A Comparison of Post-Procedural Anticoagulation in High-Risk Patients Undergoing WATCHMAN device Implantation

Short Title: Anticoagulation Following WATCHMAN Implantation

Joshua A. Cohen, MD[*]; E. Kevin Heist MD, PhD[†]; Jennifer Galvin, PA[†]; Hang Lee, PhD[‡]; Matthew Johnson, NP[†]; Michael Fitzsimons, MD[†]; Kathryn Slattery, CRNA[†]; Brian Ghoshhajra, MD[†]; Rahul Sakhuja, MD[†]; Grace Ha, MS[†]; Margaux Forsch, RN[†]; Linsheng Shi, MD[†]; Jacqueline Danik, MD[†]; Jacob Dal-Bianco, MD[†]; Danita Sanborn, MD[†]; Judy Hung, MD[†]; Jeremy Ruskin, MD[†]; M. Edip Gurol, MD[†]; Moussa Mansour, MD[†].

*Massachusetts General Hospital, Department of Medicine, Boston, MA

[†]Corrigan Minehan Heart Center, Massachusetts General Hospital, Boston, MA

[‡]Massachusetts General Hospital, Biostatistics Center, Boston, MA

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Abbreviations:

LAAC Left Atrial Appendage Closure

AF Atrial Fibrillation

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OAC Oral Anticoagulation

VKA Vitamin K Antagonist

DRT Device related thrombosis

DAPT Dual Antiplatelet Therapy

NOAC Novel Oral Anticoagulant

TEE Transesophageal Echocardiography

Corresponding Author:

Moussa Mansour, MD

Cardiac Arrhythmia Service, Heart Center, Massachusetts General Hospital

55 Fruit Street, GRB 109, Boston, MA 02114

Phone: (617) 726-5557 / Fax: (617) 724-1241 / Email: mmansour@mgh.harvard.edu

Abstract

Background:

Left atrial appendage closure (LAAC) is an alternative to long-term anticoagulation for thromboembolic protection in patients with atrial fibrillation (AF) and high bleeding risk. Short-term Warfarin use following LAAC is well-studied, while data pertaining to novel oral anticoagulant (NOAC) use in this setting is less robust. Specifically, data regarding the safety and efficacy of post-procedural NOAC use in high-risk patients is lacking.

Objective:

To compare the safety and efficacy of Warfarin and NOAC use in a high-risk patient population undergoing LAAC with the WATCHMAN device.

Methods:

From November 2015 to October 2017, 97 patients underwent LAAC with the WATCHMAN device. All patients were discussed at a multidisciplinary meeting prior to device implantation. Longitudinal data were collected and analyzed for a composite endpoint of stroke and death at 8 months, and major bleeding at 3 and 6 months.

Results:

Among the 90 patients included in the safety and efficacy analysis 43 were prescribed Warfarin and 47 were prescribed NOACs. Baseline characteristics were comparable between study groups. There were no procedural complications and no significant differences in the incidence of death and stroke at 8 months or major bleeding at 3 and 6 months.

Conclusion

For patients with Atrial Fibrillation at high risk of both thromboembolic and hemorrhagic events, NOACs as compared to Warfarin, are seem to be safe and effective for short-term anticoagulation following LAAC with the WATCHMAN Device. Further validation in large randomized controlled trials is required.

Key Words:

Left Atrial Appendage Closure

WATCHMAN Device

Novel Oral Anticoagulation

Atrial Fibrillation

Thromboembolism

Stroke

Introduction:

Left Atrial Appendage Closure (LAAC) has evolved in clinical practice as an alternative to warfarin for the prevention of thromboembolic events in patients with atrial fibrillation (AF) and concurrent high bleeding risk. The WATCHMAN device (Boston Scientific, Marlborough, MA) is currently the only FDA-approved closure device in the United States for stroke prevention and has been validated in randomized clinical trials and patient level meta-analyses (1-4). Notably, patients with contraindications to long-term oral anticoagulation (OAC) were excluded from the original clinical trial populations, and all patients received the vitamin K antagonist (VKA) warfarin following LAAC. Short-term OAC for 45 days is a standard practice felt to be necessary for device endothelialization and the prevention of device related thrombosis (DRT) (5). At present, LAAC is a Class IIb, LOE C recommendation though long-term follow up data from the PROTECT AF and PREVAIL trials have yet to be incorporated into new major society guidelines (6,7).

