Left Atrial Appendage Occlusion for Patients with Transcatheter Aortic Valve Replacement, MitraClip, Percutaneous Coronary Intervention, and Ablation for Atrial Fibrillation

Optimizing Long-Term Patient Outcomes

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KEYWORDS

• Left atrial appendage occlusion • WATCHMAN • Transcatheter aortic valve replacement • MitraClip • Percutaneous coronary intervention • Atrial fibrillation

KEY POINTS

- Patients with AF undergoing TAVR or MitraClip often present with both high stroke and bleeding risks.
- Patients undergoing complex PCI may require extended duration of dual antiplatelet therapy, which increases the risk of bleeding when combined with antithrombotic therapy for AF.
- Patients undergoing PVI with hope to "cure" AF and stop anticoagulation still present elevated stroke risk due to AF recurrence.
- Each of the above groups of patients may therefore benefit from LAA occlusion.
- Trials are underway to determine whether a staged or combined strategy is preferable for LAAO and other structural cardiac or electrophysiology procedures.

INTRODUCTION

Percutaneous left atrial appendage occlusion (LAAO) is a mature therapy for the prevention of stroke among patients who are poor candidates for long-term anticoagulation.[1] Many patients who seek care for valvular heart disease or coronary artery disease have concomitant atrial fibrillation (AF). Often, these patients demonstrate high risk of both stroke and bleeding. Therefore, a non-anticoagulant method of stroke risk reduction can be an important solution for optimizing their long-term care. In this article, we describe the clinical rationale for LAAO among patients undergoing percutaneous coronary intervention (PCI), transcatheter aortic valve replacement (TAVR), and MitraClip percutaneous mitral valve repair.

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TRANSCATHETER AORTIC VALVE REPLACEMENT

Aortic valve stenosis is a common valve disease and increases in frequency with age. Over the past decade, TAVR has demonstrated similar or superior outcomes to surgical aortic valve replacement (SAVR) among patients who are anatomically and clinically candidates for both procedures at all levels of the surgical risk spectrum, and superiority to medical therapy for patients who are considered inoperable[2–5] To optimize the care of these patients in the long term, however, we must be cognizant of their stroke risk.

Stroke After Transcatheter Aortic Valve Replacement

Although methods to reduce periprocedural stroke during TAVR is outside the scope of this article, it is important to be aware that there are numerous studies of both pharmacologic therapies and embolic protection devices aimed at reducing this complication. Importantly, although, the rate of stroke in the period between 30 days and 1 year is essentially the same as the periprocedural period and ranges between 2% and 6% in most large trials and commercial registries.[6,7] On average, approximately one-third of patients undergoing TAVR have a history of AF. In addition, although new-onset AF after TAVR is not as common as after SAVR, it is still seen in approximately 15% of patients.[8] Certainly, AF does not represent the only stroke risk factor among this group of generally elderly patients. Most of these patients are over the age of 65 years, have heart failure, and between one-third and one-half have diabetes mellitus, hypertension, and/or vascular disease. Not only are many of these comorbidities themselves independent risk factors for stroke, but they also contribute to a high CHA_2DS_2-VASc score with AF.

Anticoagulant Therapy Among Transcatheter Aortic Valve Replacement Patients

Unfortunately, although these patients would benefit from anticoagulation to abrogate their AF-related stroke risk, the same conditions that result in a high CHADS2-VASc score also contribute to their HAS-BLED score. It is well known that, among patients who have undergone TAVR, major late bleeding (MLB) events carry substantial mortality risk, which is highest for patients with AF to those who have MLB without AF (1-year mortality 48.7% versus 23.9%, respectively; 12.9% for no MLB).[9] Of course, similar to the non-TAVR population, many patients are simply never given anticoagulation due to perceived bleeding risk and most patients may simply demonstrate nonadherence to prescribed anticoagulation.[10] Given the excellent and robust randomized and registry data demonstrating the efficacy of LAAO for patients who are not good candidates for long-term anticoagulation, such as most patients in the current era who undergo TAVR, this is an important therapeutic option.

