Advanced Treatment of Hypertension for the Cardiologist

Education Partner:

Turnkey Solutions, LLC
Continuous Medical Education

Dallas, Texas
December 12, 2008
Session 2: Advanced Treatment of Hypertension for the Cardiologist

Learning Objectives

- Outline the role of renin-angiotensin-aldosterone system modulation in lowering blood pressure and preventing hypertension-associated target organ damage.
- Outline the implications of inadequately controlled hypertension for target organ damage and cardiovascular events.

Faculty

Alan H. Gradman, MD
The Western Pennsylvania Hospital, Pittsburgh
Professor of Medicine
Temple University School of Medicine
Philadelphia

Dr. Gradman is program director of the Cardiology Fellowship Training Program at The Western Pennsylvania Hospital in Pittsburgh as well as a professor of medicine at Temple University School of Medicine in Philadelphia. Dr. Gradman’s former positions include associate professor of medicine at Yale University School of Medicine and chief of the Cardiology Section at the West Haven Veterans Administration Hospital in Connecticut. Dr. Gradman received his medical degree from Washington University in St. Louis, Missouri. His postgraduate training included an internship and residency in medicine at Barnes Hospital in St. Louis. He also completed a fellowship in cardiology at Stanford University Medical Center in California. He is certified by the American Board of Internal Medicine and holds additional certification in cardiovascular diseases. He is recognized as a specialist in clinical hypertension by the American Society of Hypertension.

Joseph A. Hill, MD, PhD
Professor of Internal Medicine and Molecular Biology
James T. Willerson, MD, Distinguished Chair in Cardiovascular Diseases
Frank M. Ryburn Jr Chair in Heart Research
Chief, Division of Cardiology
University of Texas, Southwestern Medical Center
Dallas

Dr. Hill is a cardiologist-scientist whose research focuses on molecular mechanisms of remodeling in the stressed myocardium. He graduated with a medical degree and a doctorate from Duke University, Durham, North Carolina. Next, he pursued postdoctoral scientific training at the Pasteur Institute in Paris, France, followed by clinical training in internal medicine and cardiology at the Brigham and Women’s Hospital, Harvard Medical School. Dr. Hill served on the faculty of the University of Iowa for 5 years before moving in 2002 to the University of Texas Southwestern Medical Center to assume the role of chief of cardiology. Dr. Hill’s research group strives to decipher mechanisms of structural, functional, and electrical remodeling in heart disease with an eye toward therapeutic intervention.

Dr. Hill serves on numerous committees and study sections, and he lectures widely. In addition, he serves on several editorial boards, including Circulation, and the Journal of Biological Chemistry. Dr. Hill maintains an active clinical practice focusing on general cardiology, hypertension, and heart failure.

Faculty Financial Disclosure Statements

The presenting faculty reported the following:
Dr. Gradman is a consultant for AstraZeneca Pharmaceuticals LP; Daiichi Sankyo, Inc.; Merck & Co., Inc.; and Novartis Pharmaceuticals Corporation; and is on the speaker’s bureau of Boehringer Ingelheim Corporation; Daiichi Sankyo, Inc.; Merck & Co., Inc.; and Novartis Pharmaceuticals Corporation.
Dr. Hill has nothing to disclose.

Education Partner Financial Disclosure Statements

The content collaborators at Turnkey Solutions, LLC, have reported the following:
Emily A. Bakerman, RN, MS, APN-C, executive vice president, has nothing to disclose.
Drug List
Generic | Trade
--- | ---
amlodipine | Norvasc
atenolol | Tenormin
benazepril | Lotensin
captopril | Capoten
chlorthalidone | Hygroton
clonidine | Catapres, Duraclon
enalapril | Vasotec

Generic | Trade
losartan | Cozaar
olmesartan | Benicar, Olmetec
lisinopril | Prinivil, Zestril
quinapril | Accupril
ramipril | Altace
telmisartan | Micardis
valsartan | Diovan

Acronym List
ACEI | angiotensin-converting enzyme inhibitor
ARB | angiotensin receptor blocker
CAD | coronary artery disease
CCB | calcium channel blocker
CHF | congestive heart failure
CRI | chronic renal insufficiency
DBP | diastolic blood pressure
DM | diabetes mellitus
ECG | electrocardiogram
HCTZ | hydrochlorothiazide

HTN | hypertension
IHD | ischemic heart disease
ISH | isolated systolic hypertension
LVH | left ventricular hypertrophy
MI | myocardial infarction
PWV | pulse wave velocity
RAAS | renin-angiotensin-aldosterone system
SBP | systolic blood pressure
SeSBP | seated systolic blood pressure

Suggested Reading List


ONTARGET/TRANSCEND Investigators. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease trials. *Am Heart J.* 2004;148:52-61.