It has been our experience, that the majority of patients referred for LAAC have relative and in many cases absolute contraindications to long-term oral anticoagulation (OAC). As such, many of these patients were not represented in clinical trials and in fact may have been excluded. Within a "real world" high-risk population, LAAC followed by short-term OAC (with warfarin) or dual antiplatelet therapy (DAPT) has been shown to be well-tolerated (8-10). The role of the novel oral anticoagulants (NOAC) in such high-risk populations is not well-studied. As such, we sought to examine the safety and efficacy of NOACs as compared to warfarin in a high-risk population undergoing LAAC with the WATCHMAN device.

Methods:

Patient Selection:

The present study included consecutive patients who presented for LAAC with the WATCHMAN device between November 2015 to October 2017. Institutional Review Board (IRB) approval was obtained prior to data collection. Candidacy of individual patients was discussed at a multidisciplinary Stroke prEvention in Atrial FibriLlation (SEAL) meeting prior to moving forward with device implantation. SEAL meetings include cardiologists, neurologists, radiologists, and echocardiographers who meet on a monthly basis to discuss the treatment of patients with AF and challenging stroke prevention needs.

WATCHMAN Implantation Procedure:

All procedures were performed under general anesthesia and utilized fluoroscopy and intraoperative transesophageal echocardiography (TEE) for guidance. No routine screening

TEE or CT scan (to assess for left atrial size) was performed leading up to the procedure as our center's early experience found a relatively low rate of intracardiac thrombus and/or unfavorable LAA size/anatomy. Femoral vein cannulation was performed using a micropuncture needle under ultrasound guidance. Subsequent transseptal puncture was performed using a radiofrequency needle to ensure access into the left atrium along the inferior border of the fossa ovalis, anterior to the midline. A Heparin bolus was infused prior to the transseptal puncture with a goal ACT of $\geq$ 250 sec. For patients receiving warfarin, there was no interruption in anticoagulation, while those receiving NOACs held medication doses the evening before and morning of the procedure. All procedures were performed by a single experienced operator.

Data Collection and Statistical Analysis:

Longitudinal data were collected including patient characteristics and rates of death, stroke, and major bleeding. Major bleeding was defined in accordance with well-accepted societal guidelines as fatal bleeding, bleeding into a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome), or hemoglobin drop of $\geq$ 2g/dL and/or transfusion of $\geq$2 units of whole blood or packed red cells within 48 hours of index bleed (11). Data was subsequently analyzed to evaluate a primary efficacy endpoint of death and stroke at 8 months, and a safety endpoint of major bleeding at 3 and 6 months. Categorical variables are reported in count and corresponding percentage while continuous variables are reported as mean +/- standard deviation. Data was analyzed using pooled T-test, Chi Square, Fisher Exact, and survival

analysis models as appropriate utilizing EpiCalc 2000 (Brixton Health) and JMP Pro 14 (JMP®, Cary, NC). P-values of <0.05 were deemed to be significant.

Results:

Patient Population:

Ninety-seven patients were included in the study (Table 1). The WATCHMAN device was successfully implanted in 93/97 (96%) patients. In 4 patients the procedure was attempted but unsuccessful due to unfavorable left atrial appendage anatomy. Additionally, 3 patients (2 in the NOAC group, and 1 in the warfarin group) underwent successful implantation but did not meet the follow up interval of 8 months. As a result, these 7 patients were excluded from the safety and efficacy analysis, but were included in the procedural complication analysis. Within the study population, 41/ 97 (42%) were not on OAC at the time of referral to our center, 24/97 (25%) had a history of intracranial hemorrhage, and 52/97 (54%) had clinical documentation of prior falls.

Procedural Outcomes:

Of the 97 patients who underwent the procedure, there were no major procedural complications. Specifically, there was no death, stroke, hemodynamically significant pericardial effusion, major bleeding, or vascular site complication requiring intervention. After the procedure, 45 patients were treated with Warfarin and 52 with NOACs. Patients within the warfarin and NOAC groups were well-matched with regard to age, gender, comorbid conditions, prior bleeding events, thromboembolic risk, and bleeding risk, with a significant difference only in the proportion of patients with a history of congestive heart failure, and prior falls (Table 1). Anticoagulation and subsequent antiplatelet strategies following device implantation are reported in Table 2. Notably, 95% of patients in the

