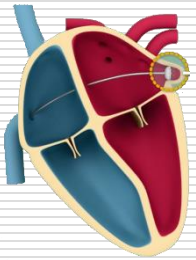
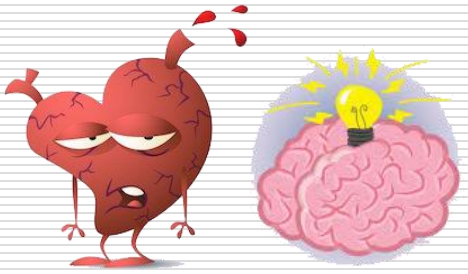
# Intervention for Stroke Prevention: LAA Closure

## Whether to Close or Not

**Tae-Hyun Yang**
*Professor of Medicine/Cardiology*

Inje University Busan Paik Hospital



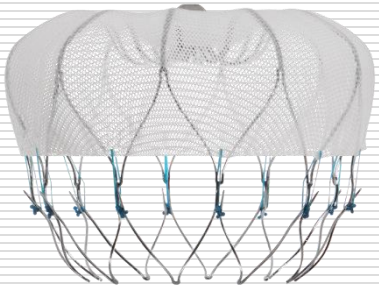


# Clinical Evidences of Left Atrium Appendage Closure

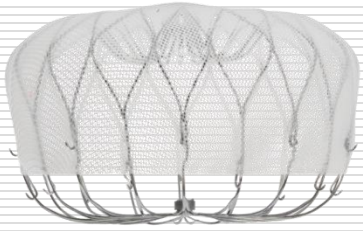
# LA Appendage Closure Devices

**WATCHMAN**
**(Boston Scientific)**

**AMPLATZER Devices**
**(Abbott [St. Jude medical])**



WATCHMAN™



WATCHMAN FLX™

ACP™

Amulet

Lariat

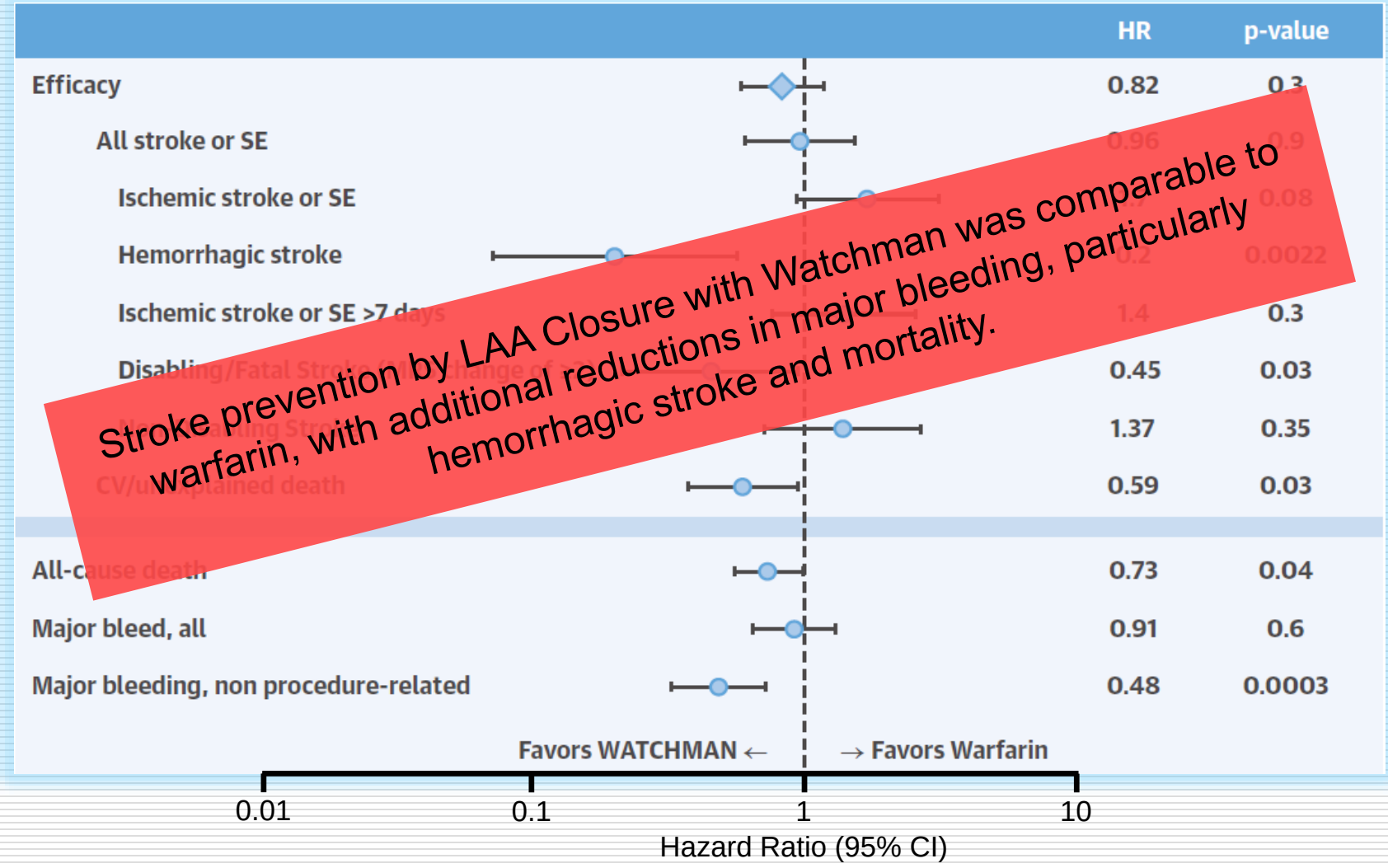
LAmbre

WaveCrest

# Clinical Evidences of WATCHMAN™

| Study | Enrollment | Enrolled Patients | Enrolled Sites | Follow-up |
|---|---|---|---|---|
| Pilot (feasibility study) | Aug 2002~Jan 2005 | 66 | 8 | Completed 5 years (US) and up to 9 years (Other regions) |
| **PROTECT AF Randomized trial** | Feb 2005~Jun 2008 | 707 | 59 | Up to 5 years |
| CAP Registry | Aug 2008~Jun 2010 | 566 | 26 | Up to 5 years |
| ASAP registry | Jan 2009~Nov 2011 | 150 | 4 | Up to 5 years |
| **PREVAIL Randomized trial** | Nov 2010~Jun 2012 | 461 | 41 | Up to 5 years |
| CAP2 registry | Sep 2012-ongoing | 1500 | 60 | Ongoing through 5 years |
| EWOLUTION registry | Oct 2013~ongoing | 1020 | 47 | Ongoing through 5 years |
| US post-approval registry | Oct 2013~May 2016 | 3822 | 169 | Ongoing |
| FLX device post-approval registry (Europe) | July 2019~ongoing | 300 | | Ongoing |

# 5-Year Outcomes of PROTECT AF and PREVAIL Trials




Stroke prevention by LAA Closure with Watchman was comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke and mortality.

J Am Coll Cardiol 2017;70:2964-2975

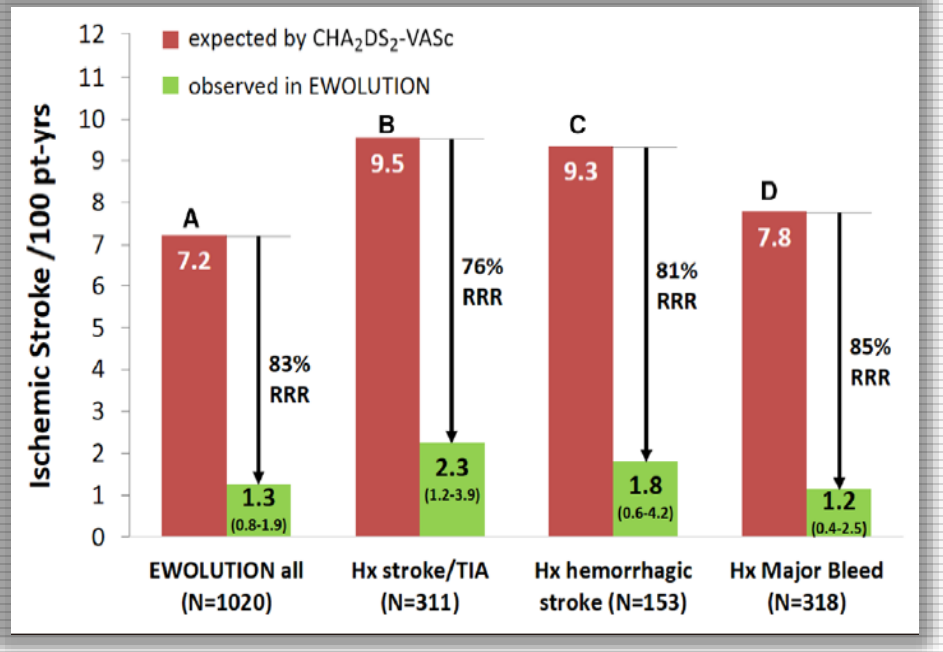
# Real-World Registry in AF Patients Receiving WATCHMAN™ (EWOLUTION 2-Year Outcome)

1,020 Patients (73.4±8.9 years) at high risk of stroke ($CHA_2DS_2$-VASc 4.5±1.6) and bleeding (HAS-BLED 2.3±1.2)

