Latest Treatments for Irregular Heartbeat

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Boulder Community Health

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Atrial Fibrillation

- Irregular heart rhythm
- Basically, the top part of the heart ("atria") don't communicate electrically with the bottom ("ventricles")
- Results in symptoms of SOB, light-headedness, and palpitations

Boulder Community Health

Causes

- High blood pressure.
- Heart attacks.
- CAD
- Abnormal heart valves.
- Heart defects you're born with (congenital)
- An overactive thyroid gland or other metabolic imbalance.
- Exposure to caffeine, tobacco or alcohol

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Diagnosis

- ECG is mandatory
- Not every "irregular heart rhythm" is AF!
- PVCs, APCs, skipped beats can all mimic feelings of AF
- AF does not have to be chronic, it can be short-lasting or come/go (i.e. PAF)

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Treatment

- Medications to control HR (i.e. beta-blockers, Ca-channel blockers) are first line
- Anti-arrhythmic medications can be used to control rhythm
- Cardioversion (either electrically or chemically) can be utilized for symptomatic AF

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But what else does AF cause?

- Stroke!!
- The left atrial appendage (LAA) which is in the left atrium can collect blood which forms clots that can break free in patients with AF
- That's why we place patients with AF who have elevated risks for stroke on blood thinners

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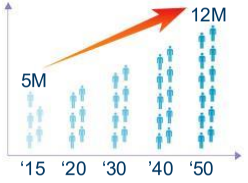
Blood Thinners

- Work very well as long as compliance is maintained and no side effects seen
- Warfarin- cheap but compliance with diet/testing an issue as well maintaining adequate levels
- NOACs- Costly, lack readily available reversal agents
- All the above can exacerbate bleeding

AF is a Growing Problem Associated with Greater Morbidity and Mortality

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

AF = most common cardiac arrhythmia, and growing



~5 M
people with AF in U.S., expected to more than double by 2050[1]

AF increases risk of stroke

5x
greater risk of stroke with AF[2]

- Higher stroke risk for older patients and those with prior stroke or TIA
- 15-20% of all strokes are AF-related
- AF results in greater disability compared to non-AF-related stroke

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1. Go AS. et al, Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association. Circulation. 2013; 127: e6-e245.
2. Holmes DR, *Seminars in Neurology* 2010;30:528–536.

AF-related strokes are debilitating

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Stroke

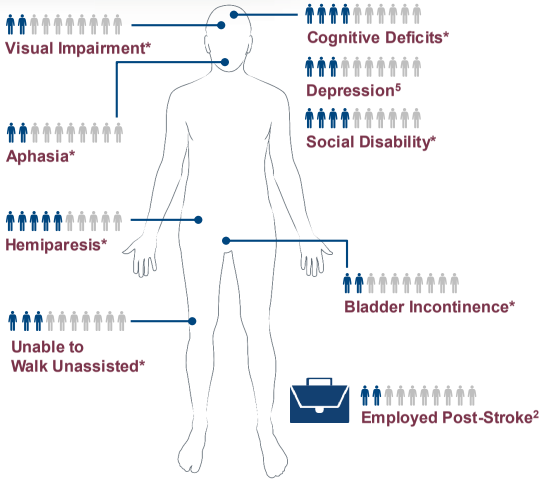
#1 cause of **adult disability** worldwide[1]

AF-related Stroke

1.5X higher **disability**[3**]

2X higher **mortality**[3**]

70% result in **death or permanent disability**[6]



*at 6 months post-stroke[4]
**compared with stroke patients without AF

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[1]Chee and Tan. *Med J Malaysia* 69.3 (2014): 119-23. [2]Sreedharan et al. *Journ of the neurological sciences* 332.1 (2013): 97-101. [3]Lamassa et al. *Stroke* 32.2 (2001): 392-398.[4]Kelly-Hayes et al. *Journ of Stroke and Cerebrovascular Diseases* 12.3 (2003): 119-126. [5]Loo and Gan. *International Journ of Stroke* 7.2 (2012): 165-167. [6]Holmes DR, *Seminars in Neurology* 2010;30:528–536.

