

# Atrial Fibrillation

## *Anticoagulation Strategies*

Owen Obel, MD  
*North Texas VA Health System*  
*UT Southwestern Medical Center*  
*Dallas*

**SOUTHWESTERN**

THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

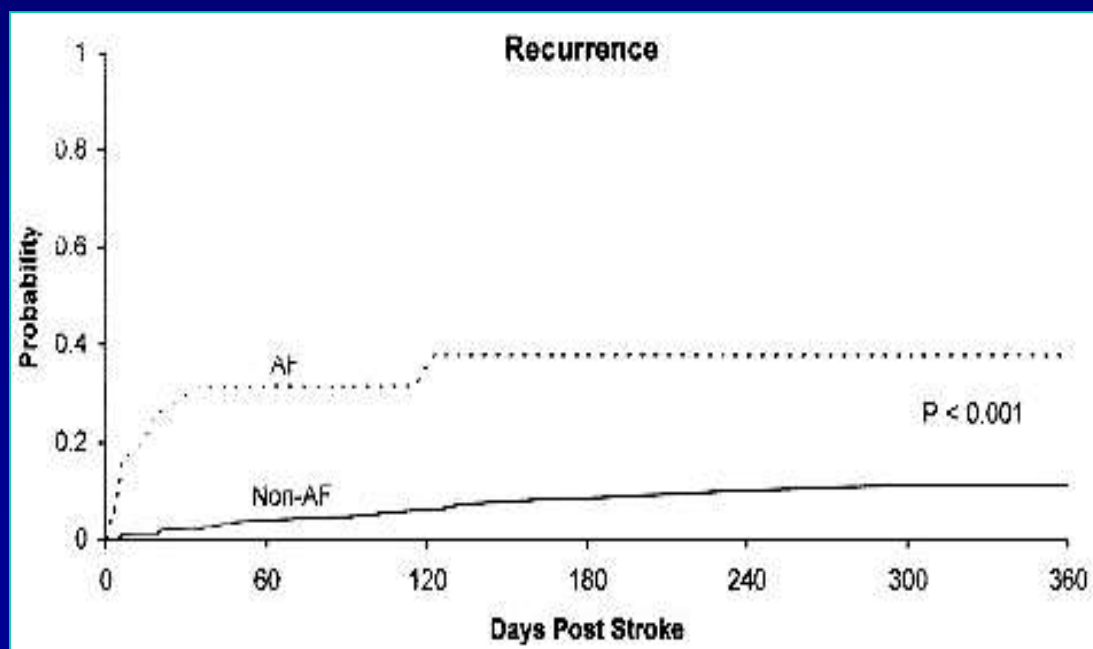
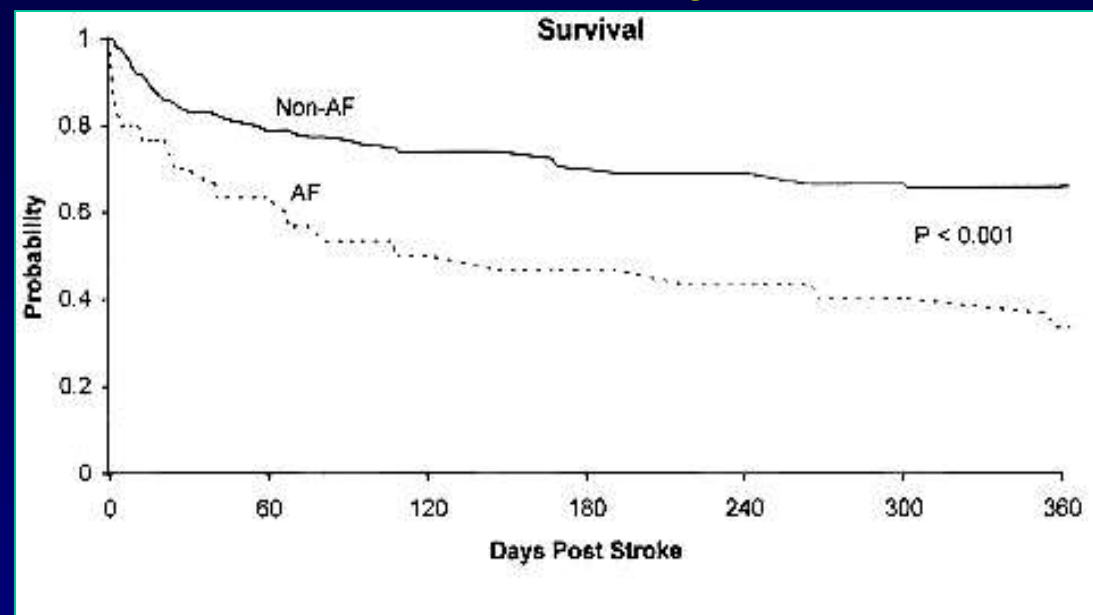


VA  
NORTH TEXAS  
HEALTH CARE  
SYSTEM

Disclosures:

- None relevant to this talk

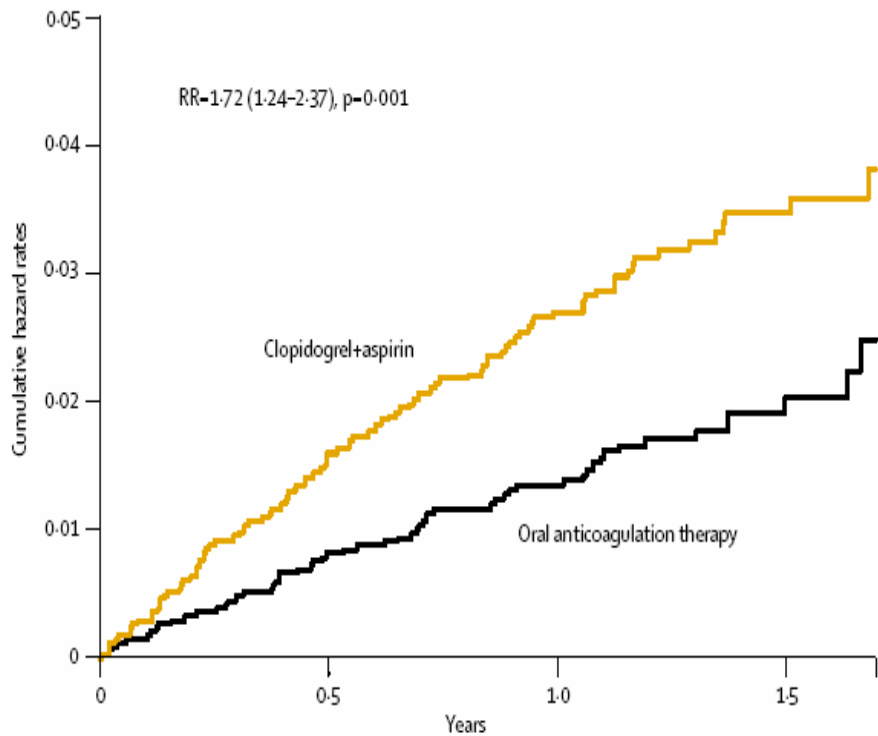
# Severity of Stroke in AF



- AF is associated with increased severity of stroke
- 30-day mortality of stroke:
  - AF 25%
  - non-AF 14%
- AF increases risk of early handicap from stroke
- Stroke recurrence more common in AF group (23%) than non-AF group (8%)

# Aspirin + Clopidogrel

## For Stroke Prevention in AF

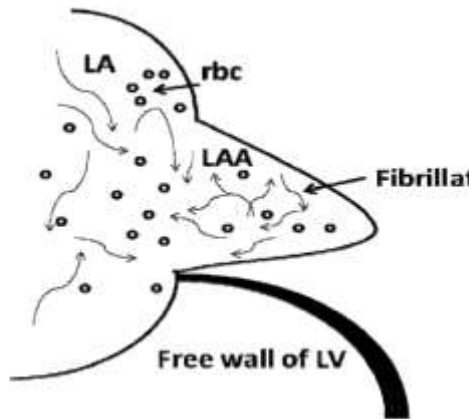


### Number at risk

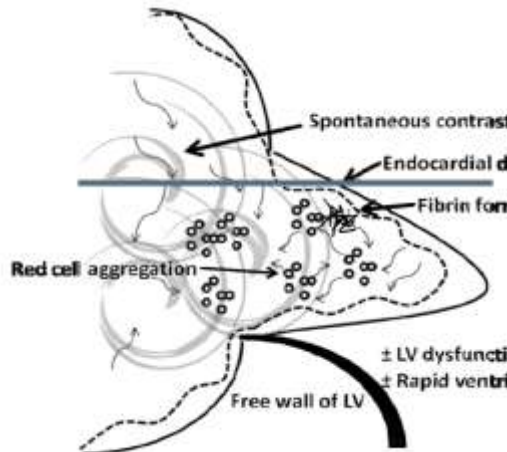
Clopidogrel + aspirin	3335	3168	2419	941
Oral anticoagulation therapy	3371	3232	2466	930

- >6000 patients with AF and one risk factor
- Warfarin vs aspirin+clopidogrel
- Stroke/periph. emb/MI/vascular death
- Stopped early due to clear superiority of Warfarin
- 15% withdrawal from warfarin (esp. as new therapy)
- Rates of major hemorrhage similar