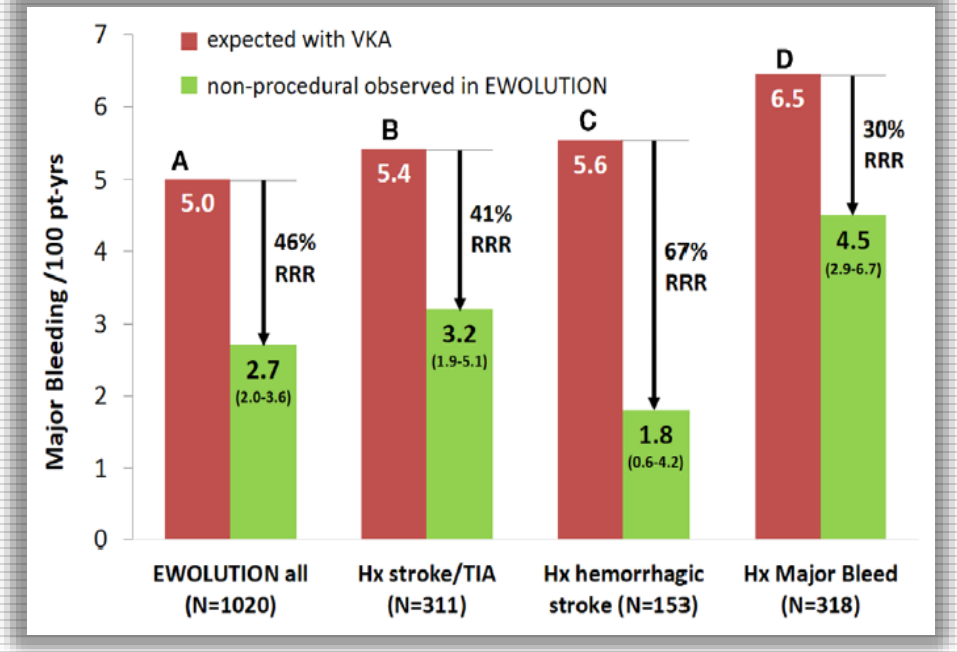
- WATCHMAN™
- Antithrombotics by discretion of physicians

- Endpoint : Ischemic stroke, TIA, SE, major bleeding
- Median FU = 2 years

## Ischemic stroke rates

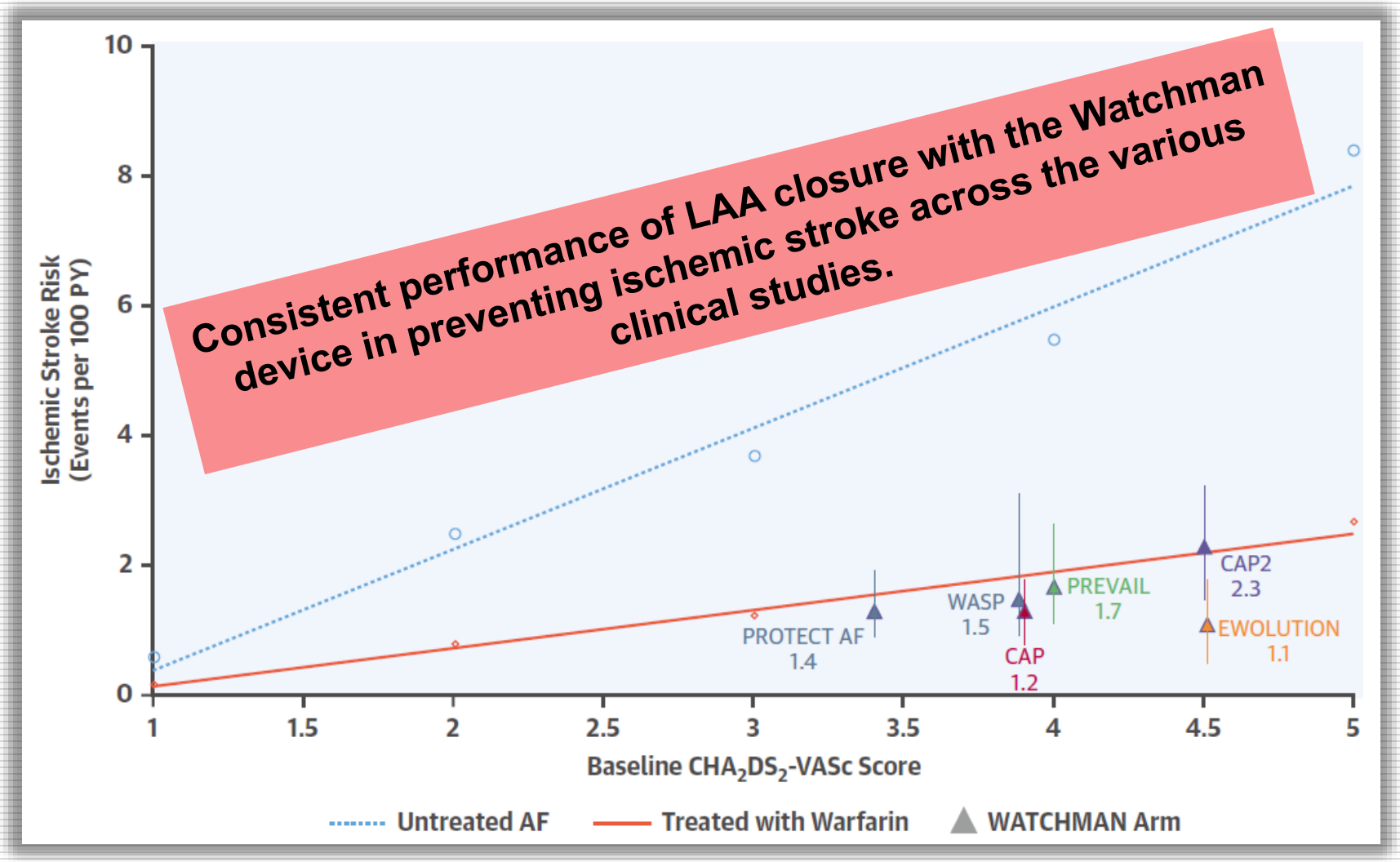



## Major bleeding rates




Circ Arrhythm Electrophysiol 2019;12:e006841

# Ischemic Stroke Rates in AF Patients As A Function of Baseline $CHA_2DS_2$-VASc Score




J Am Coll Cardiol 2017;70:2964-2975

# Clinical Evidences of Amplatzer Device™

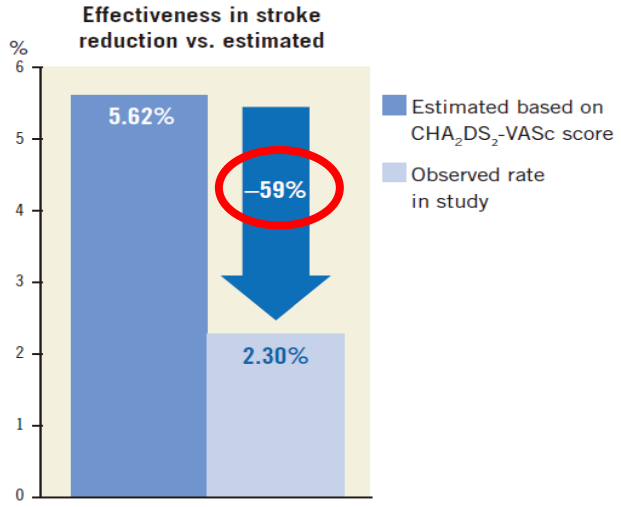
| Study | Enrollment | Enrolled Patients | Enrolled Sites | Follow-up |
|---|---|---|---|---|
| ACP multicenter registry | Dec 2008~Nov 2013 | 1001 | 22 | Completed 13 months (average) |
| Amplatzer Amulet global prospective observational study | Jun 2015~Sep 2016 | 1088 | 64 | Ongoing (1-year outcome available) |
| Amulet IDE RCT (Amulet vs. Watchman) | Aug 2015~Comleted | 1878 | 150 | Ongoing through 5 years |

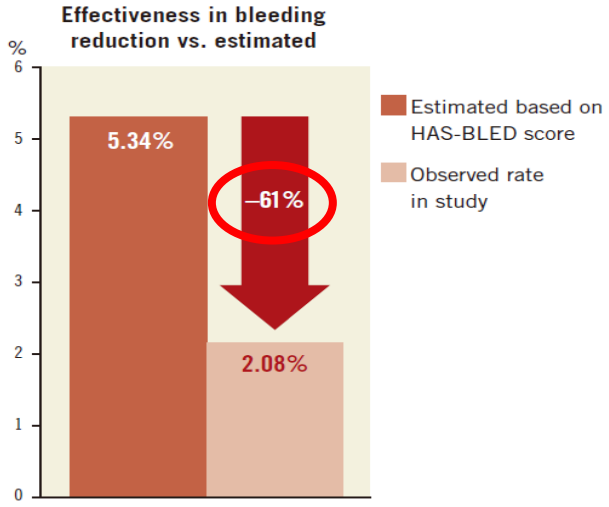
# LAA Closure for Stroke Prevention in AF (Multicenter Experience with AMPLATZER Cardiac Plug)

1,047 Patients (75±9 years) at high risk of stroke ($CHA_2DS_2$-VASc 4.5±1.6) and bleeding (HAS-BLED 3.1±1.2)

- ACP™
- Antithrombotics by discretion of physicians

- Primary endpoint : device efficacy to prevent stroke, TIA, SE
- Average FU = 13 months




| Total patients | Total patient-years | $CHA_2DS_2$-VASc score |
|---|---|---|
| 1,001 | 1,349 | 4.43 |

| Estimated stroke rate per $CHA_2DS_2$-VASc | Actual annual stroke rate (No. strokes+TIA) |
|---|---|
| 5.62% | 2.30% (31) |

| Total patients | Total patient-years | HAS-BLED score |
|---|---|---|
| 1,001 | 1,349 | 3.12 |

| Estimated bleeding rate per HAS-BLED | Actual annual bleeding rate (No. major bleeds) |
|---|---|
| 5.34% | 2.08% (28) |

