BACKGROUND: First described by Spanish physician Moses Maimonides in year 1187.

EPIDEMIOLOGY: The most common sustained arrhythmia. Lifetime risk after age 40 is 26%. 5 million Americans.

DIAGNOSIS: If age >70 and HR> 140, sinus mechanism <10% of time

- ECG with irregularly irregular rhythm, no P waves (or with very coarse, irregular F-waves)
- Irregularly irregular: varying R-R intervals with no predictable pattern
  - Other irregularly irregular rhythms: atrial flutter with variable block, wandering pacemaker (MAT with HR < 100), multifocal atrial tachycardia

APPROACH TO ATRIAL FIBRILLATION WITH RAPID VENTRICULAR RESPONSE (HR > 110)

- Is the patient unstable? Angina, hypotension/shock, acute heart failure

  ➞ Electrical cardioversion: Direct current synchronized: 120-200 Joule biphasic shock
  - Treat with 2mg IV midazolam if time permits
  - IV heparin (weight-based bolus) or SC enoxaparin (1mg/kg)

- Stable: Give 250cc NS (if no HF), one of the rate-controlling agents as below, and 2g IV Mg if patient has 2nd IV

- Caution for Pre-excitation: Wolff-Parkinson-White, Lown-Ganong-Levine, Mahaim fiber tachycardia (would expect WCT/ check baseline ECG)
  - Treat underlying cause: pain, stress/anxiety, hypoxemia, hyperthyroidism, alcohol withdrawal, β blocker withdrawal, recent surgery and fluid shifts, pneumonia, pulmonary embolism, and ischemia
  - IVF: If not in decompensated heart failure, give in 250cc boluses to improve preload and improve filling pressures (as no atrial kick). This will lower adrenergic tone, help control rate. This will also allow more meds to be given prior to hypotension. Caution if volume overloaded, hypoxemic.
  - Magnesium: 2-4g over 30 minutes
    - Magnesium prolongs the AV node refractory period
    - Hypomagnesemia present in 20% to 53% of patients with AF-RVR
    - In meta-analysis, more likely to achieve rate control in acute setting adding magnesium

Rate-controlling agents: Choose ONE of these

- Metoprolol tartrate 2.5-5mg IV q2-5 min CONCURRENT WITH 25mg PO at first dose.
  - Okay to give carefully if bronchospastic disease. Avoid if in status asthmaticus.
  - Guidelines: 15mg IV max, but can go to 30mg if monitored. Biggest mistake is not enough.
  - 5 mg IV = 12.5 mg PO (although different kinetics)

- Esmolol: Bolus ≤ 500 mcg/kg/min x 1 min then 25-300 mcg/kg/min gtt, titrate to HR < 100
  - Extremely fast elimination half-life of 2.7-4.8 minutes since metabolized in RBCs
  - BIDMC policy: CVL is preferred, but initial infusion can be started through PIV if 18g

- Diltiazem: IV bolus: 0.25mg/kg over 2 minutes (avg adult: 20mg) CONCURRENT WITH 30mg PO x1
  - Preferred if severe bronchospastic disease, also can use as a drip
  - Repeat IV bolus after 15 minutes: 0.35mg/kg
  - Drip: 5-15mg/hr titrate to HR < 120
  - BIDMC Policy: Drip generally requires ICU for monitoring, but can be done on Farr 3
  - Contraindications: Use of IV beta blockers within the past few hours, SBP<90mmHg, bypass tract, decompensated heart failure.
  - Hypotension treatment: 1g calcium gluconate over 3 minutes can lessen the hypotensive effects of CCBs without affecting the antiarrhythmic effects. Caution with tissue necrosis from extravasation, cardiac arrest from calcium.

- Amiodarone: 5-7mg/kg over 30-60min, then at rate for 1.2-1.8g/day.
  - Used acutely will provide some beta blockade. Safe in HF without shock.
  - Give 10 g total load, or until cardioversion
  - 600 to 800 mg daily in divided doses until 10 g total, then 200 mg daily as maintenance (AHA/ACC/HRS)
Contraindications: cardiogenic shock/prior amiodarone toxicity

Digoxin: Therapeutic index of 2, toxicity common.

