Treating Hypertension from Initiation to Resistance: A Case Study Approach

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Presentation

- **Review current recommendations for blood pressure targets & preferred drug classes**

- **Discuss strategies to achieve blood pressure goals including hypertensive drug classes, their mechanism of action, and when and why to use them.**

- **Discuss the evaluation and treatment of resistant hypertension.**
Focus on JNC 8

1. Does initiating antihypertensive pharmacological therapy at specific BP thresholds improve health outcomes? When should you initiate treatment?
2. Does treatment with an antihypertensive pharmacological therapy to a specified BP goal lead to improvements in health outcomes? How low should you go?
3. Do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes? How do you get there?
Presentation

- Hypertension Management: A Case Study Approach
  - Case 1
  - Case 2
  - Case 3
  - Case 4
  - Case 5
Case 1

- 45 year old male presents to the clinic for his annual physical examination. He is exercising regularly and attempts to follow a healthy diet although he states he could do better.
  - PMHx: Non contributory
  - No excess ethanol and no tobacco use
Case 1

- Physical examination:
  - Sitting blood pressure average of 2 readings:
    - 136/88 mm Hg, pulse 60
    - BMI 30
  - Remainder of the physical examination is normal
  - Review of blood pressure from his last physical 1 year ago was 134/86 mm Hg
Case 1: How would you treat this patient?

- A. Lifestyle modifications
- B. Candsartan 16 mg daily
- C. Chlorthalidone 25 mg daily
- D. Metoprolol 50 mg daily
- E. Return to clinic in 1 year
Hypertension Prevalence

- 50 million Americans have elevated blood pressure or take antihypertensive medications
- Over 2.5 million Americans under the age of 18 have high blood pressure
- 1.6-1.9% of all adolescents are diagnosed with hypertension
**Definition of Hypertension**

- **JNC 7 Classification System**

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP</th>
<th>DBP</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and &lt;80</td>
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<tr>
<td>Pre-hypertension</td>
<td>120-139</td>
<td>or 80-89</td>
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<tr>
<td>Hypertension</td>
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<td></td>
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<tr>
<td>Stage 1</td>
<td>140-159</td>
<td>or 90-99</td>
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<tr>
<td>Stage 2</td>
<td>&gt;160</td>
<td>or &gt;100</td>
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Lifestyle Modifications

- Sodium intake
- Potassium intake
- Weight reduction
- Physical Fitness
- Alcohol Consumption

Salt intake and hypertension

L. Dahl 1960
Sodium recommendations

- Previous recommendations
  - <2,300 mg for all adults
- Current recommendations
  - < 2,300 mg/day
  - < 1,500 mg/day
    - Those >50 years of age
    - African Americans
    - Those with hypertension, diabetes mellitus, or chronic kidney disease
Only 10% of adults achieve recommended dietary sodium restrictions

- 15-20% of intake is from patients adding salt to food

Government and ADA encouraging manufacturers and restaurants to reduce added salt by 50% by 2013

- Identify salt substitutes, re-formulate products
- Wal-Mart, Kraft Foods, and Campbell soups have announced goals for re-formulation of products in the next 5 years
Sodium recommendations

- Top 10 dietary sources of sodium ~45% intake
  - 1. Breads/rolls
  - 2. Cold cuts
  - 3. Pizza
  - 4. Poultry
  - 5. Soups
  - 6. Sandwiches
  - 7. Cheese
  - 8. pasta
  - 9. Meat dishes
  - 10. Snack foods

www.cdc.gov
Sodium restriction

- Cochrane Review
  - 7 clinical trials evaluating sodium restriction intervention as compared to controls
  - Mortality and CVD morbidity
    - 3 normotensive trials
    - 2 hypertensive trials
    - 1 mixed-normotensive and hypertensive
    - 1 CHF

Taylor RS et al. Am J Hypertension 2011;843-853
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Favors reduced salt</th>
<th>Favors control</th>
<th>Risk ratio</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
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<tr>
<td>1.1.1 Normotensive</td>
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<tr>
<td>HPT 1989 [36 mo]</td>
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<td>196</td>
<td>1</td>
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<tr>
<td>TOHP I 1992 [18 mo]</td>
<td>6</td>
<td>327</td>
<td>12</td>
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<tr>
<td>TOHP II 1997 [36 mo]</td>
<td>16</td>
<td>1,191</td>
<td>24</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>1,714</td>
<td>1,804</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>23</td>
<td>37</td>
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</tbody>
</table>

Heterogeneity: $\chi^2 = 0.06$, df = 1 ($P = 0.96$); $I^2 = 0$
Test for overall effect: $Z = 1.53$ ($P = 0.13$)

