130/80 is the New High: Strategies to Manage Hypertension

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Speaker has no relationship to disclose.

Objectives

- Utilize JNC 8 and the 2017 ACC/AHA Blood Pressure guidelines in adults to guide medication choices. (20 mins)
- Evaluate and compare *primary* pharmacologic agents (dosages, mechanism of action, side effects, desired effects) to help treat hypertension/renal disease in adults. (40 mins)
- Evaluate and compare pharmacologic agents (dosages, mechanism of action, side effects, desired effects) with attention to renoprotective effects. (30 mins)

Do you have any patients like these?

- Diabetes, HTN
- NSAID, diuretic users
- Cyclosporine users
- Renal artery stenosis patients
- Older adults
- GFR < 60 ml/min
- Heart Failure
- Sodium depletion, low albumin
- ASCVD

If you did nothing else except treat hypertension...

If you want to Control Blood Pressure long term:

Protect the Kidneys

Clinical Inertia

How many hypertensive people do you know

> who ONLY have hypertension?

The world changed... November 13, 2017

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA /ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood **Pressure in Adults**

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

130/80 Became the New High!

Whelton PK, Carey RM, AronowWS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughinEJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright 17 J. 2017 ACC/AHA/AAPA/ABC/ACFM/ACS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blodo pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.*Hypertension*.2017

https://doi.org/10.1161/HYP.00000000000065 Hypertension. 2017;HYP.000000 000000065 Originally published November 13, 2017

Is JNC 8 Obsolete?

ACC/AHA Categories of BP in Adults				
BP Category	SBP		DBP	
Normal	< 120 mm Hg	And	< 80 mm Hg	
Elevated	120-129 mm Hg	And	< 80 mm Hg	
	Hypertension			
Stage 1	130-139 mm Hg	Or	80-89 mm Hg	
Stage 2	<u>></u> 140 mm Hg	Or	<u>></u> 90 mm Hg	



Who gets Treatment for BP?

- Stage 1 with ASCVD, DM, CKD
- Stage 1 with ASCVD risk > 10%
- All Stage 2 patients

How do you determine ASCVD risk?

Get the free app!

ASCVD risk app!

It Goes without Saying....

Make therapeutic lifestyle changes

Lifestyle Modifications			
Intervention		Dose	SBP Impact
Weight Loss		Expect 1 mm Hg for every 1 kg reduction in body wt for overweight adults	-5 mm Hg
DASH diet	Fruits, veggies, whole grains, low fat dairy, reduced sat/trans fats		-11 mm Hg
Reduced Na intake		<1500 mg/d ideal	-5/6 mm Hg
Increased intake of K	Dietary K	3500-5000 mg/d by diet	-4/5 mm Hg
EtOH intake		Men: <u><</u> 2 drinks daily Women: <u><</u> 1 drink daily	-4 mmHg

Exercise			
		Decrease in SBP in HTN	Decrease in SBP Normotensive
Aerobic	 120–150 min/wk 65%–75% heart rate reserve 	-5/8 mm Hg	-2/4 mm Hg
Dynamic Resistance	• 90–150 min/wk • 50%–80% 1 rep maximum • 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 mm Hg	-2 mm Hg
Isometric Resistance	• 4 x 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk	-5 mm Hg	-4 mm Hg







Thiazide or Thiazide-type Diuretics

- Chlorthalidone
- Hydrochlorothiazide
- Indapamide
- Metolazone

Which one is preferred?



Chlorthalidone

- Most evidence for improved CV outcomes!
- 1.5 -2 times as potent as HCTZ
- Longer half-life (up to 72 hours vs. 6-12 hours with HCTZ)
- Longer control of SBP!!!

Clinical Resource, Comparison of Commonly Used Diuretics. Pharmacist's Letter/Prescriber's Letter. January 2017.





Chlorthalidone

• Appears to work in the ascending limb of Henle's loop (2.6 h initial diuresis occurs)

- · Excreted unchanged by the kidneys
- 7-8% will require therapy for hypokalemia

• Hypokalemia most likely in first 2 weeks, so if K is normal at 3 weeks, unlikely to have hypokalemia

• Gout?

