Updates in Cardiology

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I have no actual or potential conflicts of interest to disclose.
Updates in Cardiology - 2016

- Use of DOACs in obesity • March 2016
- Amiodarone vs Lidocaine in Cardiac Arrest • May 2016
- Andexanet Alfa for Acute Major Bleeding • August 2016
- Transcatheter Aortic Heart Valve Thrombosis • August 2016
- New Pharmacological Therapy for Heart Failure Guidelines • September 2016
Objectives

• Describe outcomes of amiodarone versus lidocaine in out-of-hospital cardiac arrest. *(How the presented topic impacts patient outcomes)*

• Direct Oral Anticoagulants *(Recommend therapeutic means to achieve clinical endpoints)*
  o Explain mechanism of andexanet alfa for reversal of Xa inhibitors.
  o Assess limitations of current literature surrounding direct oral anticoagulants in obesity.

• Differentiate between current clinical guideline recommendations for TAVR antiplatelet management, and new concerns for transcatheter aortic valve thrombosis. *(Review evidence based guidelines and best practices described)*

• New Pharmacological Therapy for Heart Failure
  o Evaluate clinical scenarios where new agents, valsartan/sacubitril and ivabradine, may improve patient outcomes. *(Identify two clinical endpoints of the presented topic)*

*Italicized objective summaries are General NDSHP Drug Therapy Case Series Objectives*
Abbreviations

• ACCF/AATS/SCAI/STS
• AF: Atrial fibrillation
• ACC/AHA/AFSA
• ARNI: Angiotensin receptor-neprilysin inhibitor
• BMI: Body Mass Index
• BNP: B-type natriuretic peptide
• CCS: Canadian Cardiovascular Society
• DAPT: Dual Antiplatelet Therapy
• DOACs: Direct Oral Anticoagulants
• ESC/EACTS: European Society of Cardiology/European Association for Cardiothoracic Surgery
• HFrEF: Heart Failure with Reduced Ejection Fraction
• LVEF: Left Ventricular Ejection Fraction
• MACCE: Major Adverse Cardiac and Cerebrovascular events
• NYHA: New York Heart Association
• PK/PD: Pharmacokinetics/Pharmacodynamics
• SAPT: Single antiplatelet therapy
• SAVR: Surgical Aortic Valve Replacement
• SSC of the ISTH: Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis
• STS: Society of Thoracic Surgeons
• TAVI: Transcatheter aortic valve implantation
• TAVR: Transcatheter aortic valve replacement
• VTE: Venous Thromboembolism
Amiodarone, Lidocaine, or Placebo for Out-of-Hospital Cardiac Arrest

New England Journal of Medicine
May 5, 2016
Out-of-Hospital Cardiac Arrest

- Accounts for 300,000 deaths per year in N. America\(^1\)
  - May have ventricular fibrillation or pulseless electrical activity as the primary rhythm
  - Rate of survival with good neurological function averages 8.5% \(^1\)
- Amiodarone vs placebo, 1999 \(^2\)
  - Amiodarone vs placebo was administered after 3 or more shocks were administered
  - Amiodarone group was more likely to survive to hospital admission (44% vs 34%, p=0.03).
- Amiodarone vs lidocaine, 2002 \(^3\)
  - Amiodarone vs lidocaine were administered for refractory ventricular fibrillation after 3 shocks, one dose of epinephrine, and one further shock.
  - Amiodarone vs lidocaine group was more likely to survive to hospital admission (22.8% vs 12%, p=0.009)

**Start CPR**
- Give oxygen
- Attach monitor/defibrillator

2 minutes

**Check Rhythm**

- If VF/VT Shock

**Drug Therapy**
- IV/IO access
- Epinephrine every 3-5 minutes
- Amiodarone for refractory VF/VT

Consider Advanced Airway
- Quantitative waveform capnography

Treat Reversible Causes

**Return of Spontaneous Circulation (ROSC)**

**Post-Cardiac Arrest Care**

**Continuous CPR**

**Monitor CPR Quality**

**Continuous CPR**
Amiodarone, Lidocaine, or Placebo for Out-of-Hospital Cardiac Arrest

- Randomized, double blinded, placebo controlled, pre-hospital trial
- Included 3000 patients with non-traumatic, out-of-hospital cardiac arrest
  - Shock refractory ventricular fibrillation or pulseless ventricular tachycardia
- Amiodarone 300 mg vs lidocaine 120 mg vs normal saline

