# Anticoagulation in Elderly AF Patients

## Drugs or Devices?

Win K. Shen, MD
Professor of Medicine
Mayo Clinic Arizona
Venice Arrhythmias, 2015

mayo

# DISCLOSURE

## Relevant Financial Relationship(s)

None

## Off Label Usage

None

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# Stroke Prevention in the Elderly
## Learning Objectives

- *A case study*
- *Summarize recent RCT: NOAC vs. Warfarin*
- *Review subgroup meta-analysis focusing on the elderly*
- *Describe specific considerations*
  - *Renal function*
- *Update clinical use of WATCHMAN in the U.S.*
- *Our patient*

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# Case Study

*A 78 year-old female, retired MD (hematologist), has had paroxysmal and persistent AF for 1 yr. She self-referred to discussed options to avoid "that rat poison", to continue skiing*

*Past medical history and ROS:*

*"Boarder line" HTN and DM; OSA on CPAP; "~ 3 glasses" wine/day*

*Exam:*

*Wt 62 Kg, BP 140/90 mmHg, HR 62 bpm, 1/6 holosystolic murmur*

*Current medications :*

*ASA 81 mg/day; lisinopril 10 mg/day; propafenone 225 mg BID, glyburide 1.25 mg qd.*

*Labs:*

*Echo mild MR, normal EF, moderate LA enlargement*

*FBS 120, Cr 1.8 (CrCl 24 cc/min)*

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# Case Study: Management
## Stroke Prevention

**What would you recommend for stroke prevention?**

1. Increase ASA to 325 mg/day
2. Add clopidogrel 75 mg/day
3. Start warfarin to target INR 2-3
4. Start dabigatran 110 mg BID
5. Start rivaroxaban 25 mg QD
6. Start apixaban 2.5 mg BID
7. Start edoxaban 30 mg QD
8. Offer WATCHMAN device

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# Case Study: Management
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*I AM SIMPLY LOST!!*

*Too Many Choices!*

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# Risk Stratification for Stroke
## Non-Valvular Atrial Fibrillation

| Risk factors | $CHADS_2$ score | $CHA_2DS_2$-VASc score | Total | $CHADS_2$ Adj risk score (%/yr) | Total | $CHA_2DS_2$-VASc Adj risk score (%/yr) |
|---|---|---|---|---|---|---|
| | | | 0 | 1.9 (1.2-3.0) | 0 | 0.0 |
| CHF | 1 | 1 | 1 | 2.8 (2.0-3.8) | 1 | 1.3 |
| HTN | 1 | 1 | 2 | 4.0 (3.1-5.1) | 2 | 2.2 |
| Age ≥75 | 1 | 2 | 3 | 5.9 (4.6-7.3) | 3 | 3.2 |
| DM | 1 | 1 | 4 | 8.5 (6.3-11.1) | 4 | 4.0 |
| Stroke/TIA/ thromboembolism | 2 | 2 | 5 | 12.5 (8.2-17.5) | 5 | 6.7 |
| Vascular disease | – | 1 | 6 | 18.2 (10.5-27.4) | 6 | 9.8 |
| Age 65-74 | – | 1 | | | 7 | 9.6 |
| Female gender | – | 1 | | | 8 | 6.7 |
| | | | | | 9 | 15.2 |
| Maximum score | 6 | 9 | | | | |

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# Clinical Characteristics Comprising the HAS-BLED Bleeding Risk Score

| Letter | Clinical characteristic | Points awarded |
|---|---|---|
| H | Hypertension | 1 |
| A | Abnormal renal or liver function (1 point each) | 1 or 2 |
| S | Stroke | 1 |
| B | Bleeding | 1 |
| L | Labile INRs | 1 |
| E | Elderly (eg, age >65 years) | 1 |
| D | NSAID or alcohol (1 point each) | 1 or 2 |

Maximum 9 points

Increased bleeding risk ≥ 3

Lip et al, JACC 2011

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# Trials of Anticoagulation for AF
## New Oral Anticoagulants vs. Warfarin

ROCKET AF

*(Rivaroxaban)*

RELY®
Study of stroke prevention in atrial fibrillation

*(Dabigatran)*

*ARISTOTLE*
*(Apixaban)*

*AVERROES*
*(Apixaban vs. ASA)*

*ENGAGE AF*
*(Edoxaban)*

- 4 trials
- 4 drugs
- Dabigatran
- Apixaban
- Rivaroxaban
- Edoxaban
- >71,000 patients with broad risk profiles

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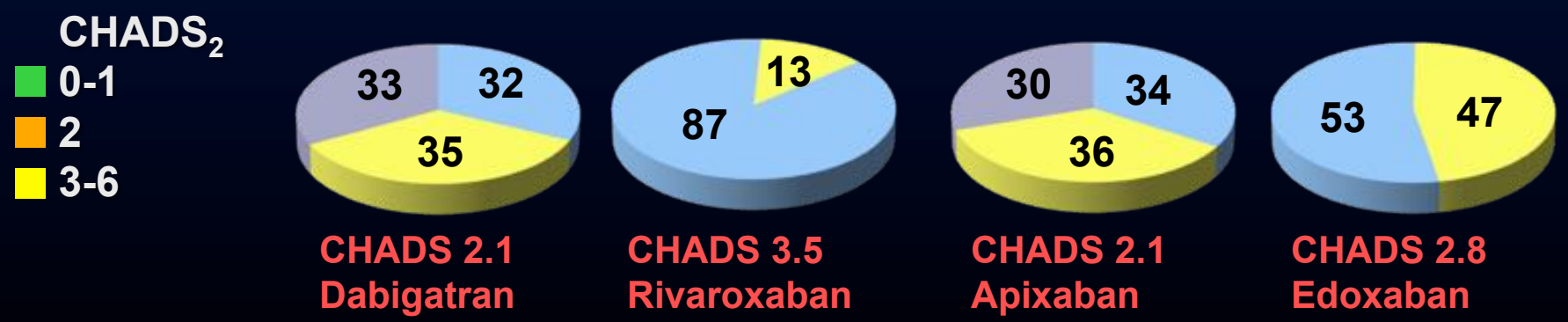
# Baseline Characteristics