warfarin group and 98% of patients in the NOAC group tolerated at least 6 weeks of OAC with almost all patients discontinuing OAC by 90 days post procedure. For unclear reasons, 5 patients were continued on OAC for >90 days by their referring physicians. At 90 days (~3 months) major bleeding occurred in 2/43 (4.7%) and 3/47 (6.4%) in the warfarin and NOAC group respectively. At 180 days (~6 months) there were no new bleeding events in the warfarin group (event rate remained at 4.7%), and one additional event 4/47 (8.5%) in the NOAC group (p=0.68). At 245 days (~8mo) there were 3 patients in the warfarin group and 1 in the NOAC group that met criteria for a composite endpoint of stroke or death (event rate 7.0% vs 2.1%; p=0.35). Specifically, there were 2 deaths and 1 stroke in the warfarin group and 1 death in the NOAC group. Despite small differences in absolute event rates there was no significant difference in a composite endpoint of death and stroke at 8 months or major bleeding at either 3 or 6 months (Table 3). Kaplan Meier curves are shown in Figure 1A-C. Among the 3 patients who died, the cause of death was septic shock following uterine surgery, urosepsis, and pneumonia.

Discussion

This study resulted in two significant findings. First, it highlights the utility of short-term NOAC use in patients with AF and concurrent high bleeding risk undergoing LAAC. Second, it reveals a lack of difference between NOAC and warfarin groups, not only in the early post-procedural period, but also when followed past the time of discontinuation of OAC and/or DAPT.

Large randomized clinical trials have demonstrated the safety and efficacy of LAAC with the WATCHMAN device. However as previously mentioned, patients undergoing this procedure in the “real world” are often comparatively sicker and have more medical comorbidities. In

addition, the aforementioned trials only used warfarin following device implantation. More recently the efficacy of LAAC in high-risk populations has been exhibited (8-10). Moreover, with the increased use of NOACs relative to Warfarin, a recent study reported on the safety and efficacy of these medications as compared to warfarin after LAAC (12). However the patient population in that study appeared healthier as demonstrated by the statistically significant differences in the mean $CHADS_2$ (2.4 vs 2.1), CHA_2DS_2-VASC (4.1 vs 3.8), and HASBLED (2.7 vs 2.4) scores between the warfarin and NOAC groups, respectively (12). Additionally, thromboembolic and bleeding events were evaluated in the majority of patients prior to discontinuation of DAPT with the longest duration of follow up occurring at 4 months post-procedure. Using $CHADS_2$, CHA_2DS_2-VASC, and HASBLED scores as a surrogate, the present study, to our knowledge, includes the highest risk patient population reported in the literature to receive NOACs following LAAC. The mean $CHADS_2$ and CHA_2DS_2-VASC, and HASBLED scores in our study population were 2.9, 4.7, 3.5 (warfarin group) and 2.9, 4.7, 3.5 (NOAC group). For reference, $CHADS_2$ and CHA_2DS_2-VASC scores in the PROTECT AF population were 2.2, 3.5 and 2.6, 4.0 in PREVAIL. Furthermore 89% of our study population had a HASBLED score ≥3, while this was the case for only 20% of patients in PROTECT AF and 30% of patients in PREVAIL. Finally, a significant number of patients had a history of intracranial hemorrhage (a commonly cited absolute contraindication to OAC), clinical documentation of prior falls, and almost half were not on OAC at the time of referral to our center. Despite significant risk, the procedure was well-tolerated with low event rates. All deaths and strokes were unrelated to the procedure and the one patient who suffered a stroke did not have evidence of device-related thrombus (DRT) on follow up TEE.

The efficacy analysis was performed at 8 months of follow up to evaluate for late events occurring after the majority of patients discontinued some form of antithrombotic therapy (NOAC or DAPT) which occurred between 3-6 months for the majority of patients. There is a known non-negligible incidence of late DRT that carries an associated increased risk of ischemic stroke. Presumably, the risk of developing DRT is highest in the early post-procedure period before device endothelialization, but recurs with cessation of OAC and/or antiplatelet therapy (13). All but 3 patients in this study underwent routine follow up with TEE at 6 weeks to assess device placement and evaluate for DRT (1 patient died prior to 6 weeks, 1 patient followed up outside of our center, and 1 patient sustained major bleeding after which the procedure was never rescheduled). This study revealed that the rate of stroke is very low, and identified no DRT or clinically significant peri-device leaks on 6 week follow up TEE. These findings (or lack thereof) provide only short-term understanding of NOACs vs warfarin as related to DRT given this is a phenomenon typically seen at 6 months or later and could be due to a lack long-term TEE data and a relatively small sample size . Larger randomized studies with long-term follow up data are necessary.