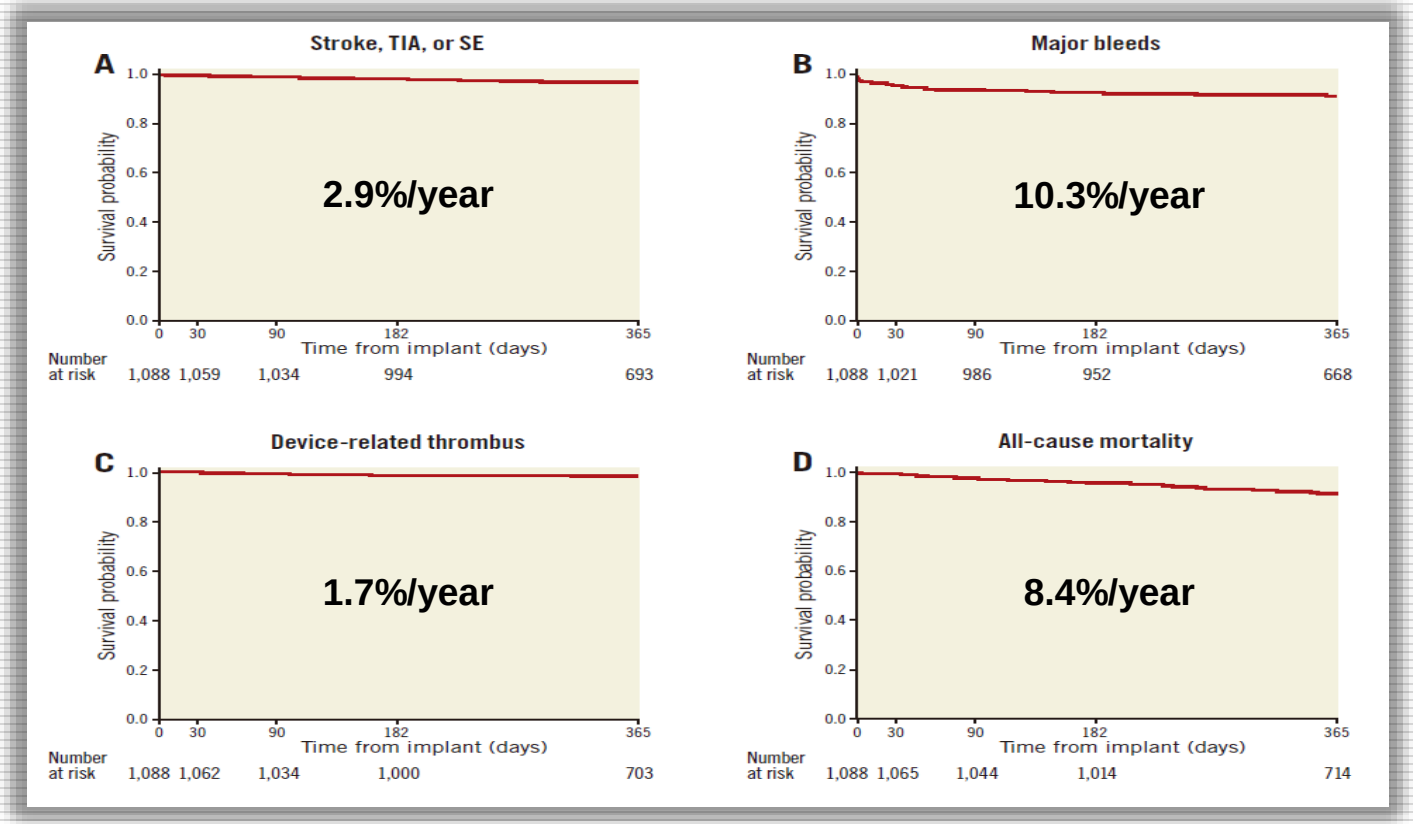
Eurointervention 2016;11:1170-1179

# One-Year Outcomes of LAAC with AMPLATZER Amulet™ (Prospective Global Amulet Observational Registry)

1,088 Patients (75±9 years) at high risk of stroke ($CHA_2DS_2$-VASc 4.2±1.6) and bleeding (HAS-BLED 3.1±1.1)

- **AMPLATZER Amulet™**
- Discharged without OAC (>80%)

- Evaluated for: Ischemic stroke, TIA, SE, major bleeding, DRT, all cause of death




Eurointervention 2018;14:e590-e597

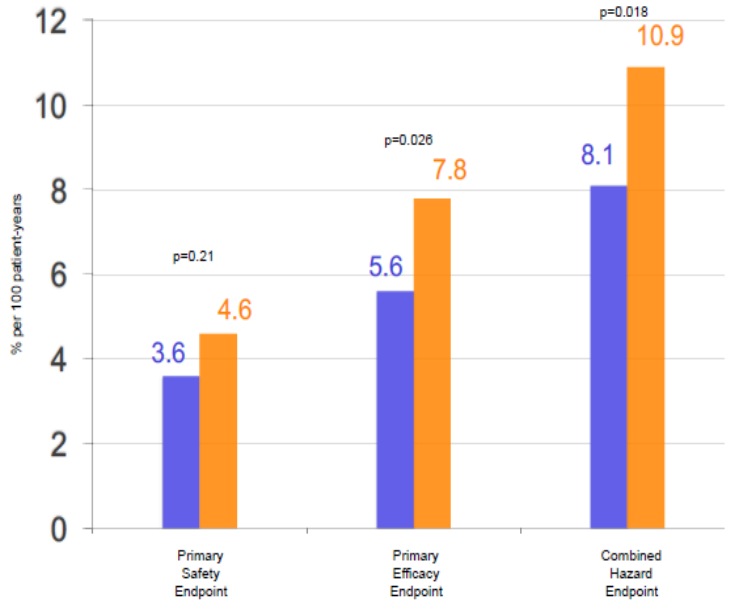
# LAA Closure vs. OAC (Propensity Score Matched Study)

1000 Patients

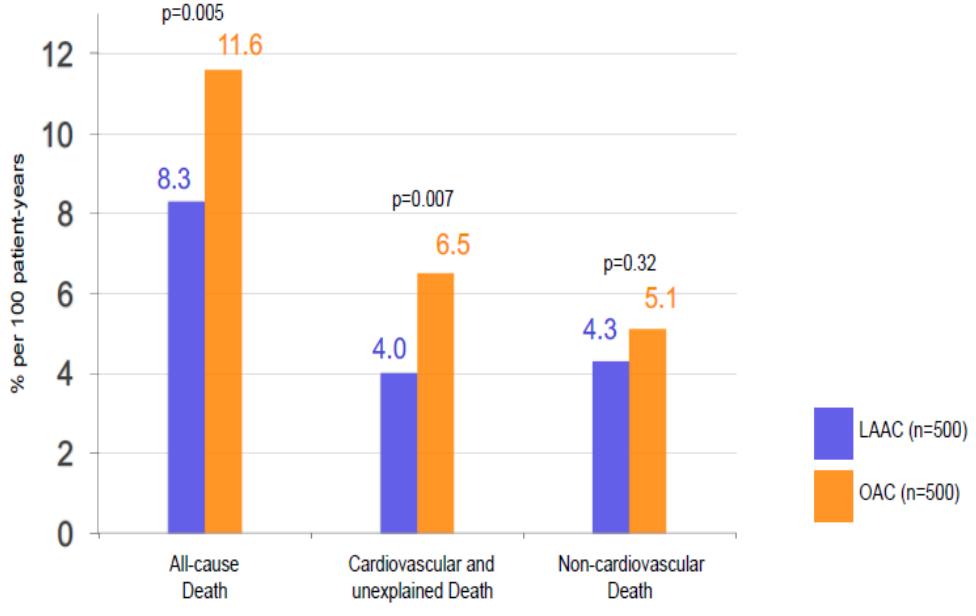
- Amplatzer devices (n=500)
- OAC or NOAC (n=500)

- Primary endpoint : All major procedural adverse events and major or life threatening
- Mean FU = 2.7 ± 1.5 years

