Boston Scientific Corporation
300 Boston Scientific Way
Marlborough, MA 01752
(508) 683-4000
www.bostonscientific.com

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Ms. Tamara Syrek-Jensen, J.D.
Director, Coverage & Analysis Group, OCSQ
Centers for Medicare and Medicaid Services
7500 Security Boulevard, C1-14-15
Baltimore, Maryland 21244

Via email: Tamara.Syrek-Jensen@cms.hhs.gov

A FORMAL NATIONAL COVERAGE DETERMINATION (NCD) REQUEST FOR PERCUTANEOUS, TRANSCATHETER, INTRALUMINAL LEFT ATRIAL APPENDAGE CLOSURE (LAAC) WITH IMPLANTED DEVICE

Dear Ms. Syrek-Jensen:

Boston Scientific is pleased that the WATCHMAN Left Atrial Appendage Closure (LAAC) Device has received FDA approval on March 13, 2015. The attached dossier constitutes a formal request by Boston Scientific for the Centers for Medicare and Medicaid (CMS) to develop an NCD for percutaneous, transcatheter, intraluminal LAAC using an implanted device.

The dossier includes information required by CMS for a complete NCD request as well as supporting documents for patient selection criteria (Directions for Use and Patient Guide) that assist with the FDA indication for the WATCHMAN Device. We have also included our perspectives on the scope of the NCD and the question that we believe should form the basis of the analysis of the clinical evidence.

We look forward to working with you and your staff during this process. Please do not hesitate to contact either me or Wendy Chan if you need additional information to proceed.

Sincerely,

Parashar Patel
Vice President, Global Health Economics & Reimbursement

Enclosure

FORMAL REQUEST FOR A MEDICARE NATIONAL COVERAGE DETERMINATION (NCD)
Percutaneous, transcatheter, intraluminal Left Atrial Appendage Closure with Implanted Device
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1. Request

a. Scope

Boston Scientific Corporation is requesting CMS open a National Coverage Analysis (NCA) for the purpose of developing national coverage for left atrial appendage closure achieved via a percutaneous, transcatheter, intraluminal approach and an implanted device. We request that CMS limit its NCA and NCD to devices that meet this description and which are FDA approved. This request for coverage is specific to the WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device which recently received FDA approval on March 13, 2015. We are not aware of any other devices meeting this description under FDA review.

Although there are other techniques used to achieve left atrial appendage (LAA) exclusion, these techniques are surgical. They require an incision and involve the use of sutures or clips or staples to achieve LAA exclusion. They are not achieved via percutaneous, vascular access, are not exclusively intraluminal, do not involve use of an implanted device, and none of them are approved by the FDA for LAA closure for stroke prevention. Our NCD request is limited to analysis of evidence supporting coverage for LAAC achieved using a percutaneous, transcatheter, intraluminal approach and an implanted device with an approved FDA indication.

CMS could consider coverage under both of the following statutory provisions:

Section 1862 (a)(1)(A) of the Social Security Act (SSA), and

Section 1862 (a)(1)(E) of the SSA

Under the first provision, CMS can find the WATCHMAN to be medically reasonable and necessary for labeled indications and can recommend hospital infrastructure and operator requirements. Under the second provision, CMS can cover the WATCHMAN under coverage with evidence development (CED). In this scenario CMS could require participation in a prospective, national audited registry that accepts all applicable devices, includes long term follow up and hospital and operator requirements.

In summary, we recommend that CMS cover percutaneous, transcatheter, intraluminal LAAC using an implanted device that has received a PMA from the FDA for the device's labeled indications. The current indications for use are below in Section 1e.

b. Benefit categories

Physician services (SSA Section 1861(r))

Inpatient hospital services (SSA Section 1861(b))

c. Hospital and Operator Requirements

Boston Scientific recommends that there should be hospital infrastructure and operator training and experience requirements for performing percutaneous, transcatheter, intraluminal LAAC procedures with an implanted device. These requirements should be similar to those that were part of the WATCHMAN pivotal IDE clinical trials.

Hospital infrastructure requirements should include:

- Experience with performing complex interventional cardiac procedures;
- Cardiac catheterization lab or electrophysiology (EP) lab with fluoroscopy capability;
- Non-invasive imaging expertise (i.e., TEE- transesophageal echocardiogram) with dedicated echocardiography support;
- Anesthesiology support for administration of general anesthesia;
- Sufficient cath lab, operating room (if required), post anesthesia recovery, intensive care and step down unit space to accommodate cases with and without complications;
- On-site emergency cardiac surgery services, if needed;

Operator requirements should include:

- Interventional or EP program where the primary implanting physician has performed > 25 interventional cardiac procedures involving a transseptal puncture (TSP) in their total experience, with at least 10 TSP procedures performed over the past 12 month period.
- The percutaneous, transcatheter, intraluminal LAAC implant is performed by an interventional cardiologist and/or an electrophysiologist. They may jointly participate in intra-procedural aspects of the implant or perform the implant procedure individually.
- Interventional cardiologist(s) and electrophysiologist(s) must receive prescribed training by the manufacturer on the safe and effective use of the device prior to performing implant procedures.

d. Proposed NCA question

CMS national coverage analyses are usually predicated on the general question: “Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?”

Our proposed question for the evaluation of the WATCHMAN Device is as follows:

“Is the evidence adequate to conclude that percutaneous, transcatheter, intraluminal left atrial appendage closure with implanted device (or WATCHMAN) improves health outcomes for Medicare beneficiaries with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores but who have an appropriate rationale to seek a non-pharmacologic alternative to warfarin?”

If the answer to this question is positive, “Is the available evidence adequate to identify the characteristics of the patient, practitioner or facility that predict which beneficiaries are more likely to experience overall benefit or harm from WATCHMAN?”

e. FDA information

The FDA recently approved the PMA application for the WATCHMAN Device on March 13, 2015. The FDA has posted the Integrated Summary of Safety and Effectiveness Data (SSED), the approval, Implant System Directions for Use, and the Patient Guide on its website: http://1.usa.gov/1FuDCFt. Section 5 of this dossier contains the Integrated Summary of Safety and Effectiveness Data, the Indications for Use and the Patient Guide. The indications for use are as follows:

Indications for use

The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc[1] scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

Patient Selection considerations

Selection among available treatment options must first take into account whether anticoagulation is indicated to reduce the risk of stroke based on $CHADS_2$ or CHA_2DS_2-VASc scores per current guidelines covering stroke risk reduction in patients with atrial fibrillation. Next, in a patient who is deemed by their physicians to be suitable for anticoagulation with warfarin, physicians and patients should consider the rationale for implantation of the WATCHMAN Device as an alternative to long-term warfarin therapy. Specific factors may include one or more of the following:

- a history of major bleeding while taking therapeutic anticoagulation therapy
- the patient's prior experience with oral anticoagulation (if applicable), which may include an inability to maintain a stable therapeutic International Normalized Ratio (INR) or inability to comply with regular INR monitoring AND unavailability of an approved alternative anticoagulation agent
- a medical condition, occupation, or lifestyle placing the patient at high risk of major bleeding secondary to trauma. Some studies of patients with a history of falls, or at risk for falls and head trauma, have shown that the benefits of anticoagulation therapy to reduce the risk of stroke outweigh the risk of major, life-threatening bleeding. An individualized benefit and risk assessment should be made in such patients.[2,3,4]
- the presence of indication(s) for long-term warfarin use, other than non-valvular atrial fibrillation (e.g. mechanical heart valve, hypercoaguable states, recurrent deep venous thrombosis).

Again, it is important to reiterate that these are considerations that apply to patients, who although suitable for warfarin, have a good reason to seek an alternative. To provide a better perspective of the population that would be candidates for the WATCHMAN Device, we have provided the **Figure 1** below.

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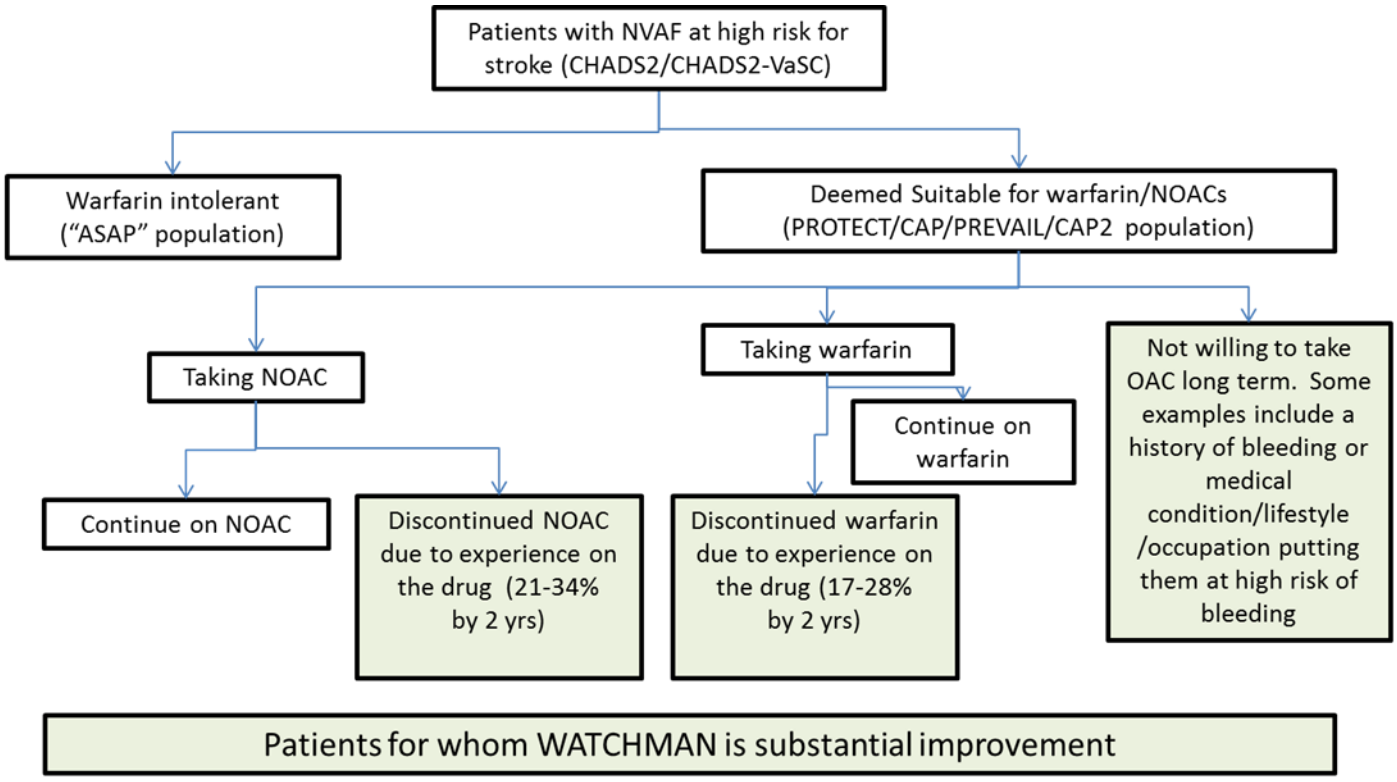
[1] January CT, Wann LS, Alpert JS, et. al., 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, Circulation, 2014; 130: e199-e267.

[2] American Geriatrics Society/British Geriatrics Society Clinical Practice Guideline for Prevention of Falls in Older Persons. J Am Geriat Soc. 2010 (http://www.americangeriatrics.org/files/documents/health_care_pros/JAGS.Falls.Guidelines.pdf)

[3] Seller MB, Newby LK. Atrial Fibrillation, Anticoagulation, Fall Risk, and Outcomes in Elderly Patients. Am Heart J. 2011; 161:241-246.

[4] Donzé J, Clair C, Hug B, et al. Risk of Falls and Major Bleeds in Patients on Oral Anticoagulation Therapy. Am J Med. 2012 Aug;125(8):773-8.

Figure 1: Candidates for the WATCHMAN Therapy



1. Jani, et al. Uptake of Novel Oral Anticoagulants in Patients with Non-Valvular and Valvular Atrial Fibrillation: Results from the NCDR-Pinnacle Registry. ACC 2014

As indicated in Figure 1 and discussed below, the four major WATCHMAN studies (PROTECT AF, CAP, PREVAIL, CAP2) studied patients who were deemed suitable for warfarin and novel oral anti-coagulants. The totality of the data from these studies shows that WATCHMAN is a safe and effective alternative to oral anticoagulation, and provides significant protection against stroke in patients who might otherwise be left unprotected.

2. Supporting medical and scientific information

Executive Summary

Atrial fibrillation is the most common sustained arrhythmia and is associated with a significantly increased risk of thromboembolic stroke. Current pharmacologic therapies to reduce this risk have important limitations for many patients. *For further information on AF, risk factors for stroke, historical treatments for stroke, and other oral anti-coagulation alternatives, please reference* ***Sections 2a, 2b, 2c, and 2d.***

A substantial number of high risk patients with nonvalvular AF who are deemed suitable for anticoagulant therapy nonetheless have an appropriate rationale to seek a nonpharmacologic alternative and many of these patients, including many Medicare beneficiaries, are currently left unprotected from the potentially devastating consequences of stroke. The clinical community urgently needs a safe and effective alternative to oral anticoagulation to reduce the risk of cardioembolic stroke in these patients. *For further*

information on why there is an urgent need for WATCHAN as a therapy option for indicated patients, please reference ***Sections 2e, 2f, and 2g.***

A substantial number of high risk patients with non-valvular AF who are deemed suitable for anticoagulant therapy nonetheless have an appropriate rationale to seek a non-pharmacologic alternative. Prior to the FDA approval of the WATCHMAN Device many of these patients, including many Medicare beneficiaries, were left unprotected from the potentially devastating consequences of stroke. The clinical community urgently needs a safe and effective alternative to oral anticoagulation to reduce the risk of cardioembolic stroke in these patients. *For further information on why there is an urgent need for WATCHAN as a therapy option for indicated patients, please reference* ***Sections 2e, 2f, and 2g.***

The WATCHMAN Device is the most comprehensively studied device supporting the reduction of cardioembolic stroke originating in the LAA. The totality of data from PROTECT AF, PREVAIL, and two continued access registries provides reasonable assurance of the safety and efficacy of WATCHMAN versus warfarin. The WATCHMAN Device offers Medicare beneficiaries a safe and effective alternative to oral anticoagulation to reduce the risk of cardioembolic stroke in patients described above. *For further information on the key clinical trials and the meta-analyses that provide support the totality of the clinical data supporting the WATCHMAN Device, please reference* ***Section 2h****.*

a. General background on Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, currently affecting more than three million Americans. In AF, the left atrium does not beat - instead it fibrillates and as a result it does not contract in any organized manner. Because of this, AF patients have a five-fold increased risk of stroke due to blood pooling in the left atrium and the predominant location for this is the left atrial appendage (LAA), a thumb-sized outpouching from the left atrium. The pooled blood can form blood clots (i.e., thrombus formation), which can break off (embolize) and go into the systemic circulation and lodge somewhere else in the body. Commonly, these clots will lodge in the brain causing a stroke. Ninety-one percent of left atrial thrombi in non-valvular atrial fibrillation have been shown to be isolated to, or originate in, the LAA.[5] The risk of ischemic stroke attributed to non-valvular AF is estimated at an average of 5% per year which is 2-7 times that of people without AF.[6]

b. Risk Factors for Stroke

Comprehensive management of the patient with atrial fibrillation requires a multifaceted approach directed at first identifying any underlying treatable causes, then controlling symptoms and protecting the

[5] Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996; 61:755-59.

[6] Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for practice guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol. 2006;48:854-906.

patient from ischemic stroke or peripheral embolism[7]. The American College of Cardiology, American Heart Association, and the European Society of Cardiology (ACC/AHA/ESC) task force recommend AF management involve three non-mutually exclusive objectives: rate control, prevention of thromboembolism, and correction of the rhythm disturbance.