Outcomes

• No significant differences in primary and secondary outcomes:
  o Survival to discharge and modified Rankin score ≤ 3
  o No significant difference between either treatment vs placebo or amiodarone vs lidocaine

• Exploratory analysis
  o Admitted to hospital
    • Significantly higher rates if received amiodarone or lidocaine vs placebo
    • No differences when amiodarone vs lidocaine

Interpretation and application to practice

• Heterogeneity of treatment effect existed based on if the arrest was witnessed or not
  o If witnessed, amiodarone and lidocaine were associated with higher survival to hospital discharge

• Placebo group more likely to require additional antiarrhythmic, and greater number of shocks

• Estimated survival rates differed less than anticipated, possibly suggesting trial is underpowered to detect a difference

Direct Oral Anticoagulants

Andexanet Alfa for Acute Major Bleeding – August 2016
Use of DOACs in obesity, ISTH recommendations – March 2016
Xa inhibitors

• Approved indications:
  o Stroke prevention in non-valvular atrial fibrillation
    • Rivaroxaban, Apixaban, Edoxaban
  o VTE treatment
    • Rivaroxaban, Apixaban, Edoxaban
  o VTE prevention
    • Rivaroxaban, Apixaban

• Compared with warfarin:
  o DOACs had lower rates of major bleeding in primary atrial fibrillation trials\(^1\)
    • Reduced relative risk of intracranial bleeding
    • Although higher rates of major gastrointestinal bleeding

• Problems exist:
  o No specific antidote for Xa inhibitors
  o Dosing in obesity
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

New England Journal of Medicine
August 30, 2016
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

• Andexanet Alfa
  o Reverses direct and indirect factor Xa inhibitors
  o Recombinant, modified human factor Xa decoy
    • Binds to Factor Xa inhibitors
    • Does not have intrinsic catalytic activity

• ANNEXA-4
  o First study in patients with acute major bleeding
  o Ongoing, multicenter, prospective, open label study
  o Patient population:
    • 67 patients, average age: 77 years
    • Major bleeding
      o Gastrointestinal bleeding: 33 patients
      o Intracranial bleeding: 28 patients
      o Other bleeding: 6 patients

## Xa Inhibitors in Obesity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Weight categories</th>
<th>Number of obese patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>RE-COVER I</td>
<td>≥ 100 kg</td>
<td>502/2539 (20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI ≥ 35</td>
<td>306/2539 (12)</td>
</tr>
<tr>
<td></td>
<td>RE-COVER II</td>
<td>&gt; 100 kg</td>
<td>438/1280 (34.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI &gt; 35</td>
<td>302/1280 (23.6)</td>
</tr>
<tr>
<td></td>
<td>RE-LY</td>
<td>≥ 100 kg</td>
<td>3099/18 113 (17.1)</td>
</tr>
<tr>
<td></td>
<td>RE-MEDY</td>
<td>≥ 100 kg</td>
<td>299/1430 (20.9)</td>
</tr>
<tr>
<td></td>
<td>RE-SONATE</td>
<td>≥ 100 kg</td>
<td>122/681 (17.9)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN DVT</td>
<td>&gt; 100 kg</td>
<td>245/1731 (14.2)</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN PE</td>
<td>&gt; 100 kg</td>
<td>345/2419 (14.3)</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN EXTENSION</td>
<td>&gt; 100 kg</td>
<td>85/602 (14.1)</td>
</tr>
<tr>
<td></td>
<td>ROCKET-AF</td>
<td>&gt; 90 kg</td>
<td>2035/7131 (28.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI &gt; 35</td>
<td>972/7131 (13.6)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>AMPLIFY</td>
<td>≥ 100 kg</td>
<td>522/2691 (19.4)</td>
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<tr>
<td></td>
<td></td>
<td>BMI &gt; 35</td>
<td>349/2691 (13.0)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>ARISTOTLE</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TIMI 48</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HOKUSAI VTE</td>
<td>&gt; 100 kg</td>
<td>611/4118 (14.8)</td>
</tr>
</tbody>
</table>

