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WATCHMAN™

Left Atrial Appendage Closure Device

Clinical Study Highlights

WATCHMAN™ Clinical – Portfolio Summary

Pilot	Early feasibility with >6 years of follow-up	N=66
PROTECT-AF	Primary efficacy, CV death, and all-cause mortality superior to warfarin at 4 years[1]	N=707
CAP Registry	Significantly improved safety results[2]	N=566
ASAP	Expected rate of stroke reduced by 77% in patients contraindicated to warfarin[3,4]	N=150
PREVAIL	Improved implant success procedure safety confirmed with new and experienced operators[5]	N=407
CAP2	579 patients enrolled in 48 sites	N=579
Meta-Analysis	Evaluation and analysis of the totality of WATCHMAN trial data[6]	N=1,877
EWOLUTION	Compilation of real-world clinical outcomes data for WATCHMAN[7,8]	N=1,025

1 Reddy, VY et al. JAMA. 2014; 312(19):1988-1998
2 Reddy, VY et al. Circulation. 2011;123:417-424;
3 Reddy, VY et al. JACC.2013 Jun 25;61(25):2551-6.
4 Sharma D et al. JACC 2016 May 10;67(18):2190-2192.
5 Holmes DR et al. JACC 2014; Jul 8;64(1):1-12
6 Reddy, VY et al. JACC 2017 Dec 19;70(24):2964-2975
7 Boersma LVA et al., Eur Heart J. 2016;37(31):2465-74.
8 Boersma LVA et al., Heart Rhythm. 2017 Sep;14(9):1302-1308.

WATCHMAN™ - Most Studied LAAC Device
Only one proven with long-term data from randomized trials and multi-center registries

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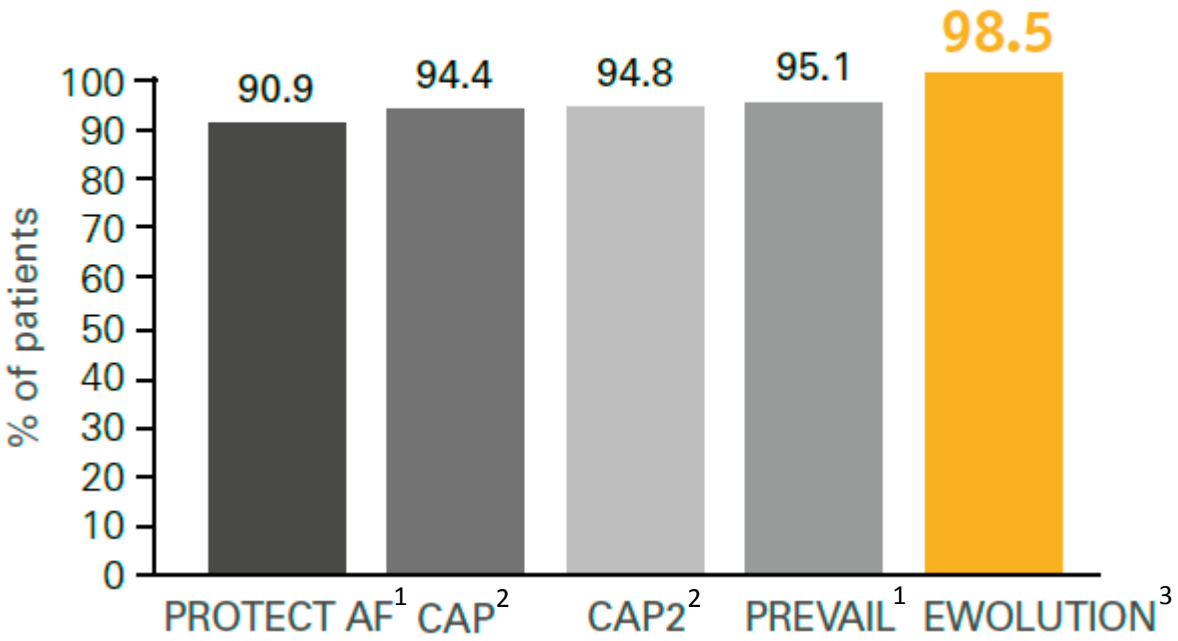
	PROTECT AF[1]	CAP Registry[1]	PREVAIL[1]	CAP2 Registry[1]	EWOLUTION[2]
Enrollment	2005-2008	2008-2010	2010-2012	2012-2014	2013-2015
Purpose	Demonstrate safety and effectiveness of the WATCHMAN implant compared to long-term warfarin	Continued Access Registry	Demonstrate safety and effectiveness of the WATCHMAN implant compared to long-term warfarin	Continued Access Registry	Collect peri-procedural safety data and long-term outcomes data for patients implanted with WATCHMAN™ in a real world clinical setting
Study Design	2:1 Randomized, non-inferiority	Non-randomized	2:1 Randomized, non-inferiority	Non-randomized	Prospective, single-arm, multi-center, real-life registry
Primary Endpoints	1. Effectiveness: Stroke, systemic embolism and cardiovascular/unexplained death 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 7 days post-randomization or WATCHMAN implant procedure 3. Safety: Death, ischemic stroke, systemic embolism and procedure/device-related complications within 7 days of implantation procedure		Primary analysis includes procedural complications, incidence of stroke, bleeding, and death

1: FDA Oct 2014 Panel Sponsor Presentation.
2: Boersma L.V.A. et al., Catheter Cardiovasc Interv. 2016 Sep;88(3):460-5.