# Thrombogenesis in AF

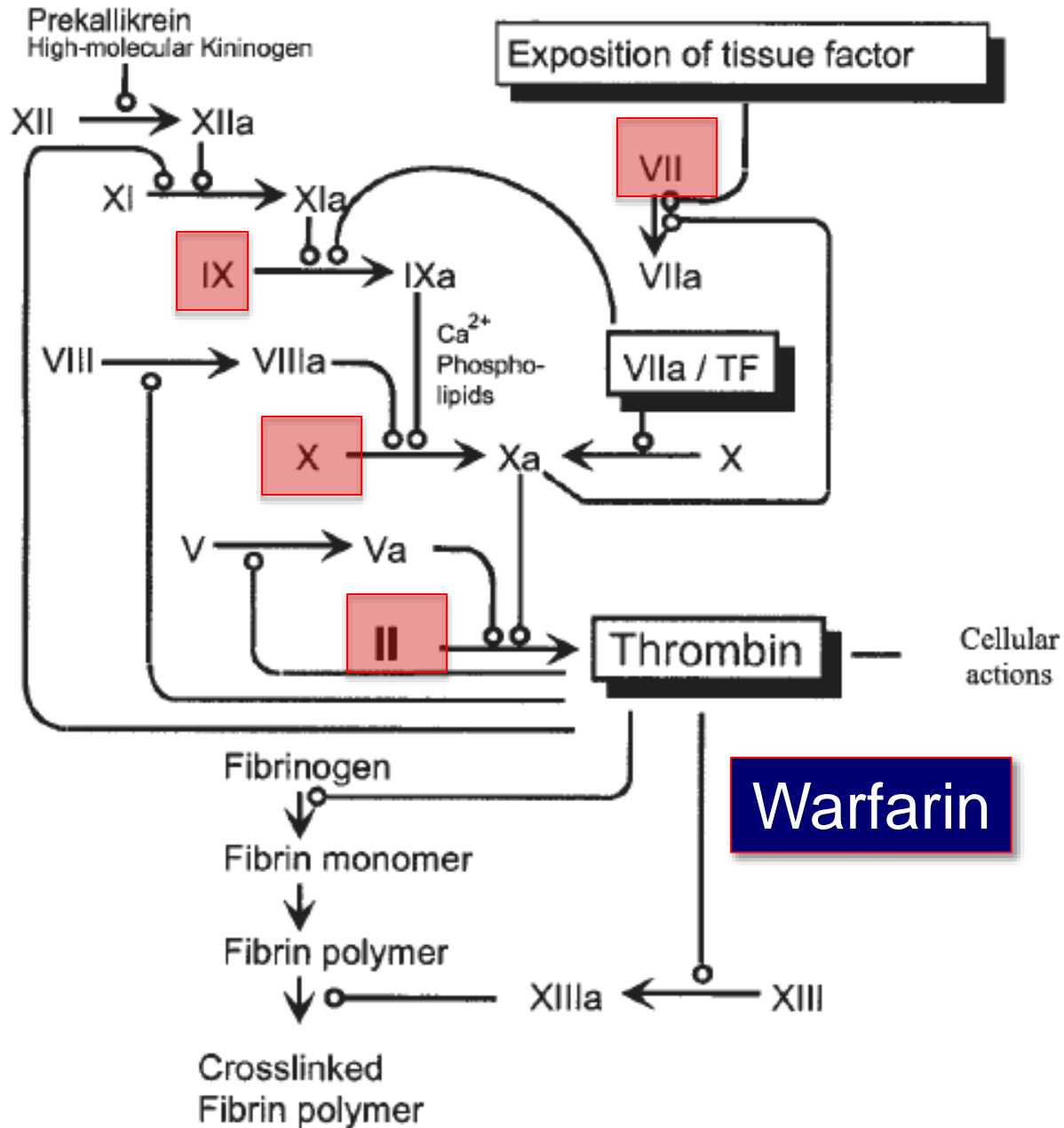


MV  
39-13-09



## Intrinsic System

## Extrinsic System



# Risk S

CHADS<sub>2</sub> score was de

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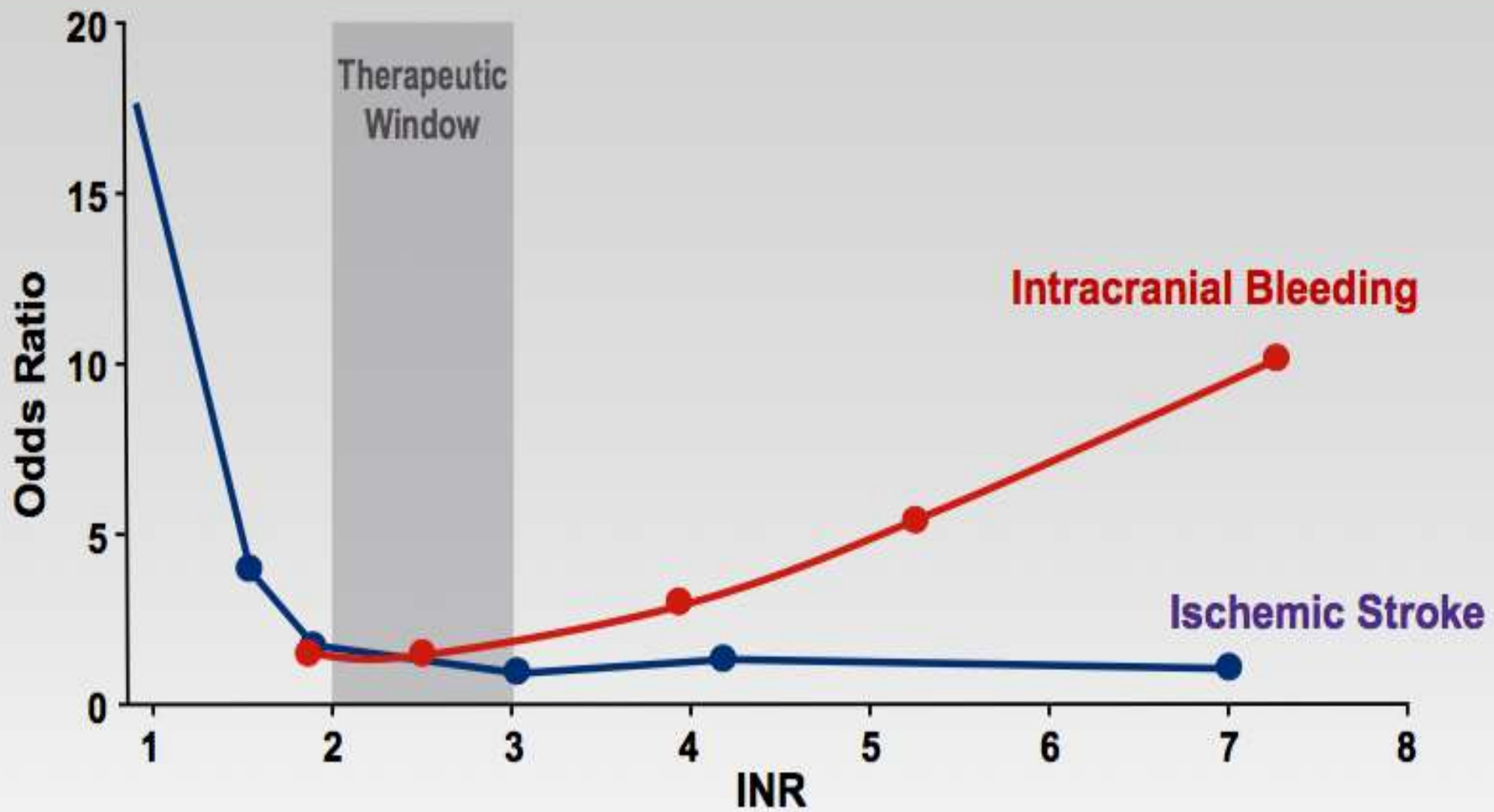
CHADS<sub>2</sub>-VASc has refined

In recent years, many hav

## (c) Adjusted stroke rate according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score

CHA <sub>2</sub> DS <sub>2</sub> -VASc score	Patients (n=7329)	Adjusted stroke rate (%/year) <sup>b</sup>
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

CHA <sub>2</sub> DS <sub>2</sub> -VASc	Score
Congestive heart failure	1
Hypertension	1
Age ≥75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Aged 65 to 74 y	1
Sex category (ie, female sex)	1
Maximum score	9





## Intrinsic System

Prekallikrein  
High-molecular Kininogen

XII → XIIa

XI → XIa

IX → IXa

VIII → VIIIa

X → Xa

V → Va

II → IIa

## Extrinsic System

Exposition of tissue factor

VII → VIIa

VIIa / TF

X → Xa

Dabigatran

Thrombin

Cellular actions

Fibrinogen

Fibrin monomer

Fibrin polymer

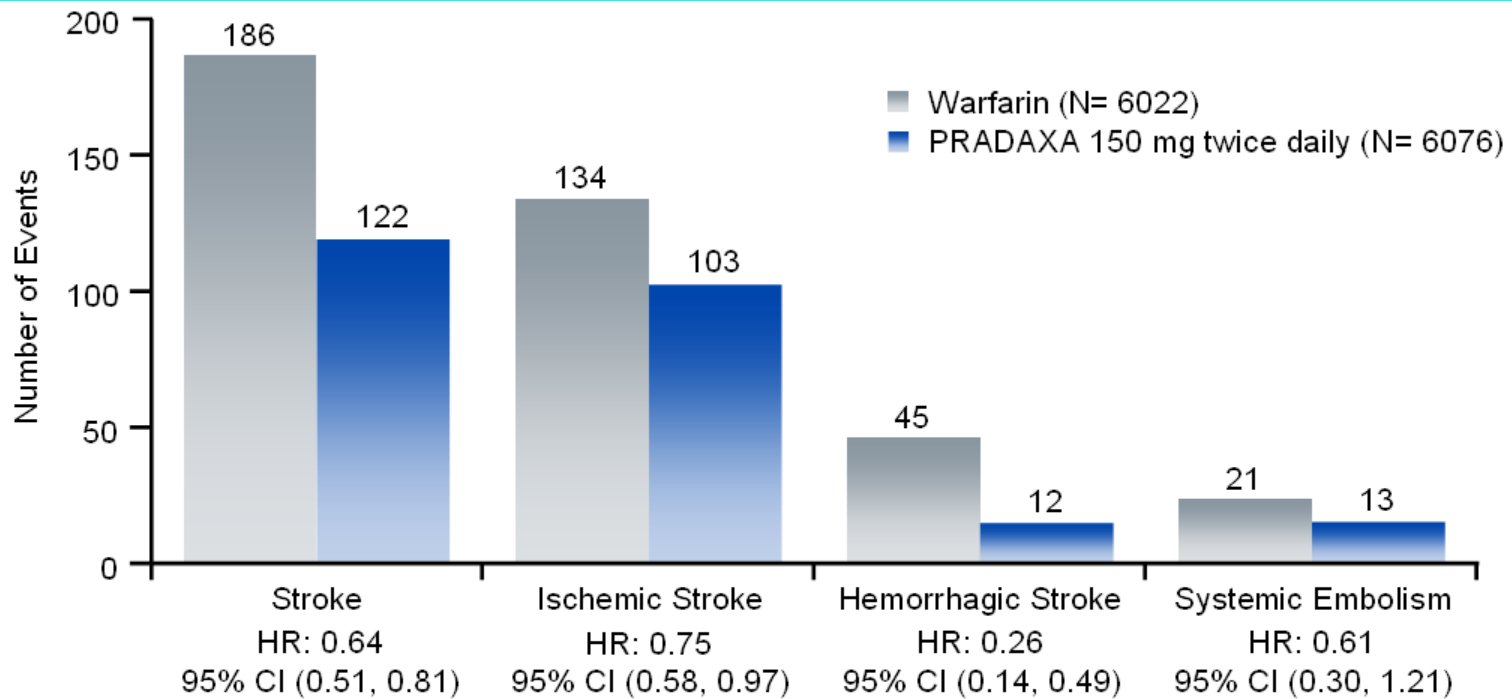
Crosslinked  
Fibrin polymer

XIIIa

XIII → XIIIa

# Direct Thrombin Inhibitors

## Dabigatran



- The risk of myocardial infarction was numerically greater in patients who received PRADAXA (1.5% for 150 mg dose) than in those who received warfarin (1.1%)

ment Group.

