

# Left Atrial Appendage Occlusion in Patients with Non-Valvular Atrial Fibrillation and History of Intracranial Hemorrhage: A Review

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## Article Info

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## Abstract

Atrial Fibrillation (AF) is associated with an increased risk of thromboembolism due to formation of intracardiac thrombus mostly in left atrial appendage. Anticoagulant agents are used to reduce the risk of thromboembolism but have concerning bleeding side effect, making their use very challenging particularly in patients with high HAS-BLED risk score. WATCHMAN device (Boston Scientific, St. Paul, Minnesota) is a Left Atrial Appendage Occlusion (LAAO) device, which was tested in two major randomized trials. PROTECT AF (Percutaneous Left Atrial Appendage Closure for Stroke Prophylaxis in Patients with Atrial Fibrillation) trial, and PREVAIL (Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation versus Long Term warfarin Therapy) trial, both evaluated WATCHMAN device's safety and efficacy compared to warfarin. These trials showed WATCHMAN device to be non-inferior to warfarin. However, patients with history of intracranial hemorrhage were excluded from these trials due to concern of increased recurrent bleeding in presence of perioperative use of anticoagulation. Purpose of this review is to evaluate existing evidence and share our experience of LAAO in this high-risk population.

## Introduction

Atrial fibrillation is the most common clinically manifested arrhythmia and is associated with complication of cardio-embolic stroke<sup>1</sup>. CHA2DS2-VASc score is the risk assessment system used to calculate the risk for a thromboembolic event in patients with atrial fibrillation and high-risk score warrants use of anticoagulation<sup>2</sup>. But patients at very high risk for cardioembolic stroke are also at high risk for bleeding due to comorbid conditions, making use of anticoagulants challenging in this population. As 90% of intracardiac thrombus are formed in the left atrial appendage, LAAO has demonstrated promising results in randomized clinical trials to reduce the risk of stroke. In this review article we will discuss LAAO to prevent thromboembolism in very high bleeding risk group of patients who were excluded from the pioneer trials of LAAO device.

## Anticoagulation in Atrial Fibrillation

Medical conditions such as congestive heart failure, hypertension and diabetes, and biographic characteristics of being female and age greater than 65 years are among the factors included in CHA2DS2-VASc risk scoring system due to their association with higher risk of embolic event<sup>3</sup>. Each CHA2DS2-VASc condition represents a risk factor, and even though the associated embolic risk rate can be

different among the many study settings and populations that have been evaluated, collectively, CHA2DS2-VASc risk score of  $\geq 2$  in men and  $\geq 3$  in women is considered moderate to high risk and initiation of anticoagulation is highly recommended<sup>4</sup>. Traditionally, these patients have been treated with warfarin. This practice is based on multiple studies that showed anticoagulation with warfarin significantly reduce stroke incidence in patients with CHA2DS2-VASc risk stratification score  $\geq 2$ <sup>5</sup>. Warfarin, being an oral vitamin K antagonist, has multiple medication interactions. Therapy may also be affected by change in diet or even acute illness. Warfarin requires frequent International Normalized Ratio (INR) monitoring. In addition, reaching a therapeutic INR level may take up to days. During this time to prevent thromboembolic events, patients should receive another anticoagulation agent, typically a low molecular weight (LMW) heparin, which can be discontinued once their INR becomes therapeutic<sup>6</sup>. Due to warfarin's challenging dosing and management, non-vitamin K oral anticoagulants also known as Direct Oral Anticoagulants (DOAC), have gained popularity. Direct Oral Anticoagulants have significantly less food and medication interactions and they do not need any frequent INR monitoring or bridging therapy. There have been multiple recent and on-going trials comparing DOAC agents with warfarin in terms of efficacy and bleeding risk. Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran (RE-LY) and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) are three pioneer trials that compared DOAC with warfarin. These trials suggested less bleeding rates with DOACs compared to warfarin<sup>7-9</sup>. With specific hepatic and renal function considerations, the 2019 AHA/ACC/HRS guidelines recommend DOAC agents over warfarin except in patients with moderate to severe mitral stenosis or any prosthetic heart valve<sup>4</sup>. Since the 2019 guidelines DOACs have gained a lot of interest but there is data that suggests intracranial hemorrhage remains a major concern even with the DOACs<sup>10</sup>.