Martin, J of Thrombosis and Haemostasis, 2016
Use of direct oral anticoagulants in obesity: Guidance from SSC of the ISTH

• Recommendations:
  o Standard dosing of DOACs in patients with:
    • BMI ≤ 40 kg/m²
    • Weight ≤ 120 kg
    • For indications including VTE treatment, VTE prevention, and prevention of ischemic stroke in non-valvular atrial fibrillation
  o DOACs should not be used in patients with:
    • BMI > 40 kg/m² or weight > 120 kg
      o Limited clinical data
      o Available PK/PD suggests decreased drug exposure, lower peak concentrations, and shorter half-lives

Martin, J of Thrombosis and Haemostasis, 2016
Transcatheter Aortic Valve Replacement

- Treatment technique for patients with severe aortic stenosis, who are not candidates for open-heart surgery
  - TAVR can improve symptoms and extend life
  - Although, rate of stroke higher in TAVR group compared with medical therapy²
    - First 30 days: ischemic events 6.7% vs 1.7%, p=0.02
    - Beyond 30 days: hemorrhagic strokes 2.2% vs 0.6%, p=0.16

Available Transcatheter Valves

Edwards SAPIEN

SAPIEN XT

CoreValve

Webb, J Am Coll Cardiol 2012;60:483–92
TAVR Guideline Recommendations

- AHA/ACC Guideline for Management of Patients with Valvular Heart Disease, 2014
  1. TAVR is recommended if patients have (1, B):
     - An indication for aortic valve replacement for aortic stenosis
     - Prohibitive surgical risk
     - Predicted post-TAVR survival > 12 months
## Antithrombotic Therapy Following TAVR

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Post-procedural antithrombotic therapy if indication for anticoagulation (AF)</td>
<td>Aspirin 75-100 mg/day + clopidogrel 75 mg/day for 6 months</td>
<td>Aspirin 80 mg/day + thienopyridine for 1-3 months</td>
<td>Aspirin 81 mg/day + clopidogrel 75 mg/day for 3-6 months</td>
<td>Low-dose aspirin + a thienopyridine early after TAVR</td>
</tr>
<tr>
<td>Long-term antithrombotic therapy</td>
<td>Lifelong aspirin 75-100 mg daily (Class IIb; LOE: C)</td>
<td>Low-dose aspirin indefinitely</td>
<td>Aspirin 81 mg/day indefinitely</td>
<td>Low-dose aspirin indefinitely</td>
</tr>
</tbody>
</table>

Lung B, European Heart Journal, 2014
Questions exist...

- Type of valve variations:
  - Sapian Valves\(^1\)
    - PARTNER trial: 6 months of dual antiplatelet therapy
  - CoreValve Study \(^2\)
    - 3 months of dual antiplatelet therapy
- Ussia, 2011\(^3\) – Patients randomized to clopidogrel/ASA or ASA alone
  - No significant differences in major adverse cardiac events at 30 days and 6 months

3: Ussia, Am J Cardiology, 2011
Dual vs Single Antiplatelet Therapy

Stroke (major, minor and TIA)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SAPT</th>
<th>DAPT</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Durand 2014</td>
<td>2</td>
<td>91</td>
<td>2</td>
</tr>
<tr>
<td>Poliacikova 2013</td>
<td>2</td>
<td>91</td>
<td>2</td>
</tr>
<tr>
<td>Ussia 2011</td>
<td>3</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>221</td>
<td>189</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.44$, df = 2 (P = 0.80); $I^2 = 0$

Test for overall effect: $Z = 0.05$ (P = 0.96)

Death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SAPT</th>
<th>DAPT</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Durand 2014</td>
<td>8</td>
<td>91</td>
<td>7</td>
</tr>
<tr>
<td>Poliacikova 2013</td>
<td>3</td>
<td>91</td>
<td>4</td>
</tr>
<tr>
<td>Ussia 2011</td>
<td>4</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>221</td>
<td>189</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.99$, df = 2 (P = 0.61); $I^2 = 0$

