Hypertension: The Latest Treatment Options
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Objectives
• Upon completion of the learning activity the participant will be able to:
  – Describe the clinical consequences of hypertension.
  – Identify antihypertensive medications with compelling indications for use in patients with comorbid conditions, hypertensive urgency and hypertensive emergency.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) JNC-8 to be Released in 2013 for Public Review, Comment, and Later, Final Publication
National Heart, Lung and Blood Institute
National High Blood Pressure Education Program

How to avoid HTN TOD?
• Avoid target organ damage in part by blunting catecholamine effect.
• Attenuate the action of angiotensin II (Ang II)
  – A potent vasoconstrictor that also stimulates adrenal catecholamine release

BP = HR (Heart Rate) X SV (Stroke Volume) X PR (Peripheral Resistance, Also Known as Peripheral Vascular Resistance {PVR})

Yield = Myocardial Remodeling, Vessel Hypertrophy, Endothelial Dysfunction
**Diuretic (thiazide)**

Examples: HCTZ, chlorthalidone

- **MOA**: Low volume sodium depletion that leads to PVR reduction
  
  \[ \text{BP=HR} \times SV \times PVR \downarrow \]

W/ HD (≥HCTZ 25 mg/dL or its equivalent), potential for negative impact on dyslipidemia, glucose control

Monitor for K, Na, Mg depletion. Calcium sparing

Less effective when Cr ≥1.8 mg/dL (159.1 µmol/L) (Loop diuretics will likely remain effective.)

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**Beta adrenergic antagonists (-lol suffix)**

Examples: Atenolol, metoprolol, propranolol

- **MOA**: Block adrenergic B-receptor sites, blunt catecholamine response
  
  \[ \text{BP=HR} \downarrow \times SV \downarrow \times PVR \downarrow \]

Use with caution with COPD, asthma, heart block.

In DM, benefit of beta blocker use outweighs the risk of worsening insulin resistance or masking hypoglycemia symptoms.

With discontinuation, taper slowly

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**Meta-analysis Results: Beta Blockers in Uncomplicated HTN**

- **Stroke**
  - Significantly higher with beta-blockers than with other antiHTN (relative risk, 1.16; 95% CI, 1.04–1.30)
  - Most problematic w/atenolol than w/ other non–beta-blocker antiHTN a (RR, 1.26; 95% CI, 1.15–1.38)

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**Source**


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**American Association of Clinical Endocrinologists**

**Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Hypertension**

Endocrine Practice Vol. 12 No 2 March/April 2006
Recommendation for HTN with DM per AACE

• “In addition to lifestyle modifications, the use of an ACEI or ARB, in conjunction with a low-dose diuretic, a calcium channel blocker, a 3rd generation beta blocker (such as carvedilol) or some combination of these agents, currently seems to be the preferred initial therapeutic regimen for patients with diabetes.”

(continued)

• “In a study of patients with type 2 diabetes and hypertension, carvedilol and atenolol had similar BP lowering effects…”

(continued)

• “…and action in decreasing left ventricular hypertrophy, but triglycerides, fasting plasma glucose, A1C and insulin levels decreased with carvedilol use but increased with atenolol therapy.”

Medication Comments

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme inhibitors (ACEI)</td>
<td>Adjust dose in renal insufficiency. Do not use in presence of bilateral renal artery stenosis. Hyperkalemia risk, especially with inadequate fluid intake, when used with aldosterone antagonist.</td>
</tr>
<tr>
<td>ACEI examples- Lisinopril, enalapril, all with -pril suffix</td>
<td></td>
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<tr>
<td>Angiotensin receptor blockers (ARB)</td>
<td></td>
</tr>
<tr>
<td>ARB examples- Losartan, telmisartan, all with -sartan suffix</td>
<td></td>
</tr>
<tr>
<td>ACEI-induced cough- can use ARB as alternative. Angioedema risk with ACEI use, less so with ARB use Do not use during pregnancy (category D).</td>
<td></td>
</tr>
</tbody>
</table>

Renin-angiotensin Cascade: What works where?
Medication Comments

Direct renin inhibitor
Example- Aliskiren (Tekturna®)
•MOA- Decreases plasma renin activity and inhibits the conversion of angiotensinogen to angiotensin I with end result less Ag II production

Use with caution in renal insufficiency.
Modest hyperkalemia risk, especially with inadequate fluid intake, when used with other potassium sparing drugs.
Rare angioedema and cough risk with use. Do not use during pregnancy (category D).