## Intrinsic System

Prekallikrein  
High-molecular Kininogen

XII → XIIa

XI → XIa

IX → IXa

VIII → VIIIa

V → Va

II → II

## Extrinsic System

Exposition of tissue factor

VII → VIIa

VIIa / TF

X → Xa

Thrombin

Rivaroxaban  
Apixaban  
Edoxaban

Cellular actions

Fibrinogen

Fibrin monomer

Fibrin polymer

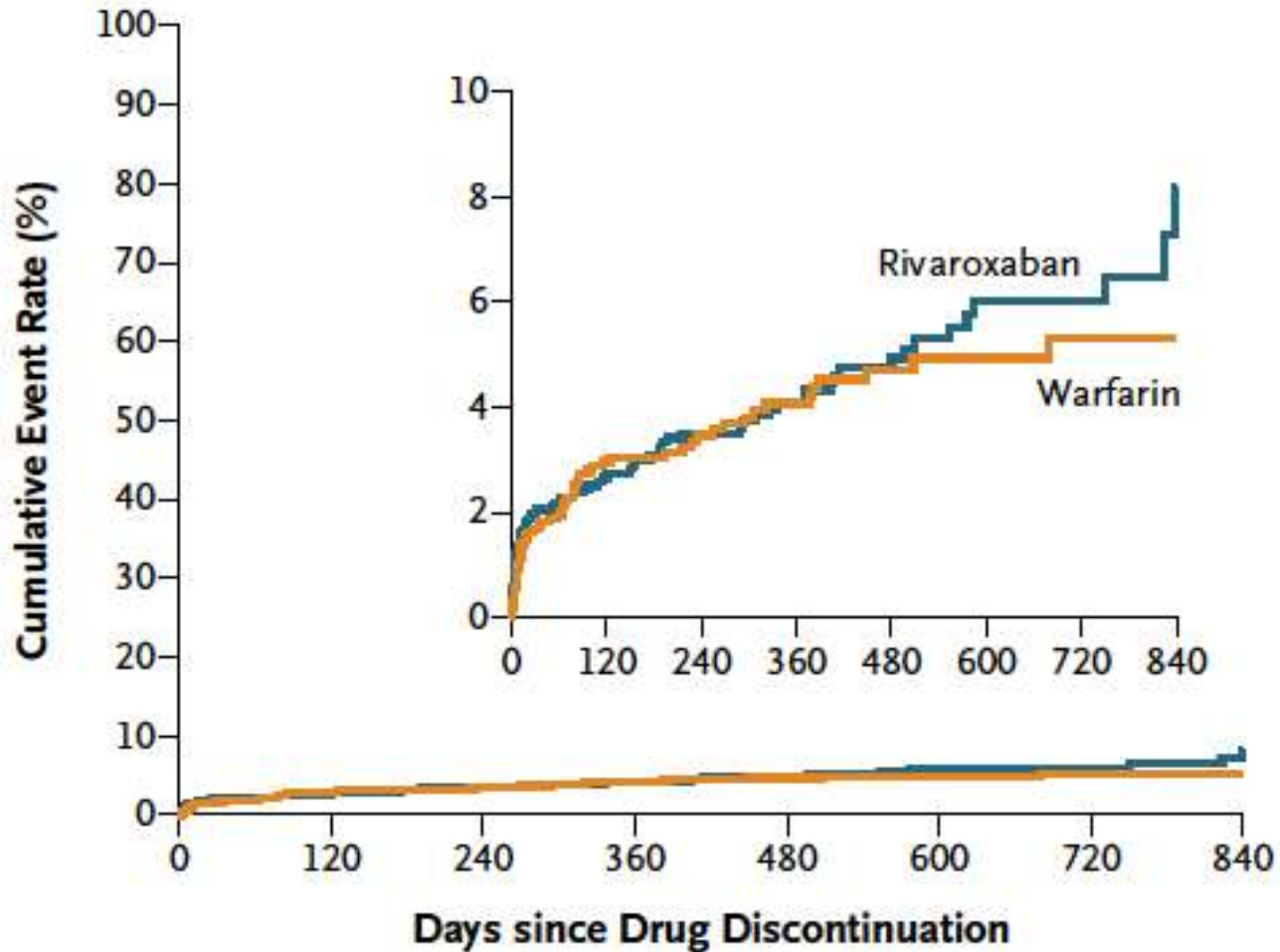
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Fibrin polymer

XIIIa

XIII

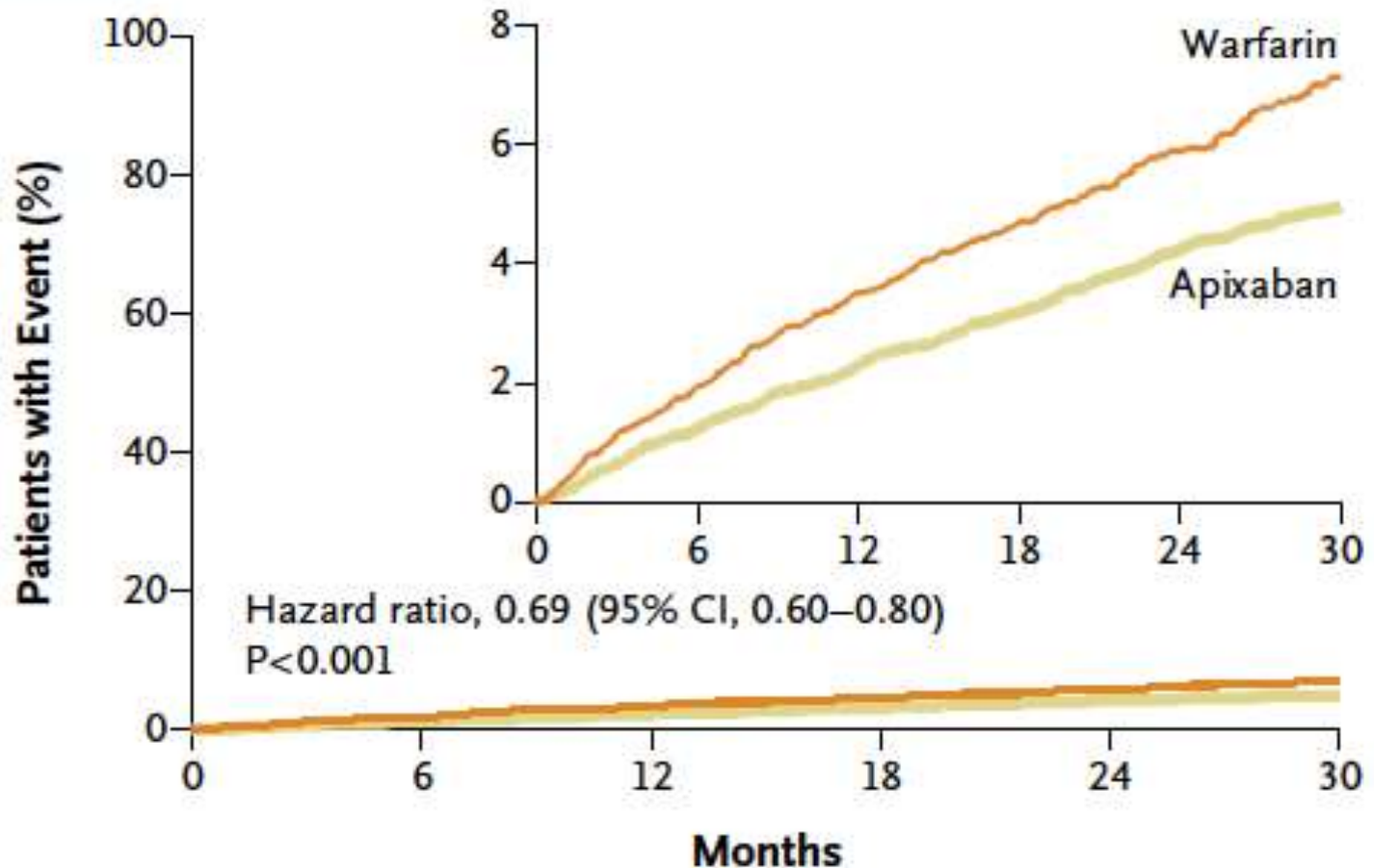
# Factor Xa Inhibitors

## B Events after Discontinuation



# Factor Xa Inhibitors

## B Major Bleeding

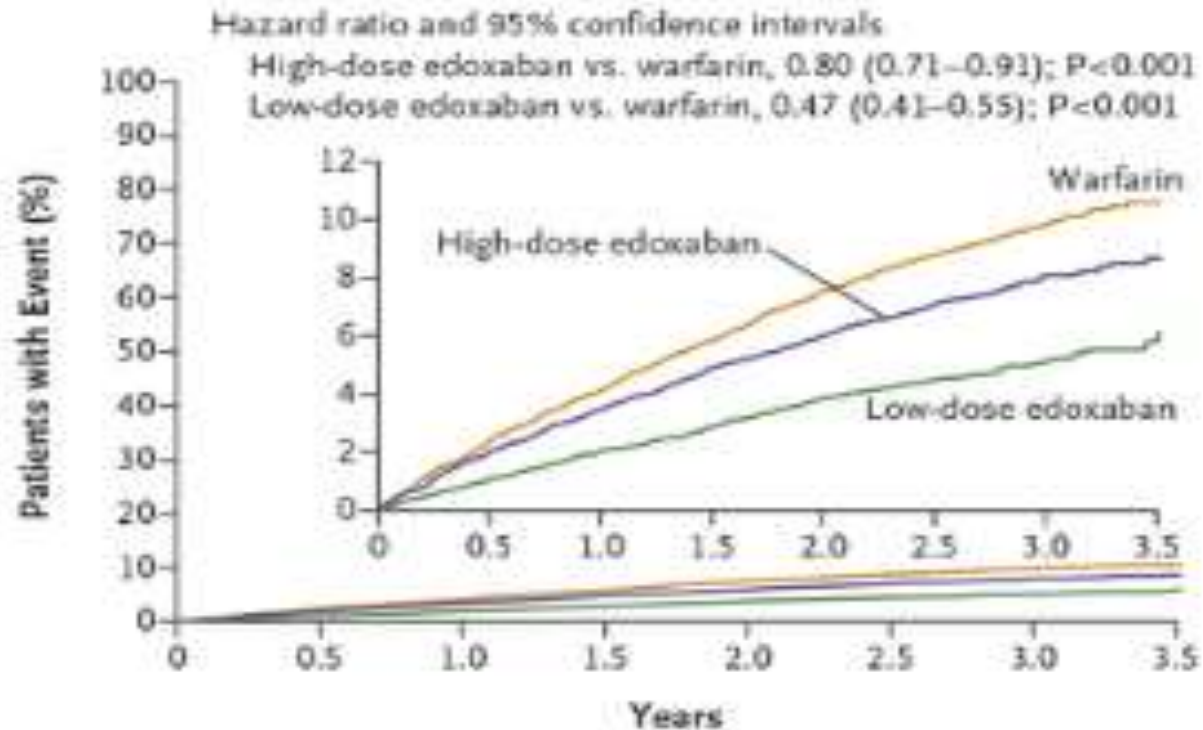


### No. at Risk

	0	6	12	18	24	30
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

# Factor Xa Inhibitors

## B Major Bleeding



### No. at Risk

Warfarin	7012	6116	5630	5278	4941	3446	1687	370
High-dose edoxaban	7012	6039	5594	5232	4910	3471	1706	345
Low-dose edoxaban	7002	6218	5791	5437	5110	3635	1793	386

