Update in the Management of AF

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Financial Disclosures

Medtronic Consulting

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?

Tests:  
- TSH

Echocardiogram: 
- Assess LV function
- Identify occult structural heart disease (valve etc)

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.

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

**Randomized**

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

Primary outcome: Mortality

3.5 ys follow up
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.

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

**Figure 1.** Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.
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

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

Yes

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 CI 15-50 ml/min)
Contraindicated if (CrCL > 95 ml/min)
AF > 48h duration

TEE

No thrombus present

Thrombus present

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

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, Rivaroxaban or Edoxaban For 3-4 weeks

Zimetbaum, Cecil 2014
Pharmacologic Management

Class 1  \( \text{Na}^+ \text{ channel blockers} \)

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

Class 2  \text{Beta Blockers} \n
Class 3:  \( \text{K}^+ \text{ channel blockers} \)

Sotalol, Amiodarone, Dofetilide, Dronedarone

Class 4:  \text{Calcium channel blockers} \n
Antiarrhythmic Medications

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

2nd line
- Sotalol
- Type 1A
- Amiodarone

Avoid
- Type 1C
- Dronedarone

↓ LVEF/CHF
- Amiodarone
- Dofetilide

CAD (nl EF)
- Sotalol
- Amiodarone
- Dronedarone

Hypertrophic Myopathy
- Amiodarone
- Sotalol

Type 1A
- Amiodarone
- Dronedarone

Type 1C
- Dronedarone

Type 1A
- Dofetilide

Disopyramide
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</th>
<th>Anti Psychotics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>Levoflox</td>
<td>amitryptyline</td>
<td></td>
<td>Cisapride</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Ciproflox</td>
<td>Desipramine</td>
<td></td>
<td>Methadone</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Erythromycin</td>
<td>Imipramine</td>
<td></td>
<td>Arsenic</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Clarithromycin</td>
<td>Fluoxetine</td>
<td></td>
<td>Sumatriptan</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Fluconazole</td>
<td>Haloperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disopyr</td>
<td>Ketoconalzole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Effect</td>
<td>Incidence</td>
<td>Recommended Monitoring</td>
<td>Special Considerations</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td>-------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>In most patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torsades de pointes</td>
<td>&lt;1%</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>20%</td>
<td></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>
<td></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>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>3–30%</td>
<td>Routine</td>
<td>Consider dose reduction</td>
<td></td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>&lt;1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean age: 65 yrs
PAF 49%, Persistant AF 51%
LA dimension: $41 \pm 7$ 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
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>Component</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq$ 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>
The rates of ischaemic stroke per 100 patient years in the Swedish Registry according to both the CHADS2 and CHA2DS2-VASc scores.
Updated 2014 AHA/HRS Guidelines

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

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

Class 2b
For patients with nonvalvular AF and a CHA\textsubscript{2}DS\textsubscript{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
Atrial Flutter
 Dopage of aspirin varied between 81 and 325 mg

- 6 original trials of stroke prevention in AF
  - BAATAF
  - AFASAK
  - CAFA
  - SPINAF
  - EAFT
  - SPAF

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

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

ACTIVE W*

ACTIVE A**

ACTIVE I

Irbesartan in ACTIVE W and A

Clopidogrel + ASA bleeding rate equivalent to warfarin therapy

COPYRIGHT
Cumulative risk of stroke for patients treated at centers with a Time in Therapeutic Range (TTR) below or above the study median (65%)

**TTR <65%**

**TTR ≥ 65%**

**ACTIVE W**

RR = 1.22 (0.75-1.97)

p=0.42

RR = 2.25 (1.45-3.49)

p=0.0003

Warfarin inhibits the C1 subunit of Vitamin K epoxide reductase (VKORC1).