Rationale for Left Atrial Appendage Occlusion and Clinical Data

Although there is some concern for thrombus located in the left atrial (LA) cavity among patients with valvular heart disease, this stems from the historic data demonstrating LA cavity clot in 30% to 40% of patients with mitral valve stenosis.[11] Our group previously analyzed the transesophageal echocardiograms of patients at Cleveland Clinic with both aortic stenosis (AS) and AF, and found that, in patients who had documented thrombus it was always localized to the LAA.[12] Therefore, LAAO would seem a reasonable strategy for stroke risk reduction in the AS/TAVR population.

Attinger-Toller and colleagues[13] provided procedural and 1-year outcomes in a group of 52 patients who underwent concomitant TAVR and LAAO using the Amplatzer Cardiac Plug (ACP) device compared with 52 patients who underwent isolated TAVR. There were no statistically significant differences in procedural complications, such as stroke, bleeding, acute kidney injury, or death. Although no patients in the TAVR-alone group had a major vascular complication, pericardial tamponade, or (expectedly) ACP embolization, each of these were seen in the combined group (frequency: 3, 1, 1, respectively). More recently, Neitlispach presented data from the TAVR/LAAO trial of 80 patients, 41 of whom underwent combined TAVR and LAAO and 39 of whom underwent TAVR alone.[14] In the per-protocol analysis, there were numerically higher rates of mortality, bleeding, and acute kidney injury among the TAVR-alone group, and a numerically higher rate of stroke in the TAVR/LAAO group (none of these results achieved statistical significance). Superiority of the combined LAAO strategy would not be expected from either of these trials owing to small patient population and limited duration of follow-up.

The WATCH-TAVR trial is currently enrolling with an expected total enrollment of 352 patients randomized in a 1:1 fashion between combined

TAVR and LAAO using the WATCHMAN device and TAVR alone. The primary endpoint is a composite of death, stroke, and bleeding, with important secondary endpoints to include quality of life, procedural costs, rehospitalization, and others. The typical work-flow for the combined procedure is highlighted in Fig. 1. At our institution, we perform the TAVR under conscious sedation as usual. Once we have confirmed the optimal valve result, our imaging colleagues introduce the transesophageal echocardiography probe (still under conscious sedation and we exchange the femoral venous sheath used for temporary rapid pacing during TAVR deployment) for the trans-septal puncture (TSP) system. The LAAO procedure is then performed using the standard technique. Once completed, protamine is given to reverse the heparin anticoagulation, all sheaths are removed, and the arterial and venous site Perclose Proglide preclosure sutures are completed. The patient is routinely discharged on the next day.

At the current time, TAVR is primarily performed for patients who are at intermediate or greater surgical risk of SAVR, and who fit the risk profiles for stroke and bleeding that are detailed above. Many of these patients are likely to benefit from LAAO, whether as a combined procedure (not currently reimbursed) or in a staged fashion. As recent studies among low-surgical-risk patients have demonstrated favorable results for TAVR, it may be that those patients have lower rates of AF, lower stroke risk/rates, and better tolerate anticoagulation.[5] Therefore, a strategy of "TAVR plus LAAO" for all patients may be unnecessary, but it is important to keep LAAO in mind as an important option for many of the TAVR patients. Interestingly, there have also been small surgical studies that have demonstrated a benefit to routine appendage closure for patients undergoing elective open-heart surgery irrespective of preoperative AFib status. This may be another data point in the discussion of the potential for benefit with combined TAVR plus LAAO.

