

## 2016 ANNUAL CONFERENCE

August 18-20 • Hyatt Regency Sarasota

Join your colleagues and friends as we celebrate  
"NPs Creating Footprints in the Sand." Earn CE while networking  
and enjoying the beautiful sun and beaches of Sarasota!

### CONFERENCE ACTIVITIES:

- Specialty Workshops
- Speakers You Want to Hear
- "An Evening of Celebration" Legislative Gala
- Update on Controlled Substances Law
- Tradeshow

### EDUCATIONAL WORKSHOPS INCLUDE:

- Commercial Drivers Medical Examiner Course
- Simulation Lab
- Basic Procedures in Dermatology
- ECG/Imaging
- More!

## OUR SPECIAL GUESTS INCLUDE...



Barbara Lumpkin, RN  
*Legendary Nurse Advocate*



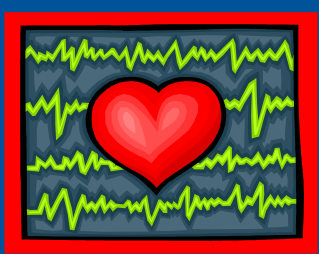
Loretta Ford, EdD, PNP, FAAN  
*Co-founder, America's First  
Nurse Practitioner Program*



Rep. Cary Pigman, MD  
*Representing Florida  
House District 55*



Sen. Denise Grimsley  
*Representing Florida  
Senate District 21*



# ATRIAL FIBRILLATION / FLUTTER: ANTICOAGULATION: USE, GUIDELINES AND CONTROVERSIES

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A.A.C.C., F.H.R.S.





# DISCLOSURES

▣ I have no disclosures to report.



# OBJECTIVES



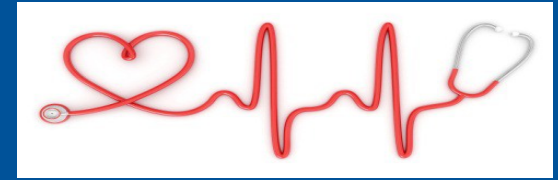
- ▣ 1. Participants will be able to discuss atrial fibrillation and atrial flutter patient indications for and against anticoagulation.
- ▣ 2. Participants be able to name and recognize the newer oral anticoagulants (NOACs).
- ▣ 3. Participants will be able to calculate stroke and bleeding scores to risk stratify patients prior to anticoagulation.

# USE OF ANTICOAGULANTS

- ▣ WHO DO WE ANTICOAGULATE?
- ▣ WHAT DO WE PRESCRIBE - WARFARIN vs NOACs
- ▣ WHY DO WE ANTICOAGULATE ?
  - ▣ Reduce Risk of Thromboembolism formation and Stroke
- ▣ WHEN ? – Indications, risk, benefits
- ▣ WHERE ? - Worldwide
  - Inpatient
  - Outpatient
- ▣ HOW do we decide to anticoagulate SAFELY?
- ▣ OR DO WE ANTICOAGULATE AT ALL??
  - ▣ **Stroke** and **Bleeding** Risk stratification Scores
    - ATRIA STROKE
    - CHADS<sub>2</sub>
    - CHADS<sub>2</sub>-MS
    - CHA<sub>2</sub>DS<sub>2</sub>-VASc
  - ATRIA BLEED
  - HAS=BLEED

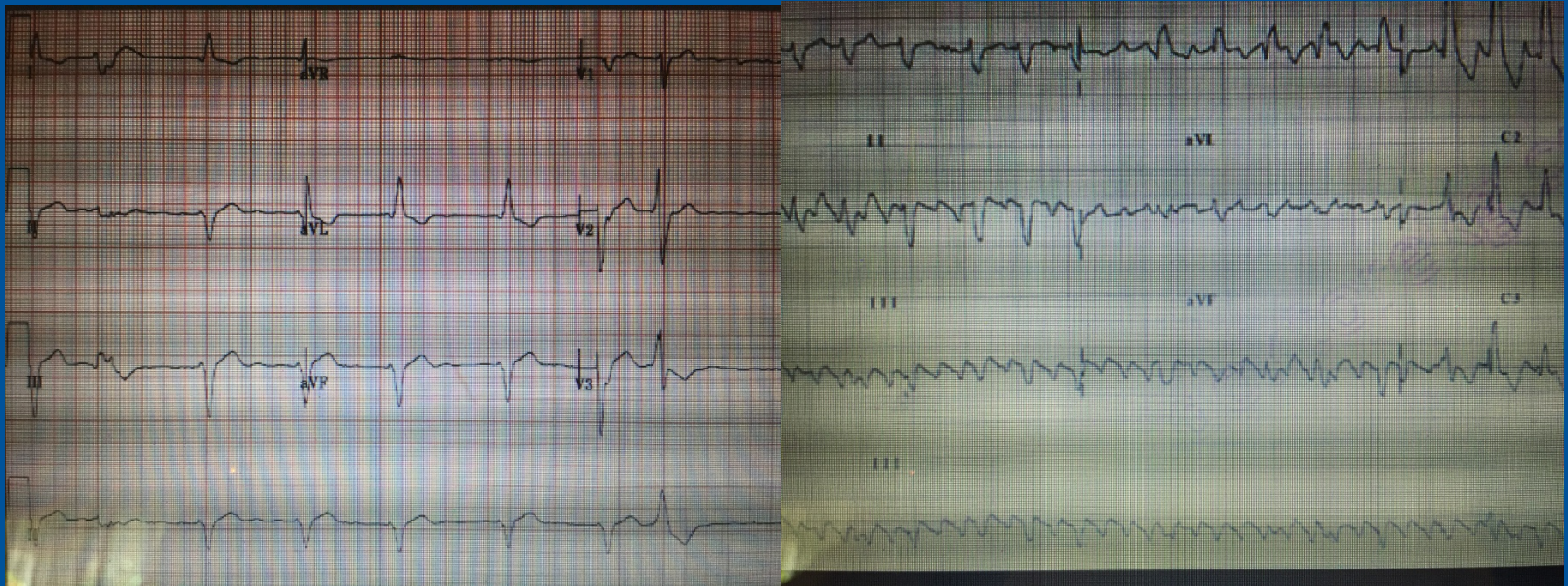


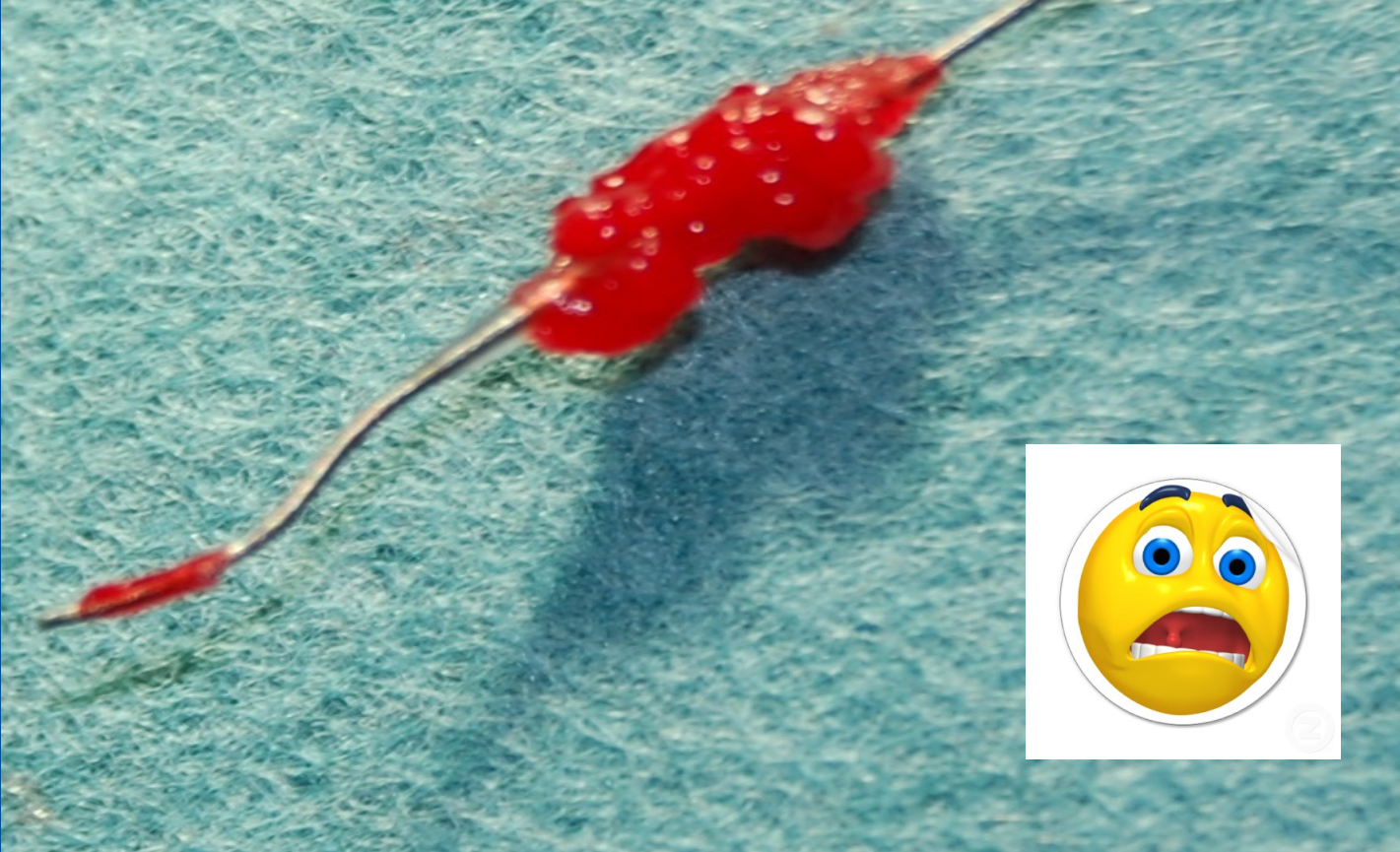
# WHO ?



