



Maurice Buchbinder, M.D.

Very Long Term Outcomes after LAAC

Maurice Buchbinder, MD, MDCM, FACC, FSCAI

Medical Director
Foundation for Cardiovascular Medicine
San Diego, California

Professor of Clinical Medicine
Stanford Hospital and Clinics
Stanford, California



Maurice Buchbinder, M.D.

DISCLOSURE STATEMENT OF FINANCIAL INTEREST

In the past 12 months, I or my spouse/partner has had a financial interest/arrangement with the organization(s) listed below.

BSCI

- Scientific Advisory Board Member
- Speaker Bureau
- Equity Ownership



Background

- PROTECT AF and PREVAIL remain the only RCTs comparing left atrial appendage closure (WATCHMAN) to OAC (warfarin) with up to 5 years follow up
- PROTECT-AF demonstrated similar stroke reduction to warfarin (at a mean of 3.8 years follow up)
 - *JAMA* 312:1988-98 (2014)
- PREVAIL produced inconclusive findings due to a warfarin cohort with an implausibly low ischemic stroke rate, relatively few patients and relatively short follow up (~10 months)
 - *JACC* 64:1-12 (2014)
- Both protocols specified 5 years of follow-up for all patients
 - 5 year follow up completed in 2013 (final)
 - 5 year follow up completed in 2017 (final)



Objectives

The objective of this presentation is to report the final 5 year results of the totality of data available for PREVAIL alone and as part of a patient-level meta-analysis including PROTECT-AF final 5 year data (as per the pre-specified analysis plan)



PROTECT AF

Superiority of Watchman over Warfarin

- RCT: Can the WATCHMAN device *replace* Warfarin

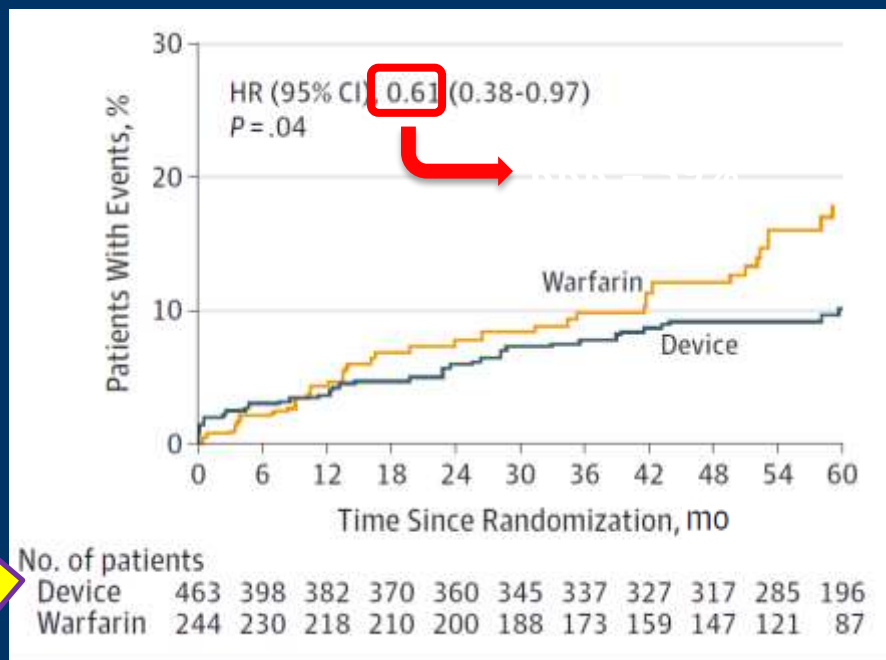
Non-Valvular AF
CHADS₂ ≥ 2

Randomization (1:2)

Anticoagulation Regimen

- Implant to 6 weeks
 - Warfarin
 - Aspirin
- 6 weeks to 6 months
 - Clopidogrel
 - Aspirin
- After 6 months
 - Aspirin

Primary Endpoint
[Stroke / SE / CV Death]

