Advances in Management of Hypertension

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Associate Dean for GME and CME

Declaration of full disclosure: No conflict of interest

Current Status of Hypertension

- Prevalence 29%; Blacks 33.5%
- About 72.5% treated; 53.5% uncontrolled (>140/90)
- Risk for poor control: Latinos, Blacks, age 18-44 and ≥80, <300% poverty, < college degree
- Better control: Any insurance, ≥2 visits, and a usual source of care

MMWR 2012;61: 703-709

Hypertension Control by Cardiovascular Disease and Risk: NHANES, 2003-04

<table>
<thead>
<tr>
<th>Condition</th>
<th>%HTN</th>
<th>%Rx</th>
<th>% Not Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Risk</td>
<td>34</td>
<td>66</td>
<td>35</td>
</tr>
<tr>
<td>Diabetes</td>
<td>85</td>
<td>96</td>
<td>54</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>83</td>
<td>95</td>
<td>53</td>
</tr>
<tr>
<td>CHF</td>
<td>86</td>
<td>98</td>
<td>50</td>
</tr>
<tr>
<td>Cardiovascular Dis</td>
<td>85</td>
<td>95</td>
<td>51</td>
</tr>
<tr>
<td>Framingham Score ≥10</td>
<td>77</td>
<td>68</td>
<td>59</td>
</tr>
</tbody>
</table>

In patients with elevated BP, my normal practice is:

1) Review the medical assistant’s recorded BP measurement

2) Retake the BP myself, using correct techniques, and record my value in the medical record
Advances in Management of Hypertension

Accurate BP Measurement

1) Seated for 5 minutes in chair
2) Arms bared and supported
3) No cigs, coffee; no talking
4) Correct fitting cuff for right arm (small cuff results in elevated BP: 3/2 mm Hg - 12/8 mm Hg)
5) First appearance of sound is SBP; disappearance is DBP
6) Two or more reading in 2 minutes averaged
7) Two visits to define HTN

Treatment Based on What Blood Pressure Measurement?

- Office clinician measures are standard, used in trials
- Home BP measurement leads to less intensive drug Rx & BP control. Identifies “white-coat” HTN
- Ambulatory monitor measures higher correlation with CVD

Clinic, Home and Ambulatory BP in Diagnosis of Hypertension

- Systematic review comparing measures in initial diagnosis
- 20 studies with 5683 patients, compared to ambulatory monitor daytime mean ≥135/85

<table>
<thead>
<tr>
<th>Measure</th>
<th>Definition</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home 135/85 mean</td>
<td>+LR = 2.28 -LR= 0.23</td>
<td>85.7%</td>
<td>62.4%</td>
</tr>
<tr>
<td>Clinic 140/90 mean</td>
<td>+LR = 2.94 +LR = 0.34</td>
<td>74.6%</td>
<td>74.6%</td>
</tr>
</tbody>
</table>


Joint National Commission 8 (JNC 8)

Three questions:
1) Does Rx at specific BP thresholds improve outcomes?
2) Does Rx to a specific BP goal improve outcomes?
3) Do various meds differ on outcomes?

Nine recommendations
ADVANCES IN MANAGEMENT OF HYPERTENSION

73 yo woman. BP=148/88. No DM. Creat 1.1. Otherwise well. On non-drug therapy. The next best step is:

1) Continue current therapy
2) Begin hydrochlorothiazide
3) Begin ace inhibitor
4) Begin calcium channel blocker
5) Begin beta blocker

Recommendations for Management of Hypertension

Recommendation 1
≥60 years:

- Lower BP at SBP ≥150 mm Hg or DBP ≥90 mm Hg
- Treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg.

Strong Recommendation – Grade A (but not unanimous)

Hypertension in the Very Elderly Trial (HYVET)

- 3845 patients ≥ 80 y, 2 years
- >160 mm Hg – goal of 150/80 mm Hg BP=173/91
- Indapamide SR 1.5 mg vs. placebo Added perindopril if needed

