Electrophysiology of the Heart

Amy Leigh Miller, MD, PhD
Cardiovascular Electrophysiology, Brigham & Women’s Hospital

Disclosures: None
Bradyarrhythmias

- Sinus node
- AV node
- His/Purkinje system
Complete Heart Block (without escape)
Mobitz I – PR lengthens, RR shortens
- typical of AV nodal block
- benign prognosis
Mobitz I... with “trifascicular block”
“Trifascicular block”
With CHB!
Severe/Symptomatic Bradycardia
History and semantics...

- “Sick sinus” - Bernie Lown, 1967 DCCV invited lecture
- “Sick sinus syndrome” – Ferrer, 1968

- Sinus Bradycardia
- Sinus Arrest
- Sinus Exit Block
- Tachy/Brady Syndrome
- Chronotropic incompetence

Abnormal vs. Pathological

• Pronounced sinus bradycardia can be benign
  – Conditioned athletes
  – Nocturnal bradycardia

• Sinoatrial function decreases with age
  – Intrinsic heart rate decreases
  – SA conduction time increases

• Acutely increased vagal tone
  – e.g., ventilated patient with deep suctioning
Etiologies of Sinus Node Dysfunction

**Intrinsic causes**
- Idiopathic degeneration (aging)
- Infarction* or ischemia
- Infiltrative diseases
  - Sarcoidosis
  - Amyloidosis
  - Hemochromatosis
- Collagen vascular diseases
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Scleroderma
- Myotonic muscular dystrophy
- Surgical trauma
  - Valve replacement
  - Correction of congenital heart disease
  - Heart transplantation
- Familial diseases
  - Infectious diseases*
    - Chagas’ disease
    - Endocarditis

**Extrinsic causes**
- Autonomically mediated syndromes
- Neurocardiac syncope
- Carotid-sinus hypersensitivity
- Situational disturbances
  - Coughing
  - Micturition
  - Defecation
  - Vomiting
- Drugs
  - β-Adrenergic blockers
  - Calcium-channel blockers
  - Clonidine
  - Digoxin
  - Antiarrhythmic agents
- Hypothyroidism
- Hypothermia
- Neurologic disorders
- Electrolyte imbalances
  - Hypokalemia
  - Hyperkalemia
• Incidence increases exponentially w/ age (~1/600 over age 65)
  – Classically episodic - “runs an erratic course with periods of normal node function alternating with abnormal behavior”
• Coexisting AV &/or intraventricular conduction block in 15-50%
  – Complete AV block in 0-12%
• Electrophysiological changes predispose to AF – bradycardia leads to…
  – Early afterdepolarizations
  – Increased dispersion of refractoriness
  – 5-10% have AF at the time of diagnosis
~22 hours into a 24 hr Holter...
Patient with normal CSM, SNRT, exercise/isuprel response.
Monitoring options for rare events

• Looping event recorder
  – Device records continuously, has memory buffer
    • Autocapture OR patient presses button upon symptom onset
    • Device captures pre-trigger and post-trigger information

• Implantable loop recorder (ILR)
  – 2-3 year battery life
  – Higher yield and/or lower cost than event/holter

• Mobile continuous outpatient telemetry (MCOT)
  – Provide “trend” information, burden of AF, often used to assess efficacy of rhythm control
Atrial Fibrillation

- Chaotic atrial electrical activity with high-rate fibrillatory potentials
- Irregularly irregular ventricular complexes
Epidemiology

- Most common arrhythmia
  - Prevalence ~0.5-1%
  - Increases with age
    - 8% over age 80y/o
  - Twice as common in men
  - Over twice as common in Caucasians as African-Americans
  - Age-adjusted incidence increasing

Prevalence of AF

Secondary Atrial Fibrillation

• Triggered by…
  – Surgery (“post-op AF”)
  – Acute illness (e.g., pneumonia, PE)
  – Hyperthyroid state
  – Myocarditis / Pericarditis
  – Drugs (EtOH, caffeine)
  – Subarachnoid hemorrhage

• Hickam’s Dictum
Consequences of AF

- Increased risk of...
  - Stroke
    - Average 5%/yr
      - TIA/CVA >7%/yr
    - 2-7x increased RR
    - Rheumatic – >15 fold increase in risk
  - Heart failure
    - AF decreases cardiac output ~5-15%
  - All-cause mortality
    - Majority cardiovascular