Chlorthalidone

May never observe the value in your clinic

- Improvement in BP is overnight
- MR FIT trial
- LDL cholesterol better with chlorthalidone than HCTZ

Hypertension. 2011;57(4):689

Chlorthalidone

- Start at 12.5 mg
- No 12.5 mg tabs
- Available: 25 mg, 50 mg tabs

Chlorthalidone

3 fixed dose combos:

• Azilsartan medoxomil/chlorthalidone (Edarbyclor 40/12.5,40/25)

Atenolol/chlorthalidone
(Tenoretic 50/25, 100/25))

• Clonidine/chlorthalidone (Clorpres .1/15, .2/15, .3/15)

Chlorthalidone

• Sensitivity reactions may occur in patients with a history of allergy or asthma, sulfonamide derived meds

• Possibility of exacerbation of lupus (SLE) with thiazide diuretics—none reported with chlorthalidone

Formerly Pregnancy Category B

Hydrochlorothiazide

- Most commonly prescribed diuretic for HTN *in the world!*
- Widely available in combo with antihypertensive agents
- Mild antihypertensive agents
- Half life 6-12 hours
- Best used as synergists, unless minimal decrease in BP needed



Take Home Point!

• Limit HCTZ to 25 mg per day of HCTZ

WHY?

And, make sure there is adequate potassium on board! WHY?





Indapamide (Lozol)

Thiazide diuretic

- Half life is about 14 hours
- Indications: HTN, salt and fluid retention associated with HF
- Disadvantage: Not found in combo with other BP meds
- Cheap! (\$4 drug)

Indapamide

Thiazide diuretic

- 1.25 mg daily; if not at BP goal after 4 weeks, increase to 2.5 mg daily
- 2.5, 5, 10 mg tabs demonstrated equal efficacy
- Consider changing plan if goal BP not achieved by 8 weeks

Thiazide Diuretics HCTZ, indapamide, chlorthalidone

- Systolic reduction: 5-16.4 mmHg
- Diastolic reduction: 2-9.3 mmHg
- Minimal decreases in potassium (consider checking potassium levels after 2 weeks of therapy)
- Keep K+ at least 4 meq/L

Metolazone

Metolazone (Zaroxolyn)

• 2.5, 5, 10 mg tabs

• More effective than other thiazides at CrCl < 30 mL/min

Clinical Resource, Comparison of Commonly Used Diuretics. Pharmacist's Letter/Prescriber's Letter. January 2017.

Ernst ME, Moser M. Use of diuretics in patients with hypertension. *N Engl J Med* 2009;361:2153-64.

Potassium-Sparing Diuretics Secondary agents

Weak antihypertensive agents

- Advantage: They spare potassium!!!!
- Good in combo with thiazide or a loop for K sparing ability
- \bullet Avoid in significant CKD eGFR , 45 ml/min

Examples: Triampterene, amiloride

Clinical Resource, Comparison of Commonly Used Diuretics. Pharmacist's Letter/Prescriber's Letter. January 2017.

Loop Diuretics

Secondary agents

Bumetanide, furosemide, torsemide

• Do not decrease BP as much as thiazides; cause excretion of more Na than thiazides

• Preferred over thiazides in patients with moderate-to-severe CKD (e.g., GFR<30 mL/min)

Preferred if symptomatic HF

JNC 8 Goal: Reach target BP < 140/90 42 y/o male with HTN, dyslipidemia, Pre-DM, obese but trying to lose weight

AM Rea

10 mg amlodipine 40 mg lisinopril 25 mg HCTZ

BP dings	PM BP Readings
142/92	146/98
148/94	152/94
150/96	146/90
140/88	148/98

1. Increase HCTZ?

- 2. Change a medication?
- 3. Add another medication?

Option 2: Change a medication Try Chlorthalidone!		
Diuretic	Average Systolic Drop	
25 mg HCTZ	-4.5 mm Hg (<u>+</u> 2.1 mm Hg)	
12.5 mg -15.7 mm Hg (<u>+</u> 2.2 mm Chlorthalidone Hg)		
Ernst ME, Carter BL, Goerdt CJ, S Bergus GR Comparative antihypertensive effe ambulatory and office blood press Hypertension 2006/47(2):352	Steffensmeier JJ, Phillips BB, Zimmerman MB, ects of hydrochlorothiazide and chlorthalidone on ure.	