According to the 2014 ACC/AHA/ESC guidelines, AF-associated stroke risk stratification is based upon CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack, Vascular disease, Age 65-74, and Sex/gender). A CHA_2DS_2-VASc score of 0 indicates aspirin as the preferred strategy, while a CHA_2DS_2-VASc score of 2 or greater indicates that oral anticoagulants are recommended. A CHA_2DS_2-VASc score of 1 leaves the treatment choice to the patient and physician, as they balance the benefit of stroke risk reduction against the potential complications of anticoagulation. Importantly, the guidelines state that for all patients "antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute and relative risks of stroke and bleeding and the patient's values and preferences."[8]

The CHA_2DS_2-VASc score represents a refinement of the previous scoring system that was in widespread clinical use: the $CHADS_2$ score. The CHA_2DS_2-VASc metric was developed and validated after the WATCHMAN Clinical Program began and was not used prospectively to screen patients in the clinical trials, but is now the recommended metric for measuring stroke risk and recommending stroke risk prophylaxis per the latest ACC/AHA/HRS Guidelines. Patients with a CHA_2DS_2-VASc score of 2 or greater have a 4 – 24% risk of ischemic stroke per 100 patient-years if left untreated. Across the WATCHMAN clinical studies, the vast majority of the patients (>95%) were high risk for stroke on the basis of a retrospectively-calculated CHA_2DS_2-VASc score of 2 or greater, and thus met guideline recommendations for warfarin anticoagulation.[9]

Current AHA/ACC/HRS guidelines recognize the need to balance the benefit of oral anticoagulation against the bleeding risk. This balance may be guided by the HAS-BLED score, which has been validated to assess the risk of bleeding on warfarin.[10,11,12] HAS-BLED risk factors include hypertension (systolic blood pressure > 160mm Hg), abnormal renal or liver function, a history of stroke or bleeding, labile INR, age (age > 65 years), use of drugs that promote bleeding, or excessive alcohol use. HAS-BLED scores

[7] Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for practice guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol. 2006;48:854-906.

[8] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JS, 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation. J Coll Cardiol 2014; 64 (21):2246-80.

[9] AHA/ACC/HRS Guidelines (2014).

[10] Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation. The task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369-2429.

[11] Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation. The Euro Heart Survey. *Chest* 2010;138:1093-1100.

[12] Lip GYH, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Europace* 2011;13:723-46.

may take on values ranging from 0 to 9. Risk levels and associated bleeding rates in events per 100 patient-years are shown in **Table 1**.

Table 1: Bleeding Rate Associated with HAS-BLED Risk Scores

HAS-BLED Score	Bleeding Risk Classification	% Bleeds / 100 Patient-Years
0	Low	1.1
1 – 2	Intermediate	1.9
≥ 3	High	4.9

c. Historical Treatment for Stroke

The current standard of care for preventing stroke in patients with non-valvular atrial fibrillation is oral anticoagulation. Anticoagulation with warfarin or one of the novel oral anticoagulation agents (NOACs) such as dabigatran, rivaroxaban, or apixaban, is well established as effective for prevention of thromboembolism, and, is still the treatment of choice for patients who can tolerate such medication over the long term. While the approved pharmacological therapies do decrease the risk of stroke for these patients, each of the approved medications also is associated with certain risks.

The most common anticoagulant used for preventing strokes in these patients is warfarin. Warfarin has been used for many years and works by interfering with the body's clot forming mechanisms. It has been extensively studied both for its therapeutic benefit and long-term sequelae and has demonstrated efficacy in stroke risk reduction. Despite its proven efficacy, long-term warfarin therapy is not well-tolerated by some patients, has a very narrow therapeutic range, and carries a high risk for bleeding complications.

The frequency of major bleeding or intracranial hemorrhage while on warfarin is 3.1 – 3.6% per year[13,14,15]. Hemorrhagic strokes due to intracranial hemorrhage on warfarin are a particular concern since these are often catastrophic resulting in death or severe disability. Although chronic warfarin therapy has been proven to reduce the risk of clinical thromboembolism in patients with non-valvular AF, patients find it difficult to adhere to the therapy and discontinuation rates have been shown to range from 17-28% over time, resulting in lack of thromboembolic protection in those who have stopped the drug.[16,17] The

[13] Connolly SJ, Ezekowitz MD, Yusuf S, et al and the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in atrial fibrillation patients. *N Engl J Med*. 2009;361:1139-51.

[14] Patel MR and the ROCKET AF Steering Committee for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.

[15] Granger CB and the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.

[16] Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke*. 2006;37:1070-4.

discontinuation risk increases over longer periods of time. The use of warfarin requires routine laboratory monitoring to achieve an International Normalized Ratio (INR) of 2.0 – 3.0. Maintaining the INR within this narrow therapeutic range can be challenging. Frequent blood tests to monitor INR are required at some cost and inconvenience to the patient. In addition, because warfarin is affected by a large number of drug and dietary interactions, INR levels can be unpredictable and difficult to manage. Chronic anticoagulation presents problems of safety and tolerability in many patients, especially those older than 75, the age group encompassing perhaps half of AF-associated strokes.[18] As a result, approximately 40-50% of high risk Medicare patients with non-valvular AF are currently left unprotected from stroke.[19]

As noted above, one major challenge in warfarin therapy is maintaining the patient within a narrow therapeutic range, INR between 2.0 and 3.0, associated with efficacy. Patients who are unable to comply with warfarin therapy and therefore only take it intermittently (effectively having a low INR), or who are sub-therapeutic despite being on warfarin, have been shown to have significantly worse outcomes than those able to maintain warfarin therapy within range.

Time in Therapeutic Range (TTR) on warfarin is a powerful indicator of overall therapeutic effect when evaluating warfarin and is correlated with outcomes.[20] TTR was maintained at a very high level in both the PREVAIL and PROTECT AF Warfarin Groups. In order to place the high TTR observed in our study's warfarin arm in context, 'real world' TTR data should be considered:

- A meta-analysis of TTR in AF patients treated with warfarin in the ambulatory setting in the US demonstrated AF patients spend, on average, only about one-half of the time within therapeutic INR in community practice, with average TTR = 51% (95% CI=47%-55%).[21] It is sobering to recognize that this average TTR achieved in real-world clinical practice represents a value that has been associated with limited or no efficacy of warfarin. In a post hoc analysis, the TTRs of patients on warfarin in a randomized trial of OAC versus dual antiplatelet therapy (clopidogrel plus aspirin)[22] were used to calculate the mean TTR for each of 526 centers and 15 countries. A wide variation was found to exist in TTR. A target threshold TTR was identified (estimated between 58% and 65%) below which there appears to be little benefit of OAC over antiplatelet therapy.

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[17] Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689-96.

[18] Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: Structure, function, and role in thromboembolism. *Heart.* 1999;82:547-55.

[19] Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689-96.

[20] Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: Observing outcomes associated with varying levels of INR control. *Thromb Res*. 2009;12437-41.

[21] Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm*. 2009;15(3):244-52

[22]Connolly SJ, Pogue J, Eikelboom J, et.al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of International Normalized Ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation*. 2008;118:2029-37.

- In a systematic examination of clinical studies, TTR in retrospective studies was median 59% (29-75%), and in prospective cohort studies 61% (56-66%).[23]
- In the context of a large, integrated health system (i.e. the VA), TTR has been assessed as a basis for quality measurement and quality improvement efforts. The mean TTR for the entire sample was 58%.[24]

The Stroke Prevention in Atrial Fibrillation III randomized clinical trial established conclusively that low-intensity, fixed-dose warfarin (INR 1.2-1.5) plus aspirin is insufficient for stroke prevention in patients with non-valvular AF at high-risk for thromboembolism.[25] This study was stopped after a mean follow-up of 1.1 years when the rate of ischemic stroke and systemic embolism (primary events) in patients given combination therapy (7.9% per year) was significantly higher than in those given adjusted-dose warfarin (1.9% per year) at an interim analysis ($p < 0.0001$), an absolute reduction of 6.0% per year (95% CI 3.4, 8.6) by adjusted-dose warfarin. The annual rates of disabling stroke (5.6% vs 1.7%, $p = 0.0007$) and of primary event or vascular death (11.8% vs 6.4%, $p = 0.002$), were also higher with combination therapy. Despite the lack of protective benefit the rates of major bleeding were, nevertheless, similar in both treatment groups.

d. Oral Anticoagulation Therapy

The clinical challenges with warfarin (described above) led to the development of newer anticoagulants, specifically targeted at various components of the coagulation cascade, often called novel oral anticoagulants (NOACs). These include dabigatran, rivaroxaban, apixaban, and edoxaban. Initial clinical trials have found these to be similar or slightly superior to warfarin in terms of stroke prevention with a lower overall risk of bleeding. Data around clinical use of these agents is limited by their relatively recent introduction into clinical care paradigms.

A summary of these anticoagulants, dabigatran (Pradaxa®)[26], rivaroxaban (Xarelto®)[27], apixaban (Eliquis®)[28], and edoxaban (Savaysa®)[29] is provided below for discussion of alternatives to warfarin therapy. Meta-analyses of the reported treatment benefits of the NOACs compared to warfarin therapy

[23] Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes*. 2008;1:84-91.

[24] Rose AJ, et al. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation: results of the Veterans Affairs Study To Improve Anticoagulation (VARIA). *Circ Cardiovasc Qual Outcomes*. 2011;4:22-9.

[25] Lancet. 1996 Sep 7;348(9028):633-8.

[26] Connolly SJ, Ezekowitz MD, Yusuf S, et al and the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in atrial fibrillation patients. *N Engl J Med*. 2009;361:1139-51.

[27] Patel MR and the ROCKET AF Steering Committee for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.

[28] Granger CB and the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.

[29] Giugliano, RP et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med 2013*: 2093-2104.

are few and vary depending on the anticoagulation control achieved by the warfarin cohorts. The data reported in contemporary clinical studies for these anticoagulants suggest all four agents are at least as efficacious as dose-adjusted warfarin. These agents have not been evaluated directly against each other.

Dabigatran (Pradaxa®)

Dabigatran is an oral direct thrombin inhibitor approved by FDA in October 2010 for preventing strokes in patients with non-valvular atrial fibrillation. Dabigatran offers similar efficacy compared to warfarin therapy without frequent blood tests for INR monitoring. Unlike warfarin, however, there is no simple, fast way to reverse the anticoagulant effect in the event of a major bleeding event.

In the RE-LY randomized clinical study, dabigatran was administered at a dose of 150 mg BID and was associated with lower rates (1.11% per year; P<0.001 for superiority) of stroke and systemic embolism but similar rates of major hemorrhage (3.11% per year) when compared to warfarin therapy (3.36% per year). The rate of hemorrhagic stroke was higher (0.38% per year) in the warfarin group as compared to 150 mg BID (0.10% per year; P<0.001) of dabigatran.[30]

While dabigatran demonstrated efficacy, it is not without risks. The most common side effect of dabigatran was bleeding, which was observed in more than 1 in 10 patients. When compared to warfarin, patients taking dabigatran had fewer life-threatening bleeds and fewer minor and major bleeds, including intracranial bleeds, but the rate of gastrointestinal bleeding was higher, mostly in patients older than 75 years. Concomitant drug use can also increase the risk of additional side effects. For example, the use of antiplatelet agents increases the risk of major bleeds with dabigatran approximately two-fold. Similar to warfarin therapy, certain populations are contraindicated to dabigatran due to increased risk of side effects. Discontinuation rates of dabigatran are high. In fact, 21% of patients taking dabigatran at its recommended dose in the pivotal trial opted to discontinue therapy within 2 years, a discontinuation rate higher than that observed for warfarin in the same study. As has been shown recently for Dabigatran, drug concentration is highly variable and dependent on renal function.[31] This may result in excess bleeding risk in the event of decline in renal function. Although monitoring of renal function is recommended, this may be of limited value in the absence of a lower dose.

One of the postulated benefits of dabigatran for use in stroke prevention in non-valvular atrial fibrillation is that the drug requires no need for ongoing dosage adjustment or drug plasma level monitoring. But the evidence base relating to bleeding complications and drug plasma levels has resulted in a current controversy over the best approach to managing potential safety problems with this drug in its clinical use, including the appropriate role of plasma level monitoring.[32]

Rivaroxaban (Xarelto®)

Rivaroxaban (Xarelto®) is a direct Factor Xa inhibitor approved by the FDA in July 2011 for prophylaxis of deep vein thrombosis (DVT) which can lead to pulmonary embolism (PE). In November 2011, the FDA approved the drug for stroke prophylaxis in patients with non-valvular atrial fibrillation.

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[30] Connolly SJ, Ezekowitz MD, Yusuf S, et al and the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in atrial fibrillation patients. *N Engl J Med*. 2009;361:1139-51.

[31] Reilly PA, Lehr T, Haerrter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients – The RE-LY Trial. *J Am Coll Cardiol*. 2014;63:321-8.

[32] Moore TJ, Cohen MR, Mattison DR. Dabigatran, bleeding, and the regulators. *BMJ*. 2014;349:g4517.

Unlike warfarin, dosage adjustments and routine coagulation monitoring are not required with rivaroxaban. However, there is no simple, fast way to specifically reverse the anticoagulant effect of rivaroxaban in the event of a major bleeding event.

In the ROCKET-AF randomized study comparing rivaroxaban with adjusted dose warfarin, the primary analysis revealed rivaroxaban was not inferior (1.7% per year; P<0.001) to warfarin (2.2% per year) in the prevention of subsequent stroke or systemic embolism. There were no significant differences in rates of major and clinically relevant non-major bleeding between the rivaroxaban (14.9% per year; P=0.44) and warfarin (14.5% per year), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%) and fatal bleeding (0.2% vs. 0.5%) in the rivaroxaban group. However, bleeding from GI sites, including upper, lower, and rectal sites, occurred more frequently in the rivaroxaban group, as did bleeding that led to a drop in hemoglobin or bleeding that required transfusion. Additionally, 14.3% of patients discontinued their treatment medication by 1 year.[33]

Apixaban (Eliquis®)

Apixaban (Eliquis®) is a direct Factor Xa inhibitor approved by the FDA in December 2012 for reducing the risk of stroke and dangerous blood clots (systemic embolism) in patients with non-valvular atrial fibrillation. Similar to other NOACs, there is no treatment currently available to rapidly and simply reverse the anti-coagulant effect of apixaban.

The randomized clinical study ARISTOTLE comparing apixaban to warfarin therapy demonstrated apixaban was not inferior to warfarin therapy for the primary outcome of all stroke and systemic embolism (1.27% per year and 1.60% per year, respectively; p<0.001 for non-inferiority; p=0.01 for superiority). Major bleeding risk also favored apixaban over warfarin therapy (2.13% per year vs. 3.09% per year; p<0.001). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group compared to 0.47% per year in the warfarin group (P<0.001). As with the other newer anticoagulants, the patient discontinuation rate of the treatment drug was high, about 25% by the end of the study.[34] Discontinuation of apixaban in the absence of adequate anticoagulation can lead to increased thrombotic events as cautioned in a black box warning.[35]

Edoxaban (Savaysa®)

Edoxaban is a new anti-clotting drug recently approved by the FDA in January 2015 to treat deep vein thrombosis (DVT) and pulmonary embolism (PE), and AF. Similar to other NOACs, there is no treatment to simply and quickly reverse the anti-coagulant effect of edoxaban. The safety and efficacy of edoxaban in treating patients with atrial fibrillation not caused by cardiac valve disease was studied in the ENGAGE-AF-TMI clinical trial.[36] The trial compared two dose levels of edoxaban with the anti-clotting drug warfarin for their effects on rates of stroke and dangerous blood clots (systemic emboli). The trial results showed

[33] Patel MR and the ROCKET AF Steering Committee for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.

[34] Granger CB and the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.

[35] US Food and Drug Administration. Eliquis (apixaban) tablets for oral use, December 2012. Downloaded from http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf

[36] Giugliano, RP et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med 2013*: 2093-2104.

the higher dose of edoxaban to be similar to warfarin for the reduction in the risk of stroke. Edoxaban demonstrated significantly less major bleeding compared to warfarin.

Summary of NOACs

Kosar and colleagues conducted a review of the new oral anticoagulants and provided a suggested approach to weighing stroke and bleeding risks when determining anticoagulation therapy.[37] The approach includes four steps: 1) Calculate patient's risk of stroke using $CHADS_2$ score; 2) Calculate patient's risk of major bleed using HAS-BLED score; 3) Balance predicted risk of stroke versus bleed; 4) Re-assess patient's risk of stroke and bleed annually, or sooner if risk criteria change. Kosar and colleagues then assess the clinical trials for dabigatran, rivaroxaban and apixaban. Using these trials, they evaluated several variables when comparing warfarin and the new OACs. The authors concluded there was no clear superiority among the new OACs when compared to warfarin.

Although NOACs carry a somewhat lower risk of bleeding compared with warfarin in the population studied, the risk is still significant at 2-3.5% annually. This risk includes the risk of major bleeding, including gastrointestinal and intracranial hemorrhage.

