Taking the Pressure Off: Selecting Add-on Therapy to Reach Goal Blood Pressure

Cincinnati, OH

October 30, 2008
11:00 AM – 12:15 PM
Session 9: Taking the Pressure Off: Selecting Add-on Therapy to Reach Goal Blood Pressure

Learning Objectives

- Incorporate JNC 7 guidelines into the management of hypertension.
- Describe the benefits of combination therapy.
- Identify effective strategies for managing hypertension in patients with diabetes to avoid end-organ damage.

Faculty

Philip Altus, MD, MACP
Professor Emeritus
Department of Internal Medicine
University of South Florida
Tampa, Florida

Dr. Altus is currently a professor emeritus of medicine in the Department of Internal Medicine at the University of South Florida and consulting physician at the James A. Haley VA Hospital in Tampa, Florida. He is a charter member of the American Society of Hypertension and a designated specialist in that field. He has served on the Board of Governors of the American College of Physicians as governor of the Florida chapter. Dr. Altus has been honored as being elected a Master of the American College of Physicians and has received its Laureate Award. He has been a course director for many continuing medical education (CME) programs and has delivered more than 250 CME presentations. He has published many articles in peer-reviewed journals and is a reviewer for the Florida Medical Journal, the American Journal of Medicine, and the Archives of Internal Medicine. His primary clinical interests are cardiovascular risk factors.

Dr. Altus received his medical degree from State University of New York Upstate Medical University in Syracuse, New York, where he also completed his postgraduate training in internal medicine.

Faculty Financial Disclosure Statement

The presenting faculty reported the following:
Dr. Altus has no financial relationships to disclose.

Drug List

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<td>bisoprolol</td>
<td>Zebeta</td>
</tr>
<tr>
<td>captopril</td>
<td>Capoten</td>
</tr>
<tr>
<td>irbesartan</td>
<td>Avapro</td>
</tr>
<tr>
<td>losartan</td>
<td>Cozaar</td>
</tr>
<tr>
<td>olmesartan</td>
<td>Benicar</td>
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<tr>
<td>spironolactone</td>
<td>Aldactone</td>
</tr>
<tr>
<td>triamterene</td>
<td>Dyrenium</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
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</thead>
<tbody>
<tr>
<td>HCTZ + amiloride</td>
<td>Moduretic</td>
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<tr>
<td>HCTZ + bisoprolol</td>
<td>Ziac</td>
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<td>Capozide</td>
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<td>HCTZ + irbesartan</td>
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<tr>
<td>HCTZ + losartan</td>
<td>Hyzaar</td>
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<td>HCTZ + spironolactone</td>
<td>Aldactazide</td>
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<tr>
<td>HCTZ + triamterene</td>
<td>Maxzide, Dyazide</td>
</tr>
</tbody>
</table>

Suggested Reading List


Taking the Pressure Off: Selecting Add-on Therapy to Reach Blood Pressure Goal

Philip Altus MD  MACP
Professor Emeritus
Department of Internal Medicine
University of South Florida
Tampa, Florida

Controlled BP = SBP <140 mm Hg and DBP <90 mm Hg.
BP = blood pressure; NHANES = National Health and Nutrition Examination Survey.
Adapted from Izzo J et al. Hypertension Primer. American Heart Association 2008

Hypertensive Patients (%)

NHANES II (1976–1980)
[Phase I]
[Phase II]
NHANES (1999–2004)

Aware
Treated
Controlled*

10
20
30
40
50
60
70
80
0

Prevalence of Hypertension in the US

Why Poor Control?
• Physician inertia
  – Reluctance to increase dosage
  – Reluctance to add additional medications
• Patient compliance/Patient reluctance
  – Patients do not want to take multiple pills
  – Side effects and cost
• Special populations are hard to get to goal
  – African Americans
  – Hispanics
  – Patients with diabetes
  – Lower socioeconomic and educational groups

Treatment of Hypertension

• Why do we treat Blood Pressure?
  – To prevent complications
• How do we prevent complications?
  – Lower the Blood Pressure
• Does it matter what drug we use?
  – Yes and No

CV Mortality Risk Doubles With Each 20/10 mm Hg BP Increment*

Meta-analysis: 1 Million Adults, 61 Prospective Studies

BP/DBP (mm Hg)
115/75
135/85
155/95
175/105

CV Mortality Risk

10
8
6
4
2
0

BP Reductions as Little as 2 mm Hg Reduce the Risk of CV Events by Up to 10%

Meta-analysis of 61 prospective, observational studies
1 million adults; 12.7 million person-years
Lower baseline blood pressure yields reduced risk for CV events; unclear if pharmacologic BP reduction will result in similar reductions in events.

