AF and Congestive Heart Failure
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Medtronic: consultant
No Conflicts regarding the discussed content for the management of atrial fibrillation

Objectives
Understand the mechanistic interactions between CHF and AF
Understand the prognosis associated with CHF and AF
Understand the preferred approaches to rate control vs rhythm control
Understand the principles of use for the new oral anticoagulants in patients with AF and CHF (to be covered mostly in lecture #2)

Aging world population
By year 2030: >20% of the US population (~71.5 million) will be 65 years or older

Age and AF and Heart Failure Prevalence

Heart Failure Prevalence in Relation to Age
Prevalence of AF by NYHA CHF Class

Pathophysiology
- Ion Channel Remodeling (shortened APD)
- Atrial Fibrosis
- Atrial enlargement (multi wavelet reentry)
- Decreased Cardiac Performance
  - Loss of atrial systole
  - Rapid VR
  - Irregular VR
  - Increased MR and TR
- Intracellular Calcium dysregulation
- Neurohumoral activation (RAAS and autonomic)
- Increased filling pressures

Associations with CHF and AF
- Hypertensive heart disease
- Coronary artery disease
- Diabetes Mellitus
- Excessive alcohol
- Obesity: 50-60% increased risk of AF (PHS and Olmstead city (JAMA 2004;292:2471))
- Significant increased risk of CHF
- Genetic Syndromes: Laminopathies (Di CI, AV conduction dz and AF)
- Familial dilated cardiomyopathies
- Mutations in SCN5A (sinus bradycardia, CM and AF)
- Hypertrophic Obstructive Cardiomyopathy
- Emery Dreyfuss Syndrome (neuromuscular diseases)
- Kidney Disease
- Tachycardia induced cardiomyopathy

Sleep Apnea, Heart Failure and AF

AF in Dialysis Patients: Prevalence of Hx of AF at DOPPS (Dialysis Outcomes Practice Patterns Study) Enrollment
Table 2. Associations with Pre-existing and Newly Diagnosed Atrial Fibrillation (2)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre-existing AF</th>
<th>Newly diagnosed AF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary Comorbid Conditions (yes vs. no)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.08 (1.94-2.25)</td>
<td>0.051</td>
<td>0.117 (0.05-0.24)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1.10 (0.68-1.82)</td>
<td>0.801</td>
<td>0.077 (0.04-0.14)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.03 (0.85-1.25)</td>
<td>0.911</td>
<td>0.114 (0.08-0.19)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>1.01 (0.67-1.53)</td>
<td>0.938</td>
<td>0.100 (0.06-0.15)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.28 (1.04-1.58)</td>
<td>0.017</td>
<td>0.114 (0.19-0.75)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.98 (0.78-1.29)</td>
<td>0.866</td>
<td>0.084 (0.05-0.14)</td>
</tr>
<tr>
<td>CVD</td>
<td>1.16 (0.97-1.40)</td>
<td>0.949</td>
<td>0.091 (0.06-0.13)</td>
</tr>
<tr>
<td>Lung disease</td>
<td>1.11 (1.00-1.22)</td>
<td>0.020</td>
<td>0.113 (0.08-0.19)</td>
</tr>
<tr>
<td>Hypertension disorder</td>
<td>1.09 (0.85-1.37)</td>
<td>0.717</td>
<td>0.102 (0.06-0.14)</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>1.12 (0.97-1.30)</td>
<td>0.843</td>
<td>0.097 (0.06-0.13)</td>
</tr>
<tr>
<td>Cancer, other than skin</td>
<td>0.83 (0.66-1.04)</td>
<td>0.066</td>
<td>0.099 (0.06-0.15)</td>
</tr>
<tr>
<td>N/A</td>
<td>0.70 (0.58-0.85)</td>
<td>0.049</td>
<td>no events</td>
</tr>
</tbody>
</table>

V Milanovic et al. 2010

Tachycardia Induced Cardiomyopathy

Presentation: typically with CHF or incidentally noticed LV dysfunction

Generally rapid ventricular rates and minimal AF

Symptoms

Mechanism is unknown

Echo generally shows global reduction in EF without dilation. ECG most often shows a narrow QRS

Prognosis of AF in association with Heart Failure

Cumulative distribution function

<table>
<thead>
<tr>
<th>Time to Death</th>
<th>Low EF</th>
<th>Hazard ratio: 1.06 (95% CI 1.23 - 1.32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AF at baseline</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>AF at baseline (Low EF)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>AF at baseline (Preserved)</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

Hospital outcomes and Mortality stratified by atrial fibrillation (AF) groups (Get with the Guidelines Heart Failure Registry) 99,810 pts: 1/3 had new or preexisting AF

Whether AF is the cause or simply a marker for worse outcomes remains uncertain

Frequency and Prognosis of HFPEF and AF

Olmsted County Study: 1983 to 2010, 939 Olmsted County, Minnesota, residents (age, 77±12 years; 61% female) newly diagnosed with HFpEF (EF ≥0.50) were evaluated.

+ 1/3 of population with AF at baseline = 2/3’s of HFPEF population develops AF over 15 yrs of follow-up
What are we trying to achieve in the management of our patients with AF?

Does it differ in patients with AF and CHF?

Goals of AF Management

- Prevent Strokes
- Control symptoms
- Reverse and prevent left ventricular dysfunction

Symptoms

Palpitations  
Chest pain  
Shortness of breath  
Fatigue

Ventricular rate  ➔  Loss of AV synchrony  
Loss of RR regularity

AV dyssynchrony  ➔  Anti arrhythmic drugs  
Catheter or surgical ablation

Loss of RR regularity  ➔  Anti arrhythmic drugs  
AV junction ablation  
Catheter or surgical ablation

When to try to Restore and Maintain Sinus Rhythm

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

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

Primary outcome: Mortality  
3.5 yrs 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
Rate v Rhythm Control in CHF

No difference in CV death, Outcome-free Survival, Quality of life, 6 min walk, HF class.

