Management of Thromboembolism Risk Related to Atrial Fibrillation

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Few Concepts….

- Atrial Fibrillation = Atrial Flutter
  - *Everytime* the word “fibrillation” is used the same rationale applies to “flutter”
- ASA and Clopidogrel (Plavix)
  - Not anticoagulants
  - Net effect is increased complications

Anticoagulation for AF, Protocol #1: Peri-Cardioversion, For *Every* Patient

- Identical for Electrical CV, Pharmacologic CV or Restoration of SR with Ablation
- 3 consecutive weeks of AC before CV
- 6 weeks AC after CV
- TEE: eliminates the 3 wks AC prior to CV
  - *But* the pt MUST be AC prior / at time of CV
- Once CV, then use CHADS-VASc Score to determine need for long term AC

Anticoagulation for AF, Protocol #2: Thromboembolism Prophylaxis

- Use risk assessment tools
- CHA_2DS_2-VASc
- Anticoagulation is indeed *forever*
  - Recognize that decision re AC can change
  - In 5 years with new Dx of DM, change to AC
  - Reassess if bleeding risk changes

CHA_2DS_2-VASc Score

Major Risks (2 pts):

- Prior CVA / TIA
- Systemic embolism
- Age ≥ 75 yo

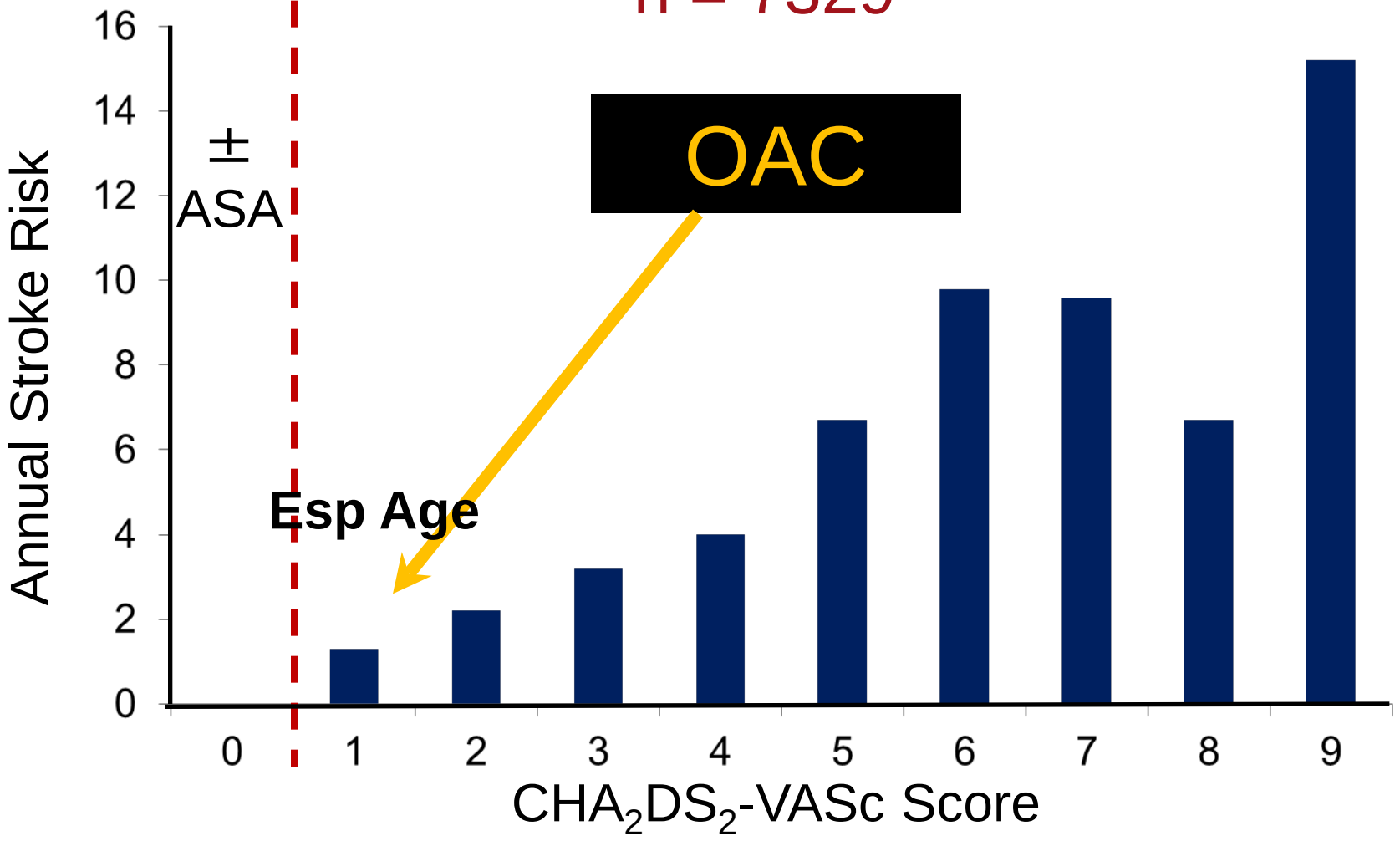
Non-Major Risks (1 pt):