HYVET Study Results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Meds</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>12.4</td>
<td>17.7</td>
<td>0.64 (0.46 - 0.95)</td>
</tr>
<tr>
<td>CVA Death</td>
<td>6.5</td>
<td>10.7</td>
<td>0.55 (0.33 - 0.93)</td>
</tr>
<tr>
<td>CHF</td>
<td>5.3</td>
<td>14.8</td>
<td>0.28 (0.17 - 0.48)</td>
</tr>
<tr>
<td>CV Death</td>
<td>23.9</td>
<td>30.7</td>
<td>0.73 (0.55 - 0.97)</td>
</tr>
<tr>
<td>Any Death</td>
<td>47.2</td>
<td>59.6</td>
<td>0.72 (0.59 - 0.88)</td>
</tr>
</tbody>
</table>
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HYVET Conclusions and Implications

- Benefits appear at 1 year of Rx
- NNT = 20 to prevent one stroke
- NNT = 10 to prevent one CHF
- Never too old to treat SBP > 160
- Goal does not have to be < 140

Recommendations for Management of Hypertension

Corollary Recommendation
≥60 years:

- If treatment results in lower SBP (e.g., <140 mm Hg) and is well tolerated treatment does not need to be adjusted.

Expert Opinion – Grade E

Recommendation 2

<60 years:

- Treat to lower BP at DBP ≥90 mm Hg
- Treat to a goal DBP <90 mm Hg.

30-59 years, Strong Recommendation – Grade A
18-29 years, Expert Opinion – Grade E

73 yo woman, BP=140/88. No DM, Creatinine 1.1. Otherwise well. On non-drug therapy. The next best step is:

1) Continue current therapy
2) Begin hydrochlorothiazide
3) Begin ace inhibitor
4) Begin calcium channel blocker
5) Begin beta blocker
Recommendation 3
<60 years:
- Treat to lower BP at SBP ≥140 mm Hg
- Treat to a goal SBP <140 mm Hg.
(Expert Opinion – Grade E)

Recommendation 4
≥18 years with chronic kidney disease (CKD) (GFR < 60 or proteinuria >30 mg alb/g creat):
- Treat to lower SBP ≥140 mm Hg or DBP ≥90 mm Hg
- Treat to goal SBP <140 mm Hg and goal DBP <90 mm Hg.
(Expert Opinion – Grade E)

Recommendation 5
≥18 years with diabetes, treat to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg
- Treat to a goal SBP <140 mm Hg and goal DBP <90 mm Hg.
(Expert Opinion – Grade E)

Intensive BP Control in Type 2 DM: ACCORD
- RCT of 4733 patients with type 2 DM
- Compare BP less than 120 mm Hg vs 140
- BP
  - 120
  - 140
- CV events plus death
  - 1.37%
  - 2.09%
- Mortality
  - 1.23%
  - 1.19%
- Stroke
  - 0.37%
  - 0.57%
- Adverse events
  - 3.3%
  - 1.3%
- In type 2 DM: treating to 120 mm Hg did not reduce the rate of composite fatal and non-fatal CV events
Recommendations for Management of Hypertension

Recommendation 6
Nonblack population, including diabetes:

Initial treatment:
- Thiazide-type diuretic
- Calcium channel blocker (CCB)
- Angiotensin-converting enzyme inhibitor (ACEI)
- Angiotensin receptor blocker (ARB).

(Moderate Recommendation – Grade B)

Thiazide Diuretics

- Very effective for systolic BP
- Do not increase sudden death
- Most effective in LVH regression
- Lipid effects are short lasting (1 y)
- Hyperglycemia only in high doses
- Still effective in early chronic kidney disease (to GFR 40-45)
- Erectile dysfunction in 20%
- More effective in Blacks and older

Efficacy of HCTZ

Messerli FH, et al. JACC 2011; 57: S90-S90

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Decrease in mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ 12.5 - 25 mg</td>
<td>6.5/4.5</td>
</tr>
<tr>
<td>HCTZ 50 mg</td>
<td>12.0/5.4</td>
</tr>
<tr>
<td>ACE-I</td>
<td>12.9/7.7</td>
</tr>
<tr>
<td>ARB</td>
<td>13.3/7.8</td>
</tr>
<tr>
<td>CCB</td>
<td>11.0/8.1</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>11.2/8.5</td>
</tr>
</tbody>
</table>

Beta Blockers

- Most effective as mono-therapy in younger persons and whites
- Adverse effects: no clear depression or sexual dysfunction, but + fatigue
- Glucose elevation with A1C increase by 0.2%
- No lasting effect on lipids
- Less efficacy in stroke prevention among those older than 60 years
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**Atenolol in hypertension: is it a wise choice?**