More importantly, adherence to long term anticoagulation therapy with any agent, including NOACs, is poor with approximately a 20% rate of discontinuing therapy over two years demonstrated in the clinical trials which led to their approval. During the RE-LY trial both doses of dabigatran had higher rates of non-adherence than warfarin. At one year, 15% and 16% of dabigatran 110mg and 150mg patients had ceased therapy, compared to 10% with warfarin[38]. At two years, 21% of dabigatran users had discontinued therapy, compared to 17% of warfarin users[39]. More recently, a study on the use of dabigatran reveals considerable site level variation in adherence[40]. Among patients with atrial fibrillation treated at 67 sites of care within the Veterans Health Administration (VHA), adherence to dabigatran ranged from 42% to 93%. Investigators observed better adherence to dabigatran among clinical sites that had a system in place for selecting appropriate dabigatran candidates, sites that included pharmacy-led patient education, and sites that regularly monitored the patients. This work adds important context to the same group's earlier work that has demonstrated that low adherence increases the risk of a poor outcome in these patients[41].

Furthermore, anticoagulation of any type must be reversed for invasive procedures and in some emergent situations, a not infrequent occurrence in the Medicare population that temporarily increases the risk of clot formation and stroke. While this poses a challenge with regard to risk of stroke during the uncovered period, management is further hampered by the fact that rapid reversal agents are not widely available for

[37] Kosar L, Jin M, Kamrul R, Schuster B, Oral anticoagulation in atrial fibrillation: Balancing the risk of stroke with the risk of bleed. Canadian family physician 2012*;* 58(8):850-858.

[38] Connelly SJ et al, Dabigatran versus warfarin in patients with atrial fibrillation, *N Engl J Med* 2009; 361(12):1139-51.

[39] Connelly SJ et al, Dabigatran versus warfarin in patients with atrial fibrillation, *N Engl J Med* 2009; 361(12):1139-51.

[40] Shore S, Ho MP, Lambert Kerzner A, et al. Site level variation in and practices associated with dabigatran adherence. *JAMA* 2015; 313:1443-1450.

[41] Shore S, Carey EP, Turakhia MP, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: Insights from the Veterans Health Administration. *Am Heart J*. 2014;167:810-7.

any of the NOACs – antidotes are under clinical development for the direct Factor Xa and thrombin inhibitors[42].

e. Need exists for device-based alternative

There is an urgent need for a safe and effective device-based therapy to reduce the risk of cardioembolic stroke as an alternative to long-term oral anticoagulation for high-risk patients with non-valvular atrial fibrillation. This need is further emphasized by several additional clinical observations that highlight the acceptance barriers, dosing difficulty, and adherence problems patients can encounter with long-term oral anticoagulant therapy (either warfarin or NOAC agents). As a consequence, many high-risk patients with non-valvular atrial fibrillation are left unprotected against cardioembolic stroke:

- The introduction of NOACs has not meaningfully increased the proportion of eligible patients receiving oral anticoagulation, and has not resolved the clinical need for a device-based alternative to long-term oral anticoagulation.

  An analysis presented at the American College of Cardiology Scientific Sessions in March 2014 examined the real-world experience with oral anticoagulants for over 24,000 US patients. The authors found considerable discontinuation of drug therapy over time, including the newly approved oral anticoagulants as well as warfarin.[43] The data demonstrate approximately 30-50% of patients cumulatively discontinue NOACs at 180 days. The March 2014 analysis adds to previously published data showing 31.8% of patients prescribed warfarin for stroke prevention in atrial fibrillation discontinue therapy within 1 year, 43.2% discontinue within 2 years, and 61.3% discontinue within 5 years.[44] The median time to discontinuation (MTD) was 2.9 years.[45] Any stroke risk reduction strategy that hinges on the biological effects of a drug is at risk of being ineffective unless the medication is adhered to in the manner prescribed, and as long as no confounding factors interfere with its bioavailability or plasma level. Clearly, in a Medicare population dealing with the challenge of polypharmacy, this fine balance is constantly in danger, and an oral regimen may be of limited applicability.

- Data published have clearly described the reasons for discontinuation of dabigatran[46], which include adverse effects in 29% of the affected patients, as well as considerations such as cost, kidney disease, and patient preference.

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[42] Greinacher A; Thiele T; Selleng K. Reversal of anticoagulants: an overview of current developments. Thrombosis and Haemostasis 2015;113:1-12.

[43] Pan X, Kachroo S, Liu X, Kawabata H, Phatak H. Real world discontinuation rates with apixaban versus warfarin, dabigatran, or rivaroxaban among atrial fibrillation patients newly initiated on anticoagulation therapy: early findings (abstract). *J Am Coll Cardiol* 2014;63(12):A415.

[44] Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes*. 2008;1:84-91.

[45] Gomes T, Mamdani M, Holbrook A, Paterson JM, Juurlink DN. Persistence with therapy among patients treated with warfarin for atrial fibrillation. *Arch Intern Med.* 2012;172:1687-9.

[46] Jacobs A, Linn D, Sipe B, Heyerly A, Bokhart G. Evaluation of reasons for dabigatran discontinuation in a community hospital and anticoagulation clinic. *Hosp Pharm* 2014;49:115-6.

- NOACs have relatively short half-lives, and effective anticoagulation may be limited by intermittent dosage, omission, or delay. A Veterans Affairs (VA) study[47] highlights the implications of NOAC non-adherence on patient outcomes. 27.8% of patients with non-valvular AF who were prescribed dabigatran were found to be non-adherent. Low adherence (decrease in proportion of days covered by the drug by 10%) was associated with an increased risk of all-cause death and stroke.

- It is not uncommon for patients to require transient interruption of OAC therapy, for example: for surgical procedures, bleeding episodes, side effects, or drug interactions. Such unprotected intervals may raise the risk of stroke relative to the level of protection the oral agent is intended to provide. Transient interruption of warfarin has been shown to require dose adjustments to regain anticoagulation control, prolonging the interval during which patients are either unprotected or at excessive bleeding risk due to over-anticoagulation since the direction of this dose change cannot be predicted.[48] Two of the NOACs (apixaban and rivaroxaban) contain a black box warning regarding the need for bridging during interruption of therapy.

NOAC agents do not have a readily available, measurable marker for dosage efficacy like warfarin, and so the therapeutic effect may not be apparent by means of a clinical surrogate. In dabigatran, for example, note has been made of significant plasma level variation with ostensibly therapeutic dosages[49]. The problem of assessing biological activity is further compounded by the absence of immediate symptomatic change while on the medication, which further adds to the likelihood of drug non-adherence or cessation over time, akin to the phenomenon seen in many chronic cardiovascular therapies.

In applying these general treatment challenges to actual patients, the above considerations underpin the identification of the population most applicable to WATCHMAN. When found to be at risk of stroke requiring anticoagulation, and suitable for warfarin therapy, the indicated population includes:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc[50] scores and are recommended for anticoagulation therapy;

- Are deemed by their physicians to be suitable for warfarin; and

- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

These are NOT patients who are intolerant to anticoagulation – such patients were not enrolled in the clinical studies that resulted in WATCHMAN approval in the US (see section (2)(h) below). However, these are patients who seek an effective alternative to warfarin in order to be protected from the stroke

[47] Shore S, Carey EP, Turakhia MP, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: Insights from the Veterans Health Administration. *Am Heart J*. 2014;167:810-7.

[48] Boros ML, Rybarczyk AM, Gallegos PJ, Zimmerman JP. Clinical impact of temporary therapy interruptions on anticoagulation control in patients treated with warfarin. *Am J Ther.* 2013;20:267-74.

[49] Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol* 2014;63:321-8.

[50] January CT, Wann LS, Alpert JS, et. al., 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, Circulation, 2014; 130: e199-e267.

risk posed by their non-valvular atrial fibrillation – in the absence of an alternative many of these patients choose to forego therapy altogether and are left unprotected against stroke and its devastating consequences.

Outside of the ASAP (ASA Plavix Registry) conducted in Europe, there is not extensive data on WATCHMAN use for patients who are intolerant to warfarin. Boston Scientific is not seeking WATCHMAN coverage for these patients under the national coverage decision as this is outside of the FDA approved indication for WATCHMAN. (We ask CMS to continue coverage for FDA-approved clinical trials, including Part B IDE trials that also meet CMS coverage requirements for such trials.)

Clinical realities demonstrate why there is a significant unmet need for new ways to prevent thromboembolism in patients with non-valvular atrial fibrillation and it is the reason why the WATCHMAN Technology was developed to address this patient subpopulation. In summary, while warfarin remains the standard of care for most patients, a significant subgroup of the warfarin-eligible patient population remains unprotected from stroke or is at high risk of bleeding complications from warfarin. The WATCHMAN Device addresses this unmet need to reduce stroke and improve health outcomes in this vulnerable group of patients.

f. Role of the WATCHMAN in Preventing Stroke in Patients with Non-valvular AF

Currently, there is no other device that has FDA approval for closure or exclusion of the left atrial appendage for stroke indication. Other LAA exclusion approaches have a 510K clearance for suture of soft tissue or LAA ligation with a concomitant open cardiac procedure but no FDA approval for the treatment of stroke originating in the LAA. Based on the indications for use, the number of physicians trained to implant the WATCHMAN, the number of sites participating in the clinical trials and the length of time needed to train new sites and users, Boston Scientific anticipates WATCHMAN volume for federal fiscal year 2016 will be 2500 to 3000 procedures with approximately 90% of those cases performed on Medicare beneficiaries. In making any projections regarding utilization, it is important to remember that WATCHMAN is not intended to be a broad replacement for oral anticoagulation and physicians will be required to extensively counsel patients and fully inform them of the relative advantages and disadvantages of both anticoagulation and the WATCHMAN Device before considering a patient for this procedure.

g. Description of Percutaneous, transcatheter, intraluminal Left Atrial Appendage Closure with Implanted Device

Overview of the Procedure

Percutaneous, transcatheter, intraluminal LAAC with a device implant is a catheter- based endovascular approach where a catheter is inserted into the femoral vein and threaded into the right atrium and across the atrial septum. The LAA closure device is deployed from the delivery system to completely close the LAA so that thrombi in the LAA cannot embolize into the systemic circulation and cause a stroke or other end organ damage due to embolic occlusion of a peripheral artery.

Detailed Description of the Procedure

The WATCHMAN Technology includes the following components:

- The WATCHMAN Access System, a unique proprietary vascular access system including a dilator and sheath
- The WATCHMAN Delivery System, which is comprised of a unique proprietary delivery catheter and a preloaded WATCHMAN Device.

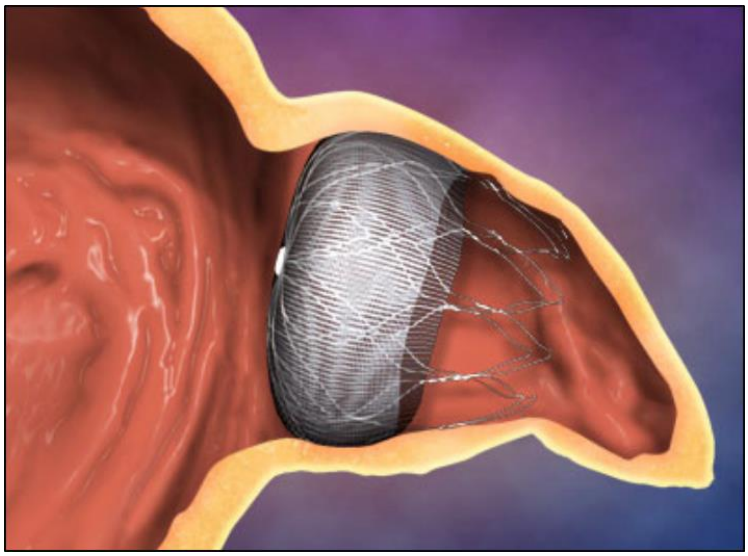
The WATCHMAN closure device consists of a fabric membrane that is fitted over a bare metal frame and looks like an umbrella. There are a row of fixation anchors around the perimeter of the frame which anchor the closure device. The frame and fabric endothelialize (become covered in tissue) during the 45 days after implant which allows the patient to discontinue anticoagulation therapy.

The procedure takes place in the catheterization or electrophysiology suite with the patient under anesthesia. Before the procedure starts, a transesophageal echocardiography transducer is placed into the esophagus so that transesophageal echocardiography (TEE) can be used to guide deployment of the closure device. Then the access system is introduced into the femoral vein and advanced to the right atrium under imaging guidance (e.g., fluoroscopy). A transseptal puncture is performed and, under imaging guidance, the catheter is advanced to the left atrium. The WATCHMAN Device is then advanced through the Access System to the intended implant location of the left atrial appendage.

The WATCHMAN Device is deployed by retracting the WATCHMAN Access System and deploying the WATCHMAN Delivery System while holding the core wire stationary. The preloaded closure device is released from the delivery catheter by turning the deployment knob on the WATCHMAN Delivery System counterclockwise until the core wire is completely disconnected from the WATCHMAN Device. The core wire provides both the support necessary to deploy the WATCHMAN closure Device and the flexibility necessary to not bias the deployment in the LAA until it has been evaluated and released. Before releasing the WATCHMAN Device from the WATCHMAN Delivery System core wire, the pre-specified device release criteria are confirmed via fluoroscopy and TEE. Please see the instructions for use in in the last section of this dossier for a more detailed description of the procedure and the device release criteria.

Following implantation in the LAA, the WATCHMAN Device self-expands so as to close the LAA ostium. (**Figure 2**). Over time, the body's natural healing response causes endothelialization of the fabric membrane on the WATCHMAN Device.

Figure 2: WATCHMAN Device in situ



h. Clinical Data Supporting Coverage of the WATCHMAN

WATCHMAN Clinical Program Overview

The WATCHMAN Left Atrial Appendage Closure (LAAC) Device has been studied in four U.S. clinical trials, two of which were controlled prospective randomized trials comparing the WATCHMAN to warfarin and the other two were continued access registries. The four studies contributing to the analysis (PROTECT AF, PREVAIL, CAP, and CAP2) represent more than 2400 patients and nearly 6000 patient-years of follow-up. We have attached the published articles describing these trials plus other WATCHMAN publications to this dossier.

These trials were developed in collaboration with FDA following guidance on use of Bayesian statistics to allow for incorporation of prior established clinical data, thus requiring smaller sample sizes and limiting patient exposure to an experimental treatment. The Bayesian concept is to consider the prior information and the trial results as part of a continual data stream, in which inferences are being updated each time new data become available. The Bayesian analysis of PROTECT AF utilized a non-informative prior. The PREVAIL study was designed to use prior information from the PROTECT AF study. Only data from those patients in PROTECT AF who would have qualified for PREVAIL under the modified entry criteria were used and given a weight of 50%. These concepts are important when it comes to understanding the post-hoc meta-analyses of the PROTECT AF and PREVAIL data.

These trials all enrolled subjects with non-valvular atrial fibrillation who were eligible for warfarin therapy according to published guidelines. In order to use warfarin as the control arm of the randomized trials, it was necessary for all patients entering the trials to be able to tolerate warfarin therapy. In addition, all patients had to be able to tolerate warfarin since every patient in the trials had at least 45 days of warfarin therapy to allow for endothelialization of the device. The intent of the WATCHMAN LAAC Device therapeutic strategy is to permit warfarin discontinuation once adequate endothelialization has been established. In each of the WATCHMAN studies, warfarin could be discontinued if echocardiographic

evidence of an adequate seal (≤ 5 mm residual flow) was present at 45 days. If the seal was not found to be adequate (> 5mm residual flow) at 45 days, warfarin was continued and TEE was repeated at 6 months and, if necessary, again at 12 months to confirm occurrence of the seal.

Eligibility criteria for trial participation were similar across the trials, with some modification to enroll higher risk patients in subsequent trials. Risk stratification was done using the $CHADS_2$ score, which is a validated stratification model, incorporated in the ACC/HRS/AHA Guideline during the time the trials were conducted. As discussed above, the guidelines have subsequently been updated to use a modified version of the $CHADS_2$ score known as CHA_2DS_2-VASc. The $CHADS_2$ score was used to guide pharmaceutical therapy by targeting the use of anticoagulation or other therapeutic options toward those patients who have the greatest risk of stroke.

The first trial was the pivotal WATCHMAN LAAC Therapy for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT AF) study. This trial was followed by three additional studies in this population: a continued access (CAP) registry following the conclusion of the PROTECT AF study; a second randomized study, the Prospective Randomized Evaluation of the WATCHMAN LAAC Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL); and a second continued access (CAP2) registry following the conclusion of the PREVAIL study. **Table 2** provides an overview of the study design of each trial, as well as results from each study.