| | RE-LY | ROCKET-AF | ARISTOTLE | ENGAGE - AF |
|---|---|---|---|---|
| Randomized (no.) | 18,113 | 14,264 | 18,201 | 21,105 |
| Age (yr) | 72±9 | 73 (65-78) | 70 (63-76) | 72 (64-78) |
| Female (%) | 37 | 40 | 35 | 38 |
| Paroxysmal AF | 32 | 18 | 15 | 25 |
| VKA naïve | 50 | 38 | 43 | 41 |
| Aspirin use | 40 | 36 | 31 | 29 |




Connolly SJ et al: NEJM 361:1139, 2009
Patel MR et al: NEJM 365:883, 2011
Granger CB et al: NEJM 365:981, 2011
Grugliano RP et al: NEJM, 2013

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# Characteristics of Novel Oral Anticoagulants

| Characteristic | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| Drug class | Direct factor IIa inhibitor | Direct factor Xa inhibitor | Direct factor Xa inhibitor | Direct factor Xa inhibitor |
| Molecular weight (daltons) | 628 | 436 | 460 | 548 |
| Protein binding (%) | 35 | >90 | 87 | 54 |
| Bioavailability (%) | 6 | 80 | 50 | >60 |
| $T_{max}$ (hrs) | 1-3 | 2-4 | 1-3 | 1-3 |
| Half-life (hrs) | 14-17 | 5-9 | 8-15 | 9-11 |
| Renal excretion (%) | 80 | 36 | 25 | 40 |
| Dialyzable | Yes | Unlikely | Unlikely | Unlikely |
| CYP metabolism | No | 30% CYP3A4, CYP2J2 | 15% CYP3A4 | <4% CYP3A4 |
| P-glycoprotein transport | Yes | Yes | Yes | Yes |

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Wittkowsky: Pharmacotherapy 31(12):1175, 2011

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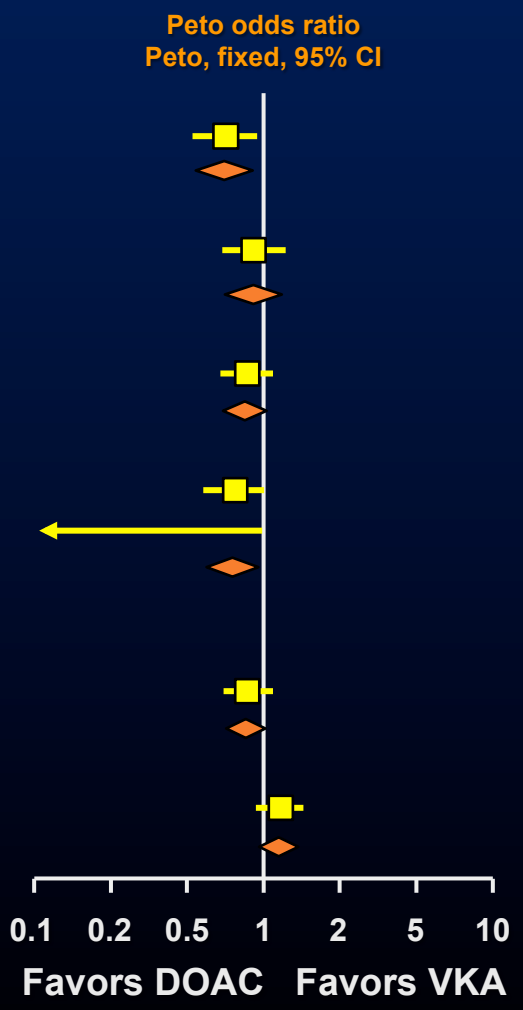
# Risk of Stroke or Systemic Embolism in the Elderly
## Age ≥ 75 Years

| Study or subgroup | DOAC Events | DOAC Total | VKA Events | VKA Total | Peto odds ratio Peto, fixed, 95% CI |
|---|---|---|---|---|---|
| **1.1.1 Dabigatran 150 mg vs VKA** | | | | | |
| Re-ly | 69 | 2466 | 101 | 2423 | 0.66 (0.49, 0.90) |
| Subtotal (95% CI) | | 2486 | | 2423 | 0.66 (0.49, 0.90) |
| **1.1.2 Dabigatran 110 mg vs VKA** | | | | | |
| Re-ly | 87 | 2349 | 101 | 2423 | 0.88 (0.66, 1.18) |
| Subtotal (95% CI) | | 2349 | | 2423 | 0.88 (0.66, 1.18) |
| **1.1.3 Rivaroxaban vs VKA** | | | | | |
| Rocket-AF | 125 | 3082 | 154 | 3082 | 0.80 (0.63, 1.02) |
| Subtotal (95% CI) | | 3082 | | 3082 | 0.80 (0.63, 1.02) |
| **1.1.4 Apixaban vs VKA** | | | | | |
| Aristotle | 79 | 2850 | 109 | 2828 | 0.71 (0.53, 0.95) |
| Aristotle-J | 0 | 45 | 2 | 23 | 0.05 (0.00, 0.95) |
| Subtotal (95% CI) | | 2895 | | 2851 | 0.70 (0.52, 0.93) |
| Heterogeneity: $Chi^2$-3.10, df=1 (P=0.08); $I^2$=68% | | | | | |
| **1.1.5 Edoxaban 60 mg vs VKA** | | | | | |
| Engage-AF-Timi 48 | 138 | 2848 | 166 | 2820 | 0.81 (0.65, 1.03) |
| Subtotal (95% CI) | | 2848 | | 2820 | 0.81 (0.61, 1.03) |
| **1.1.6 Edoxaban 30 mg vs VKA** | | | | | |
| Engage-AF-Timi 48 | 184 | 2806 | 166 | 2820 | 1.12 (0.90, 1.39) |
| Subtotal (95% CI) | | 2806 | | 2820 | 1.12 (0.90, 1.39) |