Reduced Vitamin K

Oxidized Vitamin K

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

Variants of CYP2C9 encode enzyme with reduced activity → lower maintenance warfarin dosages

Most common in Caucasians

VKORC1 genetic variants → lower maintenance warfarin dosages

Most common in Asians
Warfarin interactions

**Potentiate Warfarin**
- Acetaminophen
- Amiodarone
- Aspirin
- Antibiotics (particularly)
  - Cephalosporins, Ciprofloxacin, Erythromycin
  - Metronidazole, Trimethoprim- Sulfamethoxazole, Macrolides
- Cimetidine
- Excessive ETOH
- Fluconazole
- NSAIDS
- Sulfonamides
- Ginko Biloba, Ginseng
- Congestive heart failure

**Inhibit Warfarin**
- Azathioprine
- Carbamazepine
- Haldol
- Oral contraceptives
- Phenobarbital
- Rifampin
- Vit K containing foods (green leafy vegetables):
  - spinach, broccoli, avocado
- Coenzyme Q
- St John's wart
- Hypothyroidism
- Nephrotic syndrome
- Edema
- Hereditary coumadin resistance
Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation
THROMBOEMBOLISM ASSOCIATED WITH AURICULAR FIBRILLATION

Continuous Anticoagulant Therapy 1950

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 fibrillation as those with 15.7 per cent. The incidence of deaths and complications from intracardiac clot formation must be balanced against the similar hazards of the use of dienamid. About 20% of 100 patients dying of rheumatic heart disease and auricular fibrillation die from thromboembolism. The majority show systemic clots could theoretically be accomplished by continuous anticoagulant treatment following the establishment of the arrhythmia.
Coagulation Cascade

Initiation

VIIa/TF

Propagation

IX

IXa

Direct Thrombin Inhibitors
Ximelagatran
Dabigatran etexilate

Direct Factor Xa inhibitors
Rivaroxaban
Apixaban
Betrixaban

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

Fibrin Formation

Xa

Va

Fibrinogen

Fibrin

No interaction with food or antibiotics

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

Rapid onset and offset
Dabigatran

Gut

Dabigatran etexilate

P-gp

esterase-mediated hydrolysis

no CYP450

→

Dabigatran

Bio-availability 3–7%

$t_{1/2} = 12-17\text{h}$

15 mg qd (cr cl 15–50 ml/min)

20 mg qd

2.5 mg bid (≥2 of >80 yr,≤60 kg, cr ≥ 1.5 mg/dl)

(cr cl <15 contraindicated)

Apixaban

Gut

Apixaban

P-gp

→

Apixaban

Bio-availability 50%

$t_{1/2} = 12\text{h}$

150 mg bid

Rivaroxaban

Gut

Rivaroxaban

P-gp

→

Rivaroxaban

Bio-availability:

65% (without food)

>80% (with food)

$\sim 65\%$

$\sim 35\%$

15 mg qd

(con cl 15-50 ml/min)

20 mg qd

Edoxaban

Gut

Edoxaban

P-gp

→

Edoxaban

Bio-availability 62%

$t_{1/2} = 9-11\text{h}$

30 mg qd (Cr Cl 15-50 ml/min)

Contraindicated if (CrCL > 95 ml/min)

30 mg qd

(Cr Cl 15-50 ml/min)

Contraindicated if (CrCL > 95 ml/min)

(Cr Cl 15-50 ml/min)

Contraindicated if (CrCL > 95 ml/min)

(Cr Cl 15-50 ml/min)
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></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><strong>CHADS</strong></td>
<td>2.1</td>
<td>3.5 (50% prior stroke/TIA)</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Time in therapeutic range</strong></td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
<td>68%</td>
</tr>
<tr>
<td><strong>Ischemic End pt</strong></td>
<td>Non inferior</td>
<td>Non inferior</td>
<td>Non inferior</td>
<td>Non inferior</td>
</tr>
<tr>
<td><strong>Intracranial hemorrhage</strong></td>
<td>60% lower</td>
<td>41% lower</td>
<td>49% lower</td>
<td>46% lower</td>
</tr>
<tr>
<td><strong>Special considerations</strong></td>
<td></td>
<td></td>
<td>Sig lower all cause bleeding</td>
<td>Sig lower all cause bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CANNOT use if Cr Cl 95</td>
<td></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
**Mortality** is NOT higher with Dabigatran c/w warfarin when an ICH occurs