- CHF / LVEF ≤ 40%
- HTN
- DM
- Female Sex
- Age 65-74
- Vascular Disease

Risk Factor	Score
Congestive HF	1
HTN	1
Age ≥ 75	2
DM	1
Stroke / TIA / TE	2
Vascular Disease	1
Age 65 - 74	1
Sex (ie, female)	1
Maximum Score	**9**

Adjusted Annual Stroke Risk Using CHA_2DS_2-VASc Score

n = 7329

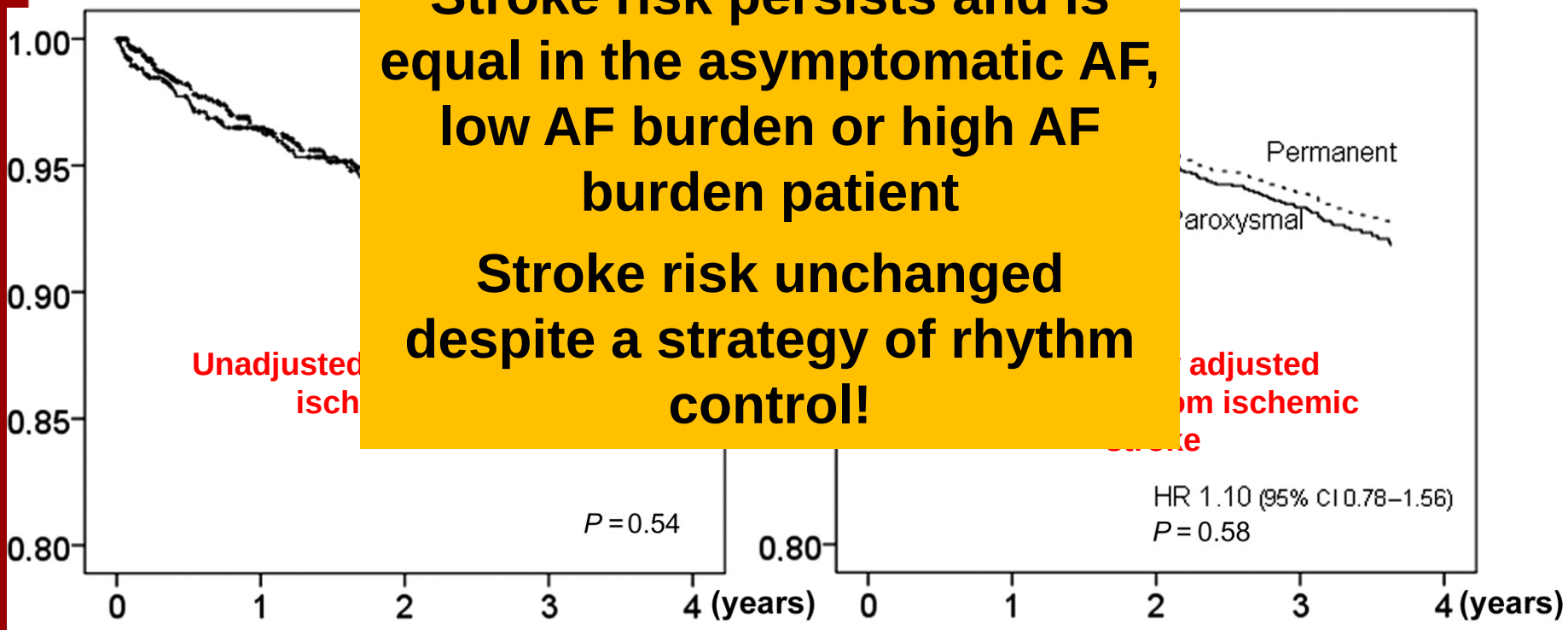


Camm AJ et al. *Eur Heart J*. 2010;31:2369-429.