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Sharma et al: Circulation 132:194, 2015

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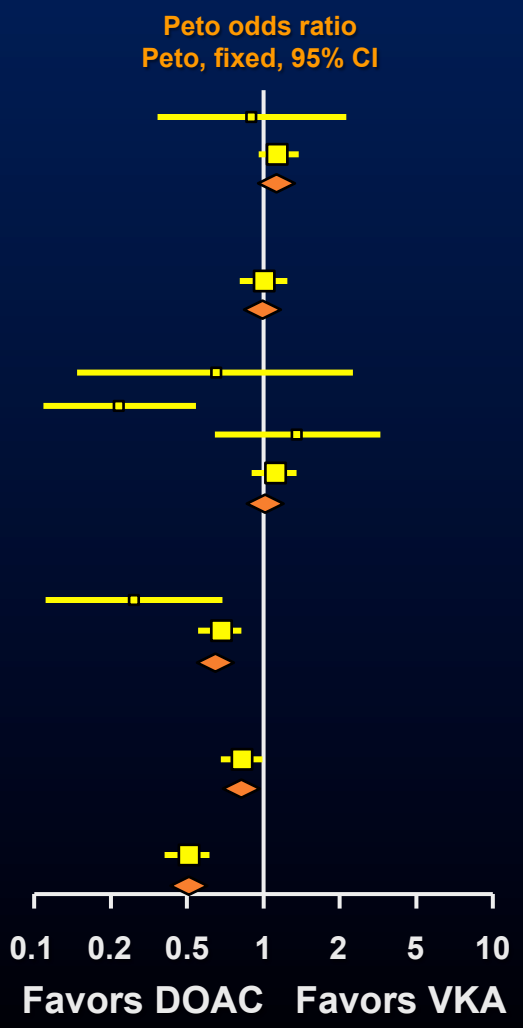
# Risk of Major Bleeding in the Elderly

## Age ≥ 75 Years

| Study or subgroup | DOAC Events | DOAC Total | VKA Events | VKA Total | Peto odds ratio Peto, fixed, 95% CI |
|---|---|---|---|---|---|
| **1.3.1 Dabigatran 150 mg vs VKA** | | | | | |
| Pooled recover studies | 8 | 231 | 10 | 262 | 0.90 [0.35, 2.32] |
| Re-ly | 227 | 2145 | 188 | 2088 | 1.20 [0.98, 1.46] |
| Subtotal (95% CI) | | 2376 | | 2350 | 1.18 [0.97, 1.44] |
| Hetereogeneity: $Chi^2$=0.32, df=1 (P=0.57); $I^2$=0% | | | | | |
| **1.3.2 Dabigatran 110 mg vs VKA** | | | | | |
| Re-ly | 187 | 2026 | 188 | 2088 | 1.03 [0.83, 1.27] |
| Subtotal (95% CI) | | 2026 | | 2088 | 1.03 [0.83, 1.27] |
| **1.3.3 Rivaroxaban vs VKA** | | | | | |
| Einstein-DVT | 3 | 215 | 5 | 223 | 0.62 [0.15, 2.52] |
| Einstein-PE | 5 | 440 | 23 | 401 | 0.24 [0.11, 0.51] |
| J-Rocket AF | 14 | 206 | 10 | 207 | 1.43 [0.63, 3.26] |
| Rocket-AF | 203 | 2688 | 179 | 2702 | 1.15 [0.93, 1.42] |
| Subtotal (95% CI) | | 3549 | | 3533 | 1.04 [0.86, 1.26] |
| Hetereogeneity: $Chi^2$=16.54, df=3 (P=0.0009); $I^2$=82% | | | | | |
| **1.3.4 Apixaban vs VKA** | | | | | |
| Amplify | 4 | 398 | 16 | 370 | 0.27 [0.11, 0.66] |
| Aristotle | 151 | 2836 | 224 | 2819 | 0.65 [0.53, 0.81] |
| Subtotal (95% CI) | | 3234 | | 3189 | 0.63 [0.51, 0.77] |
| Hetereogeneity: $Chi^2$=3.60, df=1 (P=0.06); $I^2$=72% | | | | | |
| **1.3.5 Edoxaban 60 mg vs VKA** | | | | | |
| Engage-AF-Timi 48 | 214 | 2848 | 257 | 2820 | 0.81 [0.67, 0.98] |
| Subtotal (95% CI) | | 2848 | | 2820 | 0.46 [0.38, 0.57] |
| **1.3.6 Edoxaban 30 mg vs VKA** | | | | | |
| Engage-AF-Timi 48 | 121 | 2806 | 257 | 2820 | 0.46 [0.38, 0.57] |
| Subtotal (95% CI) | | 2806 | | 2820 | 0.46 [0.38, 0.57] |

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Sharma et al: Circulation 132:194, 2015

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# Novel Drugs
## Major Exclusions