PROCEDURAL SUCCESS AND SAFETY

Implant success results



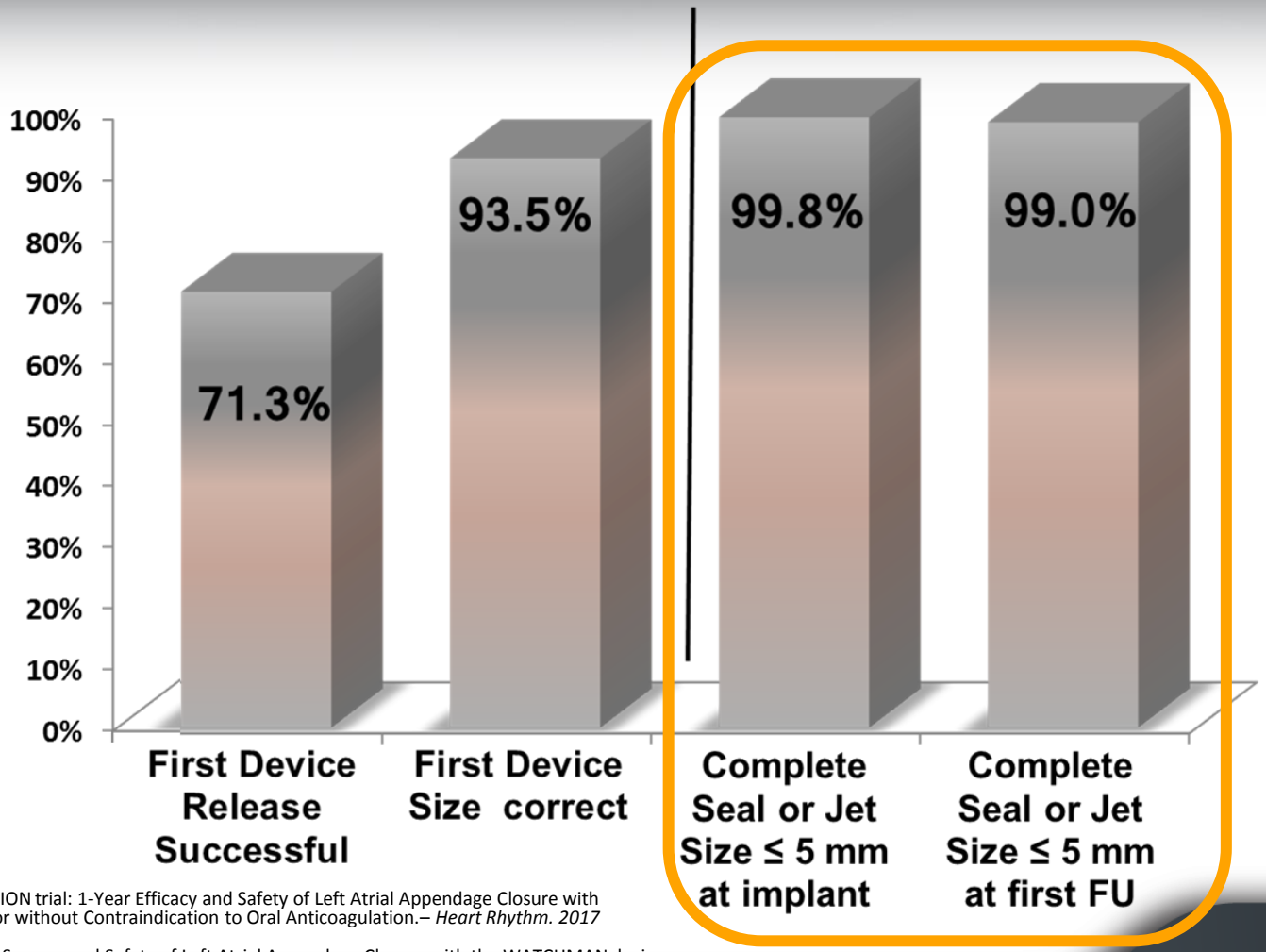
98.5%

Highest implant success rate of all WATCHMAN trials [1-3]

Implant success in EWOLUTION when compared to prior WATCHMAN studies

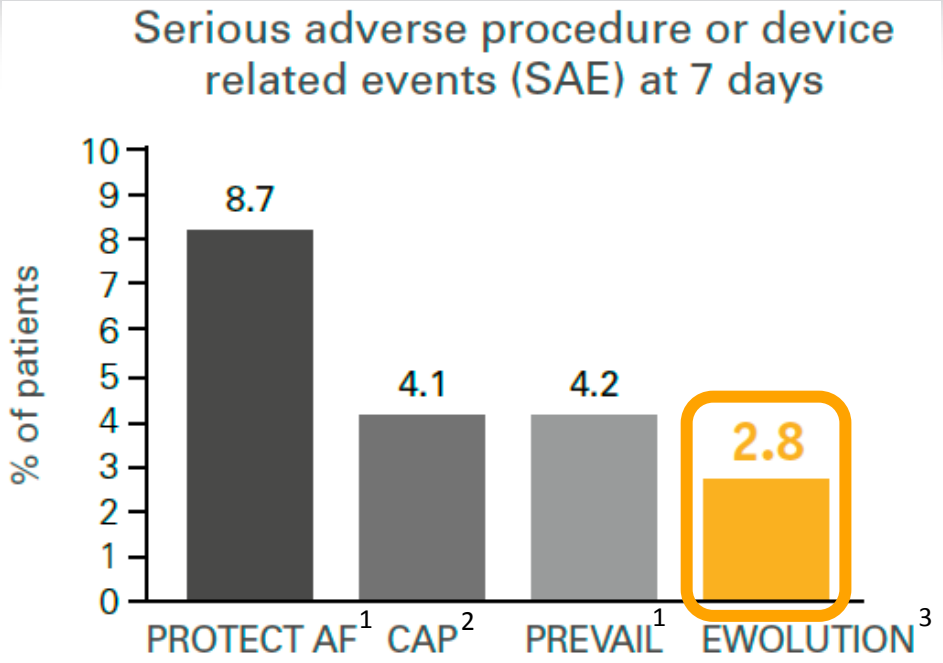
1. PREVAIL, Holmes, DR et al. JACC 2014;Vol.64, No.1
2. (2014). Circulatory System Devices Panel: WATCHMAN® Left Atrial Appendage Closure Therapy Sponsor Presentation. 2014 FDA Circulatory System Devices Panel.
3. EWOLUTION, Boersma L.V.A et al. Eur Heart J. 2016 Aug;37(31):2465-74