2014 ACC/AHA/HRS Treatment Guidelines to Prevent Thromboembolism in Patients with AF

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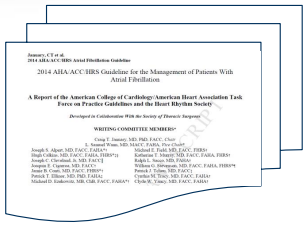
- Assess stroke risk with CHA_2DS_2-VASc score
  - Score 1: Annual stroke risk 1%, oral anticoagulants or aspirin may be considered
  - Score ≥2: Annual stroke risk 2%-15%, **oral anticoagulants are recommended**
- **Balance stroke risk reduction benefit vs. bleeding risk**



2014 AHA/ACC/HRS Guideline for the Management of Patients with AF

CHA_2DS_2 VASc Score	Recommendation
0	No anticoagulant
1	Aspirin (81-325 mg daily) or warfarin (INR 2-3)
≥2	Oral anticoagulants are recommended (warfarin (INR 2-3), dabigatran, rivaroxaban or apixaban

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January, CT, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. JACC. 2014; doi: 10.1016/j.jacc.2014.03.022

Anticoagulant Therapy Carries Risk of Intracerebral Hemorrhage or Death

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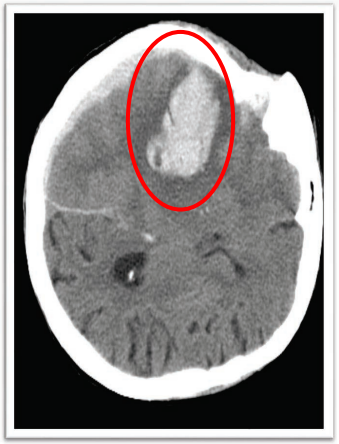

Spontaneous intra-parenchymal bleed

Hemorrhagic transformation

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Validated Scoring Systems to Assess Stroke Risks

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

CHA_2DS_2VASc Score (Stroke Risk)[3]

	Condition	Points
C	Congestive heart failure	1
H	Hypertension (SBP>160)	1
A_2	Age ≥ 75 years	2
D	Diabetes mellitus	1
S_2	Prior stroke, TIA or thromboembolism	2
V	Vascular disease (PAD, MI)	1
A	Age 65-74 years	1
Sc	Sex category (Female)	1
	TOTAL POINTS	

Score	Yearly Stroke Risk (%)		
	No Warfarin	With Aspirin[2]	With Warfarin[2]
0	0	0	0
1	1.3	1.0	0.5
2	2.2	1.8	0.8
3	3.2	2.6	1.1
4	4.0	3.2	1.4
5	6.7	5.4	2.3
6	9.8	7.8	3.4

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3. *Chest*. 2010 Feb;137(2):263-72.

Validated Scoring Systems to Assess Bleeding Risks

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

HAS-BLED Score (Bleeding risk with warfarin)[4]

	Condition	Points
H	Hypertension	1
A	Abnormal renal/liver function (1 pt each)	1 or 2
S	Hemorrhagic Stroke	1
B	Bleeding history or disposition	1
L	Labile INRs	1
E	Elderly [4]	1
D	Current drugs (medication) or alcohol use (1pt each)	1 or 2
	TOTAL POINTS	

Score	Yearly Major Bleeding Risk %
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5+	Not well validated

4. *Chest*. 2010 Nov;138(5):1093-100.