Calcium channel blockers (CCB)
Dihydropyridine (DHP) examples- Amlodipine, felodipine, others, all with -ipine suffix
NonDHP CCB examples- Diltiazem, verapamil
•MOA- Causes vasodilatation

Ankle edema, particularly with DHP
Non DHP- Caution w/BB, ≥1 degree HB
Verapamil and diltiazem shown to reduce CV mortality, proteinuria and diabetic nephropathy progression independent of ACE inhibitor use
Use with caution in presence of heart failure, renal or hepatic impairment.

Aldosterone antagonist
Examples- Spironolactone, eplerenone
•MOA- Block effects of aldosterone therefore

Hyperkalemia risk, particularly w/ ACEI, ARB use or volume depletion including excessive diuresis
Use with caution in renal impairment.

Centrally acting agents
Examples- Clonidine, methyldopa
•MOA- Works at brain BP control center

Sedation risk
Abrupt withdrawal of clonidine can lead to rebound hypertension.

Algorithm for Treatment of Hypertension

<table>
<thead>
<tr>
<th>Initial Drug Choices</th>
<th>Without Compelling Indications</th>
<th>With Compelling Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Line Therapy</td>
<td>Stage 1 Hypertension</td>
<td>Stage 2 Hypertension</td>
</tr>
<tr>
<td>BB or CCB, or ARB, or ACEI, or diuretic</td>
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</tr>
<tr>
<td>Target: &lt;140/90 mm Hg</td>
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<tr>
<td>Step 2 Therapy</td>
<td>Double the dose of the initial therapy if goal is not met.</td>
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</tr>
<tr>
<td>Target: &lt;130/80 mm Hg</td>
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<td>Target: &lt;130/80 mm Hg</td>
</tr>
<tr>
<td>Initiate second agent</td>
<td>Initiate second agent</td>
<td>Initiate second agent</td>
</tr>
<tr>
<td>Target: &lt;120/70 mm Hg</td>
<td>Target: &lt;120/70 mm Hg</td>
<td>Target: &lt;120/70 mm Hg</td>
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<tr>
<td>Initiate third agent</td>
<td>Initiate third agent</td>
<td>Initiate third agent</td>
</tr>
<tr>
<td>Target: &lt;110/70 mm Hg</td>
<td>Target: &lt;110/70 mm Hg</td>
<td>Target: &lt;110/70 mm Hg</td>
</tr>
<tr>
<td>Initiate fourth agent</td>
<td>Initiate fourth agent</td>
<td>Initiate fourth agent</td>
</tr>
<tr>
<td>Target: &lt;100/60 mm Hg</td>
<td>Target: &lt;100/60 mm Hg</td>
<td>Target: &lt;100/60 mm Hg</td>
</tr>
<tr>
<td>Initiate fifth agent</td>
<td>Initiate fifth agent</td>
<td>Initiate fifth agent</td>
</tr>
<tr>
<td>Target: &lt;90/50 mm Hg</td>
<td>Target: &lt;90/50 mm Hg</td>
<td>Target: &lt;90/50 mm Hg</td>
</tr>
<tr>
<td>Initiate sixth agent</td>
<td>Initiate sixth agent</td>
<td>Initiate sixth agent</td>
</tr>
<tr>
<td>Target: &lt;80/40 mm Hg</td>
<td>Target: &lt;80/40 mm Hg</td>
<td>Target: &lt;80/40 mm Hg</td>
</tr>
<tr>
<td>Initiate seventh agent</td>
<td>Initiate seventh agent</td>
<td>Initiate seventh agent</td>
</tr>
<tr>
<td>Target: &lt;70/30 mm Hg</td>
<td>Target: &lt;70/30 mm Hg</td>
<td>Target: &lt;70/30 mm Hg</td>
</tr>
<tr>
<td>Initiate eighth agent</td>
<td>Initiate eighth agent</td>
<td>Initiate eighth agent</td>
</tr>
<tr>
<td>Target: &lt;60/20 mm Hg</td>
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According to Up To Date

• All patients with diabetes mellitus have a goal blood pressure <140/90 mmHg.
• We suggest (weaker recommendation) an attempt to lower the systolic pressure below 130 to 135 mmHg (preferably less than 130 mmHg) if it can be achieved without producing significant side effects.

