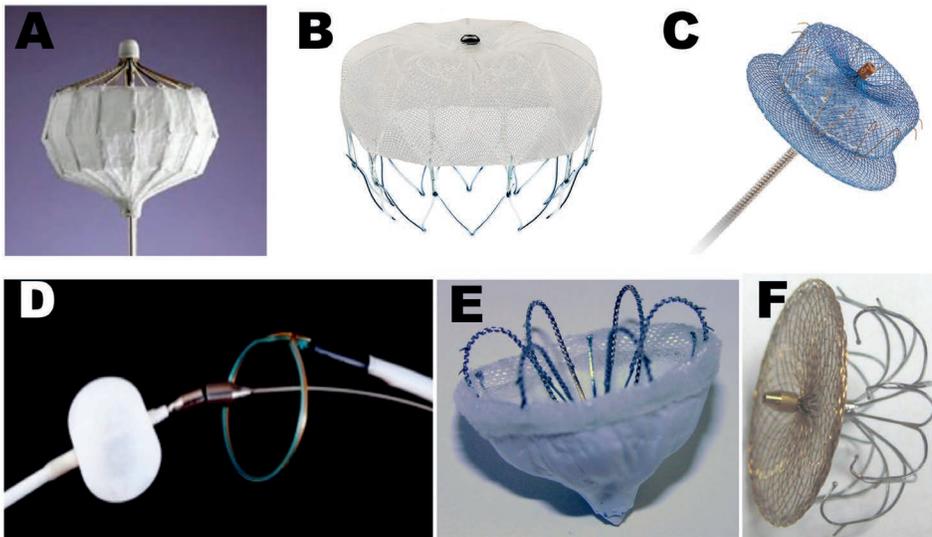
Figure 1.

Percutaneous devices for left atrial appendage occlusion. (A) PLAATO device; (B) WATCHMAN device; (C) Amplatzer Amulet device; (D) LARIAT suture delivery device; (E) WaveCrest device; (F) LAmbre device**.**

The PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation)[23] and PREVAIL (Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device In Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy)[24] studies were noninferiority trials that compared the WATCHMAN device with warfarin anticoagulation in AF patients. Inclusion required a $CHADS_2$ score ≥ 1 in PROTECT-AF, while PREVAIL-AF required a $CHADS_2$ score ≥ 2 or = 1 if additional stroke risk factors were present.[25] Patients

were randomized to either device implantation or warfarin in a 2:1 fashion. WATCHMAN-implanted patients were treated with 6 weeks of warfarin and aspirin, at which time a follow-up TEE was performed. If the TEE findings showed no thrombus or peridevice leak < 5 mm, warfarin was discontinued and aspirin and clopidogrel prescribed for 4.5 more months followed by indefinite aspirin therapy.

Stroke Protection. In PROTECT-AF, the WATCHMAN was noninferior to warfarin for the primary end point of cardiovascular/unexplained death, any

stroke, or systemic embolism at 1,065 patient-years,[23] 1,588 patient-years,[26] and 2,621 patient-years of follow-up.[27] At 2,621 patient-years, the WATCHMAN device not only met superiority criteria but also demonstrated reduced all-cause mortality (HR 0.66, 95% CI, 0.45-0.98, frequentist P = .038) and led to improved quality of life measures.[28] There were important limitations of these analyses, including a greater rate of withdrawal in the warfarin arm, an unusually high rate of hemorrhagic stroke in the warfarin group, inclusion of patients with $CHADS_2$ = 1 who may not require anticoagulation, and a large noninferiority margin.
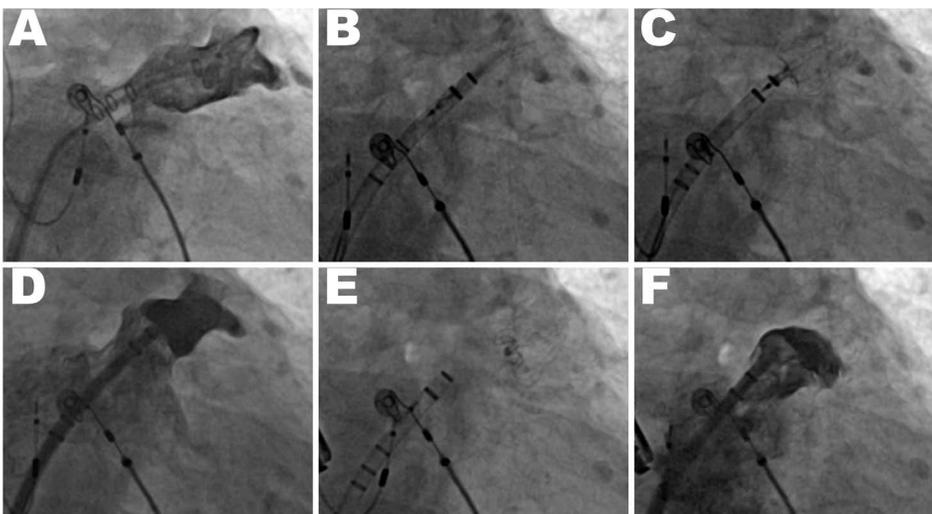