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Bleeding Risk Increases Over Patients' Lifetime

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HAS-BLED Score	Annual % Bleed Risk*	10-Year Bleeding Risk (%)**
0	0.9	8.6
1	3.4	29.2
2	4.1	34.2
3	5.8	45.0
4	8.9	60.6
5	9.1	61.5

** Assumes constant risk despite increasing age and bleeding risk is independent from bleeding risk in previous years

* Lip. JACC (2011)

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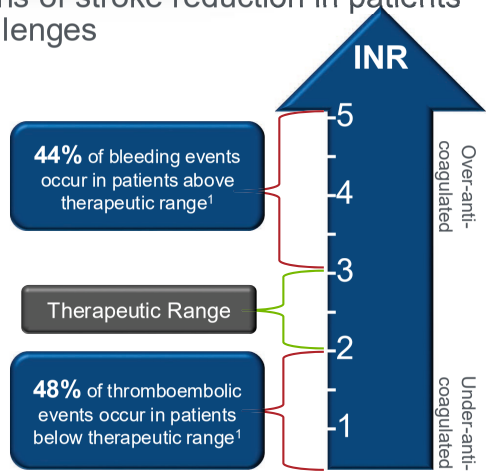
Stroke Treatment Option: Warfarin

Boston Scientific

Warfarin is an effective means of stroke reduction in patients with AF but can present challenges

- Many patients spend a significant amount of time outside of the therapeutic range.
- Warfarin tops the list for emergency hospitalizations for adverse drug events in older Americans[2]



1 Oake N, et al. *Can Med Assoc J*. 2007:176(11);1589–1594
2 Budnitz, MD, MPH. et al. *Annals of Internal Medicine*. 2007:147(11); 229

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Oral Anticoagulation is Standard of Care, but Compliance a Challenge

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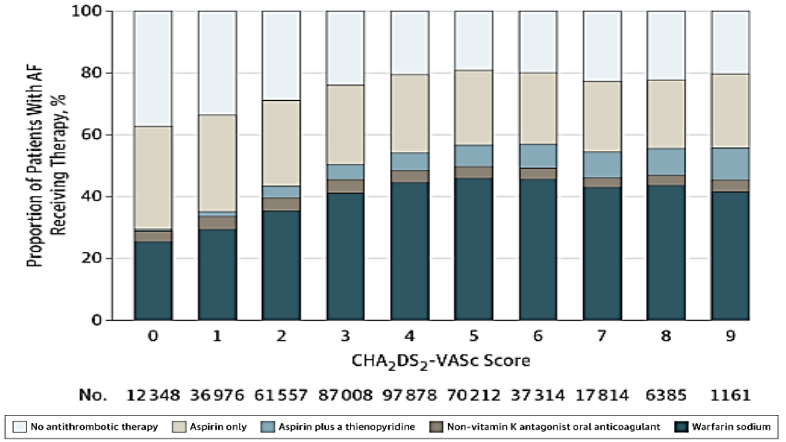
Use of OACs in AF Patients peaks at ~50%, use declines with increasing risk



1. Hsu, J et al. *JAMA Cardiol*. Published online March 16, 2016. doi:10.1001/jamacardio.2015.0374

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Despite NOAC Adoption and Ability to Switch NOACs, Adherence to Anticoagulation Remains a Challenge

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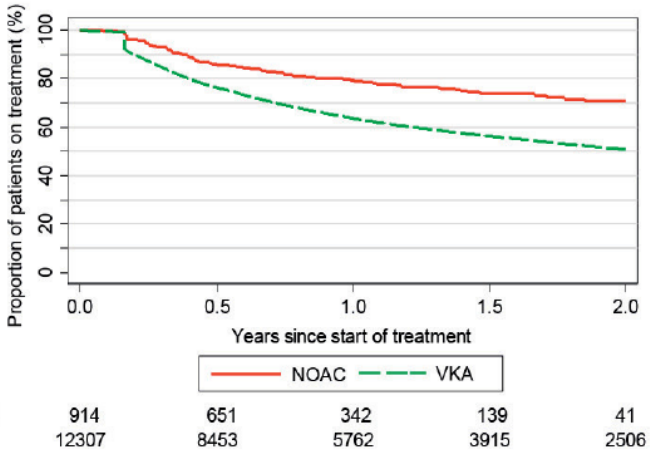
~30% of NOAC patients stop taking any drug at 2 years



NOAC	914	651	342	139	41
VKA	12307	8453	5762	3915	2506

Martinez C, et al. *Thromb Haemost.* 2015 Dec 22;115(1):31-9.