Intracranial hemorrhage can be as devastating and fatal as an embolic event and therefore decision of anticoagulation use in high risk patients is challenging. HAS-BLED risk assessment system has been used to assess the bleeding risks in individuals. Interestingly, factors such as hypertension and age above 65 years are included both in CHA2DS2-VASc and HAS-BLED scoring systems. Therefore the same factors that are associated with increased risk of embolic events are also associated with increased risk of bleeding. This puzzling issue led to search for nonpharmacological approaches for thromboembolic risk reduction.

## Left Atrial Appendage

Thrombus formation in atrial fibrillation is believed to be a consequence of blood stasis. Thromboembolism to the downstream vascular structure causes tissue damage with ischemic stroke being the most worrisome outcome. A meta-analysis study reviewing twenty three separate studies found that 446 of 3504 (13%) of patients with rheumatic atrial fibrillation and 222 of 1288 (17%) with non-rheumatic atrial fibrillation had left atrial thrombus, thrombus was present in left atrial appendage (LAA) in 254 of 446 (57%) of patients with rheumatic atrial fibrillation and in 201 of 222 (91%) of nonrheumatic atrial fibrillation patients ( $p < 0.0001$ )<sup>11</sup>. Discovery of LAA as an anatomical site of thrombus formation in AF patients led to nonpharmacological innovations aimed to mechanically occlude LAA to prevent embolization of any possible thrombus formed. The first ever percutaneous left atrial appendage transcatheter occlusion device used was PLAATO device in PLAATO (Percutaneous Left Atrial Appendage Occlusion) trial, in 2001<sup>12</sup>. Soon after, WATCHMAN device (Boston Scientific, St. Paul, Minnesota) and Amplatzer Cardiac Plug (St Jude Medical) among others were innovated and used. The PROTECT AF trial done in 2013 compared WATCHMAN device and warfarin. In this study, total of 707 patients with nonvalvular atrial fibrillation and at least 1 risk factor (age  $>75$  years, hypertension, heart failure, diabetes, or prior stroke/transient ischemic attack) were randomized in a 2:1 ratio to either receiving WATCHMAN device ( $n=463$ ) or Warfarin ( $n=244$ ). Post device implantation warfarin was continued for about 45 days. After 45 days warfarin in device group was switched to dual antiplatelet therapy (clopidogrel and aspirin) for 4.5 months and then aspirin was continued lifelong. The primary end point of this study was stroke, systemic embolism and cardiovascular death. The PROTECT AF trial found the WATCHMAN device to be non-inferior to warfarin<sup>13</sup>. It also showed higher rate of overall adverse events (about 50 percent of which were pericardial effusions requiring drainage) in the device implantation group (5.5%), as compared to warfarin (3.6%), with a relative risk of 1.53 and confidence interval of 0.95-2.70<sup>13</sup>. One year after PROTECT AF trial, in 2014, PREVAIL trial was conducted to further evaluate safety and efficacy of the WATCHMAN device. Total of 407 patients were randomized in a 2:1 ratio to WATCHMAN device group or Warfarin group. The PREVAIL trial again showed the non-inferiority of WATCHMAN device to warfarin and it showed improved safety outcomes<sup>14</sup>. WATCHMAN device was approved in 2015 by United States Food and Drug Administration for non-valvular AF. In 2017, five-year outcomes of the both PREVAIL and PROTECT AF trials confirmed these findings and suggested reduced risk of major bleeding and mortality in device group compared to warfarin<sup>15</sup>. However, patients with any history of intracranial bleed were excluded from these trials.