1.1.2 Hypertensive

|                  | Events  | Total | Events  | Total | Weight | M-H, fixed, 95% CI | M-H, fixed, 95% CI |
|------------------|---------|-------|---------|-------|--------|                   |                   |
| Chang 2006 [31 mo] | 192     | 768   | 312     | 1,213 | 98.2%  | 0.97 [0.83, 1.14]  |                   |
| Morgan 1978 [7-71 mo] | 4       | 35    | 5       | 42    | 1.8%   | 0.96 [0.28, 3.30]  |                   |
| Subtotal (95% CI) | 803     | 1,255 | 100.0%  | 0.97 [0.83, 1.13] |                   |
| Total events     | 196     | 317   |        |        |        |                   |                   |

Heterogeneity: $\chi^2 = 0.00$, df = 1 ($P = 0.96$); $I^2 = 0$
Test for overall effect: $Z = 0.36$ ($P = 0.72$)

1.1.3 Heart failure

|                  | Events  | Total | Events  | Total | Weight | M-H, fixed, 95% CI | M-H, fixed, 95% CI |
|------------------|---------|-------|---------|-------|--------|                   |                   |
| Paterna 2006 [6.4 mo] | 15    | 114   | 6       | 116   | 100.0% | 2.59 [1.04, 6.44]  |                   |
| Subtotal (95% CI) | 114     | 116   | 100.0%  | 2.59 [1.04, 6.44] |                   |
| Total events     | 15      | 6     |        |        |        |                   |                   |

Heterogeneity: Not applicable
Test for overall effect: $Z = 2.05$ ($P = 0.04$)

Figure 2 | All-cause mortality at end of trial. Duration of follow-up reported in parentheses.
Case 1: How would you treat this patient?

- A. Lifestyle modifications
- B. Candsartan 16 mg daily
- C. Chlorthalidone 25 mg daily
- D. Metoprolol 50 mg daily
- E. Return to clinic in 1 year
Type of diuretic: HCTZ vs Chlorthalidone

Ernst ME et al. Am J Hypertension 2010;23:440-446
Presentation

- Nephrology Update: A Case Study Approach
  - Case 1
  - Case 2
  - Case 3
  - Case 4
  - Case 5
Case 2

- 58 yo female comes to the clinic for routine 4 month follow up
  - Diabetes mellitus Type 2 with retinopathy and neuropathy
  - Hypertension
  - TIA in the past year
  - Current blood pressure medications
    - Lisinopril 40 mg daily
    - Chlorthalidone 25 mg daily
Case 2

- Physical examination
  - Blood pressure 134/82 mm Hg, HR 54 bpm
  - Remainder of physical examination non contributory

- Laboratory studies:
  - Creatinine 1.4 mg/dl eGFR 47 ml/min
  - Potassium 5.1 mg/dl
  - Urine protein to creatinine ratio 0.3 mg/mg
Case 2: What is the most appropriate treatment?

- A. Increase lisinopril to 40 mg twice daily
- B. Add losartan
- C. Add amlodipine
- D. Add carvedilol
- E. No change to current therapy
Definition of Hypertension

- Arbitrary cutpoints have been formulated based on cardiovascular risk
- Seventh Report of the Joint National Committee (JNC 7) is considered the standard of care
- Goals
  - <140/90 mm Hg
  - <130/80 mm Hg for those with diabetes mellitus and/or chronic kidney disease
  - Consideration for <125/75 mm Hg for those with proteinuria
Blood pressure targets in diabetics

- ACCORD Trial
- 4,733 type 2 diabetics
  - Intensive therapy SBP <120 mm Hg
  - Standard therapy SBP <140 mm Hg
- Outcome
  - Nonfatal MI, Nonfatal CVA, Death from cardiovascular causes

The ACCORD Study group NEJM 2010;1575-1585
Figure 2. Kaplan–Meier Analyses of Selected Outcomes.
Combination therapy for blood pressure control: ONTARGET Trial

- 25,620 subjects with cardiovascular disease or diabetes mellitus without congestive heart failure
  - Ramipril
  - Telmisartan
  - Combination ramipril and telmisartan

- Primary composite endpoint
  - Death cardiovascular cause, MI, stroke, or hospitalization for CHF

ONTARGET Investigators NEJM 2008
ONTARGET Trial

Figure 1. Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups.