Stroke in Atrial Fibrillation: Stockholm Cohort of AF

Stroke risk persists and is equal in the asymptomatic AF, low AF burden or high AF burden patient

Stroke risk unchanged despite a strategy of rhythm control!



At risk

	Index	1 year	2 years	3 years	4 years
PxAF	855	751	689	630	10
PermAF	1126	910	774	658	29

Friberg L et al. *Eur Heart J*. 2010;31:967-75.

Perception is Not Reality……
Use of AAD's and Maintenance of SR Does *Not* Reduce Stroke Risk.
Anticoagulation is Forever!!!

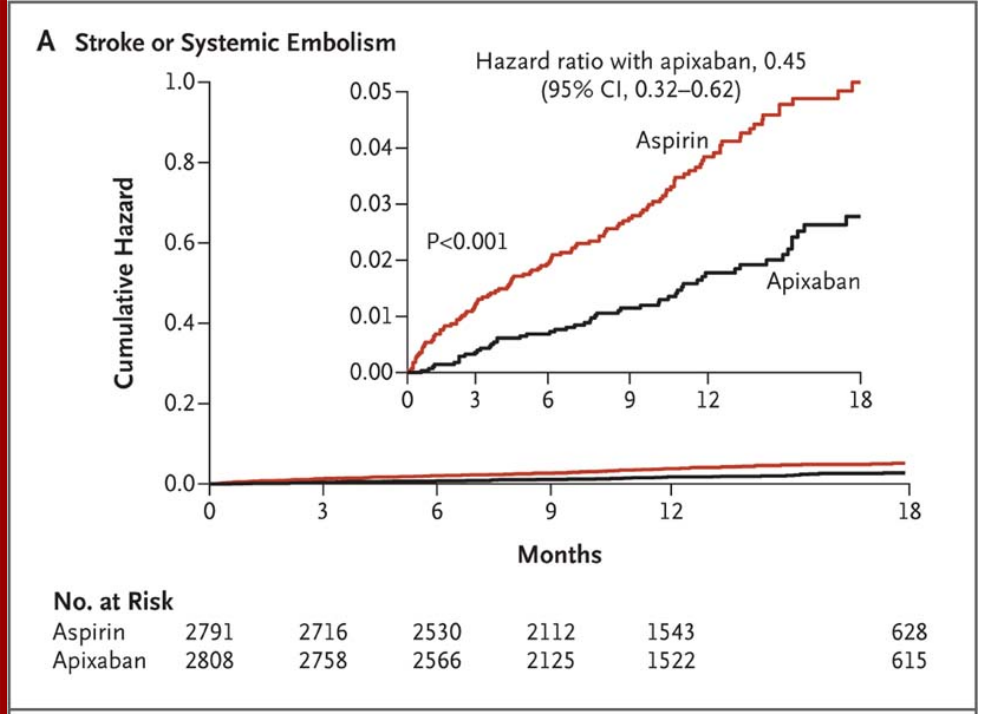
COMPARED TO WARFARIN				
	Apixaban (ARISTOTLE)	**Dabigatran 150 mg (RE-LY)**	**Rivaroxaban (ROCKET AF)**	**Edoxaban (ENGAGE AF-TIMI 48)**
Overall Mortality	↓ (p 0.047)	↔ (p 0.051)	↔ (p 0.15)	**Equal** c 60mg ↓ c 30mg (p 0.006)
Stroke and Systemic Embolism	↓ **(No decrease ischemic CVA)**	↓ **(↓ Ischemic & Hemorrhagic CVA)**	↔ **(No decrease ischemic CVA)**	↔ **(No decrease ischemic CVA)**
Major Bleeding	↓	↔	↔	↓
GI Bleeding	↔	↑	↑	↑ c 60mg / ↓ c 30mg
ICH	↓	↓	↓	↓
Indication	• stroke/embolism prevention in non-valvular AF • VTE Tx • VTE 2^0 prevention • VTE prevention after hip/knee replacement	• stroke/embolism prevention in non-	• stroke/embolism prevention in non-valvular AF VTE Tx VTE 2^0 prevention VTE prevention after hip/knee replacement	• stroke/embolism prevention in non-valvular AF • VTE Tx
Exclusions from trials	• **Valve disorders** • Stroke within 7 days • ASA > 100 or ASA+Plavix • CrCl < 25 OR SCr > 2.5 • Hgb < 9		**Valve disorder** CVA 14 days or severe CVA within 3 months ASA > 100 or ASA+Plavix CrCl ≤ 30 Hgb < 10	• **Valve disorders** • Stroke within 30 days • ASA > 100 or ASA+Plavix • CrCl < 30 • Hgb < 10
Renal Function Subgroup Analysis	• Significant S/SE redn only in CrCl 50-80 • Major bleeding significantly reduced in CrCl < 80 (no diff CrCl > 80)	• No diff in major bleeding	Significant S/SE reduction only in CrCL > 50 • No diff in major bleeding	• Harm with CrCl > 80 • Significant S/SE redn only in CrCl 50-80 • Major bleeding significantly reduced in CrCl < 80 (no Diff CrCl > 80)
Dosage Changes	If 2 out of 3: Age ≥ 80, Wt ≤ 60 Kg, SCr ≥ 1.5, ↓ dose to 2.5 mg bid	Use 75 mg bid for CrCl 15-30	Use 15 mg daily for CrCl 30-50	If CrCl > 95 (? >80), **AVOID USE** (↑ ischemic CVA due to ↓ blood levels by 30-40%)
Target (Warfarin – VKORC1 – II, VII, IX, X, C, S)	Factor Xa	Thrombin	Factor Xa	Factor Xa