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
<b>Drug interactions</b>	+++	+	++	++	++
<b>Food limitation</b>	YES	NO	NO	NO	NO
<b>Dosing</b>	QD	BID	QD	BID	BID
<b>Monitoring</b>	YES	NO	NO	NO	NO
<b>Use in 'valvular' AF</b>	YES	NO	NO	NO	NO
<b>Reversal agents</b>	YES	NO	NO	NO	NO
<b>Renal dosing</b>	NO	YES	YES	YES	YES
<b>Use in dialysis</b>	YES	NO	NO	YES	NO
<b>Bleeding c/w warfarin</b>		Neutral	Neutral	Better	Better

# Conclusions

- AF is the most common cause of ischemic stroke and is increasingly common
- The risk of stroke is dramatically reduced by effective anticoagulation with either Warfarin or NOAC agents
- The NOACs are 'novel' (!) and experience with their use is increasing
- Reversal agents for the NOACs would be very advantageous
- Triple therapy remains a challenge
- Peri-ablation use of NOACs is evolving
- Optimal bridging strategies are evolving



ADDITIONAL SLIDES

# Left atrial appendage is the major source of thrombi that cause stroke in AF patients

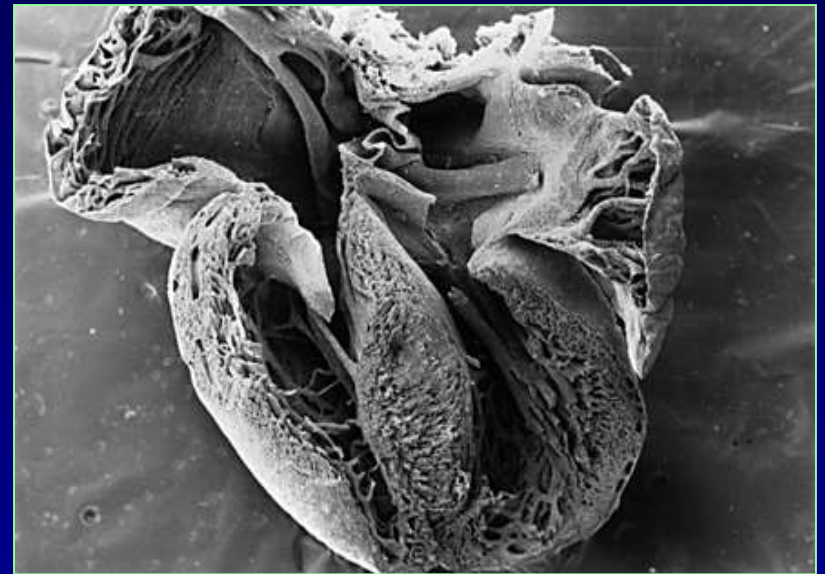
- 91% of all thrombus in patients with AF is found in the left atrial appendage (LAA)
- The four largest TEE studies comprising 1,181 patients showed that 98% of thrombi were found in the LAA

## Location of thrombi in non-rheumatic atrial-fibrillation

Setting	Total # of thrombi found in LAA and atrium	Found LAA		Found in left atrium		Reference
		Number	%	Number	%	
TEE	67	66	99%	1	1.5%	<i>Stoddard, JACC '95</i>
TEE	35	34	97	1	2.9	<i>Manning, Circulation '94</i>
Autopsy	47	35	74	12	25.5	<i>Aberg, Acta. Med. Scan. '69</i>
TEE	4	2	50	2	50.0	<i>Tsai, JFMA '90</i>
TEE	13	12	92	1	7.7	<i>Klein, Int J. Card. Imag. '93</i>
TEE & operation	11	8	73	3	27.3	<i>Manning, Circulation '94</i>
SPAF III <sup>1</sup> & TEE	20	19	95	1	5.0	<i>Klein, Circulation '94</i>
TEE	19	19	100	0	0.0	<i>Leung, JACC '94</i>
TEE	6	6	100	0	0.0	<i>Hart, Stroke '94</i>
<b>Total</b>	<b>222</b>	<b>201</b>	<b>91%</b>	<b>21</b>	<b>9.5%</b>	

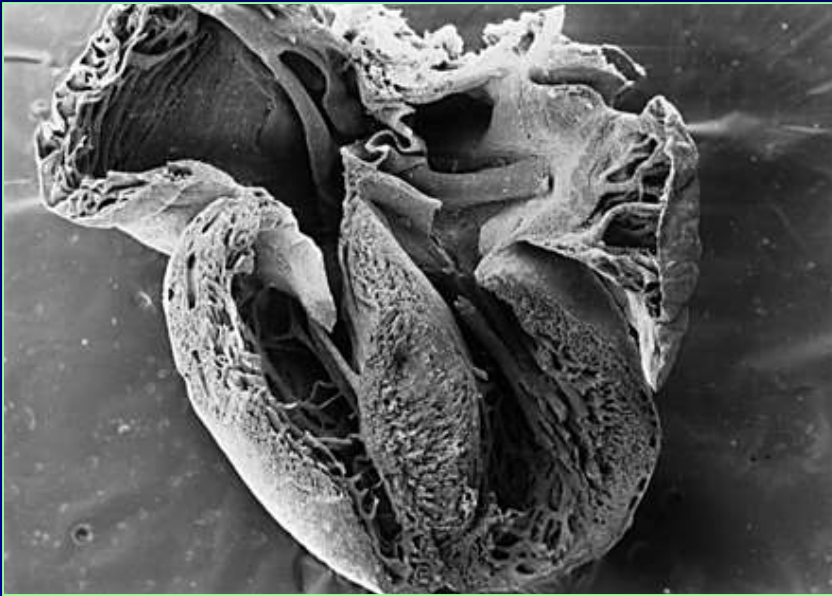
# Left Atrial Appendage

- A remnant of the original embryonic left atrium that develops during the third week of gestation.
- The main smooth walled left atrial cavity develops later and is formed from the outgrowth of the pulmonary veins.



# RAA

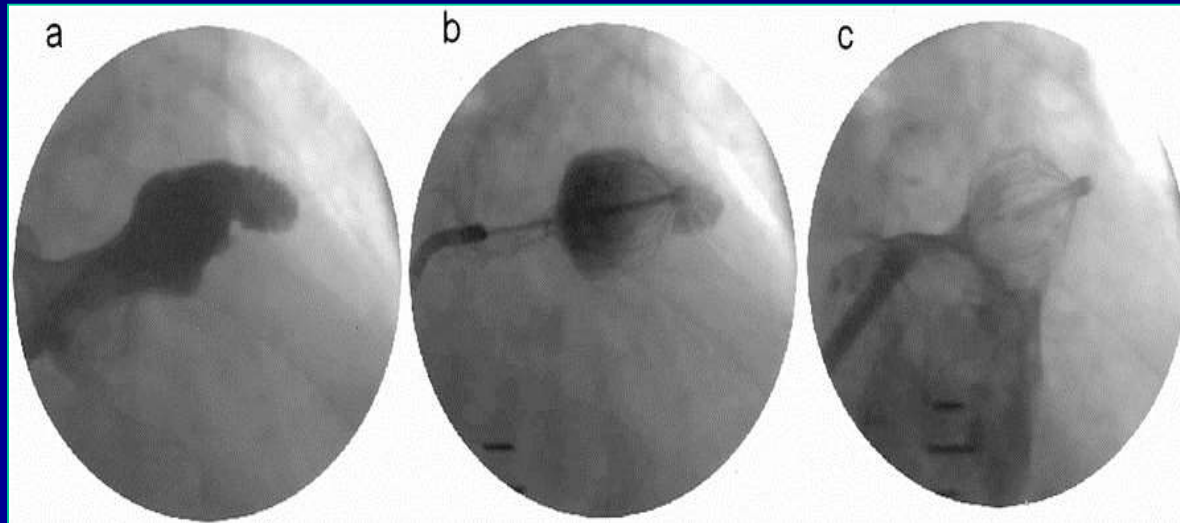
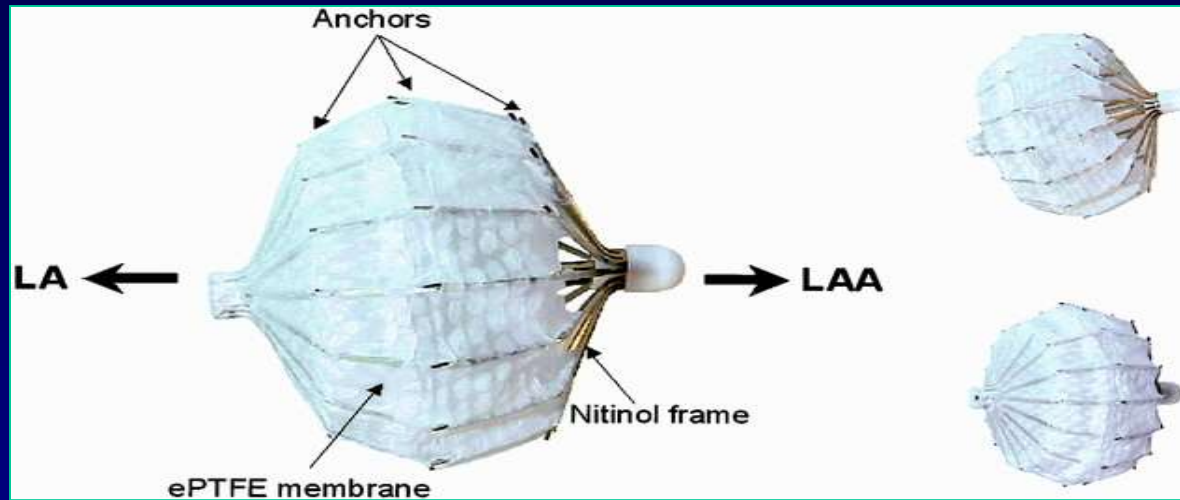
- Broad and triangular with a wide junction.