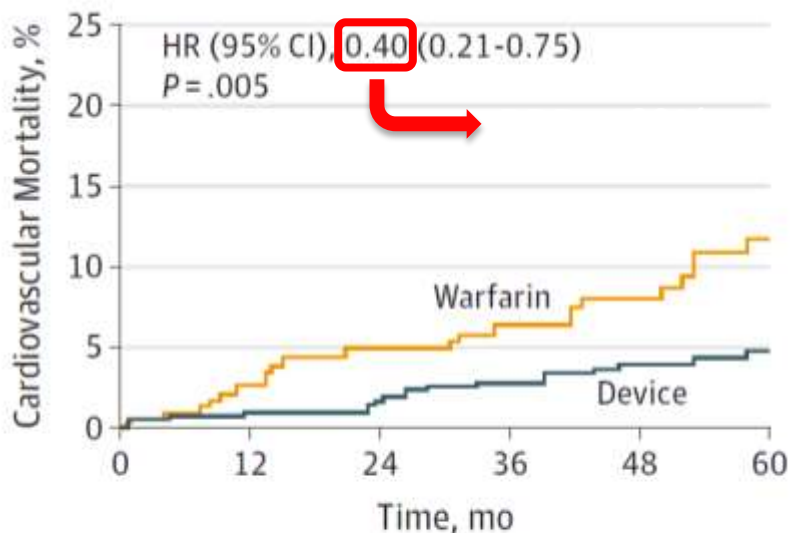


Hemorrhagic Stroke: 85%↓↓



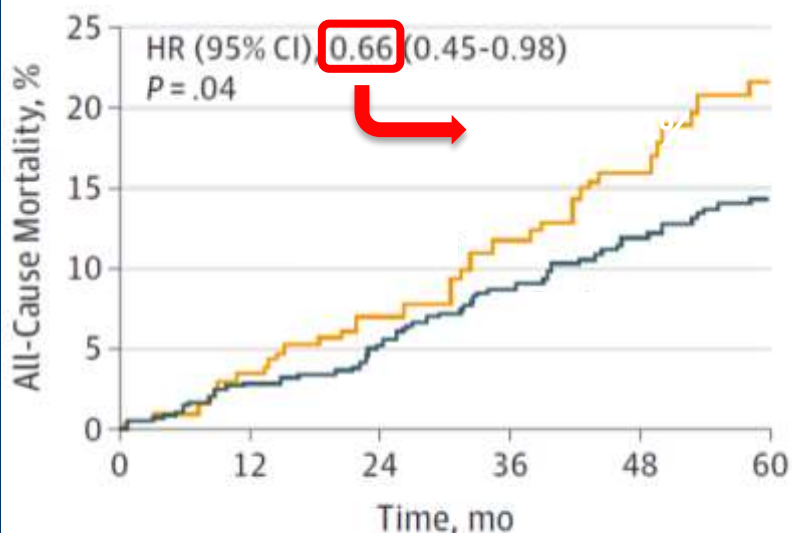
Mortality Benefit with Watchman

CV Death



463	389	372	351	328	165
244	222	204	176	147	69

All-Cause Mortality



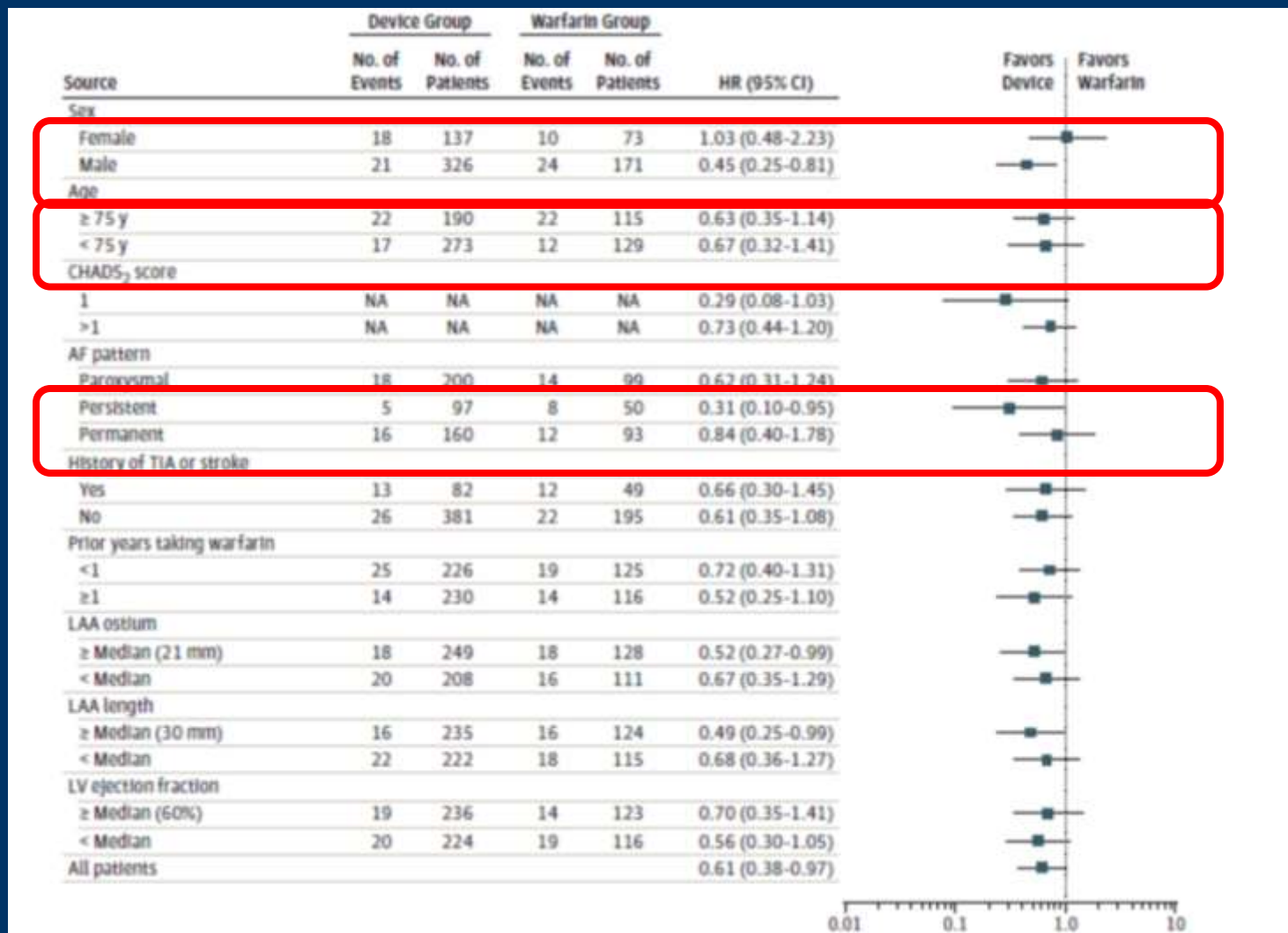
463	389	373	352	330	202
244	222	204	177	150	92