Table 2. Summary of WATCHMAN® Clinical Studies

Patient Population	Subjects with non-valvular atrial fibrillation who were deemed by their physicians to be suitable for warfarin therapy to reduce the risk of ischemic stroke and systemic embolism			
Study	**PROTECT AF**	**CAP**	**PREVAIL**	**CAP2**
Purpose	Demonstrate safety and efficacy compared to long-term warfarin	Demonstrate safety and efficacy	Demonstrate safety and efficacy compared to long-term warfarin	Demonstrate safety and efficacy
Study Design	2:1 Randomized, non-inferiority	Non-randomized	2:1 Randomized, non-inferiority	Non-randomized
Primary Endpoint	1. Effectiveness: Stroke, cardiovascular death, and systemic embolism 2. Safety: Life-threatening events which include device embolization requiring retrieval and bleeding events		1. Effectiveness: Stroke, systemic embolism, and cardiovascular/unexplained death 2. Effectiveness: Ischemic stroke or systemic embolism occurring after seven days post-enrollment 3. Safety: Death, ischemic stroke, systemic embolism and procedure/device-related complications within seven-days of the implantation procedure	
Number of Patients Enrolled	800 subjects • 93 roll-in WATCHMAN • 707 randomized ○ 463 WATCHMAN ○ 244 Control	566 WATCHMAN subjects	461 subjects • 54 roll-in WATCHMAN • 407 randomized ○ 269 WATCHMAN ○ 138 Control	579 WATCHMAN subjects
Status of Subject Follow-Up	Study Complete 2717 patient-years	Study Ongoing 2022 patient-years	Study Ongoing 860 patient-years	Study Ongoing 332 patient-years
Follow-Up Duration	5 years		5 years	

PROTECT AF Study

The PROTECT AF study was a multicenter, prospective randomized controlled study comparing the WATCHMAN Device to long-term warfarin therapy. The purpose of the study was to demonstrate that the WATCHMAN Device is safe and effective in subjects with non-valvular atrial fibrillation who were deemed by their physicians to be suitable for warfarin therapy. A 2:1 randomization allocation ratio was used with stratification by center such that for every one subject randomized to the Control arm (long-term warfarin therapy); two subjects were randomized to the Device arm to receive the WATCHMAN Device. Key eligibility criteria are provided in **Table 3**.

Table 3: PROTECT AF Key Eligibility Criteria

Key Inclusion Criteria
The subject is 18 years of age or older
The subject has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation
The subject is eligible for long-term warfarin therapy
The subject has a calculated $CHADS_2$ score of 1 or greater
Key Exclusion Criteria
The subject requires long-term warfarin therapy
The subject is contraindicated for warfarin therapy
The subject is contraindicated for aspirin
The subject has a history of atrial septal repair or has an atrial septal defect (ASD)/patent foramen ovale (PFO) closure device
Key Echo Exclusion Criteria
The subject has Left Ventricular Ejection Fraction (LVEF) <30%
The subject has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days prior to implant
The subject has a high risk PFO defined as a PFO with an atrial septal aneurysm (total excursion >15 mm or length ≥15 mm) or a large shunt (early, within 3 beats, substantial passage of bubbles)
The subject has significant mitral valve stenosis
The subject had complex atheroma with mobile plaque of the descending aorta and/or aortic arch
The subject has a cardiac tumor

The primary effectiveness composite endpoint was the rate of the composite of stroke (including ischemic and hemorrhagic), systemic embolism, and cardiovascular death (cardiovascular and unexplained). The primary safety endpoint was the rate of life-threatening events as determined by the Clinical Events Committee (CEC), which included device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion, and any bleeding related to the device or procedure that necessitated a surgical procedure. The primary statistical objective was to determine if the Device group was non-inferior to the Control group with respect to the event rate for the composite primary effectiveness endpoint.

Although PROTECT AF was not powered to show superiority of WATCHMAN to warfarin, as it was designed as a non-inferiority trial, it was also designed with the potential to demonstrate superiority. The protocol allowed for testing for superiority provided that non-inferiority was shown. The lack of power to

show superiority simply means that the study was not likely to demonstrate superiority, a priori, given the sample size and expected performance of WATCHMAN vs. warfarin.

A total of 800 subjects were enrolled in the study at 59 centers. The 800 subjects included 463 subjects randomized to the WATCHMAN Device group, 244 subjects randomized to the Control group, and 93 Roll-in WATCHMAN Device subjects.

Demographics and Baseline Clinical Features: For subjects randomized to the WATCHMAN group, the mean $CHADS_2$ score was 2.2±1.2, the mean CHA_2DS_2-VASc score was 3.2±1.4, the mean age was 72 years, 70% were male, and 92% were Caucasian. For subjects randomized to the Control group, the mean $CHADS_2$ score was 2.3±1.2, the mean CHA_2DS_2-VASc score was 3.5±1.6, the mean age was 73 years, 70% were male, and 91% were Caucasian. The two treatment groups had no statistically significant differences in baseline demographic and clinical characteristics as shown in **Tables 4** and **5**.

Table 4: PROTECT AF Baseline Demographics

Characteristic	**WATCHMAN N=463**	**Control N=244**	**P-value**
Age, years	71.7 ± 8.8 (463) (46.0, 95.0)	72.7 ± 9.2 (244) (41.0, 95.0)	0.179
Sex			0.928
Female	137/463 (29.6%)	73/244 (29.9%)	
Male	326/463 (70.4%)	171/244 (70.1%)	
Race/Ethnicity			0.779
Asian	4/463 (0.9%)	1/244 (0.4%)	
Black/African American	6/463 (1.3%)	5/244 (2.0%)	
Caucasian	425/463 (91.8%)	222/244 (91.0%)	
Hispanic/Latino	25/463 (5.4%)	15/244 (6.1%)	
Hawaiian/Pacific Islander	1/463 (0.2%)	1/244 (0.4%)	
Other	2/463 (0.4%)	0/244 (0.0%)	

Table 5: PROTECT AF Baseline Risk Factors

Characteristic	**WATCHMAN N=463**	**Control N=244**	**P-value**
$CHADS_2$ Score			0.411
1	156/463 (33.7%)	66/244 (27.0%)	
2	158/463 (34.1%)	88/244 (36.1%)	
3	89/463 (19.2%)	51/244 (20.9%)	
4	37/463 (8.0%)	24/244 (9.8%)	
5	19/463 (4.1%)	10/244 (4.1%)	

Characteristic	WATCHMAN N=463	Control N=244	P-value
6	4/463 (0.9%)	5/244 (2.0%)	
$CHADS_2$ Score (Continuous)	2.2±1.2 (463) (1.0, 6.0)	2.3±1.2 (244) (1.0, 6.0)	0.072
$CHADS_2$ Risk Factors			
Congestive Heart Failure (CHF)	124/463 (26.8%)	66/244 (27.0%)	0.9392
Hypertension	415/463 (89.6%)	220/244 (90.2%)	0.8243
Age ≥ 75	190/463 (41.0%)	115/244 (47.1%)	0.1198
Diabetes	113/463 (24.4%)	72/244 (29.5%)	0.1423
Previous TIA/Ischemic Stroke	82/463 (17.7%)	49/244 (20.1%)	0.4404
CHA_2DS_2-VASc Score			0.469
1	44/460 (9.6%)	16/239 (6.7%)	
2	105/460 (22.8%)	54/239 (22.6%)	
3	139/460 (30.2%)	64/239 (26.8%)	
4	91/460 (19.8%)	47/239 (19.7%)	
5	45/460 (9.8%)	32/239 (13.4%)	
6	27/460 (5.9%)	19/239 (7.9%)	
7	5/460 (1.1%)	5/239 (2.1%)	
8	2/460 (0.4%)	2/239 (0.8%)	
9	0/460 (0.0%)	0/239 (0.0%)	
CHA_2DS_2-VASc Score (Continuous)	3.2±1.4 (460)	3.5±1.5 (239)	0.022

Results of PROTECT AF

WATCHMAN Device implant success was achieved in 408/449 (90.9%) subjects who underwent the implant procedure.

Table 6: PROTECT Subject End of Study Summary (taken from the PROTECT Final Report0

Discontinuation Reason	Device N/463 (%)	Control N/244 (%)	Roll-in N/ 93 (%)	Total N/800 (%)
Patient successfully completed study	299/463 (64.6)	133/244 (54.5)	67/93 (72.0)	499/800 (62.4)
Death	60/463 (13.0)	44/244 (18.0)	5/93 (5.4)	109/800 (13.6)

Discontinuation Reason	Device N/463 (%)	Control N/244 (%)	Roll-in N/ 93 (%)	Total N/800 (%)
Patient Consent Withdrawn	18/463 (3.9)	44/244 (18.0)	3/93 (3.2)	65/800 (8.1)
No Device Implanted	41/463 (8.9)	0/244 (0.0)	16/93 (17.2)	57/800 (7.1)
Lost to Follow-up	22/463 (4.8)	13/244 (5.3)	2/93 (2.2)	37/800 (4.6)
Other	13/463 (2.8)	10/244 (4.1)	0/93 (0.0)	23/800 (2.9)
Outside Implant Window	10/463 (2.2)	0/244 (0.0)	0/93 (0.0)	10/800 (1.3)

There were thirteen (13) “other” reasons Device subjects exited the study: subjects that did not have the device implanted due to embolization, explant, or aborted procedure (9), medical status that made follow-up unmanageable (3) and a subject exited prior to implant due to a finding of amyloidosis (1). In the Control group there were ten (10) “other” reasons for early study exit. These included subjects that permanently discontinued warfarin therapy (6), medical conditions that did not allow for continued study follow-up (3), and a subject relocated overseas (1).

Table 7: Causes of Mortality by Treatment Group

Category	WATCHMAN (N=463)		Control (N=244)		p-value
	n	%	n	%	
Cardiovascular	18	3.9	22	9.0	0.0093
Unexplained/other	5	1.0	5	2.0	0.33
Sudden cardiac death	4	0.9	4	1.6	0.46
Heart failure	4	0.9	2	0.8	1.00
Hemorrhagic stroke	2	0.4	8	3.3	0.0041
Myocardial infarction	2	0.4	2	0.8	0.61
Ischemic stroke	1	0.2	1	0.4	1.00
Cancer	10	2.2	3	1.2	0.56
Pulmonary	9	1.9	9	3.7	0.21
Multisystem Organ Failure	6	1.3	1	0.4	0.43
Renal Failure	4	0.9	3	1.2	0.70
Other Non-Cardiovascular	4	0.9	1	0.4	0.66
Sepsis	3	0.6	1	0.4	1.00
Neurologic	2	0.4	1	0.4	1.00

All four studies employed an independent Clinical Events Committee (CEC) to review and adjudicate site-reported adverse events and ascertain their seriousness, relationship of the event to the device or procedure, and relationship of study medications to the study endpoints.[51] For example, if there was an adverse event (i.e., death) and the cause was adjudicated as undetermined or unexplained (i.e., patient died in his sleep), then it would be classified in the cardiovascular (CV) "unexplained/other" category.

Each study CEC was comprised of 2 interventional cardiologists and 1 neurologist. Additionally, the PREVAIL and CAP2 Registry CECs had a second Neurologist and Interventional Neuroradiologist participate during any meeting in which a potential stroke, TIA, or systemic embolism event was to be reviewed. The Chairperson was the same for all four studies.

In **Table 7**, this represents the final (2717 patient years of follow up) PROTECT AF dataset. There are 18 and 22 cardiovascular (CV) deaths attributed to the WATCHMAN and warfarin arms, respectively as adjudicated by the CEC. The 4 deaths under the "Other Non-CV" category that were classified as "unexplained/other" in the WATCHMAN arm were deemed by the CEC to contain enough information about the cause of death to rule out a CV-related endpoint definition but did not necessarily fall into a pre-defined cause (i.e., death attributed to motor vehicle accident or suicide) listed on the case report form. While not appropriate nor correct, if one were to include the 4 device deaths and 1 warfarin death from the "other non-CV" category in the CV death totals, the total number would be 22 for WATCHMAN and 23 for warfarin. Based on the 2:1 randomization scheme used in the trial, the true comparison would be 22 CV/unexplained deaths in the WATCHMAN arm versus 46 CV/unexplained deaths in the warfarin arm. Even in such a "worst case" analysis, WATCHMAN provides a 52% relative reduction in CV/unexplained death over warfarin.

Effectiveness: Results of the final 5 year follow-up representing 2717 patient years for the primary effectiveness endpoint of stroke, death (cardiovascular or unexplained) and systemic embolism are displayed in **Table 8.** The primary effectiveness event rate was 2.2 events per 100 patient years for the Device group and 3.7 events per 100 patient years for the Control group, resulting in a relative risk or rate ratio of 0.61. For Bayesian analysis, a posterior probability of 97.5% represents non-inferiority; ≥95% represents superiority. The criterion for non-inferiority and superiority of the WATCHMAN device vs. the control group were met and were driven by the rates of hemorrhagic stroke and cardiovascular/unexplained death in favor of the device group. The ischemic stroke rate numerically favored the control group.

Table 8. PROTECT AF Primary Efficacy Results (Intent-to-Treat) (2717 patient years)
Randomization Allocation (2 Device: 1 Control)

	WATCHMAN		Control		
	Event Rate (per 100 Pt-yrs)	**Event Rate / Subject**	**Event Rate (per 100 Pt-yrs)**	**Event Rate / Subject**	**Rate Ratio (95% Crl)***
Primary effectiveness	2.2 (40/1788)	8.6% (40/463)	3.7 (34/929)	13.9% (34/244)	0.61 (0.42, 1.07)

[51] The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors; Guidance for Clinical Trial Sponsors - Establishment and Operation of Clinical Trial Data Monitoring Committees, issued March 2006

	WATCHMAN		Control		
	Event Rate (per 100 Pt-yrs)	Event Rate / Subject	Event Rate (per 100 Pt-yrs)	Event Rate / Subject	Rate Ratio (95% CrI)*
Ischemic stroke	1.3 (24/1782)	5.2% (24/463)	1.1 (10/933)	4.1% (10/244)	
Hemorrhagic stroke	0.2 (3/1838)	0.6% (3/463)	1.1 (10/946)	4.1% (10/244)	
Systemic embolism	0.2 (3/1837)	0.6% (3/463)	0.0 (0/949)	0.0% (0/244)	
Death (CV/unexplained)	1.0 (19/1843)	4.1% (19/463)	2.3 (22/949)	9.0% (22/244)	
Ischemic stroke and systemic embolism	1.5 (26/1781)	5.6% (26/463)	1.1 (10/933)	4.1% (10/244)	
Stroke (all)	1.5 (26/1782)	5.6% (26/463)	2.2 (20/929)	8.2% (20/244)	

*Posterior probability >0.999 for non-inferiority and 0.954 for superiority

The Rate Ratio is based on the event rates per 100 pt-yrs

CrI = credible interval

Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)

Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.

Clinical data from the long term follow-up of all patients in PROTECT AF has now been published. This includes data capturing efficacy at 1065 (18 months of follow-up), 1588 (2.3 years of follow-up), and 2621 (3.8 years of follow-up) patient years.[52] The mean follow-up is now 4 years (2717 patient years) and analysis of this long term data demonstrates superior primary efficacy outcomes of the WATCHMAN Technology over warfarin. Refer to **Table 9**.

The PROTECT AF data represent the most robust clinical data set available for WATCHMAN. The table below shows the primary efficacy endpoint for WATCHMAN compared to warfarin at each of the data analyses requested by the FDA. Although we do not cross the 95% posterior probability of superiority until the 3.8 year time point for primary efficacy, the data are consistent with superiority as early as the 1.3 year (900 patient year) analysis and, in fact, the rate ratio is relatively constant thereafter, reflecting consistency of the benefit vs. warfarin from that point onward.

Table 9: PROTECT primary efficacy supports WATCHMAN benefit persistent over 4 years

Patient Years	Years of mean follow up	WATCHMAN observed rate per 100 patient years	Warfarin observed rate per 100 patient years	% Reduction vs. warfarin	*Posterior Probability		
					Non-inferiority (NI)	Superiority (S)	
900	1.3	3.4	5.0	32%	99.8%	83.7%	NI
1065	1.5	3.0	4.9	38%	>99.9%	90.0%	NI
1588	2.3	3.0	4.3	29%	>99.9%	84.6%	NI
2621	3.8	2.3	3.8	40%	>99%	96%	NI and S
2717	4.0	2.2	3.7	39%	>99.9%	95.4%	NI and S

*****For Bayesian analysis, a posterior probability of 97.5% represents non-inferiority; ≥95% represents superiority

[52] Reddy et al. JAMA (2014).

Warfarin cessation: Among subjects successfully implanted with the WATCHMAN Device, 87% discontinued warfarin therapy by 45 days, and 93% discontinued warfarin therapy by 12 months.

The long term results of PROTECT AF show that the WATCHMAN Technology provides a substantial clinical improvement as compared to warfarin in the subgroup of warfarin eligible high risk patients for reducing the risk of stroke.