# LAA

- Typically a long, tubular, hooked structure which is usually crenellated.
- A narrow junction with the venous component of the atrium.
- Trabeculated, with muscle bars largely running parallel to each other giving a comb-like appearance (hence termed pectinate muscles).

# Left Atrial Appendage Exclusion PLAATO Device



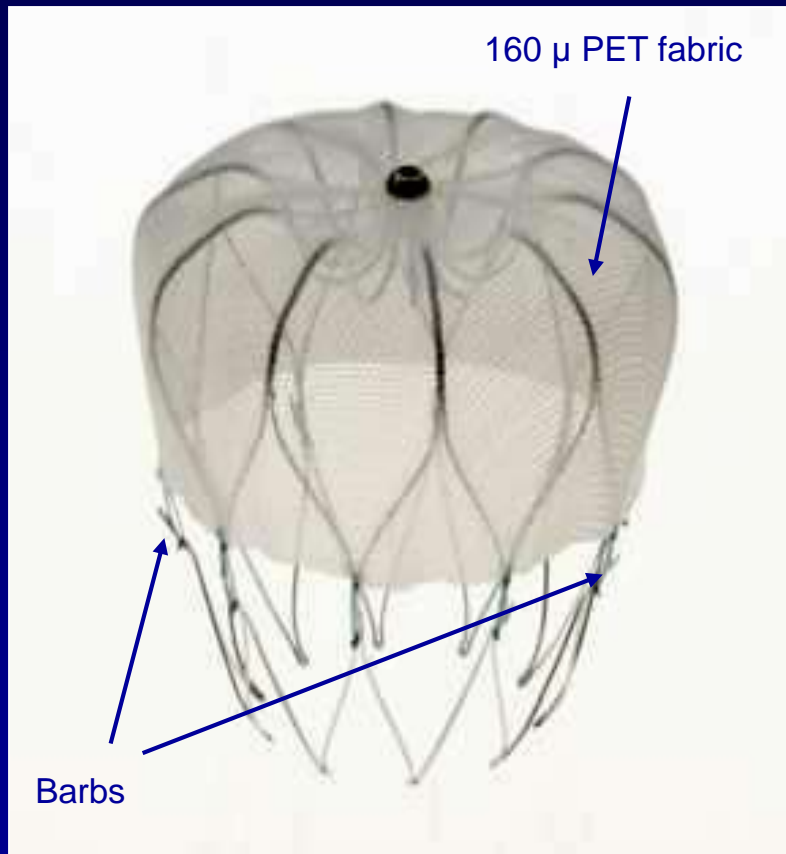
- Chest X-ray and TOE - stable implant position

- No migration, erosion, or encroachment

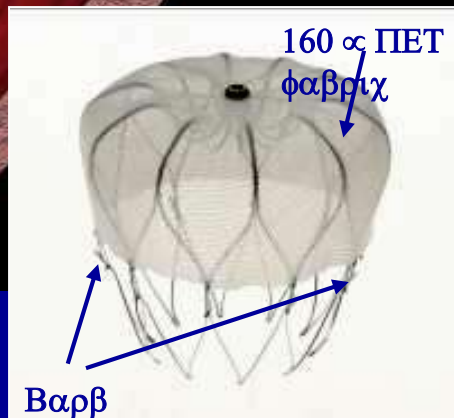
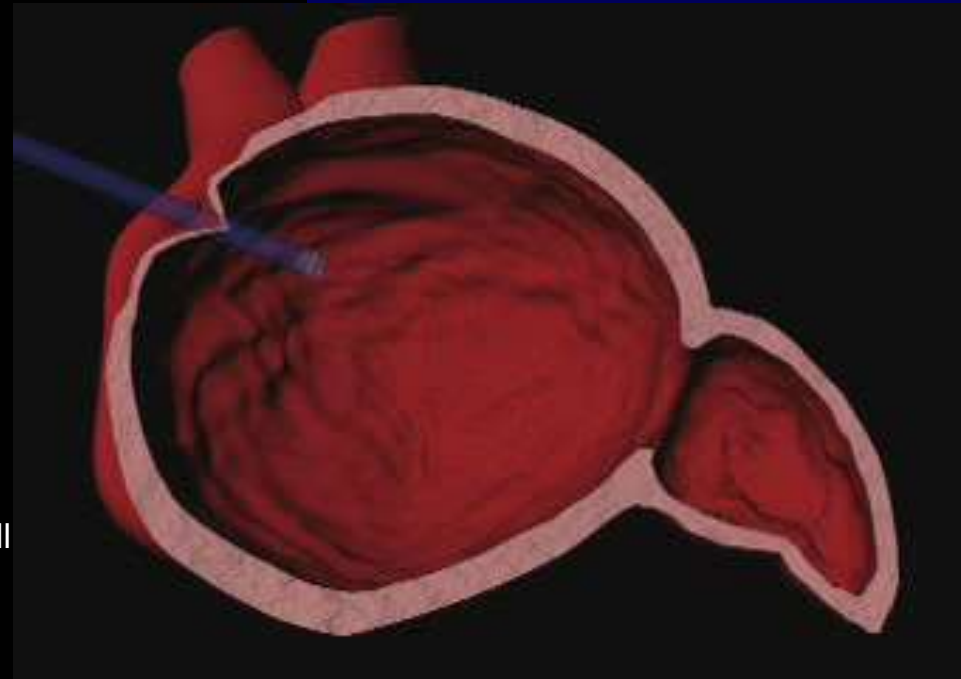
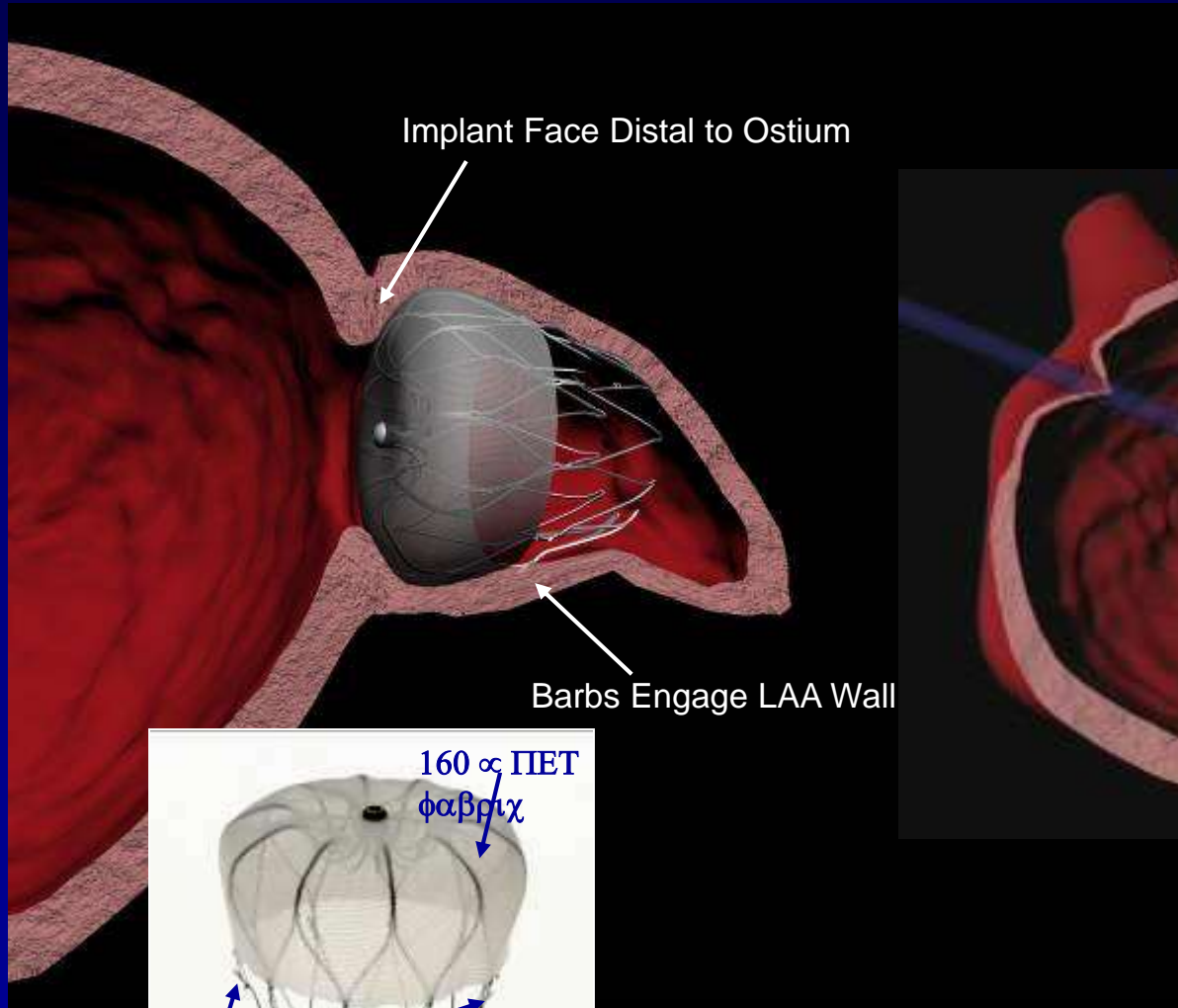
- No thrombi, no atrial shunt