Procedural results & Seal[1,2]



1: Boersma LV. Et al., EWOLUTION trial: 1-Year Efficacy and Safety of Left Atrial Appendage Closure with WATCHMAN in Patients with or without Contraindication to Oral Anticoagulation.– *Heart Rhythm. 2017 Sep;14(9):1302-1308*
2: Boersma LVA et al., Implant Success and Safety of Left Atrial Appendage Closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION Registry. Eur Heart J. 2016;37(31):2465-74.

Favorable Procedural Safety Profile



2.8%

Lowest peri-procedural risk of all WATCHMAN trials [1-3]

SAE: Serious Adverse Event - Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications[1]

[1]Includes observed PE not necessitating intervention, AV fistula, major bleeding requiring transfusion, pseudoaneurysm, hematoma and groin bleeding

1. PREVAIL, Holmes, DR et al. JACC 2014;Vol.64, No.1
2. (2014). Circulatory System Devices Panel: WATCHMAN® Left Atrial Appendage Closure Therapy Sponsor Presentation. 2014 FDA Circulatory System Devices Panel.
3. EWOLUTION, Boersma L.V.A et al. Eur Heart J. 2016 Aug;37(31):2465-74

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EFFICACY

Stroke Risk Reduction

PREVAIL Endpoints: Final 5-Year Results

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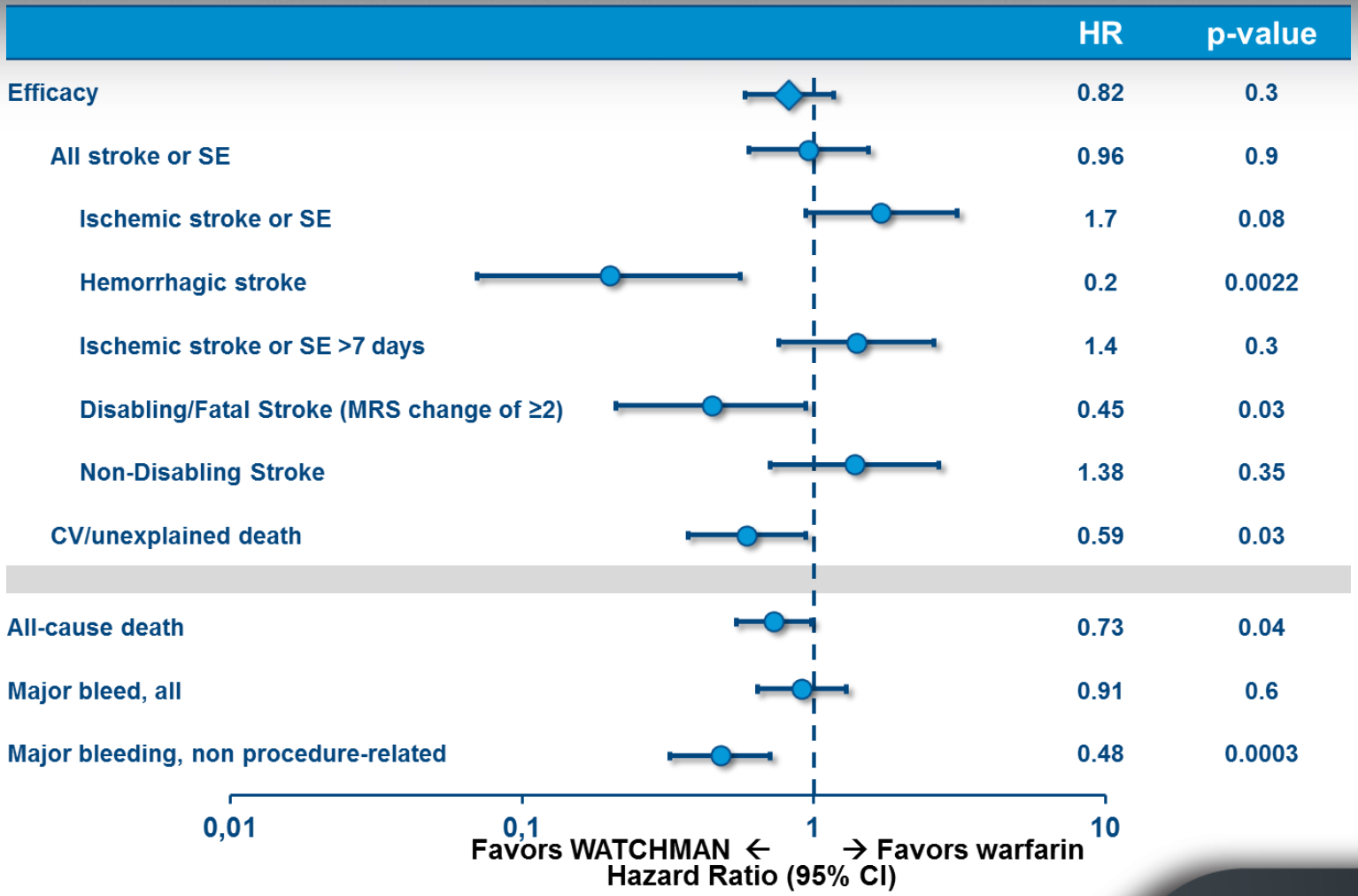
Endpoint	Definition	Final Result
Primary Safety	Acute (7-day) occurrence of death, ischemic stroke, systemic embolism and procedure or device related complications requiring major cardiovascular or endovascular intervention	✓
Primary Efficacy Composite	Comparison of composite of stroke, systemic embolism, and CV/unexplained death	✗
Primary Efficacy Ischemic Stroke/SE	Comparison of ischemic stroke or SE occurring >7 days post randomization	✓