Safety: In PROTECT AF, the primary safety endpoint was defined as freedom from occurrence of life threatening events as determined by the Clinical Events Committee. By design this includes long term complications of therapy as well as acute procedural events. The primary safety endpoint was major bleeding, device embolization, or pericardial effusion. The primary safety endpoint rate for the Warfarin Group was similar at each of the analysis time points whereas the WATCHMAN Group rate decreased with subsequent time points. A higher rate of early primary safety events in the WATCHMAN Group compared to the Warfarin Group was expected due to the invasive nature of the implant procedure. The majority of primary safety events in the WATCHMAN Group (32/60, 53.3%) occurred peri-procedurally.

Early complications were related to procedures performed by new users. The incidence of procedural related complications for the first 232 patients was 9.9% (first half of PROTECT AF). As a result, revisions were made to the implantation procedure and to physician training. After these revisions, the complication rate decreased to 4.8% for the next 231 patients enrolled in the WATCHMAN arm of the trial (second half of PROTECT AF).

After 2717 patient-years of follow-up, the primary safety rate was 3.5 events per 100 patient years for the Device group and 3.2 events per 100 patient years for the Control group resulting in a relative risk ratio of 1.08. These results are summarized in **Table 10.**

Table 10. PROTECT AF Primary Safety Results (Intent-to-Treat) (2717 patient-years)
Randomization Allocation (2 Device: 1 Control)

Device Rate (N events / total pt-yrs)	Control Rate (N events / total pt-yrs)	Relative Risk (95% CrI)	Posterior Probabilities	
			Non-inferiority	Superiority
3.5 (60/1729.6)	3.2 (29/904.9)	1.08 (0.72, 1.77)	0.993	0.315

Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)
Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.
CrI = credible interval

These data show the following:

- At 2717 patient-years (2014 Panel dataset), the primary safety endpoint rate was 3.5% for the WATCHMAN Group and 3.2% for the Warfarin Group, yielding a rate ratio of 1.08 [95% CrI (0.72, 1.77)].

- The primary safety endpoint rate for the Warfarin Group was similar at each of the analysis time points whereas the WATCHMAN Group rate decreased with subsequent time points. A higher rate of early primary safety events in the WATCHMAN Group compared to the Warfarin Group was expected due to the invasive nature of the implant procedure. The majority of primary safety events in the WATCHMAN Group (32/60, 53.3%) occurred peri-procedurally.

This outcome indicates that risks in the WATCHMAN Group were comparable to those seen in the Warfarin Group. The principal procedural-related safety events in the WATCHMAN Group were pericardial effusions, which are a known complication of intracardiac procedures. The rate of pericardial effusions decreased over the course of the study, attributable to investigator experience.

CAP Registry

Because of the relatively high complication rate early in the PROTECT trial, a subsequent study (PREVAIL) was designed and implemented to specifically test the safety profile of the procedure in the hands of new operators. PREVAIL has a very similar design to PROTECT AF, but with modifications to trial entry criteria and a minimum number of new operators. Prior to PREVAIL enrollment, the FDA established a continued access program (CAP) to allow patients a therapeutic option for the WATCHMAN Technology. CAP enrolled 566 patients and the efficacy rates in CAP were similar to those seen in PROTECT AF and procedural complication rates were similar to the rates seen in the second half of PROTECT AF after the revisions to the implantation procedure and physician training were implemented.

The CAP registry evaluated endpoints identical to those used in the PROTECT AF study although there were no pre-defined statistical hypotheses. The primary effectiveness endpoint was the successful treatment of subjects without stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism. The primary safety endpoint was the rate of life-threatening events as determined by the CEC, which included device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeding requiring transfusion, and any bleeding related to the device or procedure that necessitated a surgical procedure

The WATCHMAN Device was successfully implanted in 534/566 (94%) subjects. For the primary effectiveness endpoint, a rate of 2.6 events/100 patient-years was observed, with cardiovascular or unexplained death and ischemic stroke being the two most common events over a mean follow-up duration of 44 months as shown in **Tables 11 and 12**.

Table 11: CAP Primary Efficacy Endpoint

Event Type	Rate Per 100 Pt-yrs (N Events/Pt-yrs)	(95% CI)
Primary Efficacy	2.6 (53/2021.8)	2.0,3.4

Table 12: CAP Events Contributing to Primary Efficacy Endpoint

Type	N Events	% of Subjects
Death (Cardiovascular or Unexplained)	25	4.4%
Stroke - Ischemic	24	4.2%
Stroke - Hemorrhagic	2	0.4%
Systemic Embolism	1	0.2%

Discontinuation of warfarin among WATCHMAN subjects: Among subjects successfully implanted with the WATCHMAN Device and followed for at least 12 months, 96% discontinued warfarin therapy by 45 days, and 96% discontinued warfarin therapy by 12 months.

Serious Adverse Events: There were no procedure-related strokes or deaths during implant of the device with no long-term device migrations or erosions. The results of the CAP Registry helped confirm the findings observed both in the second half of PROTECT AF and the long term patient follow-up.

PREVAIL

The purpose of PREVAIL was to address FDA's concerns about the early complication rates in the PROTECT trial and it was specifically designed to test the safety profile of the procedure in the hands of new operators. From November 2010 to June 2012, PREVAIL enrolled a total of 407 patients, 269 of whom received LAAC with the WATCHMAN Technology and 138 assigned to warfarin therapy.

The PREVAIL study is a multicenter, prospective randomized controlled study to evaluate the safety and effectiveness of the WATCHMAN Device compared to long-term warfarin therapy. PREVAIL was a second pivotal, randomized study of the WATCHMAN Device, and the analyses of the primary endpoints included historical data from the PROTECT AF study. Key eligibility criteria are provided in **Table 13**.

Table 13: PREVAIL Key Eligibility Criteria

Key Inclusion Criteria
The subject is 18 years of age or older
The subject has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation
The subject is eligible for long-term warfarin therapy
The subject has a calculated $CHADS_2$ score of 2 or greater; Subjects with a $CHADS_2$ score of 1 may be included if any of the following apply: • The subject is a female age 75 or older • The subject has a baseline LVEF ≥30% and <35% • The subject is age 65-74 and has diabetes or coronary artery disease • The subject is age 65 or greater and has documented congestive heart failure
Key Exclusion Criteria
The subject requires long-term warfarin
The subject is contraindicated for warfarin therapy
The subject is contraindicated or allergic to aspirin
The subject has a history of atrial septal repair or has an ASD/PFO closure device
Key Echo Exclusion Criteria
The subject has LVEF <30%
The subject has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE and determined by the echocardiographer within 2 days prior to implant
The subject has a high risk PFO defined as an atrial septal aneurysm (excursion >15 mm or length >15 mm) or large shunt (early, within 3 beats and/or substantial passage of bubbles)
The subject has significant mitral valve stenosis
The subject had complex atheroma with mobile plaque of the descending aorta and/or aortic arch
The subject has a cardiac tumor

Subject Demographics and Baseline Clinical Features: For subjects randomized to the WATCHMAN group, the mean $CHADS_2$ score was 2.6±1.0, the mean CHA_2DS_2-VASc score was 3.8±1.2, the mean age was 74 years, 68% were male, and 94% were Caucasian. For subjects randomized to the Control group, the mean $CHADS_2$ score was 2.6±1.0, the mean CHA_2DS_2-VASc score was 3.9±1.2, the mean age was 75 years, 75% were male, and 95% were Caucasian. The two treatment groups had no statistically significant differences in baseline demographic and clinical characteristics as shown in **Tables 14** and **15**.

Table 14: PREVAIL Baseline Demographics

Characteristic	WATCHMAN N=269	Control N=138	P-value
Age (years)	74.0 ± 7.4 (269) (50.0 ,94.0)	74.9 ± 7.2 (138) (53.0 ,90.0)	0.260
Sex			0.146
Female	87/269 (32.3%)	35/138 (25.4%)	
Male	182/269 (67.7%)	103/138 (74.6%)	
Race/Ethnicity			0.603
Asian	1/269 (0.4%)	1/138 (0.7%)	
Black/African American	6/269 (2.2%)	1/138 (0.7%)	
Caucasian	253/269 (94.1%)	131/138 (94.9%)	
Hispanic/Latino	6/269 (2.2%)	5/138 (3.6%)	
Native American Indian/Alaskan Native	1/269 (0.4%)	0/138 (0.0%)	
Other	2/269 (0.7%)	0/138 (0.0%)	

Table 15: PREVAIL Baseline Risk Factors

Characteristic	WATCHMAN N=269	Control N=138	P-value
$CHADS_2$ Score (Categorical)			0.484
1	21/269 (7.8%)	12/138 (8.7%)	
2	137/269 (50.9%)	62/138 (44.9%)	
3	65/269 (24.2%)	36/138 (26.1%)	
4	33/269 (12.3%)	21/138 (15.2%)	
5	12/269 (4.5%)	7/138 (5.1%)	
6	1/269 (0.4%)	0/138 (0.0%)	
$CHADS_2$ Score (Continuous)	2.6 ± 1.0 (269) (1.0 ,6.0)	2.6 ± 1.0 (138) (1.0 ,5.0)	0.838
$CHADS_2$ Risk Factors			
CHF	63/269 (23.4%)	32/138 (23.2%)	0.958
History of Hypertension	238/269 (88.5%)	134/138 (97.1%)	0.003
Age ≥ 75	140/269 (52.0%)	78/138 (56.5%)	0.391
Diabetes	91/269 (33.8%)	41/138 (29.7%)	0.401
Previous TIA/Ischemic Stroke	74/269 (27.5%)	39/138 (28.3%)	0.873
CHA_2DS_2 VASc Score (Categorical)			0.300
2	19/269 (7.1%)	7/138 (5.1%)	
3	78/269 (29.0%)	44/138 (31.9%)	
4	95/269 (35.3%)	35/138 (25.4%)	
5	50/269 (18.6%)	37/138 (26.8%)	
6	20/269 (7.4%)	12/138 (8.7%)	
7	6/269 (2.2%)	3/138 (2.2%)	
8	1/269 (0.4%)	0/138 (0.0%)	

Characteristic	WATCHMAN N=269	Control N=138	P-value
CHA_2DS_2 VASc Score (Continuous)	4.0 ± 1.1 (269) (2.0 ,8.0)	4.1 ± 1.2 (138) (2.0 ,7.0)	0.399

The PREVAIL study is ongoing. Current follow-up of the 407 randomized subjects is 860 patient-years. PREVAIL follow-up visit attendance is shown in **Table 16**.

Table 16: PREVAIL Only Follow-Up Visit Attendance

Visit	WATCHMAN Attended/Expected (%)	Control Attended/Expected (%)
1 Year	234/236 (99%)	119/124 (96%)
2 Years	208/211 (99%)	96/99 (97%)
3 Years	61/62 (98%)	26/26 (100%)
4 Years	0/0 (NA)	0/0 (NA)
5 Years	0/0 (NA)	0/0 (NA)

There were three specified endpoints for the PREVAIL trial.

SAFETY ENDPOINT: Procedure-related events that required major surgical or endovascular repair. Success was defined as a 1-sided 95% upper credible bound of <2.67%. At least 20% of operators had no prior experience with the device, and 25% of patients were implanted by new operators

PRIMARY EFFICACY ENDPOINT: The rate ratio of 18-month event rates of the Device and Warfarin Groups were compared, and a risk ratio criterion (treatment over warfarin) of 1.75 was used to establish non-inferiority.

LATE-ISCHEMIC PRIMARY EFFICACY ENDPOINT: Peri-procedural events of ischemic stroke and systemic embolism >7 days post-randomization, based on a 1-tailed test, in which the null hypothesis would be rejected if either the ratio or the difference between rates in the randomized groups satisfied the non-inferiority criteria. A composite criterion for either the risk ratio or risk difference was used, with criterion of the 95% upper CrI <2.0 and <0.0275, respectively.

Statistical power was determined based on the efficacy endpoints per the Bayesian design. As FDA agreed for the study design, the PROTECT AF dataset was a valuable basis for the WATCHMAN Device performance; as a result, a portion of the data was included as an informative prior for the PREVAIL Bayesian design. All evaluation of endpoints was predefined and powered based on the pre-specified

data lock (January 2013) when all patients had completed at least 6 months of follow-up. The individual components of the composite were not powered to reach statistical conclusions.

Table 17: PREVAIL End of Study Summary (taken from the 7/31/14 PREVAIL CSR)

Discontinuation Reason	Device N/Total (%)	Control N/Total (%)
Implant Attempt Unsuccessful	13/269 (4.8%)	NA
Implant Not Attempted	4/269 (1.5%)	NA
Death	22/269 (8.2%)	13/138 (9.4%)
Subject Withdrew Consent	3/269 (1.1%)	9/138 (6.5%)
Lost to Follow-up	5/269 (1.9%)	4/138 (2.9%)
Other	2/269 (0.7%)	1/138 (0.7%)
Total	49/269 (18.2%)	27/138 (19.6%)

The most frequent reason for exit in the Device group was due to subject death, not attributed to the device. The second most frequent reason for early study termination in the Device group was due to unsuccessful implant attempt combined with implants that were not attempted which account for 17 subjects in the Device group. As indicated in the protocol, subjects with an unsuccessful implant attempt (13) were followed until the 45 day visit or resolution of adverse events, whichever was longer, and then exited by the study site. Likewise, the four (4) subjects that were randomized but did not have an implant attempt were exited from the study after the date of their scheduled procedure.

For the Control group, the most frequent reason was death which occurred in thirteen (13) subjects. The second most frequent reason was “Subject Withdrew Consent”.

The subjects with “Other” noted as the reason for study discontinuation includes two (2) Device group subjects who had an embolized WATCHMAN device and one (1) Control group subject who was withdrawn from the study by the subject’s physician due to an increased risk of continued anticoagulation which did not exist at baseline.

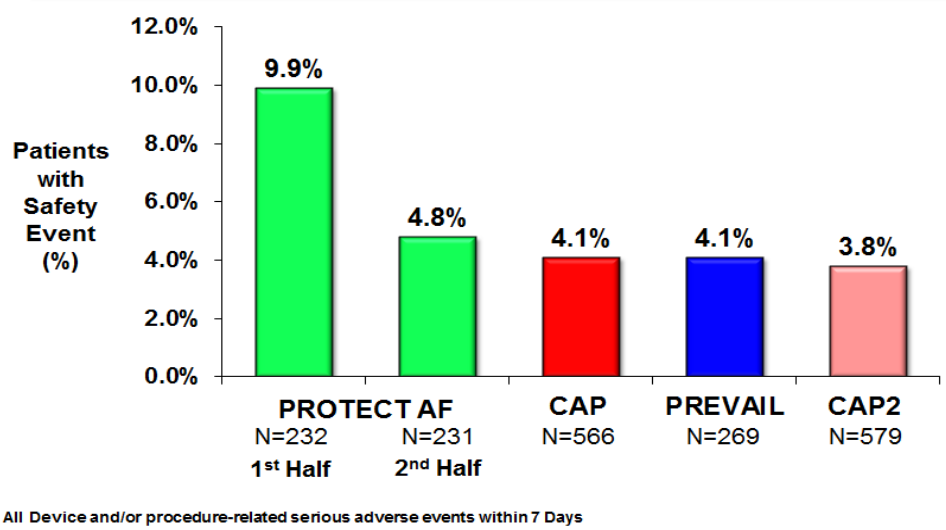
PREVAIL Safety

PREVAIL was the confirmatory trial that met and reproduced (along with the PROTECT AF data) the safety endpoint for the WATCHMAN Technology. There were six events (i.e., device embolization, AV fistula, cardiac perforation, pericardial effusion with cardiac tamponade, and major bleed requiring transfusion) meeting the primary safety endpoint definition in 269 patients. In evaluating the safety primary endpoint events, 2.2% of patients experienced an event and a one-sided 95% credible interval upper bound was 2.652%. Therefore, success of the primary safety endpoint was achieved.

With prolonged follow-up in PROTECT AF, the rate ratio of serious adverse event in the WATCHMAN cohort was comparable to that of warfarin. Additional safety data from the CAP Registry also supported a

decrease in procedure-related events. The continuous improvement in the safety profile over the WATCHMAN clinical program is similar to other complication rates in left sided heart procedures such as AF ablation.[53] See **Figure 3**.

Figure 3: WATCHMAN has a Favorable Procedural Safety Profile across demonstrated across trials



All Device and/or procedure-related serious adverse events within 7 Days

Another focus of PREVAIL was to evaluate the implant performance between both new and experienced operators. The PREVAIL study was designed to determine whether the training and technical improvements instituted during the prior PROTECT AF study could be replicated in investigators with no experience implanting the WATCHMAN LAAC Device. There were no statistically significant differences in the 7-day safety rates achieved by either cohort, which supports the conclusion that the WATCHMAN LAAC Device can be implanted safely by both experienced operators and new operators who have been trained.