No benefit to prevent MI or All-cause mortality

**ACE-I or ARB**

- 30% reduction of ESRD (dialysis) and of doubling of serum creatinine; optimal with GFR 30-60, proteinuria
- Not better tolerated than other drugs
- Regression of LVH not more than other drugs—SBP reduction
- Elevates K+
- Do not use in women < 50 y
- Works less well in Blacks as 1 drug
- Best choice in diabetes (in non-blacks)
- Don’t combine

**Calcium Channel Blockers**

- Effective in Blacks and elderly
- Effective in preventing CV events
- No increase risk of cancer
- Short acting CCB may be harmful
- Effective in systolic hypertension
- Better outcomes in latest trials

**ACCOMPLISH**

*Calcium Blockers Combined with ACE*

- Comparison of combinations: ACE-I + HCTZ vs. ACE-I + amlodipine. 3 yrs
- RCT, 11,506 patients, ≥ 65 y, 60% men, 83% White, 60% diabetes, BMI = 31
- Outcomes: CV death, MI, stroke, hospitalization for angina, resuscitation after cardiac arrest, CABG or PCI
- Funded by Novartis: USA and 4 N Europe
ADVANCES IN MANAGEMENT OF HYPERTENSION

ACCOMPLISH Results

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>Benazepril + Amlodipine</th>
<th>Benazepril + HCTZ</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Events</td>
<td>552 (9.6%)</td>
<td>679 (11.8%)</td>
<td>0.80 (0.72-0.90)</td>
</tr>
<tr>
<td>CV Death</td>
<td>107 (1.9%)</td>
<td>134 (2.3%)</td>
<td>0.80 (0.62-1.03)</td>
</tr>
<tr>
<td>All MI</td>
<td>125 (2.2%)</td>
<td>159 (2.8%)</td>
<td>0.76 (0.62-0.99)</td>
</tr>
<tr>
<td>All Strokes</td>
<td>112 (1.9%)</td>
<td>133 (2.3%)</td>
<td>0.84 (0.65-1.08)</td>
</tr>
<tr>
<td>Revasc procedure</td>
<td>334 (5.8%)</td>
<td>386 (6.7%)</td>
<td>0.86 (0.74-1.00)</td>
</tr>
</tbody>
</table>

ACCOMPLISH Conclusions

- Combination of CCB and ACE was superior to ACE/HCTZ
- BP differences of 1 mm only
- Different populations may matter
- Chlorthalidone vs. HCTZ?
- Recommendation to change practice in highest risk patients – ACE and CCB may have special benefits

53 yo African-American man, BP=148/88. DM Type 2. Creatinine 1.1. Otherwise well. On non-drug therapy. The next best step is:

1) Continue current therapy
2) Begin hydrochlorothiazide
3) Begin ACE inhibitor
4) Begin calcium channel blocker
5) Begin angiotensin receptor blocker

Recommendations for Management of Hypertension

Recommendation 7
Black population, including diabetes:

Initial treatment:
- Thiazide-type diuretic
- Calcium Channel Blocker (CCB)

General black population: Moderate Rec – Grade B
Black patients with diabetes: Weak Rec – Grade C
ADVANCES IN MANAGEMENT OF HYPERTENSION

53 yo African-American man, BP=148/88. + DM Type 2, Creatinine 1.1. Otherwise well. On non-drug therapy. The next best step is:

1) Continue current therapy
2) Begin hydrochlorothiazide
3) Begin ACE inhibitor
4) Begin calcium channel blocker
5) Begin angiotensin receptor blocker

Recommendations for Management of Hypertension

Recommendation 8
≥18 years with CKD, initial (or add-on) treatment:
- ACEI or ARB to improve kidney outcomes.
- For all CKD patients with HTN regardless of race or diabetes
Moderate Recommendation – Grade B

Recommendation 9
- If goal BP not reached within 1 month, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB).
- Assess BP and adjust the treatment regimen until goal is reached.
- If goal cannot be reached with 2 drugs, add and titrate a third drug from the list provided.

