Learning Objectives

This presentation will address the following issues:

• Beta blockers and cocaine
• Carvedilol for elevated blood pressure in heart failure
• ACE inhibitors and ARBs in coronary artery disease
• Aspirin vs. oral anticoagulation in older patients with atrial fibrillation

Case #1

AB is a 55 year-old man with a history of HFrEF (EF 30%) admitted with worsening shortness of breath and weight gain over the last several weeks’ duration. Shortly after admission, urine toxicology results are positive for cocaine. After four days of diuresis, the team plans to send AB home and is developing a discharge regimen. The intern asks for your recommendation regarding an alternative to beta blockers since they are contraindicated in this patient. What do you do?

A. Use spironolactone instead based on the RALES trial.
B. Use labetalol due to its effects on alpha receptors.
C. Use diltiazem to prevent cocaine-induced vasospasm.
D. Any evidence-based beta blocker would be acceptable.

EF = ejection fraction; HFrEF = heart failure with reduced ejection fraction
Evidence of an Interaction?

- Mechanism hypothesized from a single case report\(^1\)
- Most evidence is derived from animal models, and almost always utilized the non-selective beta blocker propranolol
- Vasospasm in early catheterization studies has been challenged by more recent data, including studies involving direct administration of cocaine\(^2\)

Evidence of an Interaction? (Continued)

- Beta blockers with \(\alpha\) effects may exert favorable hemodynamic changes\(^1,2\)
- When a myocardial infarction is observed, it is almost always accompanied by thrombus formation\(^3\)
- Retrospective studies in the emergency department indicate that beta blockers may even be helpful in this setting\(^4,5\)

### Effects of IV Cocaine Administration

Cardiac catheterization study among chronic cocaine abusers (n=6)

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Baseline</th>
<th>Cocaine</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 ± 9</td>
<td>110 ± 23</td>
<td>0.007</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>3.4 ± 0.7</td>
<td>5.5 ± 1.1</td>
<td>0.0005</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>110 ± 9</td>
<td>112 ± 11</td>
<td>0.05</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne∙sec/cm²)</td>
<td>2492 ± 578</td>
<td>1721 ± 357</td>
<td>0.003</td>
</tr>
<tr>
<td>Coronary sinus flow (ml/min)</td>
<td>233 ± 67</td>
<td>411 ± 232</td>
<td>0.09</td>
</tr>
<tr>
<td>Coronary vascular resistance (dyne∙sec/cm²)</td>
<td>37.66 ± 14.48</td>
<td>29.72 ± 17.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Coronary arterial diameter (mm)</td>
<td>2.28 ± 0.31</td>
<td>2.25 ± 0.41</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### Emergency Department Studies

Two recent retrospective studies comparing cocaine users who did or did not receive beta blockers

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Beta blocker</th>
<th>No beta blocker</th>
<th>OR (95% CI)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Datillo, et al(^1)</td>
<td>Myocardial infarction</td>
<td>6%</td>
<td>26%</td>
<td>0.17 (0.04 – 0.80)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>In-hospital mortality</td>
<td>1.7%</td>
<td>4.5%</td>
<td>0.22 (0.02 – 2.41)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Rangel, et al(^2)</td>
<td>All-cause death</td>
<td>12%</td>
<td>15%</td>
<td>0.53 (0.26 – 1.08)</td>
<td>0.080</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular death</td>
<td>NR</td>
<td>NR</td>
<td>0.29 (0.09 – 0.98)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Managing the Controversy

- Not enough evidence to recommend in all patients (e.g., young, no risk factors)
- Benefit likely outweighs risks in those with established disease or risk factors
- Patients should be provided with therapeutic options and should choose
- Beta blockers with α effects may alleviate liability concerns

Case #1

AB is a 55-year-old man with a history of HFrEF (EF 30%) admitted with worsening shortness of breath and weight gain over the last several weeks. Shortly after admission, urine toxicology results are positive for cocaine. After four days of diuresis, the team plans to send AB home and is developing a discharge regimen. The intern asks you to decide if beta blockers will be acceptable. What do you do?

A. Use spironolactone instead based on the RALES trial.
B. Use labetalol due to its effects on alpha receptors.
C. Use diltiazem to prevent cocaine-induced vasospasm.
D. Any evidence-based beta blocker would be acceptable.

Case #2

JS is a 60-year-old woman with a history of HFrEF who is admitted with CAP. Her condition improves after antibiotics. She takes the following medications for HFrEF: lisinopril 40 mg daily, metoprolol succinate 200 mg once daily, spironolactone 25 mg, and furosemide 40 mg twice daily. During her admission, her SBP ranges 140–150 mmHg. Your student suggests changing metoprolol to carvedilol 25 mg twice daily due to its α1-blocking effects. What should you do?