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Challenge: Adherence and Major bleed rates with Novel Oral Anticoagulants (NOACs)

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

Treatment	Study Drug Discontinuation Rate	Major Bleeding (rate/year)
Rivaroxaban[1]	24%	3.6%
Apixaban[2]	25%	2.1%
Dabigatran[3] (150 mg)	21%	3.3%
Edoxaban[4] (60 mg / 30 mg)	33 % / 34%	2.8% / 1.6%
Warfarin[1-4]	17 – 28%	3.1 – 3.6%

For those that remain adherent, there is an annual compounding bleeding risk

1Connolly, S. NEJM 2009; 361:1139-1151 – 2 yrs follow-up (Corrected) 2Patel, M. NEJM 2011; 365:883-891 – 1.9 yrs follow-up, ITT 3Granger, C NEJM 2011; 365:981-992 – 1.8 yrs follow-up, 4Giugliano, R. NEJM 2013; 369(22): 2093-2104 – 2.8 yrs follow-up.

Results from different clinical investigations are not directly comparable. Information provided for educational purposes only

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Non-Valvular Atrial Fibrillation (NVAF), Stroke, and Current Treatment Options

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

- AF is a Growing Problem Associated with Greater Morbidity and Mortality
  - 5x increased risk of stroke
  - 90% of clots formed in LA come from LAA
- Current treatments with warfarin or NOACS are effective, but many patients stop taking the medications
  - ~1 in 4 patients discontinue blood thinners after 2 years
- Anti-coagulation bleeding risk compounds over time; may not be viable as a long-term solution for some patients

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Connection Between NVAF-Related Stroke and the Left Atrial Appendage

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

AF Creates Environment for Thrombus Formation in Left Atrium

- Stasis-related LA thrombus is a predictor of TIA[1] and ischemic stroke[2].
- In non-valvular AF, >90% of stroke-causing clots that come from the left atrium are formed in the LAA[3].

1. Stoddard et al. Am Heart J. (2003); 2. Goldman et al. *J Am Soc Echocardiogr* (1999)
3 Blackshear JL. Odell JA., *Annals of Thoracic Surg* (1996)

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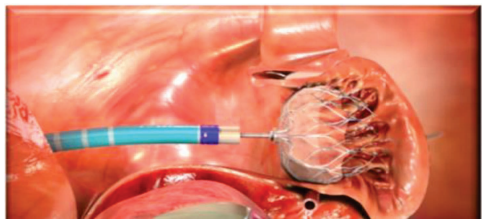
WATCHMAN LAAC Device: A One-Time Procedure

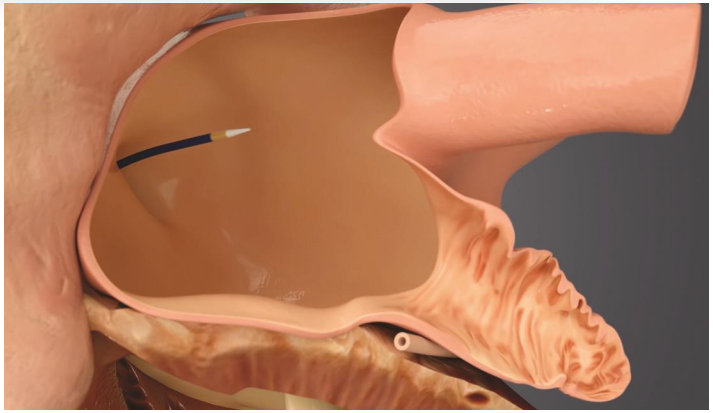
Boston Scientific

- One-time implant that does not need to be replaced
- Performed in a cardiac cath lab/EP suite by a Heart Team
- Transfemoral Access:
  - Catheter advanced to the LAA via the femoral vein
  - Does not require open heart surgery
- General anesthesia (typical)
- 1 hour procedure (typical)
- 1-2 day hospital stay (typical)



