Update in the Management of AF

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Financial Disclosures

No Conflicts regarding the discussed content for the management of atrial fibrillation
What to ask and order when a patient presents with AF?

How to decide to rate control or maintain SR?

Rate Control: Consequences of inadequate heart rate, target heart rate and how to achieve it?

Rhythm Control – how to achieve and maintain it?

Who to anticoagulate and with what?
What to ask and order when a patient presents with AF?

**Symptoms:**
- Palpitations
- Chest pain
- Shortness of breath
- Fatigue

**Circumstances:**
- Sleep – Obstructive sleep apnea
- Autonomic triggers
- Volume overload (CHF)
- Post operative
- Alcohol

**Pattern – Paroxysmal:** (terminates spontaneously)
- Persistent (remains for at least 7 days)
- Permanent (chronic)

? Family history
What to ask and order when a patient presents with AF?

<table>
<thead>
<tr>
<th>Tests</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiogram:</td>
<td>Assess LV function</td>
</tr>
<tr>
<td></td>
<td>Identify occult structural heart disease (valve etc)</td>
</tr>
</tbody>
</table>

Assess the Risk for stroke:  
- Congestive heart failure  
- Hypertension  
- Age  
- Diabetes  
- Prior Stroke/TIA  
- Vascular disease  
- Female Gender

DO NOT HAVE TO:
1. Evaluate for ischemia  
2. Restrict moderate caffeine  
3. Restrict mild ETOH
How to decide to rate control or maintain SR?

Rate v. Rhythm

Data and nuances
AFFIRM: Atrial fibrillation follow-up investigation in rhythm management

4,060 pts with clinical risk factors for stroke:
- ≥ 65 yrs old or
- < 65 with 1 or more stroke risk factors
- >6 hrs of AF in 1 or more episodes in prior 6 mos.
- Duration of continuous AF < 6 mos.

Randomized

Rate control
- Warfarin INR 2-3
- BB, CCB, Digoxin
- W/ confirmed rate control

Rhythm control
- Warfarin up to discretion of treating physician
- AAD – up to two trials

Primary outcome: Mortality
3.5 ys follow up
Figure 1. Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.

<table>
<thead>
<tr>
<th>Years</th>
<th>Rhythm control</th>
<th>Rate control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1</td>
<td>80 (4%)</td>
<td>78 (4%)</td>
</tr>
<tr>
<td>2</td>
<td>175 (9%)</td>
<td>148 (7%)</td>
</tr>
<tr>
<td>3</td>
<td>257 (13%)</td>
<td>210 (11%)</td>
</tr>
<tr>
<td>4</td>
<td>314 (18%)</td>
<td>275 (16%)</td>
</tr>
<tr>
<td>5</td>
<td>352 (24%)</td>
<td>306 (21%)</td>
</tr>
</tbody>
</table>

**P = 0.08**
No mortality advantage to a STRATEGY of rhythm v. rate control with the therapies utilized in 1997-2002.

Anticoagulation must be maintained in patients with clinical risk factors for stroke even if AADs are used to maintain SR.
When would you favor rhythm control regardless of the data? ie. even if the patient is asymptomatic

1. Young person – do you want to leave a 50 yr old in AF indefinitely?

2. Some patients don’t realize they were symptomatic until sinus rhythm is restored

3. Comparative study using ablation has not been done
Rate Control: Consequences of inadequate rate control, target heart rate and how to achieve it?
Rate control: Acute and Chronic

Consequences of inadequate rate control:

Symptoms: fatigue, dyspnea, palpitations

Tachycardia-induced cardiomyopathy
Lenient versus Strict Rate Control in Patients with AF: RACE 2 study

614 patients with permanent AF randomized to a

**Lenient RC strategy ≤ 110 bpm at rest**

or

**Strict RC strategy ≤ 80 bpm at rest**

Primary outcome: composite of death from cv causes, CHF hospitalization, stroke, bleeding and life threatening arrhythmic Events

10% prior CHF hospitalization
15% with LVEF ≤ 40%
35% with NYHA Class 2 or 3 HF symptoms

2-3 yr follow up

NEJM 2010;362:1363
AVJ ablation for rate control of Atrial fibrillation
Rhythm Control – how to achieve and maintain it?
Clear evidence of AF duration < 48 h