Warfarin cessation: Among subjects successfully implanted with the WATCHMAN Device and followed for at least 12 months, 92% discontinued warfarin therapy by 45 days, and 99% discontinued warfarin therapy by 12 months.

PREVAIL Efficacy:

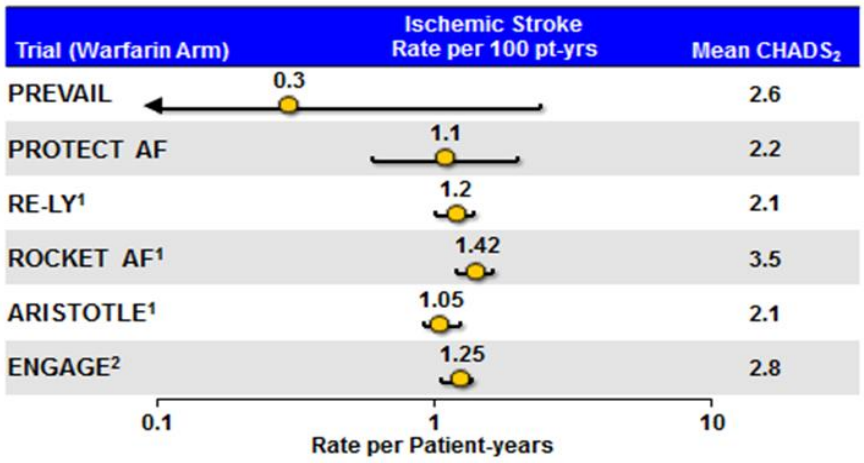
Based on the protocol pre-specified analysis data lock in January 2013, the PREVAIL data, with a mean follow-up from randomization of 11.8 +5.8 months, had achieved both the second endpoint of non-inferiority for the occurrence of late ischemic stroke and systemic embolism (i.e., those that occurred after 7 days post randomization) and the third endpoint which was the occurrence of peri-procedural events within 7 days of procedure or discharge.

For the first endpoint (composite of all stroke, systemic embolism, and cardiovascular/unexplained death), though the 18-month event rates in both trial arms were almost identical, and the rate ratio was 1.07, the upper credible interval of 1.89 crossed the upper limit of 1.75; therefore, statistically, this endpoint was not met.[54] It is important to note that, with respect to ischemic and hemorrhagic strokes, the warfarin arm

[53] Capatto. *Circulation* (2010).
[54] Holmes et al. *JACC* (2014).

was outperforming historical trials (and real-world experience as discussed in section 2c above) and the built-in expectations of the PREVAIL trial. Specifically, the rate of ischemic strokes was three times less than any warfarin control trial in the last decade, with large confidence intervals due to the very small (138) number of patients. On the other hand, the WATCHMAN arm was performing as expected and the incidence of ischemic and hemorrhagic strokes in the WATCHMAN arm was similar to that seen in PROTECT and the CAP registry. The figure below compares the performance of warfarin in PREVAIL compared to recent pharmaceutical trials.

Figure 4: Warfarin ischemic stroke rate in PREVAIL differs from other trials



1. Miller. AJC (2012) 2. Giugliano. NEJM (2013)

Based on this pre-specified primary analysis of the data which was locked in January 2013, along with long-term data in PROTECT AF and CAP, the FDA advisory panel convened in December 2013 voted 13 to 1 in favor of safety, efficacy, and benefit vs. risk profile for WATCHMAN. Patients enrolled in PREVAIL continued to be followed after the initial data lock in January 2013 in order to confirm the low procedure safety rates and to continue to collect additional efficacy data on the device. During this continued follow-up, the safety endpoint remained unchanged because all implants had been completed at the time of the initial data lock. However, there were additional ischemic events after January 2013.

After January 2013, and before June 2014 when the data were locked again, there were 15 additional primary efficacy events - 10 in the WATCHMAN arm and 5 in the warfarin arm (consistent with the 2:1 randomization scheme used in the trial). Eight of the events in the WATCHMAN arm were ischemic strokes while the warfarin arm had no new ischemic strokes (This factored into the FDA's decision to convene the 2014 Panel to reevaluate the benefit-risk profile of the WATCHMAN Device). On the other hand, there were two hemorrhagic strokes and four unexplained cardiovascular deaths in the warfarin arm and only one hemorrhagic stroke and one unexplained cardiovascular death in the WATCHMAN arm. Due to these additional events, at the time of the June 2014 data lock, PREVAIL missed the second endpoint statistically in this ad hoc analysis, even though it had made the second endpoint at the time of the pre-specified data analysis in January 2013.

Table 18 depicts the total number of events at the time of the first and second data locks as well as the incremental events between the two data locks. "PREVAIL-only" includes information from patients in the PREVAIL trial (i.e., Bayesian prior is not included). Please note that the primary efficacy rates represent

the first event (a stroke, systemic embolization, or CV death) a patient experiences. The lines for the individual components represent each event one patient experiences; therefore, the total events will not align with the number of "first" events, as one WATCHMAN patient and one warfarin patient experienced both a hemorrhagic stroke and a subsequent CV death related to that stroke.

Table 18: PREVAIL new primary efficacy events since Jan 2013 data lock equivalent when accounting 2:1 randomization

Type	**PREVIL-only (Jan 2013 Data lock)**		**PREVAIL-only (June 2014 Data lock)**		**Total New Events since Jan 2013 Data lock**	
	WATCHMAN (N event/% of patients)	**Warfarin (N event/% of patients)**	**WATCHMAN (N event/% of patients)**	**Warfarin (N event/% of patients)**	**WATCHMAN (N event/% of patients)**	**Warfarin (N event/% of patients)**
Primary Efficacy	14 (5.2%)	4 (2.9%)	24 (8.9%)	10 (7.2%)	10 (3.7%)	5 (3.6%)
Stroke-Ischemic	5 (1.9%)	1 (0.7%)	13 (4.8%)	1 (0.7%)	8 (3.0%)	0 (0.0%)
Stroke-Hemorrhagic	1 (0.4%)	0 (0.0%)	2 (0.7%)	2(1.4%)	1 (0.4%)	2 (1.4%)
Systemic embolism	1 (0.4%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death-CV /unexplained	7 (2.6%)	3 (2.2%)	8 (3.0%)	6 (4.3%)	2 (0.7%)	4 (2.9%)

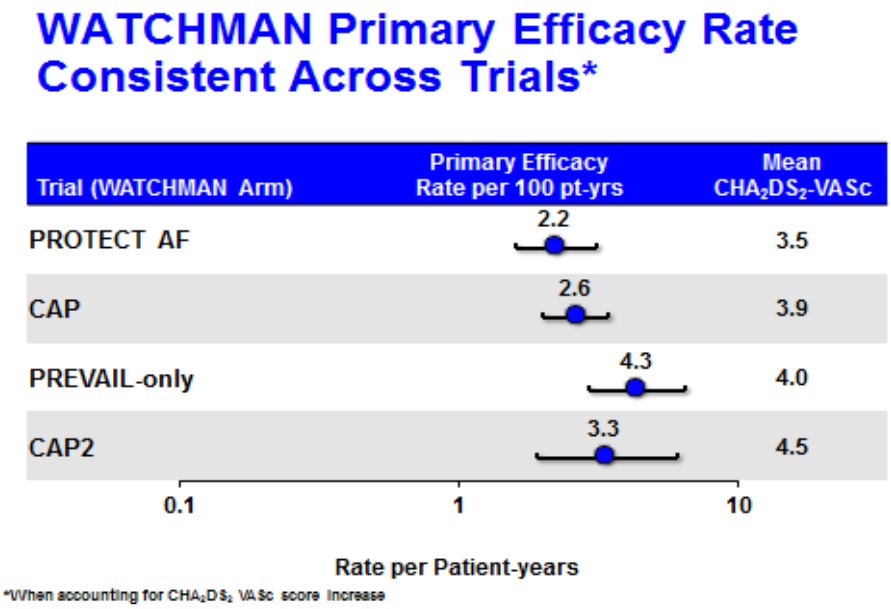
While the ischemic stroke rate in WATCHMAN was numerically higher than that in warfarin, it was consistent in the long term follow up of all WATCHMAN patients in all the trials (**Figure 5a**). In addition, the increase was commensurate with the CHA_2DS_2-VASc scores (PREVAIL 4.0 vs. 3.5 in PROTECT AF). As discussed above, the performance of the warfarin arm in PREVAIL in not representative or comparable to recent pharmaceutical trials[55] of the drug. Here, the incidence of stroke was far less than in previous trials (**Figure 5b**).

This calculation is illustrated for the CHA_2DS_2-VASc score in **Figure 5a** which shows the difference in baseline scores and the PROTECT AF, CAP, PREVAIL-only, and CAP2 ischemic stroke rates. The ischemic stroke rates for the WATCHMAN Group are consistent when extrapolated over time. The ischemic stroke rates are substantially less than the historical rate for an untreated AF population and in line with the rate expected for an AF population treated with warfarin. The Warfarin Control Group, in contrast, has an ischemic stroke rate substantially below what one would expect for a population with these risk factors (**Figure 5b**). The Warfarin Group has done better than expected while the WATCHMAN

[55] Connolly SJ. N Engl J Med (2009); Patel MR. *N EnglJMed*(2011); Granger DB. N EnglJ Med (2011).

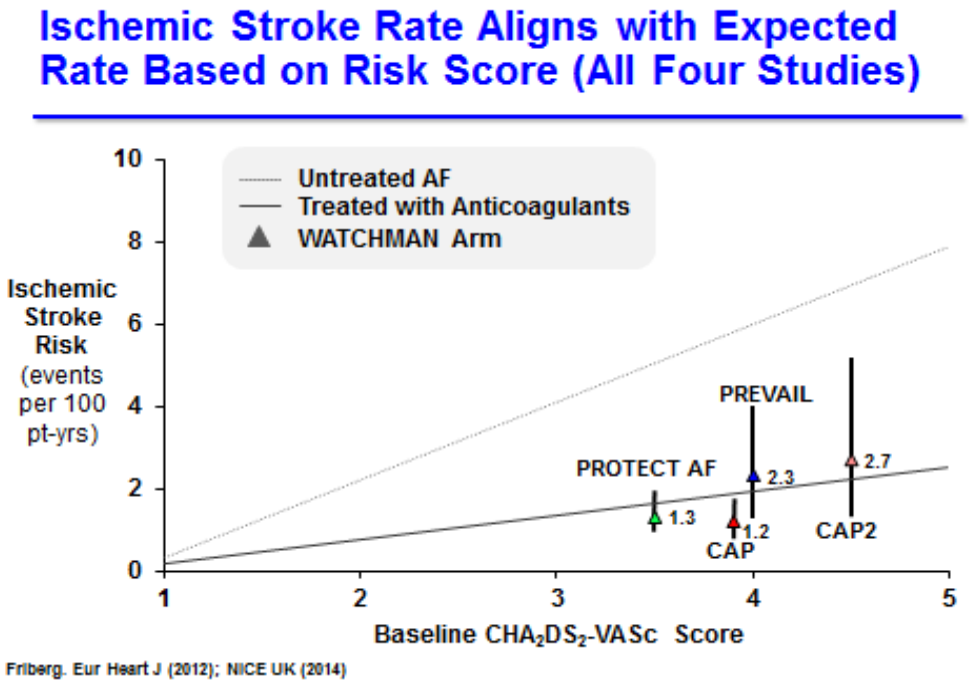
Group meets expectations and has remained consistent between the 2013 and 2014 Panel analyses. **Figure 5a** helps support the consistency in the performance for the WATCHMAN Device.

Figure 5a: Consistent WATCHMAN primary efficacy performance across all trials



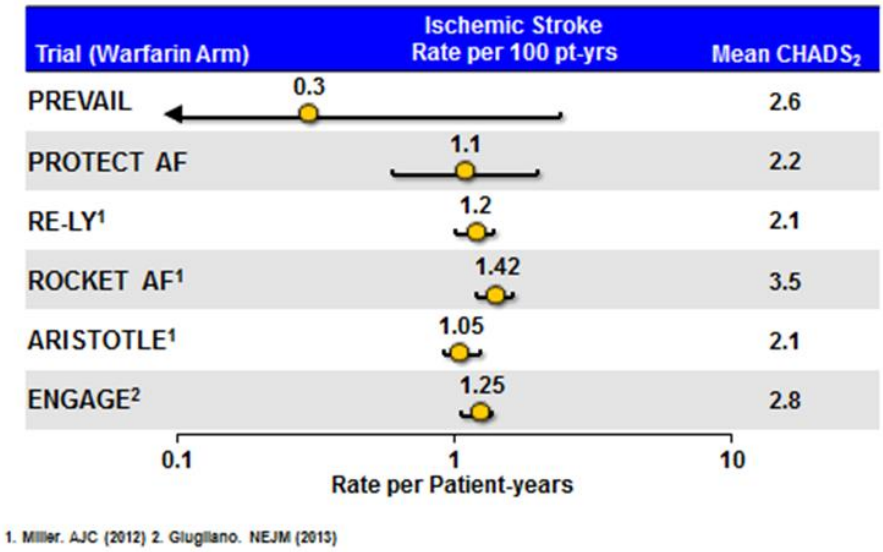
*When accounting for CHA_2DS_2 VASc score increase

**Caution should be used when interpreting CAP2 efficacy due to limited follow up in the trial (less than 6 months).



Friberg. Eur Heart J (2012); NICE UK (2014)

Figure 5b: Consistent WATCHMAN stroke performance across all trials



1. Miller. AJC (2012) 2. Giugliano. NEJM (2013)

The intent of the PREVAIL data was to be examined as part of a Bayesian analysis that included the PROTECT AF data as an informative prior, not as a stand-alone frequentist analysis. The PREVAIL data presented in isolation, without the PROTECT AF prior, are labeled “PREVAIL-only.” PREVAIL-only analyses include 24% of the total patient population and are underpowered to detect clinically meaningful differences. Consequently, it may be difficult to draw conclusions from PREVAIL-only data alone due to its small number of events. Because the primary purpose of PREVAIL was to prove safety (which it did) and was not powered to demonstrate efficacy over longer term follow-up (i.e., after the January 2013 data lock), the FDA requested three supplemental analyses consisting of the following:

- A patient-level meta-analysis that pools the results from the PROTECT AF and PREVAIL studies to obtain overall assessment of device performance.
- An imputed-placebo analysis that puts the WATCHMAN Clinical Program results into perspective by comparing the observed study rates to non-randomized published historical rates.
- A landmark bleeding analysis that examines the risk of major bleeding over the four distinct periods post-implant in which different background anticoagulant/antithrombotic medications are used.

These supplemental analyses provide a more comprehensive perspective on the safety and effectiveness of the WATCHMAN Device taking into account that PREVAIL was not powered without the informative prior from PROTECT AF to show efficacy for longer follow up.

CAP 2 Registry

As a continuation of the PREVAIL trial, the CAP2 Registry is a prospective, non-randomized, multicenter study allowing continued access to the WATCHMAN Technology during the device approval process. A cohort of 450 WATCHMAN patients was enrolled in 60 sites in the U.S and followed through their 5 year follow up visit. Enrollment began in September 2012 and ended in March 2014 (per FDA's request), but follow-up of the patients is still ongoing. Follow up time in this patient cohort is on average less than 6 months so it is too early to provide definitive efficacy conclusions. However, procedural safety in CAP2 is similar to PREVAIL.

Warfarin cessation: Among subjects successfully implanted with the WATCHMAN Device and followed for at least 12 months, 98% discontinued warfarin therapy by 45 days, and 99% discontinued warfarin therapy by 12 months.

Meta-analysis of PROTECT AF and PREVAIL data

Boston Scientific performed a patient level meta-analysis that combined the PROTECT AF and PREVAIL data. CAP and CAP2 are not included in this evaluation because these registries did not have Warfarin Control Groups. This analysis provides an additional perspective to support the efficacy of the WATCHMAN Technology and shows that the device was performing as expected compared to the warfarin control arm.

In the meta-analysis, multiple outcomes of interest are examined, starting with the primary efficacy endpoint then looking at individual outcomes: all stroke (ischemic and hemorrhagic) and associated disability, systemic embolism, cardiovascular/unexplained death and major bleeding.

Though most outcomes show non-inferiority of the WATCHMAN Technology to warfarin, a few measures are notable. For efficacy, although there were no statistical significant differences between the two groups, WATCHMAN was favored with a 21% reduction in the risk of a primary efficacy endpoint event (p=0.23). The incidence of all strokes (ischemic and hemorrhagic) was not statistically different in the WATCHMAN and warfarin arms. However, there were statistical differences while analyzing the stroke subtypes. There were more ischemic strokes in the WATCHMAN arm. However, after accounting for early procedural complications, including strokes (within 7 days post procedure) in PROTECT AF, the difference in ischemic stroke between the two arms fell below statistical significance (p=0.21). Importantly, there were significantly more hemorrhagic strokes and cardiovascular deaths in the warfarin arm compared to the WATCHMAN arm which showed a 78% and 52% reduction in those events respectively (p=0.004 and p=0.006).

