Lilly Slide Presentation – NOT FOR SYLLABUS
(See separate file for syllabus!)

Cardiology Take Home Points

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Effect of Maneuvers on Systolic Murmurs

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>Aortic Stenosis</th>
<th>Mitral Regurgitation</th>
<th>Hypertrophic Cardiomyopathy</th>
<th>Mitral Valve Prolapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Filling</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑ (and earlier)</td>
</tr>
<tr>
<td>↑ Filling</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>↑ Afterload</td>
<td>Hand Grip</td>
<td></td>
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</tr>
</tbody>
</table>

Management of Acute Pericarditis

- Aspirin (e.g., 650 mg q 4-6 h)
- NSAIAs (e.g., ibuprofen 400-800 mg q 6-8 h)
- Prednisone 60-80 mg/d (last resort)
- Colchicine

Early Hospital Care Antiplatelet Rx: INV Rx

- For UA / NSTEMI
- Dual antiplatelet therapy on presentation:
  - BEFORE PCI: Clopidogrel 60-300 mg or Prasugrel 60 mg
  - AT PCI: Clopidogrel, or Prasugrel, or GP 2b/3a
- Loading dose of ADP receptor blocker:
  - Clopidogrel 300-600 mg or Prasugrel 60 mg
- If undergo PCI, consider clopidogrel 600 mg load followed by 150 mg/d × 6 d if not high risk for bleeding
- Consider Prasugrel before angiography if risk of bleeding low and likelihood of CABG low
- If high-risk, consider upstream clopidogrel and GP 2b/3a
- Reasonable to use ASA 75-162 mg/d after PCI if concerned about bleeding

Long-term Antiplatelet Rx

- Without stenting:
  - ASA 75-162 mg/d indefinitely
  - Clopidogrel 75 mg/d for ≥1 mo and ideally up to 1 yr
- If treated with bare metal stent(s):
  - ASA 162-325 mg/d for ≥1 mo and then 75-162 mg/d indefinitely
  - Clopidogrel 75 mg/d or Prasugrel 10 mg/d for ≥1 yr
- If treated with drug-eluting stent(s):
  - ASA 162-325 mg/d for ≥3-6 mos and then 75-162 mg/d indefinitely
  - Clopidogrel 75 mg/d or Prasugrel 10 mg/d for ≥1 yr
- Reasonable to use ASA 75-162 mg/d after PCI if concerned about bleeding
- If treated with drug-eluting stent(s):
  - Consider continuation of clopidogrel or prasugrel beyond 15 mos

Clopidogrel Metabolism

- CYPs: 1A2, 2B6, 2C19
- Active Metabolite: Cl
Invasive vs. Conservative Strategy

**INVASIVE**
- Routine angiography and revascularization as indicated, within 12-24 h if high-risk, otherwise within 48 hrs

1. Refractory angina
2. Hemodynamic or electrical instability
3. Risk of ischemic events
   - Recurrent angina, angina at rest or with low-level activity
   - High-risk features on stress test
   - Troponin
   - ST depressions
   - TIMI or GRACE risk score
   - Heart failure, low EF, new or worsening MR
   - PCI in past 6 mos, prior CABG

**CONSERVATIVE**
- Coronary angiography and revascularization only if significant stress-test induced or recurrent spontaneous ischemia
1. Low TIMI or GRACE Risk score
2. Patient or physician preference in absence of high-risk features

Anticoagulant Therapy
- If INV strategy selected:
  - UFH or enoxaparin or bivalirudin
  - Fondaparinux
- If CONS strategy selected:
  - Enoxaparin or UFH or fondaparinux
- If CONS strategy & ↑ risk of bleeding:
  - Fondaparinux

Anticoagulate for ≥48 hrs and preferably for duration of hospitalization, up to 8 days (regimens other than UFH are recommended if Rx given for >48 hrs or if risk of HIT w/ prolonged UFH).