Why are we talking pit vipers and bananas?

Which Anti-Hypertensive Agents?

- **Primary Agents** Other diuretics
- Thiazides
- ACEs
- Aldosterone antagonists
- ARBs CCB DHP
- CCB non-
- DHP
- Beta Blockers

Secondary Agents

- Direct renin inhibitor Alpha 1 blockers
- Direct vasodilators
- https://doi.org/10.1161/HYP.000000000000065 Hypertension. 2017;HYP.000000000000065 Originally published November 13, 2017

RAAS (RAS)

Renin Angiotensin Aldosterone System

RAAS (RAS)

- ACE (Primary agent)
- ARB (Primary agent)
- Direct Renin Inhibitors (DRI)
- Aldosterone antagonists **(AA)**







ACE Inhibitors		
ACE I	Usual Daily Dose in mg	Daily Frequency
Benazepril	10-40	1 or 2
Captopril	12.5-150	2 or 3
Enalapril	5-40	1 or 2
Fosinopril	10-40	1
Lisinopril	10-40	1
Moxepril	7.5-30	1 or 2
Perindopril	4-16	1
Quinapril	10-80	1 or 2
Ramipril	2.5-10	1 or 2
Trandolapril	1-4	1



ACE Inhibitors

Primary Agent in 2017, HTN guidelines

• Indicated to treat HTN, HF, DM nephropathy, non-DM nephropathy, Post MI, CAD

• Slow progression of chronic kidney disease

Widespread use (4th most commonly dispensed medication)
 https://doi.org/10.1161/HYP.00000000000065 Uppertension. 2017;HYP.00000000000000065 Originally published November 13, 2017

ACE Angioedema

Angioedema 0.1% - 0.7%

Class effect of ACE-I

Toh S, Reichman ME, Houstoun M, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med 2012;172:1582-9.

Angioedema: When?

- At any time but >50% within a week of starting therapy
- 66% within 3 months
- But can occur years after

Mahoney EJ, Devaiah AK. Angioedema and angiotensin-converting enzyme inhibitors: are demographics a risk? Otolaryngol Head Neck Surg 2008;139:105-8.

After Angioedema:

• Can recur and/or persist up to 6 weeks after discontinuation (up to 17% cross reactivity)

• If switching to an ARB, consider waiting at least 4 weeks to prevent misdiagnosing an ACE-I recurrence as an ARB associated angioedema

Mahoney EJ, Devaiah AK. Angioedema and angiotensin-converting enzyme inhibitors: are demographics a risk? *Otolaryngol Head Neck Surg* 2008;139:105-8.

ACE Angioedema

• Similar risks of angioedema with aliskiren (Tekturna)

DO NOT switch to aliskiren

Toh S, Reichman ME, Houstoun M, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med 2012;172:1582-9.

When to use an ACE Inhibitor?

Hypertension

Reduce fatal/nonfatal MI in patients with hypertension plus one other CV risk factor as well as chlorthalidone or amlodipine (ALLHAT).

ALLHAT - Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. JAMA 2002;288:2981-97.

When to use an ACE Inhibitor?

Diabetic Nephropathy: Reduce risk of doubling of serum creatinine in type 1 diabetes patients

with macroalbuminuria (NNT = 11 patients for 3 years)(CAPTOPRIL).

CAPTOPRIL - The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med1993;329:1456-62.

When to use an ACE Inhibitor?

Non Diabetic Nephropathy Reduce rate of decline of GFR in patients with non-diabetic kidney disease, as well as the risk of doubling of serum creatinine or ESRD (NNT = 4 patients for 1.3 years)(REIN).

REIN - Ramipril Efficacy In Nephropathy. Lancet 1997;349:1857-63.