Test for overall effect: $Z = 0.28$ (P = 0.78)
## Dual vs Single Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SAPT Events</th>
<th>SAPT Total</th>
<th>DAPT Events</th>
<th>DAPT Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durand 2014</td>
<td>5</td>
<td>91</td>
<td>24</td>
<td>91</td>
<td>53.4%</td>
<td>0.21 [0.08, 0.52]</td>
<td></td>
</tr>
<tr>
<td>Poliacikova 2013</td>
<td>7</td>
<td>91</td>
<td>9</td>
<td>58</td>
<td>24.5%</td>
<td>0.50 [0.20, 1.26]</td>
<td></td>
</tr>
<tr>
<td>Stabile 2011</td>
<td>5</td>
<td>60</td>
<td>6</td>
<td>60</td>
<td>13.4%</td>
<td>0.83 [0.27, 2.58]</td>
<td></td>
</tr>
<tr>
<td>Ussia 2011</td>
<td>3</td>
<td>39</td>
<td>4</td>
<td>40</td>
<td>8.8%</td>
<td>0.77 [0.18, 3.22]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>281</strong></td>
<td></td>
<td><strong>249</strong></td>
<td></td>
<td>100.0%</td>
<td><strong>0.41 [0.25, 0.69]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>20</td>
<td></td>
<td>43</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Heterogeneity: Chi² = 4.49, df = 3 (P = 0.21); I² = 33%

Test for overall effect: Z = 3.41 (P = 0.0006)
Subclinical Leaflet Thrombosis

• Reduced aortic-valve leaflet motion after TAVR\textsuperscript{1}
  o 22 of 55 TAVR patients (40%)
    • Reduced leaflet motion less prevalent among patient on anticoagulation compared to dual antiplatelet therapy (0 of 8 patients versus 11 of 20 patients [55%], \( p=0.01 \))

• Transcatheter heart valve thrombosis\textsuperscript{2}
  o \( n=405 \) at 1-3 month follow-up
  o Incidence of valve thrombosis: 7%
    • 18% of these patients with thrombosis formation developed clinical obstructive thrombosis
  o No warfarin post valve implantation was independently associated with an increased risk of valve thrombosis
  o Treatment with warfarin reversed valve thrombosis findings and valve function

\textsuperscript{1} Makker, N Engl J Med, 2015
\textsuperscript{2} Hansson, JACC, 2016
TAVR for Intermediate Surgical Risk Patients

- TAVR versus surgical aortic valve replacement\(^1\)
  - Intermediate risk:
    - STS risk score of 4-8%
    - STS < 4% if conditions not represented in the risk calculation existed
  - Composite endpoint of death and disabling stroke at 2 years
    - Non significant differences – non-inferiority trial
- FDA granted approval for subsequent study in low risk populations
  - Currently enrolling
  - STS risk score < 4%

TAVR for Low Risk Patients?

• Italian OBERVANT registry, 2016¹
  o Outcomes at 3 years

<table>
<thead>
<tr>
<th></th>
<th>SAVR (n=355)</th>
<th>TAVR (n=355)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>83.4%</td>
<td>72.0%</td>
<td>0.0015</td>
</tr>
<tr>
<td>Freedom from MACCE</td>
<td>80.9%</td>
<td>67.3%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

• Widening TAVR patient population intensifies urgency to:
  o Define patient characteristics favorable for SAVR vs TAVR
  o Solidify antiplatelet/anticoagulant therapeutic goals
  o Determine clinical significance of subclinical leaflet thrombosis

Rosato, Circ Cardiovasc Interv, 2016
New Pharmacological Therapy for Heart Failure: ACC/AHA/AFSA Focused update

American Journal of Cardiology
September 2016
New Pharmacological Therapy for Heart Failure: ACC/AHA/AFSA Focused update

- Angiotensin receptor-neprilysin inhibitor (ARNI)
  - Valsartan/Sacubitril
- Sinoatrial node modulator
  - Ivabradine
Angiotensin receptor-neprilysin inhibitor

LCZ696 (ARNI)

Valsartan

- Angiotensin II
- Angiotensin I

- AT, R

- Increased sympathetic tone
- Vasoconstriction
- Increased blood pressure
- Oxidative stress

- Ventricular hypertrophy
- Remodelling
- Increased Fibrosis
- Reduced cardiac output

- Increased Aldosterone
- Fluid and water retention

Sacubitril

- LBQ657 (active metabolite)