Figure 2.

Deployment of a WATCHMAN device. (A) Initial left atrial appendage (LAA) angiogram obtained through a pigtail catheter inserted via a sheath in the LAA. (B) Sheath advancement into the LAA with the WATCHMAN inside. (C) Deployment of the WATCHMAN in the LAA. (D) LAA angiogram to verify position of initial deployment in the LAA neck. (E) Release of the WATCHMAN. (F) Final angiogram.

In the smaller PREVAIL trial,[24] the 18-month rates of the co-primary end point of cardiovascular death, any stroke, or systemic embolism were numerically similar between the WATCHMAN device and warfarin anticoagulation but the device did not achieve noninferiority because the upper bound of the 95% credible interval for the 18-month rate ratio was not lower than the prespecified noninferiority margin of 1.75. Failure to achieve noninferiority was attributed to a lower-than-expected event rate—particularly among the patients randomly assigned to warfarin—and the relatively short duration of follow-up.[24]

A recent patient-level meta-analysis[29] of all randomized WATCHMAN data included 2,406 patients with 5,931 patient-years (PY) of follow-up from the PROTECT AF and PREVAIL trials and their respective registries. It was shown that patients receiving LAA closure with the WATCHMAN device had significantly fewer hemorrhagic strokes (HR 0.22; P = .004) and cardiovascular/unexplained death (HR 0.48; P = .006) and less nonprocedural bleeding (6.0% vs 11.3%; HR 0.51; P = .006) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 vs 1.87 events/100 PY; HR 1.02; 95% CI 0.62-1.7; P = .94). There were more ischemic strokes in the device group (1.6 vs 0.9, HR 1.95, P = .05 in PROTECT-AF and 0.2 vs 1.0 events/100 PY; HR 0.22, P = .004 in PREVAIL). Both trials and registries identified similar event rates and consistent device effect in multiple subsets.

These data provide support for the mechanistic hypothesis that LAA occlusion reduces thromboembolic risk in the absence of oral anticoagulation. In PREVAIL, WATCHMAN implantation was noninferior to warfarin for the co-primary end point of ischemic stroke or systolic embolism occurring more than 7 days post randomization.

Procedural Safety versus Bleeding Risk on Anticoagulation. In PROTECT-AF, the rate of the major safety end point (excessive bleeding or a procedure-related complication) at 18 months was greater in the patients randomly assigned to the WATCHMAN compared with warfarin (RR 1.69, 95% CrI 1.01-3.19); this was driven by pericardial effusion requiring treatment and procedure-related ischemic stroke.[23,30] Most safety events in the device arm occurred within the first 7 days of the procedure.[30] Over the longer-term, however, the difference in the cumulative safety events narrowed between treatment groups due to bleeding events in the warfarin arm. Thus, at 2,621 patient-years of follow-up, there was no significant safety difference between the WATCHMAN and warfarin (RR 1.17, 95% CrI 0.78-1.96).[27]

In PREVAIL, safety events related to the procedure, including the incidence of serious pericardial effusions and procedural

stroke, were significantly reduced compared with PROTECT-AF.[24] This improved safety profile was consistent with the findings of the prospective continuing access registry that followed the PROTECT-AF trial.[30]

Although there was no difference in the overall rate of major bleeding in patients assigned to LAA closure compared with warfarin therapy over 3 years of follow-up, LAA closure significantly reduced bleeding beyond the procedural period, particularly once adjunctive pharmacotherapy was discontinued, when bleeding dropped to < 70%.[31]

Postprocedure Anticoagulation Alternatives. The ASAP (ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology) was an observational study of 150 AF patients who were ineligible for warfarin therapy, predominantly because of prior bleeding.[32] After WATCHMAN implantation, patients received clopidogrel for 6 months and aspirin indefinitely. At 14.4 ± 8.6 months, the observed rate of stroke or systemic embolism was 2.3% per year, significantly less than the expected rate of 7.3% per year based on the $CHADS_2$ score. The ASAP-TOO trial is currently under design to confirm these findings.