## Primary endpoints



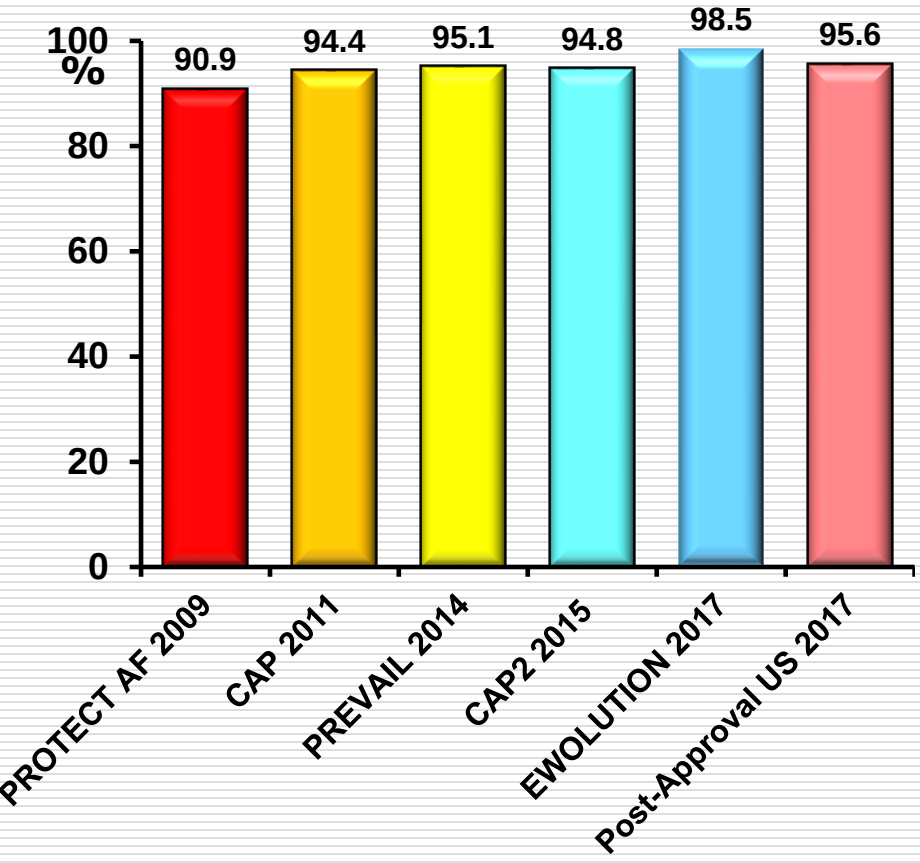

## Mortality



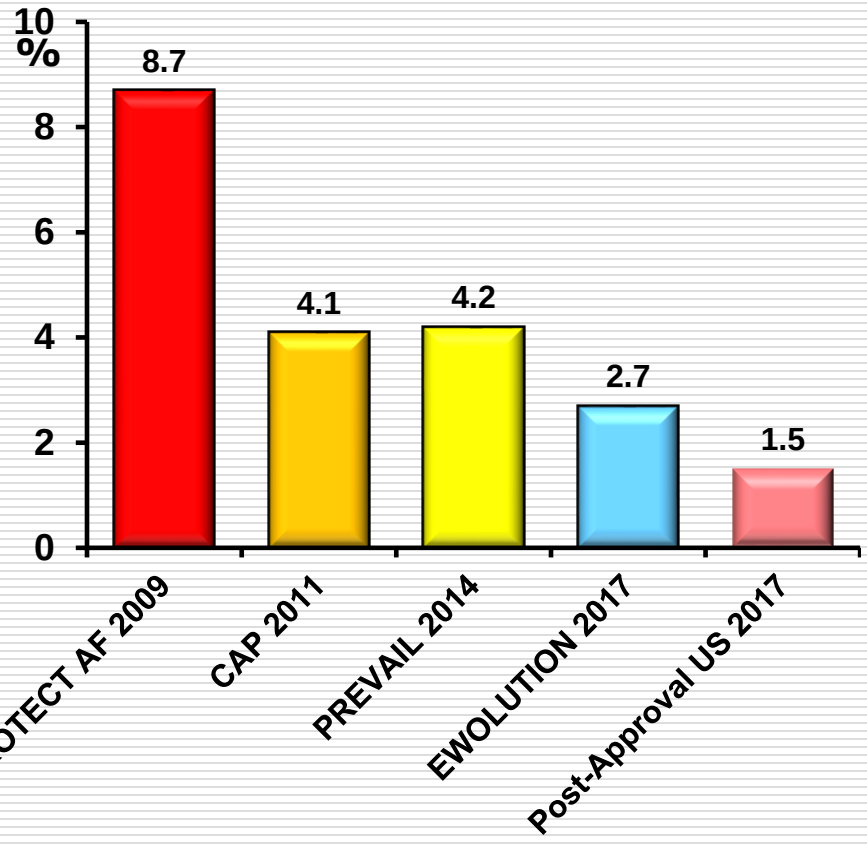

EuroPCR 2017

# Improving Procedural Results with WATCHMAN™ over Time

## Implant success rates



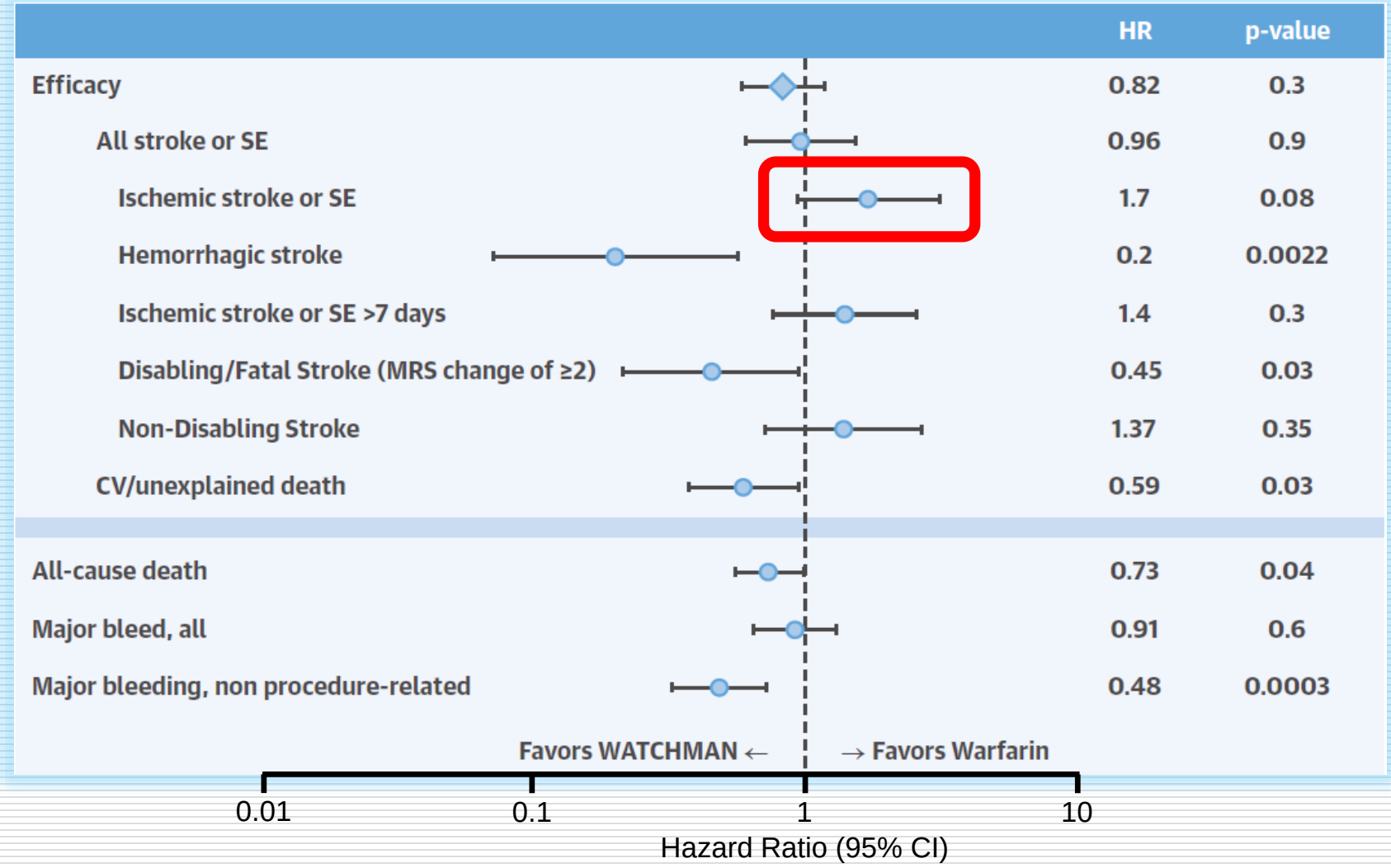

## Procedure/Device SAE




Eur Heart J 2016;37:2465-2474

# Post LAA Closure Ischemic Stroke & Device-Related Thrombus

# 5-Year Outcomes of PROTECT AF and PREVAIL Trials

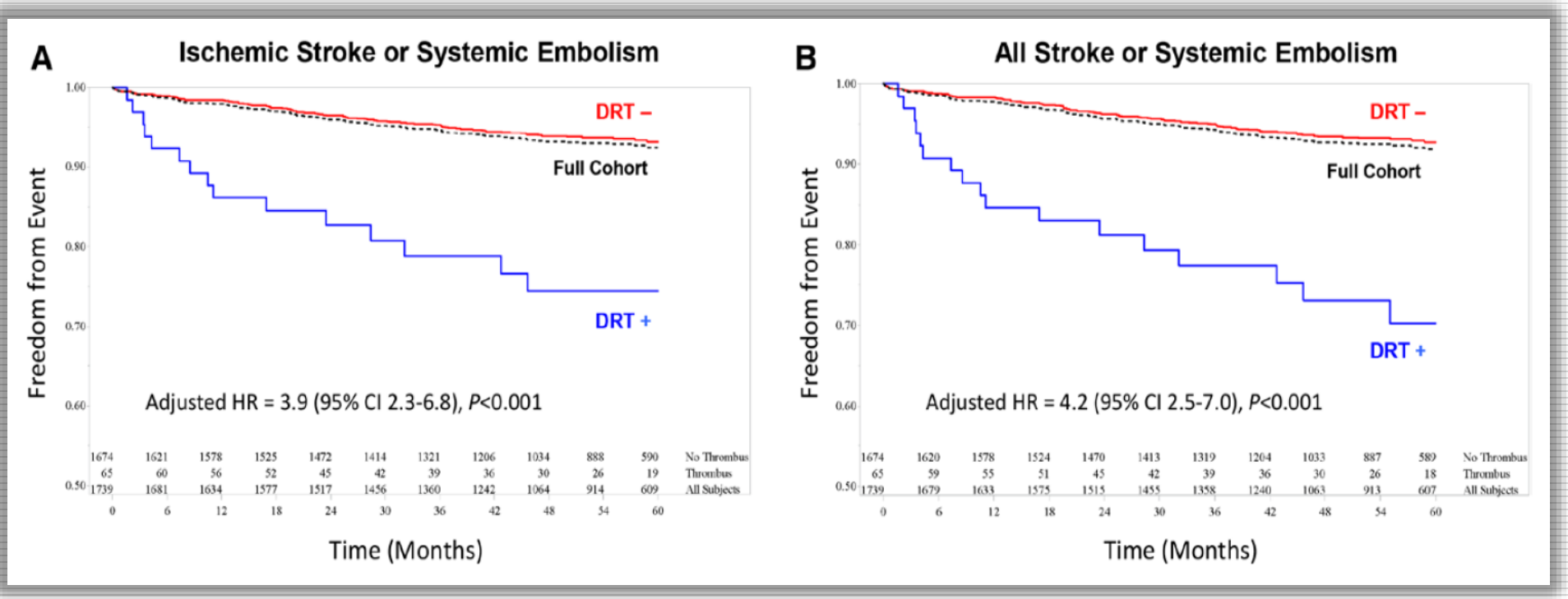



J Am Coll Cardiol 2017;70:2964-2975

# Device-Related Thrombus and Its Consequences

**1,739 patients who received an WATCHMAN implantation in PROTECT AF, PREVAIL, CAP, and CAP2**

- **Device-related thrombus was seen in 65 patients (3.74%).**



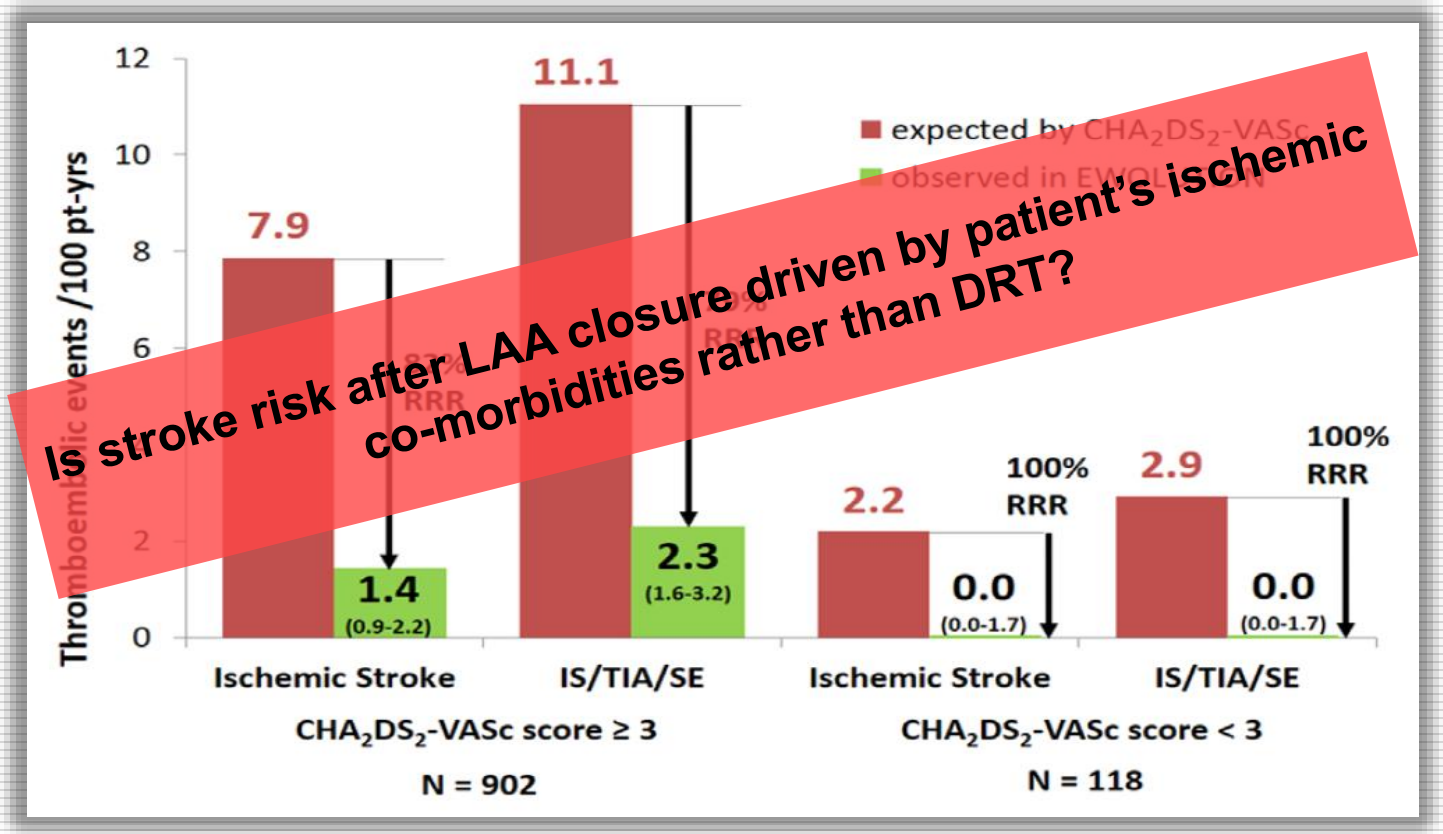

Circulation 2018;138:874-885

# Real-World Registry in AF Patients Receiving WATCHMAN™ (EWOLUTION 2-Year Outcome)

1,020 Patients (73.4±8.9 years) at high risk of stroke ($CHA_2DS_2$-VASc 4.5±1.6) and bleeding (HAS-BLED 2.3±1.2)

- WATCHMAN™
- Antithrombotics by discretion of physicians

- Endpoint : Ischemic stroke, TIA, SE, major bleeding
- Median FU = 2 years




Is stroke risk after LAA closure driven by patient's ischemic co-morbidities rather than DRT?

Circ Arrhythm Electrophysiol 2019;12:e006841

# LAA Closure in AF Patients Ineligible for OAC

## No RCT date so far

# WATCHMAN™ vs. VKA
# PROTECT AF and PREVAIL Trials

| PROTECT AF[1] | PREVAIL[2] |
|---|---|
| $CHADS_2$ of 1 or more (mean 2.2) | $CHADS_2$ of 2 or more (mean 2.6) |
| **Tolerant to VKA therapy**<br>**45 days VKA+ASA, 6 Mo DAPT, Indefinite aspirin** | **Tolerant to VKA therapy**<br>**45 days VKA+ASA, 6 Mo DAPT, Indefinite aspirin** |
| 2:1 randomization device vs. drug | 1:1 randomization device vs. drug |
| Followed with TEE 3-6-12 Mo | Followed with TEE 3-6-12 Mo |
| Primary endpoint<br>Efficacy: Stroke/SE/CV or unexplained death<br>Safety: Adverse events | Primary endpoint<br>Efficacy: Stroke/SE/CV or unexplained death<br>Safety: Adverse events |