Regimens include:
- UFH for 48 hrs
- Enoxaparin (adj for age & CrCl) for duration of hospitalization or 8 days
- Fondaparinux for duration of hospitalization or 8 days

Epidemiology of HF by EF

4596 pts discharged with HF, Olmsted County, 1987-2001

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Preserved EF</th>
<th>Depressed EF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>74.4 yrs</td>
<td>71.7 yrs</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>44.3%</td>
<td>65.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>41.4%</td>
<td>35.9%</td>
<td>0.002</td>
</tr>
<tr>
<td>HTN</td>
<td>62.7%</td>
<td>48.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>52.9%</td>
<td>63.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>33.1%</td>
<td>34.3%</td>
<td>0.61</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>41.3%</td>
<td>28.5%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Owan TE, et al. NEJM 2006; 355:251-9

BNP for Diagnosis

1586 pts presenting to EW with dyspnea

**BNP > 100 pg/mL:**
- Diagnostic Accuracy 83.4%

**BNP < 50 pg/mL:**
- Negative Predictive Value 96%

Maisel AS, et al. NEJM 2002;347:161

Optimal Dosing of RAAS Antagonists

**ATLAS**
- Lisinopril 50-100mg
- Time to Death or Hospitalization
- Favors High Dose
- HR 0.88 (0.82-0.96), P=0.002

**HEAAL**
- Losartan 150mg
- Time to Death or HF Hospitalization
- Favors High Dose
- HR 0.90 (0.82-0.99), p=0.027

Titrate as Tolerated to Doses Achieved in Clinical Trials

**β-Blocker Trials in Symptomatic HF**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target Dose (mg/d)</th>
<th>Mean Dose (mg/d)</th>
<th>Control Mean Dose (mg/d)</th>
<th>β-blocker RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>CIBIS I</td>
<td>5</td>
<td>3.8</td>
<td>11.0</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>10</td>
<td>7.5</td>
<td>13.2</td>
<td>8.8</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>BEST</td>
<td>100-200</td>
<td>76</td>
<td>17</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>MDC</td>
<td>100-150</td>
<td>108</td>
<td>11.1</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>200</td>
<td>159</td>
<td>11.0</td>
<td>7.2</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>US Carvedilol</td>
<td>12.5-100</td>
<td>45</td>
<td>14.4</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>50</td>
<td>37</td>
<td>18.5</td>
<td>11.4</td>
</tr>
</tbody>
</table>

**EMPHASIS-HF: Primary outcome**

![Graph showing hospitalization rate](image)

**What about Hydralazine and Isordil?**

*The A-HeFT Trial*

- 1050 NYHA III/IV AA pts
- Composite endpt (death, HF hosp, QOL), Terminated early
- Bidil (Hydralazine 37.5 mg + Isordil 20 mg) 2 tablets tid
- 68% at target
- Mean dose 3.8 tablets
- Contemporary bkgd Rx
  - ACEI/ARB 87 %
  - Beta blkers 75 %
  - Spironolactone 40 %
- Adverse events common
  - HA 44%     - Dizziness 29%

![Graph showing reduction in hospitalization](image)

**European Study Group on “Diastolic” Heart Failure**

To diagnose diastolic heart failure, three conditions must be simultaneously satisfied:

1. Signs and symptoms of CHF are present *(Possible)*
2. Left ventricular systolic function is normal or only mildly abnormal at time of diagnosis *(Probable)*
3. Evidence of abnormal LV relaxation, abnormal LV filling, diastolic distensibility, or diastolic stiffness should be present *(Definite)*

**Benefits of Lowering BP**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Average Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>35-40%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>20-25%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>50%</td>
</tr>
</tbody>
</table>

In stage 1 HTN and additional CVD risk factors, achieving a 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated.

**Indications For the Use of Ambulatory Blood Pressure Monitoring**

- White coat hypertension
- Informing equivocal treatment decisions
- Evaluation of nocturnal hypertension
- Evaluation of drug-resistant hypertension
- Determining efficacy of treatment over 24 hours
- Evaluation of symptomatic hypotension
- Evaluation of unusual variability

![Graph showing ambulatory BP monitoring](image)
Spironolactone is Remarkably Effective in Resistant Hypertension

- ΔSBP = 22 (21-23)
- ΔDBP = 9.5 (9-10)
- Mean blood pressure (mm Hg)

- 4th line at investigator discretion
- Median dose 25 mg
- Median f/u 1 year

*1411 ASCOT participants

10 Clues to the Diagnosis of Renal Artery Disease

- Onset of hypertension before age 30 or after the age of 55
- Exacerbation of hypertension
- Malignant hypertension
- Resistant hypertension
- Epigastric bruit
- Unexplained azotemia
- Azotemia on ACE inhibitors or ARB
- Discrepancy in kidney size
- Atherosclerosis elsewhere
- “Flash” pulmonary edema or recurrent CHF