- There have been no late complications or embolic events during follow-up

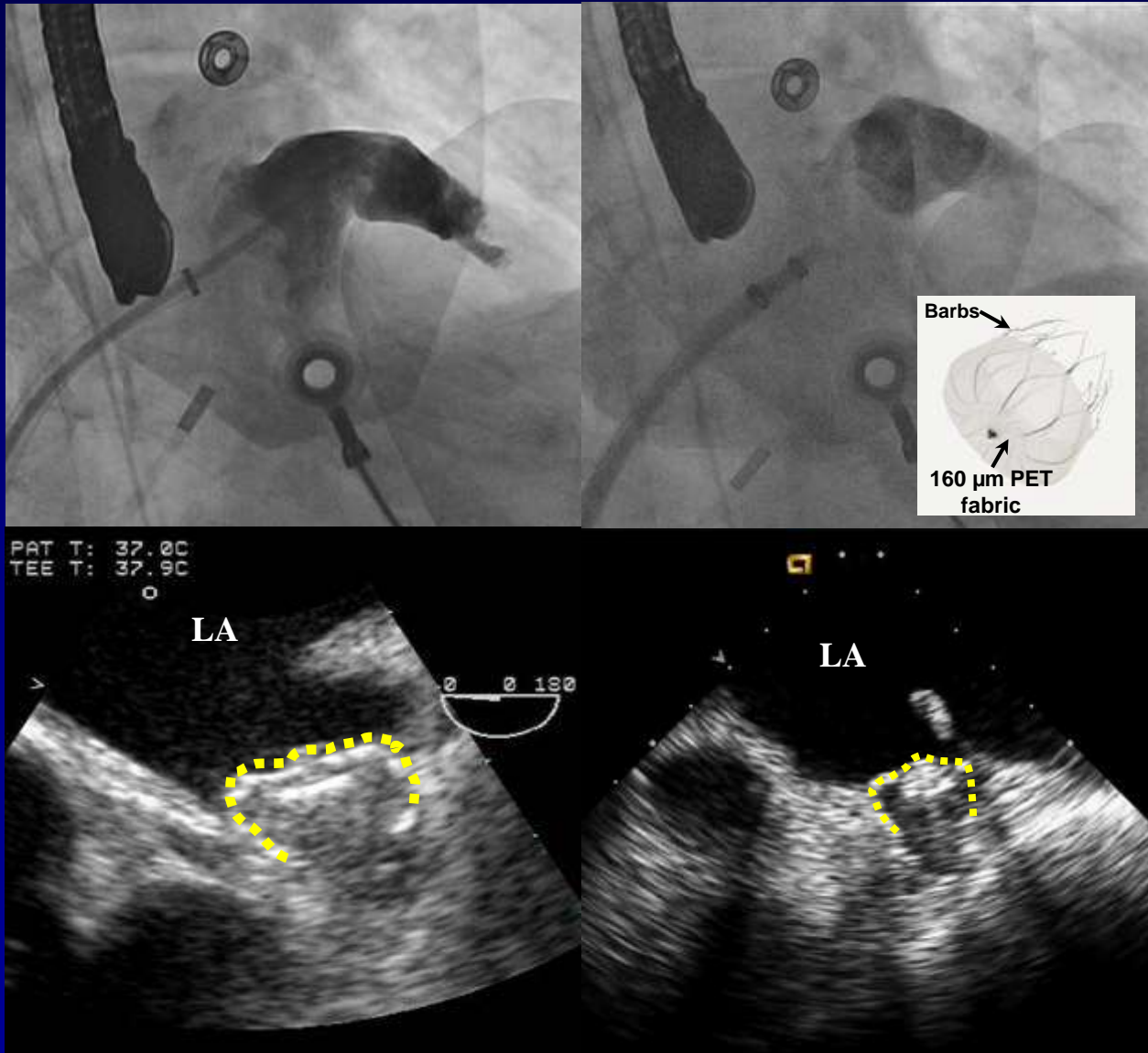
# Left Atrial Appendage Exclusion Watchman Device



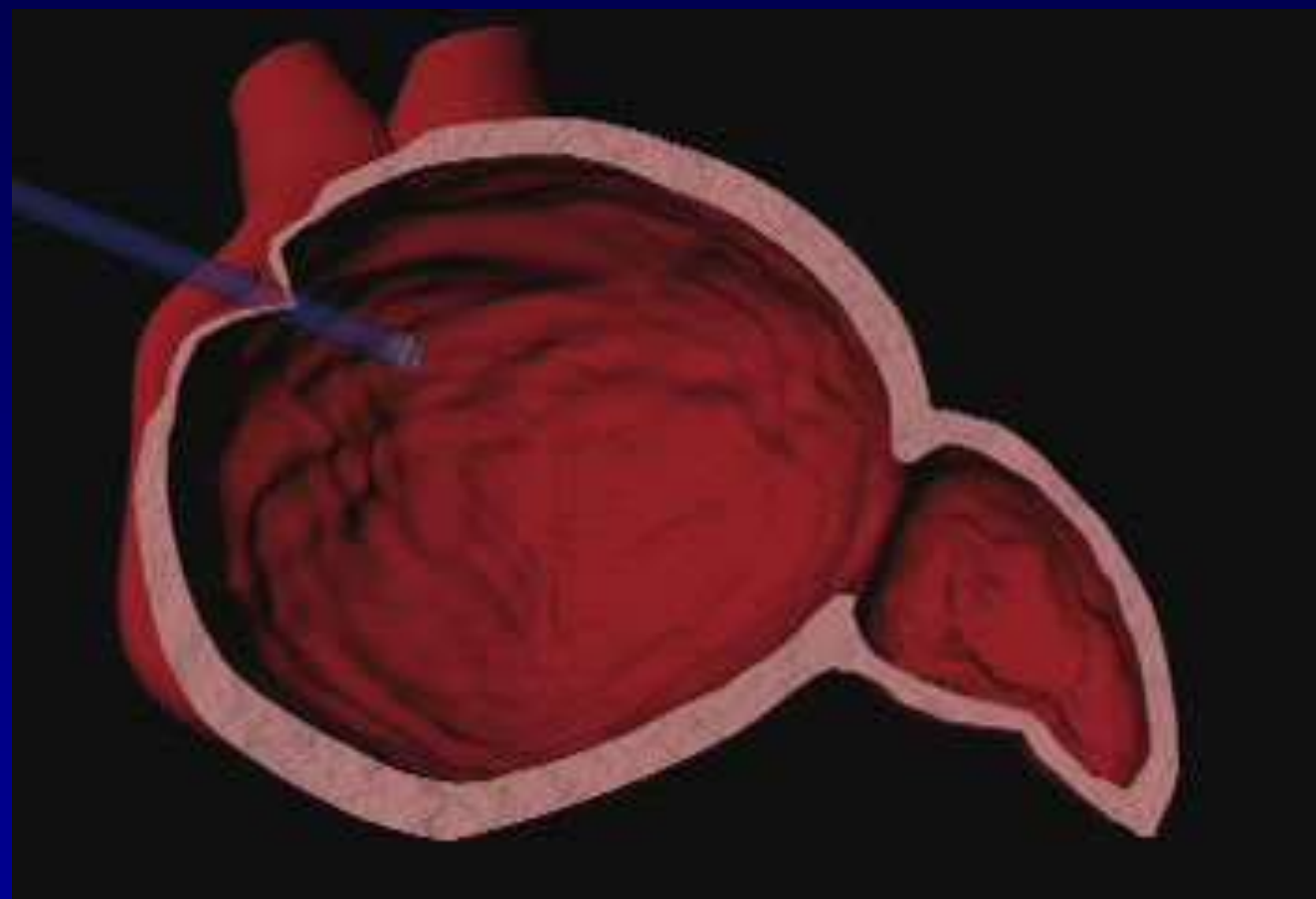
# WATCHMAN System



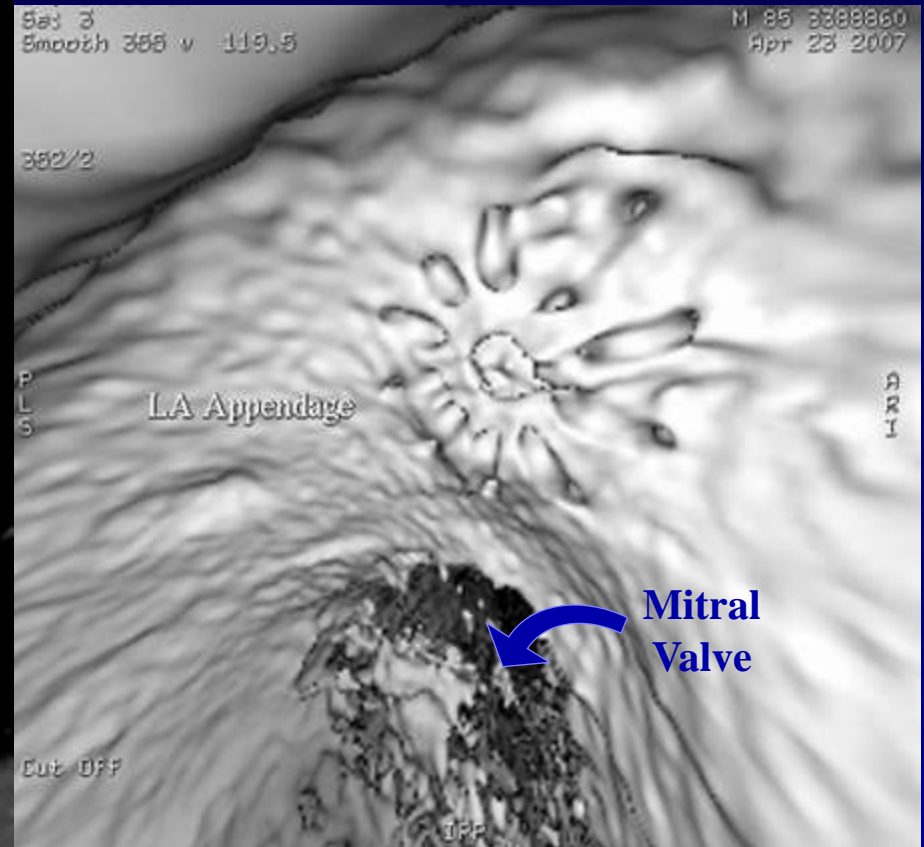
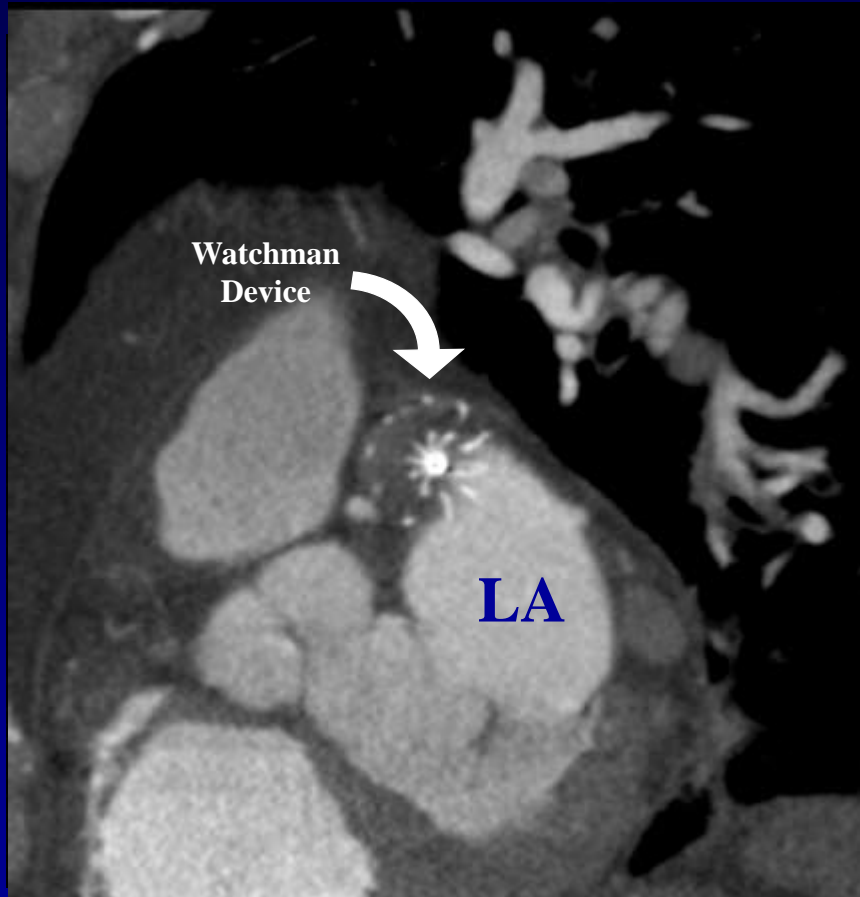
# Implant Procedure