A. Make the change to carvedilol 25 mg twice daily.
B. Increase the metoprolol succinate to 200 mg twice daily instead.
C. Change the lisinopril to sacubitril/valsartan instead.
D. Add chlorthalidone 25 mg once daily instead.
Heart Failure and α Receptors

- In V-HeFT, the α-blocker prazosin failed to improve mortality (shown left)\(^1\)
- In ALL-HAT, the α-blocker arm (doxazosin) was stopped early due to a 2x increase in incident heart failure\(^2\)
- In BEST, bucindolol, a beta blocker with α\(_1\) blocking effects was stopped early due to futility\(^3\)
- Recent studies indicate that α\(_1\) stimulation may be cardioprotective\(^4\)

Heart Failure and α Receptors (Continued)

- In patients with HFrEF (n=36), carvedilol failed to inhibit α\(_1\) receptors as measured by lower extremity vascular conduction or vasoconstrictor response\(^1\)
- Similar results observed when comparing normal (n=14) vs. HFrEF patients (n=25)\(^2\)

Putting it all together

- The α\(_1\) effects of carvedilol may make it more tolerable at initiation
- However, the effects of carvedilol on α\(_1\) dissipate with time
- Although carvedilol is an appropriate choice for patients with HFrEF, the oft-quoted pearl that it is better for hypertensive patients should be re-examined
- Changing patients from other evidence-based beta blockers for this reason wastes drug, requires another copay, and may add unnecessary complexity
**Case #2**

KT is a 55 year-old woman who presented with unstable angina, now s/p DES. She is a 55 year-old woman who presented with unstable angina, now s/p DES. She takes aspirin 81 mg once daily, ticagrelor 90 mg twice daily, atorvastatin 80 mg once daily, metoprolol tartrate 50 mg twice daily, and nitroglycerin SL tablets PRN. Vitals include SBP 124/82 mmHg and HR 74 bpm. The resident is preparing her discharge medications and says “I want to make sure I get all the checkboxes. What ACE inhibitor should we start her on?” What do you recommend?

A. Candesartan 8 mg because ARBs are better than ACE inhibitors in ASCVD.

B. Lisinopril 5 mg once daily.

C. Change the lisinopril to sacubitril/valsartan instead.

D. This patient doesn’t have a compelling indication for an ACE inhibitor.

**Case #3**

JS is a 50 year-old woman with a history of HFrEF who is admitted with CAP. Her condition improves after antibiotics. She presents her prescriptions for HFrEF: lisinopril 40 mg daily, metoprolol succinate 200 mg twice daily, spironolactone 25 mg, and atorvastatin 80 mg once daily. At admission, her SBP ranges 140-150 mmHg. Her echocardiogram indicates an EF of 55% and she has no symptoms of heart failure. She takes aspirin 81 mg once daily, ticagrelor 90 mg twice daily, atorvastatin 80 mg once daily, metoprolol succinate 200 mg once daily, and nitroglycerin SL tablets PRN. Vitals include SBP 140-150 mmHg and HR 74 bpm. The resident is preparing her discharge medications and says “I want to make sure I get all the checkboxes. What ACE inhibitor should we start her on?” What do you recommend?

A. Give enalapril 2.5 mg once daily.

B. Increase the metoprolol succinate to 200 mg twice daily instead.

C. Change the metoprolol to carvedilol instead.

D. Add chlorthalidone 25 mg once daily instead.

**SAVE**

Patients with acute coronary syndrome and asymptomatic left ventricular dysfunction (n = 2231)

**ISIS-4**

Patients with acute coronary syndrome (n = 58,050)

- Benefits more modest despite 50,000 patients (but only assessed weeks)
- Some clinical worsening in patients with low blood pressure at baseline
HOPE vs. PEACE

Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>HOPE1 (n=9297)</th>
<th>PEACE2 (n=8290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received PCI</td>
<td>17.8%</td>
<td>41.5%</td>
</tr>
<tr>
<td>Received CABG surgery</td>
<td>25.8%</td>
<td>39%</td>
</tr>
<tr>
<td>Had diabetes mellitus</td>
<td>38.5%</td>
<td>17%</td>
</tr>
<tr>
<td>On antplatelet therapy</td>
<td>76%</td>
<td>90.5%</td>
</tr>
<tr>
<td>On beta blocker</td>
<td>39.5%</td>
<td>60%</td>
</tr>
<tr>
<td>On lipid-lowering therapy</td>
<td>28.6%</td>
<td>70%</td>
</tr>
</tbody>
</table>

ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction

Endpoints

Nonfatal MI, stroke, or CV death (HOPE endpoint)