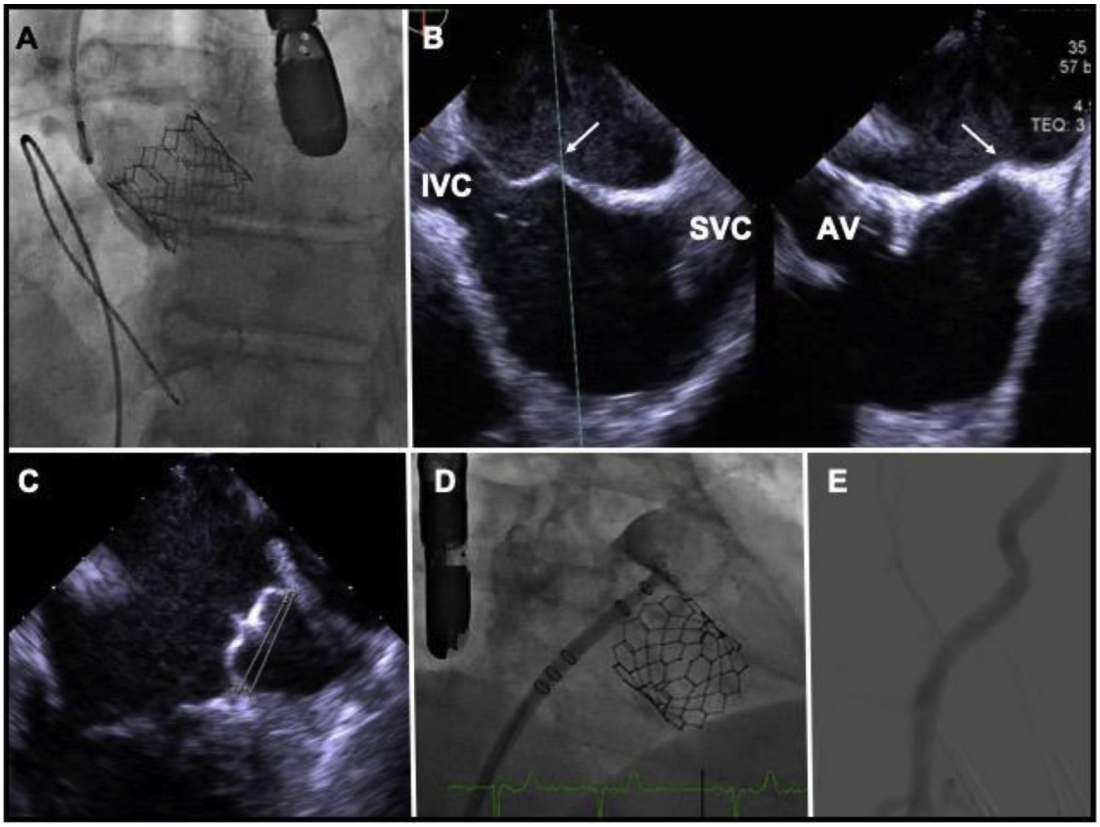

Fig. 1. Typical procedure for combined TAVR and LAAO under conscious sedation. (*A*) TAVR is performed followed by introduction of the transesophageal echocardiography (TEE) probe. (*B*) Biplane TEE demonstrates typical inferior and posterior transseptal puncture. LAAO in position by (*C*) TEE and (*D*) fluoroscopy. (*E*) Removal of TAVR delivery sheath, LAAO delivery sheath, and femoral completion angiography.

MitraClip PERCUTANEOUS MITRAL VALVE REPAIR

Those patients treated with a MitraClip for severe mitral valve regurgitation tend to be elderly and/or have numerous comorbid conditions that contribute to a high CHA_2DS_2-VASc score. Currently, the device is approved by the US Food and Drug Administration (FDA) for the treatment of patients with mitral regurgitation (MR) considered at "extreme risk" for cardiac surgery. Worldwide, more than 60,000 patients have been treated with the MitraClip, and use is expected to increase in the United States given the recent US FDA approval for its use in patients with functional MR.

Stroke Risk After MitraClip

In the commercial ACC/STS transcatheter valve therapy registry, the average age of patients undergoing MitraClip was 83 years, 63% of whom had AF.[15] Similar to the TAVR group of patients who generally have a high CHA_2DS_2-VASc score, many had a previous stroke (9%), hypertension (84%), diabetes (25%), and heart failure (98%). Many of these factors also imply an increased propensity for bleeding through a high HAS-BLED score.

Interestingly, it is possible that the treatment of MR confers a high stroke risk for patients. Nakagami and colleagues[16] analyzed 290 patients with nonrheumatic AF and varying degrees of MR. At 7.4-year follow-up, 68 patients had suffered a stroke. Among the 43 patients with moderate or severe MR, only 4 (10%) had a stroke, whereas 13 of the 52 patients (25%; $P = .047$) with none or mild MR had a stroke. Multivariate analysis demonstrated moderate or more MR as a significantly protective factor (odds ratio = 0.45; 95% CI, 0.20–0.97) for stroke. Although strictly conjectural, it is therefore possible that reducing MR among the high stroke risk group of MitraClip patients could increase their stroke risk.