RAAS (RAS)

Renin Angiotensin Aldosterone System

Angiotensin Receptor Blockers circa 1990s



Effects of Angiotensin II

- Vasoconstriction
- Aldosterone secretion
- Sympathetic stimulation
- Cardiac stimulation
- ADH secretion

ARBs			
ARB	Usual Daily Dose in mg	Daily Frequency	
Azilsartan	40-80	1	
Candesartan	8-32	1	
Eprosartan	600-800	1 or 2	
Irbesartan	150-300	1	
Losartan	50-100	1 or 2	
Olmesartan	20-40	1	
Telmisartan	20-80	1	
Valsartan	80-320	1	



ARBs

Primary Agent in 2017, HTN guidelines

• Indicated to treat HTN, HF, DM nephropathy, non-DM nephropathy, Post MI, CAD

https://doi.org/10.1161/HYP.00000000000065 Hypertension. 2017;HYP.000000000000065 Originally published November 13, 2017

ACEs and ARBs for Kidney Disease

- 1. Reduce blood pressure
- 2. Reduce proteinuria
- 3. Slow progression of kidney disease by decreasing glomerular intracapillary pressure, other mechanisms

https://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm. Accessed March 1, 2018.

ACEs and ARBs for Kidney Disease

"Beta blockers" of the kidney

• These meds slow the progression of kidney disease but,

ACEs and ARBs Kidney Disease

 Blocking angiotensin reduces kidney filtration

• Concomitant increase in serum creatinine and serum potassium

Tips for ACEs and ARBs in Kidney Disease • Use moderate dose for most patients

• Use moderate dose for most patients (Level A)

• Lower dose if severe renal impairment, HF, or age > 80

Titrate every 1-2 weeks

Monitor SCr and K at baseline, within

1-2 weeks after starting dose or

increasing dose https://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm. Accessed March 1, 2018.

SCr <u>LESS THAN 30%</u> on ACE or ARB dose

• Continue ACE or ARB as long as SCr increases LESS THAN 30% SCr

• Expect SCr to move back toward baseline as BP moves toward goal

• Recheck SCr, K, BP in 2-3 weeks

•Once stable, recheck labs 1-2 times annually

https://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm. Accessed March 1, 2018.

SCr <u>MORE THAN 30%</u> or K approaches 5.5 mEq/L

- Cut dose in half
- Decrease diuretics
- Stop meds that increase K
- Increase fluids to avoid dehydration

https://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm. Accessed March 1, 2018.

SCr <u>STAYS above 30%</u> or K <u>></u> 5.5 mEq/L

• STOP ACEI or ARB despite dose reductions or if K exceeds 5.5 mEq/L

- · Let it go back down to baseline
- Try to restart the ACEI or ARB once the labs improve

https://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm. Accessed March 1, 2018.

2 Final Thoughts on ACEs and ARBs

Of course:

- Do not use ACEs and ARBs in combination; or with a DRI
- Monitor for increased risk of hyperkalemia in patients on CKD, taking K supplements/K sparing meds

Of course:

- May cause acute renal failure in patients with severe bilateral renal artery stenosis (reduced blood flow HUGE risk factor for acute failure)
- Avoid in pregnancy!

Avoid "Triple Whammy"

Triple Whammy= risk of acute kidney injury

ACE or ARB *plus* diuretic *plus* NSAID *or* Aspirin

Triple Whammy

- ACE/ARB: reduce glomerular filtration pressure via vasodilation of the efferent arteriole
- NSAID/ASA: inhibits renal prostaglandin synthesis (inhibits dilation of renal arteries and decreases blood flow to the glomerulus)
- Diuretics decrease intravascular volume and reduce blood flow to the glomerulus
- The combo leads to reduction in renal blood flow and renal dysfunction





Triple Whammy

• Especially deleterious in elderly patients, diabetics, renal insufficiency, ascites, or HF ("double whammy" can cause acute injury)

Protection from the Triple Whammy

- Keep well hydrated
- NSAID use: 6-12 hour (not 24 hours)
- Avoid NSAID, use tramadol, acetaminophen instead, other modality

Calcium Channel Blockers Circa: Early 1980s

Calcium Channel Blockers

- Verapamil was the first
- Thought to be a beta blocker

Calcium Channel Blockers (CCBs)

- 2 Groups of calcium channel blockers:
 - 1. Dihydropyridines (DHPs)
 - 2. Non-Dihydropyridines (non-DHPs)