- Digitalis in Acute Atrial Fibrillation (DAAF) Trial
  - 0.5mg IV x 1 then 0.25 mg IV at 2 hr and 0.25mg at 6 hours (unless <50 kg)
  - Draw trough within 12-24 hours after the initial loading dose administration
  - Unlikely to be effective when high adrenergic tone is the cause of RVR
  - Inferior to amiodarone at rate control

- Study of 84 patients in Iranian ER with contraindications to BB/CCB (ex. Hypotension, heart failure) randomized to digoxin or amiodarone showed superior rates of treatment success (achieving HR 80-100 bpm) (78.6% vs. 60.5%, p < 0.001) and slower onset of action (10-180 min for amiodarone vs. 25-540 min for digoxin, p< 0.001) when followed for 12 hours.

### Rate-control agents

<table>
<thead>
<tr>
<th>Onset (IV)</th>
<th>Metoprolol tartrate</th>
<th>Esmolol</th>
<th>Diltiazem</th>
<th>Verapamil</th>
<th>Digoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset (PO)</td>
<td>1-2 hours</td>
<td>N/A</td>
<td>30-60 min</td>
<td>1-2 hours</td>
<td>1-2 hours</td>
</tr>
<tr>
<td>Duration of action</td>
<td>5 hours (dose dependent)</td>
<td>2.7-4.8 min elimination t½</td>
<td>~ 3 hrs</td>
<td>10-20min IV, 6-8hr PO</td>
<td>3-4 days</td>
</tr>
</tbody>
</table>

### CLASSIFICATION

- **Substrate**
  - Lone: < 60 years old without clinical nor echo evidence of cardiopulmonary disease, including hypertension
  - De novo: Cardiac risk factors, but no acute trigger for AF as in secondary AF
  - Secondary: MI, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, or acute pulmonary disease.

- **Chronicity**
  - Paroxysmal: terminates in < 7 days without intervention. 90% from pulmonary veins. Responds to ablation.
  - Chronic: Anything other than paroxysmal
    - Persistent: > 7 days OR requires DC/drug to cardiovert. Remodeling of atria occurs.
      - Long-standing: > 1 year
    - Permanent: Impossible/inadvisable to cardiovert. Or failed a cardioversion.

- **Presence/absence of valvular disease**
  - Valvular AF: Rheumatic mitral stenosis, prosthetic heart valve (usually mitral), or valve repair
  - CHADS2 and CHA2DS2-Vasc scores not validated in this setting. Likely all need anticoagulation
  - Nonvalvular AF: May have valvular disease, just not mitral stenosis or mitral valve replacement/repair.

### PATHOPHYSIOLOGY: Disorganized electrical impulses usually originating in the roots of the pulmonary veins

- “A-fib begets a-fib”: the longer someone is in AF, the more difficult it is to brake, likely due to remodeling as below.

- **Possible initial mechanisms**
  - Ectopic focus: ↑ automaticity, early afterdepolarizations, delayed afterdepolarizations
  - Re-entry: single, multiple. (Wavelength = refractory period x conduction velocity)

- **Remodeling**: Leads to progression from paroxysmal to permanent AF
  - Electrical: tachyarrhythmias: ↑ calcium load yields ↓ CaL-type, ↓ I, decreasing phase 2,3 and decreasing refractory period
  - Structural: Fibrosis,
  - Neurohormonal: Upregulation of adrenergic receptors
ATRIAL FIBRILLATION

Structural risk factors
- Left atrial enlargement: increased myocardial irritability from stretch
- Left ventricular hypertrophy
- Reduced LVEF

Thrombus formation: Stasis in left atrium
- Left atrial appendage is site of thrombus in 91% of detected thrombi

FIRST EPISODE OF ATRIAL FIBRILLATION

Attempt to establish underlying cause: May be reversible, although 45% of pAF have no identifiable cause
- Infection
- Hyperthyroidism
- Recent surgery
- Electrolyte imbalance: especially hypokalemia
- Sympathomimetic use
- Electrocuton
- Pulmonary disease: pulmonary embolism, COPD exacerbation
- Alcohol intake (“holiday heart”)