Rationale for Left Atrial Appendage Occlusion and Clinical Data

There has been concern that the mitral stenosis (MS) resulting from MitraClip placement could abrogate the potential benefit of LAAO in this group of patients. It is important to realize that, among most major series' of MitraClip placement, the average MV gradient after treatment is 4 mm Hg, which does not imply even moderate MS. Furthermore, placement of an LAAO device even with MS (although not an approved indication) may merit consideration in specific clinical scenarios. Among the major studies of MS patients, 47% to 100% of patients demonstrate thrombus confined to the LAA alone (with the rest of patients showing thrombus in the LA cavity or both the LA and the LAA) (Fig. 2).[11] Therefore, for those patients who do have MS after MitraClip, occluding the LAA may still provide some benefit with regard to stroke reduction among those for whom anticoagulation is strictly contraindicated.

There are limited data regarding LAAO among this group of patients. Francisco and colleagues[17] described their experience of 5 patients who underwent a combined procedure of WATCHMAN LAAO followed by MitraClip. The TSP was performed in a location to optimize for the clip (high and posterior) and the LAAO was

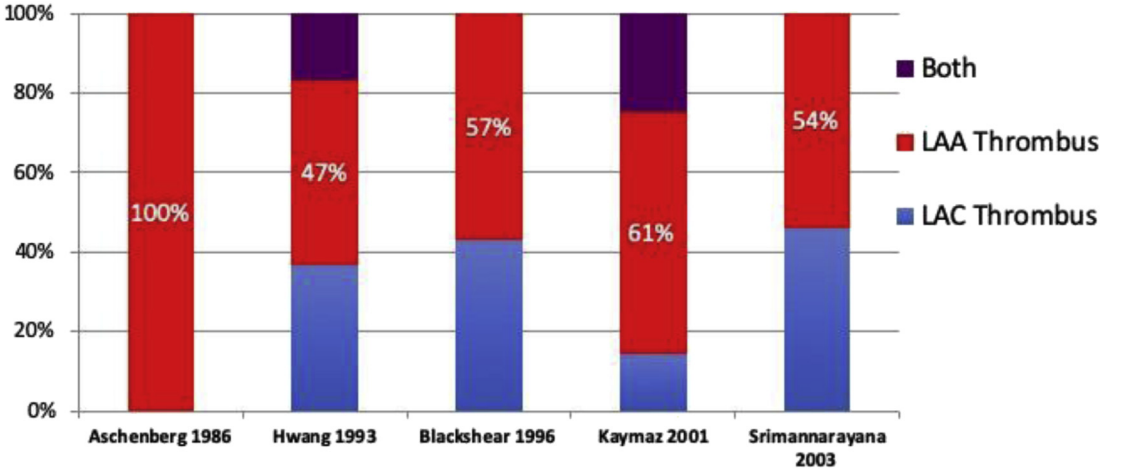

Fig. 2. Location of thrombus in patients with mitral stenosis. LAA, left atrial appendage; LAC, left atrial cavity. (*Data from* Huded C, Krishnaswamy A and Kapadia S. Percutaneous Left Atrial Appendage Closure: is there a Role in Valvular Atrial Fibrillation. J Atr Fibrillation. 2017;9:1524; with permission.)

performed first. The procedure was successful in all patients without any complications and with a good result of both devices. Four of the 5 patients had a mean MV gradient less than 2 mm Hg and one had a gradient of just under 5 mm Hg.

Given the clinical rationale provided above, a trial of combined MitraClip/LAAO is currently in the planning stage. In our practice, we generally advocate performance of the MV repair first to avoid any damage to the LAAO device with manipulation of the MitraClip device. Furthermore, it may be beneficial to confirm the existence of only mild MV gradients before performance of the LAAO, especially in patients who develop moderate or significant MS and could be reasonable candidates for oral anticoagulation.

The prevention of stroke for patients undergoing percutaneous mitral valve treatment is an important therapeutic target. Many of these patients present high stroke and bleeding risk, and LAAO may provide a beneficial alternative to long-term anticoagulation. Future trials are important to confirm the expected safety and efficacy of the combined procedure.

