

Resistant Hypertension Management

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Objectives

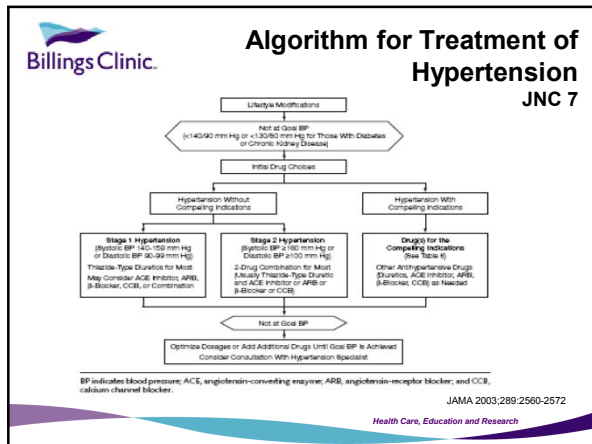
- Review recent changes to blood pressure guidelines
- Apply these principles to general patient populations
- Understand secondary causes of resistant hypertension
- Learn basic strategies for the management of patients with resistant hypertension

Hypertension 101 JNC 7

Table 1. Classification and Management of Blood Pressure for Adults Aged 18 Years or Older

BP Classification	Systolic BP, mm Hg*	Diastolic BP, mm Hg*	Lifestyle Modification	Management*	
				Without Compelling Indication	With Compelling Indication†
Normal	<120	and <80	Encourage	No antihypertensive drug indicated	Drugs‡ for the compelling indications†
Prehypertension	120-139	or 80-89	Yes	No antihypertensive drug indicated	Drugs‡ for the compelling indications†
Stage 1 hypertension	140-159	or 90-99	Yes	Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, β-blocker, CCB, or combination	Drugs‡ for the compelling indications† Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed
Stage 2 hypertension	≥160	or ≥100	Yes	2-Drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or β-blocker or CCB)	Drugs‡ for the compelling indications† Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium channel blocker.
*Treatment determined by highest BP category.
†See Table 6.
‡Treat patients with chronic kidney disease or diabetes to BP goal of less than 130/90 mm Hg.
§Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.



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2014 EVIDENCE-BASED GUIDELINE FOR THE MANAGEMENT OF HIGH BLOOD PRESSURE IN ADULTS

REPORT FROM THE PANEL MEMBERS APPOINTED TO THE EIGHTH JOINT NATIONAL COMMITTEE (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DRPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Oluwengba Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Navra, MD; Eduardo Ortiz, MD, MPH

JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427
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- “Prehypertension” no longer an entity
- Goal BP for persons < age 60 = < 140/90 mmHg
 - Initiate treatment for DBP > 90 mmHg
 - Ages 30-59: Strong Recommendation – Grade A
- Goal BP for persons 60 and over = < 150/90 mmHg
 - Strong Recommendation – Grade A
- Change in treatment algorithm

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General Nonblack Population

- “including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker”
- Alpha and beta blockers excluded for initial treatment

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General Black Population

- “including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker”
- Specifically recommending a thiazide over an ACEI in diabetics

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In patients with chronic kidney disease and HTN

- Therapy should include an ACEI or ARB to improve kidney outcomes.
- This applies regardless of race or presence of diabetes, with or without proteinuria.

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JNC 8 ...further management

- If goal BP not reached at one month increase dose or add another of the recommended first line agents
- If goal BP still not reached add a third drug

