Transcatheter Aortic Valve Replacement and Left Atrial Appendage Occlusion – A Stitch in Time?

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Abstract

Many patients have now been able to receive transcatheter aortic valve replacement (TAVR) therapy for severe aortic stenosis. These patients have atrial fibrillation and are placed on warfarin for stroke prophylaxis. The opportunity for treatment with left atrial appendage occlusion (LAAO) in place of warfarin for this population exists, especially for those with increased bleeding risk. This paper discusses the prevalence and aetiology of stroke in patients presenting for TAVR (with a focus on the risk from chronic and acute atrial fibrillation) and also the benefit of LAAO closure in this population.

Keywords

Aortic stenosis, atrial fibrillation, left atrial appendage, aortic valve replacement, transcatheter aortic valve replacement, transcatheter aortic valve implantation, left atrial appendage closure, left atrial appendage occlusion

Disclosure: Dr. Sievert's institution has ownership interest in or has received consulting fees, travel expenses or study honoraries from the following companies: Abbott, Access Closure, AGA, Angiomed, Arstasis, Atritech, Atrium, Avinger, Bard, Boston Scientific, Bridgepoint, Cardiac Dimensions, CardioKinetix, CardioMEMS, Coherex, Contego, CSI, EndoCross, EndoTex, Epitek, Evalve, ev3, FlowCardia, Gore, Guidant, Guided Delivery Systems, Inc., InSeal Medical, Lumen Biomedical, HLT, Kensey Nash, Kyoto Medical, Lifetech, Lutonix, Medinol, Medtronic, NDC, NMT, OAS, Occlutech, Osprey, Ovalis, Pathway, PendraCare, Percardia, pfm Medical, Rox Medical, Sadra, SJM, Sorin, Spectranetics, SquareOne, Trireme, Trivascular, Velocimed, Veryan. All other authors have no disclosures.

Received: 2 April 2014 **Accepted:** 12 April 2014 **Citation:** *Interventional Cardiology Review*, 2014;9(2):126–9

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Many patients with aortic stenosis have now been able to receive transcatheter aortic valve replacement (TAVR). In addition, patients with atrial fibrillation have also been able to receive left atrial appendage (LAA) occlusion for prevention of stroke. According to current studies and guidelines, LAA closure is indicated in patients with non-valvular atrial fibrillation. However, what happens if the valvular disease is treated and the atrial fibrillation persists? Can LAA closure help modify the risk of stroke in patients with aortic stenosis that receive TAVR? This query brings up issues of prevalence, indication, procedural safety and long-term outcomes.

The patients under discussion are those with aortic stenosis who are at risk for stroke due to atrial fibrillation. The Placement of Aortic Transcatheter Valves (PARTNER) trial reported one-year stroke data as 8.3 % in cohort A (high-risk operable) patients¹ and 10.6 % in cohort B (non-operable) patients.² Other registry data show that 30-day stroke risk was present in multiple registries (periprocedural stroke risk of 1.5 %, 30-day stroke rate of 4.0 %, with 30-day major stroke risk of 3.2 % and 30-day minor stroke risk of 1.0 %).^{3,4} Yet other studies indicate that roughly half of strokes within the first 30 days will be periprocedural, and half will be after the procedure.^{5–7}

Why Does Stroke Happen After Transcatheter Aortic Valve Replacement?

There are many theories addressing this question, as captured in Table 1. These include procedural risk factors and post-procedural risk factors. Some procedural risk factors are known from experience

with balloon valvuloplasty, but some are specific to valves. Serial transcranial Doppler examinations identify high-intensity transient signals (HITS) during transcatheter aortic valve implantation (TAVI), which may serve as a surrogate for microembolization.^{8–10} For example, duration of valve manipulation may be longer and lead to more HITS with self-expanding CoreValve than balloon-expandable Edwards. Of note, atrial fibrillation – both new onset and chronic – are risk factors for stroke in patients with TAVR. These theories and risk factors give rise to additional questions.

How Often is Atrial Fibrillation Present in Patients Undergoing Transcatheter Aortic Valve Replacement?