Percutaneous coronary intervention

Approximately 750,000 patients undergo PCI each year.[18] Patients with a coronary stent in place require dual antiplatelet therapy (DAPT) with aspiring (ASA) and a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) for a duration that may be variable depending on the complexity and extent of the stent procedure, as well as the indication for stenting, and generally ranges from 1 to 12 months. Among patients undergoing PCI, it is estimated that 5% to 10% have AF, many of whom therefore require anticoagulation. However, although oral anticoagulation therapy (OAT) is shown to reduce the risk of stroke or systemic embolization in AF patients, it has not been demonstrated to be effective in reducing stent thrombosis.[19] Many of these patients may, therefore, end up receiving triple antithrombotic therapy (TAT) with DAPT and OAT, which substantially increases bleeding risk.[20] Conversely, Olivier and colleagues[21] demonstrated recently that, among patients with AF undergoing PCI, approximately 50% do not receive OAT in addition to their antiplatelets, despite a relatively high stroke risk with a mean CHA_2DS_2-VASc of 3.6, most likely due to concerns about bleeding risk.

Optimizing Antithrombotic and Antiplatelet Therapy for Percutaneous Coronary Intervention Patients with Atrial Fibrillation

With the knowledge that TAT results in substantially greater bleeding risk, several investigations have been performed to determine whether single antiplatelet therapy alone with OAT is as effective with regard to ischemic endpoints but has improved safety for bleeding. First among these was the WOEST (what is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting) trial that randomized 573 patients on a vitamin K antagonist (VKA) undergoing PCI to either DAPT with clopidogrel and ASA or clopidogrel alone. Those patients who did not receive ASA demonstrated a 64% relative decrease in bleeding complications. However, the study was not powered for ischemic events so definitive conclusions cannot be made in that regard. Nevertheless, the trial provided the first major evidence for reducing TAT.

In a similar vein, the PIONEER AF-PCI (open-label, randomized, controlled, multicenter study exploring 2 treatment strategies of the direct oral anticoagulant [DOAC] rivaroxaban and a dose-adjusted oral VKA treatment strategy in subjects with AF who undergo PCI) trial randomized patients to one of 3 strategies: low-dose rivaroxaban (15 mg once daily) plus P2Y12 inhibitor, TAT using very low-dose rivaroxaban (2.5 mg twice a day) and DAPT with increase in the dose of rivaroxaban to 15 mg at the time of P2Y12 inhibitor discontinuation, and TAT with VKA plus DAPT. In each of the groups, DAPT duration was prespecified for 1, 6, or 12 months. As expected, the primary endpoint of clinically significant bleeding was reduced by the use of rivaroxaban. However, it should be mentioned that these low doses of rivaroxaban are not approved for stroke prevention in AF and, as in WOEST, the trial lacked the power to identify differences in ischemic endpoints.

Most recently, the AUGUSTUS trial was published and randomized 4614 patients taking P2Y12 inhibitor (93% clopidogrel) in a 2×2 strategy to the DOAC apixaban (5 mg twice a day) or VKA and ASA or placebo.[22] This was an important trial to independently assess the safety and efficacy of OAT and antiplatelet therapy, and among the patients 38% were treated with PCI for acute coronary syndrome. Overall, the use of apixaban (compared with VKA) led to a decrease in both bleeding and the combined endpoint of death or hospitalization. As might be expected from the above, the addition of aspirin resulted in a higher rate of bleeding. Both treatment strategies (ie, apixaban and lack of aspirin) resulted in similar ischemic endpoints compared with their comparators, although again the trial was not adequately powered to detect a difference in ischemic outcomes. Taken together, the totality of data seems to imply that, for *most* patients undergoing PCI, a strategy of a single OAT (preferably DOAC) and

P2Y12 inhibitor (usually clopidogrel) is safe and effective in patients with AF who can tolerate long-term anticoagulation.

Patients at High Risk for Stent Thrombosis

As detailed above, many studies have demonstrated the overall safety and efficacy of OAT plus single antiplatelet therapy using a P2Y12 inhibitor, as opposed to TAT, for patients with AF undergoing PCI. However, it is important to appreciate that these studies also have limited enrollment of patients with particularly high risk of stent thrombosis. Especially for these patients who may benefit from prolonged or indefinite DAPT, a non-anticoagulant stroke prevention method (ie, LAAO) may be preferable, outside of the usual indications that include high bleeding risk with OAT alone. These factors are provided in **Box 1**.

