ATRIUM CARDIOLOGY COLLABORATIVE

ATRIUM Fall Patient Safety Webinar

Cardiology Mythbusters: Vol 1

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UNIVERSITY of MARYLAND SCHOOL OF PHARMACY

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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

ACE angiotensin-converting enzyme, ARB angiotensin II receptor blocker

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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

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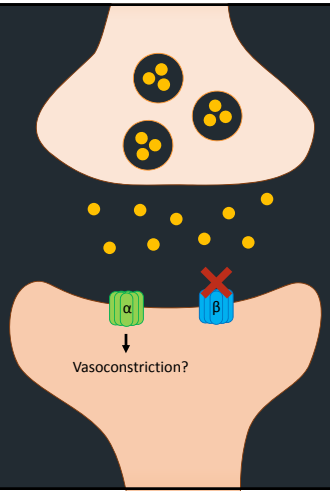

… but cocaine toxicity is complex:

- Pro-thrombotic effects
- Progressive atherosclerosis
- Ventricular remodeling

J Am Coll Cardiol. 2017 Jul 4;70(1):101-113.

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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]

(1) *Ann Emerg Med*. 1985;14: 1112-1113. (2) *Clin Cardiol*. 1992;15:253-258.

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Effects of IV Cocaine Administration

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

Hemodynamic Parameter	Baseline	Cocaine	p
Heart rate (beats/min)	71 ± 9	110 ± 23	0.007
Cardiac index (L/min/m^2)	3.4 ± 0.7	5.5 ± 1.1	0.0005
Mean arterial pressure (mmHg)	110 ± 9	112 ± 11	0.05
Systemic vascular resistance (dynes·sec/cm^5)	2492 ± 578	1721 ± 357	0.003
Coronary sinus flow (ml/min)	233 ± 67	411 ± 232	0.09
Coronary vascular resistance (dynes·sec/cm^5)	37.66 ± 14.48	29.72 ± 17.5	0.05
Coronary arterial diameter (mm)	2.28 ± 0.31	2.25 ± 0.41	0.2

IV intravenous
Adapted from *Clin Cardiol*. 1992;15:253-258.

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Evidence of an Interaction? (Continued)

- Beta blockers with α 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]

(1) *J Cardiovasc Pharmacol Ther*. 2010 Mar;15(1):47-52. (2) *Am J Med* 1993;94: (3) *Ann Intern Med* 1991;115:797– 806. (4) *Ann Emerg Med*. 2008 Feb;51(2):117-25.
(5) *Arch Intern Med*. 2010 May 24;170(10):874-9.

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Emergency Department Studies

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

Study	Outcome	Beta blocker	No beta blocker	OR (95% CI)	p
Datillo, et al[1] *Beta blocker (n=37) vs. no beta blocker (n=277)*	Myocardial infarction	6%	26%	0.17 (0.04 – 0.80)	< 0.05
	In-hospital mortality	1.7%	4.5%	0.22 (0.02 – 2.41)	< 0.05
Rangel, et al[2] *Beta blocker (n=151) vs. no beta blocker (n=177)*	All-cause death	12%	15%	0.53 (0.26 – 1.08)	0.080
	Cardiovascular death	NR	NR	0.29 (0.09 – 0.98)	0.047

CI confidence interval, NR not reported, OR odds ratio
(1) *Ann Emerg Med*. 2008 Feb;51(2):117-25. (2) *Arch Intern Med*. 2010 May 24;170(10):874-9.

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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

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Case #1

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MYTH BUSTED

A. Use spi... the RALES trial.
B. Use labe... 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

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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 α_1-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.

CAP community-acquired pneumonia, HFrEF heart failure with reduced ejection fraction

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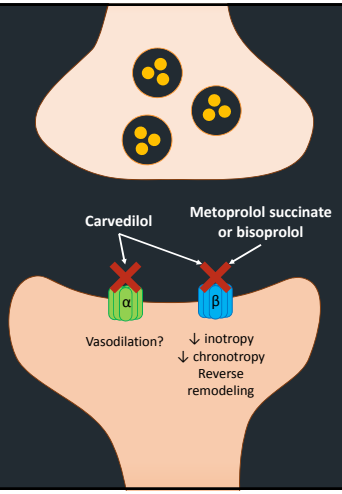

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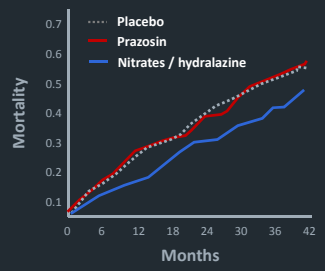
Heart Failure and α Receptors



- 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]

(1) *N Engl J Med.* 1986 Jun 12;314(24):1547-52. (2) *JAMA.* 2002 Dec 18;288(23):2981-97. (3) *N Engl J Med.* 2001 May 31;344(22):1659-67. (4) *J Pharmacol Exp Ther.* 1997 Feb;280(2):721-9.