Meta-analysis: 1 Million Adults, 61 Prospective Studies

2 mm Hg decrease in mean SBP


2 x
4 x
8 x

ARS Question 1

• According to JNC 7, Prehypertension is
  1. BP of 130/80 to 139/89
  2. Labile hypertension
  3. BP of 130/80-139/89 with a positive family history
  4. BP of 120/80-139/89
  5. A patient with the metabolic syndrome

Concepts From JNC-7

• New Classification
  – Normal: <120/80 mm Hg
  – Pre Hypertension: 120-139/80-89 mm Hg
  – Stage 1: 140-159/90-99 mm Hg
  – Stage 2: >160/100 mm Hg

• Initial Therapy
  – Thiazides are still "preferred"
  – CCBs, ACEI, BBs and ARBs are options

JNC Investigators. JAMA 2003; 289: 2560-2572

Residual Lifetime Risk for Hypertension From 55 Years of Age

Individuals who are normotensive at age 55 have a 90% lifetime risk of developing hypertension

JNC Investigators. JAMA 2003; 289: 2560-2572

JNC 7 Highlights

• High-risk conditions are compelling indications for the initial use of specific antihypertensive drug classes
• Most patients will require 2 or more antihypertensive agents to reach their goal blood pressure
• If BP is >20/10 mm Hg above goal, consideration should be given to initiating therapy with 2 agents

JNC Investigators. JAMA 2003; 289: 2560-2572

ALLHAT

• 42,000 Patients Randomized To First Line Therapy of Diuretic, ACEI, CCB, A-Blocker
• Alpha-Blocker Arm Stopped Early Because Of More CHF
• Diuretic (Chlorthalidone) Was Equal To CCBs and ACEIs (primary outcome: fatal CHD or nonfatal MI)

ALLHAT GROUP. JAMA. 2002; 288:2981-2997

ARS Question 2

• In regards to ARBs
  1. They are more cardioprotective than CCB's
  2. They are less cardioprotective than ACEI's
  3. They are more renal protective than ACEI's
  4. Combined with ACEI's they add to renal protection
  5. None of the above
VALUE

• 15,245 Patients with hypertension and at high risk for cardiovascular disease were randomized to Valsartan vs Amlodipine based Rx with a goal of < 140mm/hg
• Followed for 4.2 yrs
• Primary endpoint was 1st CV event (p=NS)
• Results suggest benefit in getting BP down sooner rather than later


VALUE: Differences in SBP With Valsartan vs Amlodipine


VALUE: Myocardial Infarction and SBP Differences at Specific Time Periods


ACEI vs ARB’s vs Both ONTARGET

• 25,620 Pts at high risk for CV events
• Randomized to receive Ramipril 10mg Telmisartan 80mg or both
• Not all pts were hypertensive
• No difference in events in either group
• More side effects (renal insufficiency and/or hypotension) in the combined Rx group


Changing Thoughts

• We need to get away from which is the best drug to what do we need to lower the BP.
• Most patients will require more than 1 drug
• Strategy in high risk patients should focus on what drug should make up the foundation for treatment to which others can be added
• Physiological combination therapy will often give a 20-30 mm Hg drop

Combination Therapy Needed to Achieve Target SBP Goals*

*All trials included some or all patients with diabetes. †Average number per patient.

Changing Thoughts

• We need to get away from which is the best drug to what do we need to lower the BP.
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Combination Therapy Needed to Achieve Target SBP Goals*

*All trials included some or all patients with diabetes. †Average number per patient.
A Changing Paradigm

- In training, we all learned to start with a low dose of an antihypertensive and slowly increase the dose.
- Now we know that early aggressive therapy will lower BP quicker and result in fewer clinical events.
- Early aggressive therapy leads to better compliance when patients are “impressed” with their results.

Altus P. USF Hypertension Conference; October 2007; Tampa, FL.