All PREVAIL analyses were pre-specified to use an informative prior that included a portion of PROTECT AF

Source: Reddy VY, et al. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. JACC 2017 Dec 19;70(24):2964-2975

Patient Level Meta-Analysis
PROTECT AF, PREVAIL 5 Years[1]



1: Reddy VY, 5-Year Outcomes After Left Atrial Appendage Closure From the PREVAIL and PROTECT AF Trials. JACC *2017 Dec 19;70(24):2964-2975*

Patient Level Meta-Analysis - PROTECT AF, PREVAIL 5 Years[1]

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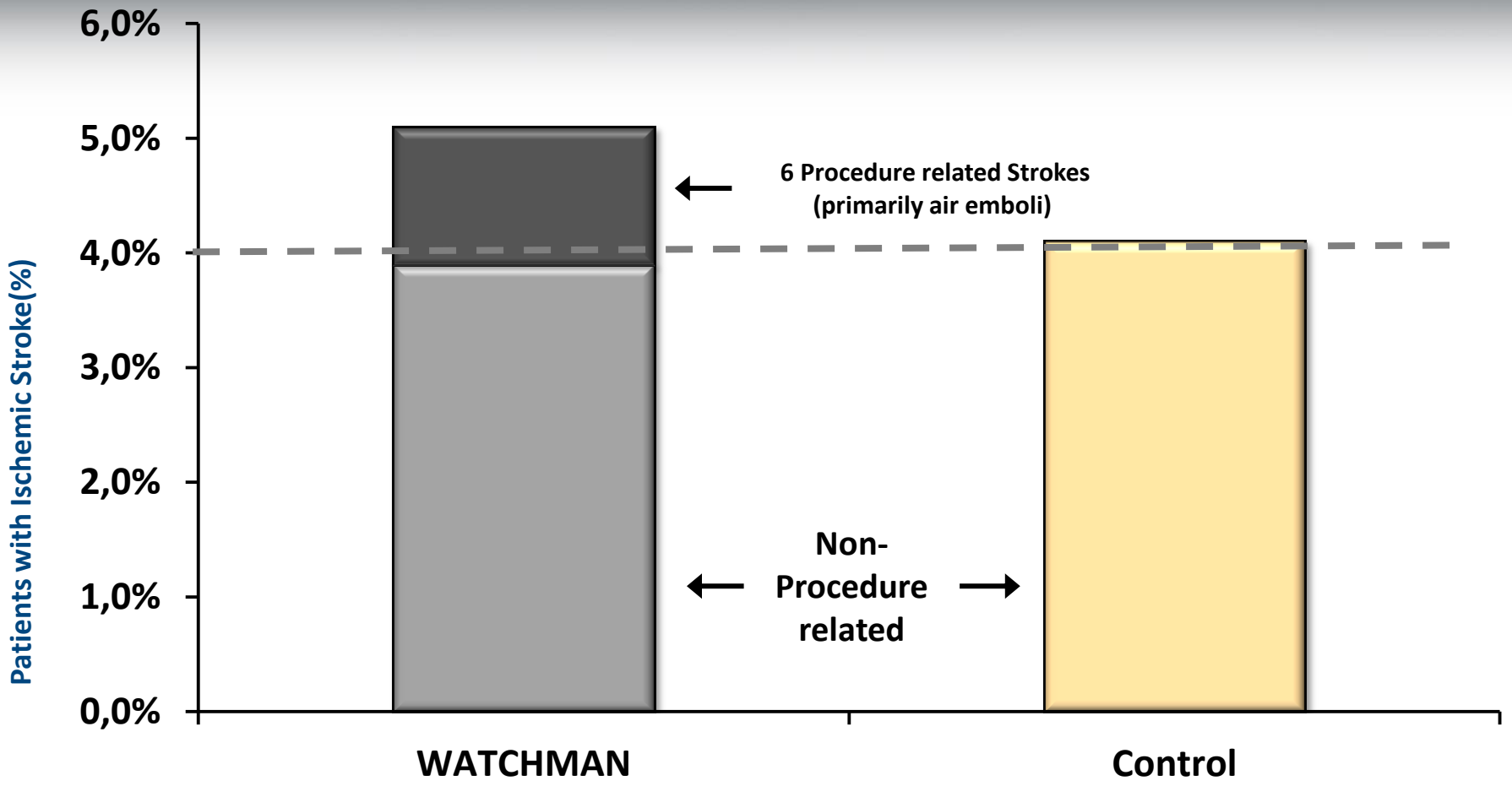
Key Outcomes:

At 5 years, WATCHMAN showed:

- **Comparable stroke risk reduction to warfarin**
- **Statistically significant reductions vs. warfarin**

1: Reddy VY, 5-Year Outcomes After Left Atrial Appendage Closure From the PREVAIL and PROTECT AF Trials. JACC *2017 Dec 19;70(24):2964-2975*

PROTECT AF Ischemic Strokes: Same Rate Once Accounting For Procedure-related Strokes



Reddy, V. et al. *Circulation* 123(4): 417-424.