To better assess the clinical impact of the different subtypes of strokes on patients, we also performed statistical tests on the disability resulting from the strokes.

Not all strokes result in equal disability risk of death. Hemorrhagic strokes are generally more severe. Data from a large Danish registry has shown that, within the first three months after stroke, hemorrhagic stroke is associated with a considerable increase in mortality, which is specifically associated with the hemorrhagic nature of the lesion[56]. In that series, compared with ischemic stroke, hemorrhagic stroke was associated with an overall higher mortality risk (HR, 1.564; 95% CI, 1.441–1.696). Additionally, resulting

[56] Anderssen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared: Stroke severity, mortality, and risk factors. *Stroke*. 2009;40:2068-72.

disability is often greater with hemorrhagic stroke and large ischemic strokes, due to the extent of cerebral damage. Clinically, it is important to determine not just whether a stroke is likely to occur, but also what kind of residual neurological deficit the patient is likely to experience. From a patient perspective, protection against ALL types of stroke is the preventive goal – along with avoidance of significant residual disability and death.

Using a validated stroke severity assessment tool (Modified Rankin Scale score), strokes that occurred were classified as "Disabling" or "Non-disabling." The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It has become the most widely used clinical outcome measure for stroke clinical trials. The scale runs from 0-6, running from perfect health without symptoms (mRS score 0) to death (mRS score 6).[57,58]

In our analyses, a disabling stroke was defined as a stroke followed by an increase in score of 2 or more in the modified Rankin Scale for neurological cause or a CV/unexplained death. This magnitude of change reflects an inability to independently perform activities of daily living or worse. Strokes not considered to be disabling were classified as non-disabling. Results are presented for PROTECT AF and PREVAIL, alone and in combination, and are detailed for disabling and non-disabling strokes, respectively, in **Table 19 and 20**. As shown previously, the relative risk of stroke due to any cause is unchanged between the WATCHMAN and Warfarin Groups (HR=1.02, p=0.93). However, those strokes that do occur are significantly less likely to be disabling for those patients randomized to receive the WATCHMAN LAAC Device compared to those seen in the warfarin arm.

Table 19: Disabling Strokes (PROTECT AF and PREVAIL-only)

	PROTECT AF	**PREVAIL-only**	**Pooled**
Hazard Ratio for WATCHMAN vs Control (95% CI)	0.33 (0.13, 0.85) p=0.021	1.14 (0.21, 6.29) p=0.88	0.44 (0.20, 0.98) p=0.044

Table 20: Non-Disabling Strokes (PROTECT AF and PREVAIL-only)

	PROTECT AF	**PREVAIL-only**	**Pooled**
Hazard Ratio for WATCHMAN vs Control (95% CI)	1.36 (0.59, 3.11) p=0.47	5.57 (0.72, 43.2) p=0.10	1.85 (0.88, 3.89) p=0.11

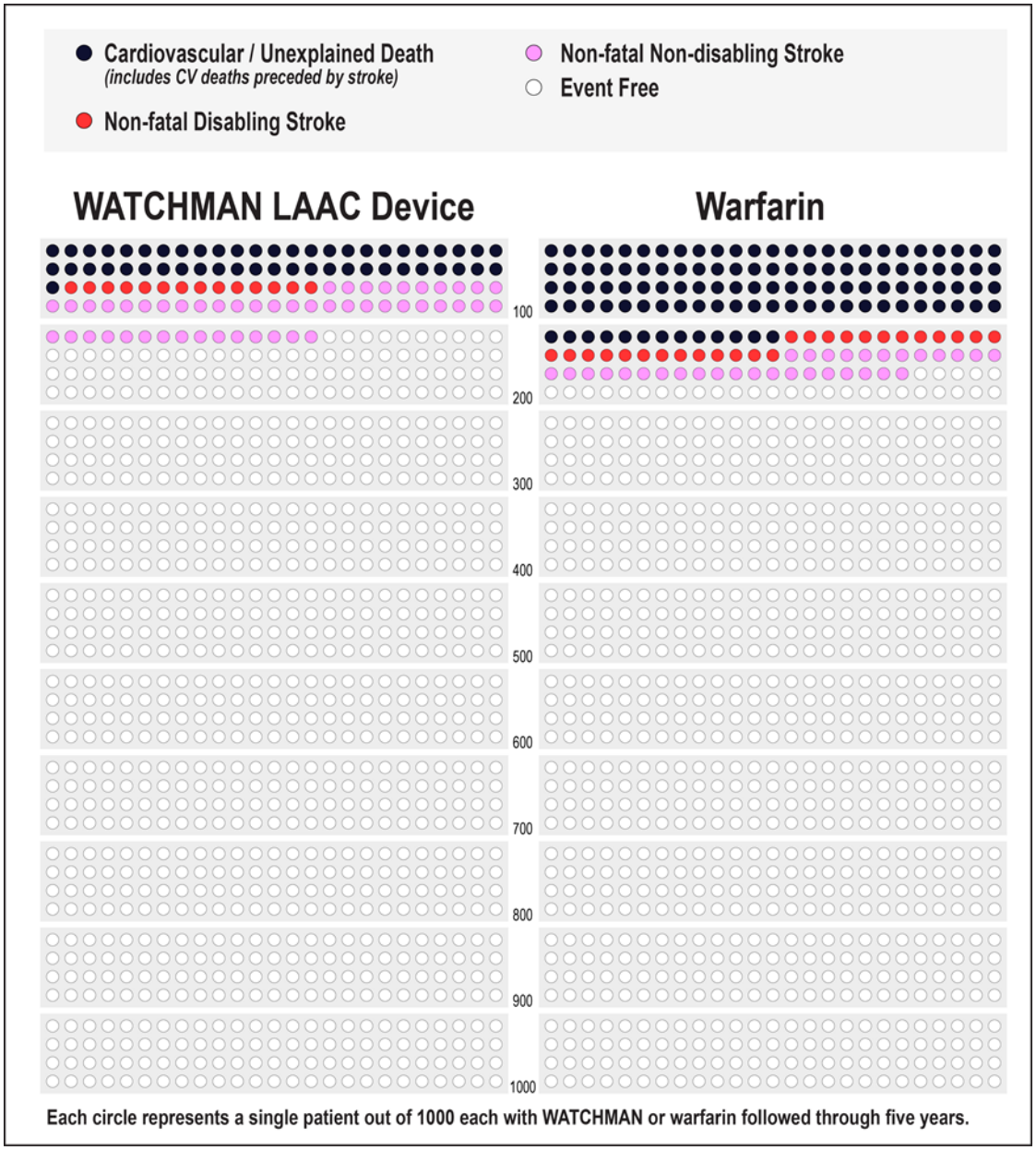
[57] Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scot Med J.*1957;2(5):200-15.
[58] van Swieten J, Koudstaal P, Visser M, Schouten H. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke.* 1988;19(5):604-7.

Understanding the relationship between stroke type, mortality risk and severity, as well as the fact that the strokes experienced by WATCHMAN patients were less disabling than those experienced by patients in the warfarin arm, can provide useful context when assessing the net benefit-risk profile of the WATCHMAN LAAC Device. [59] **Figure 6** shows this effect in a representative population of 1000 patients over 5 years of follow-up to reflect absolute changes rather than relative changes. It demonstrates stroke incidence in terms of level of disability (disabling / non-disabling as described above) rather than etiology. The WATCHMAN data are the combined data from PROTECT AF and PREVAIL. Each circle represents a single patient, and the colors represent the following events: black for cardiovascular or unexplained death (including cardiovascular death preceded by a stroke), red for disabling stroke, and purple for non-disabling stroke. When considering the individual event types experienced by each group, it becomes readily apparent that WATCHMAN significantly reduced the risk of disabling strokes compared with warfarin.

Although these results cannot be used to predict outcomes for an individual patient, they illustrate what might be expected in a large population of patients over 5 years: a reduced likelihood of CV/unexplained mortality and disabling stroke (WATCHMAN) set against a greater likelihood of a disabling stroke (warfarin).

[59] WATCHMAN FDA Panel Sponsor Presentation 2014.

Figure 6: Illustrated Benefit-risk Profile Based on Disabling/Non-disabling Strokes (Pooled PROTECT AF and PREVAIL)



Patient-level Meta-analysis Summary

Below are the major results of the WATCHMAN randomized studies:

- Primary Efficacy Endpoint: The WATCHMAN LAAC Device was associated with a 21% reduction in the risk of a primary efficacy endpoint event, though not statistically significant (p=0.23).

- Stroke and Systemic Embolism: The WATCHMAN LAAC Device is similar to warfarin in preventing all-cause stroke and systemic embolism (HR=1.02, p=0.93). It is associated with a significant decrease in the relative risk of hemorrhagic stroke (88%, p=0.004); however, the device is not as effective as warfarin in reducing the risk of ischemic stroke (HR=1.96, p=0.049).

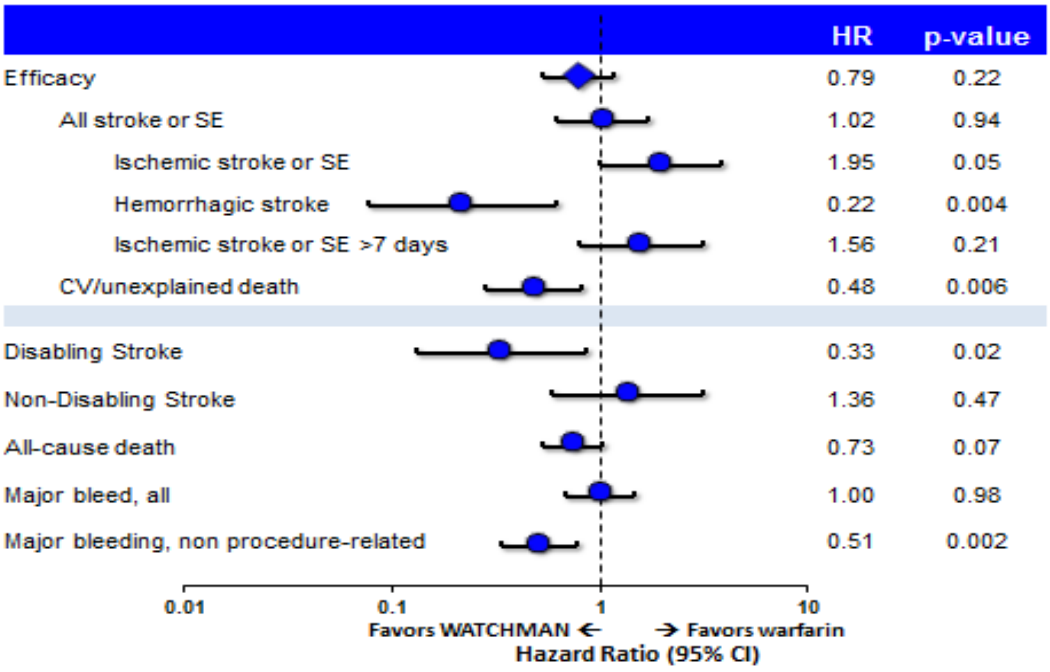
- Stroke Severity: Using the MRS instrument, those strokes occurring in the WATCHMAN device arms were significantly less likely to be disabling (49% relative reduction in disabling strokes, p=0.044) than those occurring in the Warfarin Groups.

- Major Bleeds: Warfarin can cause bleeding in anatomic locations other than the brain, such as the eye or spine. When considering all major bleeds unrelated to the implant procedure, warfarin was associated with an approximately two-fold relative increase in the risk of a major bleed (p=0.002).

- Mortality: Use of the WATCHMAN LAAC Device is associated with a 27% relative reduction in the risk of all-cause mortality, though not statistically significant (p=0.074) and a 52% relative reduction in the risk of CV/unexplained mortality (p=0.006).

When evaluating the patient-level meta-analyses, it can be concluded the WATCHMAN Device represents a reasonable alternative to warfarin. Use of the WATCHMAN Device did not change the overall rate of all-cause stroke, but it did alter the proportion of stroke subtypes: there was a reduction in hemorrhagic stroke which was offset by less effective prevention of ischemic stroke. Although the overall rate of all-cause stroke was unchanged, patients with the WATCHMAN Device were significantly less likely to have a disabling stroke. When compared to warfarin, the WATCHMAN Device yielded a significant relative reduction in the risk of major bleeding by 51% as well as a significant relative reduction in the risk of mortality due to CV or unknown causes by 52%. The patient-level meta-analysis results are shown in **Figure 7**.

Figure 7: Totality of WATCHMAN vs. warfarin data show comparable and in some measures superior outcomes



We also analyzed bleeding risks of WATCHMAN compared to historical data on long term oral anticoagulation and to no treatment at all for those at risk of stroke. Both analyses are presented below.

Imputed Placebo Analysis[60]

Many high risk warfarin-eligible patients are receiving no treatment at all and therefore left unprotected from stroke, with annual stroke rates ranging from 5.6% up to 7.1% ischemic strokes annually. In order to assess the benefit that "untreated patients" may be able to expect with WATCHMAN, the FDA asked Boston Scientific for an imputed placebo analysis. The "untreated patients" referenced in the imputed placebo analysis specifically refers to population that is deemed suitable for anticoagulation therapy, but who have an appropriate rationale to seek and alternative and who, in the absence of that alternative, choose to remain unprotected. Per our prior discussion in the "unmet clinical need" section, a substantial portion of these warfarin-eligible patients remain untreated or sub-optimally treated for non-valvular AF stroke risk. These patients would have been considered for participation in the WATCHMAN trials. Since the warfarin arm of the PREVAIL trial outperformed those of contemporary pharmaceutical trials, Boston Scientific upon FDA's request sought to compare the PREVAIL WATCHMAN results to a more robust and large warfarin database. The imputed placebo compares similar patients to those enrolled in the WATCHMAN trials using a large real-word database of similar patients that may or may not be treated with oral-anti-coagulation, but who are, eligible for treatment with these drugs. The observed ischemic strokes rates in the WATCHMAN arms of the clinical trials were compared against the estimated stroke risk of untreated warfarin-eligible non-valvular AF patients.

A placebo arm was constructed using well-established, validated literature models based on both the $CHADS_2$ and CHA_2DS_2-VASc scores. A benefit was then imputed for WATCHMAN over this placebo, and relative reduction in events was computed. Two sets of imputed placebo analyses are performed, to demonstrate consistency of the findings across different reference populations.

- The first analysis used large registry data from Gage et al. to estimate ischemic stroke risk for untreated AF patients based on both $CHADS_2$ and CHA_2DS_2-VASc scores.[61,62,63] The analysis compares these rates to measured ischemic stroke rates in the datasets for the PROTECT AF and PREVAIL-only WATCHMAN Groups and the CAP Registry. Additional comparison is provided to the published literature to put the observed risk reductions in clinical perspective.[64]

- A second analysis comparing historical ischemic stroke rates from the Swedish Atrial Fibrillation Cohort Study (Olesen 2011) to the pooled patient-level meta-analysis data described above for the PROTECT AF and PREVAIL studies. This study was chosen because it shows the risk of ischemic stroke as well as the risk of major bleeding as a function of the newer CHA_2DS_2-VASc score and

[60] Hanzel G, Almany S, Haines D, Berman A, Huber K, Kar S, Holmes D. Comparison of Imputed Placebo Versus Observed Ischemic Stroke Rates in the WATCHMAN Trials Represents a Significant Reduction in Risk (TCT2014 Presentation #176)

[61] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285(22);2864-70.

[62] Olesen JB, Lip GY, Lindhardsen J, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost* 2011;106(4):739-49.