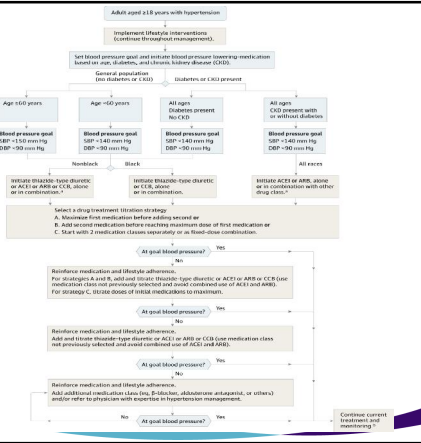


Table 4. Evidence-Based Dosing for Antihypertensive Drugs

Antihypertensive Medication	Initial Daily Dose, mg	Target Dose in RCTs, Recommended, mg	No. of Doses per Day
ACE Inhibitors			
Captopril	50	150-300	2
Fosinopril	5	20	1-2
Lisinopril	10	40	1
Angiotensin receptor blockers			
Eprosartan	400	600-800	1-2
Candisartan	4	12-32	1
Losartan	50	100	1-2
Valsartan	40-80	160-320	1
Telmisartan	75	800	1
β Blockers			
Atenolol	25-50	100	1
Metoprolol	50	100-200	1-2
Calcium Channel blockers			
Amlodipine	2.5	10	1
Diltiazem extended release	120-180	360	1
Nitrendipine	10	20	1-2
Thiazide-type diuretics			
Bendroflumethiazide	5	10	1
Chlorthalidone	12.5	12.5-25	1
Hydrochlorothiazide	12.5-25	25-100*	1-2
Indapamide	1.25	1.25-2.5	1

Abbreviations: ACE, angiotensin-converting enzyme; RCT, randomized controlled trial.
 *Current recommended evidence-based dose that balances efficacy and safety is 35-50 mg daily.

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If goal BP not achieved with 3 good drugs
and maximally tolerated doses...

RESISTANT HYPERTENSION!

INCIDENCE 5-30%

EUR HEART J. 2013 JUL;34(28):2159-2190
BMJ 2012;345:E7473

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Inability to Control BP

- Measurement errors
- Excess sodium intake
- Obesity
- Noncompliance with medical regimen
- OTC meds -- NSAIDS, sympathomimetics
- Excessive Alcohol

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Physician Factors

- Inadequate doses
- Not using diuretic in multiple med regimens
- Inertia - sometimes justified, sometimes not
- Ambulatory blood pressure monitoring

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Secondary Causes: Endocrine

- Primary Hyperaldosteronism
- Cushing's Syndrome
- Thyroid disease -- hypo or hyper
- Pheochromocytoma

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Non-endocrine causes

- Renovascular
- Obstructive sleep apnea
- Chronic renal failure
- Aortic coarctation
- Hypercalcemia
- Brain mass

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Resistant Hypertension CASE DISCUSSIONS

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Case 1

TR is a 68 yom with a history of HTN, CAD, CKD stage IV. Unable to tolerate ACE inhibitor or ARBs due to hyperkalemia. Current blood pressure medications amlodipine 10 mg daily, metoprolol tartrate 25 mg BID, clonidine 0.1 mg BID. BP 146/82 HR 60 bpm. CMP reveals K+ 4.9 mEq/L, SCr 3.1 (CrCl 28 mL/min, BUN 48, Ca2+ 10.6. Microalbuminuria 82. Which is best therapeutic plan for TR?

- a. No medication changes
- b. Start hydrochlorothiazide 25 mg daily
- c. Start furosemide 40 mg BID
- d. Change metoprolol succinate to carvedilol 6.25 mg BID

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Case 2

AM is a 32 yof with DM type 1 and HTN. Her current medications are ramipril 10 mg daily, chlorthalidone 25 mg daily, amlodipine 10 mg daily, and ethinyl estradiol 20 mcg/norethindrone 1 mg daily, insulin pump as directed. BP 145/83 mmHg, repeat 145/81 mmHg, HR 65 bpm, SCr 1.2. AM would prefer not to take any more drugs. What is the best plan for AM?

- a. Add metoprolol tartrate 25 mg BID
- b. Change chlorthalidone to hydrochlorothiazide 25 mg daily
- c. Renal artery ultrasound
- d. Patient is at goal for age, no changes

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Case 2, continued

• You see AM back in clinic 3 months later. RUS negative. She read somewhere that OCs can increase blood pressure so she decided to stop OC and see how her blood pressure does. She is now pregnant. BP 144/94. She has continued all of her home medications. She is 6 weeks gestational. She also informed the nurse at intake she has been smoking 1/2 PPD. What do you do?