WATCHMAN Implant Procedure: Imaging and Transseptal Access

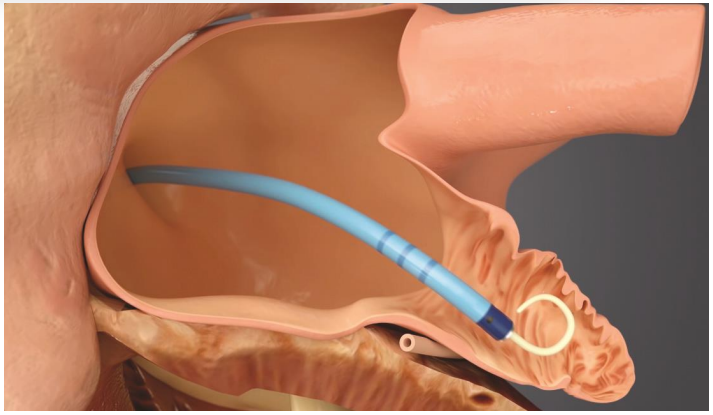
WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE



The interatrial septum is crossed using a standard transseptal access system and the procedure is performed with fluoroscopy and transesophageal echocardiography (TEE)

WATCHMAN Implant Procedure: Navigating to the LAA

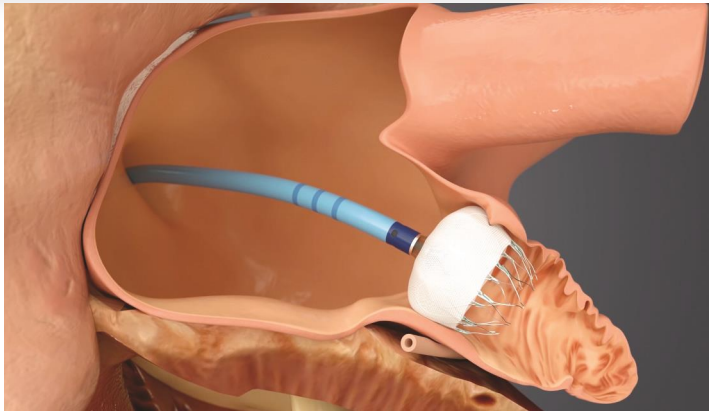
WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE



Access sheath is advanced over the guidewire into the left atrium and then navigated into the distal portion of the LAA over a pigtail catheter.

WATCHMAN Implant Procedure: Navigating to the LAA

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE



WATCHMAN is then deployed and released in the LAA.

WATCHMAN Implant Procedure: Healing after ~45 days

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

Heart tissue grows over the WATCHMAN Implant, and the LAA is permanently sealed after approximately 45 days

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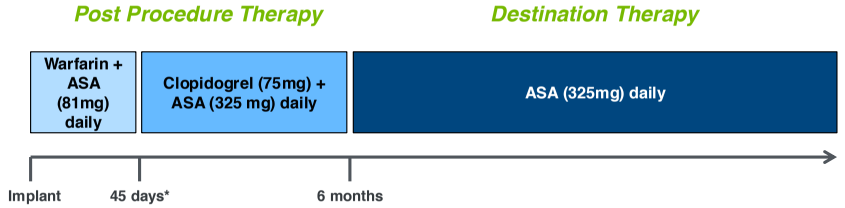
Timeline of Adjunctive Pharmacotherapy in WATCHMAN Device Patients

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE



*if leak >5mm, patients remained on warfarin + ASA until seal documented, skipping the clopidogrel + ASA pharmacotherapy