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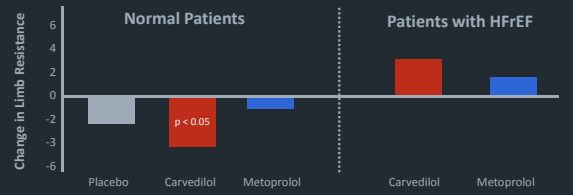
Heart Failure and α Receptors (Continued)

- 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]



HFrEF heart failure with reduced ejection fraction
N Engl J Med 1992; 327:669-77.

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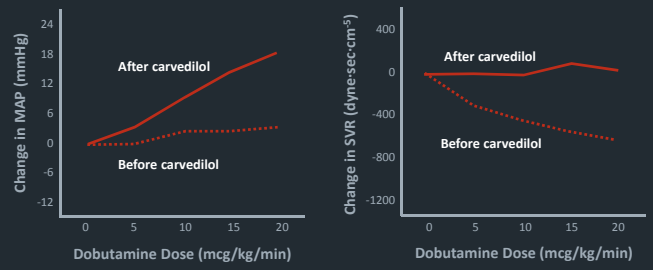
Heart Failure and α Receptors (Continued)



MAP mean arterial pressure, SVR systemic vascular resistance
Adapted from *J Am Coll Cardiol.* 2002 Oct 2;40(7):1248-58.

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Putting it αll 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

HFrEF heart failure with reduced ejection fraction

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Case #2

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A. Make th… twice daily.
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C. Change th… lisinopril to sacubitril/valsartan instead.
D. Add chlorthalidone 25 mg once daily instead.

CAP community-acquired pneumonia, HFrEF heart failure with reduced ejection fraction

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Case #3

KT 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 hyperlipidemia. 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 nitroglycerin SL tablets PRN. Vitals include BP 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. Eplerenone 50 mg based on the results of the EMPHASIS trial.
D. This patient doesn't have a compelling indication for an ACE inhibitor.

ACE antiogensin-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

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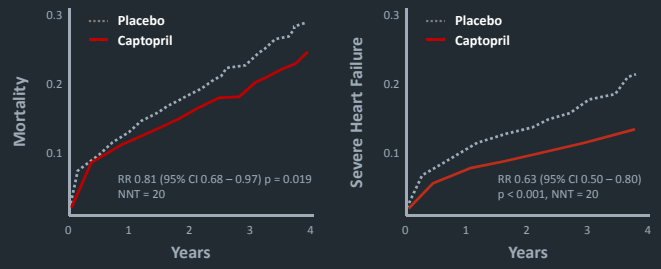
SAVE

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



N Engl J Med 1992; 327:669-77.

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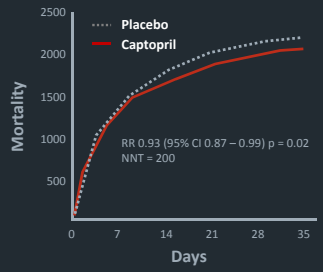
ISIS-4

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

Lancet 1995; 345: 669-85.

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HOPE vs. PEACE

Trial Characteristics	HOPE[1] (n=9297)	PEACE[1] (n=8290)
Inclusion Criterion	ASCVD or diabetes mellitus plus an ASCVD risk factor	History of ASCVD
History of Prior MI	~50%	~50%
Comparison	Ramipril vs. placebo	Trandolapril vs. placebo
Primary Endpoint	Composite of nonfatal MI, stroke, or CV death	Composite of nonfatal MI, revascularization, or CV death
Overall Outcome	Reduced risk of primary endpoint (17.8 vs. 14.0%, p < 0.001)	Did not reduce primary endpoint (22.5% vs. 21.9%, p = 0.43)

ASCVD atherosclerotic cardiovascular disease, CV cardiovascular, MI myocardial infarction
(1) *N Engl J Med* 2000;342:145-53. (2) *N Engl J Med* 2004;351:2058-68.