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Internal Carotid Artery Disease: Symptom Status Sets Revascularization Priority

<table>
<thead>
<tr>
<th>Symptomatic disease</th>
<th>Asymptomatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency!</td>
<td>Low stroke risk</td>
</tr>
<tr>
<td>Immediate revascularization</td>
<td>Revascularization requires thoughtful risk:benefit analysis</td>
</tr>
<tr>
<td>Benefit greatest within 2 weeks</td>
<td>Cumulative risk of stroke with medical therapy less than revascularization</td>
</tr>
<tr>
<td>After 12 weeks patient may now be in asymptomatic category</td>
<td>Stroke may be least cardiovascular concern</td>
</tr>
</tbody>
</table>

Obstructive Sleep Apnea

- Present in up to 85% of resistant hypertension cases
- Associated with neurohormonal activation (sympathetic nervous system, aldosterone, endothelin)
- Obesity not required (central, e.g. alcohol)
- Ask about sleep disordered breathing, difficulty sleeping, daytime sleepiness, narcolepsylke factors (awaken feeling paralyzed)
- Sleep study


Aortic Dissection: Indications for Surgery

- Acute
  - Acute Type A Dissection
  - Acute Type B Dissection with
    - Rupture
    - Malperfusion
    - Rapid Expansion
    - Marfan syndrome
- Chronic
  - Type A > 5.5 cm
  - Type A with severe aortic regurgitation
  - Type B > 6.0 cm

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AAA Surveillance & Repair

- AAAs < 4.0 cm: image every 2-3 years
- AAAs 4.0 to 5.4 cm: image every 6 months
- Repair if patients have symptoms
- Repair infrarenal aneurysm ≥ 5.5 cm

AAA Surveillance & Repair

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- Repair if patients have symptoms
- Repair infrarenal aneurysm ≥ 5.5 cm

- Follow size every 2-3 years < 4 cm
### Risk Factors for PAD

- **Decreased Risk Factors:** Smoking, Diabetes, Hypertension, Hypercholesterolemia, C-Reactive Protein
- **Increased Risk Factors:** Smoking, Diabetes, Hypertension, Hypercholesterolemia, Chronic renal insufficiency

### Differential Diagnosis of Exercise-induced Pain

- Peripheral artery disease
- Osteoarthritis of the hip or knee
- Peripheral nerve pain
  - Herniated disc
  - Sciatic nerve
  - Neuropathy (endocrinologic)
- Chronic exertional compartment syndrome
- Venous obstruction
- Muscle spasms/cramps/restless leg syndrome

### Aspirin For Prevention of CVD in Women

- Aspirin (75 to 325 mg/d) in high-risk women
  - If aspirin-intolerant: substitute clopidogrel (I B)
- Aspirin (81 mg daily or 100 mg every other day) in at risk women ≥65 years of age
- Aspirin in at risk women <65 years of age for prevention of ischemic stroke
- Aspirin in optimal risk women <65 years of age

### Aspirin For Prevention of CVD in Men

- Aspirin (75-162 mg daily) if known CHD/ASVD
- Aspirin (100-325 mg daily) following CABG surgery
  - Start within the first 48 hours after surgery to reduce the risk of saphenous vein graft failure.
  - Doses >162 mg/day may be continued for up to one year
- Aspirin (75-162 mg daily) in intermediate risk (10 year risk of CHD >10%) men

### Statins for Prevention of CVD in Women

- Statins for patients with CVD is established
  - Similar benefit in women and men
  - Relative risk reduction ~20–30%
- Statins for women with no CVD is controversial
  - Prior meta-analyses: non-significant
  - RR CHD events 0.87 (0.22–1.68), P=0.17
  - N = 11,435 women

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JUPITER Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

Statins for Prevention of CVD in Women

NEJM 2008;359:2195-2207

Petretta M. Int J Cardiol 2010;138:25

Walsh JM, JAMA 2004;291:2243
CARDIOVASCULAR RISK FACTORS AND VTE (N=63,552 meta-analysis)

**RF**
- Obesity: 2.3
- Hypertension: 1.5
- Diabetes: 1.4
- Cigarettes: 1.2
- High Cholesterol: 1.2

(Stage W. Circulation 2008; 117: 93-102)

