

Comparison of Imputed Placebo Versus Observed Ischemic Stroke Rates in the Watchman Trials Represents a Significant Reduction in Risk

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Disclosure Statement of Financial Interest

- **I, George S. Hanzel, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation**

Background

- **Atrial fibrillation is the most common arrhythmia encountered in clinical practice.**
 - **7.5-9.0 million patients in US by 2020.**
- **The LAA is the source of thrombus in 90% of patients with non-valvular AF.**
- **~40% of patients are not treated with OACs.**
- **NOACs have not increased the number of patients treated.**

Background

- **Left atrial appendage closure (LAAC) is, intuitively, an attractive strategy to reduce stroke risk in atrial fibrillation (AF).**
- **There is little data regarding LAAC therapy in patients unable or unwilling to take warfarin.**
- **We sought to assess the effectiveness of Watchman™ LAAC for stroke risk reduction compared to the imputed placebo, or predicted, event rate based on CHADS₂ and CHA₂DS₂-VASC scores.**

ASAP Trial

150 AF patients ineligible for warfarin treated with Watchman LAAC

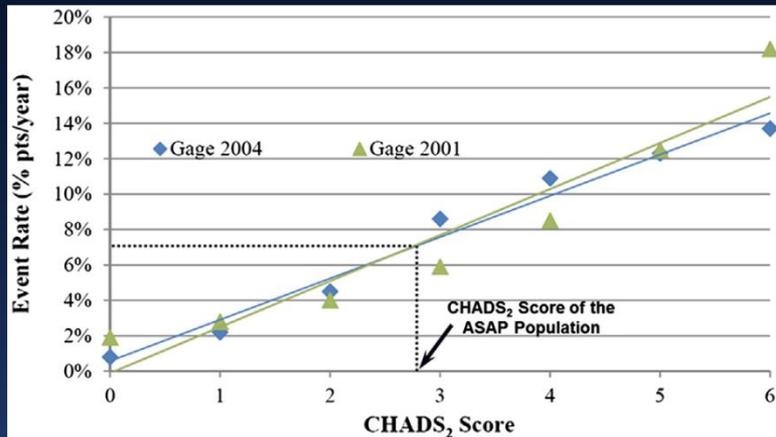


Table 4 Clinical Outcomes

	Entire Cohort Events/Patient-Years*
Primary efficacy	8/175.0 (4.6%)
Death, all cause	9/180.0 (5.0%)
All stroke	4/176.0 (2.3%)
Ischemic stroke	3/176.9 (1.7%)
Hemorrhagic stroke	1/179.1 (0.6%)