Strokes and AF

- Multifactorial – atrial stasis, hypercoagulability (?local vs systemic), endothelial dysfunction
- Risk increases with Age
  - Increased age is associated with LAE, reduced LAA flow velocity, and “smoke”
- 48 hours – not as magic as we’d like!
- “Atrial stunning” – observed after ANY type of cardioversion (spontaneous, drug, DCCV)
  - Rapid recovery in days, but can last up to 4 weeks
  - Increased duration AF predicts increased duration stunning

“Lone AF”

• Associated with better prognosis including lower thromboembolic risk

• Requirements
  – Structurally normal heart
  – No known cardiovascular/pulmonary disease
  – “Young” (<60 y/o)

• Caveats
  – Patients don’t stay young
  – Lone AF may not stay lonesome
Lone ≠ asymptomatic

- Loss of atrial kick → decreased cardiac output
  - More an issue with HCM, restrictive physiology (diastolic dysfunction), mitral stenosis
- Rapid, irregular ventricular response
  - Contractility varies with cycle length
- Decreased coronary perfusion
  - Increased coronary vascular resistance (alpha adrenergic effect)
- Tachycardia-induced cardiomyopathy
Symptomatic presentation

- Palpitations
- Lightheadedness/Pre-syncope
- Dyspnea on exertion
- Fatigue / decreased functional capacity
- Chest pain

- Monitoring demonstrates that patients can have a mix of symptomatic and asymptomatic episodes of AF
- Thromboembolic complication may be initial presentation
Syncope from AF?

• Rare...
  – Patients who are preload dependent
    • HCM
    • Aortic stenosis
  – Patients with an accessory pathway
  – Patients with sinus node dysfunction (offset pauses)
AV block can cause syncope independent of rhythm
Rate Control Options

• Beta blockers
  – Most effective class in AFFIRM
  – Negative inotropic effects

• Calcium channel blockers
  – Only drugs shown to improve QOL & exercise tolerance
  – Negative inotropic effects

• Digoxin
  – Should not be the sole agent in paroxysmal AF

• (Pacemaker)
• (AV Junction ablation)

Writing Group, 2011 ACCF/AHA/HRS Focused Update on AF, Circulation 2011.
What is a controlled rate?

- Resting rate: 60-80
- Moderate exercise: 90-115

• AFFIRM
  - Resting rate: 60-80
  - Average ≤ 100 on 18 hr Holter (with nothing above MPHR)
  - Maximum 110 bpm on 6-min walk test

• RACE II
  - Resting < 110
    - Fewer hospitalizations
    - No difference in symptoms, quality of life

*Lenient rate control appears reasonable in patients who tolerate it*
Pop Quiz

• Increased atrial rate in atrial fibrillation is associated with...
  – An increase in the ventricular rate
  – A decrease in the ventricular rate
  – No change in the ventricular rate
  – Ventricular rate is so variable in AF that it’s a meaningless distinction
How does the AV node behave?

- AV node has “decremental conduction”
  - At increasing atrial rates, conduction in the AV node will slow
    - the node protects the ventricles
    - “concealed conduction” that blocks within the node renders it transiently refractory
Atrial Fibrillation in WPW

NO nodal agents!!

Drugs of choice:
  Procainamide
  Ibutilide

Consider DCCV
“AF begets AF”

With recurrent/persistent AF

- Electrically, “remodeling” occurs quickly
  - Cardioversion success highest in first 24 hrs
  - Effective refractory periods shorten
    - Not unique to AF
    - Rapid atrial rate → Intracellular calcium loading results in calcium current inactivation → short action potential duration → short refractory period

<table>
<thead>
<tr>
<th>Structural Changes</th>
<th>Electrophysiologic Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial dilation</td>
<td>Slowed Conduction</td>
</tr>
<tr>
<td>PV dilation</td>
<td>Dispersion of ERP</td>
</tr>
<tr>
<td>Decreased contractility</td>
<td>Shortened ERP</td>
</tr>
<tr>
<td>Large PV sleeves</td>
<td>Micro-re-entry</td>
</tr>
<tr>
<td>Increased atrial compliance</td>
<td>Ectopic Activity</td>
</tr>
<tr>
<td>Fibrosis / loss of sarcomeres</td>
<td></td>
</tr>
</tbody>
</table>
Natural history of AF

- Patients will in general progress over time
  - Paroxysmal
  - Persistent (7 days)
  - Permanent

<5% of patients remain paroxysmal over decades

Rhythm Control

• On a population level, large-scale clinical trials suggest that a “rhythm control” strategy will NOT...
  – Improve quality of life
  – Decrease CHF exacerbations/hospitalizations
  – Decrease stroke risk

• Reminder – we don’t take care of populations, we take care of patients...