Price, M. J., V. Y. Reddy, et al. JACC: CV Interv 2015; 8(15): 1925-1932

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WATCHMAN is the most studied LAAC Device- Most Patients and Only One with Long-term Clinical Data

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

Key Trials	N	Highlights
PROTECT AF[1] (2005-2008)	707	Prospective, randomized 2:1, non-inferiority trial of LAA closure vs. warfarin.
CAP[2] (2008-2010)	566	Prospective registry allowing continued access to the WATCHMAN Device and gain further information prior to PMA approval.
PREVAIL[3] (2010-2012)	407	Prospective, randomized 2:1, non-inferiority trial to collect additional information on the WATCHMAN Device.
CAP2 (2012-2014)	579	Prospective registry allowing continued access to the WATCHMAN Device prior to PMA approval.
Total patients	>2,000	~6,000 Patient-Years of Follow-up

1 Reddy, et al. JAMA. 2014 ;312(19): 1988-1998.; 2 Reddy VY et al. Circulation. 2011; 123:417-424.
3 Holmes et al., JACC 2014,;4(1): 1-11.

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PROTECT AF:
WATCHMAN Disabling Stroke Reduction Superior to Warfarin

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

Significant Reduction in Disabling Strokes

	Event Rate (per 100 pt-yrs)			Posterior Probabilities, %	
PROTECT AF	**WATCHMAN** N=463	**Warfarin** N=244	**Rate Ratio (95% CrI)**	**Non-Inferiority**	**Superiority**
Stroke (all)	**1.5**	**2.2**	**0.68** (0.42, 1.37)	**>99**	**83**
Disabling	**0.5**	**1.2**	**0.37** (0.15, 1.00)	**>99**	**98**
Non-disabling	**1.0**	**1.0**	**1.05** (0.54, 2.80)	**89**	**34**

Disabling stroke defined as Modified Rankin Score 3-6

Bayesian – Posterior prob for NI must be ≥97.5%; Posterior Prob for Superiority must be >95%
Reddy, et al. JAMA. 2014

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WATCHMAN Major Bleeding Reduction Superior to Warfarin 6-months Post Procedure

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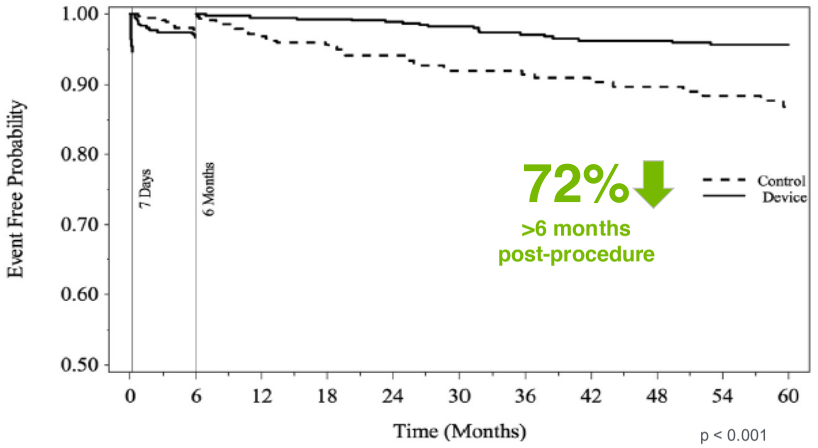
Freedom of Major Bleeding Over 3 Adjunctive Pharmacotherapy Intervals