Predicted stroke risk = 7.3%

Actual stroke risk = 1.7%

77% Reduction in ischemic stroke

Reddy VY, et al. *JACC* 2013;61:2551-2556

Methods

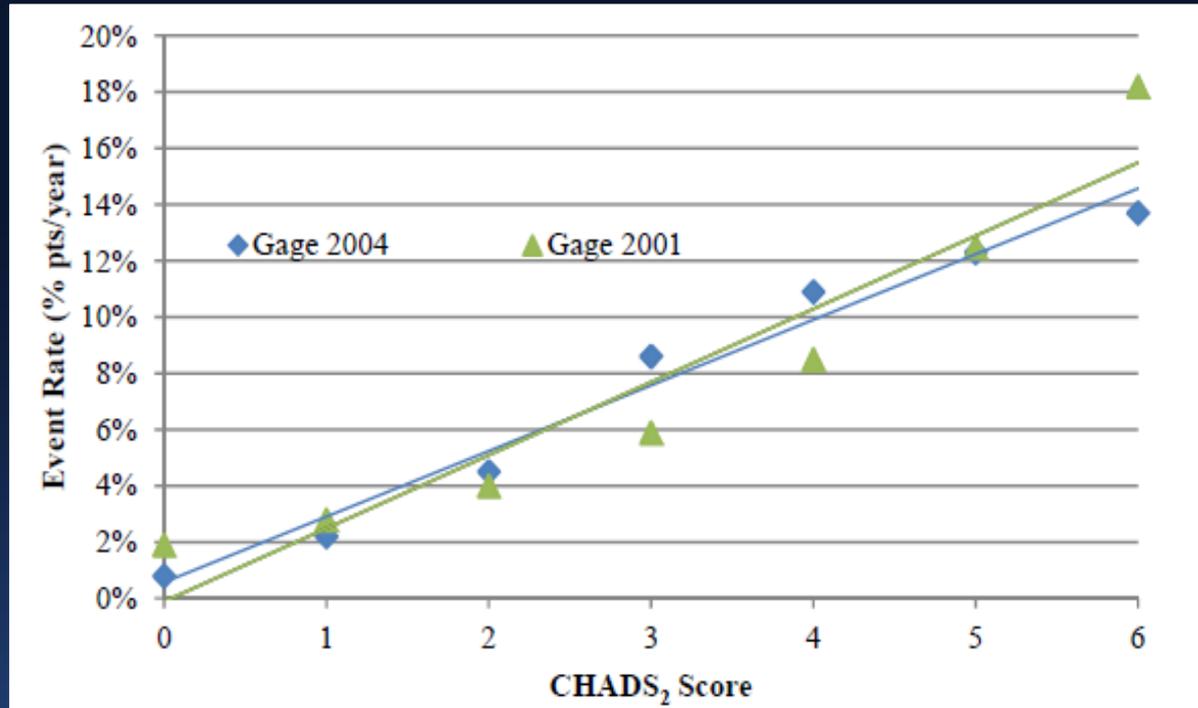
- The imputed placebo event rate in the Watchman trials (PROTECT AF, CAP, PREVAIL) was calculated using the average CHADS₂ and CHA₂DS₂-VASC scores in each study.
- The imputed placebo event rate, which is well validated in the literature, was compared with the observed ischemic stroke rate in the device arm of each individual trial.

Risk Stratification Models

Table 1 CHADS₂ Scores