- RE-LY: dabigatran 150 mg BID, 110 mg BID
  - Exclusion: cr cl ≤ 30 cc/min, BP > 180/100 mmHg
- ROCKET: rivaroxaban 20 mg QD
  - Exclusion: cr cl < 30 cc/min, > 100 mg ASA/day
  - Dose adjusted: 15 mg QD, cr cl 30 - 49 cc/min
- ARISTOTLE: apixaban 5 mg BID
  - Exclusion: cr cl < 25 cc/min, cr > 2.5, > 165 mg ASA/day
  - Dose adjusted: 2.5 mg bid (2/3): age ≥80, weight ≤60 kg, creatinine ≥1.5
- ENGAGE (edoxaban 60 mg QD)
  - Exclusion: cr cl < 30 cc/min, DAPT
  - Dose adjusted: 30 mg qd (1/4): cr cl 30 - 49 cc/min, weight ≤60 kg, use of verapamil, quinidine, dronedarone
- Renal impairment is independent risk factor for stroke, for bleeding, for death

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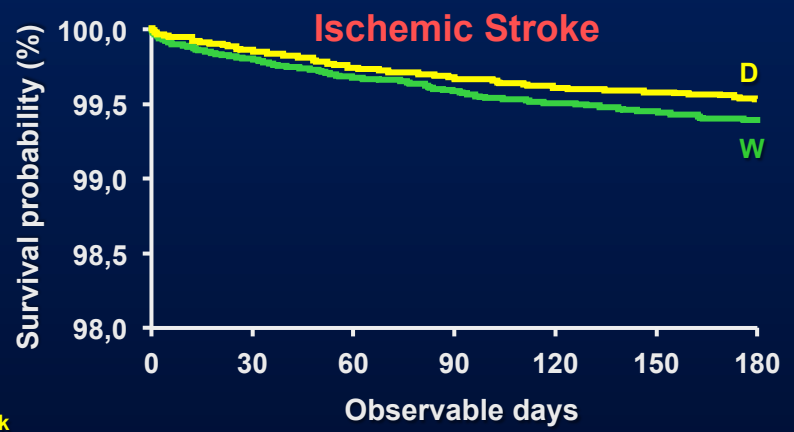
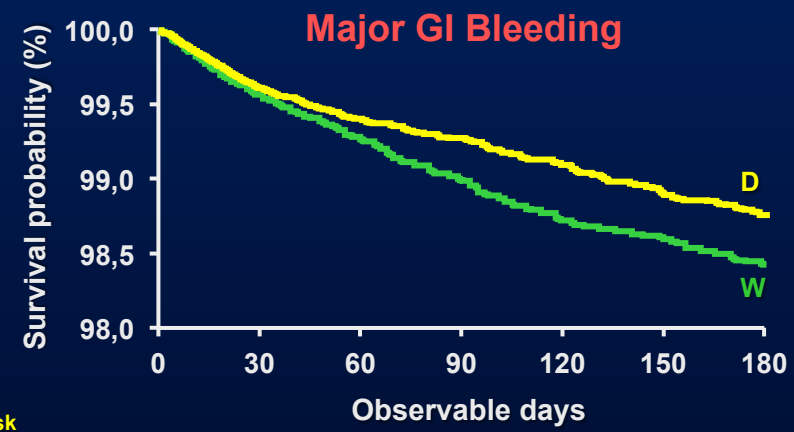
# Dabigatran in the Medicare Population
## 134,414 Participants, 2010 - 2012




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Warfarin (W) | 67,207 | 60,238 | 40,757 | 31,740 | 17,550 | 13,812 | 11,389 |
| Dabigatran (D) | 67,207 | 61,498 | 34,258 | 25,686 | 17,365 | 13,715 | 11,208 |




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Warfarin (W) | 67,207 | 60,238 | 40,757 | 31,740 | 17,550 | 13,812 | 11,389 |
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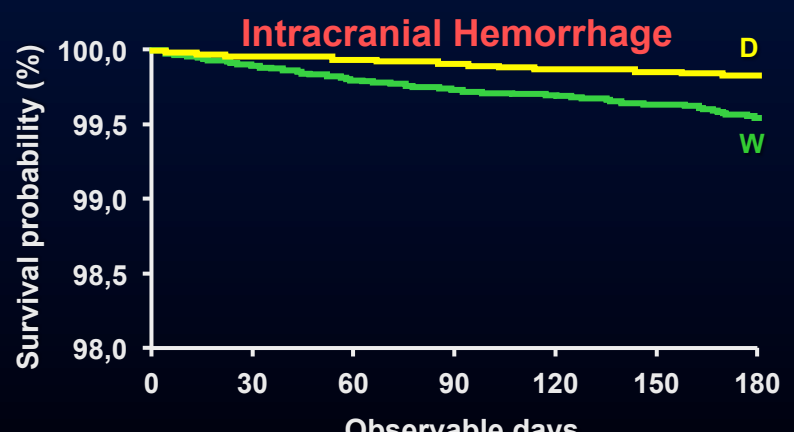


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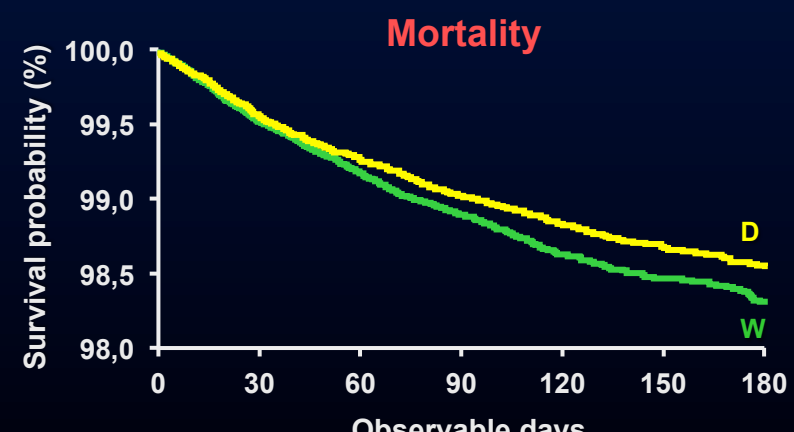


| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Warfarin (W) | 67,207 | 60,921 | 41,062 | 31,907 | 17,659 | 13,874 | 11,440 |
| Dabigatran (D) | 67,207 | 62,145 | 34,537 | 25,852 | 17,468 | 13,765 | 11,255 |