Warfarin Ischemic Stroke Rate in PREVAIL Differs from Other Trials

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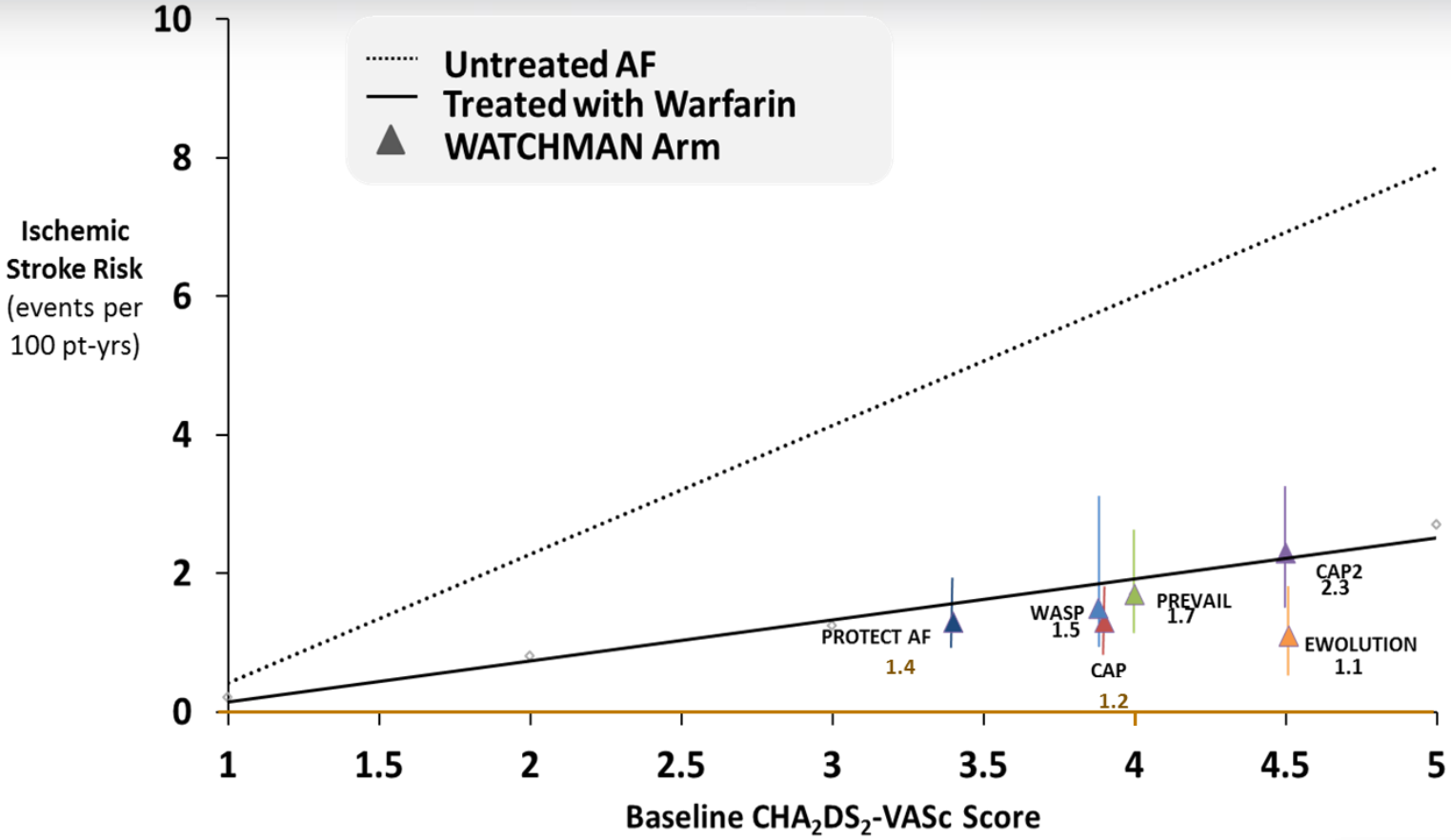
Trial (Warfarin Arm)	Ischemic Stroke Rate per 100 pt-yrs	Mean $CHADS_2$	Follow-Up (yrs)
PREVAIL[1]	0,7	2.6	5.0
PROTECT AF[1]	1,07	2.2	5.0
RE-LY[2]	1,2	2.1	2.0
ROCKET AF[2]	1,42	3.5	1.9
ARISTOTLE[2]	1,05	2.1	1.8
ENGAGE[3]	1,25	2.8	2.8