▣ Atrial Fibrillation

▣ Flutter Patients



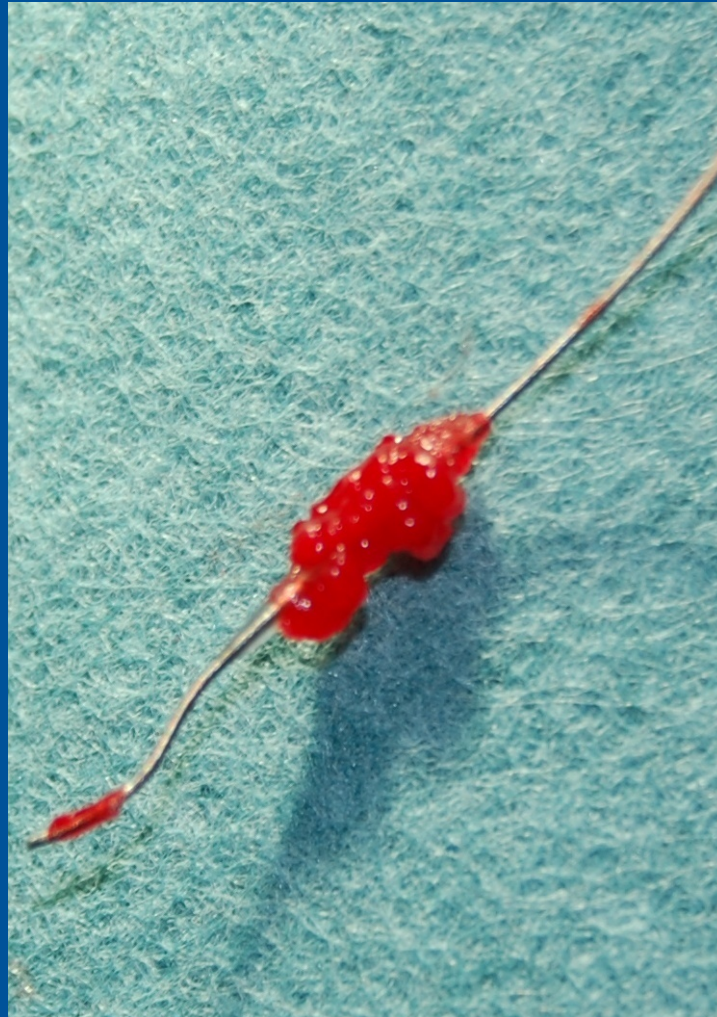




WHAT IS THAT??