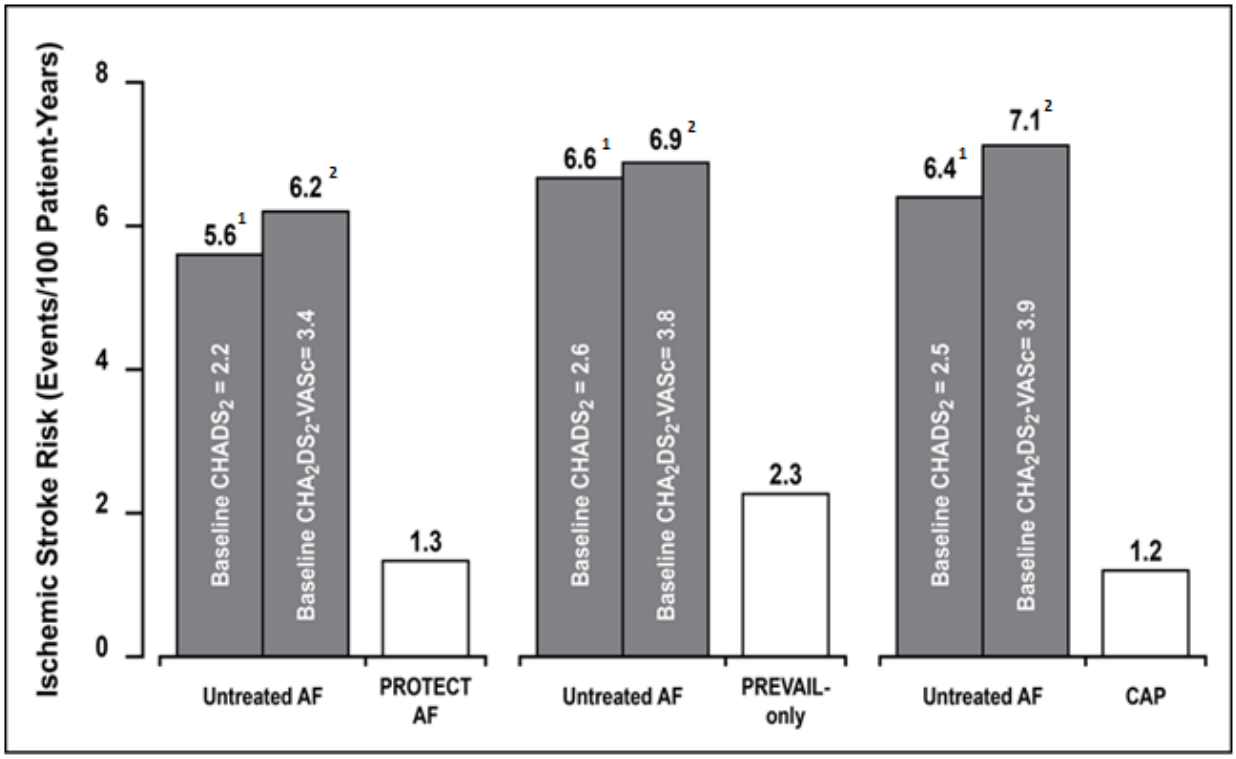
[63] Gage, BF et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation.* 2004 Oct 19;110(16):2287-92.

[64] Segal JB, McNamara RL, Miller MR, et al. Prevention of thromboembolism in atrial fibrillation. A meta-analysis of trials of anticoagulants and antiplatelet drugs. *J Gen Intern Med* 2000;15(1):56-67.

HAS-BLED scores, respectively, for AF patients who were untreated as well as treated with anticoagulants.[65]

When compared to the untreated AF rates, each of the WATCHMAN studies is associated with a substantial reduction in the risk of ischemic stroke, demonstrating a consistent and clinically meaningful response across each study. The stroke risk reduction is between 65%-81% when comparing the performance of the WATCHMAN Device to the same placebo groups used in the imputed placebo analyses. (**Figure 8**). The imputed placebo analyses show there is a strong expectation of a beneficial effect of WATCHMAN when applied as intended to the patients who are capable of taking warfarin for the short-term but who are unable or unwilling to take the drug for the long-term and who would otherwise go untreated.

Figure 8: WATCHMAN represents a large reduction in ischemic stroke over unprotected patients



[1] Gage, JAMA (2001) & Gage, Circulation (2004)

[2] Olesen, BMJ (2011)

Post hoc analysis of Bleeding risks

One of the primary goals of mechanical LAA closure is to allow the patient to be free of long-term warfarin therapy – and the associated risk for bleeding. Although the primary efficacy endpoint of the PROTECT AF and PREVAIL studies considered hemorrhagic stroke, it did not encompass other types of major

[65] Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;33:1500-10.

bleeding that may be associated with the use of warfarin. A supplemental analysis was performed to determine the relative risks of all types of bleeding.[66]

As shown in **Figure 9**, the WATCHMAN post-implant follow-up period is divided into four sub-periods based on protocol-defined, time-based landmarks. Seven days is chosen for the first sub-period because it encompasses the period of procedural risk for bleeding. The second sub-period is from 7 to 45 days, which is the period when the patient is on warfarin plus aspirin. The third sub-period is from 45 days to six months post-implant at which time the LAAC device should be endothelialized and, if confirmed by TEE, the patient may be switched to clopidogrel plus aspirin. The fourth sub-period starts at six months at which time clopidogrel may be discontinued and the patient followed on aspirin alone.

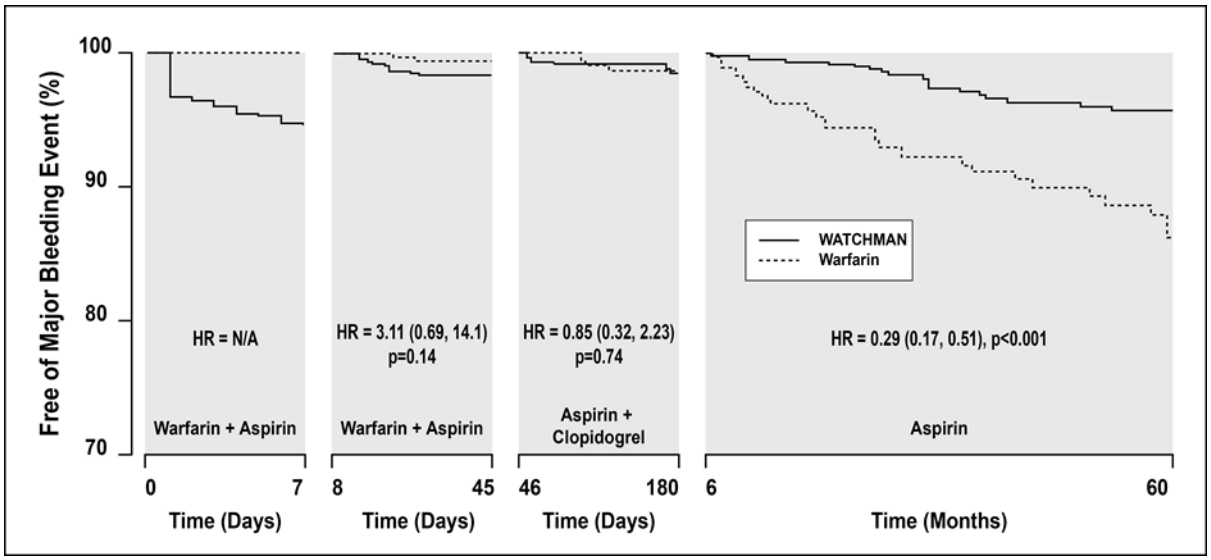
Although some bleeding events with WATCHMAN are procedural complications which occur immediately post-implant, these can be managed in-hospital under medical supervision. In contrast, bleeding events with warfarin typically occur outside the hospital setting and are more difficult to manage. An important practical distinction between bleeding that occurs at the time of the device implantation (e.g., pericardial effusion or groin hematoma) and non-procedural, anticoagulation-related bleeding is the former occurs in the hospital setting where medical care is immediately available, while the latter may occur when prompt care is not rapidly accessible.

From 7 days to 6 months, the concomitant medication required with WATCHMAN cannot be ruled out as a contributing factor to bleeding events. The 6 month period onward represents the final therapy on which the patient will be followed long-term. During this period, the hazard ratio for the risk of major bleeding is 0.29 ($p<0.001$), showing a significant relative risk reduction favorable to the WATCHMAN arm. From 6 months post-implant onward, continued use of warfarin in the Warfarin Group was associated with a 3.4-fold increase in the risk of major bleeding over WATCHMAN therapy.

The bleeding risk during the WATCHMAN implant was mitigated in the second half of the PROTECT AF trial and in all subsequent trials. Based on the **Figure 9**, there are significant bleeding reductions 6 months after implant when the WATCHMAN patients are no longer exposed to warfarin or clopidogrel therapy. Because the WATCHMAN patients are free of the burden of a life-long treatment with anti-coagulants (99% at 12 months), the bleeding risk is constant or reduced in years 1-9 post implant. Therefore, with more time, the reduced bleeding benefits of WATCHMAN continue to diverge and the magnitude of benefit increases.

[66] WATCHMAN FDA Panel Sponsor Presentation 2014.

Figure 9: Significant bleeding reduction with WATCHMAN after concomitant therapy is complete

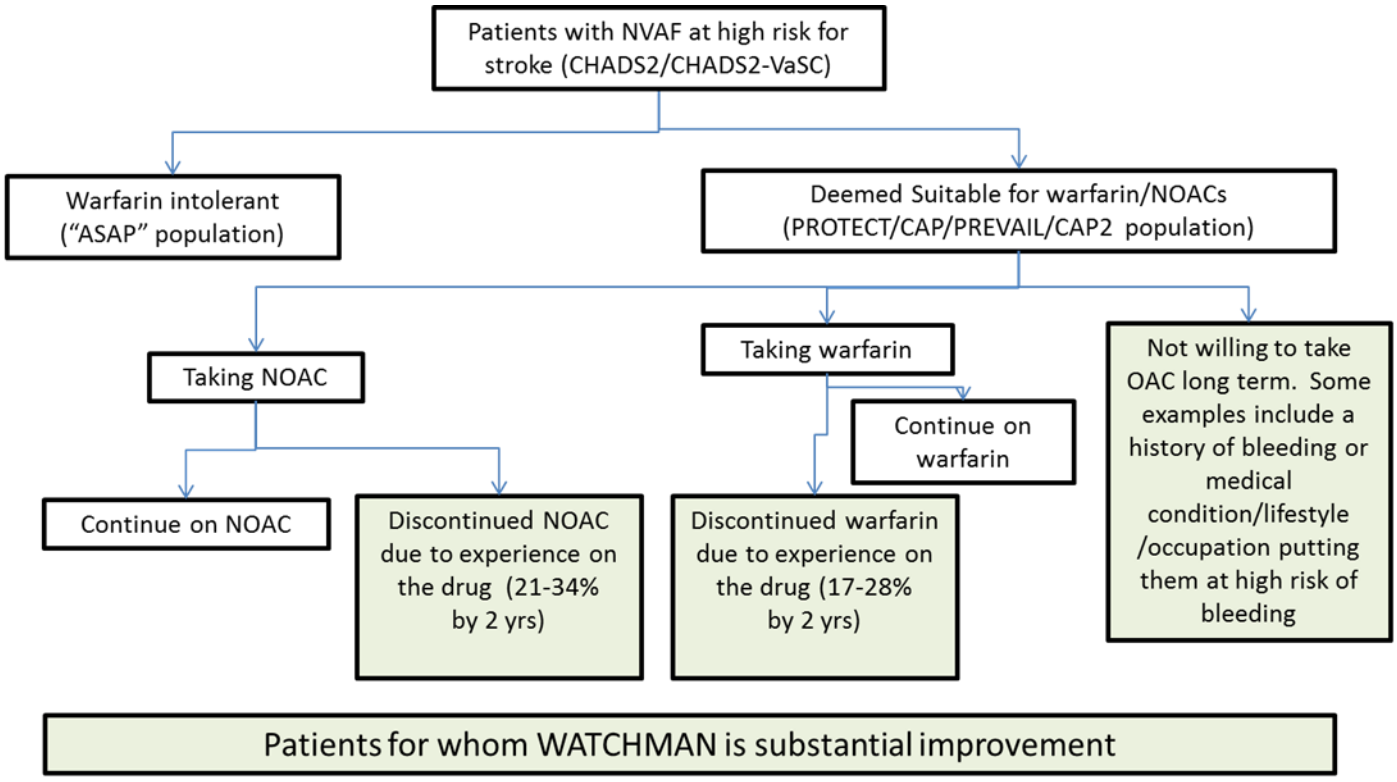


The significant reduction in bleeding after the procedure and during the post-implant medication therapy sub-period (up to 6 months) at which time long term anticoagulation is discontinued illustrates the substantial clinical benefit of the WATCHMAN Technology.

SUMMARY

The totality of the data on the WATCHMAN from the PROTECT AF study, the CAP Registry, and the PREVAIL trial demonstrate that the WATCHMAN improves the clinical outcomes of Medicare beneficiaries in preventing thromboembolism from the LAA and thus reduce the risk of stroke, systemic embolism, and cardiovascular death in high-risk patients with non-valvular atrial fibrillation who are recommended by clinical guidelines for warfarin therapy but in whom the risk posed by long term warfarin therapy outweigh the benefits. (**Figure 10**)

Figure 10: Populations Proven to Benefit from WATCHMAN



1. Jani, et al. Uptake of Novel Oral Anticoagulants in Patients with Non-Valvular and Valvular Atrial Fibrillation: Results from the NCDR-Pinnacle Registry. ACC 2014

EFFICACY

The efficacy of the WATCHMAN Closure Device in preventing thromboembolic events and cardiovascular death has been demonstrated.

- ***Investigators were able to implant the device with a high degree of success***. Implant success rates have increased from 90.9% in PROTECT AF to 94.3% in the CAP Registry and 95.1% in PREVAIL.

- ***Patients were able to successfully cease the use of warfarin***. By 45 days, warfarin cessation occurred in 87% of patients in PROTECT AF, 96% of patients in CAP, 92% of patients in PREVAIL , and 98% of patients in CAP2 that were successfully implanted with WATCHMAN. This figure improved to 93% for PROTECT AF, 96% for CAP and 99% for both PREVAIL and CAP2 at one year. Thus, the vast majority of patients to have been successfully implanted with WATCHMAN are able to discontinue warfarin, with 99% of patients in the two most recent studies able to discontinue warfarin by one year.

- ***The PROTECT AF study met its efficacy primary endpoint of non-inferiority when comparing the WATCHMAN Closure Device to warfarin, eventually reaching superiority***. This endpoint was a composite of ischemic stroke, hemorrhagic stroke, systemic embolism, or death due to cardiovascular or unknown causes encompassing 2621 patient-years of follow-up. PROTECT AF demonstrated a 40% reduction in the risk of a primary endpoint event [rate ratio= 0.60, 95% CrI (0.41, 1.05), posterior probability>0.999 for non-inferiority, 0.960 for superiority].

SAFETY

The safety of the WATCHMAN LAAC Therapy has been shown across the studies in the WATCHMAN clinical program.

- ***A substantial improvement in safety was seen early in the WATCHMAN clinical experience.*** The rate of safety events was reduced from the early PROTECT AF enrollment period to the late PROTECT AF enrollment period. Changes in training, the implant procedure, and technical aspects of the WATCHMAN device reduced the rate of safety events from 9.9% in the first half to 4.8% in the second half. The durability of this effect was evident in the CAP Registry in which the safety event rate was 4.1%.

- ***The safety endpoint in the PREVAIL study was met.*** The event rate was 2.2% with a 95% credible interval bound of 2.65%, within its pre-specified performance goal of 2.67%.

- ***The training program employed in PREVAIL was successful.*** The risk associated with the implant procedure was similar for both new and experienced operators.

3. Benefits and relevance of procedure to the Medicare population

Prior to the LAAC technology, there was a subset of Medicare beneficiaries who did not have an alternative other than long-term oral anticoagulation therapy for the reduction and management of stroke risk. The PROTECT AF, CAP, PREVAIL, and CAP2 trials had demographics reflective of the Medicare population with an average patient age > 70 years. Often these warfarin-eligible patients are left unprotected from stroke because, despite being eligible for warfarin therapy, they are unable to tolerate long-term warfarin therapy because of significant bleeding risk, challenges with adherence, and the need for regular INR monitoring and frequent dose adjustments. Although oral anti-coagulation is the standard of care, it is not ideal for all Medicare beneficiaries and studies indicate that a decline in anticoagulation use is associated with an increase risk of stroke in the Medicare population. Based on the most recent 4 year and 5 year long-term follow up results of the PROTECT AF Trial, the WATCHMAN Device offers an effective and safe alternative to warfarin for a subset of Medicare patients where warfarin therapy may not be ideal. For this subset of patients, the WATCHMAN Device provides a substantial clinical improvement in providing protection from the risk of cardioembolic stroke as effective as warfarin. In addition, it provides the opportunity for patients to cease continuation of warfarin 45 days after the required post implant treatment regimen with up to 99% of patients discontinuing warfarin by one year based on the latest two clinical trials (PREVAIL and CAP2). The totality of the data from PROTECT AF, PREVAIL, and two continued access registries provides reasonable assurance of the safety and efficacy of WATCHMAN versus warfarin in providing an effective alternative that benefits the Medicare population.

4. WATCHMAN References

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5. Supplemental Information

a. Directions for use

b. Patient guide

c. Summary of Safety and Effectiveness Data