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Graham et al: Circulation 131:157, 2015

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# Renal Function and Novel Drugs

- RE-LY, ROCKET, ARSITOTLE, ENGAGE excluded patients with eGFR < 30 ml/min
- Dabigatran is 80% renally eliminated, rivaroxaban and apixaban are ~ 30%, edoxaban ~ 40%
- Renal impairment is independent risk factor for stroke, for bleeding, for death
- 150 mg bid of dabigatran should be used cautiously in the elderly (> 80 y/o) and with renal impairment (< 50 mL/min)
- Rivaroxaban should be used at 15 mg/d with CrCl <50 cc/min
- Apixaban should be used at 2.5 mg bid with 2 of 3: Age ≥80, weight ≤60 kg, creatinine ≥1.5
- Edoxaban is less effective than warfarin in patients with eGFR > 95 cc/min

- ***Adjust dose: eGFR < 50 ml/min, age > 80, wt < 60 Kg***
- ***Do Not Use NOACs in Patients with End-Stage Kidney Disease (CrCl < 15 ml/min or on hemodialysis)***

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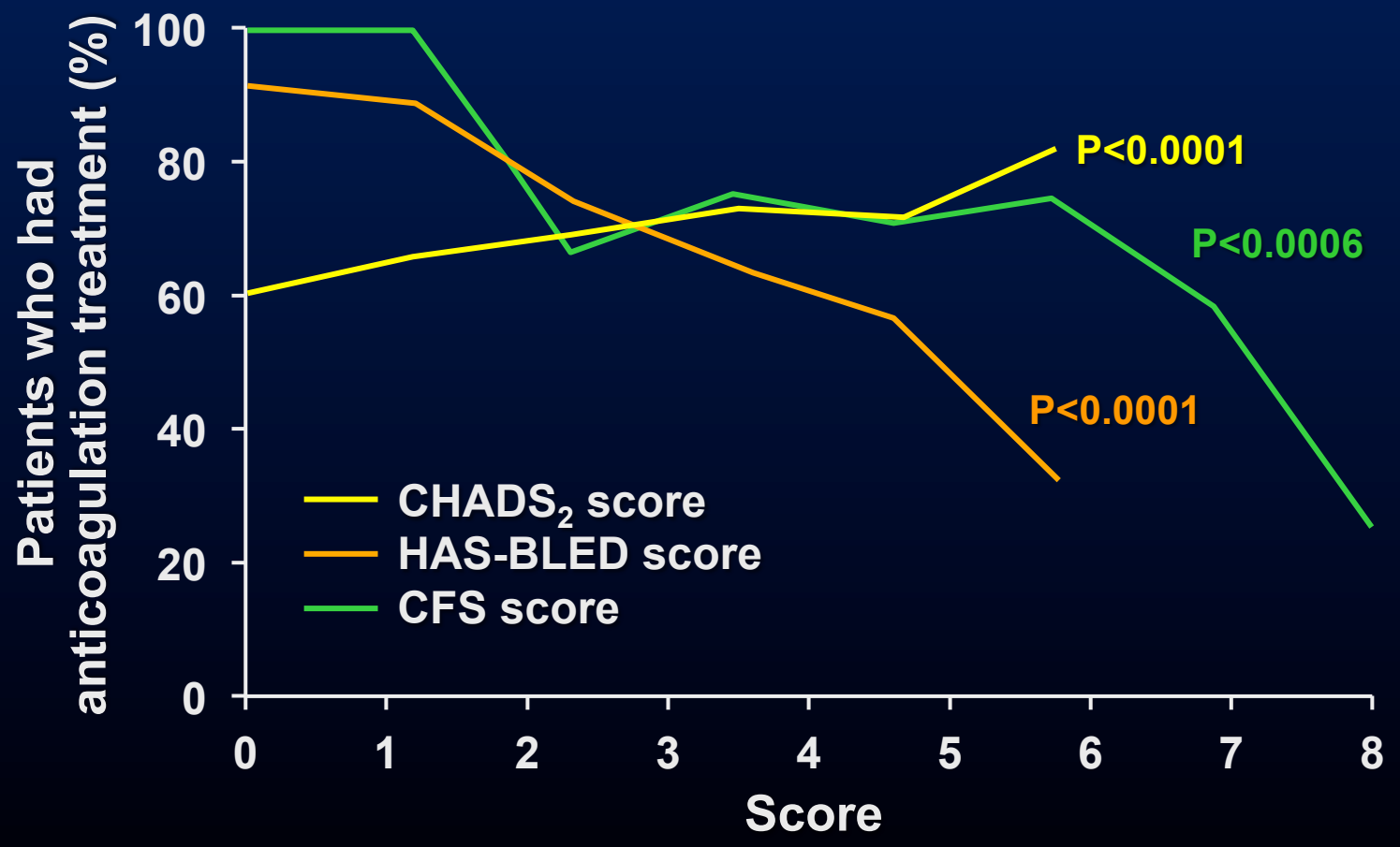
# Trends in Anticoagulant Prescriptions