1. Reddy JACC (*2017 Dec 19;70(24):2964-2975*). 2. Miller. AJC (2012). 3. Giugliano. NEJM (2013)

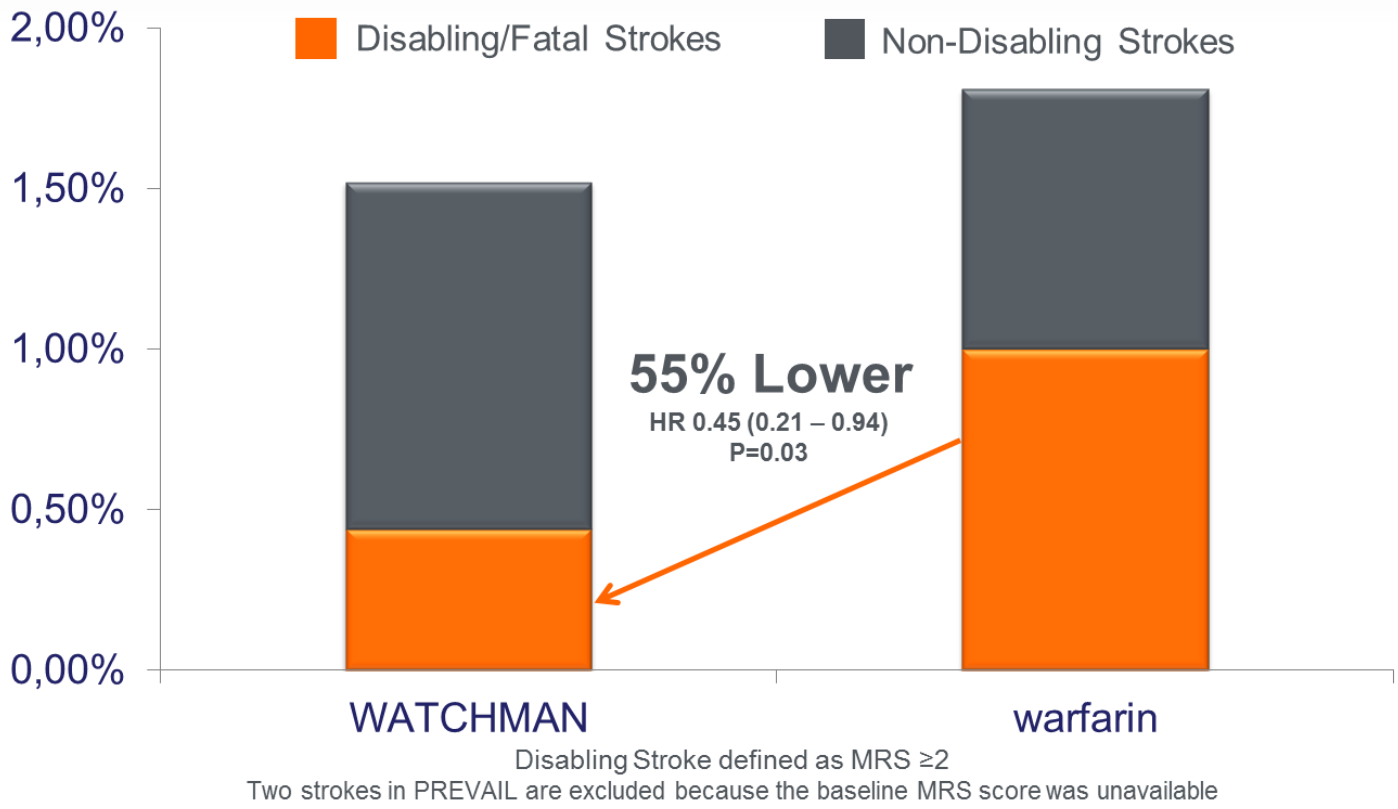
WATCHMAN Comparable to warfarin for Ischemic Stroke in 2 RCT, 4 Registries



1: Reddy VY, 5-Year Outcomes After Left Atrial Appendage Closure From the PREVAIL and PROTECT AF Trials. JACC *2017 Dec 19;70(24):2964-2975*

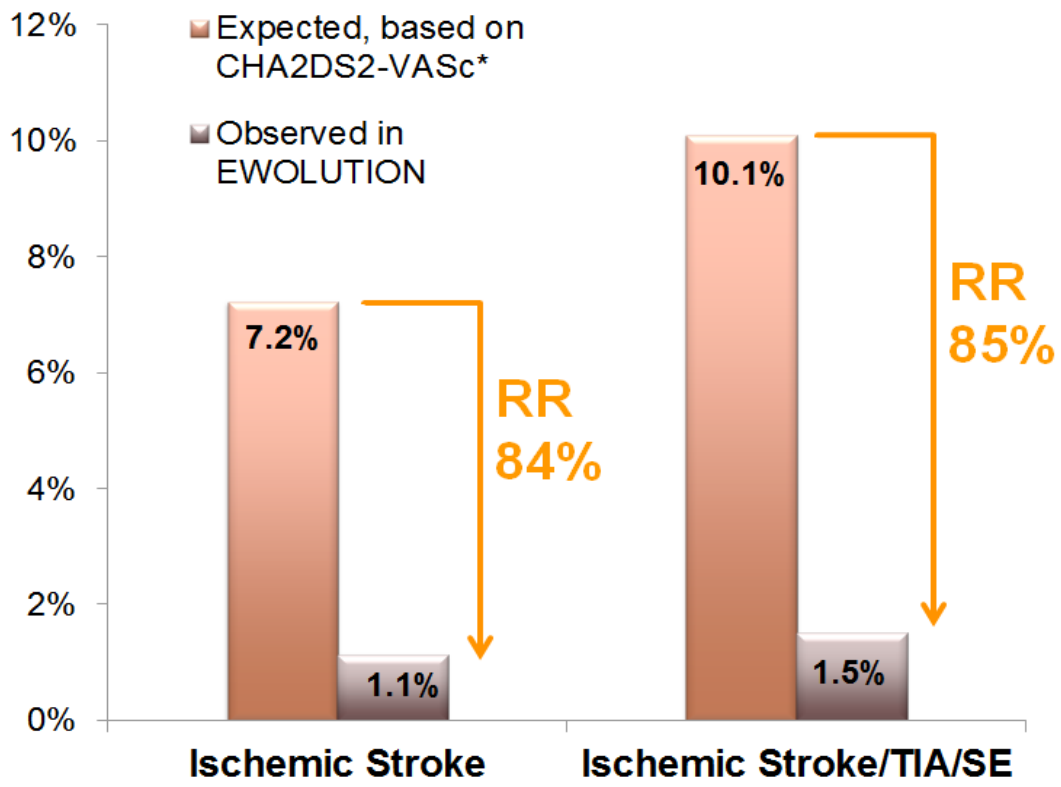
WATCHMAN Significant Reduction in Disabling Strokes

(Patient-Level Meta-Analysis)



1: Reddy VY, 5-Year Outcomes After Left Atrial Appendage Closure From the PREVAIL and PROTECT AF Trials. JACC *2017 Dec 19;70(24):2964-2975*

EWOLUTION
Effectiveness in ischemic stroke reduction – annual stroke rate[1]



84% reduction in ischemic strokes (annual stroke rate 1.1%) as compared to no therapy*.