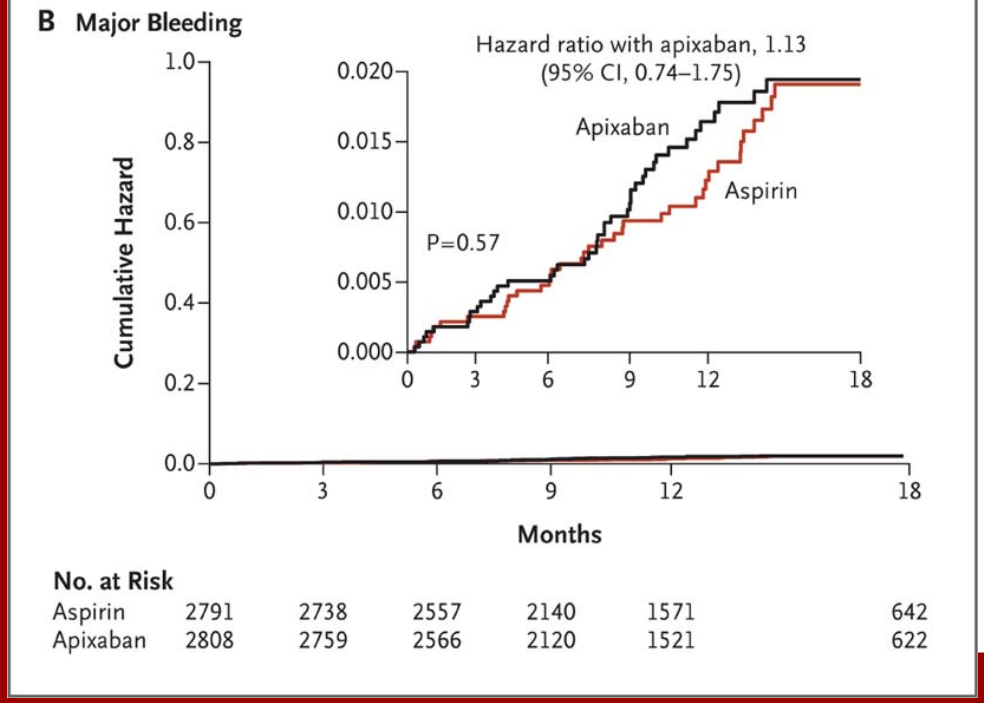
DOAC's are Better But DOAC's / Warfarin are Supported by Guidelines