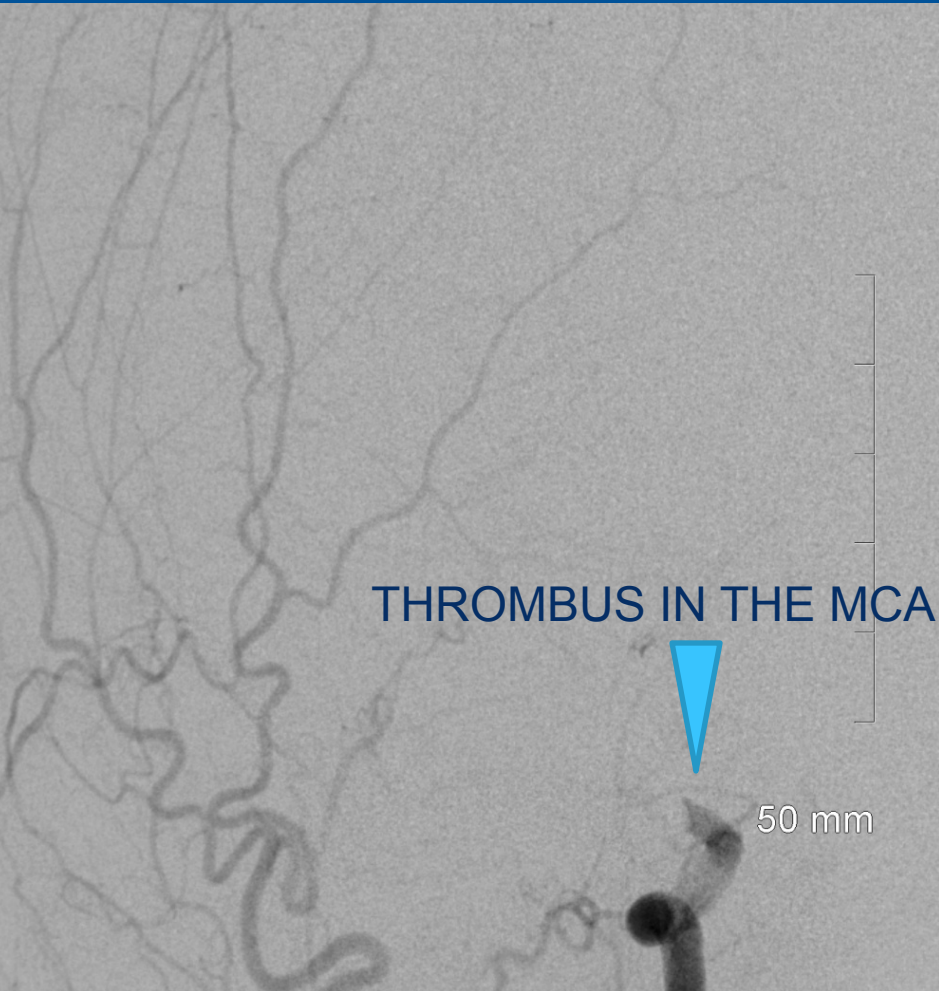
# THROMBECTOMY RESULTS



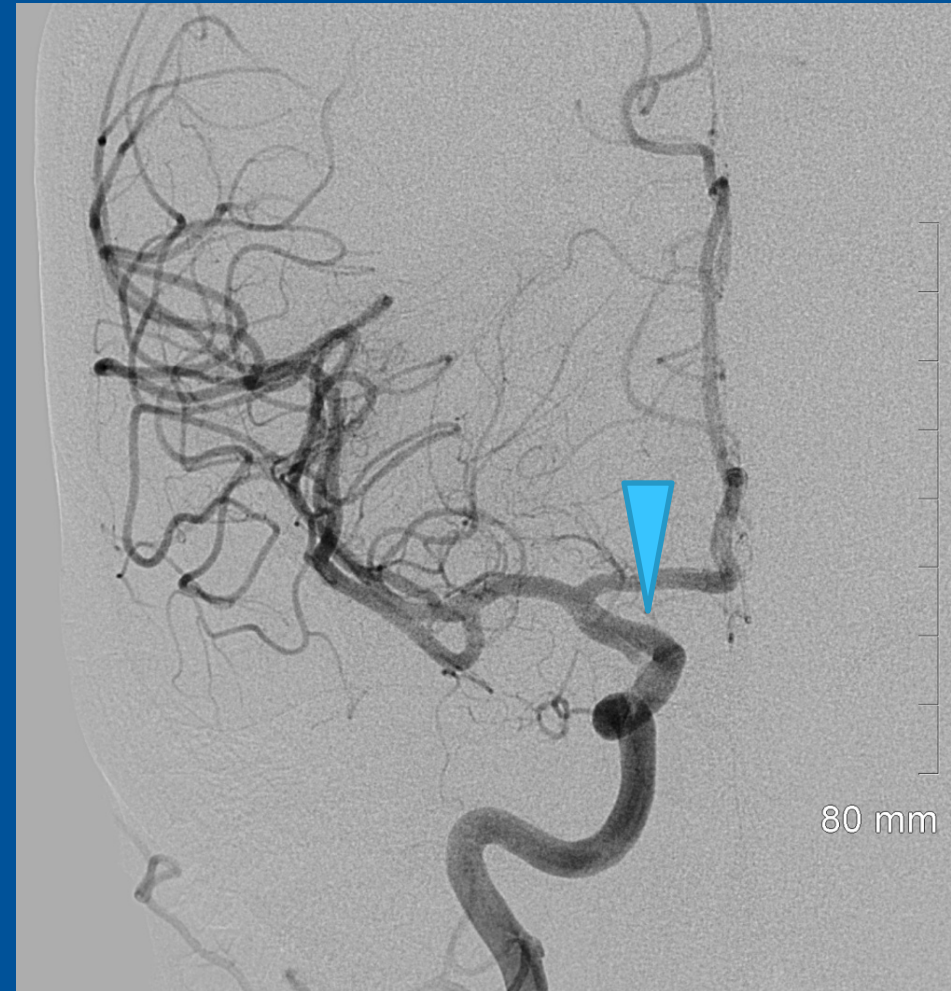
With permission

# CEREBRAL THROMBUS

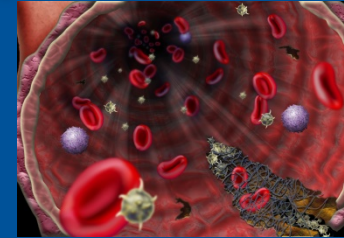
## ACUTE MCA OCCLUSION



## S/P THROMBECTOMY

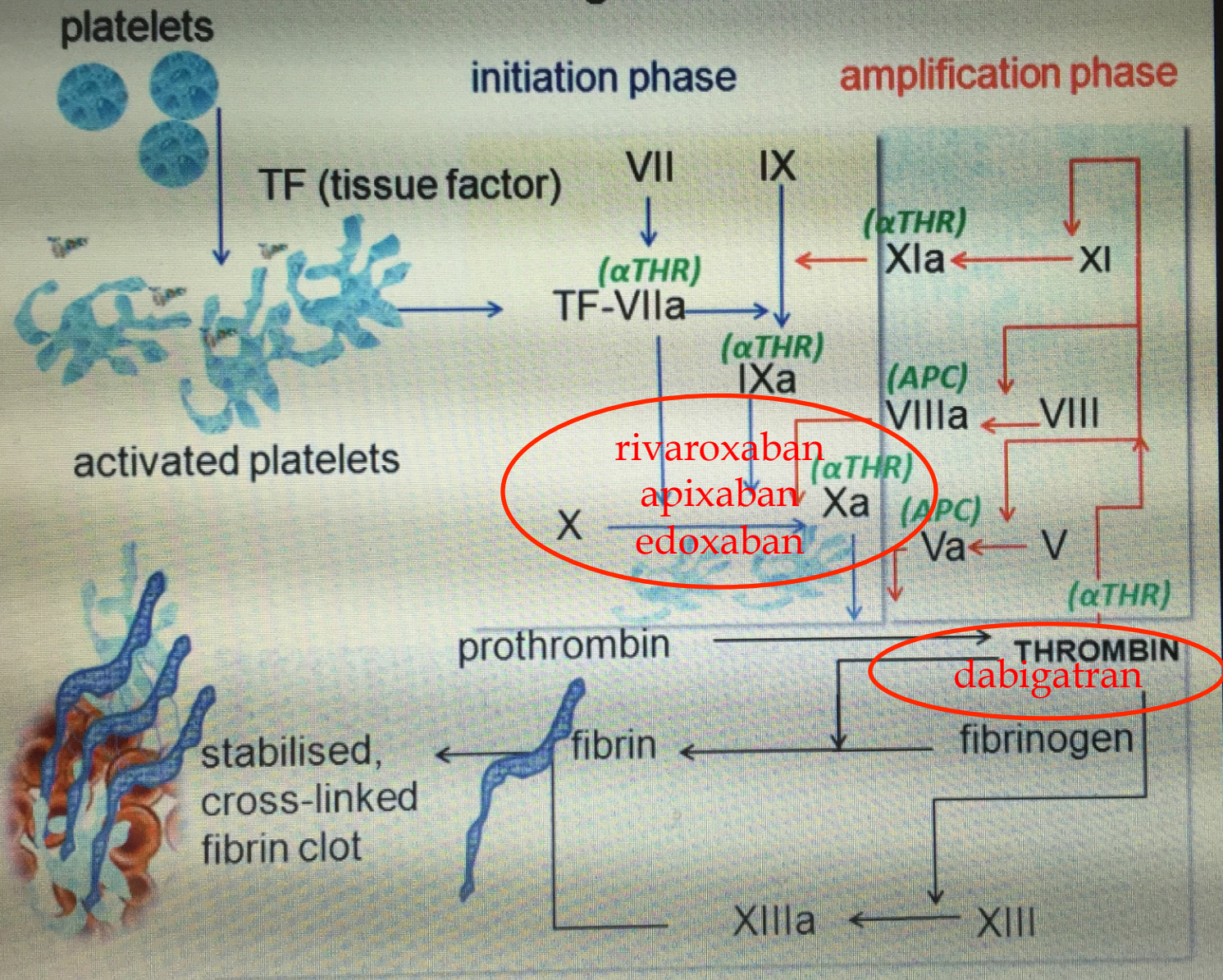


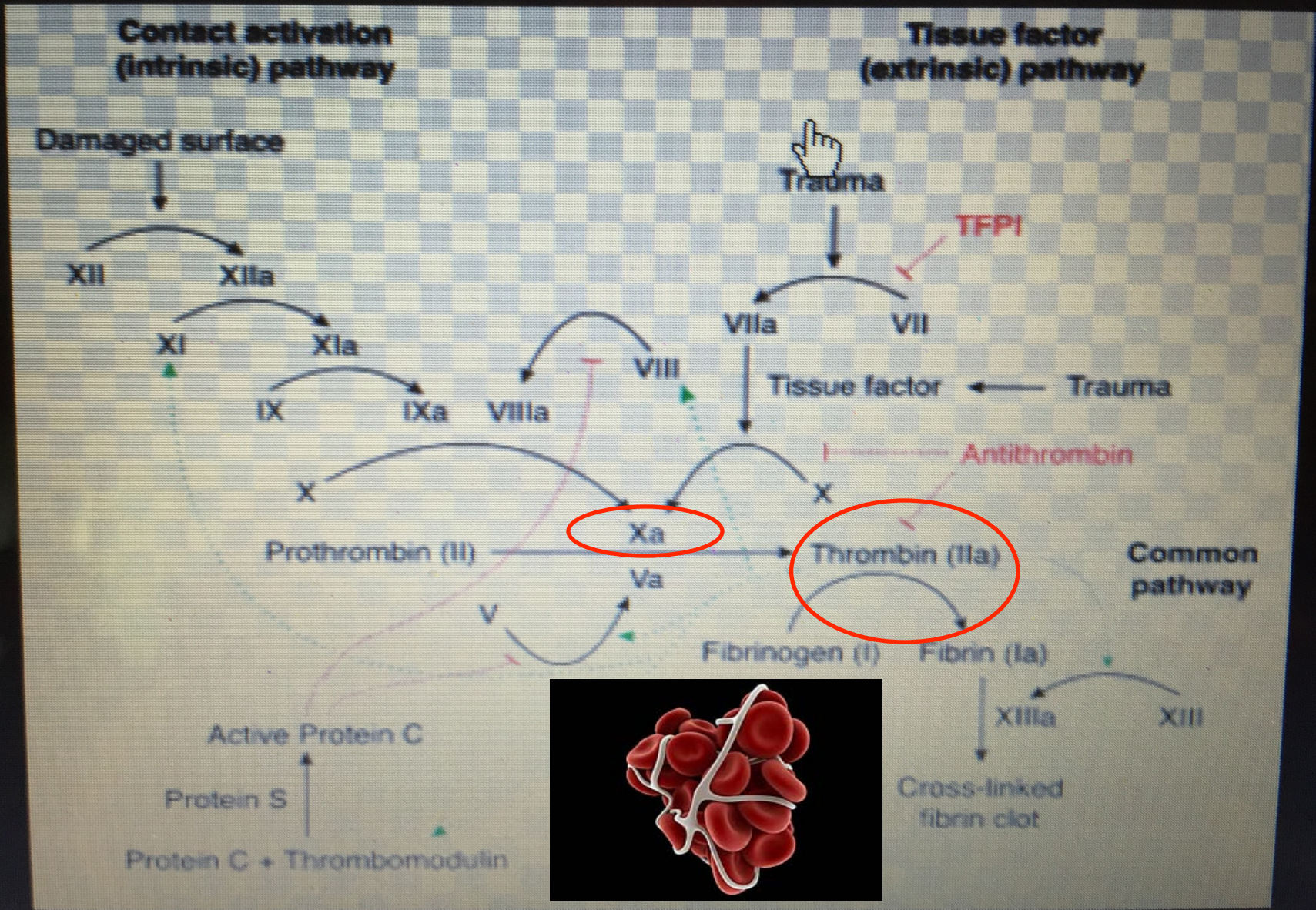
# Pathophysiology of Thrombus Formation



- ▣ Clotting triggered by inflammatory factors
- ▣ Damaged and abnormalities in blood vessel triggers clotting cascade enzymatic reactions
- ▣ The generation of thrombin (factor IIa) is central
- ▣ Prothrombin => thrombin via activated factor X (Xa)
- ▣ **THROMBUS** = intravascular clot within blood vessel or heart chamber
- ▣ **EMBOLUS** = detached thrombus carried into systemic circulation obstructing flow in smaller vessels

## Blood coagulation *in vivo*





# THROMBUS PATHOPHYSIOLOGY;

- ▣ Thrombus formation begins with Virchow's triad;
  - Stasis of blood flow
  - endothelial dysfunction / damage
  - a hypercoagulable state
- ▣ Thrombotic material associated with AF arises most frequently in the LAA
- ▣ Occurs with Stunning of the LAA with loss of flow velocities with onset AF
- ▣ Duration approximately 48 hours
- ▣ Doppler TEE is a more sensitive and specific method to visualize the clot

# THROMBUS FORMATION

- ▣ Although endothelial dysfunction has been difficult to demonstrate as distinctly contributing to thrombus formation in AF, it may, along with stasis, contribute to a hypercoagulable state.
- ▣ Systemic and/or atrial tissue levels of P-selectin
- ▣ von Willebrand factor are elevated in some patients , and AF has been associated with biochemical markers of coagulation and platelet activation that reflect a systemic hypercoagulable state

# WHAT DO WE PRESCRIBE ?

## HEPARINs

Low molecular weight – SQ – Enoxaparin

Unfractionated – IV – Heparin (Protamine Sul)

Fondaparinux – SQ – no reversible agent

## VITAMIN K ANTAGONISTS

Warfarin since 1954

## NOACs

Direct thrombin inhibitor II– Dabigatran

Reversal Agent - Idarucizumab

Direct factor Xa inhibition

Rivoxaban, Apixaban, Edoxaban – No  
reversible agents



# 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary



ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT				
	CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> <i>Additional studies with focused objectives needed</i> <b>IT IS REASONABLE</b> to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>	
				Procedure/Test	Treatment
				COR III: No benefit	No Proven Benefit
				COR III: Harm	Excess Cost w/o Benefit or Harmful to Patients