Chronic atrial fibrillation was present at a high rate in both the PARTNER cohort A: high-risk TAVR arm (40.8 %) and cohort B: inoperable TAVR arm (32.9 %). Further analysis of TAVR patients found that atrial fibrillation is a predictor of mortality regardless of type (paroxysmal, persistent or permanent). Atrial fibrillation also predicts mortality regardless of subclass (age, gender, diabetes, renal function, coronary artery disease or left ventricular ejection fraction).¹⁵ Further, pre-existing chronic atrial fibrillation was found in one study to predict stroke even after 30 days, with a hazard ratio of 2.84 and a cumulative transient ischaemic attack (TIA)/CVA hazard ratio of 1.91.⁵ However, this was not the case in other papers, namely by Stortecky et al.,¹⁵ likely due to two reasons. Firstly, these studies do not differentiate strokes at >24 hours to later strokes. Secondly, they do not differentiate strokes from 30 days to one-year as a different subgroup. Timing of the cerebrovascular event may be relevant to the cause.

How Often Does New Onset Atrial Fibrillation Occur After Transcatheter Aortic Valve Replacement?

The literature reports a rate between 7.5 and 31.9 %.^{1,2,5,14,16} Predictive factors for new onset atrial fibrillation include transapical access and large left atrial size.¹⁶ The timing of new onset atrial fibrillation is variable. About a third (36.3 %) of new onset atrial fibrillation start during the procedure, but over 50 % of cases start at over a 24 hour time period. Further, the duration of new onset atrial fibrillation is also variable, with >50 % of new onset atrial fibrillation lasting <24 hours. New onset atrial fibrillation in the first 30 days increased the odds of having atrial fibrillation again in the first year.¹⁶

Does New Onset Atrial Fibrillation After Transcatheter Aortic Valve Replacement Lead to Stroke?

There is evidence of a significant correlation. In 2012, Nombela-Franco et al.⁵ showed how new onset atrial fibrillation with onset of <24 hours, 0–30 days and 1–30 days after TAVR has an odds ratio for stroke of 2.46, 2.27 and 2.76, respectively. According to another paper, new onset atrial fibrillation in the first year after procedure has an odds ratio for stroke of 4.3.¹⁶

In total, chronic atrial fibrillation is already present in 30 % of patients undergoing TAVR; this number increases to 40–50 % when new atrial fibrillation is included.¹⁷

Preventing Stroke in Transcatheter Aortic Valve Replacement Patients with Atrial Fibrillation – Chronic and Acute Chronic Atrial Fibrillation

The optimal strategy for stroke prevention in TAVR patients with pre-existing atrial fibrillation is unknown. Patients without pre-existing atrial fibrillation in the PARTNER trial received aspirin 81 mg indefinitely with clopidogrel for three months. The American Association for Thoracic Surgery (AATS)/American College of Cardiology Foundation (ACCF)/Society for Cardiovascular Angiography and Interventions (SCAI)/Society of Thoracic Surgeons (STS) guidelines¹⁸ mention that clopidogrel can be continued for 3–6 months. The Canadian Cardiovascular Society (CCS) position statement¹⁹ recommends thienopyridine for 1–3 months. For patients with chronic atrial fibrillation, warfarin is substituted for clopidogrel.

Rodés-Cabau et al.¹⁷ analysed the evidence behind anticoagulation for patients with atrial fibrillation undergoing TAVR. They found that there was a “lack of uniformity regarding the choice of postprocedural antithrombotic treatment”. This was reflected in a German registry paper of 1,450 patients showing that 7 % of patients received aspirin and clopidogrel monotherapy, 11 % received aspirin or clopidogrel with an oral anticoagulant, 66 % of patients received dual antiplatelet therapy, and 16 % received triple therapy with aspirin, clopidogrel and an oral anticoagulant. The triple therapy was associated with an increased risk of composite of death, stroke, embolism or major bleeding (adjusted odds ratio 1.78, 95 % confidence interval [CI] 1.1–2.9).²⁰ It therefore seems that for patients with chronic atrial fibrillation who have received TAVR, the use of warfarin with dual antiplatelet therapy is associated with increased risk of bleeding.

New Onset Atrial Fibrillation

What can be done for stroke prevention in new onset atrial fibrillation? What is the necessary duration of atrial fibrillation that will mandate

Table 1: Potential Risk Factors For Stroke

Procedural Risk Factors	Post-procedural Risk Factors
Wire in atheromatous aorta	Age
Balloon valvuloplasty	Higher atherosclerotic burden
Valve positioning	Prior stroke
Duration of valve manipulation	Severe aortic insufficiency
Valve expansion	COPD
Post-dilation	Low BMI
Valve dislodgement	Diabetes
Smaller annulus valves (more calcium)	New onset atrial fibrillation
Air emboli	Chronic atrial fibrillation
Learning curve	

Information on potential risk factors for stroke collected from various studies.^{7–9,11–14}
COPD = chronic obstructive pulmonary disease; BMI = body mass index.

anticoagulation? Should anticoagulation be started at one-hour of new onset atrial fibrillation or one-day of new onset atrial fibrillation? The answer is unknown. This uncertainty in diagnosing burden of disease leads to uncertainty in prescribing appropriate stroke prophylaxis regimens.