Stroke risk Factors

No → Cardiovert

Yes →

if INR < 2
Consider heparin or equivalent therapy (low molecular weight Heparin, Dabigatran, Apixaban, Rivaroxaban or Edoxaban) then cardiovert

Continue warfarin (INR ≥ 2 or Dabigatran, Apixaban, Rivaroxaban or Edoxaban for at least one month or indefinitely if there are stroke risk factors)

Stroke Risk Factors
Age > 65
Hypertension
Diabetes Mellitus
Congestive heart failure
Prior Stroke or TIA

Drug Dosages
Dabigatran 150 mg bid, 75 mg bid if creatinine clearance < 30
Rivaroxaban 20 mg qd, 15 mg qd if creatinine clearance 15-50
Apixaban 5 mg bid, 2.5 mg bid if 2 or more (age > 80, body weight ≤ 60 kg, creatinine ≥ 1.5 mg/dl)
Edoxaban 60 mg qd, 30 mg qd (Cr Cl 15-50 ml/min)
Contraindicated if (CrCL > 95 ml/min)
AF > 48h duration

TEE

No thrombus present

Cardiovert; Warfarin, Dabigatran, Rivaroxaban, Apixaban or Edoxaban for at least one month. If risk factors present continue indefinitely

Thrombus present

Warfarin, Dabigatran, Rivaroxaban, Apixaban or Edoxaban for at least one month after which consider TEE or proceed to CV

Warfarin, Dabigatran, Rivaroxaban, Apixaban or Edoxaban for at least one month, or indefinitely if risk factors present

Warfarin, Dabigatran, Apixaban, or Edoxaban for 3-4 weeks
Pharmacologic Management

Class 1  **Na\(^+\) channel blockers**

A: Quinidine, Procainamide, Disopyramide  
B: Lidocaine, Mexilitine  
C: Flecainide, Propafenone

Class 2  **Beta Blockers**

Class 3:  **K\(^+\) channel blockers**

Sotalol, Amiodarone, Dofetilide, Dronedarone

Class 4:  **Calcium channel blockers**
Antiarrhythmic Medications

1st line
- Lone AF
  - Flecainide
  - Propafenone
  - Dronedarone

- ↓ LVEF/CHF
  - Amiodarone
  - Dofetilide

- CAD (nl EF)
  - Sotalol
  - Amiodarone
  - Dronedarone

- Hypertrophic Myopathy
  - Amiodarone
  - Sotalol

2nd line
- Type 1A
  - Sotalol
  - Dofetilide
  - Disopyramide

- Type 1C
  - Dronedarone

Avoid
Major Toxicity of Antiarrhythmic Medications

**Torsades de pointes: 2%-5%**

- Women are at > risk
- Not dose-related (type 1a)
- Dose related (Sotalol, Dofetilide)
- Bradycardia (type 1a medications)
- Post-conversion to sinus rhythm
- Hypokalemia, hypomagnesemia (diuretics)
Torsades de pointes
Drugs that pose a risk of Torsades de pointes

<table>
<thead>
<tr>
<th>AADS</th>
<th>ABXs</th>
<th>Anti Depressants Anti Psychotics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>Levoflox</td>
<td>amitryptyline</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Ciproflox</td>
<td>Desipramine</td>
<td>Methadone</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Erythromycin</td>
<td>Imipramine</td>
<td>Arsenic</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Clarithromycin</td>
<td>Fluoxetine</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Fluconazole</td>
<td>Haloperidol</td>
<td></td>
</tr>
<tr>
<td>Disopyr</td>
<td>Ketoconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Effect</td>
<td>Incidence</td>
<td>Recommended Monitoring</td>
<td>Special Considerations</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>5%</td>
<td>Baseline electrocardiogram at least once during loading period, especially if conduction disease is present; yearly thereafter</td>
<td>Consider reduction of loading dose in elderly patients and those with underlying sinoatrial or atrioventricular conduction disease; reduce dose or discontinue if QT interval exceeds 550 msec</td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>In most patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torsades de pointes</td>
<td>&lt;1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>15%</td>
<td>Aspartate and alanine aminotransferase measurements at baseline and every 6 months thereafter</td>
<td>Avoid in patients with severe liver disease</td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>3%</td>
<td>Thyroid-function tests at baseline and two or three times a year thereafter</td>
<td>Avoid in presence of preexisting, non-functioning thyroid nodule; higher incidence of thyroid effects in patients with autoimmune thyroid disease</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>&lt;3%</td>
<td>Pulmonary-function tests at baseline and if symptoms develop; chest radiograph at baseline and yearly thereafter</td>
<td>Discontinue amiodarone immediately if pulmonary effects suspected</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>25–75%</td>
<td>Routine</td>
<td>Recommend use of sunscreen with a high sun protection factor</td>
</tr>
<tr>
<td>Neurologic</td>
<td>3–30%</td>
<td>Routine</td>
<td>Consider dose reduction</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal deposits</td>
<td>100%</td>
<td>Examination at baseline if there is underlying abnormality; examinations as needed thereafter</td>
<td>Avoid in presence of preexisting optic neuritis</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>&lt;1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mean age: 65 yrs
PAF 49%, Persistant AF 51%
LA dimension: 41 ± 7 mm