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HOPE vs. PEACE Baseline Characteristics

Baseline Characteristic	HOPE[1] (n = 9297)	PEACE[2] (n = 8290)
Received PCI	17.8%	41.5%
Received CABG surgery	25.8%	39%
Had diabetes mellitus	38.5%	17%
On antiplatelet therapy	76%	90.5%
On beta blocker	39.5%	60%
On lipid-lowering therapy	28.6%	70%

CABG coronary artery bypass graft, PCI percutaneous coronary intervention
(1) *N Engl J Med* 2000;342:145-53. (2) *N Engl J Med* 2004;351:2058-68.

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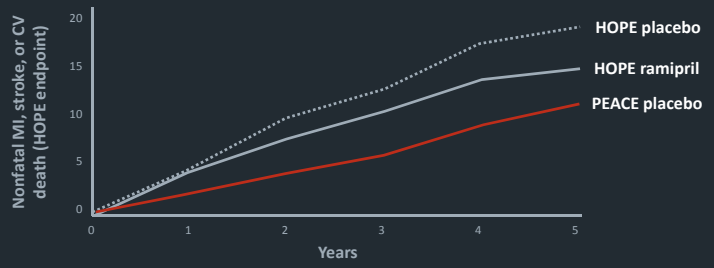
HOPE vs. PEACE Endpoints



CV cardiovascular, MI myocardial infarction
(1) *N Engl J Med* 2000;342:145-53. (2) *N Engl J Med* 2004;351:2058-68.

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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, ACS acute coronary syndrome, ARB angiotensin II receptor blocker

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Case #3

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ACE antiogensin-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

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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(CHA_2DS_2-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.

ACE antiogensin-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

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"GOMERS go to ground."

Law 2 (*The House of God*, Samuel Shem)

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Assessing Risk of Thrombosis vs. Bleeding

CHA_2DS_2-VASc

- Chronic heart failure
- Hypertension
- Age ≥ 75 years (2 points)
- Diabetes mellitus
- Stroke (2 points)
- Vascular disease
- Age 65-74 years (1 points)
- Sex (women > men)

HAS-BLED

- Hypertension
- Abnormal renal/liver function
- Stroke
- Bleeding
- Labile INR
- Elderly
- Drugs or alcohol

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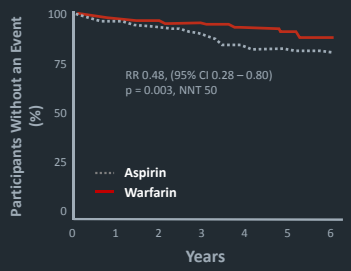
BAFTA

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

DAPT dual antiplatelet therapy
Lancet. 2007 Aug 11;370(9586):493-503. *Lancet* 2006; 367: 1903–12

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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

Arch Intern Med. 1999; 159:677-685.

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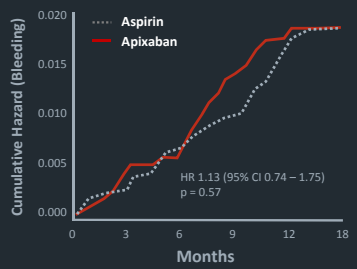
What about DOACs?

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
N Engl J Med 2011;364:806-17.

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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

DOAC direct-acting oral anticoagulant

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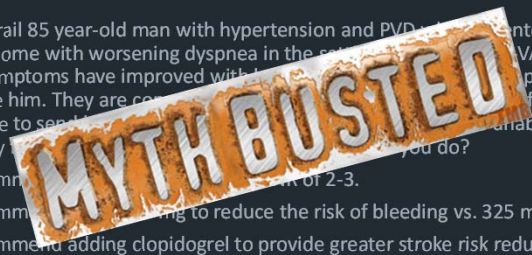
Case #4

WB is a frail 85 year-old man with hypertension and PVD [illegible] nted from his nursing home with worsening dyspnea in the [illegible] VASc score = 4). His symptoms have improved with [illegible] preparing to discharge him. They are co[illegible]fall, so they would like to sen[illegible] unable to afford the copay [illegible] you do?



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