Pathophysiology: examples of drug-mechanisms

Volume-dependent

Vaso-constrictive

Diuretics

CCBs

Combination therapy

ACEIs

ARBs

CCBs

Benefits of Combination Rx

- 2 meds in 1 pill improves compliance.
- Patients are happy when they see early significant drops in BP.
- Patients who need a 20 mm/Hg drop in BP will almost never get hypotensive with dual therapy.
- Data suggest that early BP reduction results in fewer events.


Combination Therapy

- ACE and a diuretic
- ARB and a diuretic
- Beta-blocker and a diuretic
- ACEI and CCB
- ARB and CCB

INCLUSIVE: Pts achieving goal

INCLUSIVE: Irbesartan/Hydrochlorothiazide Blood Pressure Reductions in Diverse Patient Populations trial
Goals in Treatment

• Decrease risk of classical complications
  – Coronary artery disease
  – Stroke
  – Congestive heart failure (CHF)
  – Renal disease

• A new paradigm
  – The majority of hypertensive patients have insulin resistance and many have the metabolic syndrome. Can treatment reduce the risk of new-onset diabetes?

Hypertension in the 21st Century
Trends in Complications

• Reductions in Coronary Heart Disease
  – May be related to statins, revascularization, antiplatelet Rx, better BP control

• Reductions in Stroke
  – May be related to emphasis on BP control

• Increases in Diabetes
  – May be related to increases in obesity

• Increases in Renal Disease
  – May be related to diabetes and inadequate control of BP, especially in the diabetic

Patients at High Risk

• Elderly
• Metabolic Syndrome Patients
• Diabetics
• African Americans

Patients at High Risk

• Elderly
• Metabolic Syndrome Patients
• Diabetics
• African Americans

ARS Question 3

• In regards to the elderly
  1. Patients with isolated systolic BP have shown benefit with treatment
  2. Pts over the age of 80 have shown benefit with treatment
  3. Goal BP in studies is 150mmHg systolic
  4. All of the above

Hypertension in the Elderly

• Most studies have defined elderly as >65 yo
• All of these have shown benefits with treatment especially in decreasing risk of CHF and stroke
• Pts with isolated systolic BP have also received impressive benefits with treatment
• Entry criteria is often Systolic >160 mm Hg with a goal of < 160 mm Hg or a 10 mm Hg decrease in baseline systolic
• What about the "old old"?

Hypertension in the Elderly

**HYVET**

- 3845 pts >80 yrs old with SBP>160 Rx with indapamide +/- perindopril vs placebo
- Goal BP < 150 systolic
- Rx group:
  - 30% reduction in fatal and non fatal stroke
  - 39% reduction in death from stroke
  - 21% reduction of death from any cause
  - 64% reduction in new onset CHF
- Fewer serious adverse events in Rx group


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Patients at High Risk

- Elderly
- Metabolic Syndrome Patients
- Diabetics
- African Americans

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**Risk Factors of the Metabolic Syndrome and Defining Levels**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist Circumference [Men &gt;102 cm (&gt;40 in) Women &gt;88 cm (&gt;35 in)]</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Men &lt;40 mg/dL Women &lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>≥100 mg/dL</td>
</tr>
</tbody>
</table>


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**Metabolic Syndrome Risk of Disease**

- Patients with the Metabolic Syndrome are at Significant Risk for:
  - Diabetes
  - Hypertension
  - Renal Disease
  - Cardiovascular Disease

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**When Does Diabetes Start?**

Many feel that vascular changes start 10 years prior to diagnosis

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**New Onset of Type 2 Diabetes in Hypertensives**

Does Treatment Matter?
ALLHAT: Incident Diabetes*

Diabetes defined as fasting glucose ≥ 125 mg/dL.

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

NS = not significant vs chlorthalidone.

† P < .008; ‡ P < .01; § P < .001 vs chlorthalidone.


Incidence of Diabetes (%)

<table>
<thead>
<tr>
<th>Year 2</th>
<th>Year 4</th>
<th>Year 6</th>
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<tbody>
<tr>
<td>Chlorthalidone(n=8419)</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Lisinopril(n=4958)</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Amlodipine(n=8419)</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

LIFE: Losartan and the Risk of New-Onset Type 2 Diabetes

RR=25% P<.001

VALUE: Absolute Risk for New-Onset Diabetes

Does Any Diabetic Have Normal Blood Pressure?

