



## Anticoagulation and Antidotes for A Fib

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## Financial Disclosures

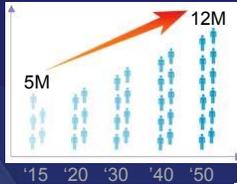
- Medtronic Consultant
- St Jude Medical Consultant



## AF is a Growing Problem Associated with Greater Morbidity and Mortality

AF = most common cardiac arrhythmia, and growing

AF increases risk of stroke



**~5 M**  
people with AF in U.S.,  
expected to more than  
double by 2050<sup>1</sup>

**5x**  
greater risk of stroke  
with AF<sup>2</sup>

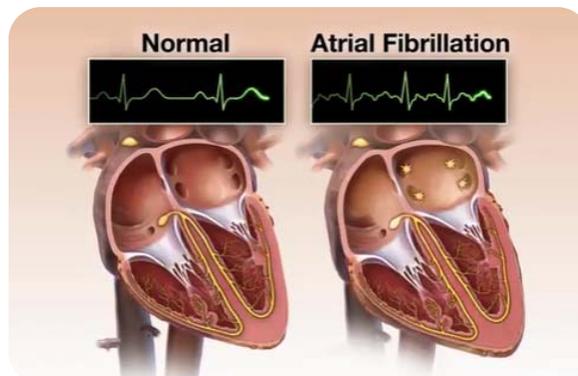
- Higher stroke risk for older patients and those with prior stroke or TIA
- 15-20% of all strokes are AF-related
- AF results in greater disability compared to non-AF-related stroke
- High mortality and stroke recurrence rate

1. Go AS, et al. Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association. *Circulation*. 2013; 127: e6-e245.  
2. Holmes DR. Atrial Fibrillation and Stroke Management: Present and Future. *Seminars in Neurology* 2010;30:528-536.



## What is Atrial Fibrillation

- Atrial Fibrillation or A fib is a heart condition that causes the upper chambers of your heart to beat too fast and in a chaotic rhythm



8 [http://medmovie.com/library\\_id/4979/topic/cvml\\_0080a/](http://medmovie.com/library_id/4979/topic/cvml_0080a/)



## PAC induced AF



## Why Afib Matters

- AF can put you at risk for other complications
  - **Blood Clots:** The irregular heart rhythm can cause blood to pool and form clots in an area of your heart called the Left Atrial Appendage (LAA)
  - **Stroke:** If a blood clot forms in the LAA, it can escape and travel through to the brain and cause a stroke
  - **Heart Failure:** If atrial fibrillation continues over a long period of time, the decreased efficiency of the heart can lead to heart failure



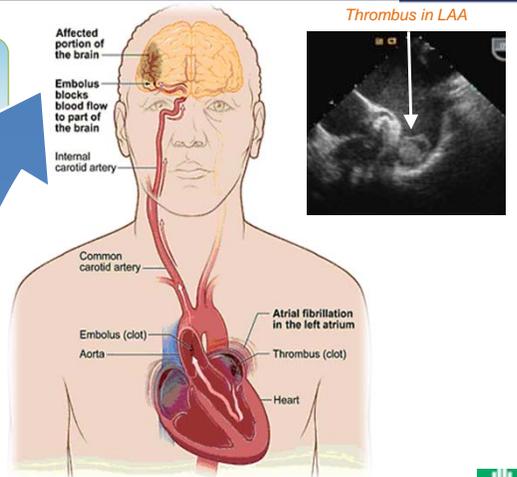
# Blood Clots & Stroke Risk

The clot lodges itself in the blood vessels of the brain, restricting blood flow and causing a stroke