Warfarin and Newer Anticoagulants

As mentioned earlier, warfarin has been used for TAVR patients in the setting of atrial fibrillation. However, this comes with multiple issues. The first is a high risk of bleeding complications,²¹ both major and minor. In addition, there are issues of compliance. Some studies have shown that only a third of all patients are eligible for warfarin, are taking warfarin in the community non-trial setting.²² Finally, the amount of time that patients taking warfarin in clinical trials with therapeutic international normalised ratio (INR) has been less than ideal, up to 38.7 % of the time. In a real-life study, patients had non-therapeutic INR up to 50 % of the time.^{23,24}

New anticoagulants, such as dabigatran, rivaroxaban and apixaban, provide great promise for stroke prophylaxis in patients with atrial fibrillation. These medications operate through mechanisms other than vitamin K antagonism, including oral direct thrombin inhibitor (dabigatran) and oral direct factor Xa inhibitor (rivaroxaban and apixaban). While the new medications were likely to decrease haemorrhagic stroke in published studies, they all are associated with an increase in major bleeding. In addition, they all have discontinuation rates of more than 20 % in a heavily controlled clinical trial setting.^{25–27} Causes for discontinuation include interactions with drugs, interactions with diet, polypharmacy, side effects, cost, nuisance bleeding or need for an invasive procedure. There has been no data looking at newer anticoagulants for chronic atrial fibrillation in patients after TAVR; however, the increased risk of bleeding and high non-compliance rate would be issues also applicable to this population.

Left Atrial Appendage Closure

There have been multiple studies showing the benefit of LAA closure. The Watchman™ device (Boston Scientific, Natick MA, US) has significant positive data. Early issues of safety and treatment failures were addressed with continued access registry, late versus early analysis with Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT-AF), and the second randomised controlled Randomized Trial of LAA Closure vs Warfarin for Stroke/ Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation (PREVAIL) trial, which all showed increasing rates of implant success with decreasing rates of vascular complications and

pericardial effusions needing intervention.²⁸ In addition, the four-year analysis of the PROTECT-AF trial showed that LAA closure was superior to warfarin, specifically in the area of all-cause mortality.²⁹ Finally, LAA occlusion was found to be effective in patients with contraindication to warfarin,³⁰ tolerant of small peri-device leaks,³¹ cost-effective³² and correlated with an improvement in quality of life.³³ The Amplatzer™ Cardiac Plug (ACP) system (St. Jude Medical, St. Paul, Minnesota, US) also has significant long-term safety and efficacy data.^{34–37}

However, all of these patients enrolled in these trials had ‘non-valvular atrial fibrillation’. This definition is often, unfortunately, unclear. What exactly is valvular atrial fibrillation?

According to the European Society of Cardiology (ESC) 2012 Valvular Heart Disease Guidelines, “It is conventional to divide AF into cases which are described as ‘valvular’ or ‘non-valvular’. No satisfactory or uniform definition of these terms exists. In this guideline, the term valvular AF is used to imply that AF is related to rheumatic valvular disease (pre-dominantly mitral stenosis) or prosthetic heart valves”.

Atrial Fibrillation and Valvular Heart Disease

Do patients with degenerative aortic stenosis treated with TAVR still count as patients with ‘valvular heart disease’? There is evidence to say that this may not be the case.

Firstly, the pathophysiological mechanism of atrial fibrillation in aortic stenosis is different than in other valvular lesions. For example, mitral regurgitation is associated with left atrial volume overload, and the left atrium is often enlarged. In aortic stenosis, there is left ventricular pressure overload, which leads to left atrial pressure overload; consequently, left atrial size is not the important outcome measure in aortic stenosis. Different valvular disorders affect the left atrium differently.³⁸

Secondly, the original papers on the presence of clot in the LAA focused on the different presence of clots based on rheumatic and non-rheumatic valve disease; however, patients with rheumatic valve disease were more likely to have mitral stenosis as opposed to aortic valve disease. Blackshear et al.³⁹ analysed the results of 23 studies, comparing a total of 3,504 patients with rheumatic valve disease and 1,288 patients without rheumatic valve disease. In this paper, there were found to be more LAA clots in the patients with non-rheumatic valve disease than in patients with rheumatic valve disease. Based on these findings, the idea arose that LAA obliteration may be an answer for atrial fibrillation without valvular heart disease. However, the vast majority of these valvular heart disease patients were patients with rheumatic mitral valve disease. It is a significant jump from patients with untreated rheumatic valvular heart disease to patients after TAVR.