	Apixaban	Dabigatran 150 mg	Rivaroxaban	Edoxaban
Bioavailability (Warfarin 100%)	50%	3-7% (↑ by 75% when pellets are taken w/o capsule shell (should NOT broken/chewed/opened) Requires pH 2-3 for absorption (coated with tartaric acid)	60-80% → Dose dependent; Food ↑ bioavailability by another 40%	62%
Time to peak effect	3-4 hrs $T_{1/2}$ ~12 hrs	1-2 hrs $T_{1/2}$ – 12-17 hrs	2-4 hrs $T_{1/2}$ – 5-9 hrs (healthy) and 11-13 hrs in elderly	1-2 hrs $T_{1/2}$ – 10-14 hrs
Metabolism	Liver: **CYP3A4** (primary) CYP1A2, 2C8, 2C9, 2C19, 2J2	**PRODRUG** → Hydrolyzed to active moiety then further metabolized thru conjugation.	Liver: **CYP3A4**/5 & CYP2J2	Minimal
Excretion	Renal 27%; Majority: Feces substrate of transport proteins: P-gp and BRCP	Oral: Renal 7%, Feces 86% Dabigatran etexilate - substrate of the efflux transporter P-gp	~33% unchanged urine (~66% metabolites in urine and feces)	Eliminated primarily as unchanged drug in the urine 50% Renal
Interactions	• ↑ - Keto/Itraconazole, HIV protease inhibitors • Mild Inc – Diltaizem • ↓ - Rifampin, carbamazepine, Phenytoin, St John's wort (inducers)	• ↑ - Dronedarone, Amio, verapamil, Quinidine, keto/Itraconazole, • ↓ - Rifampin, carbamazepine, Phenytoin, St John's wort (inducers) • mild decrease c Antacids • ↔ - Diltiazem	• ↑ - Keto/Itraconazole, HIV protease inhibitors • ↓ - Rifampin, carbamazepine, Phenytoin, St John's wort (inducers)	• ↑ - Dronedarone, Amio, verapamil, Quinidine, keto/Itraconazole, cyclosporine, tacrolimus • ↓ - Rifampin, carbamazepine, Phenytoin, St John's wort (inducers)
Reversal Agents	**Idarucizumab (Praxbind)** → Humanized antibody fragment (Fab) → Significantly exceeds thrombin affinity for binding dabigatran (350X higher) → Displaces dabigatran from thrombin and Irreversibly binds dabigatran and metabolites → Dose: 2.5 grams X2 (total dose= 5 grams) IV push or IVPB → Onset- minutes	**Andexanet alfa** → Recombinant, inactivated FXa decoy protein → Cannot form prothrombinase complex on PLT surface and Cannot bind prothrombin → Binds Xa inhibitors, ATIII complexed with LMWH → Onset: minutes → DOSING: 400mg bolus or 400mg bolus + infusion	**Andexanet alfa** → Recombinant, inactivated FXa decoy protein → Cannot form prothrombinase complex on PLT surface and Cannot bind prothrombin → Binds Xa inhibitors, ATIII complexed with LMWH → Onset: minutes → DOSING: 800mg bolus or 800mg bolus + infusion	

Why DOACs are Better

- No variability. Constant Therapy
  - Warfarin – high INR variability & low time in therapeutic window
- Greater compliance
- No monitoring
- Reduce stroke and bleeding
  - Some associated with decreased mortality
- *But…*
  - Not for valve replacement
  - Careful in kidney disease





Even With Successful Ablation of AFib…..Why I Continue Anticoagulation with DOAC but Not Warfarin

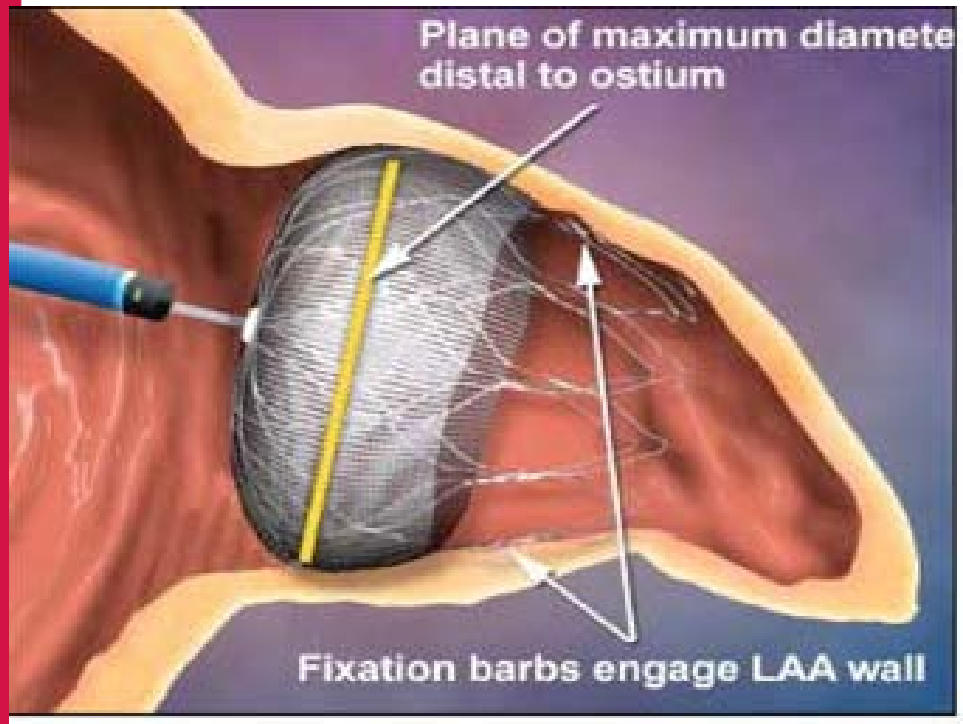
AVERROES: >5000 pts Apixaban 5 mg twice daily, vs ASA in AF pts for whom warfarin was considered unsuitable