**Advanced Treatment of Hypertension for the Cardiologist**

**ALAN H. GRADMAN, MD**

The Western Pennsylvania Hospital
Pittsburgh, Pennsylvania
Professor of Medicine
Temple University School of Medicine
Philadelphia, Pennsylvania

**CARDIOVASCULAR DISEASE IN THE US**

71.3 million Americans have cardiovascular disease

- Hypertension: 65 million
  - #1 Cardiovascular Disease
- Coronary heart disease: 13.2 million
  - Myocardial infarction: 7.2 million
  - Angina pectoris: 6.5 million
- Stroke: 5.5 million
- Congestive Heart Failure: 5 million

*Individuals aged 40–69 years, starting at blood pressure 115/75 mmHg.
CV=cardiovascular; DBP=diastolic blood pressure; SBP=systolic blood pressure.

**Published Guidelines Have Set Clear Treatment Goals**

**JNC 7 / ADA / NKF / ISHIB Guidelines for Hypertension and Patients at High Risk**

<table>
<thead>
<tr>
<th>Condition</th>
<th>SBP/DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertension</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>High-risk hypertension</td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>

ADA=American Diabetes Association
NKF=National Kidney Foundation
ISHIB=International Society on Hypertension in Blacks
*History of CVD event, stroke, transient ischemic attack, evidence of target-organ damage (e.g., left ventricular hypertrophy, microalbuminuria), CHF, or high-risk for CHF (e.g., metabolic syndrome).


**Optimizing Hypertension Treatment**

**Goal: Maximum endpoint reduction**

- Emphasis on systolic blood pressure
- Lower BP target in selected subgroups
- Prompt achievement of target BP
- Evidence-based drug selection
- Combination therapy
- RAAS blockade

**CV Mortality Risk Doubles with Each 20-mmHg SBP or 10-mmHg DBP Increment**

Note: 17 randomized, placebo-controlled treatment trials (68,000 subjects)—14 diuretic and 3 beta-blocker-based trials, all differences are statistically significant

**Effects of Antihypertensive Drug Treatment on Cardiovascular Events**

CHF=Chronic Heart Failure
CVD=Coronary Heart Disease
 strokes
CVD deaths
CHD events

Adapted from Neaton JD, Wentworth D. Arch Intern Med. 1992;152:56–64.

### Death Rate Per 10,000 Person-years

<table>
<thead>
<tr>
<th>DBP (mmHg)</th>
<th>SBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>&lt;120</td>
</tr>
<tr>
<td>120-139</td>
<td>120-139</td>
</tr>
<tr>
<td>140-159</td>
<td>140-159</td>
</tr>
<tr>
<td>160-179</td>
<td>160-179</td>
</tr>
<tr>
<td>&gt;180</td>
<td>&gt;180</td>
</tr>
</tbody>
</table>

ISH = Isolated Systolic Hypertension


### Multiple Risk Factor Intervention Trial (MRFIT) ISH Associated With Highest Death Rate

### Systolic Hypertension Pathophysiology

- **Young Elastic Vessels**
  - SYSTOLE
  - DIASTOLE
  - Stroke Volumes
  - AORTA
  - Resistance Arterioles
  - PRESSURE (FLOW)

- **Old Inelastic Vessels**
  - SYSTOLE
  - DIASTOLE
  - Stroke Volumes
  - AORTA
  - Resistance Arterioles
  - PRESSURE (FLOW)

Increased Systolic
Decreased Diastolic

CASE STUDY: Physical Examination

- Height: 5’ 10”
- Weight: 177 lbs
- BMI: 25.4 kg/m²
- Waist circumference: 34”
- BP: 148/74 mm Hg (on medication)
- Pulse: 68 bpm
- Soft pansystolic murmur along LLSB; no râles, JVD, or peripheral edema noted
- The remainder of the physical examination is unremarkable

CASE STUDY: Physical Examination

- **HTN = hypertension; MI = myocardial infarction.**

TEST YOUR KNOWLEDGE

**Case: 71M, CAD, HTN**

What should be the target BP in this patient?

1. <140/90 mm Hg
2. <130/80 mm Hg
3. <120/80 mm Hg
4. Depends on his fasting glucose
Age and Reflected Waves

**YOUNGER PATIENT**

PWV 8 m/sec

**OLDER PATIENT**

PWV 12 m/sec

Systolic Augmentation Pressure

FORWARD-TRAVELING WAVE

BACKWARD-TRAVELING WAVE

ACTUAL (COMPOSITE) WAVE

PWV = Pulse Wave Velocity


AHA Scientific Statement: Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease

CAMELOT/NORMALIZE Come to Fruition!!!