Maurice Buchbinder, M.D.

PROTECT AF: Watchman vs Warfarin

Benefit by Sub-Groups



V.Reddy, H.Sievert, J.Halperin et al, *JAMA*, 312:1988 (2014)



Methods

PREVAIL

PREVAIL efficacy endpoints were never designed to be analyzed without the informative prior from PROTECT AF.

- **1st Primary efficacy:** Comparison of rate ratios of 18-month event rates for composite of stroke, SE, and CV/Unexplained death; Upper CrI 1.75 for NI

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



Maurice Buchbinder, M.D.

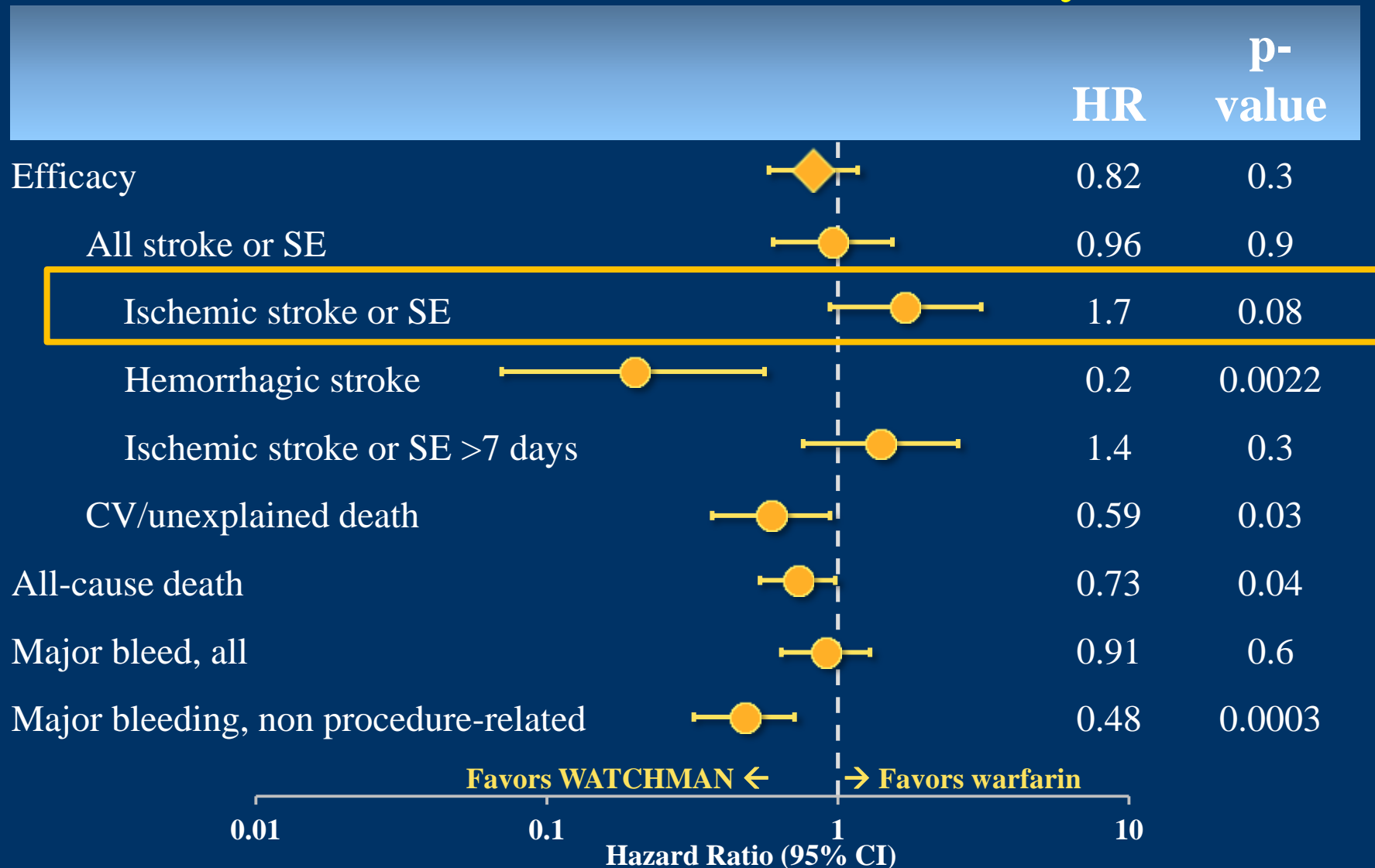
Demographics: Combined Cohort Endpoint for Patient-Level Meta Analysis