Higher hospitalization rates (46% vs 39% p=.006) and cost with rhythm control.

Bradyarrhythmias ↑ in rhythm control group.

When should we disregard the results of AFFIRM and AF CHF?

Patients in whom the atrial contribution to filling is important (> 20% of ventricular filling)

Severe Diastolic Dysfunction:
- Aortic Stenosis
- Restrictive cardiomyopathy
- Hypertrophic cardiomyopathy

Atrial fibrillation + Newly discovered LV dysfunction

Tachycardia
- Reduced EF

Rate control
- 6 weeks of confirmed rate control
- Reduced EF
- Normalized EF

Rate control: Acute and Chronic

"When fibrillation is present, the rate of ventricular action is one of the most important indications of the gravity of the condition as a whole."

FIBRILLATION OF THE AURICLES: ITS EFFECTS UPON THE CIRCULATION.

BY THOMAS LEWIS, M.D.

(From the Cardiographic Department of the University College Hospital Medical School, London.) J Exp Med 1912

Rate control: Acute and Chronic

Consequences of inadequate rate control:

Symptoms: fatigue, dyspnea, palpitations

Tachycardia-induced cardiomyopathy
Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens

JACC 1999;33(2):304

Lenient versus Strict Rate Control in Patients with AF: RACE 2 study

614 patients with permanent AF randomized to:
- Lenient RC strategy ≤ 110 bpm at rest
- 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% w LVEF ≤ 40%
35% w NYHA Class 2 or 3 HF symptoms

2-3 yr follow up

≈ 70% for strict control

Combination therapy for rate control in AF
RACE 2 Study

Beta Blockers in Heart Failure (reduced LV fxn) and AF

Despite similar rates of HR slowing - Less benefit in AF than SR

Amiodarone as a rate controlling agent in CHF patients: CHF STAT
Circulation 1998

Rate control at 3 weeks persisted thereafter

Effectiveness and Safety of Digoxin Among Contemporary Adults With Incident Systolic Heart Failure: Kaiser Permanente
AVJ ablation and Heart Failure

Role of AV Nodal Ablation in Cardiac Resynchronization in Patients With Coexistent Atrial Fibrillation and Heart Failure: A Systematic Review

Rate Control in AF and HFrEF

Class I
1. Control of resting heart rate using either a beta blocker or a nondihydropyridine calcium channel antagonist is recommended for patients with persistent or permanent AF and compensated HF with preserved EF (HFrEF). (Level of Evidence: B)

2. In the absence of pre-excitation, intravenous beta blocker administration (or a nondihydropyridine calcium channel antagonist in patients with HFrEF) is recommended to slow the ventricular response to AF in the acute setting, with caution needed in patients with overt congestion, hypotension, or HF with reduced LVEF. (Level of Evidence: B)

3. In the absence of pre-excitation, intravenous digoxin or amiodarone is recommended to control heart rate acutely in patients with HF. (Level of Evidence: B)

4. Assessment of heart rate control during exercise and adjustment of pharmacological treatment to keep the rate in the physiological range is useful in symptomatic patients during activity. (Level of Evidence: B)

5. Digoxin is effective to control resting heart rate in patients with HF with reduced EF. (Level of Evidence: C)

Rate Control in AF

Class Ia
1. A combination of digoxin and a beta blocker (or a nondihydropyridine calcium channel antagonist for patients with HFrEF), is reasonable to control resting and exercise heart rate in patients with AF. (Level of Evidence: B)

2. It is reasonable to perform AV node ablation with ventricular pacing to control heart rate when pharmacological therapy is insufficient or not tolerated. (Level of Evidence: B)

3. Intravenous amiodarone can be useful to control the heart rate in patients with AF when other measures are unsuccessful or contraindicated. (Level of Evidence: C)

4. For patients with AF and rapid ventricular response causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by either AV node ablation or a rhythm-control strategy. (Level of Evidence: B)

5. For patients with chronic HF who remain symptomatic from AF despite a rate-control strategy, it is reasonable to use a rhythm-control strategy. (Level of Evidence: C)

Rate Control in AF

Class IIb
1. Oral amiodarone may be considered when resting and exercise heart rate cannot be adequately controlled using a beta blocker (or a nondihydropyridine calcium channel antagonist in patients with HFrEF) or digoxin, alone or in combination. (Level of Evidence: C)

2. AV node ablation may be considered when the rate cannot be controlled and tachycardia mediated cardiomyopathy is suspected. (Level of Evidence: C)

3. Lenient rate control (HR ≤ 110bpm) is reasonable for ax pts with preserved EF (Level of Evidence: B)
Anti arrhythmic Drugs and Heart Failure

Pharmacologic Management

Class 1: \( \text{Na}^+ \) channel blockers
- A: Quinidine, Procainamide, Disopyramide
- B: Lidocaine, Mexilitine
- C: Flecainide, Propafenone

Class 2: Beta Blockers

Class 3: \( \text{K}^+ \) channel blockers
- Sotalol, Amiodarone, Dofetilide, Dronedarone

Class 4: Calcium channel blockers

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Antiarrhythmic Medications

Lone AF
- 1st line: Flecainide, Propafenone, Dronedarone
- 2nd line: Sotalol, Type 1A Amiodarone