Finally, not all prosthetic valves are alike. Compared with mechanical valves, bioprosthetic valves have a lower risk of stroke, as low as 1.3 ± 0.3 %.⁴⁰ With a different stroke rate, there is even more evidence that the valve replacement type plays a significant role in the overall anticoagulation strategy.

How Will Left Atrial Appendage Closure Decrease the Stroke Risk in Transcatheter Aortic Valve Replacement?

There are four main areas where there is risk of stroke in patients undergoing TAVR. These include:

- TAVR procedural risk;
- risk of clot in the LAA;
- risk of clot on the valve; and
- risk of clot elsewhere.

LAA closure only affects the risk of clot in the LAA. As soon as the valve has been replaced in aortic stenosis, the risk of clot in the LAA should be similar to patients with ‘non-valvular’ atrial fibrillation. The atrium is not excessively dilated, such as in mitral stenosis or mitral regurgitation. This would be the area where LAA occlusion may have an impact.

For the TAVR procedural risk, LAA closure does not have a significant impact. This may account to 50 % of strokes that happen in the first 30 days, as these occur in the first 24 hours. All steps of the procedure add to the risk, especially valve advancement and positioning.⁸ The key to success here may be smaller sheaths, better delivery systems and easier to position valves. Carotid protection systems may also provide a reduction in risk, but this has not yet been proven. In fact, placement of the carotid protection system can lead to an embolic risk or interference with the TAVI valve delivery system.⁷

The risk of thrombus on the valve is difficult to estimate. The guidelines therefore point to aspirin (indefinitely) and clopidogrel (1–6 months), as listed in the ACCF/AATS/SCAI/STS guidelines⁴¹ and the CCS guidelines.¹⁹ Use of LAA closure to replace warfarin is not likely to change this risk, and dual antiplatelet strategy should be continued.

Finally, there can be clots in other areas. These include left atrium (outside of the LAA), left ventricle, aorta and carotids. TAVR may increase left-sided outflow and decrease stasis, which may decrease the risk of stroke from thrombus in the left atrium or left ventricle. Use of smaller delivery systems or a transaortic/transapical strategy may also decrease risk of stroke from an atherosclerotic aorta. Risk of stroke from carotid artery disease would be similar.

LAA closure is therefore only likely to help decrease part of the overall stroke risk for these patients, but may help in patients with atrial fibrillation, where the risk of stroke from the LAA is increased.

Among Patients Receiving Transcatheter Aortic Valve Replacement, Who Are the Best Candidates for Left Atrial Appendage Occlusion?

The best candidates for LAA occlusion with TAVR are those with chronic atrial fibrillation and established contraindications to anticoagulation or a high bleeding risk (i.e. for both warfarin-ineligible and warfarin-eligible patients). Many patients who are candidates for TAVR have a high bleeding risk and are often withheld warfarin, making them preferential candidates for LAA occlusion.⁴² Other candidates include those patients with a high risk of drug–drug interaction or warfarin non-compliance. Patients with coronary artery stenting that need dual antiplatelet therapy also benefit from being off warfarin and being treated with LAA occlusion; this removes the risk of prolonged anticoagulation and/or triple therapy.

Patients that have to take warfarin for other reasons should not be candidates for LAA occlusion (e.g. patients with pulmonary embolism, deep vein thrombosis or haematological abnormality).

When should LAA closure happen? There is evidence that this can be done in the same setting as TAVR, as reported in 10 % of patients in

a case series published by Nietlispach et al.⁴³ Multiple case reports have also demonstrated safety of TAVR immediately followed by LAA occlusion.^{44–46} This takes advantage of transoesophageal guidance (and if used, general anaesthesia) for both procedures. In addition, the patients may be able to tolerate a LAA occlusion complication (e.g. embolisation⁴⁵ and tamponade) if the aortic valve obstruction has been treated prior (personal communication, Fabien Nietlispach, 10 April 2014). Other centres have performed TAVI first with LAA occlusion to follow.⁴⁷

In the case of chronic atrial fibrillation, the TAVR should be performed first as this is the more clinically important intervention. In addition, there is no evidence to show that LAA closure will change the procedural stroke rate. LAA closure may take place immediately or early within the first month after TAVR to prevent intermediate and late stroke. For centres that plan to do both in the same setting, this requires careful patient selection, planning and operator experience. In this case, the dual antiplatelet therapy that is used for TAVR may also be used for post-LAA occlusion management. ■

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