No significant differences in medication related Adverse events.

Significant reduction in embolic And hemorrhagic strokes in amiodarone group
Non Pharmacologic maintenance of sinus rhythm

Catheter based percutaneous pulmonary vein isolation

Surgical AF ablation: Minimally invasive MAZE
Full open surgical Maze
LSPV

Left atrium

Veno-atrial junction

Myocardial sleeve

Lung hilum
Percutaneous Pulmonary Vein Isolation

Optimal Candidates: Failed at least one antiarrhythmic drug

Success: 70% reduction in symptoms or cure
10-15% likelihood of second procedure

Risks: 1% risk of stroke, < 1% risk of esophagoatrial fisutula, 1% risk of tamponade
Facts and Fiction about PVI

Facts
• Most patients feel better
• Most have a reduction in the burden of AF
• Do not know the long term efficacy
• 30% of patients remain on an antiarrhythmic drug

Fiction
• PVI is a curative procedure
• PVI can be performed as a way to get off anticoagulation
• The procedure has become more effective
Thromboembolic risk and prophylaxis in Atrial Fibrillation
Stroke Prevention

Antiarrhythmic Therapy ≠ Sinus Rhythm ≠ Diminished Stroke Risk
<table>
<thead>
<tr>
<th>CHADS VASC</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular Disease (MI, PAD, Aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 64-75</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
</tr>
</tbody>
</table>

Not included: Renal Insufficiency - eGFR < 45 mL/min stroke risk + 4/100 patient-years

Go et al. Circulation 2009
25% of strokes in the > 80 yr age group are attributable to AF  Wolfe et al Framingham Heart Study

<table>
<thead>
<tr>
<th>Age and Stroke risk</th>
<th>%/patient year</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59 yrs</td>
<td>1.3</td>
</tr>
<tr>
<td>50-69 yrs</td>
<td>2.2</td>
</tr>
<tr>
<td>70-79 yrs</td>
<td>4.2</td>
</tr>
<tr>
<td>80-89 yrs</td>
<td>5.1</td>
</tr>
</tbody>
</table>
Updated 2014 AHA/HRS Guidelines

Class 1
For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA$_2$DS$_2$-VASc score of 2 or greater, oral anticoagulants are recommended.

Class 2a
For patients with nonvalvular AF and a CHA$_2$DS$_2$-VASc score of 0, it is reasonable to omit antithrombotic therapy.

Class 2b
For patients with nonvalvular AF and a CHA$_2$DS$_2$-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered.

Reduced importance of Aspirin

Neutral on NOAC v. warfarin
Stroke risk in Intermittent v. Permanent AF

Hart et al. SPAF J Am Coll Cardiol 2000;35:183:
Hohnloser J Am Coll Cardiol 2007;50:2156

Figure 1  Incidence of Stroke or Non-CNS Systemic Embolism According to Type of AF
Cumulative hazard rates of stroke and non-central nervous system (CNS) systemic embolisms in patients with paroxysmal (P) versus sustained (S) atrial fibrillation (AF) treated with aspirin plus clopidogrel or oral anticoagulation.

Atrial Flutter
Left Atrium

Left Ventricle

Left Atrial Appendage With Clot
Aspirin and thromboembolic prophylaxis in AF

- 6 original trials of stroke prevention in AF

<table>
<thead>
<tr>
<th>BAATAF</th>
<th>Trend toward stroke reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td></td>
</tr>
<tr>
<td>CAFA</td>
<td></td>
</tr>
<tr>
<td>SPINAF</td>
<td></td>
</tr>
<tr>
<td>EAFT</td>
<td></td>
</tr>
<tr>
<td>SPAF</td>
<td>Significant reduction in stroke risk</td>
</tr>
<tr>
<td>(325 mg)</td>
<td></td>
</tr>
</tbody>
</table>
Dosage of aspirin varied between 81 and 325 mg.