- a. Stop ACE inhibitor, initiate labetalol, referral for smoking cessation counseling
- b. Stop ACE inhibitor, see her back in clinic. Referral for smoking cessation
- c. Stop ACE inhibitor, chlorthalidone, see her back in clinic. RX Nicotine 21 mg/day patches same day.
- d. Stop ACE inhibitor, initiate labetalol. RX Nicotine 14 mg/day patch and referral for smoking cessation. 1 week BP follow up

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Case 3

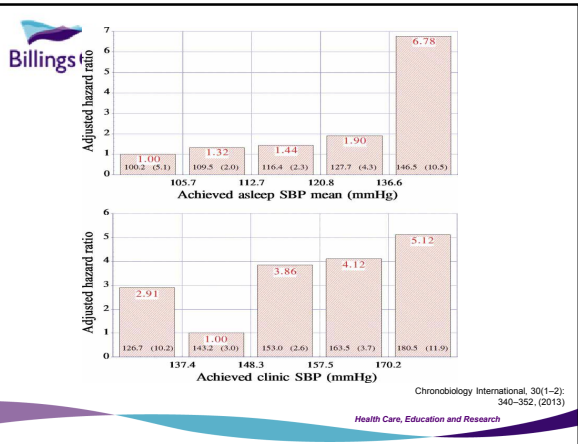
MZ is a 45 yof with uncontrolled HTN. Her home BP readings have ranged from 145-159/90s the last month. She is currently taking lisinopril 40 mg daily, felodipine 10 mg/day, atenolol 25 mg/day. She takes all of her medications in the morning with breakfast. SCr 1.4 mg/dL (CrCl 40 mL/min), K+ 3.4 mEq/L, Na+ 135 mg/dL, Last echo EF 50-59%, HR 68 bpm, and microalbumin/SCr= 39. What is next best step to control her blood pressure?

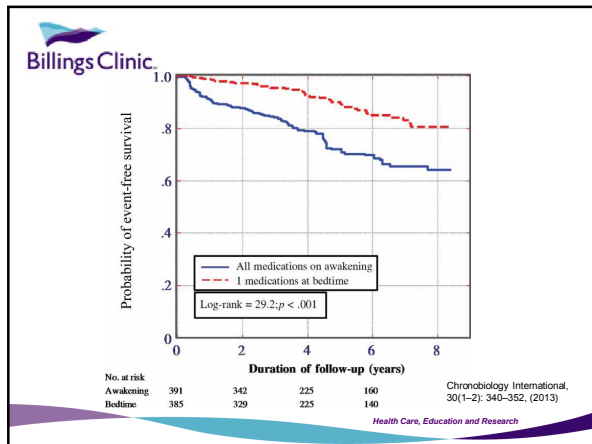
- a. Increase atenolol to 50 mg/day
- b. Add furosemide 20 mg BID
- c. Add hydrochlorothiazide 25 mg daily
- d. Increase atenolol to 50 mg/day and change to bedtime dosing

Cardiovascular Risk of Resistant Hypertension: Dependence on Treatment-Time Regimen of Blood Pressure-Lowering Medications

Diana E. Ayala, Ramón C. Hermida, Artemio Mojón & José R. Fernández (2013)

Chronobiology International: The Journal of Biological and Medical Rhythm Research, 30:1-2, 340-352





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Authors conclusions:
 “Among patients with resistant hypertension, ingestion of at least one hypertension medication at bedtime, compared with all medications upon waking, resulted in improved ambulatory BP control and fewer hard and soft CVD events”

Note: Statistical significance for CCBER and BBER, trend for ARB

Chronobiology International, 30(1-2): 340-352, (2013)
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Case 3, cont

You see MZ back in clinic in 1 month. She did not tolerate increase of atenolol (dizziness, low HR). You had added hydrochlorothiazide 25 mg daily. She is taking all of her medications in the am except atenolol in the evening. Her blood pressure today is 148/92. What is your plan for MZ?

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Case 4

HZ is a 78 yom patient with history of resistant HTN, CAD, CHF, DM, HLD. He is currently taking furosemide 40 mg BID, KCl 20 mEq BID, enalapril 20 mg daily, carvedilol 12.5 mg BID to control his blood pressure. He feels like he has been more forgetful lately. He is planning to get his medications bubble packed from ALF starting this week. He has been managing all of his medications himself. His in office blood pressure is BP 156/89. HR 55 bpm. What is the next best step for the management of HZ's hypertension?