Major bleeding was evaluated at 3 and 6 months to account for both early and late events. Notably, 96% of the NOAC population was on full dose OAC as recommended by respective FDA approved label, and 84% of the warfarin population was followed by an Anticoagulation Management System (AMS) with a historical time in therapeutic range of 74%. Although there was a slight trend toward higher major bleeding events in the NOAC group (4 NOAC vs 2 warfarin; p=0.68) upon further review, it was found that one patient was no longer on NOAC therapy (Aspirin 81mg monotherapy) at the time of major bleed while another was on both Rivaroxaban and Plavix due to recent drug eluting stent placement. As

such, these events cannot be attributed solely to NOAC therapy. All major bleeding events that occurred in this study were gastrointestinal hemorrhages.

The findings of the present study are important given the prevalence of NOACs and known logistical advantages conferred by their utilization in clinical practice. Such advantages include rapid time to therapeutic anticoagulation (eliminating the need to bridge with parenteral therapy), lack of routine laboratory monitoring, and minimal dietary and drug-drug interactions. As a result, NOACs can aid in procedural workflow and provide a less cumbersome short-term option for even the highest-risk patients undergoing LAAC.

Limitations:

This study is limited by a relatively small sample size and is retrospective in nature. As with any non-randomized, retrospective study without propensity matching, selection bias is possible. Small sample size may also lead to the study being underpowered to detect events such as DRT and stroke. In addition, all procedures were performed by a single experienced operator. It should be mentioned that warfarin was given uninterrupted while NOACs were given in a minimally interrupted fashion (doses held evening before and morning of procedure). As such, it is difficult to compare periprocedural complications (specifically those related to vascular access and bleeding) between groups. Finally, these results may not be applicable to all NOACs as the overwhelming majority of patients in the NOAC group received Apixaban.

Conclusion:

Within a patient population at high risk for both thromboembolic and major bleeding complications NOACs, as compared to Warfarin, are safe and effective for short-term anticoagulation following LAAC with the WATCHMAN Device. These findings require

further validation in larger randomized controlled trials with the inclusion of long term follow up data.

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Figure 1A: Death and Stroke at 8 months

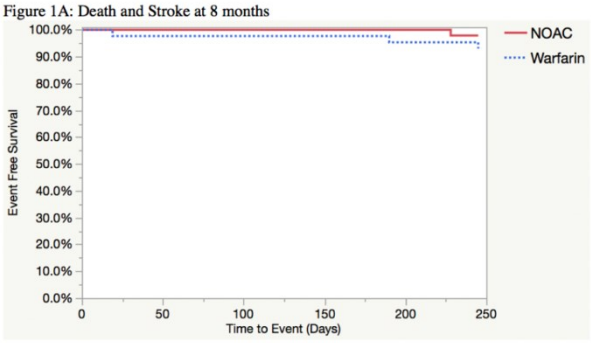

Figure 1B: Major Bleeding at 3 months

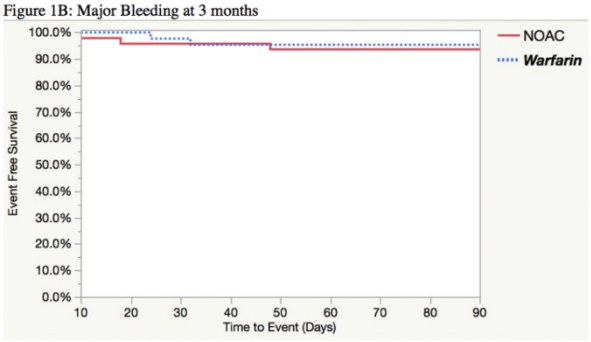

Figure 1C: Major Bleeding at 6 months

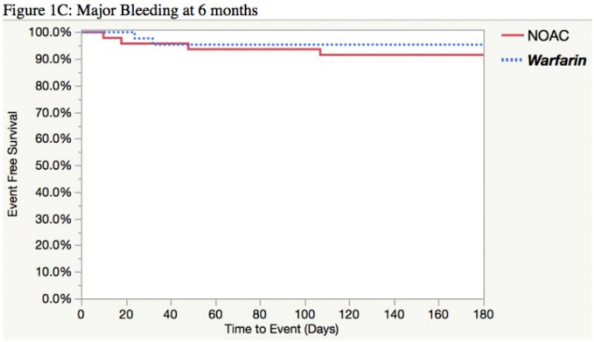

Figure 1A: Survival curves comparing event free survival from both death and stroke at 8 months in warfarin and NOAC groups.