Avoid: Type 1C Amiodarone

Heart failure and ventricular ionic current changes

Could predispose to proarrhythmia in potassium channel blocking drugs

Dofetilide Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
<th>Patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMERALD</td>
<td>European/Australian trial of Conversion and maintenance efficacy and safety in AF and AFL: Dofet v Sotalol</td>
<td>548 pts</td>
<td>Abstract 2000</td>
</tr>
<tr>
<td>SAFIRE-D</td>
<td>Conversion efficacy tested in AF and AFL: Dofetol for maintenance of SR</td>
<td>325 pts</td>
<td>Circulation 2000;102:2385</td>
</tr>
<tr>
<td>DIAMOND CHF</td>
<td>Safety of dofetilide in patients with HF, LVEF ≤ 35%</td>
<td>1518 pts</td>
<td>NEJM 1999;341:897</td>
</tr>
<tr>
<td>DIAMOND AF</td>
<td>Persistent AF conversion and maintenance</td>
<td>508 pts</td>
<td>Circulation 2001</td>
</tr>
<tr>
<td>DIAMOND MI</td>
<td>With 7 ds of Acute MI and LVEF ≤ 35%</td>
<td>1510 pts</td>
<td>Lancet 2000;356:2052</td>
</tr>
</tbody>
</table>

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Heart failure and ventricular ionic current changes

Could predispose to proarrhythmia in potassium channel blocking drugs

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Dofetilide in patients with congestive heart failure and left ventricular dysfunction

1518 patients (391 w AF at baseline) LVEF ≤ 35%
Survival rates of patients treated with dofetilide (A) or placebo (B) who converted or did not convert to SR.

Conversion to SR: 59% vs. 34% (placebo)
SR at 1 year: 79% vs. 42%, P<0.001
Reduced hospitalizations for worsening of heart failure (29% vs. 40%)


**Dosage of Dofetilide Adjusted for Creatinine Clearance**

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Initial Adjustment for ∆QTc ≥15% or QTc &gt;500</th>
<th>Dofetilide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>500 μg BID</td>
<td>250 μg BID</td>
</tr>
<tr>
<td>40–60</td>
<td>250 μg BID</td>
<td>125 μg BID</td>
</tr>
<tr>
<td>20–39</td>
<td>125 μg daily</td>
<td>125 μg daily</td>
</tr>
<tr>
<td>&lt;20</td>
<td>Not recommended</td>
<td></td>
</tr>
</tbody>
</table>

**Verapamil** increases peak plasma concentrations of dofetilide by increasing intestinal blood flow.

**Cimetidine** inhibits renal cationic secretion of dofetilide and prolongs its half-life.

**Ketoconazole**, (inhibitor of the CYP3A4), prolongs the nonrenal clearance of dofetilide and this interaction may become significant in patients with renal dysfunction.

*Diamond Trials: 0.9% in AF and MI, 4% in CHF*

**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>amitryptiline</td>
<td>Cisapride</td>
<td></td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Ciproflox</td>
<td>Desipramine</td>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Erythromycin</td>
<td>Imipramine</td>
<td>Arsenic</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Clarithromycin</td>
<td>Fluoxetine</td>
<td>Sumatriptan</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>Fluconazole</td>
<td>Haloperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disopyr</td>
<td>Ketoconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2007 AJC
667 patients with CHF, 103 (15%) had AF at baseline. 51 were randomized to amiodarone and 52 to placebo. Dose of amiodarone 400 mg.


Mean age: 65 yrs
PMF 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

<table>
<thead>
<tr>
<th>Chemical structure</th>
<th>Amiodarone</th>
<th>Dronedarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodinated benzofuran</td>
<td>Non-iodinated benzofuran</td>
<td></td>
</tr>
</tbody>
</table>
| Metabolism | CYP2D4 mediated oxidation
Very active metabolite |
| CYP2A4 mediated oxidation
Extensive first pass metabolism 15% absorption 3 fold increase with food
Metabolite not very active |
| T1/2 | 50 days
15-24 hours |
| Channels | I_{Kr}, I_{Na}, I_{to}, I_{Ca,L}, I_{ACh}, I_{f}, non-competitive α and β antagonist |
| I_{Kr}, I_{Na}, I_{to}, I_{Ca,L}, I_{ACh}, I_{f}, non-competitive α and β antagonist |
Dronedarone: Large trial to assess safety – hospitalizations and all cause mortality

**ATHENA:** A Trial with Dronedarone to Prevent Hospitalization or Death in Patients with Atrial Fibrillation (and atrial flutter)

- 3700 patients – increased to 4300. Follow up of at least 1 year

**Inclusion Criteria:**

1. Patients aged 75 years or older, or patients aged at least 70 years with one or more of the following risk factors at baseline:
   - Hypertension (taking antihypertensive drugs of at least two different classes)
   - Diabetes
   - Prior cerebrovascular accident (stroke or transient ischemic attack) or systemic embolism
   - Left atrium diameter greater than or equal to 50 mm by echocardiography
   - Left ventricular ejection fraction less than 0.40 by 2D-echocardiography.
2. Availability of one ECG within the last 6 months, showing that the patient was or is in AF/AFL
3. Availability of one ECG within the last 6 months, showing that the patient was or is in sinus rhythm

**Study Population**

- 25% in AF at time of randomization
- 60% Structural heart disease
- 30% CAD
- 20% Class 2/3 CHF
- 12% LVEF < 45

**Results:**

- Dronedarone associated with:
  - No difference in all cause mortality
  - Reduction in cardiovascular mortality related to reduction in arrhythmic death
  - Decreased hospitalizations related to ↓ AF and ↓ acute coronary syndromes
- Safety in CHF population

**Permanent Atrial fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS)**

A Randomized, Double Blind, Placebo Controlled, Parallel Group Trial for Assessing the Clinical Benefit of Dronedarone 400mg BID on Top of Standard Therapy in Patients With Permanent Atrial Fibrillation and Additional Risk Factors