Echocardiogram: Evaluates for valve disease, pericardial effusion, left atrial size, LVEF
Blood tests: CBC/diff, U/A, TSH/FT4, electrolytes, renal function, and hepatic function
Imaging: Chest X-ray to evaluate for pulmonary processes

Is this truly the first episode of atrial fibrillation? Can’t be sure. Up to 50% of episodes of paroxysmal atrial fibrillation are asymptomatic, even in patients who also experience symptomatic episodes.
- Thus, even if it is patients first symptomatic episode of AF, they still require anticoagulation/TEE prior to cardioversion.
- If the patient has a pacemaker/ICD/loop recorder, it can be interrogated to see if this is truly the first episode.

APPROACH TO THE STABLE PATIENT

Rate control versus rhythm control: The two predominant management strategies; either attempting to convert and maintain sinus rhythm (rhythm control) or allowing AF to persist, but attempting to slow the ventricular rate (rate control)
- Large clinical trials AFFIRM\(^1\) and RACE\(^2\) demonstrated no mortality benefit with antiarrhythmics versus rate control only, and had ↑ arrhythmia and a similar requirement for anticoagulation
- AFFIRM\(^3\) criticisms: Mean age 70 with only 3.5 year follow up
  - Younger patients not represented in these trials
  - Long term detrimental effects of AF not captured:
  - New data suggests increased dementia if long term AF (rhythm control may be better)

Rate control: Default strategy
- Target heart rate: RACE II\(^2\) compared strict versus lenient rate control and found no difference in death from cardiovascular causes, hospitalization for HF, stroke, embolism, bleeding, and life threatening arrhythmic events. Thus, a lenient rate control strategy is commonly accepted.
  - Strict rate control: <80 bpm at rest or <110 bpm during a 6-minute walk
  - Lenient rate control: <110 at rest is better for patients with LVEF > 40%
- Beta blockers are superior to calcium channel blockers
  - In the AFFIRM trial, 70% of patients on beta blockers achieved rate control versus only 56% of patients on calcium channel blockers\(^1\).

Rhythm control: Recurrence of AF reduced from 71-84% (no antiarrhythmics) to 30-50% (w/antiarrhythmics)\(^3\)
- Relative indications
  - Persistent symptoms (palpitations, chest pain, heart failure)
  - Inability to control rate
  - Age < 65. This group is less well represented in trials which favored rate control.
  - Left atrial size < 5.0cm. Patients with smaller atrial are more likely to maintain sinus rhythm
- Pharmacological therapy: Drugs are used to maintain sinus rhythm and as an adjunct to ↑ success of electrical cardioversion. For cardioversion to sinus rhythm, drugs are almost never used alone.
Effectiveness

- **Amiodarone** (200-400mg QD) most efficacious: 52% likely to be in sinus rhythm at 1 year
  - Not first line if structurally normal heart since significant side effects:
    - Pulmonary complications: 5-15% (reduced DLCO, infiltrates, cough)
    - Hyper/hypothyroidism: 2-24%
    - Elevated AST/ALT: 15-50%
    - Paresthesias/peripheral neuropathy: 3-30%
  - **Surveillance testing**
    - Baseline labs: “PFTs, TFTs, LFTs”: pulmonary function testing, thyroid, liver
    - Annual testing: Chest X-ray (PFTs not necessary after initial)
    - Biannual testing (Q6 months): LFTs, TFTs

- **Dofetilide** (125 - 500 mcg BID): 44% likely to be in sinus rhythm at 1 year
  - Risk of torsades: 3.3%, with 76% of cases occurring within 3 days of initiation: why patients need to be in-house for initiation.