CHADS ₂ Score		CHA ₂ DS ₂ VASC Score	
Risk Factor	Score	Risk Factor	Score
CHF	1	CHF/LF dysfunction	1
Hypertension	1	Hypertension	1
Age ≥ 75 yrs	1	≥75 yrs	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA	2	Stroke/TIA	2
		Vascular disease	1
		65–74 yrs	1
		Female sex	1

Rate of Ischemic Events in Untreated AF Patients According to CHADS₂ Score



Gage 2001: 1733 AF Medicare beneficiaries discharged without warfarin

Gage 2004: 2580 AF patients treated with aspirin in multicenter warfarin trials

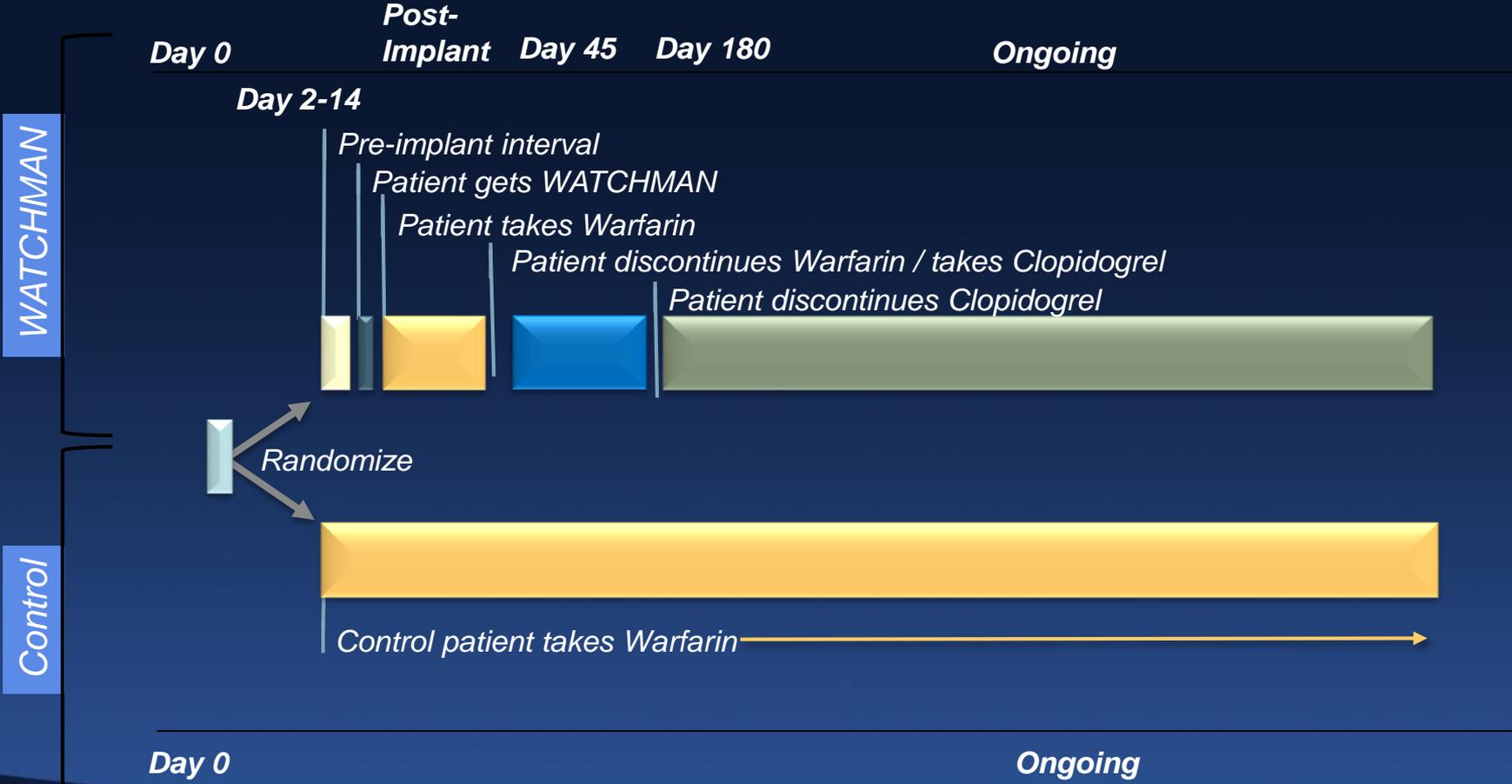
Gage et al. *Circulation* 2004;110:2287-2296