According to Up To Date
(continued)

• We recommend a goal blood pressure of less than 130/80 mmHg in patients with diabetic nephropathy and proteinuria (≥500 mg/day). Patients with microalbuminuria are treated similarly to diabetic patients without proteinuria.

Hypertension in the Elderly

ACCF/AHA
Expert Consensus Document
Available at http://content.onlinejacc.org/cgi/content/full/j.jacc.2011.01.008, accessed 1.23.13.

Developed in collaboration with the American Academy of Neurology, Association of Black Cardiologists, American Geriatrics Society, American Society of Hypertension, American Society of Nephrology, American Society for Preventive Cardiology, and the European Society of Hypertension

Hypertension in the Elderly

“There is a dramatic increase in the prevalence of hypertension with aging; by age 70 years, the majority of people have hypertension.”

Mean Blood Pressure According to Age, Sex, and Ethnic Group in U.S. Adults

Hypertension in the Elderly
(continued)

• In older adults, hypertension is characterized by an elevated systolic blood pressure (BP) with normal or low diastolic BP, due to age-associated stiffening of the large arteries.
Pathophysiology of Hypertension in the Elderly

- Flow-mediated arterial dilation, primarily mediated by endothelium-derived nitric oxide, declines markedly with aging.
- Neurohormonal profile of older hypertensive adults characterized by increased plasma norepinephrine, low renin, and low aldosterone levels.

Non-pharmacologic Lifestyle Measures Shown Beneficial in Elderly Hypertensive Subjects

- Regular physical activity
- Sodium restriction
- Weight control
- Smoking cessation
- Avoidance of excessive alcohol intake

Target Blood Pressure Goals in the Elderly

- Although the optimal BP treatment goal in the elderly has not been determined, a therapeutic target of <140/90 mmHg in persons aged 65-79 years and a SBP of 140-145 mmHg, if tolerated, in persons aged ≥80 years is reasonable.

Risk of Adverse Outcomes Among Elderly CAD Patients by Age and BP

- Diuretics, ACE-inhibitors, angiotensin receptor blockers, calcium antagonists, and beta blockers have all shown benefit on CV outcomes in randomized trials among elderly cohorts. The choice of specific agents is dictated by efficacy, tolerability, presence of specific comorbidities, and cost.
Antihypertensive Treatment-related Side Effects

• The high prevalence of both CV and non-CV comorbidities among the elderly dictates need for great vigilance to avoid treatment-related side effects such as:
  – Electrolyte disturbances.
  – Renal dysfunction.
  – Excessive orthostatic BP decline.

General Pharm Rule in Prescribing for the Elder: In this era of “treat to goal,” be aware the age-related variations in therapeutic target.

AACE Medical Guidelines for Clinical Practice for Developing a Diabetes Comprehensive Care Plan

• For older adults who are frail or with anticipated life expectancy of = 5 years, A1C goal should be = 8%, as the risks of hypoglycemia outweigh the benefits of stringent glycemic control.

Risk Factors for Rhabdomyolysis in Statin Users

• From most to least potent
  – Nearly 6-fold to 2.5 fold increase
  – Older age
  – High statin dosage
  – Renal disease
  – Female gender

Compelling Indications for Use of Select Meds in Elder w/HTN

• Heart failure
  – Thiazide diuretic, beta blocker, ACEI, ARB, CCB, aldosterone antagonist
• Post myocardial infarction
  – Beta blocker, ACEI, ARB, aldosterone antagonist
Compelling Indications for Use of Select Meds in Elder w/HTN (continued)

- CAD or high CVD risk
  - Thiazide diuretic, beta blocker, ACEI, CCB
- Angina pectoris
  - Beta blocker, CCB

Compelling Indications for Use of Select Meds in Elder w/HTN (continued)

- Aortopathy/aortic aneurysm
  - Thiazide diuretic, beta blocker, ACEI, CCB

Compelling Indications for Use of Select Meds in Elder w/HTN (continued)

- Diabetes mellitus
  - Thiazide diuretic, beta blocker, ACEI, ARB, CCB
- Chronic kidney disease
  - ACEI, ARB

Compelling Indications for Use of Select Meds in Elder w/HTN (continued)

- Recurrent stroke prevention
  - Thiazide diuretic, ACEI, ARB, CCB

You see, Sam, a 68 YO man...