1° outcomes: stroke, systemic arterial embolism, myocardial infarction or cardiovascular death
2° outcomes: CV death

Age ≥65 and at least 6 months of AF

**Estimated Enrollment:** 10800

**Study Start Date:** July 2010

**Estimated Study Completion Date:** 2013

**Estimated Primary Completion Date:** 2013 (Final data collection date for primary outcome measure)

**Risk of the First Coprimary Outcome (Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).**

**Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death).**

**Hypertrophic Obstructive Cardiomyopathy and Disopyramide**

**Reduction in LVOT gradient with Disopyramide**
Disopyramide for HCM

Cardiovascular:
- TdP
- HF exacerbation in patients with low EF

Non Cardiovascular: Anticholinergic side effects
- Blurry vision abates in days
- Constipation, Urinary hesitancy
- Mestilon (Pyridostigmine) 90 – 180 mg bid

118 HCM patients followed for 3.1 ± 2.6 years; dose 432 ± 181 mg/day m 97% on beta blockers

Non Pharmacologic Rhythm Control in AF and CHF

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 esophageal fistula, 1% risk of tamponade

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**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

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**AF Ablation and HF**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study design</th>
<th>N</th>
<th>Inclusion</th>
<th>AF pattern</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan 2008 NEJM</td>
<td>Randomized</td>
<td>81</td>
<td>LVEF&lt;40, failed AAD</td>
<td>Persistent</td>
<td>PVI ± CFAEs vs AVJ+BIV</td>
<td>88% AF free and sig increase in EF and QOL in PVI grp.</td>
</tr>
<tr>
<td>MacDonald 2011</td>
<td>Randomized</td>
<td>41</td>
<td>LVEF&lt;35</td>
<td>Persistent</td>
<td>PVI ± linear and focal CFAE vs pharm rate control</td>
<td>50% AF free in PVI grp. SR had sig increase in EF.</td>
</tr>
<tr>
<td>Jones 2013</td>
<td>Randomized</td>
<td>52</td>
<td>LVEF &lt;35</td>
<td>Persistent</td>
<td>PVI ± linear and focal CFAE vs pharm rate control</td>
<td>88% AF free in PVI grp.</td>
</tr>
<tr>
<td>Hunter 2014 CAMTAF</td>
<td>Randomized</td>
<td>50</td>
<td>LVEF&lt;50</td>
<td>Persistent</td>
<td>PVI ± linear and focal CFAE vs pharm rate control</td>
<td>81% AF free in PVI grp at 6mos., 73% at 12 mos. more in LVEF.</td>
</tr>
</tbody>
</table>

**Cardiac Resynchronization Therapy**

**EF ≤ 35%**
- LBBB with QRS ≥ 120ms
- Class 2, 3 or 4 HF

**In AF:**
- On medical therapy or post AVJ ablation to allow 100% pacing

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**AF, Heart Failure and Thromboembolic Risk and Prophylaxis**

- 560 pts with HF
  - Mean EF 27%
  - CRT
  - AHRE > 3.8/8 day
- 9X more likely to Develop a TE (p<.006)
- AHRE > 180 bpm
  - Atleast 14 mind
  - 370 days of flup
Thromboembolic Prophylaxis: Where are we, what have we learned recently and where should we go? Current Standards and New Paradigms

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Thromboembolism in AF: First Principles we use in daily management

Clots form in the LAA in patients with AF
Cardioversion of AF results in a period of potentially increased stroke risk
The risk for clot formation in AF develops after 48 hours of continuous AF
Long term risk of stroke is related to non-rhythm associated factors
The frequency of AF (paroxysmal v permanent) does not influence AC decisions

AF, Heart Failure and Thromboembolic Risk and Prophylaxis
More to come

Thank You

Disclosure of Financial Relationships
Peter Zimetbaum, MD, FACP, FACC, FHRS
Has disclosed relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

Medtronic

AF and the association with clot formation

1814 William Wood (Edinburgh): First description “ball” thrombus in the LA in a pt with MS
1847 Virchow: Thrombi can embolize to the systemic or pulmonary circulation
1909 Welch: Description of cardiac thrombosis – structure, formation and etiology of clots
1930: Harvey and Levine: Autopsy series 1913-29, 2091 records
Mural thrombi: LV (31), RA (12), LA (206), LV (4)
“Auricular fibrillation definitely increases the incidence of auricular thrombosis”

1942: Hay and Levine: Pts with same age and Valve lesions (MS) were compared at autopsy.
105 AF (49% LA clot)
80 SR (14% LA clot)

American Heart Journal

1894, 1943, No. 1

Original Communications

AF AND AURICULAR FIBRILLATION AS INDEPENDENT FACTORS IN AURICULAR VESSEL THROMBOSIS

Harrison D. Hall, MD; and Kaushik J. Lavoro, MD

Boston, Mass.
Anticoagulation and AF

1947 Wright: First to use Warfarin to prevent embolism. Am J Med

1950 Askey and Cherry: Clinical trial of AC in a population with NVAF as well.
- 10 pts with AF and RHD, 10 pts with non-valvular AF. 13 had a prior stroke (7RHD, 6 NVAF).
- 4 recurrent strokes – 3 in unanticoagulated states

Recommend: Warfarin for RHD + AF but not yet for NVAF without prior embolus due to difficulty managing it in older pts and the lack of good data.