<b>LEVEL A</b> Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	
<b>LEVEL B</b> Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	
<b>LEVEL C</b> Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	
Suggested phrases for writing recommendations <sup>†</sup>	<p>should</p> <p>is recommended</p> <p>is indicated</p> <p>is useful/effective/beneficial</p>	<p>is reasonable</p> <p>can be useful/effective/beneficial</p> <p>is probably recommended</p> <p>or indicated</p>	<p>may/might be considered</p> <p>may/might be reasonable</p> <p>usefulness/effectiveness is unknown/unclear/uncertain or not well established</p>	COR III: No Benefit	COR III: Harm
Comparative effectiveness phrases <sup>‡</sup>	<p>treatment/strategy A is recommended/indicated in preference to treatment B</p> <p>treatment A should be chosen over treatment B</p>	<p>treatment/strategy A is probably recommended/indicated in preference to treatment B</p> <p>it is reasonable to choose treatment A over treatment B</p>		<p>is not recommended</p> <p>is not indicated</p> <p>should not be done</p> <p>is not useful/beneficial/effective</p>	<p>potentially harmful</p> <p>causes harm associated with excess morbidity/mortality</p> <p>should not be done</p>



# Contraindications to Anticoagulation

1. Advance Age
2. Unsteady gait
3. History of falls
4. Dementia
5. History of prior life threatening bleed (GIB, ICH, Hemorrhagic CVA, etc.)
6. History of medication non-compliance
7. Allergy
8. Occupational Risk
9. Pregnancy
10. Macular Degeneration
11. Other



# Physician Practices Regarding Contraindications to Oral Anticoagulation in Atrial Fibrillation

- ▣ Contraindications to OAC therapy among patients with AF are common but subjective. Many patients with reported contraindications were receiving OAC, suggesting that the perceived benefit outweighed the potential harm posed by the relative contraindication.



# Selected Risk Factors and Biomarkers for AF

## Clinical Risk Factors References

- ▣ Increasing age
- ▣ Hypertension
- ▣ Diabetes mellitus
- ▣ MI
- ▣ VHD
- ▣ HF
- ▣ Obesity
- ▣ Obstructive sleep apnea
- ▣ Cardiothoracic surgery
- ▣ Smoking
- ▣ Exercise
- ▣ Alcohol use
- ▣ Hyperthyroidism
- ▣ Increased PP (S-D)
- ▣ European ancestry
- ▣ Family history
- ▣ Genetic variants



# ATRIA Stroke Risk Score

- ▣ Hx; Stroke +8
- ▣ Age <65 = 0; <74 = +3; <84 = +5; ≥85 = +6
- ▣ Female +1
- ▣ Diabetes Mellitus +1
- ▣ Congestive Heart Failure +1
- ▣ Hypertension +1
- ▣ Proteinuria +1
- ▣ eGFR <45 (MDRD equation) or ESRD +1
- ▣ Low Risk (0-5 Points), <1% Annual Risk of Ischemic Stroke.