Characteristic	Device N=732	Control N=382	p-value
Age, years	72.6±8.4	73.5±8.6	0.09
Sex, male	69.4	71.7	0.42
CHADS ₂ Score	2.3±1.1	2.4±1.2	0.06
CHA ₂ DS ₂ -Vasc Score	3.6 ± 1.4	3.9 ± 1.5	0.02
Risk Factors			
CHF	25.5	25.7	0.97
Hypertension	89.2	92.7	0.06
Age ≥ 75 years	40.4	43.2	0.38
Diabetes	27.9	29.6	0.55
Prior Stroke/TIA	22.1	23.6	0.59
AF Pattern			
Paroxysmal	45.2	44.5	0.82
Persistent	24.9	23.3	0.56
Permanent	27.6	30.1	0.38
Unknown	1.4	0.8	0.56
Paced	1.0	1.3	0.56



Maurice Buchbinder, M.D.

Patient-Level Meta-Analysis PROTECT AF and PREVAIL 5 years





Results

PROTECT AF and PREVAIL Event Rates

PROTECT-AF Subjects						PREVAIL Subjects				
	Device (n=463)		Control (n=244)		p-value	Device (n=269)		Control (n=138)		p-value
	No. of Events	Rate *	No. of Events	Rate *		No. of Events	Rate *	No. of Events	Rate *	
2:1 Randomization										
Primary Efficacy: Stroke/SE/CV Death	40 / 1787.7	2.24	34 / 929.4	3.66	0.04	37 / 1038.3	3.65	15 / 530.4	2.94	0.47
All Stroke	26 / 1781.7	1.46	20 / 929.4	2.15	0.23	19 / 1042.4	1.97	7 / 530.4	1.29	0.32
Ischemic Stroke	24 / 1781.7	1.35	10 / 932.8	1.07	0.49	17 / 1043.1	1.68	4 / 533.3	0.73	0.13
Hemorrhagic Stroke	3 / 1837.7	0.16	10 / 945.6	1.06	0.005	2 / 1084.6	0.18	3 / 538.0	0.54	0.23
Systemic Embolism	3 / 1837.1	0.16	0	n/a	n/a	1 / 1080.6	0.09	0 / 540.9	n/a	n/a
CV/Unexplained Death	19 / 1843.2	1.03	22 / 948.9	2.32	0.009	18 / 1084.7	1.79	10 / 540.9	1.98	0.76