Patients at High Risk

- Elderly
- Metabolic Syndrome Patients
- Diabetics
- African Americans
**Approach to BP in the Diabetic**

- Goal BP for patients with diabetes is <130/80 mm Hg
- Pts with high pulse pressures (180/70 mm Hg) may have trouble getting to this level
- Pts with BP of 150/95 mm Hg can get to this level
- New onset type 2 diabetics with SBP of 135 mm Hg need treatment

**BP Treatment in the Diabetic**

- Goal BP is <130/80 mm/Hg
- JNC-7 recommended that if BP is >20/10 mm Hg over your goal, consideration should be given to starting with 2 drugs
- Almost all patients will require at least 2 drugs to get to goal
- Since blocking the renin-angiotensin system is suggested, a combination ACE or ARB with either a diuretic or CCB makes sense

**The Hypertensive Diabetic Patient**

- Special concerns
  - Cardiovascular disease
  - Renal disease
  - Peripheral vascular disease
  - Retinopathy
  - Neuropathy

**The Hypertensive Diabetic Patient**

- Special concerns
  - Cardiovascular disease
  - Renal disease
  - Peripheral vascular disease
  - Retinopathy
  - Neuropathy
UKPDS Mean Blood Pressures

<table>
<thead>
<tr>
<th>Baseline BP (mm Hg)</th>
<th>Mean BP Over 9 yrs (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>Less tight control</td>
<td>160/94</td>
</tr>
<tr>
<td>Tight control</td>
<td>161/94</td>
</tr>
<tr>
<td>Difference</td>
<td>1/0</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP = blood pressure; UKPDS = United Kingdom Prospective Diabetes Study.

ADVANCE

• 11,140 diabetics with average BP 145/81
• Randomized to Perindopril/Indapamide vs placebo followed for an average of 4.3 years
• Placebo BP: 140/77 mm/Hg
• Treatment BP: 135/75 mm/Hg


ADVANCE Results

HOT Trial: BP Control Reduces CV Events

Diabetes Subgroup

<table>
<thead>
<tr>
<th>Achieved</th>
<th>65.2 mm Hg</th>
<th>63.2 mm Hg</th>
<th>61.1 mm Hg</th>
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<tbody>
<tr>
<td>26.4</td>
<td>20.5</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>18.8</td>
<td>14.4</td>
<td>11.9</td>
<td></td>
</tr>
</tbody>
</table>

Goal of Therapy: Target DBP

HOT = Hypertension Optimal Treatment; MI = myocardial infarction.

Syst-Eur Trial: Effect of SBP Control on All CV Events

Diabetic Patients

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Placebo</th>
<th>Active Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Patients</td>
<td>57.6</td>
<td>22.0</td>
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<tr>
<td>62% Risk Reduction</td>
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</table>

Nondiabetic Patients

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Placebo</th>
<th>Active Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Patients</td>
<td>31.4</td>
<td>23.5</td>
</tr>
<tr>
<td>25% Risk Reduction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Syst-Eur = Systolic Hypertension in Europe.
The Hypertensive Diabetic Patient

- Special concerns
  - Cardiovascular disease
  - Renal disease
  - Peripheral vascular disease
  - Retinopathy
  - Neuropathy

Prevalence of CKD Stages 1-3

Trends in End-stage Renal Disease

Death Rate from Kidney Disease

**Pre-ARS Question 5**

- Treatment for a diabetic hypertensive with microalbuminuria should be
  1. Diuretic
  2. Non Dihydropyridine Calcium Blocker
  3. ACE or ARB
  4. Thigh dose ACE or ARB even if BP is controlled on lower dose
  5. Any treatment that lowers BP to goal
IRMA 2: Study Design
590 patients with hypertension, type 2 diabetes, microalbuminuria (albumin excretion rate 20–200 µg/min), and normal renal function

Screening/Enrollment
- 590 randomized
  - Placebo*
  - Irbesartan 150 mg*
  - Irbesartan 300 mg*

Double-blind treatment
- Up to 5 weeks
- 2-year follow-up


IRMA 2: Primary Endpoint—Time to Overt Proteinuria


INNOVATION: Transition from Microalbuminuria to Overt Nephropathy
- Japanese patients with diabetes, microalbuminuria, and normal renal function
- Randomized to telmisartan 80 mg, telmisartan 40 mg, or placebo
- Primary endpoint: progression to frank nephropathy
- Minimum treatment 1 year; average 1.3 years