# CHADS<sub>2</sub> SCORE

Risk factor	Score
CHF	1
HTN	1
AGE $\geq$ 75yr	1
DM	1
CVA/TIA	2
<b>Maximum score</b>	<b>6</b>

**SCORE  $\geq$  2  $\Rightarrow$  AC**

# METABOLIC SYNDROME: CHADS<sub>2</sub>-MS

- Metabolic Syndrome Risk Factors
  - Elevated BMI,
  - Elevated Triglyceride
  - Low HDL-C

# CHA<sub>2</sub>DS<sub>2</sub>-VASc Score

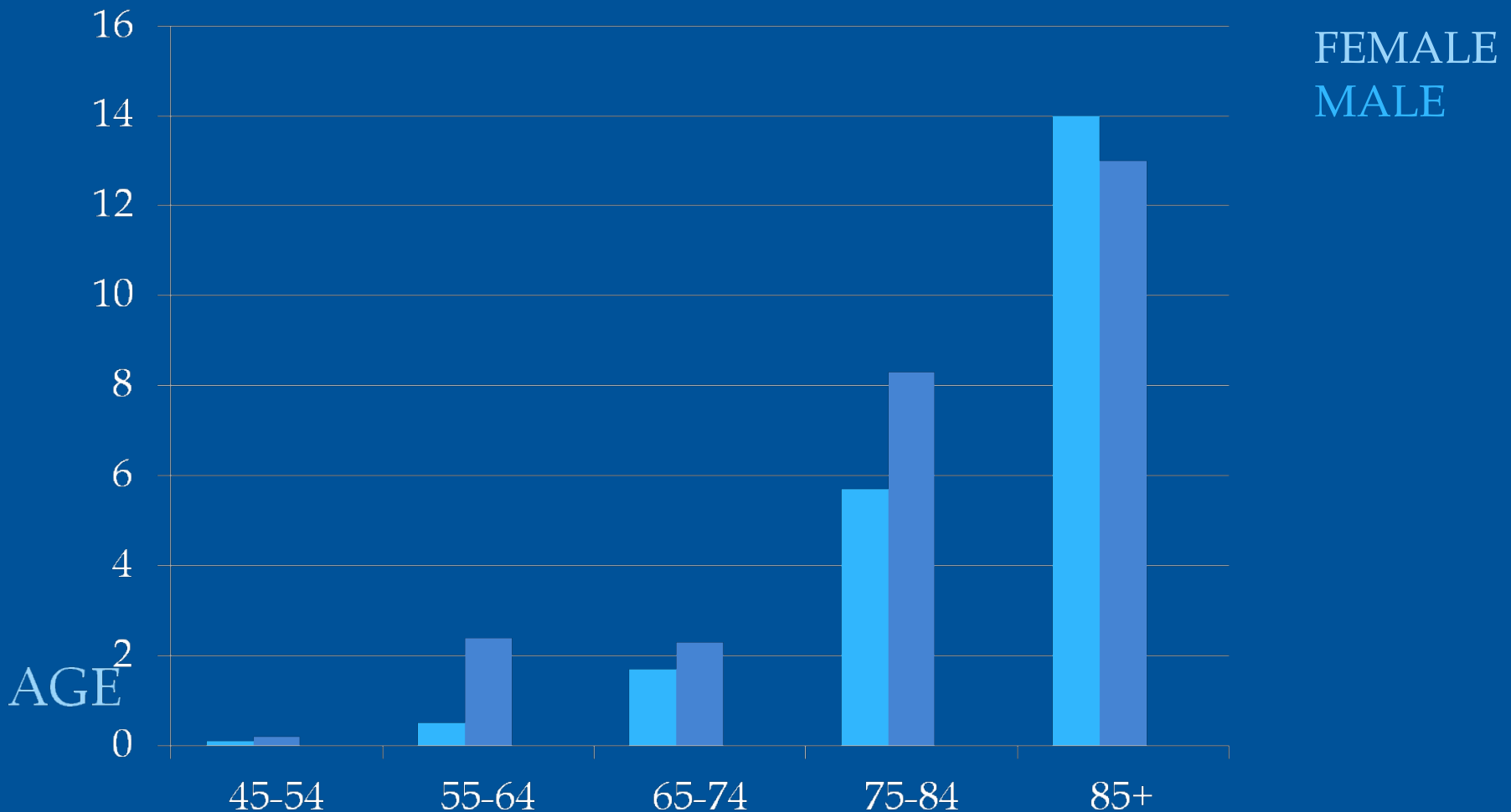
<b>C:</b> Congestive heart failure (or LV dysfunction )	(Points: 1 )
<b>H:</b> Hypertension:	(Points: 1 )
<b>A<sub>2</sub>:</b> Age >75 years	(Points: 2 )
<b>D:</b> Diabetes Mellitus	(Points: 1 )
<b>S<sub>2</sub>:</b> Prior Stroke or TIA or thromboembolism	(Points: 2 )
<b>V:</b> Vascular disease (prior MI, PAD or aortic plaque)	(Points: 1 )
<b>A:</b> Age 65-74 years	(Points: 1 )
<b>Sc:</b> Sex category ( female gender)	(Points: 1 )

**SCORE  $\geq$  2 => AC**

# ECHOES Study 2012

## Gender Prevalence of AF

in the general population and in high-risk groups:



# CHA<sub>2</sub>DS<sub>2</sub>-VASc



- ▣ CHA<sub>2</sub>DS<sub>2</sub>-VASc vs CHADS<sub>2</sub>
  - performed better in predicting patients at high risk,
  - low risk by CHA<sub>2</sub>DS<sub>2</sub>-VASc were truly at low risk for TE
- ▣ CHA<sub>2</sub>DS<sub>2</sub>-VASc  $\geq 2 \Rightarrow$  Warfarin @ 2.0-3.0
  - ▣ OR NOACs
- ▣ CHA<sub>2</sub>DS<sub>2</sub>-VASc = 1  $\Rightarrow$  No AT or AC; ASA
- ▣ CHA<sub>2</sub>DS<sub>2</sub>-VASc = 0  $\Rightarrow$  may OMIT AT

# ADJUSTED STROKE RATE

## CHADS<sub>2</sub>

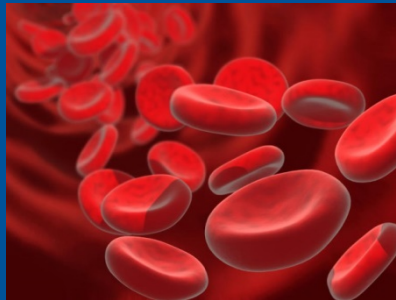
0	1.9% /yr
1	2.8% /yr
2	4.0% /yr
3	5.9% /yr
4	8.5% /yr
5	12.5% /yr
6	18.2% /yr

## CHA<sub>2</sub>DS<sub>2</sub>-VASc

0	0% /yr
1	1.3% /yr
2	2.2% /yr
3	3.2% /yr
4	4.0% /yr
5	6.7% /yr
6	9.8% /yr
7	9.6% /yr
8	----- /yr
9	15.20% /yr

# HAS-BLED Score for Bleeding Risk

Risk Factor	Score
• HTN – Sys >160mmHg	1
• Abn renal/liver function, drugs, ETOH	1 or 2
• Stroke	1
• Bleeding tendency	1
• Labile INR	1
• Age >65	1



**Low Risks = 0-2**  
**Risks of Bleeding = >3**

# ATRIA Bleeding Risk Score

- ▣ Anemia (Warfarin)
  - Female – Hgb <12; Male <13; +3
- ▣ Severe renal disease/HD
  - GFR <30ml/min or Dialysis +3
- ▣ Age  $\geq 75$  +2
- ▣ Prior Hemorrhage +1
  - GIB, ICH
- ▣ HTN +1

Low risk <4:

# Specific Patient Groups and AF

Hypertrophic  
Cardiomyopathy:  
Class I

Anticoagulation **is**  
indicated in patients  
with HCM with AF  
**independent** of the  
CHA2DS2-VASc score  
(*Level of Evidence: B*)

AF complicating ACS  
**URGENT  
CARDIOVERSION**



of new onset AF in setting  
of ACS, pulmonary disease,  
WPW, arrhythmias is  
recommended for patients  
with **Hemodynamic**  
compromise, ongoing  
**ischemia**, or inadequate **rate**  
control.