Price, M. J., V. Y. Reddy, et al. JACC: CV Interv 2015; 8(15): 1925-1932

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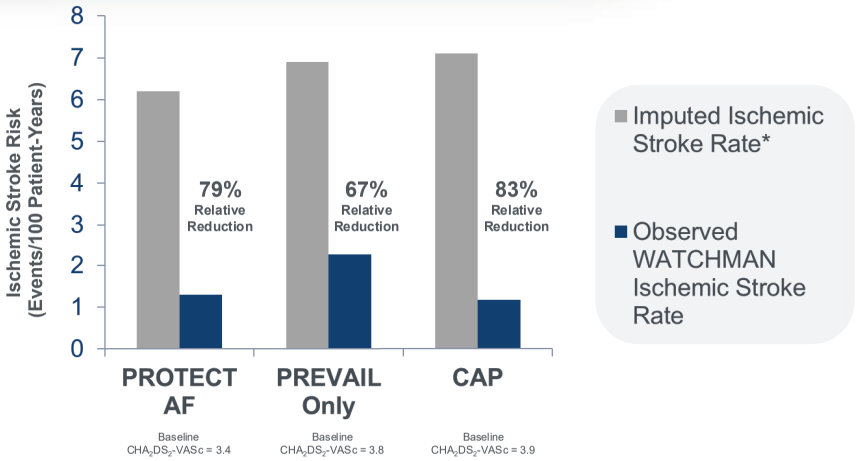
WATCHMAN Reduced Ischemic Stroke Compared to No Therapy

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE



* Imputation based on published rate with adjustment for CHA_2DS_2-VASc score (3.0); Olesen JB. Thromb Haemost (2011)

FDA Oct 2014 Panel Sponsor Presentation. Hanzel G, et al. TCT 2014 (abstract)

Results from different clinical investigations are not directly comparable. Information provided for educational purposes only

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WATCHMAN is the most studied LAAC Device with Long-term Clinical Data

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

	Results	
Safety	WATCHMAN procedure is **safe**	95% implant success; ~4% complication rates[1]
Primary Efficacy	WATCHMAN **comparable** to warfarin	21% reduction in events (p=0.22)[3]
All-Stroke	WATCHMAN **comparable** to warfarin	67% reduction in disabling strokes (P_s=98%)[2]; 78% reduction in hemorrhagic strokes (p=0.004)[3]
CV / Unexp death	WATCHMAN **superior** to warfarin	52% reduction in events (p=0.006)[3]
Major Bleeding	WATCHMAN **comparable** to warfarin; **superior** to warfarin **post-procedure**	52% reduction post-procedure (p=0.002); 72% reduction after 6-months (p=0.001)[4]
Warfarin	WATCHMAN allows the **majority** of patients to **discontinue warfarin**	92% of patients discontinue after 45-days; 99% of patients discontinue after 1 year[5]

1. WATCHMAN FDA Panel Sponsor Presentation. Oct 2014.; 2 Reddy, et al. JAMA. 2014 ;312(19): 1988-1998.
3 Holmes, DR et al. JACC. 2015;65(24):2614-2623.; 4 Price, M. J., V. Y. Reddy, et al. JACC: CV Interv 2015; 8(15): 1925-1932; 5.Holmes, DR et al. JACC 2014; 64(1): 1-12.

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Patient Populations

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

Non-Valvular A-Fib Population

High Risk for Stroke (CHA_2DS_2-VASC ≥ 2)

Balance stroke risk reduction benefit vs. bleeding risk

Tolerant to OAC

Patients w/ appropriate rationale to seek a non-pharmacologic alternative to warfarin
- History of bleeding
- Fall risks / previous trauma
- Non-compliant / Labile INR's
- Lifestyle

Contraindicated

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WATCHMAN™ Device Patient Selection

The WATCHMAN
thromboembolism
with non-valvular
– Are at increas
on $CHADS_2$ o
for anticoagul
– Are deemed
and
– Have an app
alternative to
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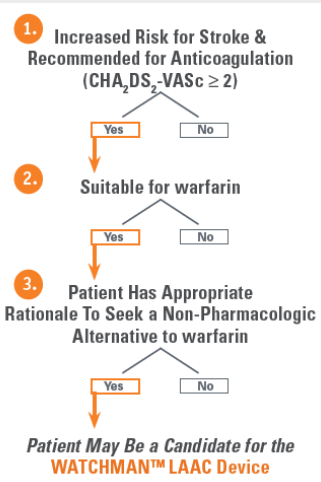