• Reminder – drug “cardioversion” has the same stroke risk as electrical DCCV

Pharmacotherapy in AF

• *Drugs that cardiologists love*…
  – *ACE Inhibitors/ARBs*
  – *Statins*

• *Drugs that nobody should love*
  – Amiodarone
  – Flecainide
  – Propafenone
  – Sotalol
  – Dofetilide

• *The drug that people really wanted to fall in love with*
  – Dronedarone
<table>
<thead>
<tr>
<th>Drug Class</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium channel blockers</td>
<td>Class IA</td>
</tr>
<tr>
<td></td>
<td>Class IB</td>
</tr>
<tr>
<td></td>
<td>Class IC</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Class II</td>
</tr>
<tr>
<td>Potassium channel blockers</td>
<td>Class III</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Class IV</td>
</tr>
</tbody>
</table>

**Phase 0**
- Na influx

**Phase 1**
- K out

**Phase 2** – slow inward CA

**Phase 3**
- K out

**Phase 4** – slow K out/ Na in

Class IA
Block Na channels & outward rectifying K -
Slow conduction, increase refractoriness →
Increase AP duration and QTc

• Procainamide –
  – historical drug of choice in patients with AF and WPW

• Quinidine –
  – *Historical role in AF*
  – *Poorly tolerated in up to 50% of patients*

• Disopyramide –
  – *Negative inotropic effects – rarely seen except in patients with HCM or vagally-mediated AF*
Class IC
Flecainide, Propafenonone

- Most potent Na blockers
- PR and QRS increases are dose-related
- QRS increase >20%
  - dose reduction indicated
- Slowed conduction can paradoxically increase rates -
  - transition to 1:1 conduction
  - Nodal agent MUST be given with Class IC agents
  - “Pill in pocket” drugs

Propafenone Toxicity

- Use-dependent
  - stress test to see drug’s maximal effect at prescribed dose

- Proarrhythmic
  - CAST (Cardiac Arrhythmia Suppression Trial) 1989 – increased mortality post MI (VF arrest)
Class III
K channel blockers –
increase QTc, risk of torsades

- **Dofetilide**
  - FDA restrictions re: prescribing
  - Require inpatient initiation - QTc increase of 15% or >500 (>550 in pts with BBB) – mandatory dose reduction for dofetilide

- **Sotalol**
  - A relatively weak beta-blocker
  - Reverse use-dependence
  - Inpatient initiation with QTc monitoring

- **Ibutilide** – IV formulation only

- **Amiodarone** –
  - can prolong QT but rarely associated with Torsades

- **Dronedarone**
Drug-induced long QT
Amiodarone

- Class III but actually affects everything – Na blocker, K blocker, beta blocker, CCB
  - Major effect acutely is depression of AV node – i.e., rate control, not rhythm control!
    - *Not FDA approved for acute AF*
- Large volume of distribution – half-life ~55 days
- Hepatic metabolism- biliary and intestinal excretion
- Toxicity –
  - Derm (Photosensitive rashes, Grey/blue discolouration of skin), Thyroid (2%), Pulmonary fibrosis, Corneal deposits, CNS/GI disturbance, Pro-arrhythmic effects, Heart block, Nightmares (25%), Abnormal LFT (20%), drug interactions (digoxin, warfarin))
How well do they work?

<table>
<thead>
<tr>
<th></th>
<th>Rate Control</th>
<th>Rhythm Control</th>
<th>Duration f/u (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFFIRM</td>
<td>35</td>
<td>63</td>
<td>5</td>
</tr>
<tr>
<td>RACE</td>
<td>10</td>
<td>39</td>
<td>2.3</td>
</tr>
<tr>
<td>PIAF</td>
<td>10</td>
<td>56</td>
<td>1</td>
</tr>
<tr>
<td>STAF</td>
<td>11</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>HOT CAFE</td>
<td></td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>