ACS and AF + **CHA2DS2-  
VASc (score  $\geq 2$ ), = >**  
**AC with warfarin is**  
recommended unless  
contraindicated

# Summary of Recommendations

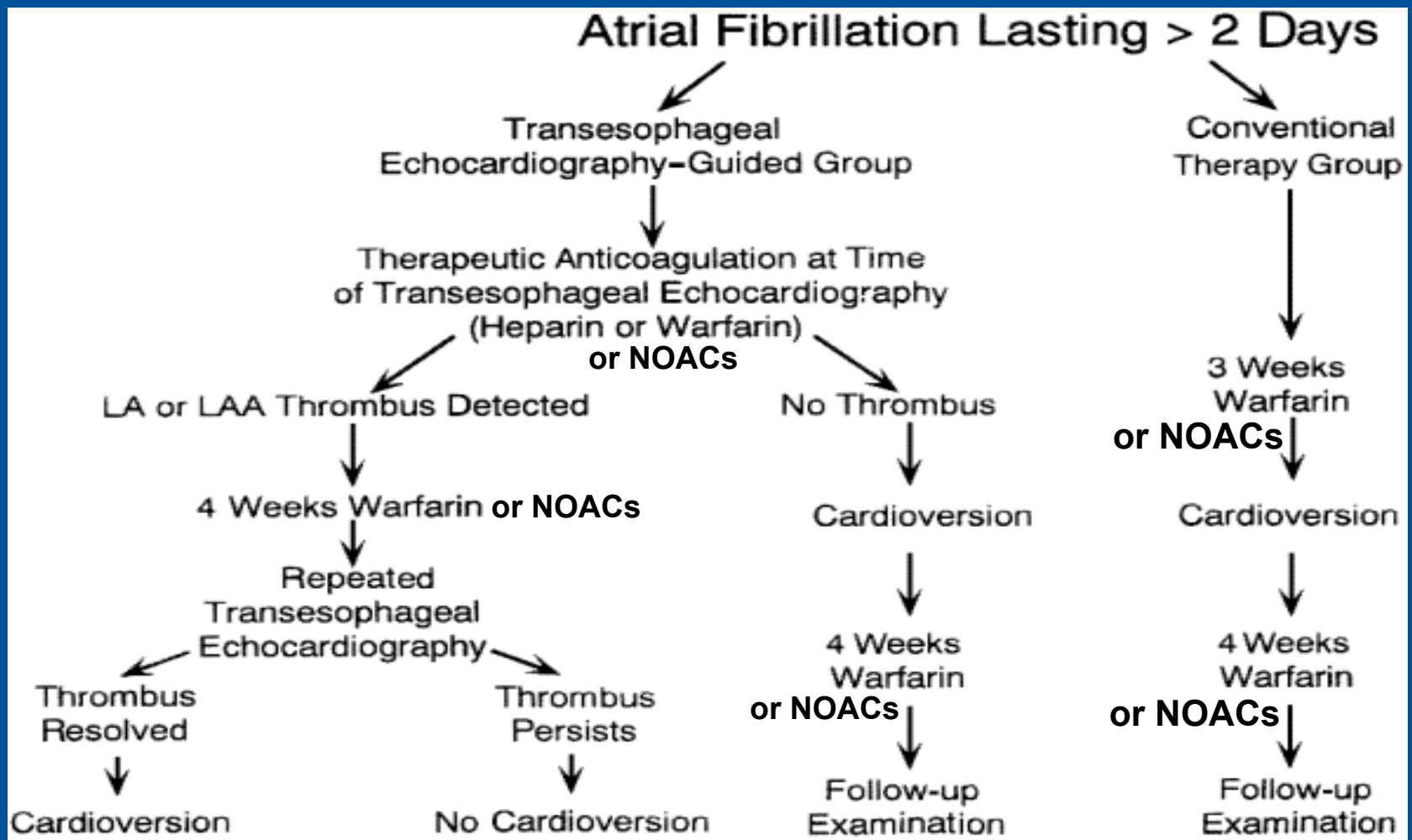
- ▣ Based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences
- ▣ CHA<sub>2</sub>DS<sub>2</sub>-VASc Score = recommended to assess stroke risk
- ▣ Warfarin Only => mechanical heart valves.
  - Target INR intensity should be based on the type and location of prosthesis
- ▣ Prior CVA/ TIA, or CHADS-VASc score  $\geq 2$ , =
  - warfarin , dabigatran, rivaroxaban, apixaban, or edoxaban
- ▣ Warfarin  $\leq$  Q WK initiation & Q MO when stable
- ▣ Unable to maintain therapeutic INR => NOAC

# Summary of Recommendations

- ▣ Re-eval need for AC PRN
- ▣ Bridging with Mech Valve = LMWH or UFH;
  - should balance risks of stroke and bleeding
- ▣ No Mech Valve = bridging = balance stroke + bleeding vs. duration of time
- ▣ Check GFR prior to direct thrombin or factor Xa inhibitors,
  - re-ck PRN
- ▣ AF1 = AF recommendations
- ▣ NVAf + CHADS-VASc score of 0 = reasonable to omit AC
- ▣ With CHADS-VASc score  $\geq 2$  ESRD (CrCl  $< 15$  mL/min) or HD = reasonable for Warfarin



# ANTICOAGULATION FOR CARDIOVERSION



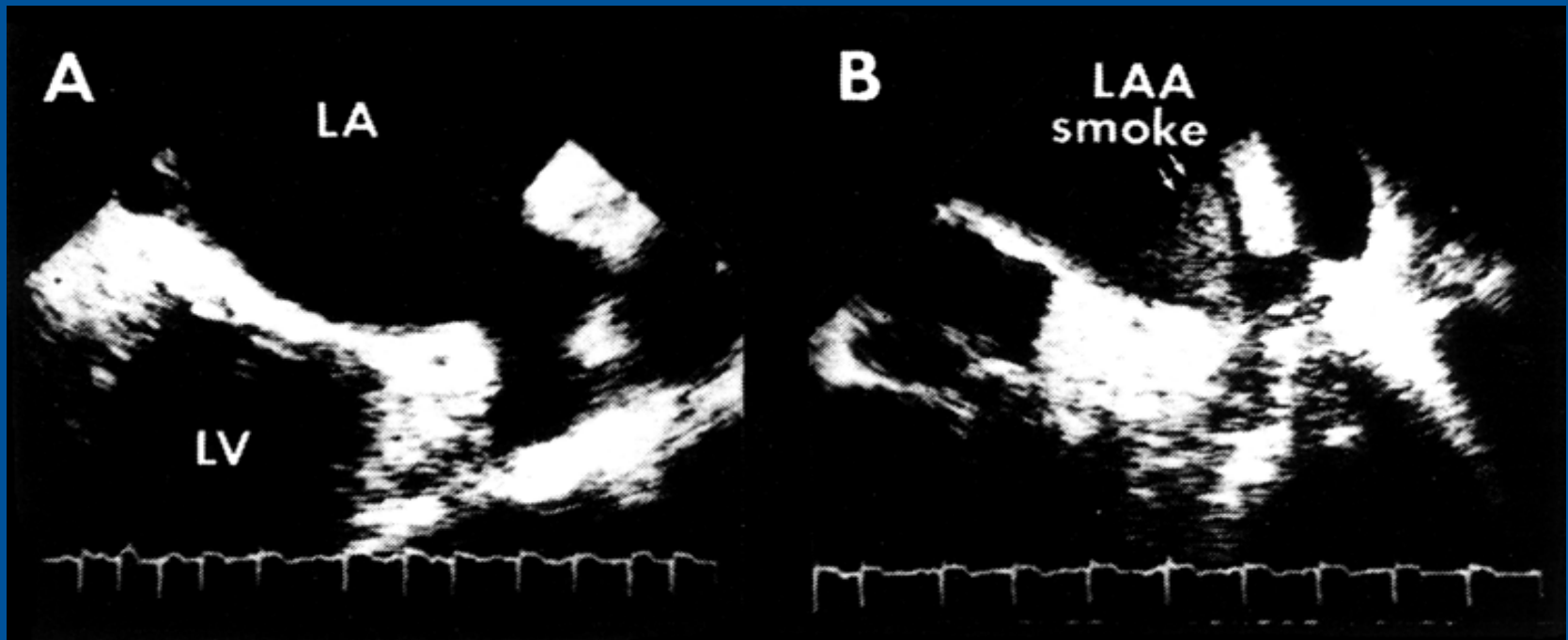
# ATRIAL FIBRILLATION CARDIOVERSION



SO WHAT HAPPENS INSIDE THE  
CHAMBERS DURING AN  
ELECTRICAL CARDIOVERSION ??



# Increase in Spontaneous Echo Contrast (“Smoke”) Following Electrical Cardioversion



**Left atrial appendage (LAA) before (A) and after (B) cardioversion**

Grimm RA. J Am Coll Cardiol. 1993;22(5):1359–1366.