The blood clot dislodges from the LAA and travels through arterial system

The stagnant blood becomes an ideal environment for a blood clot to form

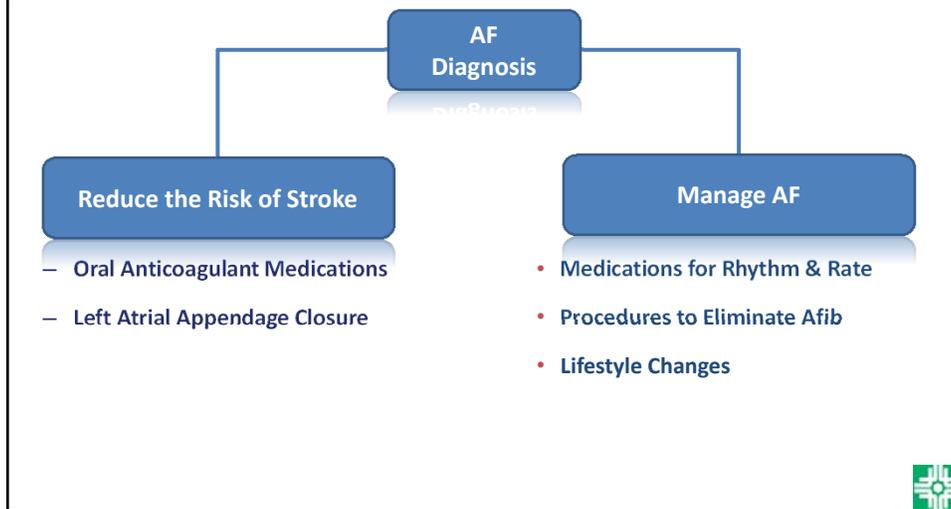
Fibrillation causes blood to stagnate in the left atrial appendage



## Did you know?

- Approximately **1 in 3** people with atrial fibrillation will have a stroke in his or her lifetime<sup>3</sup>
  - More than **90%** of stroke-causing clots that come from the heart originate in the LAA
  - Afib-related strokes are more frequently fatal and disabling<sup>4,5</sup>
- 

## Goals of treatment



## Oral Anticoagulant Medications (Blood Thinners)

- **Common blood thinners include**
    - warfarin
    - apixaban
    - dabigatran
    - rivaroxaban
    - edoxaban
  - Most people can take blood thinners for years without serious side effects
  - But because blood thinners help prevent clots by thinning the blood, they also increase the risk of bleeding<sup>2</sup>
- 

# CHA2DS2-VASc

## CHA2DS2-VASc score and stroke risk

Risk factors for stroke and thromboembolism in non-valvular AF	
Major risk factors	Clinically relevant non-major risk factors
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (eg, LV EF ≤40 percent) Hypertension - diabetes mellitus Female sex - age 65 to 74 years Vascular disease*
Risk factor-based approach expressed as a point based scoring system, with the acronym CHA <sub>2</sub> DS <sub>2</sub> -VASc (NOTE: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65 to 74	1
Sex category (ie, female sex)	1
<b>Maximum score</b>	<b>9</b>

Eur Heart J 2010; 31:2369



# Warfarin

- Inhibits Vit K dependent coagulation factors
- Metabolism – Liver CYP450
- ½ life 20-60h
- Dose adjusted to INR 2-3
- Many drug & food interactions
- Common drugs that increase the INR –  
Quinolones, Erythromycins, Tetracycline  
antifungals, Isoniazid, Amio, Propafenone,  
Gemfibrozil, Niacin, Pantoprazole, Paroxitene,  
Rouvastatin



## Dabigatran

- Direct thrombin inhibitor
- Indicated for the prevention of stroke & thromboembolism in nonvalvular AF
- No liver CYP 450 metabolism; Primarily urine excretion
- 1/2 life 12-17 hrs
- CrCl >50 ml/min - dose 150mg bid
- CrCl 30-50 ml/min - dose 75 mg bid



## Rivaroxaban

- Factor Xa inhibitor
- Indicated for the prevention of stroke & thromboembolism in nonvalvular AF. Also indicated for the prevention & tx of DVT/PE.
- Metabolism - Liver CYP450; Urinary excretion 66%
- 1/2 life 5-9 hrs; 11-13 hrs in the elderly
- CrCl >50 ml/min - dose 20 mg daily
- CrCl 15-50 ml/min - dose 15 mg daily



# Apixaban

- Factor Xa inhibitor
- Indicated for the prevention of stroke & thromboembolism in nonvalvular AF
- Metabolism - Liver CYP450; Urine excretion 27%
- 1/2 life 12 hrs
- Dose 5 mg bid
- Creat >1.5, age >80, wt <60 kg - dose 2.5 mg bid



# Inappropriate dosage

- Inappropriate dosing of non-vitamin K antagonist oral anticoagulants (NOACs) for [atrial fibrillation](#) (AF) was common in a large US cohort study, including inappropriate dosage reductions when there weren't renal indications for them and failures to drop the dosages when renal dysfunction called for it<sup>[1]</sup>.
- Such practices can lead to NOAC overdosing and underdosing that can compromise the drugs' safety without improving their effectiveness.
  - published June 5, 2017 in the Journal of the American College of Cardiology.