1978 Wolf: Framingham heart study – In NVAF patients – 5.6% increased stroke risk.

AF Cardioversion and Stroke Risk

1989 Manning et al. Pulsed doppler evaluation of atrial mechanical function after CV
• In the absence of AC in patients with AF of > 48 hours duration: 1-2% risk of stroke within the first month post CV
• Risk is believed to be related to return of atrial mechanical function
  - Duration of AF
  - Time to return of atrial mechanical function
    - AF ≤ 2 weeks: 48 hours
    - 2-6 weeks: Within one week
    - > 6 weeks: One month
  - Majority of embolic events post cardioversion occur within the first 10 days
  - Risk of stroke post cardioversion can be reduced to < 1% with 3-4 weeks of AC

1993 Manning et al. TEE guided CV

Stroke Risk Factors

Age > 65
Hypertension
Diabetes Mellitus
Congestive heart failure
Prior stroke/TIA

No
Cardiovert

If INR < 2
Consider heparin or equivalent therapy
Use molecular weight heparin, Dabigatran, Apixaban, Rivaroxaban than cardiovert.

Continue warfarin (INR 2-2.5) or
Dabigatran, Apixaban or Rivaroxaban for at least one month or indefinitely if there are stroke risk factors.

Anticoagulation and AF

1986 ACCP and NHLBI Guidelines: long term warfarin for: RHD + AF
- NVAF + syst embolism
1989 ACCP 2 Guidelines: long term warfarin for NVAF + DCM, HCM, CHF or thyrotoxicosis
1989-1991: RCTs (AFASAK, BAATAF, SRAF, CASE, SPINAF) warfarin v placebo for NVAF (no RHD)
1992 ACCP 3 Guidelines: long term warfarin for NVAF + DCM, HCM, CHF or thyrotoxicosis
1995 ACCP 4 Guidelines: long term warfarin for NVAF – Use of CHADS score

1993 ACCP 5 Guidelines: long term warfarin for NVAF – Use of CHA2DS2-VASc score

AF Cardioversion and Stroke Risk

1989 Manning et al. Pulsed doppler evaluation of atrial mechanical function after CV
• In the absence of AC in patients with AF of > 48 hours duration: 1-2% risk of stroke within the first month post CV
• Risk is believed to be related to return of atrial mechanical function
  - Duration of AF
  - Time to return of atrial mechanical function
    - AF ≤ 2 weeks: 48 hours
    - 2-6 weeks: Within one week
    - > 6 weeks: One month
• Majority of embolic events post cardioversion occur within the first 10 days
• Risk of stroke post cardioversion can be reduced to < 1% with 3-4 weeks of AC

1993 Manning et al. TEE guided CV

Zimetbaum, Cecil 2014
TEE documented thrombi

- Clots are present in 13% of all comers with AF (including those with duration estimated < 48 hrs)
- Clots appear to resolve rather than become organized
- Majority (89%) will resolve after 4 weeks of warfarin
- Routine use of a "screening" TEE after one month of AC (but no prior TEE demonstrating clot) does not reduce the risk of emboli and isn't cost effective. However – in particularly high risk settings (RHD, prior stroke, severe LV dysfunction) this approach is reasonable
- TEE documented thrombi – anticoagulate for 4 weeks – repeat TEE

Collins, Manning Circulation 1995

CHADS VASC

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</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 on MRI</td>
<td>2</td>
</tr>
</tbody>
</table>

Not included: Renal Insufficiency – eGFR < 45 mL/min

Stroke risk + 4/100 patient-years

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 (9%) 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)

- Mean age: 65 yrs
- Male: 70%
- Parox AF: 45%
- HTN: 37%
- DM: 13%
- CHF: 10%
- TIA/Stroke: 2.5%


Does adding anti platelet therapy to warfarin add value in patients with AF and vascular disease?

Antithrombotic Treatment in Patients With Heart Failure and Associated Atrial Fibrillation and Vascular Disease · A Nationwide Cohort Study (1997-2009)

Warfarin v. Warfarin + antiplatelet rx

No difference in risk of Thromboembolism or MI

Bleeding risk was significantly increased (HR 1.31; 95% CI 1.09-1.57)

Combination Anti Platelet Therapy

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

Does adding anti platelet therapy to warfarin add value in patients with AF and vascular disease?

Antithrombotic Treatment in Patients With Heart Failure and Associated Atrial Fibrillation and Vascular Disease · A Nationwide Cohort Study (1997-2009)

17,414 patients – hospitalized with HF and coexisting CAD or PVD

Warfarin v. Warfarin + antiplatelet rx

No difference in risk of Thromboembolism or MI

Bleeding risk was significantly increased (HR 1.31; 95% CI 1.09-1.57)
Anticoagulation and Antiplatelet Rx

- Risk of bleeding on triple therapy: 16% annual risk of bleeding [Arch Int Med 2010; 170:1433]
- VKA + P2Y12 inhibitor (clopidogrel 75mg) reduced the bleeding rates associated with triple therapy without an increase in CV events (WOEST study and subsequent registry) [Lancet 2013;381:1107, JACC 2013;62:981]

What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stentimng

Registry of >37,000 patients with vascular dz+CHF
Mean CHADS VASc of 5
29,660 had no AF and a significantly better prognosis than the 7000 w AF
Same risk in prevalent and incident AF groups
The addition of antiplatelet Rx to VKA did NOT reduce the rate of MI, TE, Coronary/Mi death but did increase bleeding risk [JACC 2014;63:2689]