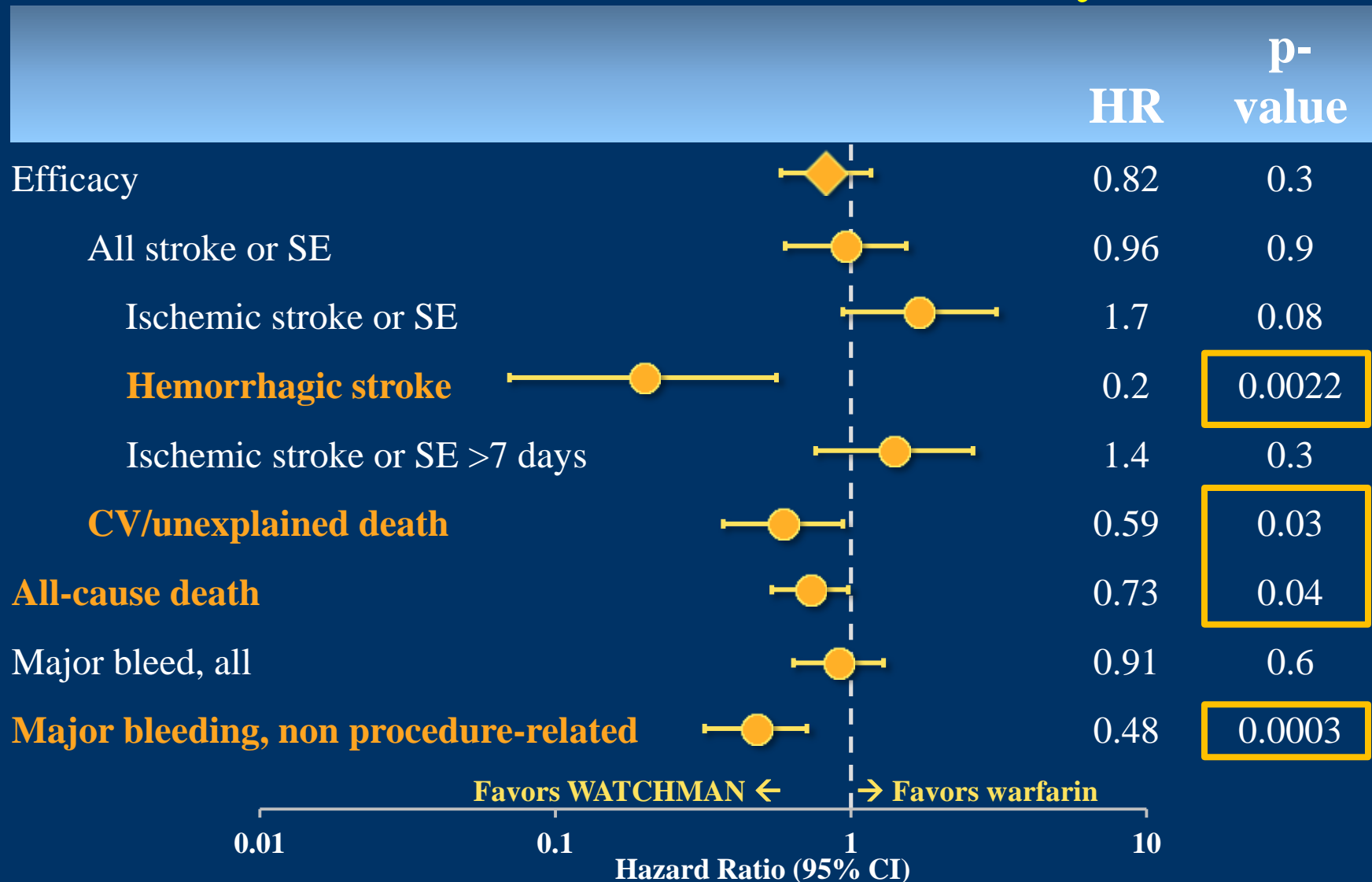
* Events are per 100 patient-years

2:1 randomization
Control Group continues to overperform
Rate = 0.7%



Maurice Buchbinder, M.D.