CCB DHP			
ССВ	Usual Daily Dose in mg	Daily Frequency	
Amlodipine	2.5-10	1	
Felodipine	5-10	1	
Isradipine	5-10	2	
Nicardipine SR	5-20	1	
Nifedipine LA	60-120	1	
Nisoldipine	30-90	1	
 Avoid use in patients with HFrEF; amlodipine may be used if required Associated with dose-related pedal edema, which is more common in women than men 			



CCB non-DHP			
ССВ	Usual Daily Dose in mg	Daily Frequency	
Diltiazem SR	180-360	2	
Diltiazem ER	120-480	1	
Verapamil IR	40-80	3	
Verapamil SR	120-480	1 or 2	
Verapamil delayed onset ER	100-480	Evening	
 Avoid routine use with beta block heart block Do not use in patients with HFrEf Drug interactions with diltiazem a 	ers due to increased risk o = ind verapamil(CYP3A4 ma	of bradycardia and	

Drug interactions wi moderate inhibitor)

True or False

Amlodipine is a better choice to treat a patient's HTN/proteinuria than diltiazem.

Calcium Channel Blockers

Anti-Proteinuric Effect

- Diltiazem and verapamil (non-DHPs)
- Decrease proteinuria by 30%
- DHPs increased proteinuria by 2%
- Similar effects if used in combo with ACE or ARB

Kidney Int. 2004;65(6):1991

CCB Indications

- Hypertension (DHP)
- DM with proteinuria (non-DHP) ACE preferred

CCB Indications

- May be preferred drugs, especially the DHPs, for patients with asthma and COPD
- Theoretical advantage of opposing muscle contraction in tracheobronchial muscle contraction
- Inhibiting mast cell degranulation
- Reinforcing bronchodilator effect of beta agonists

CCB Anti-Proteinuric Effect

ACEI, ARBs, and non DHP CCBs have a greater antiproteinuric

effect than other antihypertensive classes in hypertensive patients with DKD. (Strong)

https://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm. Accessed March 1, 2018.

CCB Anti-Proteinuric Effect

DHP CCBs when used to treat hypertension in the absence of ACE inhibitors or ARBs, are less effective than other agents in slowing progression of DKD. (Strong)

https://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm. Accessed March 1, 2018.

CCB Anti-Proteinuric Effect

- Non-DHPs decreased proteinuria by 30%
- DHPs increased proteinuria by 2%
- Similar effects if used in combo with ACE or ARB

https://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm. Accessed March 1, 2018. Kidney Int. 2004;65(6):1991

Hypertension Management

"Wise Old Owl"

Chronopharmacology

WHEN we take meds can make a difference in pharmacokinetics and pharmacotherapeutics

BP management, and overall 24 hour BP

Chronopharmacology

Strategy for timing of medications:

Deliver the drug in high concentrations when it's needed most!

Which Meds at Nighttime?

- •Calcium channel blockers
- •ACEs
- •ARBs

24 Hour Blood Pressure

BP is about 15% lower during the evening and nighttime vs daytime

The Big Dipper The Little Dipper

Nocturnal BP

 BP is about 15% lower at nighttime vs daytime values ("Physiologic Dipping")

Non-Dippers= BP falls < 10% while sleeping

Non-Dipper

Nocturnal BP

The problem occurswhen you "SKIP the DIP"...

- Predictor of CV events
- Greater incidence of LVH, HF, target organ damage
- Associated with microalbuminuria, faster progression of nephropathy

J Hypertens. 2010;28(10):2036.

Restoring the Dip? Nocturnal Treatment

- •Shifting one antihypertensive med to PM may help restore "the dip"
- •How long?
- •Long term benefit? Reduces 24 hour mean BP

Transplantation. 1995;59(9):1270. Am J Kidney Dis. 1999;33(1):29.

New Patient to my Practice

57 y/o male with HTN, dyslipidemia, Pre-DM.