AF and CAD: Anticoagulant choices

Coronary Stent

Acute CS

Stable CAD

CHADS 0

CHADS ≥1

CHADS ≤1

CHADS ≥2

CHADS ≤1

CHADS ≥2

ASA

OAC

ASA Clopidogrel

ASA Clopidogrel

ASA Clopidogrel

ASA Clopidogrel

OAC

Prasugrel likely has a higher intracranial bleeding rate than clopidogrel

NOACS and PCI in AF

<table>
<thead>
<tr>
<th>Pioneer AF-PCI Study</th>
<th>RE-DUAL PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open label Randomized Study 2100 patients</td>
<td>Open label Randomized Study 2100 patients</td>
</tr>
<tr>
<td>Riva 15 qd</td>
<td>Riva 15 qd</td>
</tr>
<tr>
<td>P2Y12 2.5bid</td>
<td>ASA P2Y12</td>
</tr>
<tr>
<td>ASA</td>
<td>ASA</td>
</tr>
<tr>
<td>Warf</td>
<td>ASA</td>
</tr>
<tr>
<td>2-3</td>
<td>100 bid</td>
</tr>
<tr>
<td>Dabi</td>
<td>Dabi</td>
</tr>
<tr>
<td>150 bid</td>
<td>150 bid</td>
</tr>
<tr>
<td>P2Y12</td>
<td>P2Y12</td>
</tr>
<tr>
<td>ASA</td>
<td>ASA</td>
</tr>
<tr>
<td>Warf</td>
<td>P2Y12</td>
</tr>
<tr>
<td>2-3</td>
<td>100 bid</td>
</tr>
<tr>
<td>Dabi</td>
<td>Dabi</td>
</tr>
<tr>
<td>150 bid</td>
<td>150 bid</td>
</tr>
<tr>
<td>P2Y12</td>
<td>P2Y12</td>
</tr>
<tr>
<td>ASA</td>
<td>ASA</td>
</tr>
<tr>
<td>2-3</td>
<td>100 bid</td>
</tr>
</tbody>
</table>

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%  ACTIVE W  TTR ≥ 65%

Warfarin

S- Warfarin  CYP 2 C9

Variants of CYP2C9 encode enzyme w reduced activity  lower maintenance warfarin dosages

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

Warfarin is most common in caucasians

Warfarin genotype  lower maintenance warfarin dosages

Most common in Asians

Reduced Vitamin K

Oxidized VitK

VKORC1 genetic variants  lower maintenance warfarin dosages

Most common in Asians

Up to 25% of patients with difficulties managing warfarin dosing have a polymorphism of VKORC1 or less commonly CYP2C9

THROMBOEMBOLISM ASSOCIATED WITH AURICULAR FIBRILLATION

Connecting Anticoagulant Therapy

JOHN MORTON ASATY, M.D.

CLIFTON & ORMARJ, M.D.

Los Angeles

About three time more patients will be catastrophically injured or die from warfarin therapy compared to those with inferiority. At present, the prevalence of death and complications from intracranial clot formation must be balanced against the similar hazards of the use of this medication. About 20 of 100 patients dying of intracranial hemorrhage from thromboembolism. The majority show systemic clinical and the dangers of the drug. It is probable that fewer anticoagulant drugs will be available and that fewer patients will be classified with age, sex, the medications. Anticoagulation is not the solution. About 250 patients dying of intracranial hemorrhage from thromboembolism. The majority show systemic
Coagulation Cascade

initiation

Vila/TF

no interaction with food or antibiotics

propagation

IXa Vlla

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

Rapid onset and offset

Fibrin Formation

Fibrinogen Fibrin

Fibrin

direct thrombin inhibitors

Kexologtran

Dabigatran etexilate

Direct Factor Xa inhibitors

Rivaroxaban

Apixaban

Indirect Factor Xa inhibitors

Fondaparinux

Eptaparinux

Important interactions involving CYP 3A4 and P-glycoprotein

Substrate

Inhibitors of CYP 3A4 and P-gp (Will increase levels of NOAC)

Action

Apixaban

Ketoconazole (azoles in general)

Ritonavir, Clarithromycin

Apixaban 2.5 bid

Stop if on 2.5 bid

Rivaroxaban

Dabigatran

Ketoconazole, Dronedarone

Important interactions involving CYP 3A4 and P-glycoprotein

Substrate

Inducers of CYP 3A4 and P-gp (Will decrease levels of NOAC)

Action

Apixaban

Rifampin, carbamazepine, phenytoin, St John’s wort

Avoid

Rivaroxaban

Dabigatran

Rifampin

New Anticoagulant Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>RelY</td>
<td>(18,113)</td>
<td>(14,264)</td>
<td>(21,107)</td>
</tr>
<tr>
<td>Dose</td>
<td>110 bid</td>
<td>20 qd</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>mg CHADS2</td>
<td>2.1</td>
<td>3.5 (50% Stroke/TIA)</td>
<td>2.1</td>
</tr>
<tr>
<td>Time in therapeutic range (INR)</td>
<td>54%</td>
<td>55%</td>
<td>62%</td>
</tr>
<tr>
<td>Ischemic endpt</td>
<td>150 superior (1.1%/yr)</td>
<td>3.5 (50% Stroke/TIA)</td>
<td>41% reduction in hemorrhagic stroke</td>
</tr>
<tr>
<td>intracranial bleeding</td>
<td>150 60% reduced in (10.6%/yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>death</td>
<td>3.10%/yr</td>
<td>3.02%/yr</td>
<td>3.02%/yr</td>
</tr>
</tbody>
</table>

RELY-ABLE Study

The long term Multi-Center Observational Study of Dabigatran Treatment in patients with Atrial Fibrillation

Follow up of the RELY study to further assess the efficacy and safety of two doses of dabigatran treatment in AF

Randomized, DB, Parallel

5,851 pts

Median follow up 2.3 yrs

110 mg

150 mg

Major bid 2.99%/yr

Stroke/emb 0.14%/yr

Death 3.10%/yr

2.94%/yr

0.13%/yr

3.02%/yr

Conc 2013

Concerns regarding New Oral Anticoagulants

Haven't been around very long

Safety in the elderly

Safety in patients with renal insufficiency

Safety in patients with valve disease

Absence of an antidote

Concerns for lack of reversibility for intracranial bleeding
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