Lefebvre et al: Canadian Journal of Cardiology 1e7, 2015

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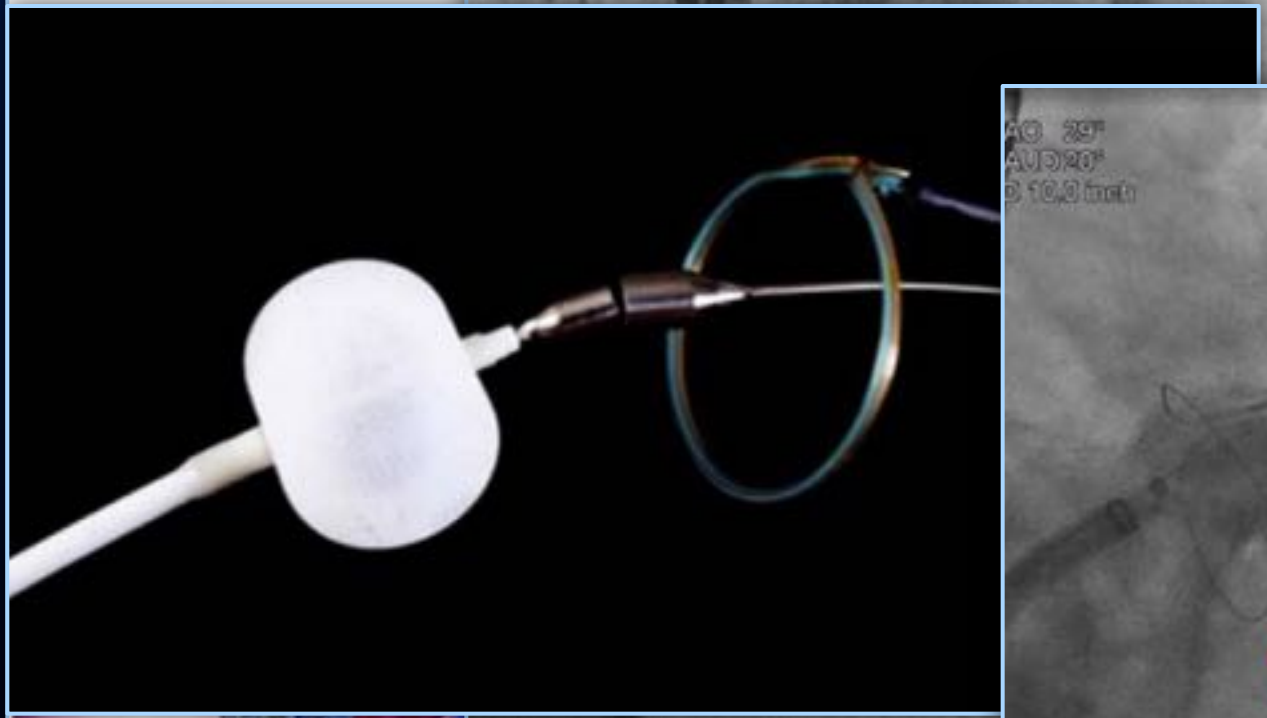
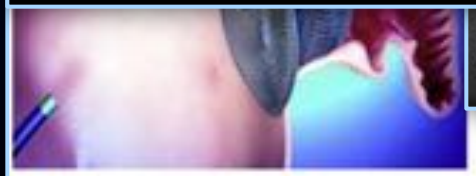
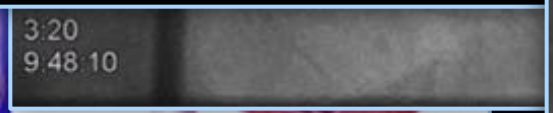
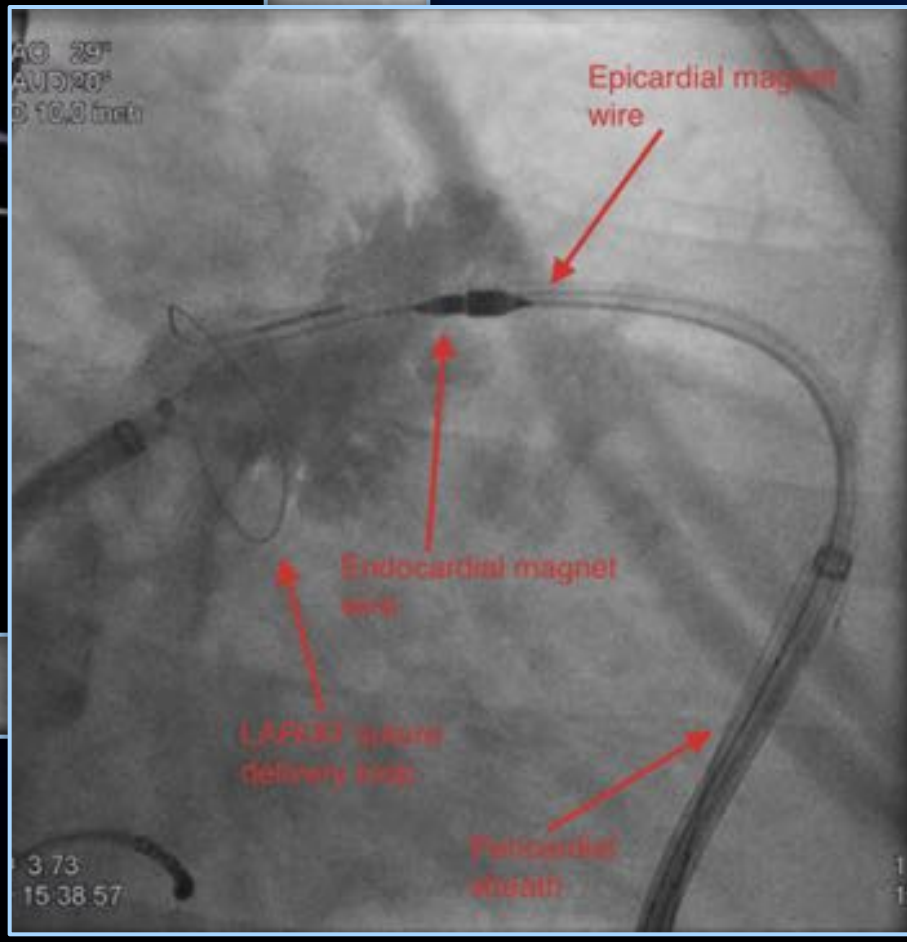
# Amplatzer