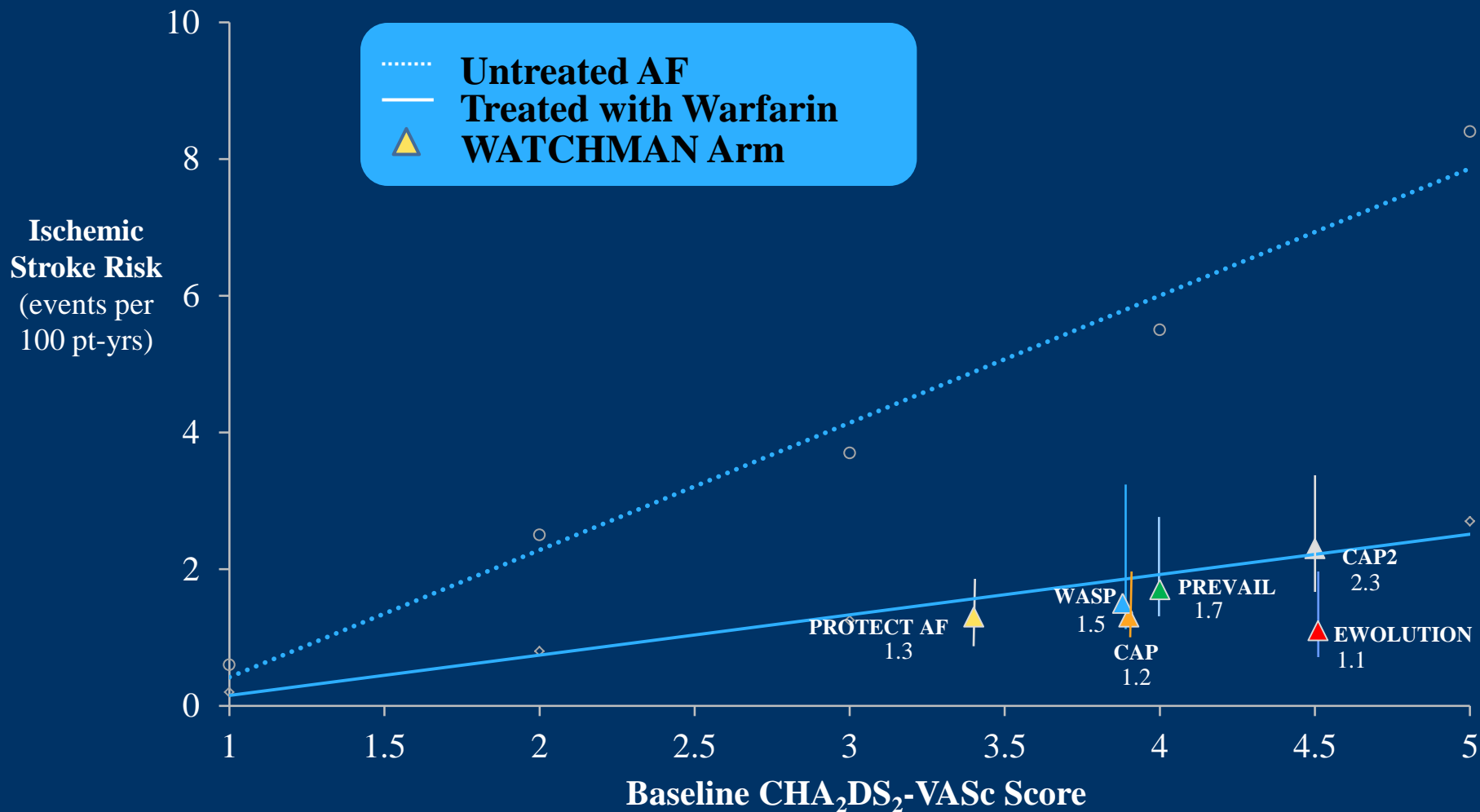
Patient-Level Meta-Analysis PROTECT AF and PREVAIL 5 years