The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.
ONTARGET trial

- Pre-specified analysis of Kidney outcomes
  - Dialysis, doubling serum creatinine, or death
    - 13.5% in ramipril
    - 13.4% in telmisartan
    - 14.5% in combination arm
      - HR 1.09 (1.01, 1.18)
  - Risk of serious adverse events
    - HR 1.33 (1.22, 1.44) disfavoring combination therapy

Mann et al Lancet 2008
ALTITUDE Trial

- ALTITUDE Study
  - Type 2 Diabetes mellitus with microalbuminuria
    - Aliskiren
    - Ace inhibitors or ARBs
  - Outcomes of cardiovascular and renal morbidity and mortality
- December 2011
  - DSMB halted trial
    - Increase incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension in combination arm
Indications for combination therapy: Chronic kidney disease

**Diabetic Kidney Disease**

- Microalbuminuria
  - Level of evidence D: No clinical evidence that supports recommendation for combination therapy

- Macroalbuminuria
  - Level of evidence I: Limited clinical evidence that supports recommendation for combination therapy and awaiting further clinical trial evidence for guidance
Indications for combination therapy

- **Nephron-D Study**
  - Type 2 Diabetes mellitus with macroalbuminuria
    - Losartan
    - Losartan and Lisinopril

- **VALID Study**
  - Type 2 Diabetes mellitus with macroalbuminuria
    - Benazepril and valsartan
    - Valsartan
    - Benazepril
Indications for combination therapy: Chronic kidney disease

Non-Diabetic Kidney Disease

- Proteinuria <500 mg per day
  - Level of evidence I: Limited clinical evidence that supports recommendation for combination therapy and awaiting further clinical trial evidence

- Proteinuria ≥500 mg per day
  - Level of evidence C: Limited clinical evidence that supports recommendation for combination therapy but favor use while awaiting further clinical trial evidence
Blood pressure targets

- JNC 8
  - ? Raising targets for diabetics based on ACCORD study to SBP 140 mm Hg
  - Avoidance of combination therapy in those with microalbuminuria

- SPRINT trial
  - ? Raising targets for CKD stage 3 with CVD risk factors
    - SBP <120 mm Hg vs SBP 140 mm Hg
Case 2: What is the most appropriate treatment?

- A. Increase lisinopril to 40 mg twice daily
- B. Add losartan
- C. Add amlodipine
- D. Add carvedilol
- E. No change to current therapy
Presentation

- Nephrology Update: A Case Study Approach
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Case 3

- 40 yo Caucasian man comes to clinic for ER follow up for increased dyspnea on exertion, headache and high blood pressures of 180/120 mm Hg
- At that time he was started on amlodipine
- No past medical history and not previously taking any prescribed medications
Case 3

- Physical examination
  - Blood pressure 178/95 mm Hg
  - Remainder of physical examination non contributory except for a S 4 gallop and mild lower extremity edema bilaterally

- Laboratory studies:
  - Creatinine 4.0 mg/dl eGFR 22 ml/min
  - Potassium 4.3

- Echocardiogram with diastolic dysfunction
Case 3

- A. Start lisinopril
- B. Refer for MRA of the renal arteries
- C. Add carvedilol
- D. Schedule renal arteriogram
- E. No change to current therapy
Case 3

- He underwent a renal arteriogram and found to have a 70% occlusion of the left renal artery and near 100% occlusion of the right renal artery.
- Bilateral renal artery stenting was performed.
- Repeat creatinine 1.3, blood pressure 130/70.
Secondary hypertension

- Less than 5% of all individuals with hypertension
- Characterized by an underlying cause that if corrected will result in a cure

Etiologies
- Chronic kidney disease
- Renovascular Disease
- Hyperaldosteronism
- Pheochromocytoma
- Illicit drug use
- Obstructive sleep apnea
Clues for secondary hypertension

- Severe/resistant hypertension
- Accelerated hypertension with previous control
- Age <30 years
  - Non-obese
  - Caucasian ethnicity
- Negative family history of hypertension
Initial evaluation

- Laboratory studies
  - Potassium, creatinine, urinalysis, TSH, calcium
  - Hypokalemia
    - Plasma renin activity, aldosterone:renin ratio
  - Plasma metanephrines
- Medication/Drug review
  - OCPs, urine toxicology screening
- Radiology studies
  - Imaging studies for renovascular disease, chronic kidney disease, Abdominal CT/MRI for pheochromocytoma or adrenal pathology
Renovascular Disease

- ACC/AHA 2005 Practice Guidelines
- Do not screen for renovascular disease unless there is a plan for intervention

Circulation 2006;113:e463
Renovascular Disease

- ASTRAL Trial
  - 806 patients with unilateral atherosclerotic renal disease
    - Revascularization + medical therapy
      - Angioplasty +/- stenting
    - Medical therapy alone
      - Statin therapy
      - Antiplatelet agents
      - Optimal blood pressure control
  
- Primary outcome: Kidney function

- Secondary outcomes:
  - Blood pressure control, time to renal and major cardiovascular events, and mortality

NEJM 2009;361:1953-1962
Renovascular Disease: Kidney function
Renovascular Disease: Blood pressure control
Renovascular Disease: When to Screen