- ANP BNP CNP
- Adrenomedullin
- Substance P
- Bradykinin
- Others

- Neprilysin

- Decreased sympathetic tone
- Vasodilatation
- Lower blood pressure

- Decrease ventricular hypertrophy
- Decrease fibrosis
- Anti-remodelling
- ? Reduce myocardial injury

- Decreased Aldosterone
- Diuresis
- Natriuresis

Bavisha, European Heart Journal, 2015
• Dosing:
  o Staring dose:
    • In patients taking > 10 mg/day enalapril or > 160 mg/day of valsartan or equivalent dose of another ACE inhibitor or ARB
      o Sacubitril 49 mg/valsartan 51 mg twice daily.
  o Escalating doses:
    • Double the dose after 2-4 weeks to the target of sacubitril 97 mg/valsartan 103 mg twice daily
  o Reduced dose:
    • Initiating at sacubitril 24 mg/valsartan 26 mg BID can be considered if:
      o Previously not taking or low dose ACE/ARB therapy
      o Severe renal impairment (eGFR < 30 ml/min/1.73m2)
      o Moderate hepatic impairment
Sacubitril/valsartan (Entresto®) Dosing

• Concomitant use of ACE inhibitor is contraindicated
  o 36 hour washout period is required before initiating sacubitril/valsartan

• Dosing considerations:
  o Difference in bioavailability between valsartan salt formulations
    • Valsartan (Entresto) 103 mg = valsartan (Diovan) 160 mg
  o Dosing in clinical trials was based on total of both components
    • 200 mg = 97/103 mg
Guideline Recommendations

• Patients with symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. ¹ (I, BR)

• ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.¹,²,³ (III Harm)
  o Oral neprilysin inhibitors in combination with ACE inhibitors can result in angioedema

• ARNI should not be administered to patients with a history of angioedema.¹ (III Harm)

2: Packer, Circulation, 2002
3: Kostis, Am J Hypertension, 2004
Angiotensin-Nephrilysin Inhibition vs Enalapril in Heart Failure

• Double-blinded, randomized trial
  o Included single-blind screening phase with each drug prior to randomization to ensure an acceptable side effect profile
  o n=8399

• Patients included:
  o Symptomatic patients with HFpEF (NYHA class II, III, or IV)
  o EF of 40% or less
    • Changed to 35% by amended protocol mid study
  o BNP >150 pg/ml OR BNP >100 pg/ml if patient had been hospitalized for HF in previous 12 months
  o Patients taking any dose of ACE inhibitor or ARB were considered
    • Were required to tolerate a stable dose of beta-blocker and ACEi/ARB equivalent to at least of enalapril 10 mg daily for at least 4 weeks prior

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization for worsening heart failure</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Angiotensin-Neprilysin Inhibition vs Enalapril in Heart Failure

• Limitations:
  o “Drug run in” study design is controversial
    • 2079 patients excluded during this 4 week period
  o Amended study protocol with modifications to inclusion criteria
    • EF inclusion changed from 40% to 35%
  o Enalapril was dosed up to 10 mg BID vs heart failure goal dose of valsartan
    • Some of efficacy of new treatment related to more significant blood pressure reduction in treatment group?

Ferrari, Intern Emerg Med, 2015
Ivabradine Mechanism

Sinus node
The pacemaker of the heart

Ivabradine selectively inhibits the I f current in the sinus node

Ivabradine reduces the slow diastolic depolarization phase

Heart rate reduction

ΔHR

0 mv
-40 mv
-70 mv
Ivabradine 5 mg bid

- Check resting heart rate
  - 2 weeks

- Check resting heart rate

  - heart rate > 60 bpm
    - Ivabradine 7.5 mg bid

  - heart rate 50-60 bpm
    - Ivabradine 5 mg bid

  - heart rate < 50 bpm
    - Ivabradine 2.5 mg bid

- or symptoms related to bradycardia

**Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dose reduction.**

**Older people:** In patients aged 75 years or more, a lower starting dose should be considered (2.5 mg twice daily) before up titration if necessary.
Ivabradine (Corlanor®)