Results

WATCHMAN Comparable to Warfarin for Ischemic Stroke

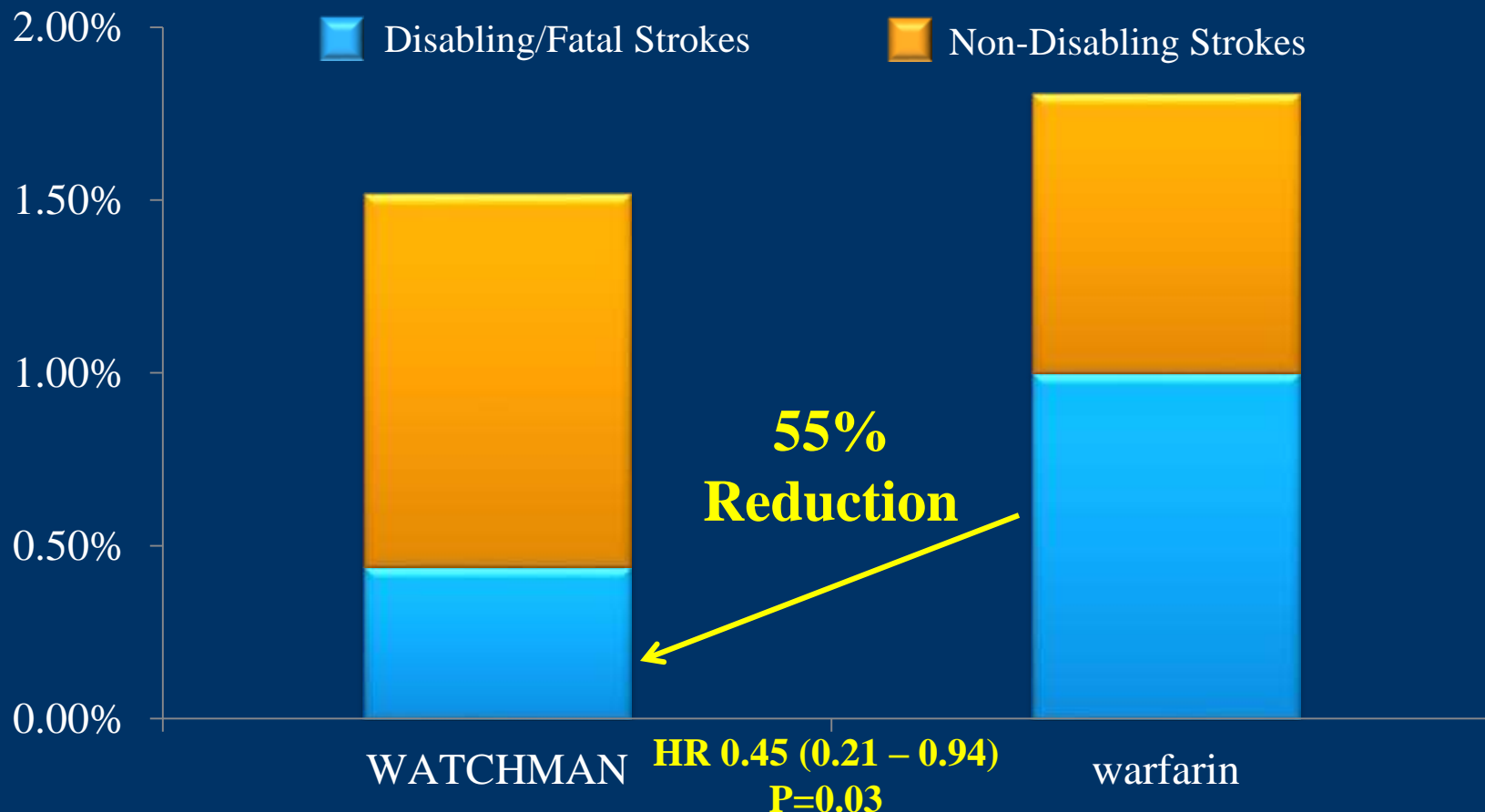




Maurice Buchbinder, M.D.

Patient-Level Meta-Analysis

WATCHMAN Superior Reduction in Disabling Strokes



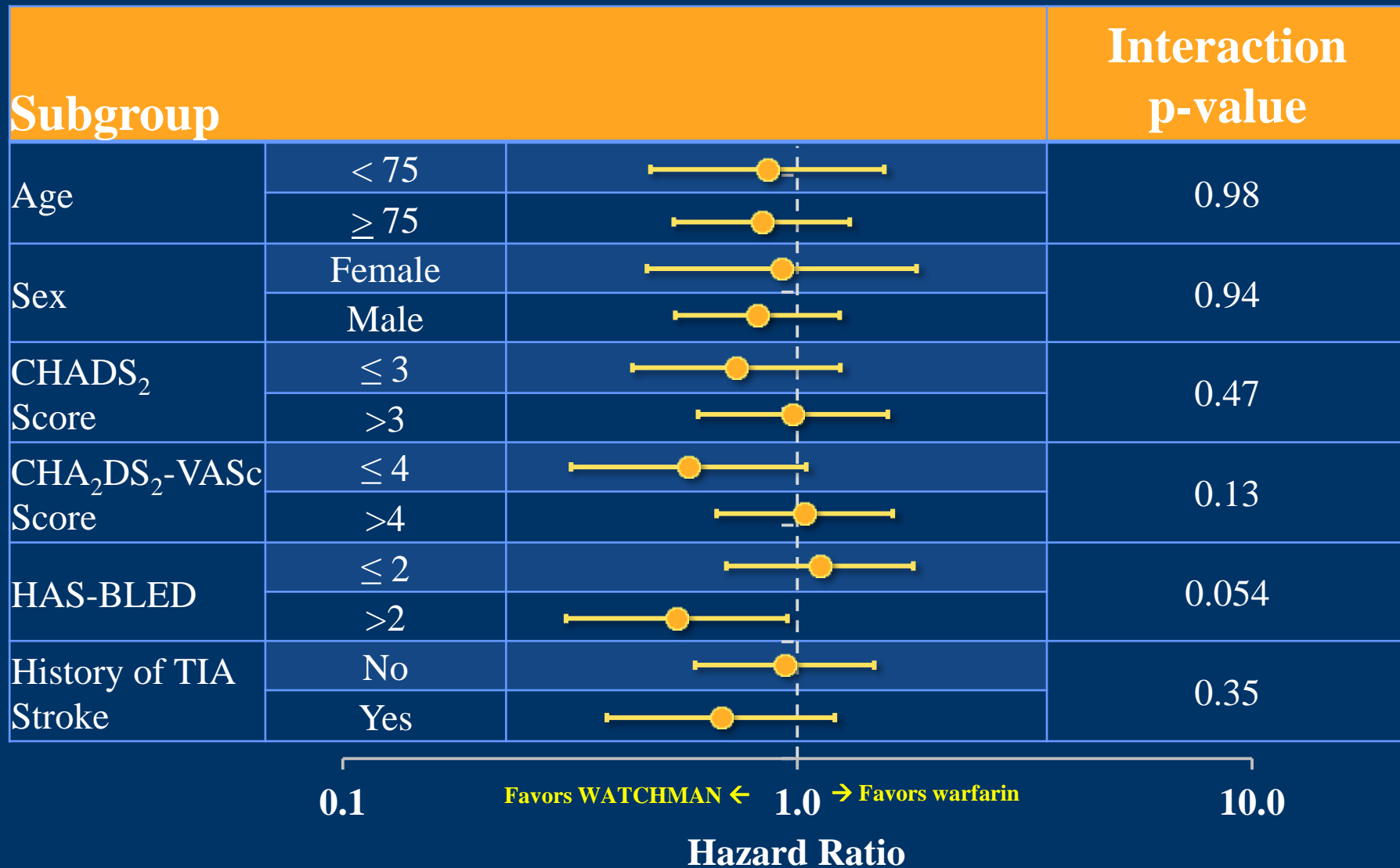
Disabling Stroke defined as MRS ≥ 2

Two strokes in PREVAIL are excluded because the baseline MRS score was unavailable