Dronedarone

- Iodine moiety removed from amiodarone
  - Similar acute electrophysiological effects
- Cardiac adverse effects: bradycardia, QT prolongation
- CYP3A4 metabolism
  - verapamil/dilt should be started at low doses given possible potentiation to dronedarone’s effects
  - Increases digoxin levels ~2-3 fold
- BID dosing
## Dronedarone (re: placebo)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Days to recur</th>
<th>Risk Ratio</th>
<th>Recurrence Rate</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAFNE</td>
<td>60</td>
<td>0.45</td>
<td>65%</td>
<td>0.72</td>
</tr>
<tr>
<td>EURIDIS</td>
<td>96</td>
<td>0.78</td>
<td>37%</td>
<td>0.77</td>
</tr>
<tr>
<td>ADONIS</td>
<td>158</td>
<td>0.73</td>
<td>37%</td>
<td>0.86</td>
</tr>
<tr>
<td>ATHENA</td>
<td>498</td>
<td>0.75</td>
<td>45%</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Meta-analysis – Relative Risk 0.82
Risk Ratio re: Amiodarone (DIONYSUS): 1.51

- Rate control (ERATO trial as well as AF recurrences in EURIDIS, ADONIS, DAFNE, and ATHENA) - significantly better than placebo and additive effect w/ other rate control agents

JACC 2010 55(15):1569-76.
Trial Experience with Dronedarone

• Safety –
  – ATHENA – nonpermanent AF and risk factors
    • Dronedarone decreased CV hospitalizations
  – ANDROMEDA – enrolled (class II-IV) recently decompensated CHF +/- AF
    • Premature termination for increased mortality with dronedarone
    • Increased mortality reflected worsening CHF
FDA approval

• indicated to reduce the risk of cardiovascular hospitalization
• patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with...
  – a recent episode of AF/AFL
  – associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%)
• who are in sinus rhythm or who will be cardioverted

Boxed Warning - Class IV heart failure or symptomatic heart failure with a recent decompensation
Trial Experience with Dronedarone

• Safety –
  – ATHENA – nonpermanent AF and risk factors
    • Dronedarone decreased CV hospitalizations
  – ANDROMEDA – enrolled (class II-IV) recently decompensated CHF +/- AF
    • Premature termination for increased mortality with dronedarone
    • Increased mortality reflected worsening CHF
  – PALLAS – first trial in permanent AF
    • Premature termination for doubling of mortality, stroke, and CHF with dronedarone
Real World Experience with Dronedarone

- CHF – postmarketing reports of CHF prompted label change regarding new/worsened CHF
- Torsades des pointes – very rare but has been observed with Dronedarone
- Drug Interactions with Dabigatran and Warfarin
- Liver toxicity – rare but can be fulminant, necessitating liver transplant
  - LFT monitoring now recommended
- Pulmonary toxicity???
Rhythm Control Decision Tree

No ♥ Dz

Hypertension

“Substantial” LVH

No… Yes…

CAD

Dofetilide Dronedarone Sotalol

CHF

Amiodarone Dofetilide

Amiodarone Dofetilide

Dronedarone Flecaainide Propafenone Sotalol

PVI
AF Ablation

- Catheter Pulmonary Vein Isolation
  - No role acutely
  - Elective procedure
  - 2nd line (after meds)
  - Blanking period
  - 1-yr success ~60-80%
    - Success improves with multiple ablations
    - “Reconnections” occur
    - Atypical flutters
  - Risks: Stroke ~1%, Tamponade ~1%, Death 0.1-0.7%

- Surgical Ablation
  - Technical advances continue

BMJ 336:914.
While a variety of atrial arrhythmias can trigger AF, AFL is the rhythm most associated with AF.

The two rhythms can interchange:
- “Fibrillation organizes…”
- “Flutter degenerates….”

Rate control is much more challenging in AFL.
Typical Atrial Flutter
Typical Atrial Flutter

Counterclockwise right atrial circuit
Cavo-tricuspid isthmus dependent

Ao = aorta, CS = coronary sinus, IVC = inferior vena cava, PA = pulmonary artery, RV = right ventricle, SVC = superior vena cava, TV = tricuspid valve.
Drug therapy vs first-line ablation for atrial flutter

**Antiarrhythmic Drug Therapy**
- sotalol, amiodarone
- flecainide, procainamide, propafenone

**RF Ablation**
- Atrial Flutter Recurrence: 93%
- Atrial Fibrillation: 60%
- Sinus rhythm last f/u: 36%

mean follow-up: 22 months

Slide courtesy of William Stevenson
Natale et al J Am Coll Cardiol 2000
Murgatroyd – Handbook of Cardiac Electrophysiology
“Not Typical Flutter”