**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

**FDA Recommendations:**
- Dabigatran: Contraindicated in pts with mechanical valves (REALIGN STUDY)
- Rivaroxaban: Not recommended for bisprosthetic valves
- Apixaban: Not recommended for use with prosthetic valves

**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</td>
<td>60-80</td>
<td>&gt; 12 hours</td>
<td>&gt; 12 hours</td>
<td>&gt; 12 hours</td>
</tr>
<tr>
<td>wear off</td>
<td>hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and</td>
<td></td>
<td>Dabigatran: Idarucizumab (phase 2)</td>
<td></td>
<td>Apixaban: Andexanet (phase 2)</td>
</tr>
<tr>
<td>reversal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reversing agent**

- PCC: prothrombin complex concentrates (vit K dependent factors 2,7,9,10)
- Recombinant activated factor 7 – directly activates thrombin on the platelet surface

**Event Rates by age in RELY**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110</th>
<th>Dabigatran 150</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yearly stroke rates, ≥ 80</td>
<td>1.9</td>
<td>1.8</td>
<td>2.7</td>
</tr>
<tr>
<td>(n=3,016)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yearly stroke Rates, &lt; 80</td>
<td>1.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>(n=15,097)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yearly major bleeds, ≥ 80</td>
<td>5.3</td>
<td>6.2</td>
<td>4.7</td>
</tr>
<tr>
<td>(n=3,016)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yearly major bleeds, &lt; 80</td>
<td>2.4</td>
<td>2.7</td>
<td>3.4</td>
</tr>
<tr>
<td>(n=15,097)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Factors associated with a risk of ICH in RELY:**

<table>
<thead>
<tr>
<th>Factor</th>
<th>RR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Europe</td>
<td>0.34</td>
<td>0.001</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>1.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Age per year</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Factors associated with a risk of ICH in ROCKET AF:**

<table>
<thead>
<tr>
<th>Factor</th>
<th>RR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin use</td>
<td>1.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>1.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Age per year</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior thienopyridine use</td>
<td>1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Heart Failure and the Novel Oral Anticoagulants**

- **Dabigatran**
  - Study: RELY (18,113)
  - Dose: Dabigatran 100 bid, Dabigatran 150 bid
  - Avg CHADS 2.1
  - Time in therapeutic range (INR) 64%
  - Ischemic endpt (GFR 30-49)
  - Bleeding: No excess on Dabi

- **Rivaroxaban**
  - Study: ROCKET AF (14,264)
  - Dose: Rivaroxaban 20 qd
  - Renal adjustment to 15 mg qd
  - Avg CHADS 3.5 (50% Stroke/TIA)
  - Time in therapeutic range (INR) 55%
  - Ischemic endpt (GFR 30-49)
  - Bleeding: 2.32%/yr

- **Apixaban**
  - Study: ARISTOTLE (18,201)
  - Dose: Apixaban 5 mg Bid
  - Renal adjustment 2.1
  - Avg CHADS 62%
  - Time in therapeutic range (INR) 62%
  - Ischemic endpt (GFR 30-49)
  - Bleeding: 2.5%/yr
Mortality is NOT higher with Dabigatran c/w warfarin when an ICH occurs

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabi 150</th>
<th>Dabi 110</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n/n)</td>
<td>% (n/n)</td>
<td>% (n/n)</td>
</tr>
<tr>
<td>All intracranial</td>
<td>36% (32/90)</td>
<td>35% (13/37)</td>
<td>41% (11/27)</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>41% (19/46)</td>
<td>64% (7/11)</td>
<td>64% (8/14)</td>
</tr>
<tr>
<td>Spont</td>
<td>45% (19/42)</td>
<td>64% (7/11)</td>
<td>70% (7/10)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>0% (0/4)</td>
<td>0% (0/5)</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% (1/10)</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>

Why less CNS bleeding with NOACs?

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

Dabigatran concentrations and Patient characteristics

Both dosages of dabigatran were associated with a 5 fold variation in dabigatran concentrations (wide therapeutic range)

Renal function was the major determinant of variation

Trough concentration and Patient Age

Peri Procedure Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creat Clearance (ml/min)</th>
<th>Half live (hrs)</th>
<th>How long to discontinue (days)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>12-17</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>30-50</td>
<td>10-33</td>
<td>27</td>
<td>4</td>
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<tr>
<td>15-30</td>
<td>17-17</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
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<td></td>
<td>2</td>
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<tr>
<td>Dabigatan</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>15-30</td>
<td>17-18</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>10-16</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>28-29</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>30-34</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-30</td>
<td>12-17</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>15-30</td>
<td>12-17</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>15-30</td>
<td>12-17</td>
<td>17</td>
<td>2</td>
</tr>
</tbody>
</table>

Where are we going?

Left atrial appendage as a target for thromboembolic risk reduction

Can we improve patient and physician compliance?

AF burden and tailored anticoagulation
LAA exclusion:

**Anatomy**
- Function: Releases ANP
- Small contribution to cardiac filling
- Distension of the LAA may result in sympatho/vagal reflexes

**Function of the LAA**
- 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

**Techniques**

---

1063 patients referred for PVI
Pre procedure CT = 678
65 (10%) had prior stroke/TIA