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**Lin and Knight: Progress in Cardiovascular Diseases 195, 2015**

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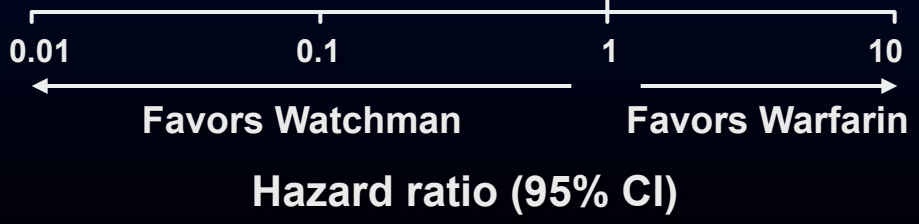
# WATCHMAN
## Meta-Analysis

| | HR | P |
|---|---|---|
| Efficacy | 0.79 | 0.22 |
| All stroke or SE | 1.02 | 0.94 |
| Ischemic stroke or SE | 1.95 | 0.05 |
| Hemorrhagic stroke | 0.22 | 0.004 |
| Ischemic stroke or SE >7 days | 1.56 | 0.21 |
| CV/Unexplained death | 0.48 | 0.006 |
| All-cause death | 0.73 | 0.07 |
| Major bleed, all | 1.00 | 0.98 |
| Major bleeding, non procedure-related | 0.51 | 0.002 |




Holmes et al: J Am Coll Cardiol 65:2614, 2015

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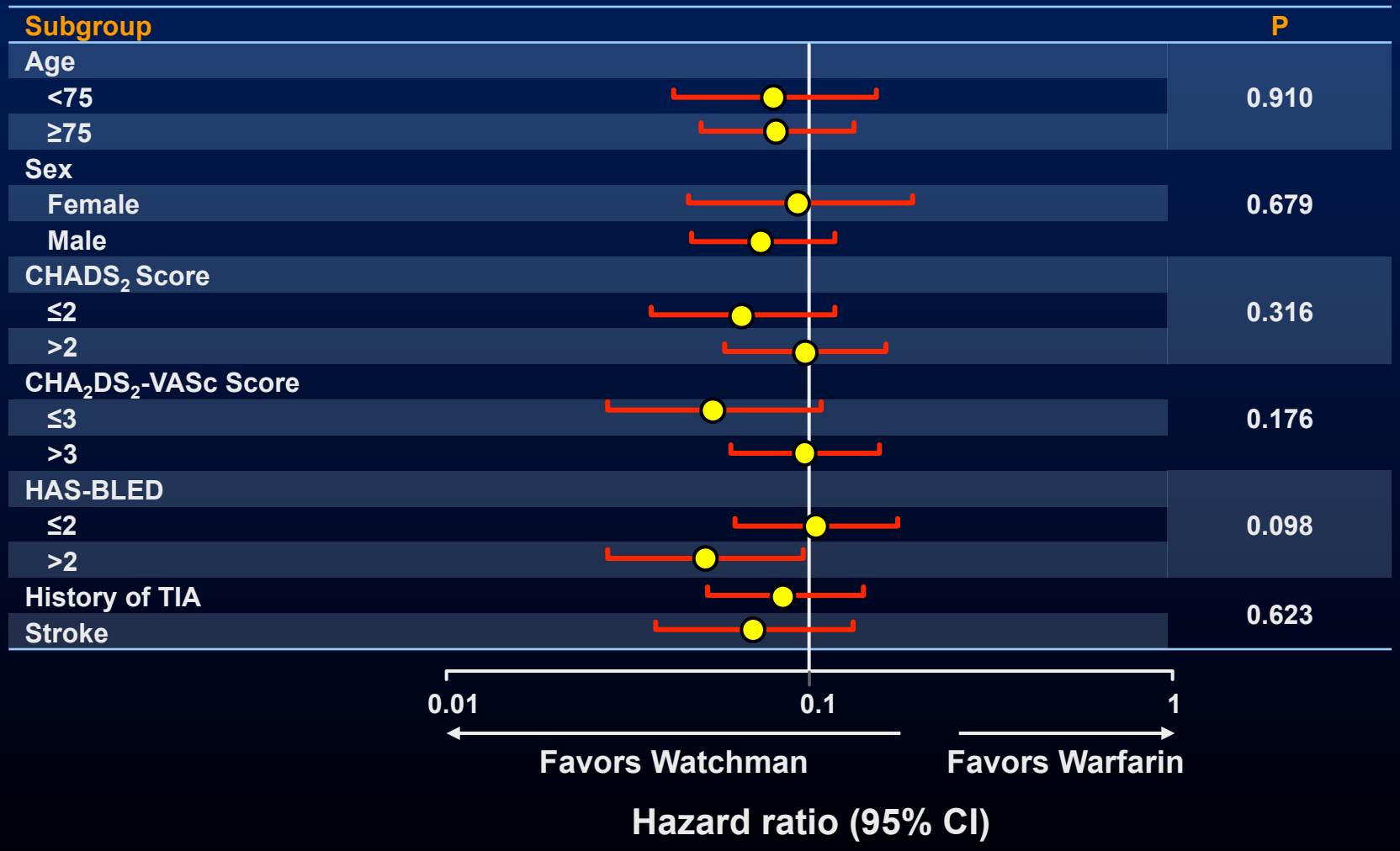
# WATCHMAN Pooled Data
## PROTECT AF/PREVAIL