*Effectiveness in stroke reduction vs. estimated in the absence of therapy for comparable CHA_2DS_2-VASc scores based on Friberg et al. EHJ 2012

1: Boersma LV. Et al., EWOLUTION trial: 1-Year Efficacy and Safety of Left Atrial Appendage Closure with WATCHMAN in Patients with or without Contraindication to Oral Anticoagulation.– *Heart Rhythm. 2017 Sep;14(9):1302-1308*

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EFFICACY

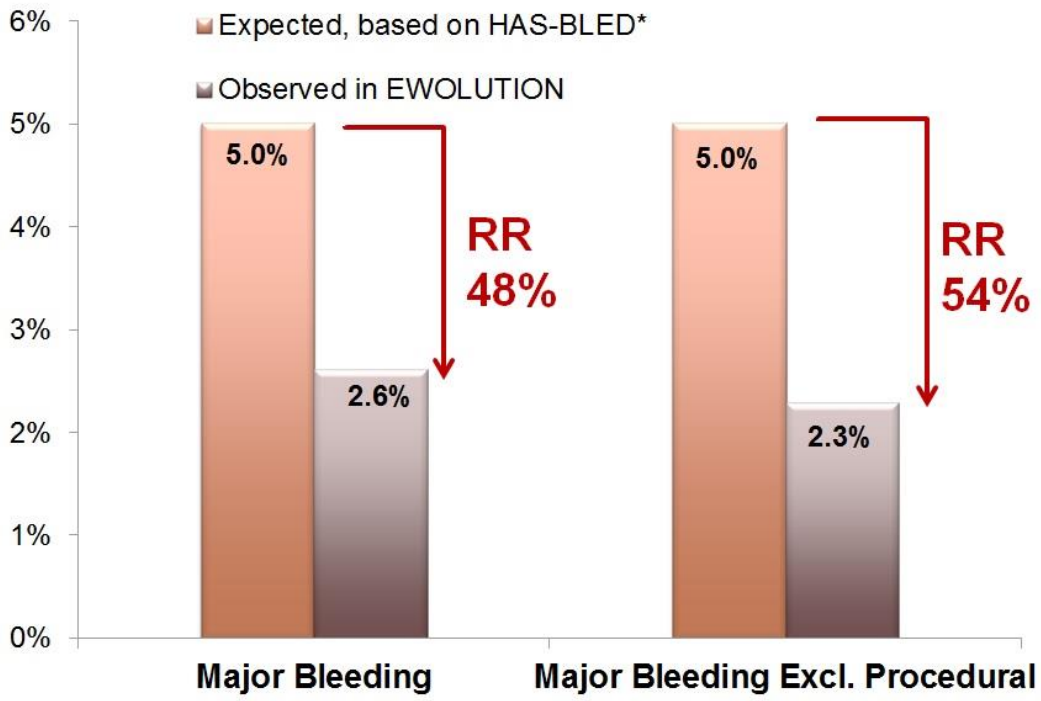
Bleeding Reduction

Bleeding Risks Compound Over Time

CHA_2DS_2-VASc* Score	Annual % Stroke Risk	HAS-BLED** Score	Annual % Bleed Risk	10-Year Bleeding Risk (%)***
0	0	0	0.9	8.6
1	1.3	1	3.4	29.2
2	2.2	2	4.1	34.2
3	3.2	3	5.8	45.0
4	4.0	4	8.9	60.6
5	6.7	5	9.1	61.5

* 2014 AHA / ACC / HRS Guidelines
** Lip. JACC (2011)
*** Assumes constant risk despite increasing age and bleeding risk is independent from bleeding risk in previous years

EWOLUTION
Effectiveness in bleeding reduction – Annual bleeding rate[1]



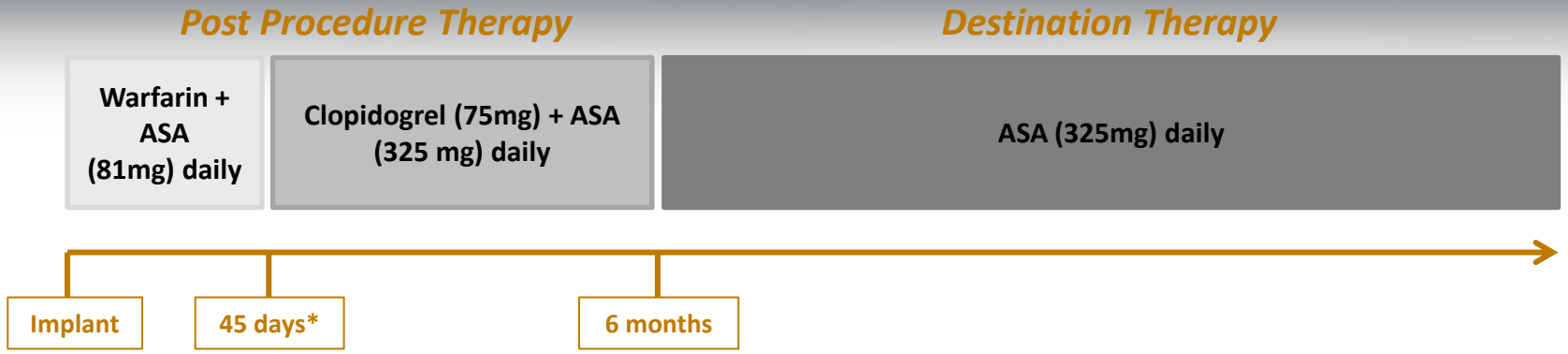
48% reduction in major bleeding events compared to warfarin.

54% reduction in major bleeding events if excluding periprocedural bleeding.