1: Lancet 2009;374:534-542, 2: J Am Coll Cardiol 2014;64:1-12.

# ASAP-TOO Trial

## Assessment of WATCHMAN™ or None in OAC Contra-indicated Patients

888 Patients with $CHA_2DS_2$-VASc ≥ 2 who are deemed ineligible for OAC

2 → WATCHMAN™

1 → SAPT or None

- Primary effectiveness endpoint : time to first occurrence of ischemic stroke or SE
- 1º safety endpoint: all death, ischemic stroke, SE or device or procedural SAE
- FU = up to 60 months

### The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) trial

David R. Holmes, MD, Vivek Y. Reddy, MD, Maurice Buchbinder, MD, Kenneth Stein, MD, Myriah Elletson, Martin W. Bergmann, MD, Boris Schmidt, MD, Jacqueline Saw, MD, FRCPC

#### Study objectives

The ASAP-TOO study is designed to establish the safety and effectiveness of the Watchman left atrial appendage closure device in patients with nonvalvular AF who are deemed ineligible for OAC. The primary effectiveness end point is the time to first occurrence of ischemic stroke or systemic embolism. The primary safety end point includes all-cause death, ischemic stroke, systemic embolism, or device- or procedural-related event requiring open cardiac surgery or major endovascular intervention.

#### Study design

This is a multinational, multicenter prospective randomized trial. Patients meeting the inclusion criteria with $CHA_2DS_2$-VASc score ≥ 2 and who are deemed by 2 study physicians to be unsuitable for OAC will be randomized in a 2:1 allocation ratio to Watchman versus control. Control patients will be prescribed single antiplatelet therapy or no therapy at the discretion of the study physician. Up to 888 randomized subjects will be enrolled from up to 100 global investigational sites. Both device group and control patients will have follow-up visits at 3, 6, and 12 months and then every 6 months through 60 months.

#### Summary

This trial will assess the safety and efficacy of Watchman in this challenging population of high–stroke risk AF patients.