RISK FACTORS FOR POOR PROGNOSIS: LABS/ RV

1. Elevated biomarkers (troponin) (European Heart J 2010; 31: 1836)
2. Right ventricular dysfunction: ECHO (Arch Intern Med 2005; 165: 1777)
3. Right ventricular enlargement: 
   - CT—(Circ Cardiovasc Imaging 2010; 3: 491-500)
   - ECHO—(Circulation 2010; 122: 1124)

Clinical evaluation
- Anatomic size of PE
- RV size/ function
- Cardiac biomarkers

Low Risk
- Anticoagulation Alone
  - (Basic)

High Risk
- Anticoagulation + Lysis/Embolectomy
  - (Advanced)

THROMBOLYSIS IN PE REMAINS CONTROVERSIAL

- Evidence for lysis in massive PE consists of 1 RCT with 8 patients.
- Submassive PE thrombolysis trials total < 1,000 patients.
- A European RCT (“PEITHO”) is enrolling 1,000 submassive PE patients. Endpoint: Reduce death/shock from 13% to 8%.

FIBRINOLYSIS FOR PE: AHA PE GUIDELINES 2011

- **Massive PE**: with acceptable risk of bleeding complications
- **Submassive PE**: severe RV dysfunction, or major myocardial necrosis, or worsening respiratory insufficiency, with low risk of bleeding

(Circulation 2011; 123: 1788-1830)

IVC FILTERS FOR PE: AHA PE GUIDELINES 2011

- Contraindications to anticoagulation
- Recurrent PE despite adequate anticoagulation
- Very poor cardiopulmonary reserve, “including those with massive PE”

(Circulation 2011; 123: 1788-1830)
WARFARIN PHARMACOGENOMICS
1. Cytochrome P450 2C9 genotyping identifies mutations associated with impaired warfarin metabolism.
2. Vitamin K receptor polymorphism testing can identify whether patients require low, intermediate, or high doses of warfarin.

(Clin Pharmacol Ther 2010; 87: 572-578)

NOVEL ORAL ANTICOAGULANTS
1. Dabigatran: an oral DTI—twice daily (renal clearance)
2. Rivaroxaban: direct factor Xa inhibitor (renal clearance)—once or twice daily
3. Apixaban: direct factor Xa inhibitor (hepatic clearance)—twice daily
4. Edoxaban: direct factor Xa inhibitor (hepatic clearance)—once daily

(Circulation 2010; 121: 1523-1532)

DOES HYPERCOAGULABILITY PREDICT RECURRENT VTE?
• **Probably:** lupus anticoagulant, protein C or S deficiency
• **No Evidence:** heterozygous Leiden or prothrombin gene mutation

(European Heart Journal 2008; 29: 2276-2315)

ACCP VTE RX DURATION GUIDELINES 8TH EDITION
1. For **provoked** VTE, 3 months of anticoagulation.
2. For **unprovoked** proximal DVT or PE and low bleeding risk, indefinite duration anticoagulation if consistent with patient preference.

(CHEST 2008; 133: 454S)

ACCP VTE RX IN CANCER: GUIDELINES 8TH EDITION
1. At least 3 months of LMWH monotherapy.
2. Then administer LMWH or warfarin as long as the cancer is active.

(CHEST 2008; 133: 454S)

Atrial Fibrillation
• Chaotic atrial electrical activity with high-rate fibrillatory potentials
• Irregularly irregular ventricular complexes
CHADS<sub>2</sub>

| C | Congestive Heart Failure / LVEF | 1 |
| H | Hypertension (>140/90 or Med Rx) | 1 |
| A | Age ≥ 75 years | 1 |
| D | Diabetes Mellitus | 1 |
| S<sub>2</sub> | h/o Stroke / TIA | 2 |

Risk Treatment

0 | Low | Aspirin |
1 | Moderate | ASA or Warfarin |
2 | High | Warfarin |

CHADS<sub>2</sub>-VASc

| C | Congestive Heart Failure / LVEF | 1 |
| H | Hypertension (>140/90 or Med Rx) | 1 |
| A<sub>2</sub> | Age ≥ 75 years | 2 |
| D | Diabetes Mellitus | 1 |
| S<sub>2</sub> | h/o Stroke / TIA / Thromboembolism | 2 |
| V | Vascular disease | 1 |
| A | Age 65-74 years | 1 |
| Sc | Sex category (female gender) | 1 |