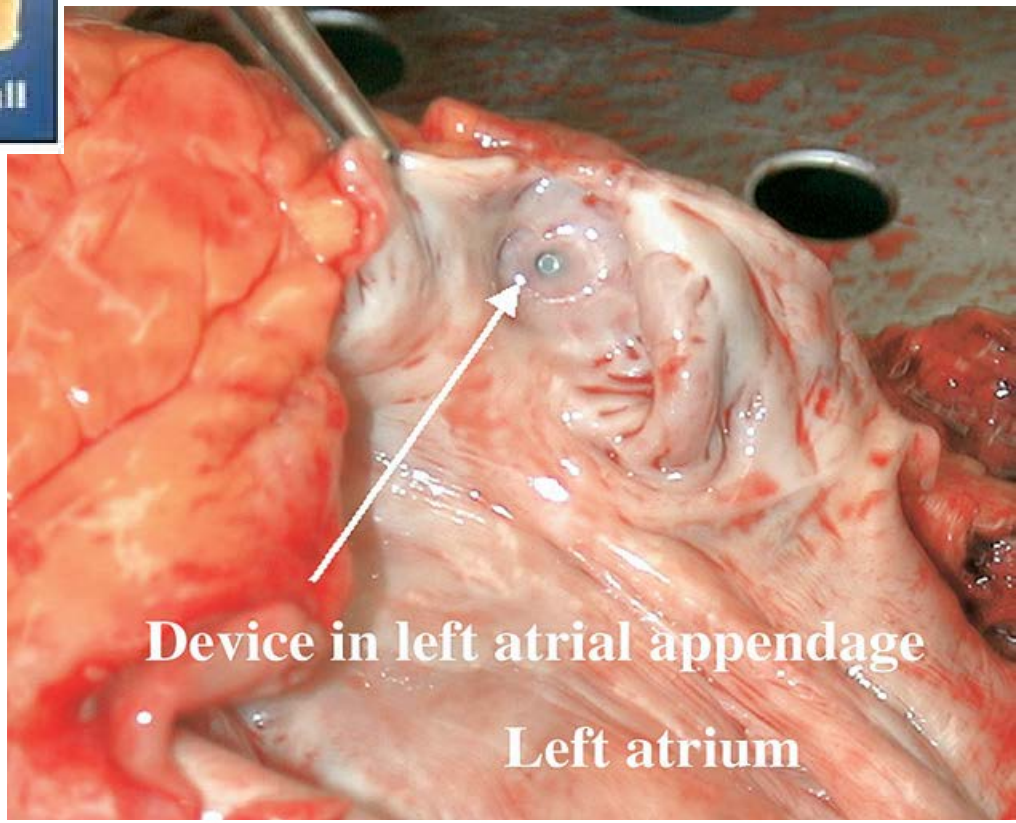
Apixaban reduced stroke

Apixaban vs ASA No difference in bleeding

New Thinking

- So why switch from Apixaban to ASA?
- Even for CHADSVASc = 0 or 1?
- Not all anticoagulants are the same
  - DOACs are not warfarin…so everything needs to be carefully reconsidered