Figure 1B: Survival curves comparing event free survival from major bleeding at 3 months in warfarin and NOAC groups.

Figure 1C: Survival curves comparing event free survival from major bleeding at 6 months in warfarin and NOAC groups.

Table 1: Patient Characteristics

	Warfarin Group	NOAC Group	P-Value
Number of Patients	n=45	n=52	
Age (years)	76.8 (+/- 7.5)	76.9 (+/- 8.7)	p=0.93
Sex (female)	19 (42.2)	17 (32.7)	p=0.33
CHF	22 (48.9)	13 (25)	p=.01*
HTN	41 (91.1)	46 (88.5)	p=0.67
DM	9 (20)	12 (23.1)	p=0.71
Stroke/TIA/Thromboembolism	16 (35.6)	23 (44.2)	p=0.38
Vascular Disease	22 (48.9)	27 (51.9)	p=0.77
$CHADS_2$ Score	2.9 (+/- 1.2)	2.9 (+/- 1.3)	p=0.96
CHA_2DS_2-VASC Score	4.7 (+/- 1.5)	4.7 (+/- 1.5)	p=0.94
Prior ICH	10 (22.2)	14 (26.9)	p=0.59
Prior GIB	23 (51.1)	17 (32.7)	p=0.07
Prior Falls	17 (37.8)	35 (67.3)	p=0.004*
HASBLED	3.5 (+/- 0.8)	3.5 (+/- 1.0)	p=0.88
Paroxysmal AF	12 (26.7)	23 (44.2)	p=0.07
Persistent AF	32 (71.1)	29 (55.8)	p=0.12
EF (%)	58.7 (+/- 10.9)	59.9 (+/- 11.7)	p=0.61

Creatinine (mg/dL)	1.6 (+/- 1.6)	1.2 (+/- 0.5)	p=.05[†]
On OAC at Referral	18 (40)	23 (44.2)	p=0.67

Categorical variables are reported in count and corresponding percentage while continuous variables are reported as mean +/- standard deviation. AF: Atrial Fibrillation. CHF: Congestive Heart Failure. DM: Diabetes Mellitus. EF: Ejection Fraction. GIB: Gastrointestinal Bleed. HTN: Hypertension. ICH: Intracranial Hemorrhage TIA: Transient Ischemic Attack. A p-value of <0.05 was considered to be statistically significant.

[†]When carried out to further decimal places the p value is >0.05, thus the result is not statistically significant.

Table 2: Post Procedural Oral Anticoagulant Strategies

	Warfarin Group (n=43)	NOAC Group (n=47) Apixaban (41), Rivaroxaban (4), Dabigatran (2)
6 weeks of OAC	39 (90.7)	19 (40.4)
6-12 weeks OAC[†]	1 (4.7)	23 (57.4)
<6 weeks OAC	2 (4.7)	1 (2.1)
4.5 months DAPT (after OAC)	17 (39.5)	7 (14.9)
No DAPT	5 (11.6)	35 (74.5)
Most Common Antithrombotic Strategy	6 weeks OAC/4.5mo DAPT/ASA 81-324 indef.	3mo OAC/No DAPT/ASA 81-325 indef.

Rates are reported as proportions and corresponding percentages. ASA: Aspirin. DAPT: Dual Antiplatelet Therapy. OAC: Oral Anticoagulation.

[†]Five patients (1 Warfarin and 4 NOAC) were continued on OAC for >12 weeks by their referring physicians for unclear reasons.

Table 3: Primary Composite and Safety Endpoints

	Stroke and Death (8mo)	Major Bleeding (3mo)	Major Bleeding (6mo)
Warfarin	3 (7.0)	2 (4.7)	2 (4.7)
NOAC	1 (2.1)	3 (6.4)	4 (8.5)
Fisher Exact Testing	p=0.35	p=1.0	p=0.68
Rates are reported a counts and corresponding percentages. P value of <0.05 was considered to be statistically significant. NOAC: Novel Oral Anticoagulant			