Patient-Level Meta-Analysis

No Significant Difference In Outcomes By Patient Subset





Summary

PREVAIL 5 year follow-up demonstrates:

- 2nd primary endpoint meets non-inferiority while the 1st endpoint remains unchanged
- No significant differences between WATCHMAN and warfarin for primary efficacy measures despite an implausibly low rate of ischemic stroke (0.73%) in the control arm

Meta-Analysis of PROTECT AF and PREVAIL with 5 year follow-up demonstrates:

- Comparable efficacy and stroke rates, with no significant difference across subgroups
- No significant differences in ischemic stroke rates versus warfarin
- Significant, superior reductions in disabling strokes, non-procedural bleeding, and mortality



Conclusion

Long term 5-year outcomes of 2 RCTs demonstrate

- LAAC with the Watchman device provides stroke prevention in NVAf patients to a similar degree as oral anticoagulation
- By minimizing major bleeding, particularly hemorrhagic stroke, LAAC results in less disability or death than warfarin

For patients who are poor candidates for long-term oral anticoagulation, left atrial appendage closure is a reasonable strategy for stroke prophylaxis



5-Year Outcomes After Left Atrial Appendage Closure

From the PREVAIL and PROTECT AF Trials

Vivek Y. Reddy, MD,^{a,b} Shephal K. Doshi, MD,^c Saibal Kar, MD,^d Douglas N. Gibson, MD,^e Matthew J. Price, MD,^f Kenneth Huber, MD,^g Rodney P. Horton, MD,^h Maurice Buchbinder, MD,^b Petr Neuzil, MD, PhD,^b Nicole T. Gordon, BSEE,ⁱ David R. Holmes, Jr, MD,^j on behalf of the PREVAIL and PROTECT AF Investigators

ABSTRACT

BACKGROUND The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial demonstrated that left atrial appendage closure (LAAC) with the Watchman device (Boston Scientific, St. Paul, Minnesota) was equivalent to warfarin for preventing stroke in atrial fibrillation, but had a high rate of complications. In a second randomized trial, PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), the complication rate was low. The warfarin cohort experienced an unexpectedly low ischemic stroke rate, rendering the efficacy endpoints inconclusive. However, these outcomes were based on relatively few patients followed for a relatively short time.

OBJECTIVES The final results of the PREVAIL trial, both alone and as part of a patient-level meta-analysis with the PROTECT AF trial, are reported with patients in both trials followed for 5 years.

METHODS PREVAIL and PROTECT AF are prospective randomized clinical trials with patients randomized 2:1 to LAAC or warfarin; together, they enrolled 1,114 patients for 4,343 patient-years. Analyses are by intention-to-treat, and rates are events per 100 patient-years.

RESULTS For the PREVAIL trial, the first composite coprimary endpoint of stroke, systemic embolism (SE), or cardiovascular/unexplained death did not achieve noninferiority (posterior probability for noninferiority = 88.4%), whereas the second coprimary endpoint of post-procedure ischemic stroke/SE did achieve noninferiority (posterior probability for noninferiority = 97.5%); the warfarin arm maintained an unusually low ischemic stroke rate (0.73%). In the meta-analysis, the composite endpoint was similar between groups (hazard ratio [HR]: 0.820; $p = 0.27$), as were all-stroke/SE (HR: 0.961; $p = 0.87$). The ischemic stroke/SE rate was numerically higher with LAAC, but this difference did not reach statistical significance (HR: 1.71; $p = 0.080$). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAAC (HR: 0.20; $p = 0.0022$; HR: 0.41; $p = 0.03$; HR: 0.59; $p = 0.027$; HR: 0.73; $p = 0.035$; HR: 0.48; $p = 0.0003$, respectively).

CONCLUSIONS These 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial, demonstrate that LAAC with Watchman provides stroke prevention in nonvalvular atrial fibrillation comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke, and mortality. (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; [NCT00129545](#); and Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; [NCT01824411](#)) (J Am Coll Cardiol 2017;■:■-■) © 2017 Published by Elsevier on behalf of the American College of Cardiology Foundation.



Maurice Buchbinder, M.D.

Thank You