# Transesophageal Echocardiogram

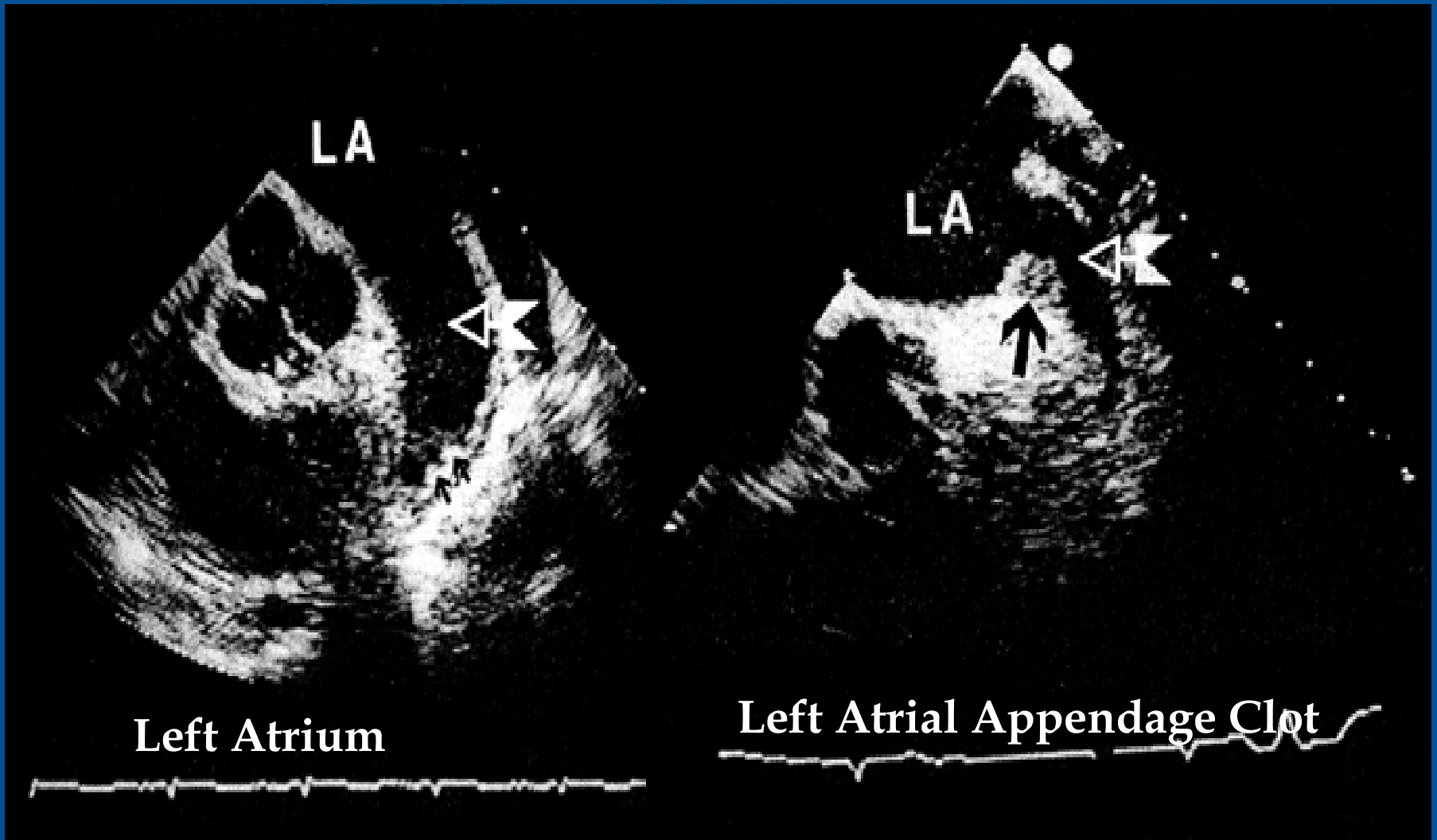
- ▣ Thromboembolic event is presumably due to left atrial clots/thrombus.
- ▣ Most clots are in left atrial appendage but poorly visualized by transthoracic echo (TTE).
- ▣ Transesophageal echo (TEE) is more sensitive (92%) and specific (98%) for detecting left atrial clot.

# LAA ANATOMY



- ▣ A long, narrow, tubular, wavy, hooked appendage with multiple pectinate muscles
- ▣ Multi-lobed: >80 % have two or more lobes, these lobes often lie in different planes

# ECHO WITH LAA CLOT



# INPATIENT AF ANTICOAGULATION



## ▣ HEPARINs

### ■ UNF

- ▣ Heparin – IV Protocol - **Protamine sulfate**

### ■ LMWH

- ▣ Enoxaparin – SQ: antithrombotic that inhibits factor Xa by increasing inhibition rate of clotting proteases that are activated by antithrombin III; **Protamine sulfate is less effective at reversing enoxaparin compared to heparin,**
- ▣ Fondaparinux – SQ: chemically related to low molecular heparins; Factor Xa inhibitor; **No reversal agent;**

# OUTPATIENT ORAL ANTICOAGULATION

- ▣ WARFARIN –inhibits liver's synthesis of Vit K dependent clotting factors II,VII, IX, X, and anticoagulant proteins C and 5

- ▣ DABIGATRAN – Factor II      - P-glycoprotein
- ▣ RIVARXOABAN – Factor Xa - CYP3A4 & P-glycoprotein
- ▣ APIXABAN - Factor Xa      - CYP3A4 & P-glycoprotein
- ▣ EDOXABAN Factor Xa      - CYP3A4 & Prostaglandin transporter

# WARFARIN

- ▣ 1948 Pesticide for rats and mice
- ▣ 1950s Safe for preventing thromboembolism & thrombosis
- ▣ 1954 Approved as medication
- ▣ 1955 Prescribed for Dwight Eisenhower after MI
- ▣ Prior to NOACs most widely prescribed oral anticoagulant drug in North America
- ▣ Multiple brand names

# WARFARIN : NOACs

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Administration	Once a day	Twice a day	Once a day	Twice a day	Once a day
Target	Vitamin K-dependent factors	Factor II	Factor Xa	Factor Xa	Factor Xa
Time to peak effect	3-5 d	1 h	2.5-4 h	3 h	1-2 h
Dose	Variable	150 mg twice a day and 110 mg twice a day	20 mg every day (15 mg every day for renal impairment)	5 mg twice a day (2.5 mg twice a day for high risk)	30 mg every day and 60 mg every day (with adjustment for high exposure)
Half-life	40 h	12-14 h	7-11 h	12 h	9-11 h
Interactions	Multiple	Inhibitors of P-glycoprotein transporter†	Inhibitors of CYP 3A4 and P-glycoprotein transporter†	Inhibitors of CYP 3A4 and P-glycoprotein transporter†	Inhibitors of CYP 3A4 and prostaglandin transporter†
Renal clearance, %	0	80	35	25	40
Anticoagulation monitoring	Required	Not required	Not required	Not required	Not required
Antidote	Vitamin K	Idarucizumab	None	None	None

Renal function	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Normal Mild Impairment	Dose adjusted for INR 2.0-3.0	150mg BID CrCl = 30ml/min	20mg HS CrCl = 50 ml/min	5.0 or 2.5mg BID
Moderate Impairment	Dose adjusted for INR 2.0-3.0	150 or 75mg BID CrCl = 30ml/min	15 mg HS (CrCl 30-50 mL/min)	5.0 or 2.5 mg BID
Severe Impairment	Dose adjusted for INR 2.0-3.0	75mg BID CrCl = 15-30ml/min	15 mg HS (CrCl 15-30 mL/min)	No recommendation, See section 4.2.2.2
End-Stage CKD Not on Dialysis	Dose adjusted for INR 2.0-3.0	Not recommended (CrCl <15 mL/min)	Not recommended (CrCl <15 mL/min)	No recommendation, See section 4.2.2.2
End-Stage CKD on Dialysis	Dose adjusted for INR 2.0-3.0	Not recommended (CrCl <15 mL/min)	Not recommended (CrCl <15 mL/min)	No recommendation, See section 4.2.2.2