- **Sotalol** (40-160mg BID): 32% likely to be in sinus rhythm at 1 year
  - Prolongs QTc
  - Contraindicated with decreased LVEF
    - **SWORD trial**: Gave sotalol vs. placebo to patients post-MI attempting to decrease arrhythmic mortality, but increased it in all patients and in particular those with low LVEF (RR 4.0 vs. 1.2 p=0.007). This is extrapolated to the AF population

- **Ibutilide**: Used in the acute setting only
  - 1mg if > 60 kg or 0.01 mg/kg if < 60 kg
  - Up to 80% effective at converting atrial fibrillation to sinus rhythm in ICU setting, of which 92% converted within 1 hour
  - Cardioversion rate not significantly better than amiodarone

Choosing an antiarrhythmic drug

- **Structurally normal heart**: No LVH, ↓ LVEF, valve disease, CAD, or history of MI
  - First line: Flecainide, propafenone, sotalol
  - Second line: Amiodarone, dofetilide
  - Propafenone and flecainide can cause 1:1 atrial flutter due to slowing atrium, can cause sudden cardiac death. *Need concurrent beta blockade to prevent this.*
  - “Pill in pocket” approach: patients take flecainide or propafenone after palpitations

- **With comorbid heart failure (systolic or diastolic)**
  - Amiodarone or dofetilide
    - Amiodarone if concurrent LVH (septal thickness > 1.4 cm)
    - Dofetilide

- **With comorbid coronary artery disease**
  - First line: Sotalol
  - Second line: Amiodarone, dofetilide

- **With an accessory pathway**
  - Procainamide, disopyramide, ibutilide, or amiodarone may be considered for hemodynamically stable patients

- **Electrical cardioversion**: Considerations for elective procedure. If unstable, cardiovert immediately.
  - **Indications**: Consider after a first episode of AF of recent onset, symptomatic patients, patients with heart failure (atria contribute up to 20% of cardiac output)
  - 150 J biphasic with progressive increase in energy if immediate return of AF (ERAF)
Consider procedural sedation (consult anesthesia)

- DCCV: 70-90% successful
  - If elective, often use adjunctive antiarrhythmic to maximize chance of success
  - Diurese patients to euvoolemia to minimize atrial stretch, which predisposes to AF

- Predictors of success of cardioversion:
  - Left atrial dimension < 4.5-5 cm
  - Reversible: ex. hyperthyroid, pericarditis, pulmonary embolism, or cardiac surgery
  - No hypertension or hypertensive heart disease
  - Normal left ventricular systolic function
  - Shorter duration of AF
  - Younger age
  - Lower thoracic impedance (not obese)

- Peri-procedural anticoagulation/transesophageal echocardiogram:
  - The requirements mirror the study protocol for the ACUTE trial (Assessment of Cardioversion Using Transesophageal Echocardiography Investigators) which compared 3 weeks of therapeutic warfarin to TEE. Both groups received 4 weeks of warfarin following DCCV. There was no difference in the rate of stroke at 8 weeks in the TEE group versus the conventional group (0.8% vs 0.5%, p=0.50)\(^{18}\)
  - The risk of thromboembolism after cardioversion without anticoagulation is approximately 7%\(^{19}\).
  - Need therapeutic anticoagulation (INR 2-3 or adherence to newer agents) for 3 weeks prior to cardioversion OR a transesophageal echocardiogram confirming absence of atrial clot.
  - Need anticoagulation for at least 4 weeks AFTER cardioversion to normal sinus rhythm due to persistent "stunning" of atrial following successful cardioversion.
    - Even after successful cardioversion, pulsed wave Doppler assessments of A-waves (atrial contribution of filling) do not return to normal until 3+ weeks after successful cardioversion.\(^{20}\)
  - Some argue that anticoagulation is not necessary for a first episode of atrial fibrillation, however, even if this is the first episode of symptomatic/observed atrial fibrillation, up to 50% of patients with paroxysmal atrial fibrillation experience asymptomatic episodes, even if they also experience symptomatic episodes.\(^{10}\)
    - The exception is a confirmed first episode if the patient has a pacemaker, ICD, or loop recorder which can be interrogated to confirm.