Aspirin is no longer recommended.

In the European Guidelines.
Low dose aspirin (150-200 mg) for prevention of stroke in low risk patients with atrial fibrillation
Japan Atrial Fibrillation Stroke Trial Stroke 2006

Hypothesis: low utilization (8%) of AC in Japan due to concerns for bleeding. 47% use of aspirin in Japan but at low dose due to concerns for GI bleeding.

Patient characteristics (matched)
N = 903
Mean age 65 yrs
Male 70%
Parox AF 45%
HTN 37%
DM 13%
CHF 10%
TIA/Stroke 2.5%

Excess bleeding and GI intolerance associated w aspirin

Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE)

AF (at least 2 episodes of AF in last 6 months) + ≥ 1 stroke risk factors (≥ 75 yrs, HTN, LVEF < 45, TIA/P emb, PVD, age 55-74 + DM or CAD)

ACTIVE W*  ACTIVE A**  ACTIVE I

Warfarin      v ASA +     ASA +        ASA +  Irbesartan
Clopidogrel    placebo                 Clopidogrel               in ACTIVE W and A
ASA 75 to 100 mg
Clopidogrel 75 mg

* Lancet 2006;367:1903
** N Engl J Med 2009;360:2066

Combination Anti Platelet Therapy

Clopidogrel + ASA bleeding rate equivalent to warfarin therapy
Cumulative risk of stroke for patients treated at centers with a Time in Therapeutic Range (TTR) below or above the study median (65%)
Warfarin inhibits the C1 subunit of Vitamin K epoxide reductase (VKORC1).

Variants of CYP2C9 encode enzyme with reduced activity, leading to lower maintenance warfarin dosages. Most common in Caucasians.

VKORC1 genetic variants lead to lower maintenance warfarin dosages. Most common in Asians.

Upto 25% of patients with difficult to manage warfarin dosing have a polymorphism of VKORC1 or less commonly CYP2C9.
### Warfarin interactions

<table>
<thead>
<tr>
<th>Potentiate Warfarin</th>
<th>Inhibit Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Haldol</td>
</tr>
<tr>
<td>Antibiotics (particularly)</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Cephalosporins, Ciprofloxacin, Erythromycin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Metronidazole, Trimethoprim-Sulfamethoxazole, Macrolides</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Cimetidine</td>
<td></td>
</tr>
<tr>
<td>Excessive ETOH</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
</tr>
<tr>
<td>NSAIDS</td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td></td>
</tr>
<tr>
<td>Ginkgo Biloba, Ginseng</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Vit K containing foods (green leafy vegetables):</td>
<td></td>
</tr>
<tr>
<td>spinach, broccoli, avocado</td>
<td></td>
</tr>
<tr>
<td>Coenzyme Q</td>
<td></td>
</tr>
<tr>
<td>St John’s wart</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td></td>
</tr>
<tr>
<td>Hereditary coumadin resistance</td>
<td></td>
</tr>
</tbody>
</table>
Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation

Fuster, V. et al. Circulation 2006;114:e257-e354
THROMBOEMBOLISM ASSOCIATED WITH AURICULAR FIBRILLATION

Continuous Anticoagulant Therapy

JOHN MARTIN ASKEY, M.D.
and
CLIFFORD B. CHERRY, M.D.
Los Angeles

About three times as many patients with rheumatic heart disease and auricular thrombi as those without these conditions are associated with auricular fibrillation. About 15.7 per cent of patients with these conditions are at risk of thromboembolism. The prevention of thromboembolism is probably impossible with usual anticoagulant therapy. Therefore, it is probable that safer anticoagulant drugs will be available eventually. At present, the incidence of deaths and complications from intracardiac clot formation must be balanced against the similar hazards of the use of dicumarol. About 20 of 100 patients dying of rheumatic heart disease and auricular fibrillation die from thromboembolism. The majority show systemic symptoms of embolism. In some cases, the embolism is lethal. In others, the embolism is subclinical.
Coagulation Cascade