INNOVATION: Results
Progression to overt nephropathy
- 80 mg: 16.7%
- 40 mg: 22.6%
Microalbuminuria remission
- 80 mg: 21.2%
- 40 mg: 12.8%


Microalbuminuria Take-Home Messages
- For equal BP reduction, irbesartan was more renal protective than usual care
- For equal BP reduction, a higher dose of ARB yielded greater renal protection
- Blocking angiotensin II is beneficial
- Maximum doses should be used

IDNT: Study Design
1715 patients with hypertension, type 2 diabetes, and proteinuria ≥900 mg/day

Screening/Enrollment
- Double-blind Treatment
  - Irbesartan*
  - Placebo/Control group*
  - Amlodipine*

Minimum follow-up: ~2 years (average follow-up 2.6 years)

IDNT = Irbesartan Diabetic Nephropathy Trial. N=1715.
*Adjunctive antihypertensive therapies (excluding ACEIs, ARBs, and CCBs) could be added to all groups to help achieve target BP levels.

Subjects (%) vs Follow-up (months) for IDNT: Primary Endpoint—Time to Doubling of Creatinine, ESRD, or Death.

- Intasartan
- Amlodipine
- Control

Follow-up (months)
0 6 12 18 24 30 36 42 48 54 60

Patients (%) vs SBP (mm Hg) for IDNT: Renal Outcomes Based on SBP:
- Doubled Serum Creatinine Concentration or ESRD

RENAAL: Study Design
- 1513 patients with type 2 diabetes and renal disease
- Randomized to losartan or placebo + conventional antihypertensive agents (eg, CCB, diuretic, α-blockers)
- Followed for 3.4 years
- Urinary albumin:urinary creatinine = 300; serum creatinine = 1.3–3.0 mg/dL
- Primary outcome of serum creatinine concentration doubling, ESRD, or death

RENAAL: Results
Losartan group:
- 16% reduction in primary endpoint
- 25% decrease in doubling of creatinine concentration
- 28% decrease in ESRD
- Benefits not due to BP differences

IDNT and RENAAL: Take-Home Messages
- For equal BP reduction, the ARB was more renal protective than other antihypertensives
- Blocking angiotensin II is beneficial
- Maximum doses should be used
- BP needs to be lowered for benefit

Patients at High Risk
- Elderly
- Metabolic Syndrome Patients
- Diabetics
- African Americans

IDNT: Renal Outcomes Based on SBP

Patients (%) vs SBP (mm Hg)

>149 141–149 134–140 <134
ARS Question 6

• The African-American Hypertensive typically:
  1. Should not be treated with ACEi or ARB since they have lower renin levels and don’t respond well
  2. Have more angioedema with ACEi’s
  3. Get more renal protection from a CCB
  4. Have less LVH than white hypertensives since they have lower renin levels

Hypertension in African Americans

• Prevalence is higher and onset is sooner
• African Americans are at increased risk for
  – Stroke
  – Renal Disease
  – LVH
• There are data suggesting that RAAS blockers may decrease the risk of these events and when used with a diuretic or CCB provide excellent BP lowering

Post-ARS Question

• A new patient with type 2 diabetes well controlled on diet has also been told that her BP was “a little high.” She takes no medications.
• PE: BP: on 3 separate readings is 156/93
• You would
  1. Start HCTZ
  2. Start a Calcium Channel Blocker
  3. Start an ACE or ARB
  4. Start a BB for BP control and cardioprotection
  5. Start a combination ACE or ARB with HCTZ

Post-ARS Question

• Treatment for a diabetic hypertensive with microalbuminuria should be
  1. Diuretic
  2. Non Dihydropyridine Calcium Blocker
  3. ACE or ARB
  4. High dose ACE or ARB even if BP is controlled on lower dose
  5. Any treatment that lowers BP to goal

Conclusions

• Hypertension is a major problem, and we can do a better job in getting patients to goal
• Many patients will require multiple medications; combination therapy has the potential to improve compliance and get patients to goal quickly
• Goals of treatment are lowering BP and reducing complications
• Many hypertensives will develop type 2 diabetes
• Recent studies suggest that blocking the renin-angiotensin system may decrease this risk
• Aggressive treatment is indicated to reduce events