*Effectiveness in bleeding reduction vs. estimated under VKA therapy for comparable HAS-BLED scores based on Lip et al. JACC 2011

1: Boersma LV. Et al., EWOLUTION trial: 1-Year Efficacy and Safety of Left Atrial Appendage Closure with WATCHMAN in Patients with or without Contraindication to Oral Anticoagulation.– *Heart Rhythm. 2017 Sep;14(9):1302-1308*

72% Major Bleeding Reduction Long Term Post-6 months



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

	LAAC (n=732)		Long-term warfarin (n=382)		Rate Ratio	P value
	Bleeding Rate (n events / N at risk)	Event Rate per 100 pt-yrs (n events / N at risk)	Bleeding Rate (n events/N at risk)	Event Rate per 100 pt-yrs (n events / N at risk)		
Overall	10.8 (79/732)	3.5 (79/2268)	11.3 (43/382)	3.6 (43/1187)	0.96	0.84
Post Procedure	5.9 (40/682)	1.8 (40/2255)	11.3 (43/381)	3.6 (43/1180)	0.49	0.001
Destination	3.2 (19/601)	1.0 (19/1958	9.7 (35/360)	3.5 (35/1004)	0.28	<0.001

Overall period defined as after randomization to the end of follow-up; post-procedural period as >7 days after randomization to the end of follow-up; destination therapy period as beyond 180 days post-randomization, when patients assigned to LAA closure were eligible to receive aspirin alone.

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

Bleeding Outcomes after Left Atrial Appendage Closure Compared with Long-term Warfarin

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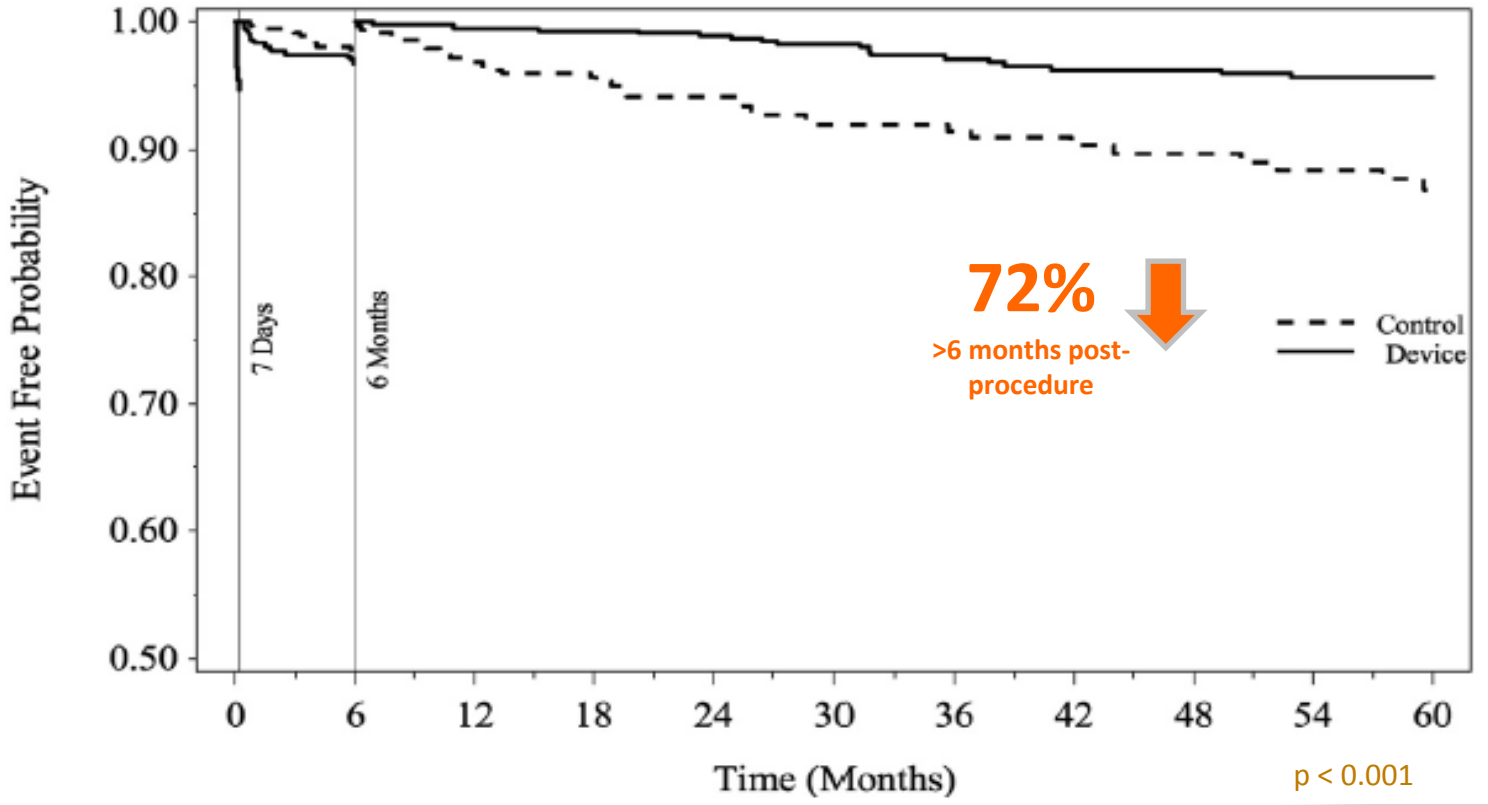
Freedom of Major Bleeding Over 3 Adjunctive Pharmacotherapy Intervals



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

Conclusion

- WATCHMAN LAAC is a proven and safe therapy
- WATCHMAN is the only LAAC device with 5-year efficacy data from 3 major studies
- WATCHMAN demonstrated **comparable stroke risk reduction** and **statistically significant reductions** in **disabling/fatal strokes**, **major non-procedure related bleeding** and **mortality** compared to warfarin[1]:
  - 55% reduction in disabling/fatal stroke
  - 52% reduction in major non-procedure related bleeding
  - 41% reduction in CV/unexplained mortality

1. Reddy VY et al. JACC *2017 Dec 19;70(24):2964-2975*