Am Heart J 2017;189:68-74, RCT#NCT02928497

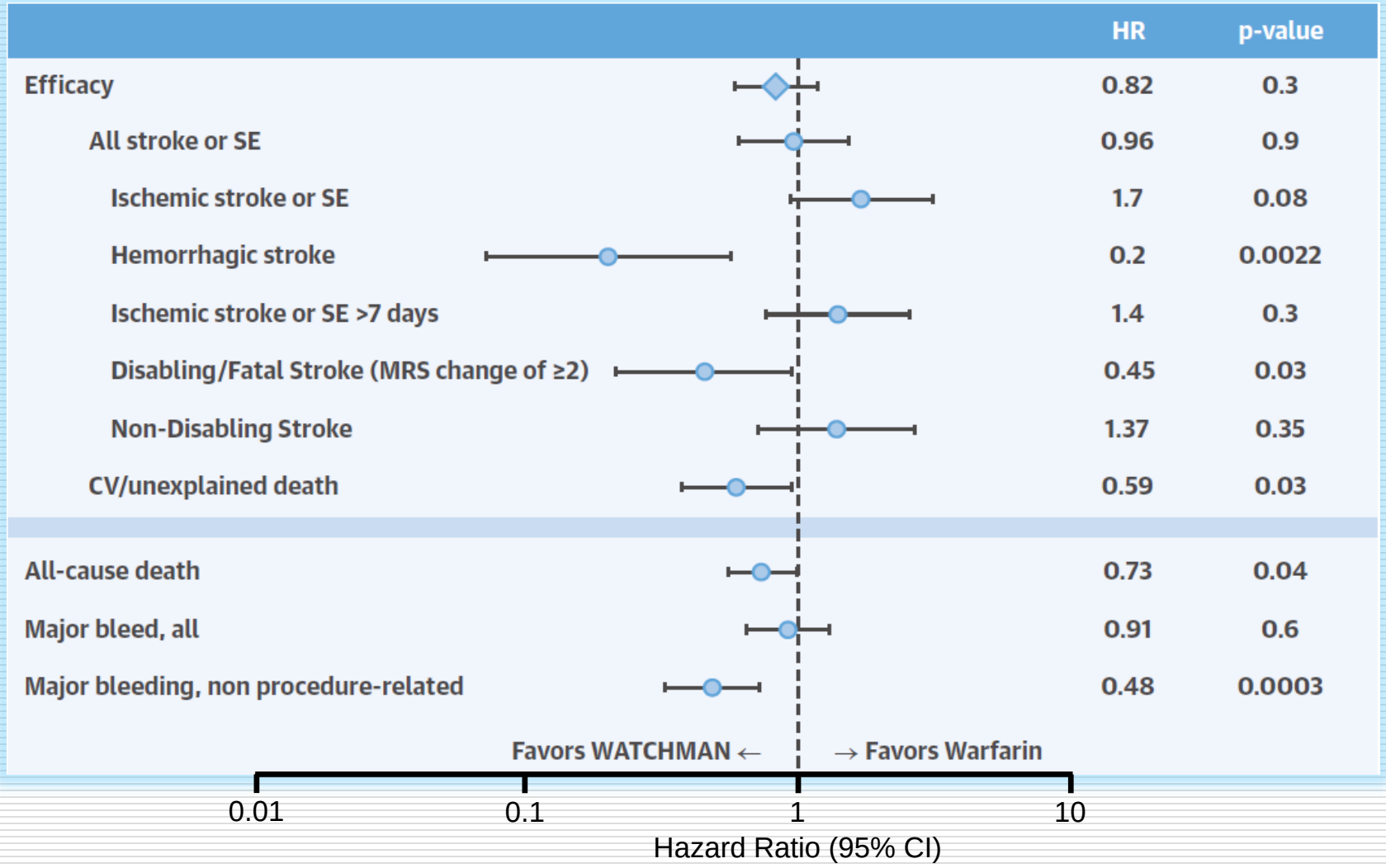
# STROKE-CLOSE Trial

## Prevention of Stroke by AMPLATZER Amulet™ in AF Patients after ICH


RCT#NCT02830152

# LAA Closure versus NOAC

# 5-Year Outcomes of PROTECT AF and PREVAIL Trials



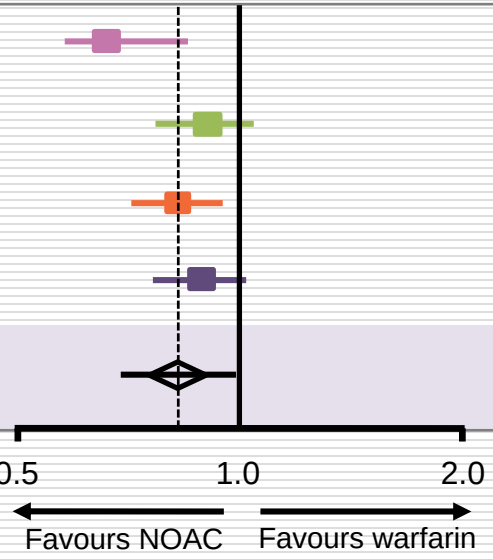

J Am Coll Cardiol 2017;70:2964-2975

# Meta-Analysis

## 71,633 Randomized Non-valvular AF Patients in 4 Trials (RE-LY, ROCKET AF, ARISTOLE, ENGAGE AF-TIMI 48)

**Primary efficacy: Stroke or systemic embolization**

| Study | NOAC (events) | Warfarin (events) | RR (95% CI) | RR (95% CI) | *P* value |
|---|---|---|---|---|---|
| RE-LY* | 375/6,076 | 199/6,022 | | **0.66** (0.53–0.82) | 0.0001 |
| ROCKET AF† | 269/7,081 | 306/7,090 | | **0.88** (0.75–1.03) | 0.12 |
| ARISTOTLE‡ | 212/9,120 | 265/9,081 | | **0.80** (0.67–0.95) | 0.012 |
| ENGAGE AF-TIMI 48§ | 296/7,035 | 337/7,036 | | **0.88** (0.75–1.02) | 0.10 |
| **Combined (random)** | **911/29,312** | **1,107/29,229** | | **0.81** (0.73–0.91) | **<0.0001** |




Data are n, unless otherwise indicated.
Heterogeneity: $I^2$ 47%, *P*=0.13

*Dabigatran 150 mg BID; †Rivaroxaban 20 mg OD; ‡Apixaban 5 mg BID; §Edoxaban 60 mg OD.
Doses were reduced for apixaban, rivaroxaban and edoxaban in a subset of patients according to prespecified criteria.

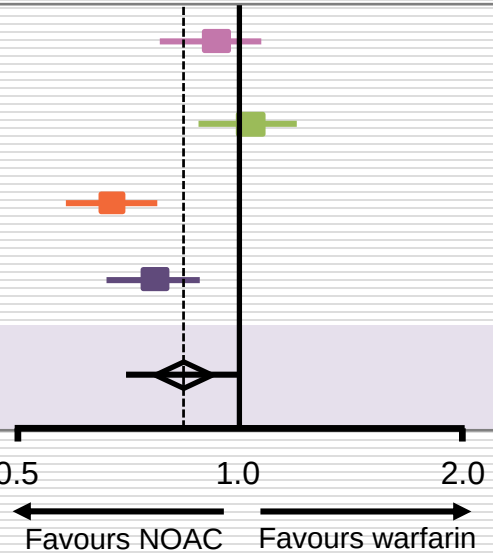
Lancet 2014;383:955-962

# Meta-Analysis

## 71,633 Randomized Non-valvular AF Patients in 4 Trials (RE-LY, ROCKET AF, ARISTOLE, ENGAGE AF-TIMI 48)

**Primary safety: Major bleeding**

| Study | NOAC (events) | Warfarin (events) | RR (95% CI) | *P* value |
|---|---|---|---|---|
| RE-LY* | 375/6,076 | 397/6,022 | **0.94** (0.82–1.07) | 0.34 |
| ROCKET AF† | 395/7,111 | 386/7,125 | **1.03** (0.90–1.18) | 0.72 |
| ARISTOTLE‡ | 327/9,088 | 462/9,052 | **0.71** (0.61–0.81) | <0.0001 |
| ENGAGE AF-TIMI 48§ | 444/7,012 | 557/7,012 | **0.80** (0.71–0.90) | 0.0002 |
| **Combined (random)** | **1,514/29,287** | **1,802/29,211** | **0.86** (0.73–1.00) | **0.06** |




Data are n, unless otherwise indicated.
Heterogeneity: $I^2$ 83%, *P*=0.001.

*Dabigatran 150 mg BID; †Rivaroxaban 20 mg OD; ‡Apixaban 5 mg BID; §Edoxaban 60 mg OD.
Doses were reduced for apixaban, rivaroxaban and edoxaban in a subset of patients according to prespecified criteria.

Lancet 2014;383:955-962

# Prague-17 Trial

## LAA Closure versus NOACs in High-Risk AF Patients

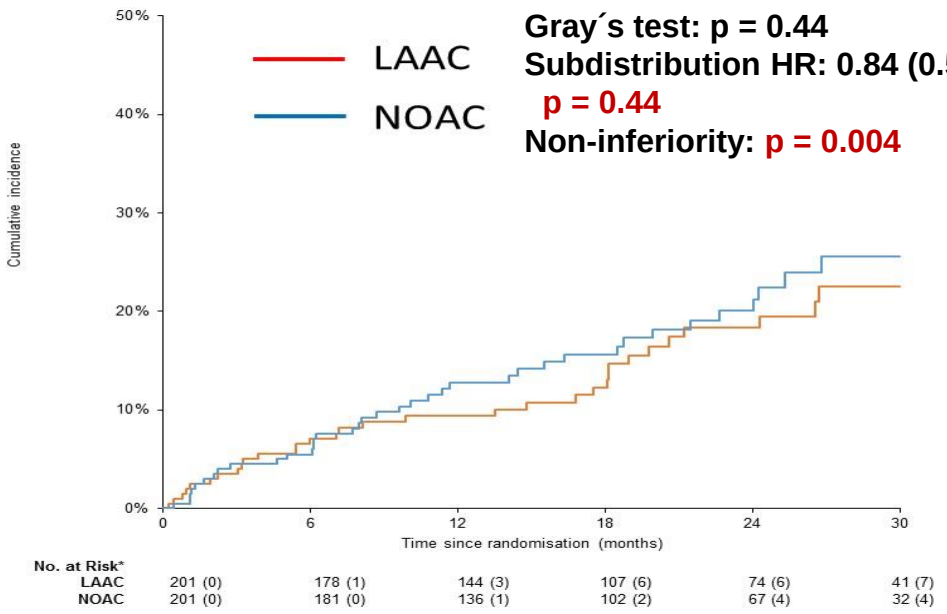
402 AF Patients with one of below:
I: Hx of bleeding requiring int/hos
II: Hx of SE on OAC
III: $CHA_2DS_2$-VASc ≥ 3 & HAS-BLED ≥ 2

1 → **WATCHMAN™ or Amulet™**
DAPT for 3 Mos and ASA indefinitely

1 → Apixaban (preferred), Rivaroxaban, or Dabigatran

- Primary endpoint : composite of stroke, TIA, SE, significant bleeding, CV death or periprocedural or device related complications
- Primary hypothesis: LAAC is noninferior to NOAC for primary endpoint

**Primary endpoint: ITT population**




ESC 2019, RCT#NCT02426944

# Prague-17 Trial

## LAA Closure versus NOACs in High-Risk AF Patients

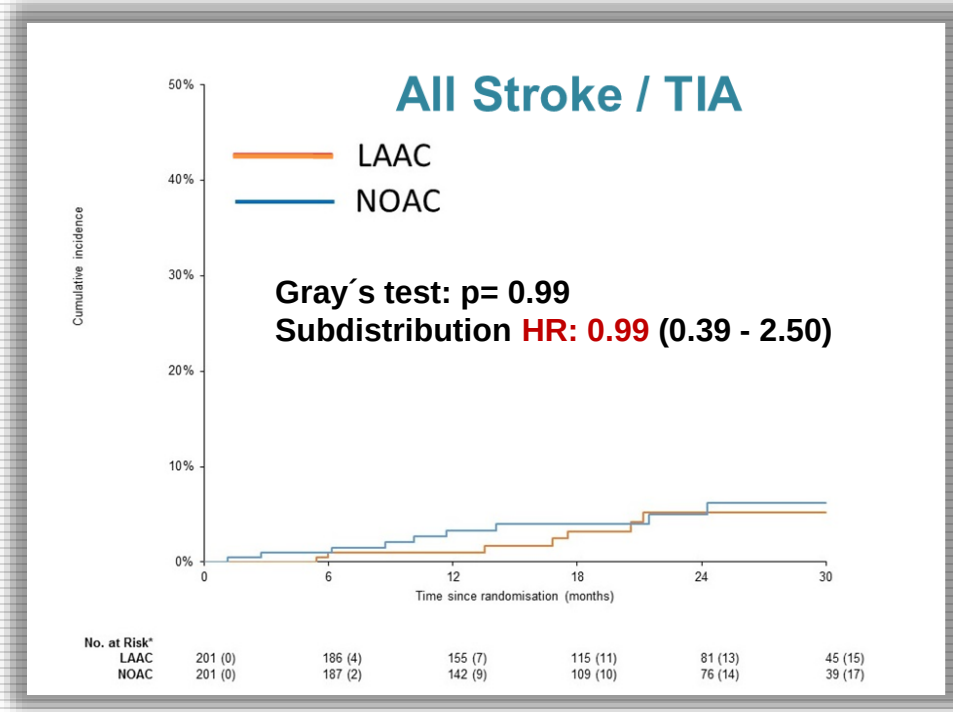
402 AF Patients with one of below:
I: Hx of bleeding requiring int/hos
II: Hx of SE on OAC
III: $CHA_2DS_2$-VASc ≥ 3 & HAS-BLED ≥ 2