Initiation

VIIa/TF

Propagation

IX

IXa

Xa

Va

II

Direct Thrombin Inhibitors
Ximelagatran
Dabigatran etexilate

Direct Factor Xa inhibitors
Rivaroxaban
Apixaban
Betrixaban

Fibrin Formation

Indirect Factor Xa inhibitors
(require thrombin as Cofactor, Sub Q)
Fondaparinux
Idraprarinux

No interaction with food or antibiotics

No need to monitor
(Minimum protein binding and predictable pharmacokinetics)

Rapid onset and offset

**Dabigatran**

- Gut
  - esterase-mediated hydrolysis
  - Bio-availability: ~3–7%
  - P-gp - Dabigatran
  - t½ = 12–17h
  - 150 mg bid

**Rivaroxaban**

- Gut
  - Bio-availability: 66% (without food) >80% (with food)
  - P-gp - Rivaroxaban
  - t½ = 5.9h (young) 11-13h (elderly)
  - 15 mg qd (Cr Cl 15-50 ml/min)

**Apixaban**

- Gut
  - Bio-availability: 50%
  - P-gp - Apixaban
  - t½ = 12h
  - 5 mg bid

**Edoxaban**

- Gut
  - Bio-availability: 62%
  - P-gp - Edoxaban
  - t½ = 9-11h
  - 60 mg qd

**Dosages**

- 2.5 mg bid (≥2 of >80 yr, ≤60 kg, cr ≥ 1.5 mg/dl)
  - (Cr Cl <15 contraindicated)
- 15 mg qd (Cr Cl 15-50 ml/min)
  - Contraindicated if (CrCL > 95 ml/min)
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>RELY 18,113</td>
<td>ROCKET AF 14,264</td>
<td>ARISTOTLE 18,201</td>
<td>ENGAGE AF 21,105</td>
</tr>
<tr>
<td>CHADS</td>
<td>2.1</td>
<td>3.5 (50% prior stroke/TIA)</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Time in therapeutic range</td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
<td>68%</td>
</tr>
<tr>
<td>Ischemic End pt</td>
<td>Non inferior</td>
<td>Non inferior</td>
<td>Non inferior</td>
<td>Non inferior</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>60% lower</td>
<td>41% lower</td>
<td>49% lower</td>
<td>46% lower</td>
</tr>
<tr>
<td>Special considerations</td>
<td></td>
<td>Sig lower all cause bleeding</td>
<td>Sig lower all cause bleeding</td>
<td>CANNOT use if Cr Cl 95</td>
</tr>
</tbody>
</table>
Worries with these new agents

Can’t reverse

particularly if there is an intracranial bleed

Can’t use with valvular heart disease
Why less CNS bleeding with NOACs?

**Initiation**
- VIIa/TF

**Propagation**
- IX
- IXa
- Xa
- Va
- II

**Fibrin Formation**
- IIa (Thrombin)

**Warfarin blocks tissue Factor VIIa-mediated thrombosis – perhaps important in CNS hemostasis**

- **Direct Thrombin Inhibitors**
  - Ximelagatran
  - Dabigatran etexilate

- **Direct Factor Xa inhibitors**
  - Rivaroxaban
  - Apixaban
  - Edoxaban

- **Indirect Factor Xa inhibitors**
  - (require thrombin as Cofactor, Sub Q)
  - Fondaparinux
  - Idraparinux
## Peri Procedure Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creat Clearance (ml/min)</th>
<th>Half life (hrs)</th>
<th>How long to discontinue (days)?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>High bleeding risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-17</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>&gt;50</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>30-50</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>15-30</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11-13 (elderly)</td>
<td>2</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>&gt;50</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>30-50</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>15-30</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>2</td>
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<tr>
<td></td>
<td></td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Apixaban</td>
<td>&gt;50</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>30-50</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>15-30</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

High bleeding risk: Neuro, Cardiac, Urological (prostate/kidney), Liver/Spleen, Polyp resection
Antidotes for the New Oral Anticoagulants

**Andexanet alfa** (recombinant modified factor Xa molecule – acts as decoy): Antidote for Apixaban and Riva (and other factor Xas)

First part of phase 3 study (AHA 2014) – 8 doses of apixaban to 33 healthy volunteers
- single IV bolus for 33 --- 95% reversal w/in 2 minutes but lasted only 1-2 hrs
  (endpt = anti factor Xa levels)

Second part (early 2015) – IV bolus then 2 hr continuous infusion
Annexa-R study part 1 and 2: 41 volunteers – same protocol and findings for rivaroxaban