HOPE placebo

HOPE ramipril

PEACE placebo

ACE Inhibitors and ARBs after ACS

- Should use in patients with an ejection fraction < 40%, hypertension, diabetes mellitus, or chronic kidney disease
- Should use in other high-risk patients (e.g., risk factors not adequately controlled, not re-vascularized)
- May be reasonable short-term in lower risk patients if benefits outweigh risks of adverse effects
- Unlikely to provide benefit in low-risk patients with stable coronary disease

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker

ASCVD, atherosclerotic; MI, myocardial infarction

References:
Case #3
KT is a 55 year-old woman who presented with unstable angina. She is a 55 year-old woman who presented with unstable angina, now s/p DES. She quit smoking 2 years ago and has a history of hypertension. Her echo indicates an EF of 55% and she has no symptoms of heart failure. She takes aspirin 81 mg once daily, ticagrelor 90 mg twice daily, atorvastatin 80 mg once daily, metoprolol tartrate 50 mg twice daily, and labetolol 200 mg three times daily. Her Z.A. lab values include BP 124/82 mmHg, HR 74 bpm. Her ejection fraction is 55%. She has no symptoms of heart failure. She takes aspirin 81 mg once daily, ticagrelor 90 mg twice daily, atorvastatin 80 mg once daily, metoprolol tartrate 50 mg twice daily, and labetolol 200 mg three times daily. Her Z.A. lab values include BP 124/82 mmHg, HR 74 bpm. Her ejection fraction is 55%.

Case #4
WB is a frail 85 year-old man with hypertension and PVD who presented from his nursing home with worsening dyspnea in the setting of AF (CHA2DS2-VASc score = 4). His symptoms have improved with beta blockade and the team is preparing to discharge him. They are concerned about bleeding in the setting of a fall, so they would like to send him home on aspirin instead of warfarin (he is unable to afford the copay for a DOAC on his Part D plan). What should you do?
A. Recommend warfarin titrated to an INR of 2-3.
B. Recommend aspirin 81 mg to reduce the risk of bleeding vs. 325 mg.
C. Recommend adding clopidogrel to provide greater stroke risk reduction vs. aspirin alone.
D. Recommend no anticoagulation.

Assessing Risk of Thrombosis vs. Bleeding

“GOMERS go to ground.”
Law 2 (The House of God, Samuel Shem)
BAFTA

Patients aged ≥ 75 years with atrial fibrillation

- Difference driven largely by difference in ischemic strokes
- No differences in major hemorrhage or hemorrhagic stroke
- Added to ACTIVE-W, which showed a 20% lower risk of bleeding with warfarin vs. DAPT in atrial fibrillation


What about fall risk?

- Falls are rarely captured in atrial fibrillation trials
- Researchers integrated results from atrial fibrillation trials and fall risk trials (50 studies total) into a Markov decision model
- Fall risk did not modulate risk of bleeding with antithrombotic strategy selected
- Patient would need to fall 300 times/year for risk of bleeding from fall to outweigh risk of benefit of stroke risk reduction


What about DOACs?

AVERROES: apixaban vs. aspirin in atrial fibrillation (n=5599)

- Apixaban reduced risk of stroke or systemic embolism by 55% but did not increase risk of bleeding (shown left)
- Similar efficacy/safety outcomes observed in older subgroup in major DOAC trials
- All DOACs associated with lower risk of intracranial hemorrhage vs. VKA

DOAC, direct acting oral anticoagulant; VKA, vitamin K antagonist

Summary

- Risk of fall-related bleeding overestimated in older patients with atrial fibrillation
- Aspirin is unlikely to ameliorate bleeding risk and provides less protection from stroke compared to warfarin or DOAC therapy
- Warfarin is safe in older patients
- DOACs have not been specifically studied in older patients
  - However, DOACs have comparable to better safety profiles overall
  - With exception of dabigatran, safety trends appear to be comparable in older subgroups
Case #4

WB is a frail 85 year old man with hypertension and PVD who presented from his nursing home with worsening dyspnea in the setting of AF (CHA2DS2-VASc score = 4). His symptoms have improved with beta blockade, and the team is preparing to discharge him. They are concerned about the risk of a fall, so they would like to recommend an anticoagulant. What do you do?

A. Recommend warfarin titrated to an INR of 2-3.
B. Recommend aspirin 81 mg to reduce the risk of bleeding vs. 325 mg.
C. Recommend adding clopidogrel to provide greater stroke risk reduction vs. aspirin alone.
D. Recommend no anticoagulation.

ACE = angiotensin converting enzyme, ARB = angiotensin II receptor blocker, ASCVD = atherosclerotic cardiovascular disease, BP = blood pressure, DES = drug-eluting stent, EF = ejection fraction, HR = heart rate, PRN = as needed, SL = sublingual