The use of NOACs as a peri-implant anticoagulation regime has been recently reported.[33] In five centers, 214 patients received NOACs (46% apixaban, 46% rivaroxaban, 7% dabigatran, and 1% edoxaban). Compared to a control group receiving uninterrupted warfarin (n = 212), the rates of periprocedural complications, including bleeding events, were similar (2.8% vs 2.4%, P = 1). At follow-up, the rates of device-related thrombosis (0.9% vs 0.5%, P = 1), composite of thromboembolism or device-related thrombosis (1.4% vs 0.9%, P = 1), and postprocedure bleeding events (0.5% vs 0.9%, P = .6) were also comparable between the NOAC and warfarin groups.

Post-Approval Outcomes Data. Post-approval data registries add insights into the WATCHMAN device performance outside the controlled settings of a clinical trial. The European EWOLUTION registry included 1,021 subjects[34] at high risk of stroke (average $CHADS_2$ score: 2.8 ± 1.3, CHA_2DS_2-VASc: 4.5 ± 1.6) and moderate-to-high risk of bleeding (average HAS-BLED score: 2.3 ± 1.2). The device was successfully deployed in 98.5% of patients, and the overall 30-day mortality rate was 0.7%. The most common adverse event occurring within 30 days of the procedure was major bleeding requiring transfusion.

In the United States, Reddy et al. reported data on 3,822 consecutive cases.[35] Implantation was successful in 3,653 (95.6%). Implanting physicians performing these procedures (n = 382) included 71% new, nonclinical trial implanters who performed 50% of the procedures. Procedural complication

rates included 39 pericardial tamponades (1.02%; 24 treated percutaneously, 12 surgically, and 3 fatal), 3 procedure-related strokes (.078%), 9 device embolizations (.24%; 6 requiring surgical removal), and 3 procedure-related deaths (.078%).

Amplatzer Cardiac Plug (ACP) and Amplatzer Amulet (ACP 2)

The ACP (St. Jude Medical) is a first-generation self-expanding nitinol mesh that consists of a distal lobe and proximal disk, each with a sewn polyester patch, connected by a short central waist (Figure 1 C).[36] The distal lobe acts as an anchor within the LAA, and the proximal disk covers the mouth of the LAA from the LA side; thus, the mechanism of LAA occlusion differs from that of the WATCHMAN, which occludes the LAA from within the appendage itself. In 2013, the second-generation Amplatzer Amulet device was released in Europe.[37] It incorporates several changes from the ACP, including increased disk diameter and waist/lobe lengths and a recessed end-screw on the disk, among other changes. The Amulet device showed fewer leaks in a small single-center trial when compared to the ACP.[38]

Clinical data with the ACP and Amulet derive from several small observational studies, many of which are retrospective in design or involve a single center or operator.[36-43] Most of the patients enrolled in these studies were intolerant or had contraindications to oral anticoagulation and were treated with aspirin and clopidogrel during the postprocedural period. The most frequent safety events appear to be pericardial effusions and device embolization, occurring at similar rates as the WATCHMAN experience. A randomized trial is necessary to robustly assess safety and efficacy in preventing thromboembolic events, as the strategies of implantation and closure differ from those of the WATCHMAN device. Moreover, most of the published studies of the ACP do not include patients who are candidates for oral anticoagulation. After an initial randomized clinical trial comparing ACP with oral anticoagulation was terminated, the Amulet device is now undergoing a device-to-device comparison against the WATCHMAN device.