<table>
<thead>
<tr>
<th>Area of Concern</th>
<th>BP Target (mm Hg)</th>
<th>Lifestyle Modification</th>
<th>Specific Drug Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>General CAD prevention</td>
<td>&lt;140/90</td>
<td>Yes</td>
<td>Any effective antihypertensive drug or combination</td>
</tr>
<tr>
<td>High CAD risk</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>ACEI or ARB or CCB or thiacarb diuretic or combination</td>
</tr>
<tr>
<td>Stable angina</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>B-Blocker and ACEI or ARB</td>
</tr>
<tr>
<td>LVD</td>
<td>&lt;120/80</td>
<td>Yes</td>
<td>ACEI or ARB and G-blocker and cholesterol, antiprostacyclin, and thiacarb or loop diuretic and hydralazine/beta blocker (should)</td>
</tr>
</tbody>
</table>

*Diabetes mellitus, chronic kidney disease, known CAD or CAD equivalent (coronary artery disease, peripheral arterial disease, abdominal aortic aneurysm), or 10-year Framingham risk score >10%.

CAMELOT Study Design

Comparison of Amlodipine Versus Enalapril to Limit Ischemic Occurrences of Thrombosis

- Placebo-controlled, multicenter, randomized, double-blind, comparative, parallel trial

Patients With CAD and DBP <100 mmHg on Standard-of-Care Therapies* (n=1,997)

Initial sample size was 3,000 patients. This was reduced in an amendment to 2,000.


CAMELOT: 31% Reduction in Primary Outcome with Amlodipine Compared to Standard Care

<table>
<thead>
<tr>
<th>Drug</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.20</td>
<td>0.15</td>
<td>0.10</td>
<td>0.05</td>
<td>0.00</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>0.15</td>
<td>0.10</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

P < 0.001

Cumulative CV events (proportion)

No. at risk

Placebo 655 588 558 525 488

Enalapril 673 608 572 553 529

Amlodipine 663 623 599 574 535

Primary outcome = incidence of CV events


CAMELOT: Similar BP Reductions from Baseline with Amlodipine and Enalapril

Placebo  50       50       50       50       50

Amlodipine 48       48       48       48       48

Enalapril  52       52       52       52       52

P < 0.001

CAMELOT: Cardiovascular Event Rates and Hazard Ratios

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>0.75</th>
<th>1.00</th>
<th>1.25</th>
<th>1.50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>0.75</td>
<td>1.00</td>
<td>1.25</td>
<td>1.50</td>
</tr>
</tbody>
</table>

CHF=congestive heart failure; CI=confidence interval; MI=myocardial infarction; PCI=percutaneous coronary intervention; TIA=transient ischemic attack.

CAMELOT: Continuous Relationship
Between Rate of Atheroma Progression
and Change in SBP
LOWESS plot for combined amlodipine and enalapril drug-treatment groups

LOWESS=Locally Weighted Scatterplot Smoothing

LOWESS plot for combined amlodipine and enalapril drug-treatment groups

Change in percent
atheroma volume (%)
0.5
1.0
1.5
2.0
2.5
Progression
Regression

Change in systolic BP (mm Hg)
-2.0
-1.5
-1.0
-0.5
0
0.5
1.0
1.5
2.0
2.5

CAMELOT – IVUS Substudy
274 Subjects with coronary stenosis >15% and DBP >100 mm Hg. 2 years

Change in atheroma volume (%)
-30 -20 -10 0 10 20

Sipahi et al. JACC. 2006;45:833-838.

Antihypertensive Rx Effects
Endpoint Reductions

BP Reduction
Specific Drug Effects

What are the best drugs for hypertension?

Relationships Between BP Components
and Change in Atheroma Volume on
Multivariable Analysis

Correlation
Coefficient
p Value
| SBP     | 0.16 | 0.006 |
| DBP     | 0.08 | 0.16  |
| Pulse Pressure | 0.14 | 0.02  |

*Based on raw transformed data and adjusted for baseline atheroma volume, LDL, HDL cholesterol, and baseline BP. For each blood pressure component, the average values observed throughout the study period were used. Since 2 patients had incomplete laboratory data, the results of 272 patients are shown.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Sipahi et al. JACC. 2006;45:833-838.