AM Meds: 10 mg amlodipine	BP LOG Day 1-7 Ave BP	
100 mg losartan	135/82	6 AM
12.5 mg HCTZ	140/90	6 AM
Baby ASA	138/90	8 PM
	132/88	10 PM
<i>PM Meds:</i> 40 mg pravastatin 1000 mg metformin	134/84	5 AM
	138/88	5:30 AM
	136/86	7 PM

New Patient to my Practice			
57 y/o male with HTI Pre-DM.	N, dyslipide	emia,	
AM Meds: 100 mg losartan	BP LOG After switch Ave BP		
12.5 mg HCTZ	130/76	5 AM	
<i>PM Meds:</i> 10 mg amlodipine 40 mg pravastatin 1000 mg metformin Baby ASA	124/82	6 AM	
	118/74	8 PM	
	122/78	10 PM	
	124/76	6 AM	
	130/80	5 AM	
	126/76	10 PM	



New Patient to my Practice Consider d/c'ing the				
HCTZ?				
AM Meds: 100 mg losartan		BP LOG After switch Ave BP		
12.5 mg HCTZ		130/76	5 AM	
<i>PM Meds:</i> 10 mg amlodipine 40 mg pravastatin 1000 mg metformin Baby ASA	1	124/82	6 AM	
		118/74	8 PM	
		122/78	10 PM	
		124/76	6 AM	
		130/80	5 AM	
		126/76	10 PM	

A Drug Combo You'll NEVER find

CCB plus a thiazide diuretic

"Calanide" "Verapamilide"

No Synergism!!!!!

Add thiazide diuretics

to ACEs, ARBs, BBs, direct renin inhibitors, etc.

WHY No Synergism???

Maybe because they both work by causing renal sodium excretion and vasodilation

Triple Combo Products

- Amlodipine, HCTZ, aliskiren (Amturnide)
- Amlodipine, HCTZ, valsartan (Exforge HCT)

Combining 2 Synergistic Drugs

Decreases BP about 5x more than doubling the dose of a single drug!

BMJ. 2009;338:b1665.

What about lower extremity edema? • Occurs in up to 1 in 3 patients

- DHPs more likely than non-DHPs
- Dose dependent
- Occurs bilaterally
- NOT caused by fluid overload!

Why lower extremity Edema?

Secondary to arteriolar dilation, then increased capillary pressure, and fluid shift

Strategies to "Fix it"

• Diuretics do NOT work because it is not fluid overload!

- Add an ACE or ARB
- Switch: non-DHP-edema is less likely

Caution with other drugs that are 3A4 inhibitors

CCB Drug Interactions

- CCBs require CYP3A4 enzymes for metabolism
- Watch out for drug reactions with 3A4 inhibitors (macrolides, some statins, grapefruit juice)

http://www.fda.gov/Drugs/DevelopmentApprovalPr ocess/DevelopmentResources/DrugInteractionsLa beling/ucm093664.htm#PgpTransport. (Accessed February 12. 2018).

CCB Drug Interactions

Non-DHPs more involved in drug interactions

- Example 1: atorvastatin plus diltiazem is deleterious
- Example 2: atorvastatin plus amlodipine (Caduet) is safe

Grapefruit Juice Interactions

- Grapefruit juice inhibits the CYP 3A4 in the intestinal wall (first pass effect)
- Greatest effect seen with the non-DHPs

http://www.fda.gov/Drugs/DevelopmentAppro valProcess/DevelopmentResources/DrugInte ractionsLabeling/ucm093664.htm#PgpTrans port. (Accessed February 12, 2018).

How long does it inhibit metabolism of drugs?

3 days up to 14!

Grapefruit Juice Interactions

- 85 Interactions identified
- Increased risk of bleeding with ticagrelor (Brilinta)
- Grapefruit exposure PERMANENTLY knocks out 3A4 enzymes; in 24 hours, about 50% 3A4 enzymes "restocked"
- Full recovery of 3A4 enzymes takes about 72 hours or longer http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ DrugInteractionsLabeling/ucm093664.htm#PgpTransport. (Accessed February 12,

Grapefruit Juice Interactions

- Grapefruit juice permanently inactivates the CYP 3A4 enzymes in the small bowel wall
- Doesn't affect liver CYP 3A4 (IV meds are not affected by grapefruit)
- Takes 48-72 hours to replace 3A4s in gut

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ DrugInteractionsLabeling/ucm093664.htm#PgpTransport. (Accessed February 12,

What Determines Severity of Reaction?

- Degree of drug exposure
- Therapeutic index of affected drug
- Quantity of grapefruit consumed
- Elderly are always at increased risk because they tolerate changes less well than their younger counterparts

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ DrugInteractionsLabeling/ucm093664.htm#PgpTransport. (Accessed February 12,

What constitutes "grapefruit juice"?