**Idarucizumab**: humanized antibody fragment – binds to dabigatran. Phase 1 studies (healthy, elderly/renal impaired completed).
- Phase 3 (RE-VERSE AD ongoing, n=200-300) – life threatening bleeding
- Primary End point: reversal of dTT or ECT
  --- SINGLE DOSE (5 grams IV)
Andexanet alfa to be reviewed by FDA 2/18

Idarucizumab (fully humanized antibody Fragment) approved by FDA 10/15
Valvular Disease and AF:

- Excessive stroke risk in rheumatic mitral stenosis
- Prosthetic valves – need for long term AC

RELY  Hx of prosthetic valve or hemodynamically relevant valve disease expected to require surgery during the study

ROCKET AF Hemodynamically significant MS or prosthetic valves (allowed annuloplasty w or w/out ring, commissurotomy and/or plasty were allowed

ARISTOTLE Moderate to severe MS or prosthetic valves

ENGAGE AF Moderate to severe MS or mechanical valves

FDA Recommendations:

- Dabigatran: Contraindicated in pts with mechanical valves (REALIGN STUDY)
  - Not recommended for bioprosthetic valves
- Rivaroxaban: No specific recommendations
- Apixaban: Not recommended for use with prosthetic valves
Valvular Disease in DOAC Trials

With VHD, Treated With Higher-Dose NOACs or Warfarin

Central Illustration: SSEE and Major Bleeding in Patients Without and With VHD. Treated With Higher-Dose NOACs or Warfarin

Table 2: Frequency of Valvular Heart Disease Subtypes in Patients Randomized in RELY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 Trials

<table>
<thead>
<tr>
<th>VHD Subtype</th>
<th>RELY (n = 17,568)</th>
<th>ROCKET-AF (n = 8,877)</th>
<th>ARISTOTLE (n = 193)</th>
<th>ENGAGE AF-TIMI 48 (n = 2,503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.10% (CI: 2.85%–3.37%)</td>
<td>SSEE</td>
<td>1.75% (CI: 1.64%–1.87%)</td>
<td>131 (2.7%)</td>
<td>254 (9.9%)</td>
</tr>
<tr>
<td>2.25% (CI: 1.99%–2.52%)</td>
<td>Major Bleeding</td>
<td>3.26% (CI: 3.03%–3.50%)</td>
<td>366 (13.0%)</td>
<td>387 (15.3%)</td>
</tr>
<tr>
<td>0.0% (CI: 0.0%–0.0%)</td>
<td>Stroke</td>
<td>4.8% (CI: 4.5%–5.1%)</td>
<td>883 (24.3%)</td>
<td>887 (26.8%)</td>
</tr>
<tr>
<td>0.0% (CI: 0.0%–0.0%)</td>
<td>Major Bleeding</td>
<td>0.0% (CI: 0.0%–0.0%)</td>
<td>817 (20.7%)</td>
<td>2,924 (11.7%)</td>
</tr>
</tbody>
</table>

AF and Coronary stent: Triple therapy v Dual therapy

Approximately 900,000 PCIs/yr in US 10% have AF

**WOEST**: (What Is the Optimal Antiplatelet and Anticoagulant Therapy in patients With Oral Anticoagulation and Coronary Stenting)

**ISAR-TRIPLE** (Intracoronary Stenting and Antithrombotic Regimen Testing of a Six-Week Versus a Six-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting)

**PIONEER AF – PCI** Rivaroxaban: reduced dose

- 15 mg + P2Y12
- 2.5 bid mg + DAPT
- Warfarin + DAPT

**REDUAL AF**: Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation

- P2Y12 inhibitor + Dabigatran 150 or 110 bid
- Less bleeding, equal efficacy, Lower mortality c/w warfarin + DAPT

Warfarin + single antiplatelet agent provided similar protection with less bleeding than triple therapy

Limitations: moderate sized
Triple therapy will be replaced by DOAC + single antiplatelet agent in Patients with recent coronary stent
Pioneer Study: Safety study of PCI with AF ac indication

2236 Patients were screened for eligibility
- 112 Did not meet eligibility criteria

2124 Were enrolled in the trial
- 338 Were in 1-mo DAPT stratum
- 737 Were in 6-mo DAPT stratum
- 1049 Were in 12-mo DAPT stratum