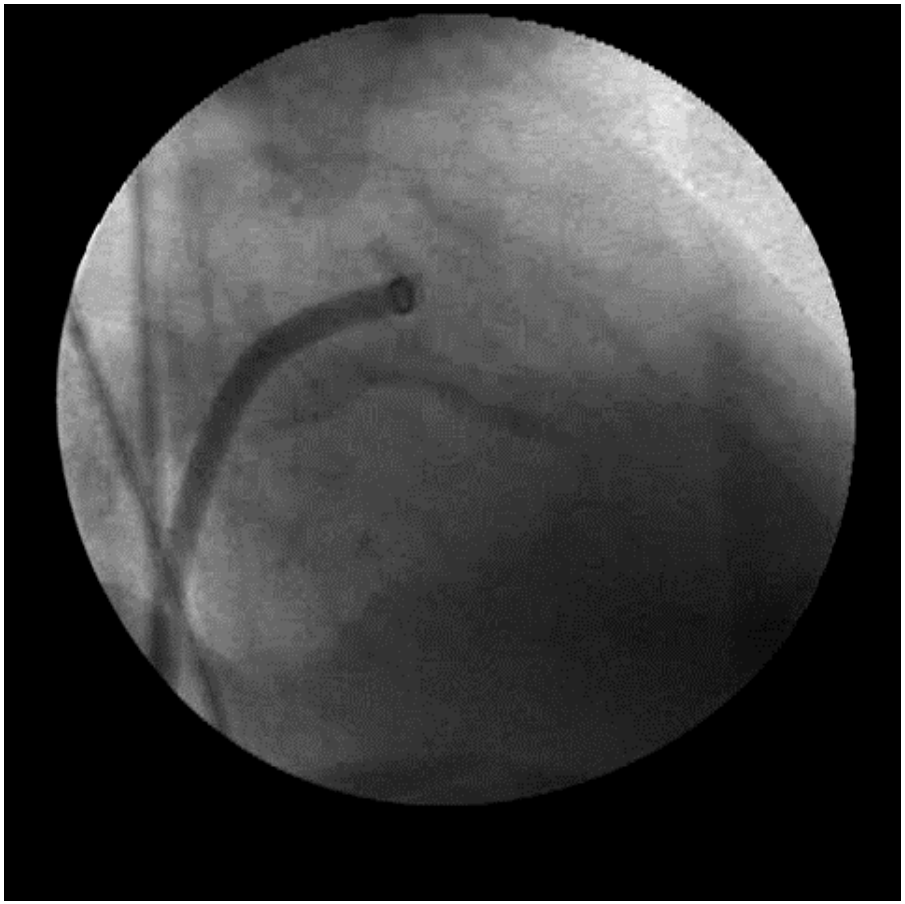


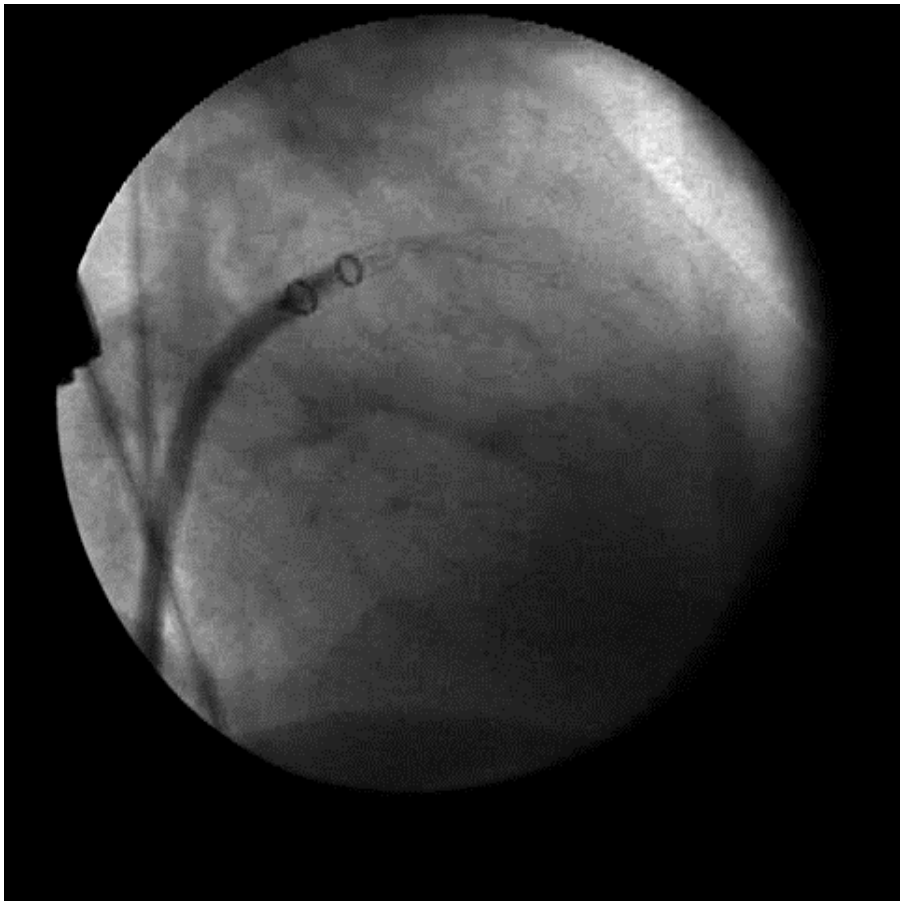


European Heart Journal (2012) 33, 698–704

Left Atrial Appendage Occlusion

- Occlusion of LAA = Mechanical Anticoagulation
- Wall off the left atrial appendage





PROTECT-AF:
Primary Efficacy Endpoint

Event	Watchman Group (n = 463)		Warfarin Group (n = 244)		Rate Ratio (Watchman/Warfarin) (95% CrI)	Posterior Probabilities	
	Events/ Patient-Years	Observed Rate (Events per 100 Patient-Years) (95% CrI)	Events/ Patient-Years	Observed Rate (Events per 100 Patient-Years) (95% CrI)		Non-inferiority	Superiority
Primary Efficacy Endpoint	39/1720.2	2.3 (1.7, 3.2)	34/900.8	3.8 (2.5, 4.9)	0.60 (0.41, 1.05)	>0.999	0.960
Stroke	26/1720.7	1.5 (1.0, 2.2)	20/900.9	2.2 (1.3, 3.1)	0.68 (0.42, 1.37)	0.999	0.825
Ischemic Stroke	24/1720.8	1.4 (0.9, 2.1)	10/904.2	1.1 (0.5, 1.7)	1.26 (0.72, 3.28)	0.780	0.147
Hemorrhagic Stroke	3/1774.2	0.2 (0.0,0.4)	10/916.2	1.1 (0.5, 1.8)	0.15 (0.03, 0.49)	>0.999	0.999
Systemic Embolization	3/1773.6	0.2 (0.0, 0.4)	0/919.5	0.0	NA	-	-
Cardiovascular Death	17/1774.3	1.0 (0.6, 1.5)	22/919.4	2.4 (1.4, 3.4)	0.40 (0.23, 0.82)	>0.999	0.995

No difference in stroke
Reduction in hemorrhagic stroke with Watchman
resulted in reduction in CV Death