8 oz of grapefruit juice *or* one whole grapefruit

Tangelos, limes (2 oz.), Seville oranges

What constitutes "grapefruit juice"?

Seville

oranges are bitter and often used to make... orange

marmalade!

What about other citrus fruits?

NO PROBLEMS with oranges, tangerines, citrons, lemons

What about other fruits? Maybe... Cranberries Pomegranate juice

Do you have a specific strategy for Managing HTN in a patient with lower airway disease?

Lower Airway Disease

- •Beta Blockers
- •ACE inhibitors
- •ARBs
- Diuretics
- •CCB
- •Sympathetic Blockers



Beta Blockers (BB)

Asthma

- BB can increase bronchial obstruction (ophthalmic BB)
- •BB can cause airway reactivity
- Make inhaled SABA, LABA ineffective

Beta Blockers (BB) COPD

- Consider a cardioselective BB (metoprolol, nebivolol, etc.)
- •Mild or moderate COPD
- May reduce mortality and exacerbations

Rutten FH, Zuithoff NP, Hak E, Grobbee DE, Hoes AWArch. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. Intern Med. 2010;170(10):880.

ACE Inhibitors

Asthma/COPD

- •Not first line in patients with lower airway disease (LAD)
- •No data supports that ACE cough is more prevalent in patients with LAD
- Difficult to differentiate ACE cough if one occurs?

Diuretics

Asthma/COPD

Potassium Issues

- SABA use drives potassium into cells (decreases plasma K concentration up to .5 – 1 meq/L)
- Oral steroid causes increased excretion of urinary potassium
- What about an infection that produces an exacerbation?

Second Issue with Diuretic

COPD

Metabolic alkalosis

- •COPD plus chronic hypercapnia, diuretic induced metabolic alkalosis
- •Met alk suppresses ventilatory drive (this worsens hypercapnia....)

Recommendation

Asthma/COPD •12.5 – 25 mg HCTZ daily •Avoid chlorthalidone (low K, more potent)

The "Go to" drug class....for a lower airway patient

Asthma

•Calcium Channel Blocker! •Especially the DHPs (nifedipine, nicardipine)

Barnes PJ. Clinical studies with calcium antagonists in asthma. Br J Clin Pharmacol. 1985;20 Suppl 2:289S.

Why? Asthma

- Opposes muscle contraction in tracheobronchial smooth muscle
- Inhibits mast cell degranulation
- Nifedipine antagonizes bronchoconstrictive effects of antigen, histamine, cold air
- Does not suppress asthma symptoms

Am Rev Respir Dis. 1986;134(2):262. Br J Clin Pharmacol. 2002;53(3):243.

Alpha 2 Blockers Asthma

•Clonidine

- •Methyldopa
- Increased bronchial reactivity to inhaled histamines

Barnes PJ. Br J Clin Pharmacol. Clinical studies with calcium antagonists in asthma.1985;20 Suppl 2:289S

Summary HTN in LAD				
	Asthma	COPD		
Alpha Blocker	×	Caution		
Beta Blocker	×	√/Caution		
Calcium Channel Blocker (DHPs)	~	V		
ACE	√	√		
ARB	✓	✓		
Diuretic	Caution	Caution		



Take Home Point

When you treat HTN in LAD... CCB, ACE, and ARB. Consider hypokalemia with diuretics.

Summary

Which Anti-Hypertensive Agents? Primary Agents Secondary Agents

Thiazides

- ACEs
- ARBs
- CCB DHP
- CCB non-
- DHP
- Other diuretics
- Aldosterone
 antagonists
- Beta Blockers
- Direct renin inhibitor
- Alpha 1 blockers
- Direct vasodilators
 https://doi.org/10.1161/HYP.00000000000065 Hypertension. 2017;HYP.00000000000065
 Originally published November 13, 2017

Thiazides: Primary Agents

•Think Chlorthalidone

RAAS: Primary Agents

• ACEs

• ARBs

CCBs: Primary Agents

DHPs ("pines")Non-DHPs

Clinical Inertia

Thank you!

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