– Clockwise Flutter
  • Right atrium, clockwise circuit, CTI dependent

– Atypical Flutter
  • Not CTI dependent
  • Right or left-sided
  • Increasing incidence (post PVI)

– Atrial tachycardia
  • Ablation often a first-line approach, depending on circuit location, other comorbidities
  – pharmacologic management sometimes attempted prior to ablation
Anticoagulation

- Consideration is INDEPENDENT of “Rhythm Control”
  - Ablation is not (yet) curative
  - Drugs generally will fail given enough time

- Risk is a continuum
  - “Moderate” risk patients benefit from therapeutic anticoagulation
  - Rare major risk factors don’t appear in the scoring (e.g., mitral stenosis, prosthetic valve)

- “Paroxysmal” AF is **not** lower risk

- Same rules apply in AFL as AF

- Given the higher risk peri-cardioversion, anticoagulation peri-cardioversion is necessary independent of risk score
# CHADS²

<table>
<thead>
<tr>
<th>C</th>
<th>Congestive Heart Failure / ↓ LVEF</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension (&gt;140/90 or Med Rx)</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Age ≥ 75 years</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S₂</td>
<td>h/o Stroke / TIA</td>
<td>2</td>
</tr>
</tbody>
</table>

## Risk Treatment

<table>
<thead>
<tr>
<th>Risk</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
</tr>
<tr>
<td>1</td>
<td>ASA or Warfarin</td>
</tr>
<tr>
<td>2</td>
<td>Warfarin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C</th>
<th>Congestive Heart Failure / ↓ LVEF</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension (&gt;140/90 or Med Rx)</td>
<td>1</td>
</tr>
<tr>
<td>A₂</td>
<td>Age ≥ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S₂</td>
<td>h/o Stroke / TIA / Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>V</td>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sc</td>
<td>Sex category (female gender)</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Level</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Nothing / Aspirin</td>
</tr>
<tr>
<td>1</td>
<td>Moderate</td>
<td>Warfarin (or ASA)</td>
</tr>
<tr>
<td>2</td>
<td>High</td>
<td>Warfarin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc</th>
<th>CHADS$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>1.3%</td>
</tr>
<tr>
<td>2</td>
<td>2.2%</td>
</tr>
<tr>
<td>3</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>5</td>
<td>6.7%</td>
</tr>
<tr>
<td>6</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

Warfarin: Target INR

Annual Major Bleeding Rates on warfarin in major trials

Writing Group, 2011 ACCF/AHA/HRS Focused Update on AF, Circulation 2011.
European AF Trial Study Group, NEJM 1995 333:5.
Historically...
In trials – patients are in therapeutic range 60-65% of the time
In real life – patients are in therapeutic range <50% of the time
Dabigatran

• Dabigatran Etexilate (pro-drug)
  – 6.5% bioavailability
  – Half-life 12-17 hrs
  – 80% renal excretion
  – Must be stored in its original packaging (controls moisture exposure)
    • If removed from packaging, discard after 30 days
  – Interolance –
    • GI symptoms (dose dependent) in >10% of patients
  – Drug levels influence by dronedarone
Stroke / Systemic Embolism

Cumulative Hazard Rate

- Warfarin
- Dabigatran, 110 mg
- Dabigatran, 150 mg
### Table 3. Safety Outcomes,

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran, 110 mg, vs. Warfarin</th>
<th>Dabigatran, 150 mg, vs. Warfarin</th>
<th>Dabigatran, 150 mg vs. 110 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
<td>Relative Risk (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative Risk (95% CI)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.80 (0.69–0.93)</td>
<td>0.003</td>
<td>0.93 (0.81–1.07)</td>
</tr>
<tr>
<td>Life threatening</td>
<td>0.68 (0.55–0.83)</td>
<td>&lt;0.001</td>
<td>0.81 (0.66–0.99)</td>
</tr>
<tr>
<td>Non–life threatening</td>
<td>0.94 (0.78–1.15)</td>
<td>0.56</td>
<td>1.07 (0.89–1.29)</td>
</tr>
<tr>
<td>Gastrointestinal†</td>
<td>1.10 (0.86–1.41)</td>
<td>0.43</td>
<td>1.50 (1.19–1.89)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>0.79 (0.74–0.84)</td>
<td>&lt;0.001</td>
<td>0.91 (0.85–0.97)</td>
</tr>
<tr>
<td>Major or minor bleeding</td>
<td>0.78 (0.74–0.83)</td>
<td>&lt;0.001</td>
<td>0.91 (0.86–0.97)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.31 (0.20–0.47)</td>
<td>&lt;0.001</td>
<td>0.40 (0.27–0.60)</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>0.94 (0.80–1.10)</td>
<td>0.45</td>
<td>1.07 (0.92–1.25)</td>
</tr>
<tr>
<td>Net clinical benefit outcome‡</td>
<td>0.92 (0.84–1.02)</td>
<td>0.10</td>
<td>0.91 (0.82–1.00)</td>
</tr>
</tbody>
</table>
# Dabigatran 150 mg vs. 110 mg