0 | Low | Nothing / Aspirin |
1 | Moderate | Warfarin (or ASA) |
2 | High | Warfarin |

PPM Indications include…

- Sinus node dysfunction / symptomatic bradycardia
  - Sinus rate <40 – “reasonable” / “may be considered” to implant in absence of symptoms
  - Tachy/Brady (rapid atrial arrhythmia alternating with sinus brady)
- Symptomatic chronotropic incompetence
- Unexplained syncope with evidence of abnormal sinus func
- Unexplained syncope with (+) CSM (>3 sec asystole)
- AVB with symptoms
  - Enable medication therapy (e.g., beta blockers)
  - High-grade AVB (Mobitz II or 3<sup>rd</sup> degree)
  - Any AVB resulting in R-R >3.0 seconds in sinus (5 seconds, AF), escape rate <40, escape below AVN
  - Prolonged HV (>100 ms) or infra-His block at EPS
- Permanent pacing should be avoided if cause of bradycardia is transient...
  - Lyme disease, Increased vagal tone, Drug toxicity

Hypertrophic Cardiomyopathy

- Predictors of risk –
  - Abnormal blood pressure response to exercise
  - Family hx cardiac arrest
  - History of VT / cardiac arrest
  - Unexplained syncope
  - NVST on Holter monitor
  - Severe wall thickness (≥ 30mm)

Defibrillators

- Secondary Prevention
  - History of cardiac arrest
  - History of sustained VT (no requirement of hemodynamic instability!!)
  - Syncope and (+) EPS
- Primary Prevention – all presume optimal medical rx
  - EF 35%, Class II/III, >40 days post MI
    - New dx nonischemic – 3 month requirement
  - EF 30%, ischemic CMP, >40d post-MI, >90d post revasc
  - EF 40%, ischemic CMP, NSVT, (+) EPS
  - Unexplained syncope with significant LV dysfunction
  - Genetic syndrome with high risk features
- All indications assume >1 yr life expectancy with “acceptable functional status”
Severe Aortic Stenosis
Surgical Treatment

<table>
<thead>
<tr>
<th>Indication</th>
<th>ACC/AHA1</th>
<th>ESC2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2006</td>
<td>2007</td>
</tr>
<tr>
<td>Symptoms</td>
<td>I(B)</td>
<td>I(B)</td>
</tr>
<tr>
<td>Need for CABG/Ao Surgery</td>
<td>I(C)</td>
<td>I(C)</td>
</tr>
<tr>
<td>LVEF &lt; 0.50</td>
<td>I(C)</td>
<td>I(C)</td>
</tr>
<tr>
<td>Abnormal ETT</td>
<td>IIb(C)</td>
<td>IIa or b(C)</td>
</tr>
<tr>
<td>Rapid Progression/Delay</td>
<td>IIb(C)</td>
<td>IIa(C)</td>
</tr>
<tr>
<td>AVA &lt; 0.6cm²</td>
<td>IIb(C)</td>
<td>-----</td>
</tr>
<tr>
<td>Severe LVH (≥15mm)</td>
<td>-----</td>
<td>IIb(C)*</td>
</tr>
</tbody>
</table>

1. Bonow R et al. J Am Coll Cardiol 2006;48;148

Indications for AVR
Severe AR
Class I

- Symptoms
- Mild-moderate LV dysfunction (EF < 0.50)
- Need for other cardiac or aortic surgery

ACC/AHA Valve Guidelines 2006

Aortic Regurgitation
Vasodilator Therapy

Chronic MR
Medical Therapy

No role for vasodilator therapy in asymptomatic, normotensive patients with chronic severe MR and normal LV function

Infective Endocarditis Prophylaxis
AHA Guidelines 2007

- Prophylaxis for dental procedures is recommended only for patients with the highest risk of adverse outcomes from IE.
  - Prosthetic valve
  - Previous IE
  - Congenital heart disease*
  - Cardiac transplant survivor with VHD

- Prophylaxis is not recommended for GI or GU procedures.

Circulation 2007. Published online 4/19/07.
SYNDROMES ASSOCIATED WITH CONGENITAL HEART DISEASE

• DOWN’S: AV Canal, VSD, Primum ASD
• TURNER’S: Coarctation, AS
• NOONAN’S: PS
• WILLIAM’S: SVAS, PS
• HOLT-ORAM: Secundum ASD
• MARFAN: Aortic aneurysm, MVP