Recommendation 9
- Do not use an ACEI and an ARB together in the same patient.
- If goal cannot be reached using the drugs in rec 6 drugs from other classes can be used.
- Referral to a specialist may be indicated

Expert Opinion – Grade E
ADVANCES IN MANAGEMENT OF HYPERTENSION

**Table 4: Evidence-Based Dosing for Antihypertensive Drugs**

<table>
<thead>
<tr>
<th>Antihypertensive Medication</th>
<th>Initial Daily Dose, mg</th>
<th>Target Dose in 7 Days, mg</th>
<th>No. of Doses per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>50</td>
<td>150-200</td>
<td>2</td>
</tr>
<tr>
<td>Enalapril</td>
<td>5</td>
<td>20</td>
<td>1-2</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eprosartan</td>
<td>400</td>
<td>600-800</td>
<td>1-2</td>
</tr>
<tr>
<td>Candesartan</td>
<td>4</td>
<td>12-32</td>
<td>1</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>50</td>
<td>300</td>
<td>1-2</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40-80</td>
<td>160-320</td>
<td>1</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>75</td>
<td>300</td>
<td>1</td>
</tr>
<tr>
<td>ARBs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren</td>
<td>25-50</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50</td>
<td>100-200</td>
<td>1-2</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>2.5</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Diltiazem extended release</td>
<td>120-180</td>
<td>360</td>
<td>1</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10</td>
<td>20</td>
<td>1-2</td>
</tr>
<tr>
<td>Thiazide type diuretics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
<td>5</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Chlorothalidone</td>
<td>12.5</td>
<td>37.5-50</td>
<td>1</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>12.5-25</td>
<td>25-100</td>
<td>1-2</td>
</tr>
<tr>
<td>Indapamide</td>
<td>1.25</td>
<td>1.25-2.5</td>
<td>1</td>
</tr>
</tbody>
</table>

**Strategies to Dose BP Meds**

1) One drug, titrate to max, add second
2) One drug, add second before max of initial
3) Two drugs at same time, separate or as combo

**What About Other Drugs?**

- Spironolactone
- Beta blockers
- CNS sympatholytics: Clonidine
- Little reason to use methyldopa
- Alpha-1 blockers: OK but inferior as single drug and tachyphylaxis
- Labetalol good 5th or 6th choice
- Direct vasodilators - hydralazine or minoxidil - need more diuretics
- Peripheral adrenergic antagonists

**Individual Lifestyle Modifications for Hypertension Control**

- Weight loss if overweight: 5-20 mm Hg/10-kg weight loss
- Limit alcohol to ≤ 1 oz/day: 2-4 mm Hg
- Reduce sodium intake to ≤100 meq/d (2.4 g Na): 2-8 mm Hg in SBP
- DASH Diet: 6 mm alone; 14 mm plus Na
- Physical activity 30 min/day: 4-9 mm Hg
- Habitual caffeine consumption not associated with risk of HTN
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Table 6: Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Population</th>
<th>Goal BP, mm Hg</th>
<th>Initial Drug Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 Hypertension</td>
<td>General (HD y)</td>
<td>&lt;130/80</td>
<td>Thiazide-type diuretic, ACEI, ARB, or CCB, or CCB</td>
</tr>
<tr>
<td></td>
<td>General (HD y)</td>
<td>&lt;125/75</td>
<td>Thiazide-type diuretic, ACEI, ARB, or CCB, or CCB</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;140/90</td>
<td>ACEI or ARB or CCB</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>&lt;140/90</td>
<td>ACEI or ARB or CCB</td>
</tr>
<tr>
<td></td>
<td>CKD with proteinuria</td>
<td>&lt;130/80</td>
<td>ACEI or ARB or CCB</td>
</tr>
<tr>
<td>SHEP 2013</td>
<td>General (HD y)</td>
<td>&lt;120/70</td>
<td>Thiazide-type diuretic, ACEI, ARB, or CCB, or CCB</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;130/80</td>
<td>ACEI or ARB or CCB</td>
</tr>
<tr>
<td>CHMP 2013</td>
<td>General (HD y)</td>
<td>&lt;120/80</td>
<td>Thiazide-type diuretic, ACEI, ARB, or CCB, or CCB</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;130/80</td>
<td>ACEI or ARB or CCB</td>
</tr>
<tr>
<td>AHA 2013</td>
<td>Diabetes</td>
<td>&lt;130/80</td>
<td>ACEI or ARB or CCB</td>
</tr>
<tr>
<td>RHEO 2014</td>
<td>General (HD y)</td>
<td>&lt;120/70</td>
<td>Thiazide-type diuretic, ACEI, ARB, or CCB, or CCB</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;130/80</td>
<td>ACEI or ARB or CCB</td>
</tr>
<tr>
<td>NHBP 2013</td>
<td>Black, lower risk</td>
<td>&lt;130/80</td>
<td>Thiazide-type diuretic, ACEI, ARB, or CCB, or CCB</td>
</tr>
<tr>
<td></td>
<td>Target organ damage</td>
<td>&lt;130/80</td>
<td>Thiazide-type diuretic, ACEI, ARB, or CCB, or CCB</td>
</tr>
</tbody>
</table>