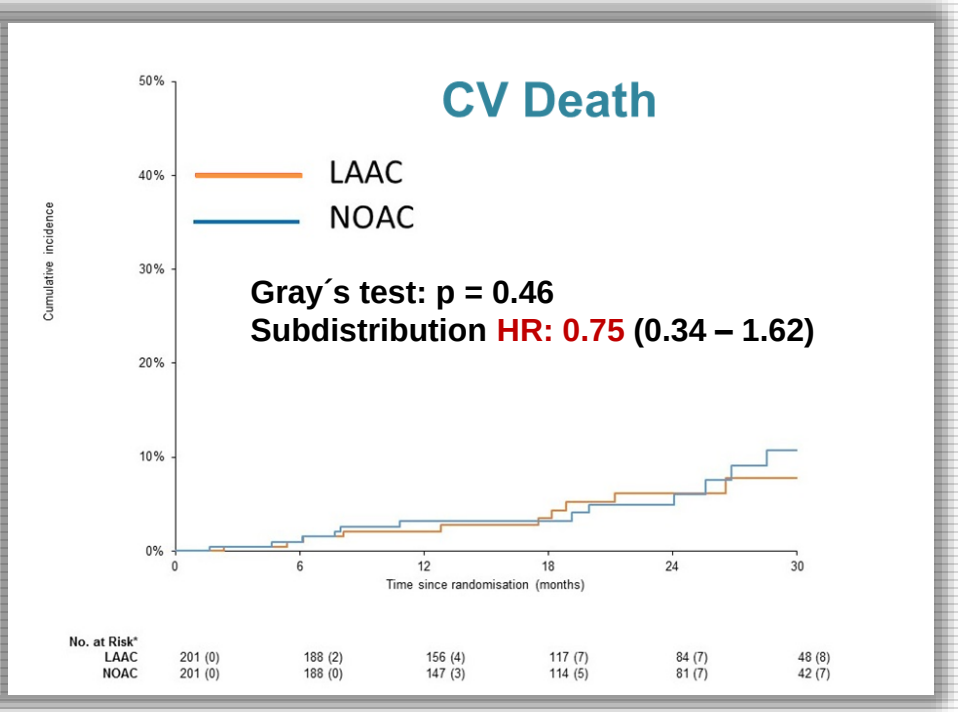
1 → **WATCHMAN™ or Amulet™**
DAPT for 3 Mos and ASA indefinitely

1 → Apixaban (preferred), Rivaroxaban, or Dabigatran

- Primary endpoint : composite of stroke, TIA, SE, significant bleeding, CV death or periprocedural or device related complications
- Primary hypothesis: LAAC is noninferior to NOAC for primary endpoint

**ITT population**




ESC 2019, RCT#NCT02426944

# Prague-17 Trial

## LAA Closure versus NOACs in High-Risk AF Patients

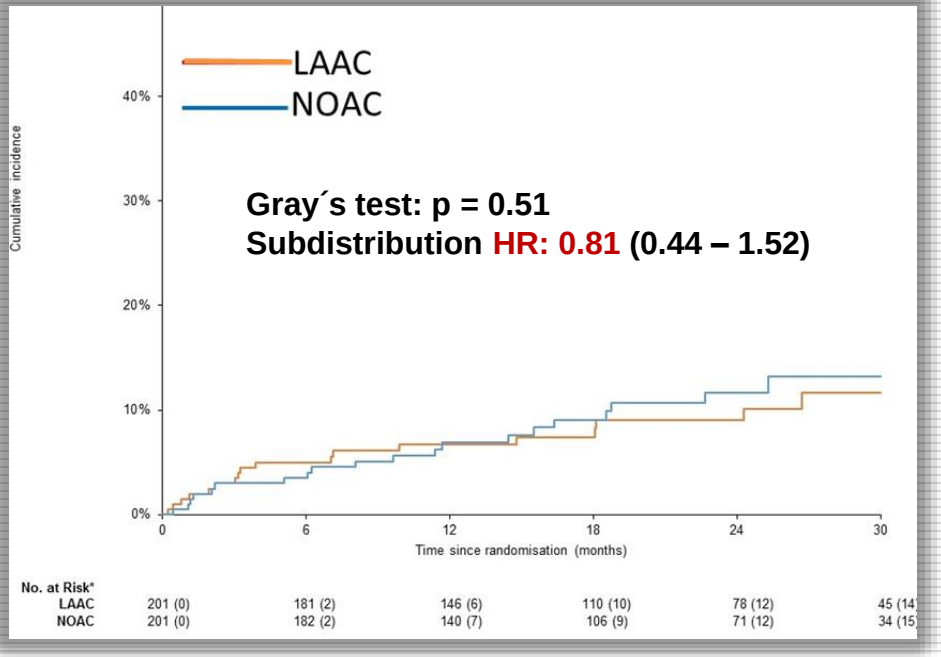
402 AF Patients with one of below:
I: Hx of bleeding requiring int/hos
II: Hx of SE on OAC
III: $CHA_2DS_2$-VASc ≥ 3 & HAS-BLED ≥ 2

1 → **WATCHMAN™ or Amulet™**
DAPT for 3 Mos and ASA indefinitely

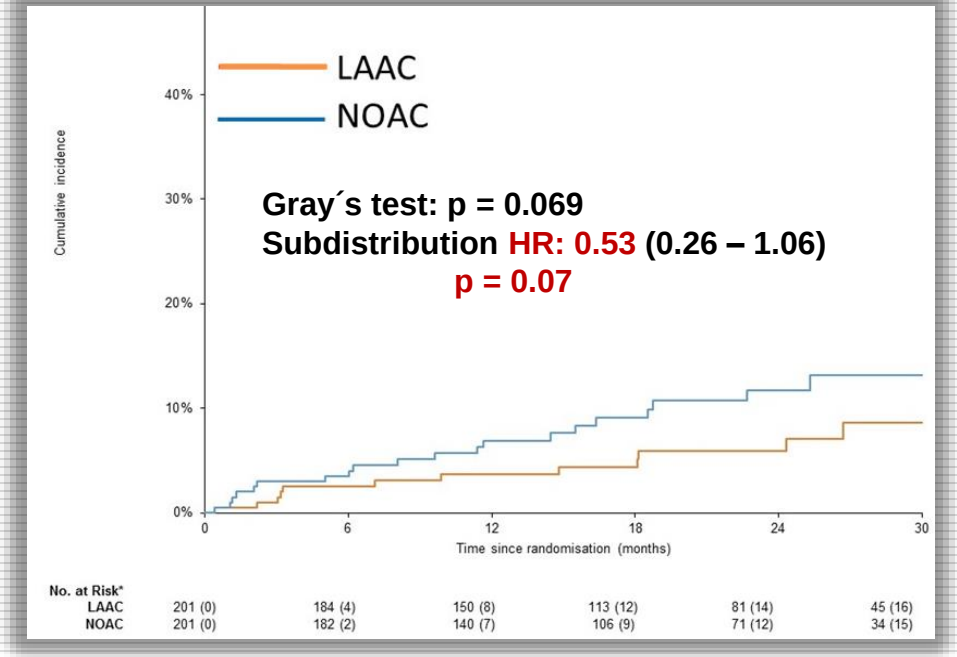
1 → Apixaban (preferred), Rivaroxaban, or Dabigatran

- Primary endpoint : composite of stroke, TIA, SE, significant bleeding, CV death or periprocedural or device related complications
- Primary hypothesis: LAAC is noninferior to NOAC for primary endpoint

### Clinically significant bleeding




### Non- procedure clinically significant bleeding




ESC 2019, RCT#NCT02426944

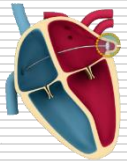
# Other Ongoing RCTs
## LAA Closure versus NOACs in High-Risk AF Patients

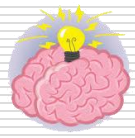
| | ***CLOSURE-AF*** | ***OCCLUSION-AF*** | ***STROKECLOSE*** |
|---|---|---|---|
| Treatment groups | LAAC *vs.* NOAC/Warfarin | Watch/Amulet *vs* NOAC | Amu *vs* NOAC/α-plt/None |
| Post-LAAC regimen | DAPT | -- | DAPTx6wk → ASAx6mo |
| Study sample size | 1512 | 750 | 750 |
| Follow-up | 24 months | 24 – 60 months | 60 months |
| Primary endpoint | Stroke / SE / CV death<br>Major bleeding | Stroke / SE / All-death<br>Major bleeding | Stroke / SE / All-death<br>Major bleeding |
| Target population | CHADS-VASc ≥ 2, and<br>HASBLED ≥ 3, *or*<br>Hx cranial/spinal bleed, *or*<br>Hx major bleed, *or*<br>CKD (GFR < 30) | Ischenuc stroke w/in 6 mo, *or*<br>TIA + MRI+ w/in 6 mo | CHADS-VASc ≥ 2, *and*<br>ICH w/in 6 mo |
| Expected date of completion of primary results | February 2021 | August 2022 | May 2022 |