Gage et al. *JAMA* 2001;285:2864-2870

Watchman Trials: PROTECT AF, CAP, PREVAIL

PROTECT AF	CAP	PREVAIL
Randomized 2:1 Watchman vs Warfarin	Registry	Randomized 2:1 Watchman vs Warfarin
CHADS ₂ ≥ 1	CHADS ₂ ≥ 1	CHADS ₂ ≥ 2
Warfarin candidates	Warfarin candidates	Warfarin candidates

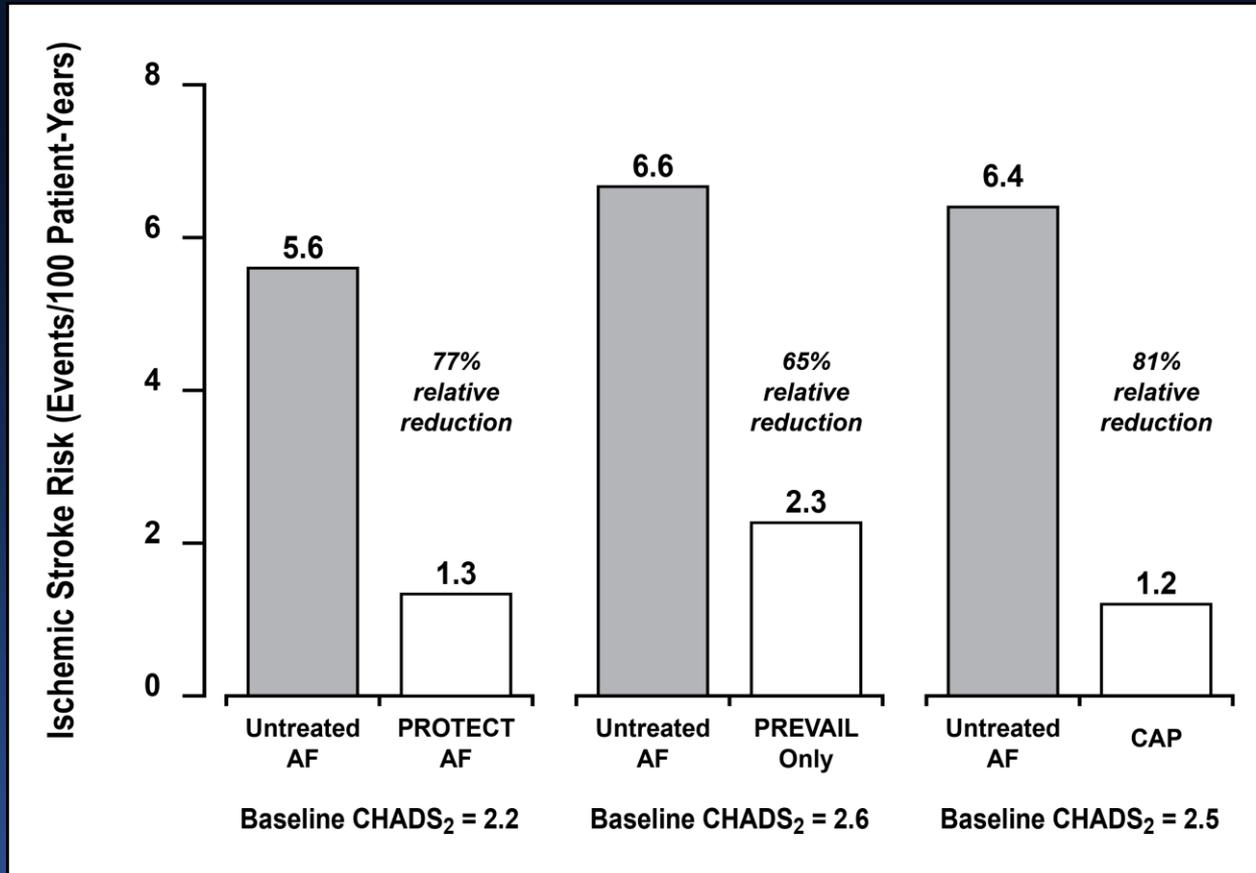
Patient Study Timeline



Baseline Demographics: PROTECT AF, CAP, PREVAIL

	PROTECT AF	CAP	PREVAIL
n	463	566	269
Patient-Year FU	2717	2022	860
Age	72	74	74
CHF	26.8%	19.1%	23.4%
Hypertension	89.2%	88.9%	88.5%
Age ≥ 75	41.0%	51.8%	52.0%
Diabetes	24.4%	24.9%	33.8%
Prior TIA or Stroke	17.7%	30.4%	27.5%
CHADS ₂ Score	2.2 ± 1.2	2.5 ± 1.2	2.6 ± 1.0
CHA ₂ DS ₂ -VASC	3.5 ± 1.6	3.9 ± 1.5	4.0 ± 1.2
Warfarin DC 45d/1year	86.8%/93.2%	95.8%/96.4%	92.2%/99.3%

CHADS₂ Imputed Placebo vs Observed Ischemic Stroke Rates in the Watchman Trials



CHADS₂ Imputed Placebo vs Observed Ischemic Stroke Rates in the Watchman Trials

	CHADS ₂	Imputed Ischemic Stroke Rate	Observed WATCHMAN Ischemic Stroke Rate	Relative Risk Reduction
PROTECT AF	2.2	5.6-5.7	1.3 (0.9-2.0)	77% (64%-84%)
PREVAIL	2.5	6.6	2.3 (1.3-4.0)	65% (39%-80%)
CAP	2.6	6.4	1.2 (0.8-1.8)	81% (72-88%)

CHA₂DS₂-VASC Imputed Placebo vs Observed Ischemic Stroke Rates in the Watchman Trials

	CHA ₂ DS ₂ -VASC	Imputed Olesen 2011 Ischemic Stroke Rate	Observed WATCHMAN Ischemic Stroke Rate	Relative Risk Reduction
PROTECT AF	3.4	6.2	1.3	79%
PREVAIL	3.8	6.9	2.3	67%
CAP	3.9	7.1	1.2	83%

Olesen JB, et al. *Thromb Haemost* 2011;106(4):739-749

Conclusions

- In this analysis, LAAC with Watchman is associated with a significant reduction in ischemic stroke compared with an imputed placebo, or expected, event rate derived from the CHADS₂ and CHA₂DS₂-VASC scores.
- The relative risk reduction is clinically meaningful and consistent across all trials.
- The relative risk reduction is similar to that seen in historical trials comparing warfarin to placebo.
- This analysis suggests that LAAC with Watchman may provide a reduction in stroke risk for patients not receiving anticoagulation therapy.