- a. Ambulatory blood pressure monitoring
- b. Echocardiography
- c. Hydralazine
- d. Urine metanephrine measurement

Office versus Ambulatory Blood Pressure Study (OvA)

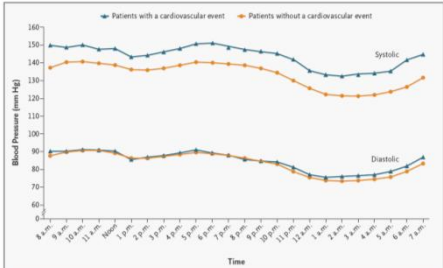
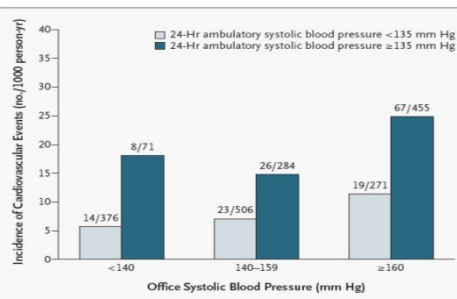


Figure 1. Hourly Means of Systolic and Diastolic Blood Pressure Derived from 24-Hour Ambulatory Blood-Pressure Recordings Obtained at Base Line (Visit 3) in the 1963 Participants.

NEJM 2003; 348:2407-2415

OvA



NEJM 2003; 348:2407-2415

Case 5

SP is a 55 yof who has 5 year history of uncontrolled HTN. Currently she is taking chlorthalidone 25 mg/day, benazepril 40 mg qhs, and amlodipine 10 mg daily. BP 160/94 mmHg. CMP reveals a SCr 0.9, K+ 4.1. She has not tolerated beta blocker or alpha-blocker therapy (dizziness).

Which of the following is the most appropriate next step in management?

- a. Discontinue chlorthalidone, start furosemide 20 mg BID
- b. Retrial terazosin 1 mg qhs
- c. Obtain kidney Doppler ultrasonography
- d. Obtain a plasma aldosterone-plasma renin activity ratio

Aldosterone-to-renin ratio (ARR)

- ARR > 20 positive
 - sensitivity 78-89%
 - specificity 71-83%
- Acelajado and Calhoun, *Cardiol Clin* 28 (2010) 639-654
- Confirm with oral sodium loading, saline infusion, fludrocortisone suppression, or captopril challenge

Higher aldosterone levels in Resistant Hypertension

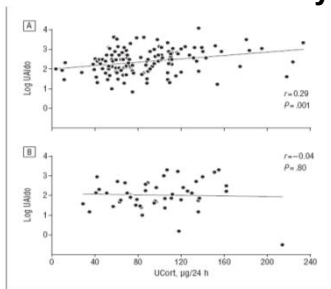


Figure 2. Correlation between 24-hour urinary aldosterone (UAldo) (reference range, 2-16 µg/24 h) and urinary cortisol (UCort) (reference range, 56-286 µg/24 h) levels in patients with resistant hypertension (A) and controls (B).

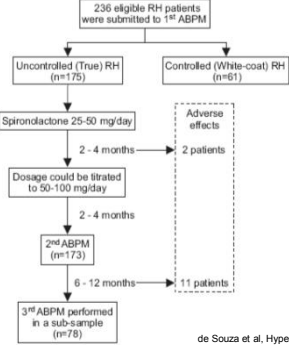
Gaddam et al. *Arch Intern Med*. 2008;168(11):1159-1164

Case 6

58 yo Hispanic female with HF-REF, CAD, and HTN. Taking furosemide 40 mg/day, lisinopril 40 mg/day, amlodipine 10mg/day, metoprolol tartrate 25 mg BID. She tried terazosin but d/c'd due to dizziness. BP today 148/79, repeat 145/81. HR 58 bpm. SCr 1.2 K+ 3.9, Na 142. Which change is best for patient?

- a. Start spironolactone 25 mg daily
- b. Add hydralazine 25 mg TID
- c. Increase metoprolol to 50 mg BID
- d. Add Diltiazem 120 mg CD daily

Effect of spironolactone in RH



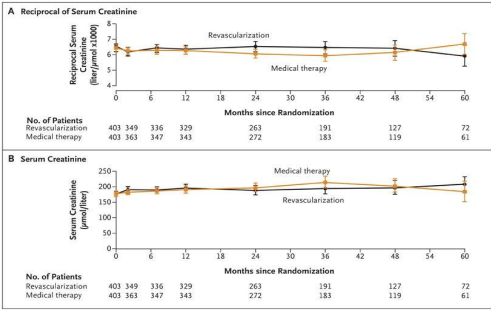
Case 7

GB is a 76 yom who is being seen for history of resistant hypertension. He is a 1 PPD smoker. Last month he was started on atenolol 25 mg daily, in addition to taking hydralazine 25 mg TID, indapamide 2.5 mg daily. He did not tolerate amlodipine (peripheral edema/constipation) or lisinopril (angioedema). In office blood pressure 164/94 mm Hg, and pulse rate is 60/min. He does have some trace edema. CMP reveals SCr 1.7 mg/dL, CrCl 29 mL/min. What is the next best step for GB.