...who is in for a sick visit with a CC of a skin rash but who states he otherwise feels well.
- He has a hx of HTN but has not taken medications for the past 6 months.
- BP=220/112
- Cardiac=+S4, no murmur
- Abd=No bruit
You see Tim, a 68 YO man...

- who is in for a sick visit with a CC of a skin rash.
- He has a hx of HTN but has not taken medications for the past 6 months.
- When questioned further, he admits to a 4-day history of increasing shortness of breath, headache and blurred vision.
- BP=220/112

Tim (continued)

- Cardiac=+S4, S3, Gr II/ VI holosystolic murmur with radiation to the axilla
- Neck veins=8 cm at 45 degrees
- Abd=No bruit

What is the difference?

- Tim
  - HTN urgency?
  - HTN emergency?
- Sam
  - HTN urgency?
  - HTN emergency?

Hypertensive Crises: Emergencies per JNC-7

- Hypertensive emergency defined
  - Severe elevations in BP (>180/120 mmHg) complicated by evidence of impending or progressive target organ dysfunction (TOD)
- Goal of treating HTN emergency
  - Immediate BP reduction (not necessarily to normal) to prevent or limit target organ
Hypertensive Crises: Emergencies per JNC-7 (continued)

- Goal of treating HTN emergency (cont.)
  - Examples of TOD=Hypertensive encephalopathy, intracerebral hemorrhage, acute MI, acute left ventricular failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysm or eclampsia.

Hypertensive Crises: Emergencies per JNC-7 (continued)

- Goal of therapy in hypertensive emergencies
  - Reduce mean arterial BP by no more than 25 percent (within minutes to 1 hour), then if stable, to 160/100–110 mmHg within the next 2–6 hours.
- Risk of excessive falls in pressure
  - Can precipitate renal, cerebral or coronary ischemia.

HTN Urgency per JNC-7

- “Unfortunately, the term ‘urgency’ has led to overly aggressive management of many patients with severe, uncomplicated hypertension. Aggressive dosing with intravenous drugs or even oral agents, to rapidly lower BP is not without risk.”

HTN Urgency per JNC-7 (continued)

- “Oral loading doses of antihypertensive agents can lead to cumulative effects causing hypotension, sometimes following discharge from the ER.”

HTN Urgency per JNC-7 (continued)

- “Patients with hypertensive urgencies may benefit from treatment with an oral, short-acting agent such as captopril, labetalol, or clonidine followed by several hours of observation.”

HTN Urgency per JNC-7 (continued)

- “However, there is no evidence to suggest that failure to aggressively lower BP in the ER is associated with any increased short-term risk to the patient who presents with severe hypertension.”
**Medication Doses for Use in HTN Urgency**

- **Captopril 12.5 to 25 mg**
  - Onset of action
    - PO route=15-30 min
    - SL route=10-20 min
  - Duration of action
    - PO route=6-8 h
    - SL route=2-6 h
  - Repeat up to 50 mg or as needed

- **Clonidine 0.1-0.2 mg PO**
  - Onset of action
    - 30-60 min
  - Duration of action
    - 8-16 h
  - Repeat with 0.05 to 0.1 mg every 1 to 2 hours to a maximum dose of 0.6 to 0.7 mg

- **Labetalol 200-400 mg PO**
  - Onset of action
    - 1-2 h
  - Duration of action
    - 2-12 h
  - Repeat every 2-3 h

**What about additional or follow-up medications?**

- **Furosemide 20-40 mg**
  - Brisk BP reduction with rapid onset of action
- **CCB**
  - Nifedipine SR 30 mg x 1 or felodipine 5 mg x 1
  - Relatively rapid onset of action with 24 h duration of activity

**Source**


**End of Presentation**

Thank you for your time and attention.

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