## LAO Device in Patients with Intracranial Bleed History

Even though WATCHMAN device does not require long term anticoagulation therapy to prevent thromboembolism, patients must still be able to tolerate minimum of 6 weeks of anticoagulation to prevent device related thrombus. Due to presumed risk of recurrent bleeding, patients with intracranial hemorrhage history were not included in any of the WATCHMAN trials mentioned. Therefore, currently there is not enough evidence based recommendations for this high-risk group of patients for thromboembolism prevention.

In our retrospective observational study done in 2020 we addressed this gap in knowledge. We studied total of 16 patients with non-valvular AF, median CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 4.5 and median HAS-BLED score of 4. All patients had history of intracranial hemorrhage with 7 (43.7%) intraparenchymal hemorrhage, 7 (43.7%) subdural hemorrhage and 2 (12.5%) subarachnoid hemorrhage with 56% being male. These patients have a minimum interval of more than 60 days between the intracranial hemorrhage and procedure. All 16 patients had WATCHMAN device implantation and received anticoagulation therapy for 45 days that was switched to dual antiplatelet therapy for 4.5 months and thereafter aspirin indefinitely. Patients were followed for longest follow up of 27 months with a mean follow up of 23 months and no clinical bleeding events were noted in any of the patients<sup>16</sup>. There were also no events of device related thrombus, systemic thromboembolism and mortality, but the small number is a limitation of this study.

Another study using 38 patients with AF and prior intracranial bleed showed similar findings of safety with LAAO device and short-term anticoagulation use. 60% of patients in this study had intra-parenchymal, 24% had subdural bleed and 16% had subarachnoid bleed history. All these patients completed post device short term anticoagulation therapy with no major bleeding complications reported up to 13.4 months follow up period<sup>17</sup>.

Safety of LAA device in high risk bleeding patients was also suggested by a study performed in Netherlands and published in 2019. This study had 73 patients with 50 (69%) of them having previous intracranial bleeding history. The rest of patients in study had gastrointestinal bleeding (18%) or multiple foci of bleeding (22%). Four nonfatal major bleeding events (5.5%) from 30 days until 35.5 months of follow up were reported, one of which was intracranial bleed. 6 total ischemic strokes were observed, resulting in an annualized stroke rate of 2.9% compared to a calculated expected stroke rate of 6.7%. Overall, the study concluded that these patients had both lower ischemic stroke rate and lower recurrent bleeding rates

than expected rates based on their CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores<sup>18</sup>.

Data from Evaluating Real-World Clinical Outcomes in Atrial Fibrillation patients receiving the WATCHMAN device published in 2019 also has promising results for LAAO in patients with history of intracranial bleeding. Out of 1025 patients, 153 patients had prior history of intracranial hemorrhage. Use of anticoagulation post procedure was less as only 11% of the 153 patients received oral anticoagulants; 27% received single antiplatelet or no antithrombotic, and 62% received dual antiplatelet agents. The observed stroke, embolism, and bleeding at 2-year follow up were 1.8/100 patient-years (81% RRR), 2.6/100 patient-years (80% RRR), and 1.8/100 patient-years (67% RRR), respectively. Although there was less use of oral anticoagulant perioperatively in patients with intracranial bleed history, these data overall suggest safety and efficacy of WATCHMAN device implant in this high-risk population<sup>19</sup>. There is also an emerging data regarding the use of short term dual antiplatelet following LAAO. A recent meta-analysis of 83 observational studies with 12326 patients comparing short term oral anticoagulation vs dual antiplatelet by Osman et al. reported no difference in bleeding, stroke, device related thrombus and all-cause mortality<sup>20</sup>.

## Conclusion

Left Atrial Appendage closure devices have shown effectiveness in thromboembolism prevention in large clinical trials that excluded patients with history of intracranial bleed due to presumptive risk of bleeding related to procedure and short-term anticoagulation therapy. There are small observational studies in addition to Real-World Clinical Outcomes' overall data analysis that suggest LAAO devices could be safe, effective and feasible in this unique high-risk group of patients.

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