- a. Start losartan 50 mg daily
- b. Increase indapamide to 5 mg daily
- c. Obtain Doppler ultrasonography of the renal arteries
- d. Obtain kidney angiography



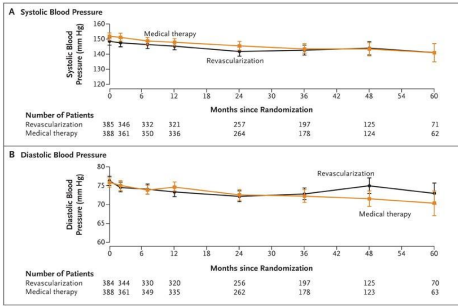
ASTRAL: Renal Artery Stenosis



The ASTRAL Investigators. N Engl J Med 2009;361:1953-1962. Health Care, Education and Research



ASTRAL: Renal Artery Stenosis



The ASTRAL Investigators N Engl J Med 2009;361:1953-1962. Health Care, Education and Research



Effectiveness of Management Strategies for Renal Artery Stenosis: A Systematic Review

Ethan Balk, MD, MPH; Gowri Raman, MD; Mei Chung, MPH; Stanley Ip, MD; Athina Tatsioni, MD; Alvaro Alonso, MD; Priscilla Chew, MPH; Scott J. Gilbert, MD; and Joseph Lau, MD *Ann Intern Med.* 2006;145(12):901-912

Conclusions: Available evidence does not clearly support one treatment approach over another for atherosclerotic renal artery stenosis.

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Causes of resistant hypertension

- Improper blood pressure measurement
 - Home blood pressure monitoring. BC grant
- Volume overload and pseudotolerance
 - Excessive Na intake
 - Kidney disease-volume retention
 - Inadequate diuretic therapy
- Drug induced
 - Nonadherence—education, healthcare team, affordable/tolerated, SMBP
 - NSAIDs, cocaine, amphetamines, sympathomimetics, OCs, adrenal steroids, cyclosporine, erythropoietin, licorice, dietary supplements
- Associated conditions
 - Alcoholism
 - Obesity
 - Clinical inertia by provider to titrate

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Suggested Approach to Resistant Hypertension

1. Establish goal BP
 - Uncomplicated HTN < 140/90
 - Accept <150/90 if age >60 and no diabetes or CKD
2. Clinical judgment rules the day

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Suggested Approach to Resistant Hypertension

3. Establish that resistance is real
 - Meds used are at good doses, compliance
 - Eliminate other substances (ETOH, NSAIDS, etc)
 - Home BP monitoring, consider ambulatory monitoring

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Suggested Approach to Resistant Hypertension

- 4. Consider secondary hypertension workup
 - Especially hyperaldosteronism
 - Renal artery stenosis if sudden increase or flash pulmonary edema

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Suggested Approach to Resistant Hypertension

- 5. Be certain diuretic is adequate
 - If edema present -- increase thiazide, consider chlorthalidone if using indapamide or hydrochlorothiazide
 - Loop diuretic if necessary or GFR <40
Consider using furosemide bid or change to torsemide daily

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Suggested Approach to Resistant Hypertension

- 6. Addition of spironolactone -- especially if overweight or has sleep apnea

Caution: Renal insufficiency
Watch potassium
Consider reducing other med dosages

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Suggested Approach to Resistant Hypertension

7. Consider changing beta blocker to combined alpha/beta blocker (labetolol or carvedilol) or add alpha blocker

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Suggested Approach to Resistant Hypertension

8. Consider adding arteriolar vasodilator or central alpha-2 agonist

- hydralazine, minoxidil
 - » Hydralazine (tachycardia), use with beta blocker
 - » minoxidil (edema), use with diuretic
- clonidine, guanfacine, methyldopa
 - » Avoid in HF, rebound HTN if w/drawal quickly

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Questions????

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