LARIAT® Procedure

The LARIAT device (SentreHEART, Inc.) is designed to ligate the LAA through the delivery of a surgical suture via a combined transseptal and subxiphoid approach (Figure 1 D).[44,45] The system has FDA approval for "suture placement and knot-tying for use in surgical applications where soft tissue are (*sic*) being approximated." However, its design is conceived and applied clinically to LAA ligation. LAA anatomy has to be favorable as assessed by preprocedural cardiac computed tomography, and an LAA diameter > 40 mm, presence of lobes behind the
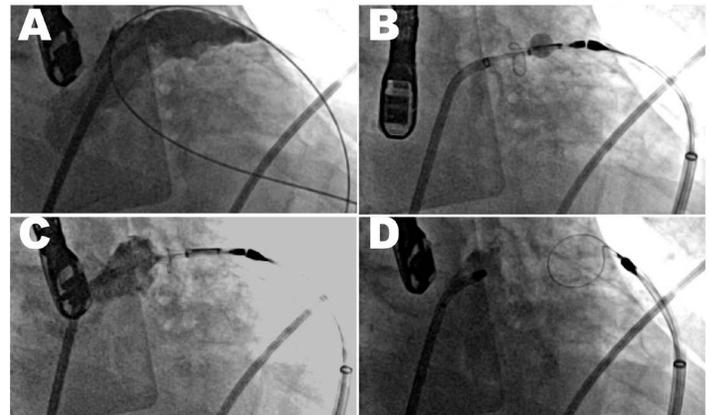

Figure 3.
Deployment of a LARIAT left atrial appendage (LAA) suture. (A) Initial LAA angiogram. (B) Endocardial and epicardial magnet-tipped wires snapped together. Balloon over endocardial wire aids in echocardiographic guidance. Snare has been advanced over the wires and is closed over the LAA. (C) Contrast injection in the left atrium shows complete occlusion. (D) After suture delivery, the snare is opened and retracted. Contrast injection shows a closed stump.

pulmonary artery, or a posteriorly oriented appendage should be avoided. A micropuncture or 17-G epidural needle is used to advance a guidewire and then a 14F sheath into the pericardial space. A magnet-tipped guidewire is advanced transseptally to the anterior aspect of the LAA, and a second magnet-tipped guidewire is advanced into the pericardium toward the LAA. The magnets snap together to form a rail, over which the LARIAT snare is advanced and closed at the mouth of the LAA using transesophageal echocardiography and fluoroscopic guidance. This snare contains a preloaded surgical knot (Figure 3).

To date, the safety and efficacy of LAA closure with the LARIAT has been limited to small observational studies.[45-49] The first reported series included 92 patients who were poor candidates or ineligible for warfarin therapy.[45] Successful closure (residual leak < 1 mm) was achieved in 96% of cases. Significant pericardial effusions occurred in three patients, and pericarditis occurred in two patients. At 1-year follow-up, 55% of the patients remained on warfarin therapy and there were no thromboembolic events. Price et al.[48] compiled retrospectively collected data from eight sites in the United States and a total of 154 unselected patients. In nine patients, the LARIAT device was not deployed due to access or delivery issues. Of the remaining 145 patients, successful LAA ligation was achieved acutely in 92%, which was 86% of the attempted patients. Follow-up postdischarge imaging of the LAA was available in 63 patients, of whom 79% had persistent complete LAA ligation. Significant procedural complications occurred, including major bleeding (9%), right ventricular perforations (n = 2), and LAA

perforation (n = 1) requiring emergency surgery (n = 3). On postdischarge follow-up, strokes occurred in two patients, and pericardial and pleural effusions occurred in three patients each. A total of four deaths occurred post procedure. These data highlight that despite comparable rates of acute success at LAA ligation, the LARIAT device can be associated with higher rates of complications than previously reported when applied to an unselected population of patients deemed to be at high risk of stroke and bleeding, the standard clinical indications.

In the absence of efficacy studies showing stroke protection, two particular concerns are the occurrence of LAA stump thrombi (four cases) and the significant rate of incomplete LAA closure (up to 21%). Similar results were reported by Miller et al.[49] in a series of 41 patients from four centers. Despite achieving complete acute LAA closure using the LARIAT system in 38 patients (93%), incomplete closure was detected on follow-up imaging in 24% of the patients. Two patients required surgical repair of an LAA perforation. One patient (2%) had a transient ischemic attack, and eight (20%) developed pericardial effusions requiring pericardiocentesis. Similarly, despite the high acute technical success, the incidence of complications and significant LAA leaks raise concerns about its safety when applied to unselected populations. In fact, the FDA issued a safety communication in July 2015 based on the finding of 45 adverse events, including six patient deaths during a review of the Manufacturer and User Facility Device Experience (MAUDE) database.[50] Thrombus at the LAA ligated stump has been reported, although the real incidence remains unknown in the absence of prospective data collection sets.[51–55]

In sum, from the small amount of data available, the LARIAT appears to provide high rates of acute anatomic closure, although procedural morbidity is not uncommon. Robust clinical efficacy data is absent.