- Catheter ablation: Pulmonary vein isolation (PVI)
  - Indications: significantly symptomatic, paroxysmal AF patients who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease\(^{5}\).
  - Technique: Wide area circumferential ablation (around right and left veins).
  - Outcomes: 60-80% success, if second procedure, another 60-80% success\(^{1}\).
    - Best candidates with paroxysmal AF.
    - Worse if continuous AF >3 years and/or LA size >5cm. If poor candidate, success <40%.
    - May have improved responsiveness to antiarrhythmic drugs if AF recurs
    - Anticoagulation should continue for 2 to 3 months for atrium endothelium to recover.
  - Complications
    - Cardiac tamponade (1.2%), CVA (0.94%), atrioesophageal fistula (0.1%), death (0.1%)\(^{1}\)
    - Pulmonary vein stenosis (1-3%): progressive dyspnea, hemoptysis\(^{1}\)
  - Evidence base
    - \(\Rightarrow\) ThermoCool AF: At 9 mo, ablation superior to antiarrhythmics, treatment failure occurred in 8.8% of antiarythmics group compared to 4.9% in catheter ablation group, HR 0.3 (p<0.001).
    - \(\Rightarrow\) CABANA trial: Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial, ongoing, final results available in 2017.

- AV Nodal Ablation and Pacemaker Implantation
  - Indications: When the rate cannot be controlled with drugs or they are associated with significant side
effects (ex. symptomatic bradycardia with the tachy-brady syndrome)

- If patient expected to pace > 40% of the time, RV pacing may worsen EF
- Type of pacemaker
  - Single chamber: Default
  - Dual chamber: if AF is paroxysmal and patient has functioning sinus node
  - Biventricular: If EF < 40% and expected to pace > 40% of the time
- Maze procedure: Left atrial appendage excised. Creates a “maze” of functional myocardium allowing normal activity but interfering with microreentry.
  - Usually only performed in patients undergoing cardiac surgery for some other reason

- Adjunctive therapies
  - Yoga improves symptoms, arrhythmia burden, HR, BP, anxiety and depression scores.

ANTICOAGULATION: To prevent stroke from cardioembolism.

- Deciding whether to anticoagulate a patient with atrial fibrillation is based on the benefit derived from reducing risk of stroke balanced against their risk of bleeding, the major complication of anticoagulation
  - Not all episodes of bleeding are the same; should be divided into intracranial bleeding (50% fatal), and other bleeding (ex. GI bleed in this setting is only 2-3.6% fatal).
- Background: Stasis of atria leads to clot formation. Up to 20% of all strokes attributed to cardioembolism.
- Stratifying risk of thromboembolism
  - CHADS2 score: 1 point for CHF, HTN, Age>75, DM, 2 for prior ischemic stroke/TIA/thromboembolism
  
  \[
  \begin{array}{|c|c|c|}
  \hline
  \text{CHADS}_2 \text{ Score} & \text{Warfarin} & \text{No warfarin} \\
  \hline
  0 & 0.25 & 0.49 \\
  1 & 0.72 & 1.52 \\
  2 & 1.27 & 2.50 \\
  3 & 2.20 & 5.27 \\
  4 & 2.35 & 6.02 \\
  5 \text{ or } 6 & 4.60 & 6.88 \\
  \hline
  \end{array}
  \]

  - Patients with CHADS2 scores ≥ 2 should be anticoagulated
  - Patients with a CHADS2 score of 0 should have aspirin 81mg
  - Patients with CHADS2 score of 1 are controversial (there is no consensus), and the CHA2DS2-VASc score should be used to see where they lie on the intermediate risk spectrum
    - CHA2DS2-VASc score: CHF, HTN, Age (>75 years 2pts, 65-74 1pt), DM, previous CVA/TIA (2 pts), vascular disease, Age 65-74 years, sex (female 1 pt, male 0 pt)
    - May be superior to CHADS2 when risk is intermediate

- Risk of bleeding
  - Falls: Not an absolute contraindication to anticoagulation
    - Patients need to fall 295 times per year before the risk of fall-related subdural hemorrhage would outweigh the benefit of stroke prevention.
  - HAS-BLED score: HTN (SBP>160), Abnormal renal function (CrCl < 50 ml/min), stroke, bleeding history, Labile INR (<60% in therapeutic range), Elderly (>65-70), Drugs (ASA, NSAID, EtOH use).
    - Score ≥ 3 suggests caution and regular follow-up.
  - “Triple therapy”: patients with AF and a concurrent indication for clopidogrel (ex. coronary stent)
    - If CHADS2 0-1, likely ASA and clopidogrel best without an oral anticoagulant
    - If CHADS2 ≥ 2, use HAS-BLED score
      - If HAS-BLED ≥ 3, likely ASA and clopidogrel best without an oral anticoagulant
      - If HAS-BLED < 3, consider “triple therapy” with ASA+clopidogrel+anticoagulant
    - For all patients on “triple therapy”, should take steps to minimize risk of bleeding
      - ASA 81mg (not 325mg)
      - Consider starting a PPI to prevent GI bleeding
  - PIONEER-AF TRIAL (An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment...
Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention

- Inclusion criteria: NVAF within last year who just underwent PCI
- Exclusion criteria: History of stroke/TIA, GI bleeding within 12 months, CrCl < 30, anemia of unknown cause with Hgb < 10 g/dL, stent thrombosis within 1 year, planned CABG, and others
- Comparison groups, randomized within 72 hours of sheath removal after PCI:
  - **Group 1**: Rivaroxaban 15mg QD (or 10mg if CrCl 30-50) + P2Y₁₂ (clopidogrel 75mg QD in 85%+)
  - **Group 2**: Rivaroxaban 2.5mg BID + aspirin 75-100mg QD + P2Y₁₂ (clopidogrel 75mg QD in 85%+)
  - **Group 3**: Warfarin + aspirin 75-100mg QD + P2Y₁₂ (clopidogrel 75mg QD in 85%+)

- Outcomes:
  - Bleeding at 12 months: 16.8% group 1, 18% group 2, 26.7% group 3 (HR 1 vs 3 was 0.59, p<0.001, HR 2 vs 3 was 0.63, p<0.001)
  - Major adverse cardiovascular event (death from CV cause, MI, or stroke): 6.5% in group 1, 5.6% in group 2, 6.0% in group 3 (p>0.05 for both comparisons)
  - Stent thrombosis rates were “low and similar among the three groups”
- Criticisms: Not blinded, not powered for efficacy, little ethnic diversity

- Choosing an anticoagulant
  - Factors to consider when choosing an anticoagulant:
    - Renal function: Does the patient have CKD and/or are they likely to have AKI
    - Adherence/Cost: A drug is 0% effective if not taken/too expensive
    - Drug interactions: Most important with warfarin, but other agents affected by CytP450
  - Take home points from clinical trial data and guidelines:
    - Once-daily dosing is only available with warfarin or apixaban
    - No direct comparisons of new agents are available, but extrapolations show all agents have similar rates of stroke/embolism but apixaban has a lower risk of major hemorrhage
    - Aspirin (75-325mg daily) + clopidogrel may be used for patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than bleeding).

### Atrial Fibrillation Anticoagulation Randomized Clinical trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial name</th>
<th>Avg. CHADS₂</th>
<th>Stroke or systemic embolism</th>
<th>Intracranial hemorrhage</th>
<th>Major bleeding</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran vs. warfarin</td>
<td>RE-LY (2009) N=18,113</td>
<td>2.1</td>
<td>1.11 vs. 1.69% Dabig. noninferior</td>
<td>0.3% vs. 0.74% Dabig. superior</td>
<td>3.11% vs. 3.36% Dabig. superior</td>
<td>3.64% vs. 4.13% Not significant</td>
</tr>
<tr>
<td>Rivaroxaban vs. warfarin</td>
<td>ROCKET-AF (2011) N=14,246</td>
<td>3.5</td>
<td>2.12 vs 2.42% Riva. noninferior</td>
<td>0.49% vs. 0.74% Riva. superior</td>
<td>3.6% vs 3.45% Riva. inferior</td>
<td>1.87% vs 2.21% Not significant</td>
</tr>
<tr>
<td>Apixaban vs. warfarin</td>
<td>ARISTOTLE (2011) N=18,201</td>
<td>2.1</td>
<td>1.6% vs. 3.7% Apixa. superior</td>
<td>0.4% vs. 0.4% Not significant</td>
<td>2.1% vs 3.1% Apixa. superior</td>
<td>3.5% vs. 4.4% Apixa. superior</td>
</tr>
<tr>
<td>Edoxaban vs. warfarin</td>
<td>ENGAGE AF TIMI 48 (2013), N=20,500</td>
<td>81% 2-3 19% 4-6</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
</tr>
</tbody>
</table>

- **Major bleeding**: reduction in the hemoglobin level of at least 2 g/dl, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ

### Novel Anticoagulants Dosing and Metabolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Dose</th>
<th>t₁/₂</th>
<th>Metabolism</th>
<th>Side effects</th>
<th>Contraindications</th>
</tr>
</thead>
</table>

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ATRIAL FIBRILLATION

Dabigatran

<table>
<thead>
<tr>
<th>Pradaxa™</th>
<th>Factor II (thrombin) inhibitor</th>
<th>150mg PO BID</th>
<th>15h</th>
<th>80% renal</th>
<th>Dyspepsia (&gt;15%)</th>
<th>CrCl &lt; 15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>75mg PO BID if CrCl 15-30</td>
<td></td>
<td>20% hepatic</td>
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<td></td>
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</tbody>
</table>

Rivaroxaban

<table>
<thead>
<tr>
<th>Xarelto™</th>
<th>Factor Xa inhibitor</th>
<th>20mg PO QD</th>
<th>5h</th>
<th>33% renal</th>
<th>None (except bleeding)</th>
<th>CrCl &lt; 15</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>15mg PO QD if CrCl 15-50</td>
<td></td>
<td>67% hepatic</td>
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Apixaban

<table>
<thead>
<tr>
<th>Eliquis™</th>
<th>Factor Xa inhibitor</th>
<th>5mg PO BID</th>
<th>12h</th>
<th>25% renal</th>
<th>None (except bleeding)</th>
<th>CrCl &lt; 15</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>2.5mg PO BID if Cr &gt;1.5, age &gt; 80, weight &lt; 60 kg</td>
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<td>75% hepatic</td>
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Edoxaban

<table>
<thead>
<tr>
<th>Lixiana™</th>
<th>Factor Xa inhibitor</th>
<th>60mg PO QD</th>
<th>9h</th>
<th>40% renal</th>
<th>Unknown</th>
<th>In phase III clinical trials</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>30mg PO QD if CKD</td>
<td></td>
<td>60% hepatic</td>
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</tbody>
</table>

APPROACH TO THE BLEEDING PATIENT ON ANTICOAGULANTS FOR ATRIAL FIBRILLATION

- Obtain coagulation panel: If PT/PTT not prolonged, the anticoagulant is unlikely to be causing the bleeding
- Supportive care
  - Stop the offending drug. Hemostasis will return in 12-24 hrs with FXa inhibitors. May take 48 h w/DTI
  - Activated charcoal if drug was ingested < 2 hours ago
  - Diuresis to support elimination of compound
  - Direct pressure to bleeding area if possible, hemostatic agents (ex. aminocaproic acid)
  - Transfusion if indicated
- Reversing anticoagulation
  - Warfarin: Vitamin K (will reverse the effect in 24 hours), FFP
  - Novel anticoagulants
    - Dabigatran: Hemodialysis is an option since it has low protein binding
    - Factor Xa-inhibitors
      - Andexanet alfa (ANNEXA-4 Study): Single-group study of patients who had bleeding within 18 hours of taking Factor Xa inhibitor.
        - Specific anticoagulants included in the study: Rivaroxaban (48%), apixaban (46%), enoxaparin (6%)
        - Site of bleeding: GI (49%), intracranial (42%), other (9%)
        - Median time from arrival in ED to administration of andexanet bolus: 4.8 ± 1.9 hours
        - Doses used:
          - If last dose > 7 hrs ago: 400mg over 15-30 min, then 480mg gtt over 2 hrs
          - If last dose < 7 hrs ago: 700mg over 15-30 min, then 960mg gtt over 2 hrs
        - Outcomes:
          - Efficacy: Hemostasis (79%)
          - Safety: Thrombotic events (18%), including 1 MI, 5 CVA, 7 DVT, 1 PE (within 30 days). However, only 27% of patients restarted anticoagulation within 30 days
          - FFP unlikely to be effective since it has to overwhelm effects of the drug (unlike warfarin where FFP repletes the absent coagulation factors)
          - Prothrombin complex concentrate (PCC): 25-50 U/kg (inactive PCC), 50-100 U/kg (active PCC)
          - Recombinant Factor VIIa (rVIIa): 60-90 mcg/kg

SOURCES