Derived from ClinicalTrials.gov

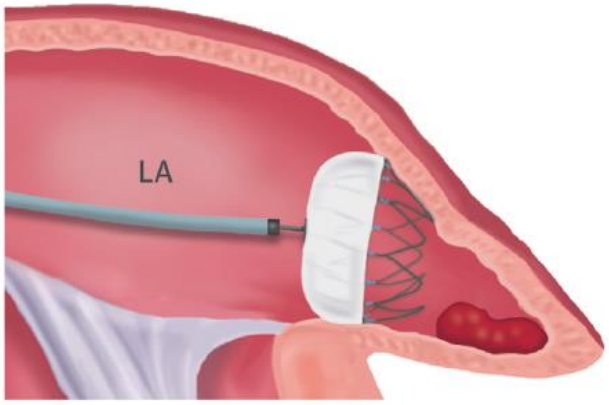
# Summary

- RCT (PROTECT AF, PREVAIL), registries, and propensity matched data showed that LA appendage closure is at least non-inferior to Vitamin K antagonists in OAC eligible patients.
- Post-procedural ischemic stroke and device-related thrombus remain an unresolved issue.
- Evidences are needed for LA appendage closure in patients with long-term contraindication to OAC. RCTs (ASAP-TOO, STROKE-CLOSE) are currently underway.
- RCT (Prague-17) comparing LA appendage closure to NOAC showed that LAA closure is non-inferior to NOACs in high ischemic/bleeding risk patients. Other RCTs are currently underway.

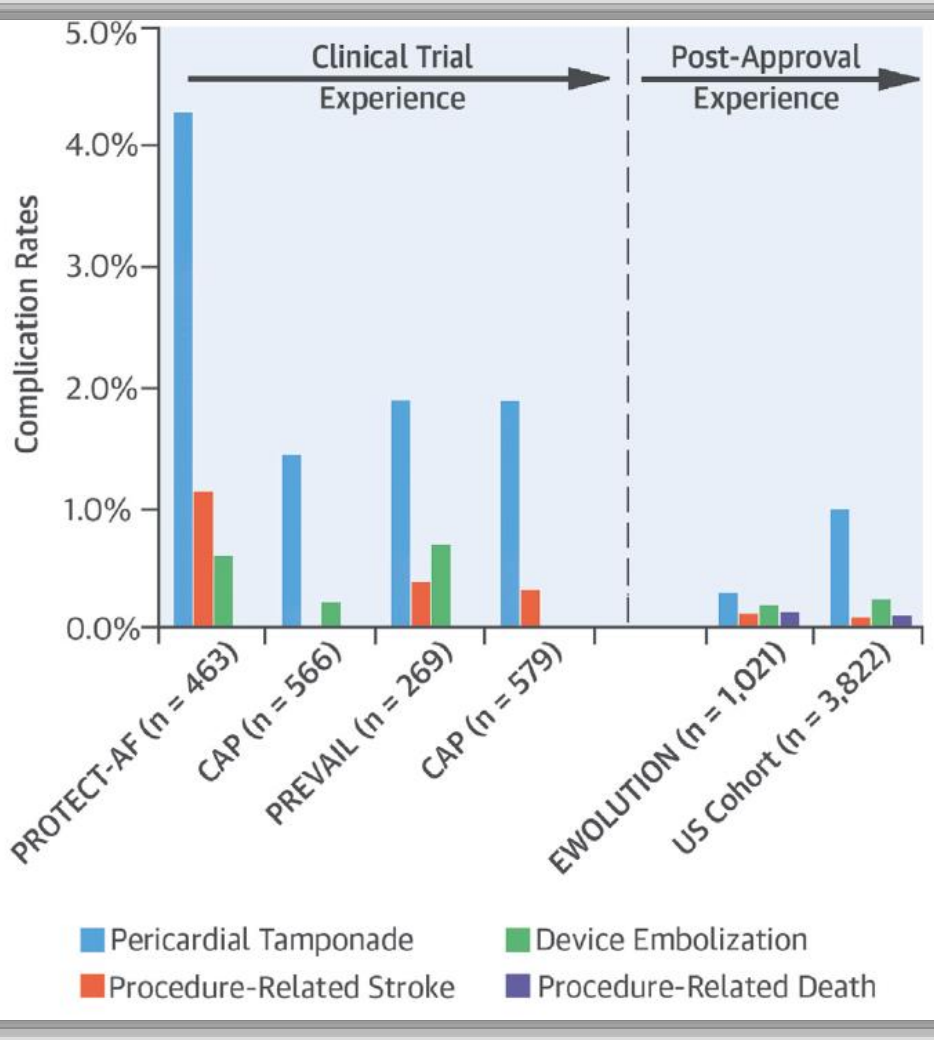




# Major Complication Rates Across WATCHMAN™ Clinical Studies




| Procedural Parameters | Aggregate Clinical Data |
|---|---|
| Number of Procedures | 6,720 |
| Implantation Success, % | 94.9% |
| **Complication Rates** | |
| Pericardial Tamponade | 1.24% |
| Procedure-Related Stroke | 0.18% |
| Device Embolization | 0.25% |
| Procedure-Related Death | 0.06% |



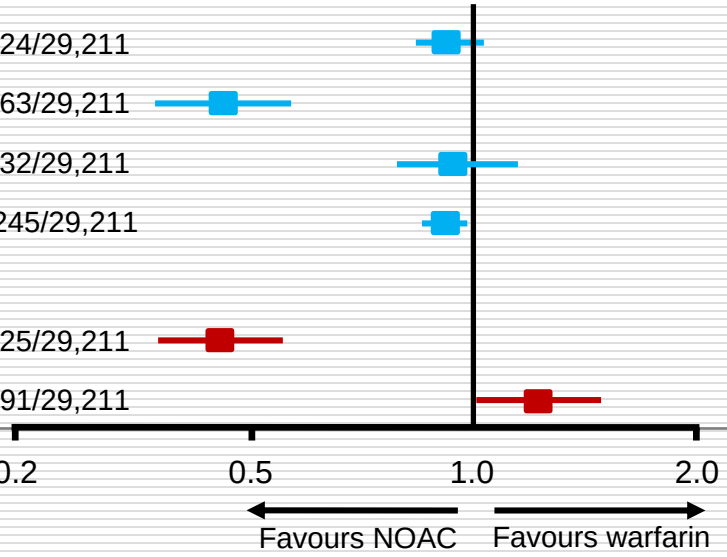

J Am Coll Cardiol 2017;69:253-261

# Meta-Analysis

## 71,633 Randomized Non-valvular AF Patients in 4 Trials (RE-LY, ROCKET AF, ARISTOLE, ENGAGE AF-TIMI 48)

### Secondary efficacy and safety outcomes

| | NOAC (events) | Warfarin (events) | RR (95% CI) | RR (95% CI) | *P* value |
|---|---|---|---|---|---|
| **Efficacy** | | | | | |
| Ischemic stroke | 665/29,292 | 724/29,211 | | 0.92 (0.83-1.02) | 0.10 |
| Hemorrhagic stroke | 130/29,292 | 263/29,211 | | 0.49 (0.38-0.64) | <0.0001 |
| MI | 413/29,292 | 432/29,211 | | 0.97 (0.78-1.20) | 0.77 |
| All-cause mortality | 2022/29,292 | 2245/29,211 | | 0.90 (0.85-0.95) | 0.0003 |
| **Safety** | | | | | |
| ICH | 204/29,287 | 425/29,211 | | 0.48 (0.39-0.59) | <0.0001 |
| GI bleeding | 751/29,287 | 591/29,211 | | 1.25 (1.01-1.55) | 0.04 |




Data are n, unless otherwise indicated.
Heterogeneity: Ischemic stroke $I^2$ 32%, *P*=0.22; hemorrhagic stroke $I^2$ 34%, *P*=0.21; MI $I^2$ 48%, *P*=0.13; all-cause mortality $I^2$ 0%, *P*=0.81; ICH $I^2$ 32%, *P*=0.22; **GI bleeding $I^2$ 74%, *P*=0.009**

*Dabigatran 150 mg BID; †Rivaroxaban 20 mg OD; ‡Apixaban 5 mg BID; §Edoxaban 60 mg OD.
Doses were reduced for apixaban, rivaroxaban and edoxaban in a subset of patients according to prespecified criteria.

Lancet 2014;383:955-962

# 2019 AHA/ACC/HRS Focused Update of Atrial Fibrillation

**Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits**

Referenced studies that support new or modified recommendations are summarized in Online Data Supplements 1 and 2.

| COR | LOE | Recommendations |
|---|---|---|
| I | A | 1. For patients with AF and an elevated $CHA_2DS_2$-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. Options include:<br>• Warfarin (LOE: A) (S4.1.1-5–S4.1.1-7)<br>• Dabigatran (LOE: B) (S4.1.1-8)<br>• Rivaroxaban (LOE: B) (S4.1.1-9)<br>• Apixaban (LOE: B) (S4.1.1-10), or<br>• Edoxaban (LOE: B-R) (S4.1.1-11)<br>**MODIFIED**: This recommendation has been updated in response to the approval of edoxaban, a new factor Xa inhibitor. More precision in the use of $CHA_2DS_2$-VASc scores is specified in subsequent recommendations. The LOEs for warfarin, dabigatran, rivaroxaban, and apixaban have not been updated for greater granularity as per the new LOE system. (Section 4.1. in the 2014 AF Guideline) The original text can be found in Section 4.1 of the 2014 AF guideline. Additional information about the comparative effectiveness and bleeding risk of NOACs can be found in Section 4.2.2.2. |
| I | B | |
| I | B | |
| I | B-R | |
| I | A | 2. NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) (S4.1.1-8–S4.1.1-11).<br>**NEW**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding. |