Holmes et al: J Am Coll Cardiol 65:2614, 2015

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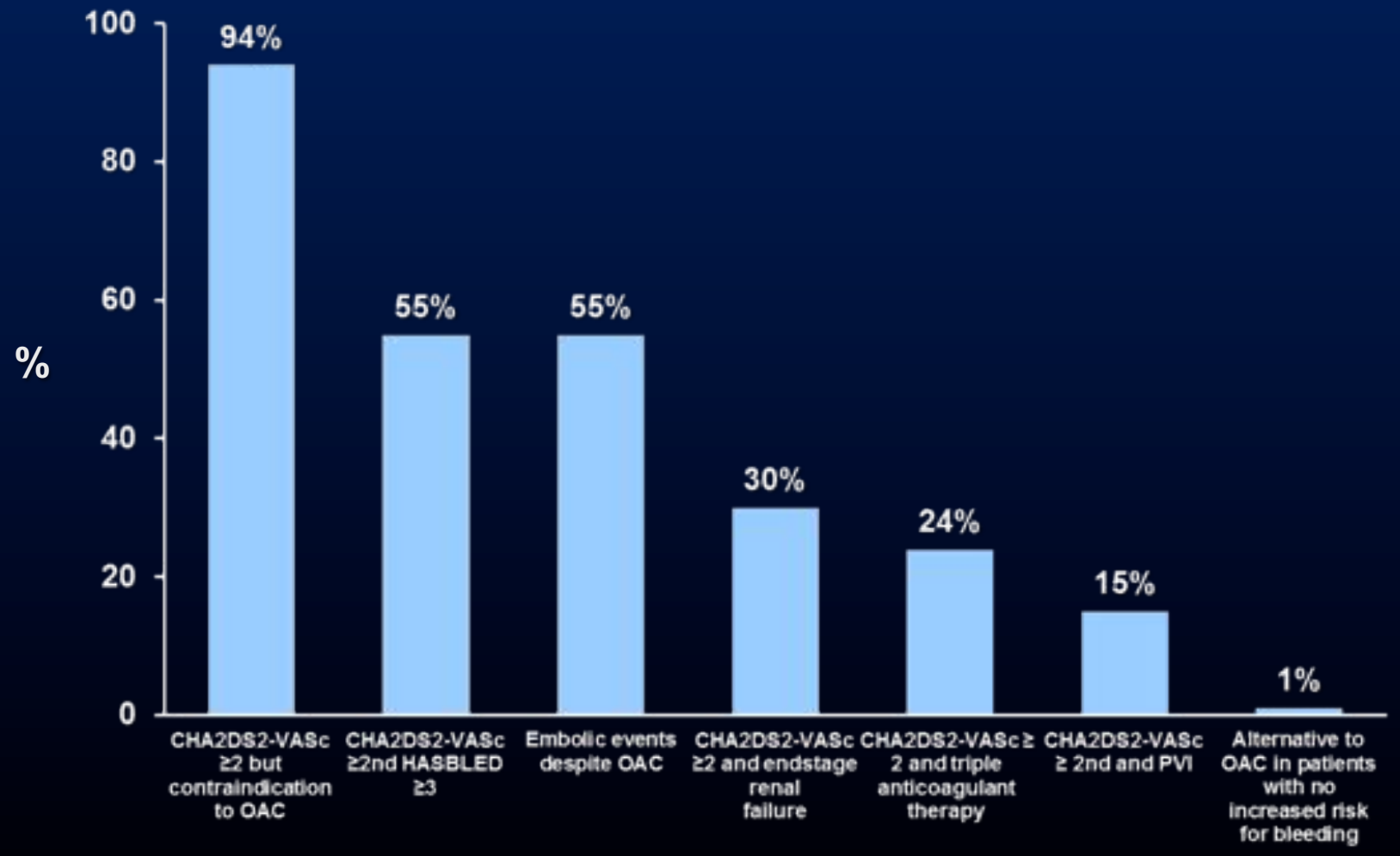
# Indications for LAA Closure
## EHRA Survey (33 Centers)




Pison et al: Europace 17, 642, 2015

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# Case Study

Our patient: a 78 year-old female, retired MD (hematologist), has had paroxysmal and persistent AF for 1 yr. She self-referred to discussed options to avoid "that rat poison", to continue skiing

CHADS-VASc 5; HAS-BLED 4

OAC vs. LAA closure: goals and risks were reviewed; she prefers LAA closure

Underwent WATCHMAN implantation: 0.5 cm pericardial effusion; no tamponade; warfarin x 6 wks followed by ASA 325 mg and clopidogrel x 6 months, than ASA 325 mg alone

Follow-up at 1 year: doing well on ASA; TEE peri-device leak ~ 25% of the LAA diameter

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# Anticoagulation in the Elderly
## OAC vs. LAA Closure

***OAC***

- ***Effective in stroke prevention***
- ***Long track record***
- ***Bleeding concerns***
- ***NOAC Dose adjustments for elderly with renal insufficiency***

***LAA Closure***

- ***RCTs have shown non-inferiority to warfarin***
- ***Procedural complications***
- ***No comparison studies to NOACs***
- ***Technology and techniques are evolving***
- ***Pts at increased risk for bleeding or with contraindications to OAC***

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CP996705-26

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# Stroke Prevention in Elderly with AF

## *AC or Devices?*

## Venice 2015

mayo

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