## Specific reversal agents

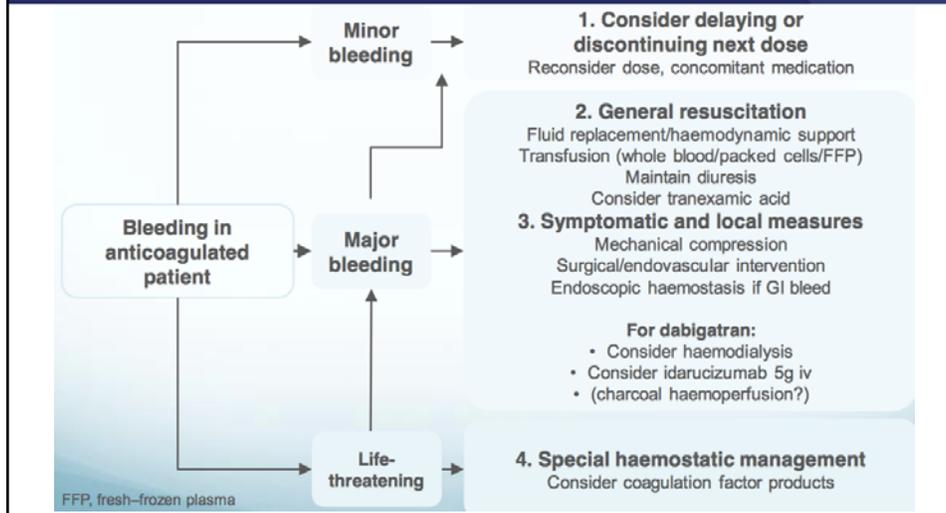
	Andexanet alfa	Idarucizumab	Aripazine
Structure	Human rXa variant	Humanized Fab fragment	Synthetic small molecule
Target	FXa inhibitors	Dabigatran	Universal
Binding	Competitive	Non-competitive. High affinity	Non-covalent Hydrogen bond
Phase 2 results	Rapid, complete reversal	Rapid, complete reversal	Complete reversal
Phase 3 trial	ANNEXA-4	REVERSE-AD	

## Acute Major Bleeding Definition

- Acute overt major bleeding is defined by at least one of the following:
  - Is potentially life-threatening (e.g., with signs or symptoms of hemodynamic compromise, etc.;
  - Associated with a fall in hemoglobin level by  $\geq 2$  g/dL, OR a Hb  $\leq 8$  g/dL if no baseline Hb is available OR, expected to fall to  $\leq 8$  g/dL with resuscitation;
  - In a critical area or organ, such as, intraspinal, retroperitoneal, intra-articular or pericardial, intracranial \* , or intramuscular with compartment syndrome.



# Bleeding Management Protocols



## REVERSAL AGENT FOR DABIGATRAN

IDARUCIZUMAB

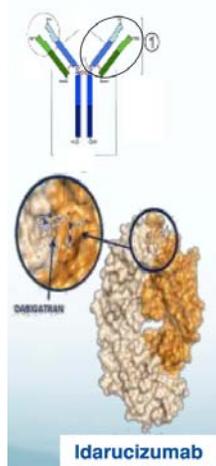


# Idarucizumab

- Drug Class: Monoclonal antibody fragment
- MOA: binds to drug compound (dabigatran) to neutralize its effect
  - Affinity is 350x higher than thrombin
  - Binds free and thrombin bound dabigatran
- Approved for:
  - Reversal of dabigatran for emergency
    - Surgery/urgent procedures
    - Life-threatening or uncontrolled bleeding



## Idarucizumab: specific reversal agent for dabigatran



- ⇒ Humanized Fab fragment
- ⇒ Binding affinity ~350 × higher than dabigatran to thrombin
- ⇒ No procoagulant or anticoagulant effects expected
- ⇒ IV administration, onset of action within 1 min  
Short half-life
- ⇒ Supports haemostasis in preclinical studies in pigs and mice



# Idarucizumab

- Dosage and Administration:
  - 5gm IV
    - Administer in two consecutive 2.5 gm infusions
  
- Warnings/Adverse Reactions:
  - Warning: Thromboembolic risk (reversal)
  - Adverse: hypokalemia (7%), delirium (7%), constipation (7%) , pyrexia (6%), pneumonia (6%), headache (5% in healthy volunteer study)