CMS Mandatory Criteria for WATCHMAN

- CHADS2 ≥ 2 or CHA2DS2-VASc ≥ 3
- D*ocumented evidence* of a *formal shared decision* interaction between the patient and an independent, non-interventional physician using an evidenced-based decision making tool on oral anticoagulants
- Short-term warfarin OK, but deemed unable to take long-term oral anticoagulation
  - Not for pts actively bleeding or absolute contraindication
- Must be performed in a hospital with structural heart disease or electrophysiology program.
- Must be trained by the manufacturer
- Patients must be enrolled in a prospective national registry

Thank You

ACTIVE Trials: Clopidogrel + Aspirin

AF + risk factors: Age ≥75 yrs, HTN, prior stroke/TIA, LVEF<45%, PAD, age 55–74 yrs + CAD or diabetes

Primary outcome: Stroke, systemic embolism, MI, or CV death

ACTIVE-W

Anticoagulation-eligible

Warfarin (INR 2-3)

Clopidogrel + Aspirin

Open-label
Non-inferiority
n=6500

Stopped by DSMB

ACTIVE-A

OAC Contraindications or Unwilling

Aspirin + Placebo

Clopidogrel + Aspirin

Double-blind
Superiority
n~7500

Irbesartan, 300 mg/day vs placebo
N ≈ 9000

ACTIVE-I

ACTIVE Investigators. *Lancet.* 2006;367:1903-12.
ACTIVE Investigators. *Am Heart J.* 2006;151:1187-93.