AGENT	DOSE	COMMENTS
Vitamin K	1=10mg IV/PO	<ul style="list-style-type: none"> <li>• Infusion reactions rare; administer over 20-30 min</li> <li>• Takes 6 (IV) to 24 (PO) hours to reverse warfarin</li> <li>• Large doses can cause warfarin resistance on Resumption</li> </ul>
Protamine Sulfate	12.5-50 mg IV	<ul style="list-style-type: none"> <li>• Full reversal of unfractionated heparin</li> <li>• 60%-80% reversal of LMWH</li> <li>• No reversal of fondaparinux</li> </ul>
Idarucizumab	Infuse 5-g dose IV as 2 consecutive 2.5-g infusions or give as a bolus injections by injecting both 2.5-g vials consecutively	<ul style="list-style-type: none"> <li>• New and expensive</li> <li>• Refrigerate</li> </ul>

# Converting Anticoagulants to and from Dabigatran

Current Anticoagulant	Anticoagulant to be Converted to	Procedure
Warfarin (INR 2-3)	Dabigatran	Discontinue warfarin and start dabigatran when INR <2.0
Dabigatran	Warfarin (INR 2-3)	<ul style="list-style-type: none"> <li>• CrCl &gt;50 ml/min: start warfarin 3 days before stopping dabigatran</li> <li>• CrCl 31-50 ml/min: start warfarin 2 days before stopping dabigatran</li> <li>• CrCl 15-30 ml/min: start warfarin 1 day before stopping dabigatran</li> <li>• CrCl &lt;15 ml/min: no recommendation</li> </ul>
LMWH, heparin	Dabigatran	Start dabigatran 0-2 hours before administration of last heparin/ LMWH dose, or at same time as discontinuation of infusional heparin
Dabigatran	LMWH, heparin	<ul style="list-style-type: none"> <li>• CrCl &gt; 30 ml/min: start 12 hours after last dose of dabigatran</li> <li>• CrCl &lt; 30 ml/min: start 24 hours after last dose of dabigatran</li> </ul>

# RE-LY TRIAL

## DABIGATRAN vs WARFARIN

### ▣ Conclusions

- ▣ In patients with atrial fibrillation, Dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage.
- ▣ Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

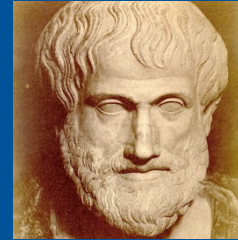
# ROCKET-AF TRIAL

## RIVAROXABAN VS WARFARIN

- ▣ **Conclusions**
- ▣ In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.



# ARISTOTLE TRIAL APIXABAN vs WARFARIN



- ▣ **Conclusions**
- ▣ In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

# META-ANALYSIS OF RANDOMISED TRIALS

## EFFICACY AND SAFETY OF NOACS VS WARFARIN

- ▣ Data for all 4 NOACs;
  - AF patients with CVA or systemic TE ;
- NOACs = Benefit profile,
  - ↓ CVA
  - ↓ Mortality
  - ↓ intracranial hemorrhage
  - ↑ GIB
  - Similar major bleeding as for warfarin
  - The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients.

# STROKE RISK REDUCTIONS: RANDOMIZED TRIALS OF ANTITHROMBOTIC AGENTS IN ATRIAL FIBRILLATION.

- **OVERVIEW**
- ▣ PLACEBO/CONTROL vs ANTIPLATELET => 22%
- **ACTIVE-A**
- ▣ ASA vs CLOPIDOGRIL+ASA => 28%
- **OVERVIEW ACTIVE-W**
- ▣ CLOPIDOGRIL +ASA vs WARFARIN => 43%
- **RE-LY**
- ▣ WARFARIN vs DIBIGATRAN 150mg => 36%
- **ROCKET AF**
- ▣ WARFARIN vs RIVAROXABAN => 12%
- **ARISTOTLE**
- ▣ WARFARIN vs APIXABAN => 21%

**SCALE OF 10  
STROKES ON  
PLACEBO/CONTROL**

# AC + ANTIPLATLET

- ▣ SPAF III & Copenhagen Atrial Fibrillation + AFASAK (Atrial Fibrillation, Aspirin, and Anticoagulation)
  - ▣ ASA, and Anticoagulation
  - ▣ low-dose oral AC = INR <1.5 + ASA =>
- ▣ added little protection against CVA compared with aspirin alone in patients with AF

# NASPEAF TRIAL ASA DURING HIATUS

In the larger Spanish National Study for Primary Prevention of Embolism in Nonrheumatic Atrial Fibrillation study, patients were stratified into a high-risk group (n 495) with AF and rheumatic mitral stenosis or AF and a history of stroke, TIA, or systemic embolism, and a lower-risk group (n 714) with AF and age greater than 60 y, hypertension, or HF (445).

Aspirin may be given temporarily during the hiatus, but the maintenance regimen should then consist of the combination of

**CLOPIDOGREL 75 mg daily, + WARFARIN**

(INR 2.0 to 3.0) for 9 to 12mo, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event.

# EUROPEAN HEART RHYTHM ASSOCIATION

Practical Guide on the use of new oral anticoagulants in  
patients with non-valvular atrial fibrillation:  
executive summary

- ▣ EHRA = NOAC CARD
- ▣ correct intake;
- ▣ contact information;
- ▣ renal function;
- ▣ concomitant medication, etc.;
- ▣ [www.NOACforAF.eu](http://www.NOACforAF.eu)

# CONTROVERSIES

- ▣ LAA excision is a class IIb recommendation during scheduled open heart surgery – do you need AC thereafter;
- ▣ Selection of patients for long-term oral anticoagulation;
- ▣ NOACs with elderly, reversibility, and use with multiple anti-platelet drugs;
- ▣ NOACs off label use;

# DABIGATRAN CONTROVERSY

- ▣ January 9, 2013, the Institute for Safe Medication Practice (“ISMP”), one month post release
- ▣ Bleeds were about 5 times more likely than warfarin to result in death
- ▣ 500% more likely to die as a result of a major bleed if you are on Dabigatran instead of warfarin
- ▣ Total disconnect between results from ISMP and RE-LY trial?

# Characteristics of the Ideal Anticoagulant

1. Equivalent efficacy to warfarin at least
2. Predictable response
3. Wide therapeutic window
4. Low inter and intra-patient variability
5. Fixed oral dosing QD
6. Low potential drug and dietary interactions
7. No need for regular coagulation monitoring
8. Fast onset and offset of action
9. Low incidence and severity of adverse effects
10. Cost effective for all
11. Responsible and accurate TV advertising

# Limitations of Warfarin

- Frequent monitoring necessitating regular clinic attendance
- Narrow therapeutic window
- Slow onset and offset of action, requiring 3-6 days to reach therapeutic levels
- Long half-life
- Numerous drug and dietary interactions
- Genetic polymorphisms exist which confer increased sensitivity or resistance to warfarin
- Unpredictable pharmacodynamics and pharmacokinetics leading to inter and intra-individual variability in dose and metabolism

# Potential Limitations of New Anticoagulants

- ▣ No reversal for Rivoxaban, Apixaban, Edoxaban
- ▣ Lack of validated tests to monitor anticoagulant effect
- ▣ It is difficult to assess compliance
- ▣ A method of anticoagulant bridging prior to surgery has not been established
- ▣ Unknown long-term safety profile
- ▣ Unknown true cost-effectiveness compared to warfarin
- ▣ No head-to-head studies of new agents
- ▣ Dabigatran and apixaban require twice daily dosing, which may promote noncompliance
- ▣ Dabigatran has been associated with GI side-effects

# OBJECTIVES REVIEW

- ▣ 1. Participants will be able to discuss atrial fibrillation and atrial flutter patient indications for and against anticoagulation.
- ▣ 2. Participants will be able to name and recognize the newer oral anticoagulants (NOACs).
- ▣ 3. Participants will be able to calculate stroke and bleeding scores prior to prescribing anticoagulant medications.

# CONCLUSION

- ▣ 1. We need to reduce risk of stroke for patients able to take anticoagulation medications.
- ▣ 2. Utilize the trial data and recommendations to guide our decisions with initial and continued lifetime anticoagulation.
- ▣ 3. Recognize the utility of multiple AT and AC agents indication for simultaneous therapy.
- ▣ 4. We need to protect out patients from risk of stroke with early detection and appropriate anticoagulation with atrial fibrillation.



A tropical beach scene with white sand, turquoise water, and a blue sky with clouds.

# Florida

THANK YOU VERY MUCH  
FOR YOUR ATTENTION