• Unique side effects:
  o 14.5% of patients experience luminous phenomena
    • Brightness in a fully maintained visual field
    • Due to blockage of the Ih ion channels in the retina
    • Symptoms are mild and reversible, resulted in discontinuation of about 1% of patients in clinical trials

• Contraindications:
  o Acute decompensated heart failure
  o Sick sinus syndrome, sinoatrial block, or 3rd degree AV block unless a functioning pacemaker is in place
  o Severe hepatic impairment

• Drug interactions:
  o 3A4 inducers and inhibitors
Sinoatrial node modulator: Ivabradine

- Guideline recommendation (COR IIa, LOE B-R): can be beneficial to reduce HF hospitalization for patients with:
  - Symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF <35%)
  - And receiving a beta blocker at maximum tolerated dose
  - And in sinus rhythm with a heart rate of 70 bpm or greater at rest

Yancy, Circulation. 2016
Ivabradine and outcomes in chronic HF (SHIFT)

- Randomized, double-blind, placebo-controlled trial
  - N=6558, 677 centers in 37 countries
- Inclusion:
  - Sinus rhythm with resting HR > 70 bpm
  - Stable, symptomatic chronic heart failure, with a hospitalization for HF within previous 12 months AND left ventricular EF < 35%
  - Required to be at optimum and stable background medication treatment for at least 4 weeks

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<tr>
<th></th>
<th>Ivabradine (n=3241)</th>
<th>Placebo (n=3264)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death or hospital admission for worsening heart failure</td>
<td>793 (24%)</td>
<td>937 (29%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mortality endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>503 (16%)</td>
<td>552 (17%)</td>
<td>0.092</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>449 (14%)</td>
<td>491 (15%)</td>
<td>0.128</td>
</tr>
<tr>
<td>Other endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission for worsening HF</td>
<td>514 (16%)</td>
<td>672 (21%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Ivabradine and outcomes in chronic HF (SHIFT)

- Limitations:
  - Number of patients on goal beta-blocker therapy
    - Patients on goal therapy: 23%
    - Patients receiving 50% or more of target dose: 49%
  - Subgroup analysis: benefit of ivabradine diminished in patients with lower baseline heart rates (<77 beats per minute)

Swedberg, Lancet, 2010
Heart Failure Guideline
Conclusions

• Sacubitril/valsartan
  o Patients tolerating an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality
  o Recognizing flaws in clinical trial
    • Amended protocol
  o Cost associated with new medication may be limiting factor

• Ivabradine
  o May be beneficial to reduce hospitalizations
    • Patients should be optimized on beta-blocker first
Assessment Question #1:

JD is a 62 year old male, who was admitted to your intensive care unit with hemodynamic instability and right heart strain on ECHO. He was diagnosed with a pulmonary embolism and has been on a heparin infusion with therapeutic aPTTs for the past 48 hours. Providers are asking for your opinion on long term anticoagulation:

- Scr: 0.9
- Weight: 135 kg

A: Apixaban 10 mg BID for the first 7 days, followed by 5 mg BID. No clinical differences have been seen in obese patients, no matter how extreme of weight.

B: Apixaban 10 mg TID: dose should be increased given weight, and shortened half life in extreme obesity

C: Given extreme weight, ISTH guidelines would suggest warfarin in patients > 120 kg.
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Assessment Question #2:

BG is 65 year old female with systolic heart failure (EF = 30%). She has been started on lisinopril 10 mg daily and metoprolol succinate 50 mg daily. She is tolerating these medications well, and is coming into your clinic for a check up, and to optimize her medication therapy.

- BP: 109/60 mmHg
- HR: 67 bpm
- Renal function: stable at baseline SCr of 0.9

To optimize BG’s medication regimen, you decide to:

A: Continue to increase lisinopril and metoprolol to goal
B: Add ivabradine to further lower HR, which has morbidity benefits in preventing hospital admissions.
C: Discontinue lisinopril, as blood pressure is getting low. Optimize metoprolol dose for better heart rate and blood pressure control.
D: Optimize dose of lisinopril as blood pressure allows in the future. Increase dose of metoprolol. Ivabradine should not be started until metoprolol optimized and if HR still > 70 bpm.
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References

• Martin K, et al. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J of Thrombosis and Haemostatis. 2016; 14: 1308-1313