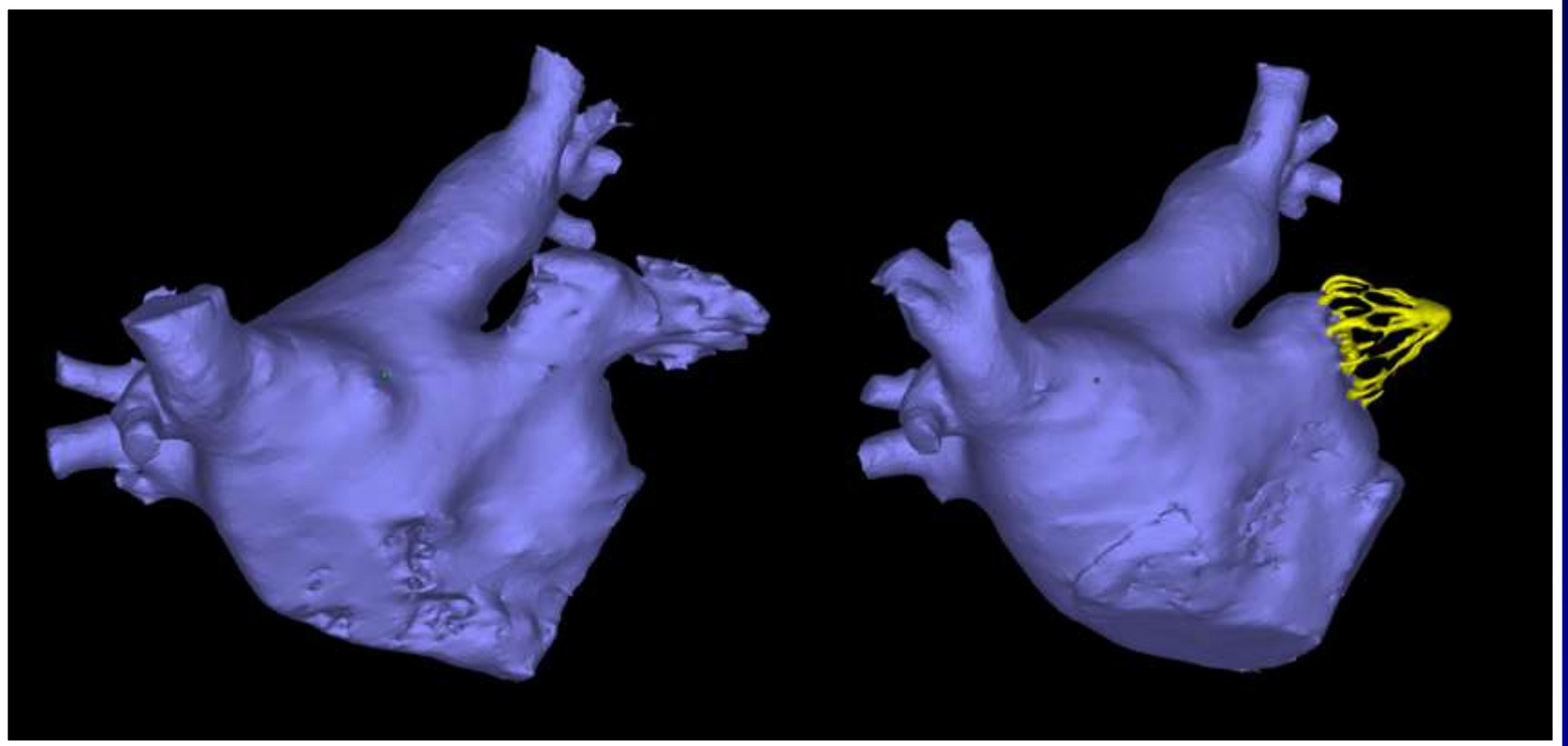




# One-Year Follow-Up



# One-Year Follow-Up



# WATCHMAN: Gross Pathology



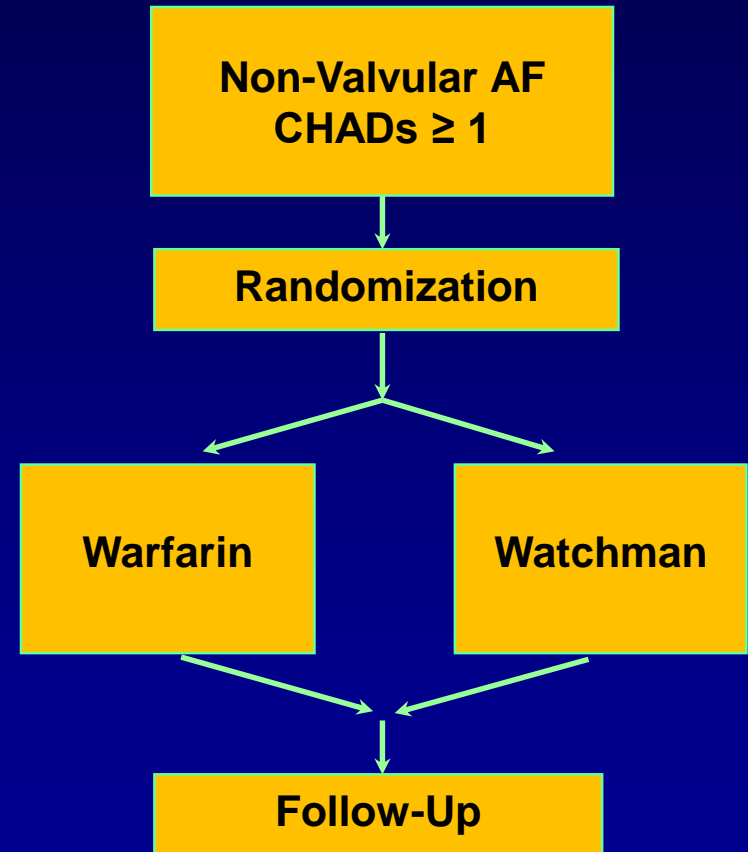
Canine – 45 days



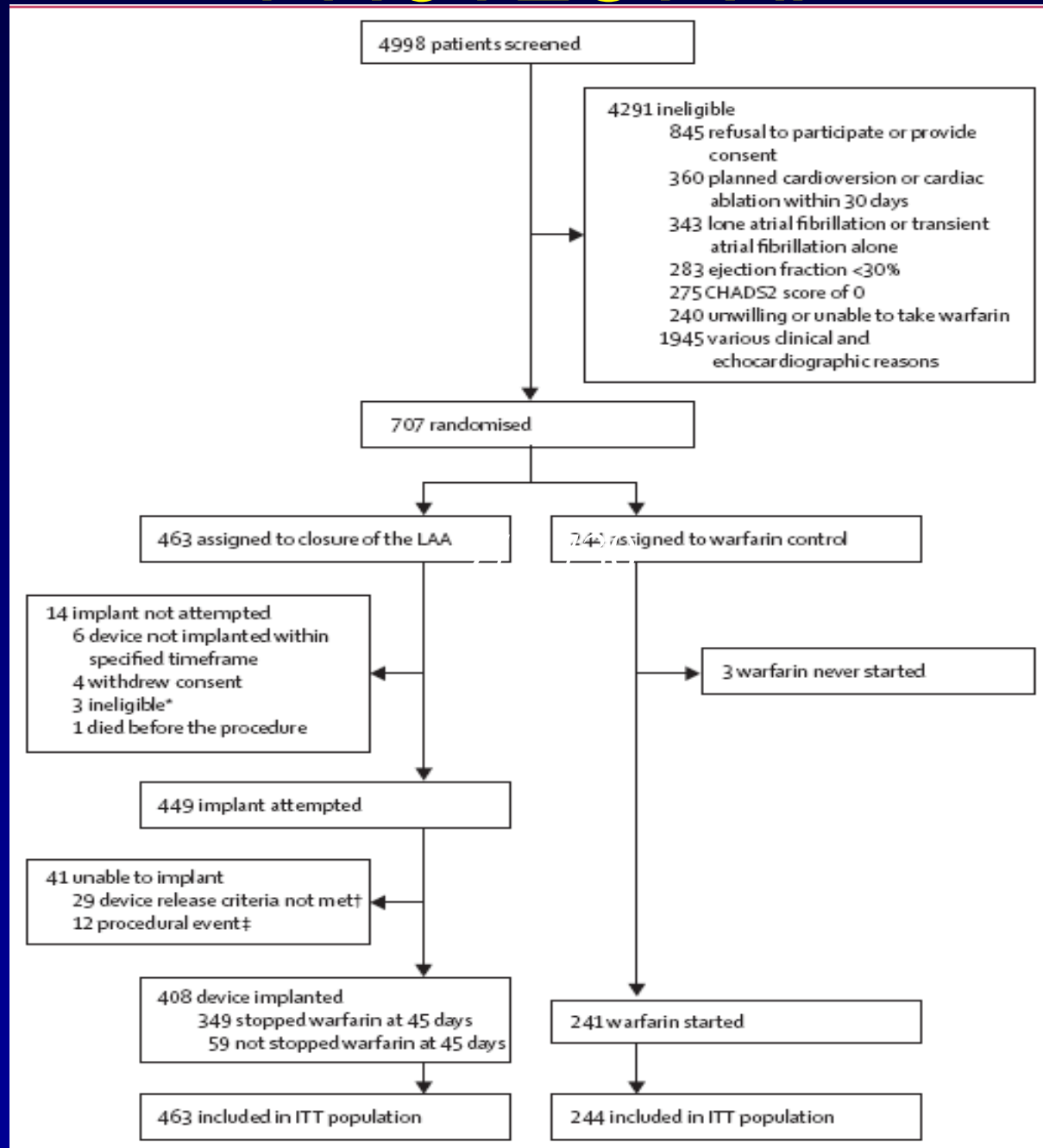
Human @ Autopsy – 9 months  
(death 2° abdominal aortic aneurysm)