### Mortality Rates of ICH by Treatment Arm in RELY

#### Intention to treat analysis

<table>
<thead>
<tr>
<th></th>
<th>Warfarin %(n/n)</th>
<th>Dabi 150 %(n/n)</th>
<th>Dabi 110 %(n/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All intracranial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral</td>
<td>36%(32/90)</td>
<td>35%(13/37)</td>
<td>41%(11/27)</td>
</tr>
<tr>
<td>Spont</td>
<td>41%(19/46)</td>
<td>64%(7/11)</td>
<td>64%(9/14)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>0%(0/4)</td>
<td>0%(0/0)</td>
<td>50%(2/4)</td>
</tr>
<tr>
<td>Subdural</td>
<td>28%(5/20)</td>
<td>21%(5/24)</td>
<td>20%(2/10)</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>25%(10/36)</td>
<td>14%(2/14)</td>
<td>20%(1/5)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>31%(5/16)</td>
<td>30%(3/10)</td>
<td>20%(1/5)</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>38%(3/8)</td>
<td>50%(1/2)</td>
<td>0%(0/3)</td>
</tr>
<tr>
<td>Spont</td>
<td>75%(3/4)</td>
<td>100%(1/1)</td>
<td>0%(0/1)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>0%(0/4)</td>
<td>0%(0/1)</td>
<td>0%(0/2)</td>
</tr>
</tbody>
</table>

Dabi 100 v. Warf
RR 1.6
P=0.76

Dabi 150 v. Warf
RR 1.4
P=0.28

*Hart R G et al. Stroke 2012;43:1511-1517*
Why less CNS bleeding with NOACs?

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

**Initiation**

**Propagation**

**Fibrin Formation**

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

**Targets for new Oral anticoagulants**

Direct Thrombin Inhibitors
- Ximelagatran
- Dabigatran etexilate

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

**Fibrin**

**Fibrinogen**

**IIa (Thrombin)**

**II**

**Va**

**Xa**

**IXa**

**VIIa/TF**

**IX**
# 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>Dabigatran</td>
<td>&gt;50</td>
<td>12-17</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>30-50</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>15-30</td>
<td>27</td>
<td>&gt;5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low bleeding risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>&gt;50</td>
<td>11-13 (elderly)</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>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High bleeding risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>&gt;50</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>30-50</td>
<td>17</td>
<td>3</td>
</tr>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low bleeding risk</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

High bleeding risk: Neuro, Cardiac, Urological (prostate/kidney), Liver/Spleen, Polyp resection
## Management of bleeding with anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to wear off and reversal of</td>
<td>60-80 hours</td>
<td>&gt; 12 hours</td>
<td>&gt; 12 hours</td>
<td>&gt; 12 hours</td>
</tr>
<tr>
<td>Reversing agent</td>
<td>Vit K IV 12 hr</td>
<td>PO 24 h</td>
<td>FFP</td>
<td>PCC immed</td>
</tr>
<tr>
<td></td>
<td>PCC (3000 Units)</td>
<td>Recombinant factor VIIa</td>
<td>Recombinant factor VIIa</td>
<td>Recombinant factor VIIa</td>
</tr>
</tbody>
</table>

- **Kcentra – PCC – 4 factors (2,7,9,10)** – Non activated – more rapid correction of INR than with FFP
- **FEBA: PCC which is Activated (activated factor 7 + other 3 factors)** = probably more thrombogenic

- **PCC prothrombin complex concentrates (vit k dependent factors 2,7,9,10)**
- **Recombinant activated factor 7** – directly activates thrombin on the platelet surface
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 apixa to 33 healthy volunteers, single IV bolus for 33 --- 95% reversal 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)

Approved 10/15

Likely to apply for accelerated FDA approval
Valvular Disease and AF:

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELY</td>
<td>Hx of prosthetic valve or hemodynamically relevant valve disease expected to require surgery during the study</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>Hemodynamically significant MS or prosthetic valves (allowed annuloplasty w or w/out ring, commissurotomy and/or plasty were allowed)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Moderate to severe MS or prosthetic valves</td>
</tr>
<tr>
<td>ENGAGE AF</td>
<td>Moderate to severe MS or mechanical valves</td>
</tr>
</tbody>
</table>

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
Antithrombotic Prophylaxis: Take homes

- 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
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.
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

Prevail   Extension trial – pending
APPROVED IN EUROPE
Cryptogenic stroke

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
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

No. at Risk
Control  220  200  197  194  184  184  184  167
ICM      221  198  194  191  186  182  173

30% by 3 years
Thank You