<table>
<thead>
<tr>
<th>LAA Shape</th>
<th>Total</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken wing</td>
<td>306(45%)</td>
<td>24(36.9%)</td>
<td>282(46%)</td>
</tr>
<tr>
<td>Cactus</td>
<td>125(18.4%)</td>
<td>15(23.1%)</td>
<td>110(17.9%)</td>
</tr>
<tr>
<td>Windsock</td>
<td>179(26.4%)</td>
<td>15(23.1%)</td>
<td>164(26.8%)</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>68(10%)</td>
<td>11(16.9%)</td>
<td>57(9.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LA Trabeculation</th>
<th>Total</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>171(25%)</td>
<td>15(23.1%)</td>
<td>161(25.3%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>395(56.4%)</td>
<td>32(48.6%)</td>
<td>363(59.4%)</td>
</tr>
<tr>
<td>Extensive</td>
<td>197(28.4%)</td>
<td>18(27.7%)</td>
<td>179(26.8%)</td>
</tr>
</tbody>
</table>

| LA Orifice DM CM | 2.74 ± 0.7 | 2.26 ± 0.5 | 2.78 ± 0.7 |
| LA Length CM    | 5.55 ± 1.18 | 5.06 ± 1.17 | 5.61 ± 1.17 |

**Percutaneous LAA Ligation**

Watchman – permeable mesh requires 45 days of AC post implant.
Protect: 700 pts 2:1 device v warfarin
Not 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
Preval: Extension trial – pending
APPROVED IN EUROPE

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Atricure Atriclip
Where are we going?

Can we improve patient and physician compliance?

Fear of bleeding
Fear of falls

Do you believe it is reasonable to leave a Low CHADS score patient with permanent AF on no AC? (eg. a 64 year old male with permanent AF)

Does the risk change over time with or without the development of more CHADS risk factors?

How helpful is the CHADS\(_2\) system?

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>CHADS 0-1</th>
<th>2026</th>
<th>ASA</th>
<th>no. of events (%/yr)</th>
<th>Apixaban</th>
<th>no. of events (%/yr)</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVERROES</td>
<td>2026</td>
<td>18 (1.6)</td>
<td>10 (0.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>6,183</td>
<td>51 (0.9)</td>
<td>Apixaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RELY</td>
<td>N</td>
<td>10 (0.9)</td>
<td>4.4 (0.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS 0-1</td>
<td>5,775</td>
<td>1.06</td>
<td>Dab 110</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTIVE W</td>
<td>N</td>
<td>2 (0.4)</td>
<td>22</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CHADS 1</td>
<td>2436 (36%)</td>
<td>0.65</td>
<td>Dab 150</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>2 (0.4)</td>
<td>Warf 1.05</td>
<td></td>
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</tr>
</tbody>
</table>

AF burden and stroke risk

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>CHADS 2.2</th>
<th>1.4 yr flup</th>
<th>3045 pts, AHRE (&gt;175 bpm for &gt; 20 seconds) CHADS 2 was 2.2 +/- 1.2 Characterized as zero (20 seconds to hours on all days) or high (on at least one day) Anticoagulant use was uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSERT</td>
<td>3080</td>
<td>CHADS 2.2</td>
<td>2.5 yr flup</td>
<td>Low burden → 1.1%/yr ≤ 0.86 hours on all days High burden → 2.4%/yr ≥ 0.87 to 3.63 hours on at least one day Independent of CHADS</td>
</tr>
</tbody>
</table>

Is the rhythm really responsible for the stroke risk associated with AF?

Shanmugan et al. 2012
560 CRT patients in two prospective studies
15 patients (2%) had thromboembolic events Atrial tachyarrhythmia ≥ 3.8 hours a day HR 3.9; P = 0.006 for stroke c/w no AF
27% were in AF at the time of stroke

2012 Circulation 2012
2580 pts, AHRE (>190 bpm for > 3 minutes in first 3 months = 261 patients enrolled) 18% of pts identified to have AF received warfarin CHADS 2 was 2.2 +/- 1.2

Shanmugan et al. 2012
11 patients (2%) had thromboembolic events Atrial tachyarrhythmia ≥ 3.8 hours a day HR 9.4; P = 0.006 for stroke c/w no AF 27% were in AF at the time of stroke

1,756 patients with a prior stroke and no documented AF: Relationship of CHADS and CHADS VASC and Stroke risk unrelated to AF

Stroke types: Cardioembolic, Large vessel thrombosis, Small vessel thrombosis

Lacunar

The higher the CHADS\(_2\)/CHA\(_2\)DS\(_2\)-VASc Score the greater the risk of stroke INDEPENDENT of AF
Presence and Duration of Atrial Fibrillation Detected by Continuous Monitoring: Crucial Implications for the Risk of Thromboembolic Events

- Retrospective analysis of 568 patients with PAF and a Medtronic AT 500 implanted
- At least 3 symptomatic episodes in prior year
- One episode in month prior to device implantation

- Primary objective: Incidence of stroke in relation to CHADS score AND AF duration
- Secondary objective: Evaluate AF detection through continuous and intermittent (simulated) monitoring

Starting and stopping anticoagulation based on burden of AF: Can we reduce the days on AC based upon AF recurrence?

High risk of stroke: Low burden with high CHADS2 score and High burden with low CHADS2 Score

Remote Monitoring of Cardiac Rhythm

N=166 (29%)
N=179 (32%)
N=223 (39%)

High risk of stroke: Low burden with high CHADS2 score
High burden with low CHADS2 Score

Remote Monitoring of Cardiac Rhythm

Zimetbaum, Waks, Ellis, Passman PACE 2013
Patient cannot have AF > 30 min total burden per day and cannot have a single continuous episode > 6 min per day in the 30 days prior to enrollment.

Patient must be on an oral anticoagulant from the class of direct thrombin or Factor Xa inhibitors (e.g., Dabigatran, Rivaroxaban, Apixaban) for at least one month prior to enrollment.

AF Monitoring
1. Scheduled Daily Transmission
2. Patient Initiated Transmission
3. Alert Triggered Transmission

AF Duration ≥ 1 Hour

Anticoagulation

Continue Anticoagulation

Freedom from AF Duration ≥ 1 Hour for 30 consecutive days

YES STOP Anticoagulation

Start ASA

NO

Thank You