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110mg</th>
<th>Dabigatran 150mg</th>
<th>D 150mg vs. D 110 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number rate/yr</strong></td>
<td><strong>Number rate/yr</strong></td>
<td><strong>Relative Risk 95% CI</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>Stroke and systemic embolism</td>
<td>1.53 %</td>
<td>1.11 %</td>
<td>0.73 0.58-0.91</td>
</tr>
<tr>
<td>Ischemic/unspecified stroke</td>
<td>1.34 %</td>
<td>0.92 %</td>
<td>0.69 0.54-0.88</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.12 %</td>
<td>0.10 %</td>
<td>0.85 0.39-1.83</td>
</tr>
<tr>
<td>Major Hemorrhage</td>
<td>2.67 %</td>
<td>3.11 %</td>
<td>1.17 1.01-1.36</td>
</tr>
<tr>
<td>GI Major Hemorrhage</td>
<td>1.12 %</td>
<td>1.51 %</td>
<td>1.36 1.09-1.70</td>
</tr>
<tr>
<td>Net Clinical Benefit</td>
<td>7.09 %</td>
<td>6.91 %</td>
<td>0.98 0.89-1.08</td>
</tr>
</tbody>
</table>
FDA Approval of Dabigatran

• 150 mg dose approved in US
  – 150 and 110 mg doses both approved in Canada
• “…concluded that encouraging the “play it safe” option for patients and physicians represented an undesirable stimulus to use a less-effective regimen and would lead to unnecessary strokes and disability”
• “…decision…was based on our inability to identify any subgroup in which use of the lower dose would not represent a substantial disadvantage”
Further analysis of RE-LY major bleeding risk

• 110 mg
  • <75 - Lower risk of bleeding re: warfarin
  • ≥75 – similar risk of bleeding re: warfarin

• 150 mg
  • <75 – lower risk of bleeding re: warfarin
  • ≥ 75 trend towards higher risk of bleeding re: warfarin

• Age interaction not observed w/ intracranial bleeding

“…at higher ages, the lower dabigatran dose might be considered a means to reduce the risk of bleeding in selected patients who are at high risk of bleeding.” “…decision…was based on our inability to identify any subgroup in which use of the lower dose would not represent a substantial disadvantage”
Novel Anticoagulants

- Oral Direct Thrombin inhibitors
  - Dabigatran

- Oral Xa Inhibitors
  - Rivaroxaban
    - ROCKET-AF – reduced stroke/embolism rate re: warfarin (2.2% vs. 1.7%) without a difference in major bleeding (preliminary results presented at AHA 2010)
    - Approved for prevention of venous thromboembolism; FDA meeting to discuss possible AF indication FDA 9/8/11
  - Apixaban
    - AVERROES – in patients with contraindications to warfarin, stroke/embolism reduced from 3.7% to 1.6% relative to ASA without an increase in bleeding (NEJM 2011)
  - Betrixaban
  - Edoxaban
Issues with novel anticoagulants

- No antidote – cannot reverse
- No monitoring
  - Overdose / elevated levels due to drug effect
  - DC cardioversion / procedural considerations
- Longterm followup –
  - drug interactions
  - compliance/discontinuation
- Cost / Insurance
- Correct risk/benefit ratio (e.g., low dose dabigatran)
Key Points

• “Cardioversion” & stroke risk – independent of CHADS & method of CV
• Ablation is first-line management for AFL, WPW, many SVT’s (e.g., AVNRT) but not AF
• Antiarrhythmics can be proarrhythmic
• Sporadic nature of bradyarrhythmias can make it challenging to diagnose them