Ablation of atrial fibrillation

Stroke prevention after AF ablation is a fundamental aspect of ongoing patient management. The decision to continue or discontinue anticoagulation following an ablation is a complicated one. An important contributing factor is to determine the success or failure of the ablation procedure in preventing future AF. Stopping anticoagulation in a high CHA_2DS_2-VASc patient thought to have no recurrence of AF based on lack of symptoms may put the patient at high risk of stroke. In fact, it is recognized that up to 56% of patients who are perceived to have a successful ablation actually continue to have asymptomatic AF, thus setting the stage for ill-informed decisions regarding the discontinuation of oral anticoagulation.[23] Therefore, the current HRS/ACC/AHA guidelines recommend oral anticoagulation based on the CHA_2DS_2-VASc score and not on the perceived outcome of ablation.[24] Conversely, continuing anticoagulation in the patient with true nonrecurrence exposes the patient to a needless lifelong strategy of oral anticoagulation and the associated compounded risk of bleeding that increases with age.

Box 1
High-risk percutaneous coronary intervention features that may benefit from prolonged dual antiplatelet therapy

- Previous stent thrombosis
- "Last remaining" coronary
- Diffuse multivessel CAD
- Chronic kidney disease
- Implantation of 3 or more stents
- Bifurcation PCI with 2 stents
- Total stent length greater than 60 mm
- PCI of chronic total occlusion

Abbreviations: CAD, coronary artery disease; PCI, percutaneous coronary intervention.

Adapted from Capodanno et al. Management of Antithrombotic Therapy in Atrial Fibrillation Patients Undergoing PCIJ. J Am Coll Cardiol 2019;74:83-99; with permission.

Rationale for Left Atrial Appendage Occlusion with or After Pulmonary Vein Isolation

With the above background and given that percutaneous LAAO has been shown to be effective in ischemic stroke prevention and in avoiding bleeding risk, LAAO after AF ablation would seem a reasonable choice. This could address both issues mentioned above: protection from ischemic stroke in high CHA_2DS_2-VASc patients with subclinical AF with a lower bleeding risk and relief from long-term anticoagulation for those who have no AF recurrence. In this regard, a recent meta-analysis suggested that stopping anticoagulation in high CHA_2DS_2-VASc score post-AF ablation patients was associated with a higher stroke risk, and continuation of oral anticoagulation was associated with a higher incidence of intracranial hemorrhage.[23,25,26] Along the same lines, the Society of Thoracic Surgeons provides a class II recommendation for surgical LA appendage closure for patients undergoing a cardiac surgery that includes AF ablation.[27]

From a technical and logistical standpoint, concomitant AF ablation and LAA closure is very attractive given that access to the left atrium is already established. Such a strategy may also decrease resource utilization by compressing all the resources and risks into a single procedure because many of the steps of AF ablation and LAAO are shared. There have been several studies that have explored the feasibility and safety of this approach.[28–30] Phillips and colleauges[31,32] have shown that the combined procedure is associated with excellent short-term and long-term outcomes. In a group of 98 patients with an average CHA_2DS_2-VASc score of 2.6 ± 1.0, the observed stroke risk at 5 years was 0.5% per year among those who underwent AF ablation and LAAO compared with a similar cohort of patients who were not anticoagulated who suffered a stroke rate of 5.1%.[32,33]

The OPTION trial (NCT03795298), which is currently enrolling, will be the largest randomized

study to compare continued oral anticoagulation with LAA closure with the next-generation WATCHMAN FLX in 1600 AF ablation patients. It will enroll patients with a CHA_2DS_2-VASc score of 2 or higher in men and 3 or higher in women. LAA occlusion can be concomitant with or within 6 months of previous AF ablation. The primary effectiveness endpoint is a composite of stroke (including ischemic and/or hemorrhagic), all cause death, and systemic embolism at 36 months. The secondary endpoint will test noninferiority for major bleeding. Follow-up is 36 months and the study is planned to conclude in 2021.

In summary combined AF ablation and LAA closure is a logical progression of current AF management to decrease the risk of embolic stroke and bleeding complications on this high-risk population.

SUMMARY

Interventional cardiologists and electrophysiologists perform various procedures to improve the quality and longevity of life for their patients. In this regard, the mitigation of stroke risk in those patients with AF may be ignored when considering the other more acute or urgent situations, such as severe coronary or valvular heart disease requiring treatment or symptomatic AF necessitating ablation. However, we must keep this long-term stroke risk in mind in order to optimize patients' overall outcomes. Percutaneous LAAO may be an important option for those who present with both high stroke and bleeding risk. Currently ongoing studies will help provide objective data in this arena where our subjective assumption of benefit seems well-founded.

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