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* Please refer to product DFU for more specific details on patient selection

WATCHMAN™ Device Patient Selection

"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"

- History of major bleeding while taking anticoagulation therapy
- Patient's prior experience with OAC (if applicable):
  - *inability to maintain stable INR*
  - *inability to comply with regular INR monitoring and unavailability of an approved alternative OAC*
- Medical condition, occupation, or lifestyle placing patient at high risk of major bleeding secondary to trauma

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* Please refer to product DFU for more specific details on patient selection

CMS National Coverage Decision Criteria for Coverage

CMS will cover percutaneous LAAC implants when specific criteria are met:

Documented in medical record

- Eligible patients must have a $CHADS_2$ score ≥ 2 or a **CHA_2DS_2-VASc score ≥ 3**
- Patients must be **suitable for short-term warfarin**, but deemed **unable to take long-term oral anticoagulation**
- **Documented evidence of a formal shared decision interaction between the patient and an independent non-interventional physician** using an OAC evidence-based decision tool

- *LAA Registry*: Patients must be enrolled in a prospective national registry
- *Operator requirements:* IC or EP or cardiovascular surgeon must have performed at least 25 transseptal punctures (TSP) through intact septum
  - Must maintain at least 25 TSP over a two year period (at least 12 are LAAC)
- *Facility Requirements*: The procedure must be furnished in a hospital with an established structural heart disease (SHD) and/or electrophysiology (EP) program

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Patient Example #1: High Bleeding Risk

- Age: 80; Involved Grandfather; NVAF, Congestive Heart Failure, Hypertension, Diabetes
- CHA_2DS_2-VASc score: 5; HAS-BLED score: 2
- Although patient is suitable for warfarin, he is currently taking 15 mg rivaroxaban daily
- Has a history of recurrent falls, resulting in both a broken hip and cerebral contusion after falling on separate occasions. His physician believes his medical condition places him at high risk of major bleeding secondary to trauma

Is he a candidate for WATCHMAN?

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Case description for educational purposes; Not a real patient case

Patient Example #2: Struggle with Compliance

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

- Age: 68; Retired, Volunteer; NVAF, Hypertension, Vascular Disease
- CHA_2DS_2-VASc score: 4; HAS-BLED score: 3
- Currently taking 5 mg warfarin
- Unable to comply with regular INR monitoring due to her proximity to the clinic and cannot afford novel oral anticoagulant (NOAC) medication

Is she a candidate for WATCHMAN?

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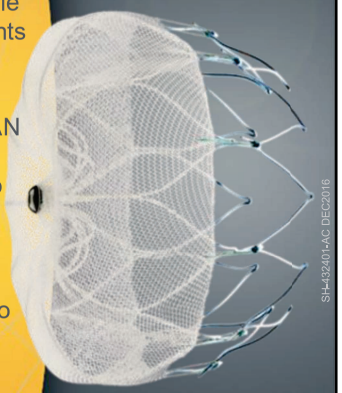
Case description for educational purposes; Not a real patient case

WATCHMAN Is A Safe, Effective, One-time Procedure For Appropriate NVAF Patients

Boston Scientific

- The WATCHMAN Implant has been proven to be a safe and effective alternative to long-term oral anticoagulants (OACs)[1]
- Left atrial appendage closure (LAAC) with WATCHMAN may eliminate the need for long-term warfarin use in patients with non-valvular atrial fibrillation (NVAF) who have a reason to seek an alternative to OACs
- The WATCHMAN Implant has been proven to offer stroke risk reduction comparable to warfarin—and also reduces the long-term risk of bleeding associated with warfarin use.[2]



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1. Holmes DR. *JACC* 2014;64(1):1-12. 2. Holmes DR. *JACC* 2015;65(24):2614-2623.

Thank You!!

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