- Indications for possible intervention:
  - Failure of anti-hypertensive therapy
  - Intolerance of anti-hypertensive therapy
  - Progressive kidney failure with bilateral renal artery disease
  - Fibromuscular dysplasia
Renovascular Disease: When to Screen

- **How to Screen?**
  - Gold standard
    - Renal Arteriography
  - Others
    - MRA renal arteries
    - CTA renal arteries
    - Duplex doppler ultrasonography
  - Ace renogram no longer recommended for screening due to low sensitivity and specificity of the test
Presentation

- Nephrology Update: A Case Study Approach
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  - Case 5
Case 4

- 56 yo Caucasian man presents to clinic for a blood pressure check
  - Home blood pressure readings typically in the 150/90 mm Hg range
  - Morbid obesity
  - Obstructive sleep apnea
  - Hypertension
  - Glucose intolerance
Case 4

- Physical examination
  - Blood pressure 154/88 mm Hg
  - Remainder of physical examination non contributory except abdominal obesity and 1+ bil LE edema
- Current medications
  - Lisinopril 40 mg twice daily
  - Chlorthalidone 25 mg daily
  - Carvedilol 25 mg twice daily
Case 4

- A. Add clonidine
- B. Add spironolactone
- C. Add verapamil
- D. Change HCTZ to lasix 40 mg daily
- E. No change to current therapy
Management of resistant hypertension

- Defined as failure to achieve target blood pressure on maximal dose of 3 anti-hypertensive agents
  - Risk factors
    - Aging
    - Obesity
    - Sleep apnea
    - CKD
An Approach to Achieving BP Goal in Resistant Hypertension

Initiate Treatment for Hypertension
(if systolic BP \( \geq 20 \) mmHg above goal)
START RAS Based Combination therapy
(including thiazide diuretic* or CCD)
Recheck within 3-4 weeks
if BP Still Not at Goal (140/90, general population, 130/80 mm Hg diabetes, CKD) and agents used are a maximal tolerated dose
Evaluate with Home or 24-hour ambulatory Blood Pressure and eliminate exogenous substances that raise pressure as well as secondary causes

Negative
Consider adding vasodilating β blocker** or Aldosterone Receptor Blocker if obese or has sleep apnea

Positive
Consider altering timing of medication-if non-dipper dose at bedtime or after dinner
If adding meds, consider vasodilating β blocker**
Or Aldosterone Receptor Blocker if obese or has sleep apnea
Recheck within 3-4 weeks
If BP Still Not at Goal

Refer to Clinical Hypertension Specialist†

Management of resistant hypertension

- Addition of spironolactone or eplerenone in obese subjects or those with sleep apnea
  - Mean decrease in blood pressure -25/12 mm Hg
  - ASCOT trial
    - Addition of spironolactone to other bp agents
      - Mean decrease in blood pressure -21.9/9.5 mm Hg
  - Concern for hyperkalemia when added to ace/ARB in CKD

Chapman N et al. Hypertension 2007;839-845
Case 4

- A. Add clonidine
- B. Add spironolactone
- C. Add verapamil
- D. Change chlorthalidone to lasix 40 mg daily
- E. No change to current therapy
Presentation

- Nephrology Update: A Case Study Approach
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  - Case 3
  - Case 4
  - Case 5
Case 5

- 48 yo African American man is being seen in the clinic after hospital follow-up for accelerated hypertension
  - Home blood pressure readings typically in the 175/100 mm Hg range
  - Compliant with medications
  - No illicit drug use
Case 5

- Physical examination
  - Blood pressure 178/108 mm Hg
  - Remainder of physical examination non contributory except 1+ bil LE edema
- Current medications
  - Nifedipine 90 mg twice daily
  - Spironolactone 50 mg daily
  - Metoprolol 100 mg twice daily
Case 5

- A. Add clonidine
- B. Add lasix
- C. Add minoxidil
- D. Refer for renal sympathetic denervation
- E. No change to current therapy
Symplicity Hypertension 2 Trial

- 106 patients with resistant hypertension
- SBP >160 mm Hg on ≥ 3 anti-hypertensive agents
- Randomized
  - Renal sympathetic denervation
  - Control with medication adjustment

Symplicity HTN 2 Trial Investigators. Lancet 2010;1903-1909
Renal Sympathetic Denervation
Renal Sympathetic Denervation

- July 2011
  - FDA grants approval for US trial for renal denervation
  - Medtronic planning multi-centered Symplicity 3-Hypertension trial
  - Recruitment of sites and participants ongoing
Case 5

- A. Add clonidine
- B. Add lasix
- C. Add minoxidil
- D. Refer for renal sympathetic denervation
- E. No change to current therapy