# PROTECT-AF: Overview

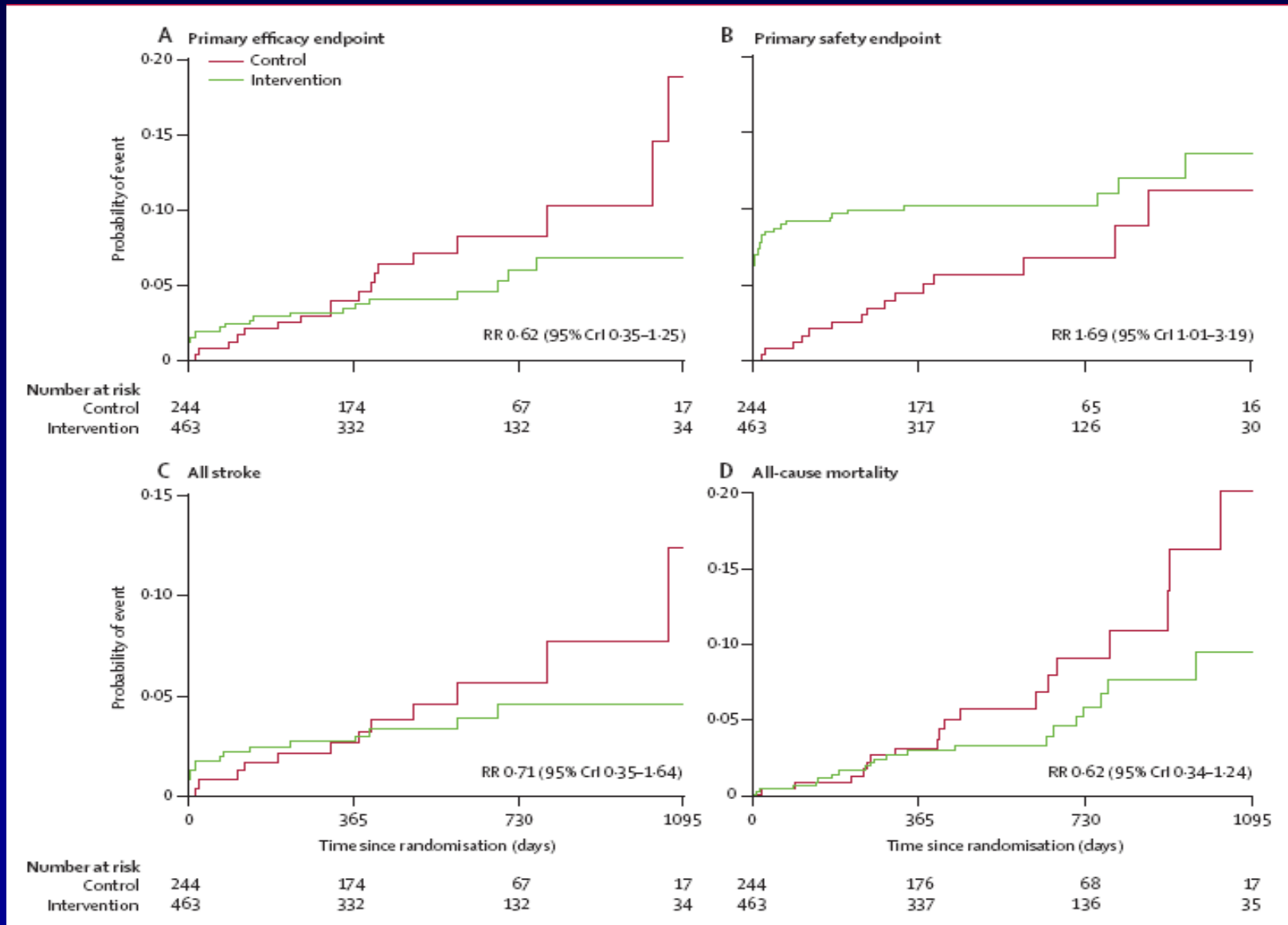
- Prospective, Randomized-Controlled Trial
  - Can the WATCHMAN device replace Warfarin?
- Endpoint:
  - Noninferiority trial
  - Efficacy: Stroke, cardiovascular death, systemic embolism
  - Safety: Major Bleeding Events
- Protocol:
  - Randomized patients to either the WATCHMAN device or continued Warfarin (2:1)



# PROTECT-AF

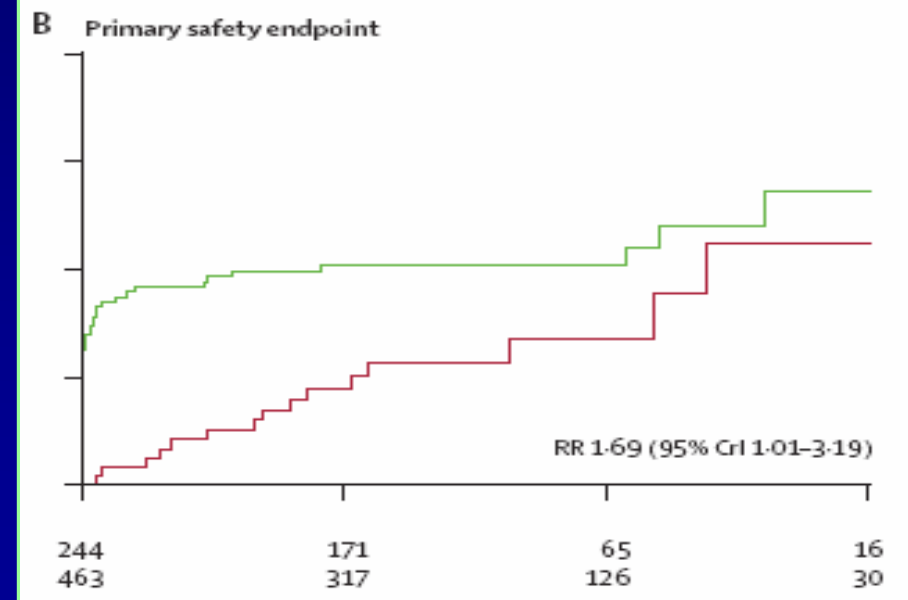
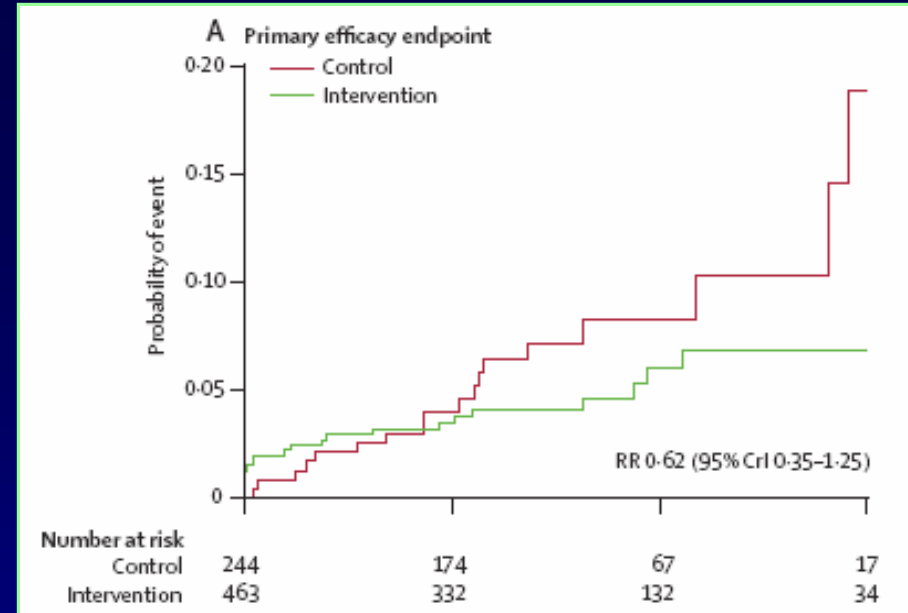


# PROTECT-AF: Results



# PROTECT-AF - Results

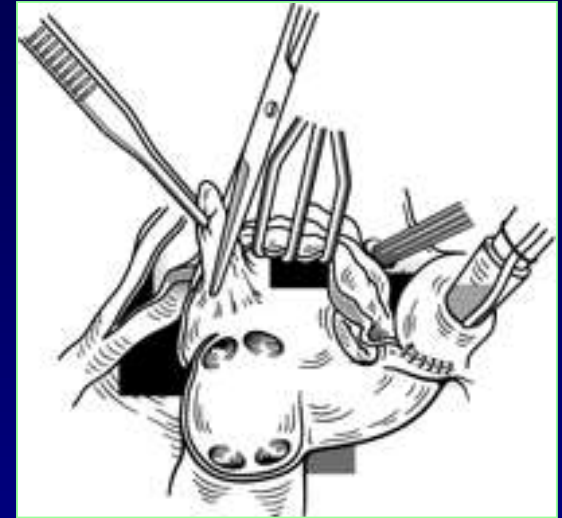
- AF + at least 1 risk factor
- 2:1 randomization
  - ↳ LAA closure (intervention) **463**
  - ↳ Warfarin (INR 2-3) **244**
- Stroke, CV death, systemic embolism
- Non-inferiority trial
- 99.9% chance that intervention not inferior to Warfarin, efficacy slightly better for LAA closure
- Safety endpoint significantly more common with LAA closure (most episodes occurred on day of procedure)
- Serious cardiac effusions were most common adverse event, 3 device embolizations





# Surgical Experience

- Paucity of Data
- Amputation vs. Closure
- <50% are truly eliminated
- Useful when surgery is otherwise indicated



# CONCLUSIONS

- Atrial fibrillation is a major cause of stroke
- Stroke in AF tends to be severe
- Effective means exist for reasonable protection against stroke in AF
- Conventional anticoagulation with warfarin is challenging and carries bleeding risk
- Novel anti-thrombin agents may offer excellent alternatives
- Mechanical left atrial appendage closure is under investigation