\*Resume anticoagulation as soon as medically appropriate\*



## RE-VERSE-AD (Idarucizumab)

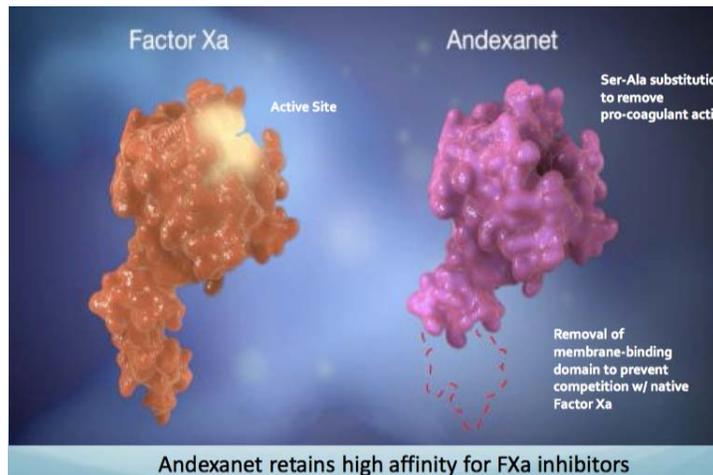
Main Inclusion Criteria	Main Exclusion Criteria
<p><b>Group A: Bleeding patients</b></p> <ul style="list-style-type: none"> <li>• Overt bleeding judged by MD to require a reversal agent</li> <li>• Currently taking dabigatran</li> <li>• ≥18 years of age</li> </ul>	<p><b>Group A: Bleeding Patients</b></p> <ul style="list-style-type: none"> <li>• Minor bleeds (epistaxis, haematuria) that can be managed with standard supportive care</li> <li>• No clinical signs of bleeding</li> </ul>
<p><b>Group B: Patients requiring emergency surgery or procedure</b></p> <ul style="list-style-type: none"> <li>• Condition requiring emergency surgery or invasive procedure where adequate haemostasis is required (emergency = next 8 hrs)</li> </ul>	<p><b>Group B: Patients requiring emergency surgery or procedure</b></p> <ul style="list-style-type: none"> <li>• Surgery or procedure which is elective or with low risk of uncontrolled or unmanageable bleeding</li> </ul>

# REVERSAL AGENT FOR RIVAROXABAN, APIXABAN, EDOXABAN

ANDEXANET ALFA

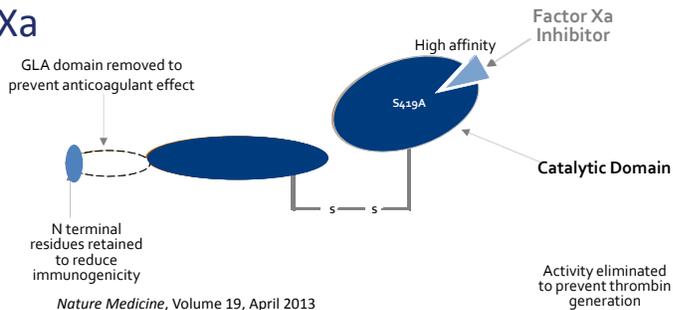


## Andexanet Binds Factor Xa Inhibitor



## Andexanet alfa: Recombinant Modified Human Factor Xa

- Specifically designed to reverse anticoagulant effects of fXa inhibitors
- Acts as a fXa decoy to bind molecules that target and inhibit fXa



## Andexanet alfa Dose Selection

**Acute major bleeding  $\leq$  18 hours of last dose of apixaban, edoxaban, rivaroxaban, or enoxaparin**

**Andexanet IV bolus and 2 hour infusion**

Pts on apixaban or  
>7 h from last rivaroxaban dose

**Bolus 400 mg  
+  
Infusion 480 mg @ 4 mg/min**

Pts on enoxaparin, edoxaban or  
 $\leq$ 7 h from last rivaroxaban dose

**Bolus 800 mg  
+  
Infusion 960 mg @ 8 mg/min**



## Safety Assessment

- Anticoagulation re-started in 18 patients (27%) by 30 days
- Thrombotic events occurred within 3 days of andexanet in 4 (6%) patients and by 30 days in 12 (18%)
- Therapeutic anticoagulation was re-started in only 1 patient before a thrombotic event occurred
- 10 deaths occurred by 30 days (15%), of which 6 were cardiovascular



Thank You