709 Were assigned to group 1
- 15 mg + clopidogrel

709 Were assigned to group 2
- 2.5 bid mg + DAPT

706 Were assigned to group 3
- Warfarin + DAPT

NEJM 2016
**REDUAL AF: Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation**

2725 randomized

<table>
<thead>
<tr>
<th>Group</th>
<th>Therapy</th>
<th>Dose</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P2Y12 inhibitor + Dabigatran</td>
<td>110 mg bid</td>
<td>981</td>
</tr>
<tr>
<td>2</td>
<td>P2Y12 inhibitor + Dabigatran</td>
<td>150 mg bid</td>
<td>763</td>
</tr>
<tr>
<td>3</td>
<td>P2Y12 inhibitor + aspirin + warfarin</td>
<td></td>
<td>981</td>
</tr>
</tbody>
</table>

Outside of US • 80 years of age; • 70 years of age in Japan + 110 mg dose or triple therapy

**Exclusions:** Bioprosthetic or mechanical valve, severe renal insufficiency

**Mean Follow up:** 14 months

**NEJM 2017**

Clopidoogrel or ticagrelor

Asa 1 mo with BMS 3 mo with DES
Amyloid angiopathy

Suspect in older pts with MRI Findings of:

- History of lobar intracerebral hemorrhage
- Evidence of microbleeds
- Superficial hemosiderosis

? Increased risk of bleed with any anticoagulant or antithrombotic
CROMIS 2 Study

Multicenter observational cohort study
Patients with a TIA or ischemic stroke, started on anticoagulation and imaged with MRI

Hypothesis: neuroimaging biomarker (cerebral microbleeds) improves the predictive ability of clinical risk scores for intracranial hemorrhage

The presence of Diabetes Was another important risk for ICH
LAA exclusion: Remnant of the embryonic LA which forms during the 3rd week of gestation.

Body of the LA forms later as an outgrowth of the PVs.

Function: Releases ANP. Small contribution to cardiac filling. Distension of the LAA may result in sympathetic/vagal reflexes.
Percutaneous LAA Ligation

Watchman – permeable mesh requires 45 days of AC post implant.

Protect: 700 pts 2:1 device v warfarin
Met non inferiority but higher device complication rate – mostly effusions

Subsequent report of 150 chads (2) pts unable to take warfarin – lower rate of stroke compared w matched group on clopidogrel

Prevalent Extension trial – pending
APPROVED IN EUROPE
200,000 strokes/year in US

Current standard is 48 hours of Arrhythmia monitoring

Treatment is anti platelet therapy
If no AF or other source of embolism identified (carotids, aorta, LV, PFOs)

30% Cryptogenic
20% Embolic
15% Small vessel
30% Large vessel
5% Other
447 Patients were enrolled

6 Were excluded
   4 Did not meet eligibility criteria
   2 Withdrawed consent

441 Underwent randomization

221 Were assigned to ICM
   208 Had ICM inserted
   13 Did not have ICM inserted

12 Crossed over to control
   12 Exited the study
   3 Died
   1 Was lost to follow-up
   5 Withdraw
   3 Were withdrawn by investigator

220 Were assigned to control
   220 Received standard of care

6 Crossed over to ICM
   13 Exited the study
   2 Died
   1 Was lost to follow-up
   7 Withdraw
   3 Were withdrawn by investigator

221 Were included in intention-to-treat analysis

220 Were included in intention-to-treat analysis

Figure 1. Enrollment and Randomization of the Study Participants and Follow-up through 6 Months.
Representative strip of atrial fibrillation from a REVEAL/LINQ
Detection of Atrial Fibrillation by 12 Months

Hazard ratio, 7.3 (95% CI, 2.6–20.8)
P<0.001 by log-rank test

30% by 3 years
Key Points

• Elderly are at greatest risk of stroke
• Risk of intermittent or paroxysmal AF is equal to chronic AF
• AF ablation or use of AA Drugs DOES NOT allow discontinuation of anticoagulants
• Risk of clot formation exists with atrial flutter
• Aspirin DOES NOT count as effective thromboembolic prophylaxis for AF
Next Steps

Look for new recommendations for anti thrombotic/anticoagulant therapy for AF patients with recently implanted stents

Left atrial appendage exclusion or closure devices are options for patients who CANNOT take an oral anticoagulant – decisions to select this option should be made with a multidisciplinary review

DOACS can be used in patients with valve disease EXCEPT for Mechanical valves or Mitral Stenosis
Thank You