Select a drug treatment titration strategy

**2014 Hypertension Guideline Management Algorithm**

- Adult aged ≥ 18 years with hypertension
  - Set blood pressure goal and initiate blood pressure lowering medication based on age, diabetes, and chronic kidney disease (CKD)
  - General population (no diabetes or CKD)
    - Nonblack
      - Initiate thiazide-type diuretic or CCB, alone or in combination
    - Black
      - Initiate thiazide-type diuretic or CCB, alone or in combination
- Diabetes or CKD present
  - Select a drug treatment titration strategy

**2014 Hypertension Guideline Management Algorithm**

- 2014 Hypertension Guideline Management Algorithm
  - Select a drug treatment titration strategy
  - All ages
    - Diabetes present
      - No CKD
        - Blood pressure goal: SBP < 140, DBP < 90
      - CKD present
        - Blood pressure goal: SBP < 140, DBP < 90
    - No diabetes
      - Blood pressure goal: SBP < 140, DBP < 90
  - All ages
    - Diabetes or CKD present
      - Blood pressure goal: SBP < 140, DBP < 90
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Key Points of JNC 8

1) ≥60 yo: goal ≤150
2) Others <140/<90 (including DM, CKD, race/ethnicity)
3) Non blacks: thiazide, CCB, ACEI, ARB
4) Blacks: thiazide, CCB
5) CKD: ACEI or ARB

One Other Key Point

Take the BP accurately yourself, and record it in the medical record.
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Table 1: Strength of Recommendation

<table>
<thead>
<tr>
<th>Topic</th>
<th>JNC 7</th>
<th>2014 Hypertension Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitions</td>
<td>Written by expert committee on a range of study designs</td>
<td>Written by expert committee on a range of study designs</td>
</tr>
<tr>
<td>Treatment goals</td>
<td>Defined by expert committee on a range of study designs</td>
<td>Defined by expert committee on a range of study designs</td>
</tr>
<tr>
<td>Lifestyles</td>
<td>Defined by expert committee on a range of study designs</td>
<td>Defined by expert committee on a range of study designs</td>
</tr>
<tr>
<td>Drug therapy</td>
<td>Defined by expert committee on a range of study designs</td>
<td>Defined by expert committee on a range of study designs</td>
</tr>
<tr>
<td>Scope of target</td>
<td>Defined by expert committee on a range of study designs</td>
<td>Defined by expert committee on a range of study designs</td>
</tr>
<tr>
<td>Source of evidence</td>
<td>Defined by expert committee on a range of study designs</td>
<td>Defined by expert committee on a range of study designs</td>
</tr>
</tbody>
</table>

Table 2: Evidence Quality Rating

<table>
<thead>
<tr>
<th>Type of Evidence</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled analyses of moderate and large trials</td>
<td>High</td>
</tr>
<tr>
<td>Pooled analyses of small trials</td>
<td>Moderate</td>
</tr>
<tr>
<td>Meta-analyses of observational studies</td>
<td>Moderate</td>
</tr>
<tr>
<td>Randomized clinical trials</td>
<td>High</td>
</tr>
<tr>
<td>Nonrandomized clinical trials</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Table 3: Strategies to Lower Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Start one drug, titrate to maximum dose, and add second drug</td>
<td>If goal BP is not achieved with the initial drug, titrate the dose to the maximum recommended dose. Add a second drug to achieve goal BP.</td>
</tr>
<tr>
<td>B</td>
<td>Start one drug and then add a second drug before achieving maximum dose</td>
<td>If goal BP is not achieved with the initial drug, add a second drug as soon as possible.</td>
</tr>
<tr>
<td>C</td>
<td>Begin with 2 drugs at the same time, either as a single pill combination</td>
<td>If goal BP is not achieved with 2 drugs, add a third drug to achieve goal BP.</td>
</tr>
</tbody>
</table>

Table 4: Comparison of Current Recommendations With JNC 7 Guidelines

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