Other Devices

Several other LAA closure devices with published human results are currently in development and some are available outside the United States:

The WaveCrest LAA occluder (Coherex Medical) is unique in that device implantation is a 2-step process (Figure 1 E): first, the proximal expanded polytetrafluoroethylene cap/occluder is positioned, and then the distal anchors are deployed. Incorporation of foam into the edges of the occluder could potentially enhance LAA sealing. This device currently has a CE mark, and initiation of a pivotal trial within the United States is planned.

The LAmbre™ LAA occluder (LifeTech Scientific Corp.) is a self-expanding nitinol device consisting of a distal, hook-embedded umbrella and a proximal covering disk, both with sewn-in PET fabric (Figure 1 F).[56,57] A short, articulating central waist connects the umbrella and cover. The device is advanced through a relatively low-profile delivery sheath (8-10F).

The AEGIS system (Aegis Medical) is an entirely percutaneous epicardial approach that uses an epicardial LAA grabber device to facilitate delivery of a suture loop to the mouth of the LAA. The device has been tested in canines and in a small feasibility study in humans.[58,59]

The Transcatheter Patch (Custom Medical Devices) uses a balloon-deliverable porous polyurethane foam material, the distal end of which is coated with an alkaline pH-activated surgical adhesive that is inactive during delivery but activated by infusion of an alkaline solution through the delivery catheter.[60] This bioabsorbable adhesive provides the initial fixation method. A small feasibility study was performed in 20 patients and acute success was achieved in 17 of them.[60]

The Occlutech Occluder (Occlutech International AB) consists of a nitinol mesh covered with polyurethane coating and a loop anchor. The first-in-man experience involving 30 patients was recently published.[61] While the device has not been FDA approved, it was available in Europe. However, a recall for device dislodgements in September 2016 has led to temporary suspension of shipping and sales of this device.[62]

The Cardia Ultraseal (CoRRect Medical GmbH) also uses a nitinol frame and a proximal sail. The first-in-man experience involving six patients was recently published.[63]

LIMITATIONS: THE LEFT ATRIAL APPENDAGE AS A SOURCE OF THROMBOEMBOLISM

Stroke risk is influenced by multiple factors unaffected by LAA closure. It is important to recognize that not all strokes in AF can be prevented by LAA-targeted therapies since up to 25% of strokes in AF patients can be linked to intrinsic cerebrovascular disease,[6] and AF is often associated with other LAA-independent risk factors for stroke. The $CHADS_2$ or CHA_2DS_2VASc scores[7,8] are useful to estimate the annual risk of thromboembolic events and select patients that benefit from anticoagulation,[9] yet they do not include any parameters of LAA function or anatomy.

These facts are important when interpreting clinical trial results. Even a technically flawless, complication-free, "perfect" LAA exclusion cannot be expected to completely eliminate stroke risk in all AF patient populations, since risk factors for stroke in AF increase the risk of non-LAA-related stroke. Oral anticoagulation may provide stroke protection beyond its effects

on LAA thrombi. Additionally, novel oral anticoagulants (NOACs) are noninferior or superior to warfarin for prevention of stroke and systemic embolism and do not require ongoing monitoring.[1-4] The final role for LAA exclusion will depend on the ability to demonstrate comparable clinical efficacy and safety to NOACs or acceptable outcomes when NOACs are contraindicated. At this point, compelling data are still absent. With those caveats in mind, the LAA remains a worthwhile target to prevent strokes in AF.

CONCLUSION

Approaches to close the LA appendage are becoming part of the management of AF as an alternative to oral anticoagulation for suitable patients.[64] A plethora of devices and procedures are currently being tested.

KEY POINTS:

- The left atrial appendage is an important source of stroke in patients with atrial fibrillation.
- The WATCHMAN device has been validated as an alternative to oral anticoagulation in patients with atrial fibrillation.
- Other strategies and devices to close the left atrial appendage are currently being tested.

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