ALLHAT
Primary Outcome*
No significant differences among the 3 treatment groups

Cumulative Event Rate (%)
0 2 4 6 8 10 12 14
Time to Event (y)
0 1 2 3 4 5 6 7

No. at Risk
Chlorthalidone 15205 14977 14930 15129 15268 15340 15385 15392 15363
Amlodipine besylate 9986 9574 9707 9863 9920 9973 10178 215
Lisinopril 9654 9355 9123 7711 7642 3392 1770 175

*Fatal coronary heart disease event or non-fatal myocardial infarction.

VALUE: Primary Composite Cardiac Endpoint

Cumulative Event Rate (%)
0 4 8 12 16
Time (months)
0 6 12 18 24 30 36 42 48 54 60 66

Number at Risk
Valsartan 7600 7449 7407 7366 7326 6272 6236 6209 6181 2162 1474
Amlodipine 7566 7409 7367 7327 7286 7242 6298 6264 6236 6208 1474

HR=1.03; 95% CI=0.94–1.14; P=0.49


VALUE: Primary Composite Cardiac Endpoint

Cumulative Event Rate (%)
0 4 8 12 16
Time (months)
0 6 12 18 24 30 36 42 48 54 60 66

Number at Risk
Valsartan 7600 7449 7407 7366 7326 6272 6236 6209 6181 2162 1474
Amlodipine 7566 7409 7367 7327 7286 7242 6298 6264 6236 6208 1474

**VALUE: Analysis of Results Based on BP Control at 6 Months**

*Pooled Treatment Groups*

<table>
<thead>
<tr>
<th>Event</th>
<th>Odds Ratio</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal/Non-fatal cardiac events</td>
<td>0.75</td>
<td>(0.67–0.83)</td>
</tr>
<tr>
<td>Fatal/Non-fatal stroke</td>
<td>0.55</td>
<td>(0.46–0.64)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.79</td>
<td>(0.71–0.88)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.86</td>
<td>(0.73–1.01)</td>
</tr>
<tr>
<td>Heart failure hospitalizations</td>
<td>0.64</td>
<td>(0.55–0.74)</td>
</tr>
</tbody>
</table>

Controlled patients† (n = 10755)

Non-controlled patients (n = 4490)

*P < 0.01

†Systolic blood pressure <140 mm Hg at 6 months.


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**JNC 7 Summary: Clinical Trials and Guideline Basis for Compelling Indications for Individual Drug Classes**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Odds Ratio</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Diuretic</td>
<td>BB</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Post-myocardial infarction</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Diabetes</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Modified based upon data published subsequent to JNC-7.


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**Advanced Treatment of Hypertension for the Cardiologist**

**JOSEPH A. HILL, MD, PhD**

Professor of Internal Medicine and Molecular Biology
James T. Willerson, MD Distinguished Chair in Cardiovascular Diseases
Frank M. Ryburn, Jr, Chair in Heart Research
Chief, Division of Cardiology
University of Texas, Southwestern Medical Center
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**Role of RAAS Activation in the Development of Cardiovascular Complications**

Ang II

Mechanical stress
Oxidative stress
Vasconstriction
Endothelial dysfunction
Growth factors
Cytokines
Inflammation

Angiotensin II

Advanced Treatment of Advanced Treatment of Hypertension for the Hypertension for the Cardiologist

**The Spectrum of Cardiovascular Disease**

**The Clinical Cardiovascular Disease Continuum**

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**The Clinical Cardiovascular Disease Continuum**

Mortality

Sudden death

Remodeling

End-stage heart disease

Chronic kidney disease

1. Exercise stress test
2. Echocardiogram
3. Cardiac catheterization
4. 1 and 2
5. All of the above

**Prevalence of LVH in Hypertension**
- Other than age, LVH is the strongest predictor of adverse CV outcomes in individuals with hypertension.\(^1\)
- Prevalence of LVH is dependent on the method of evaluation.
  - Electrocardiography: 3% to 8% of patients with mild to moderate essential hypertension
  - Echocardiography: 12% to 30% of unselected adults with hypertension
- Prevalence of LVH may be >90% in patients with sustained severe or malignant hypertension vs 10% of patients with new onset of malignant hypertension or preeclampsia.

**Angiotensin II and LVH**
- AT\(_1\) promotes the development of LVH
- AT\(_2\) inhibits the development of LVH
- Hyper trophy
  - DNA synthesis \(\rightarrow\) protein synthesis
  - Gene reprogramming skeletal α-actin \(\uparrow\)
  - ANP \(\uparrow\)
  - β-MHC \(\uparrow\)
- Necrosis
- Cardiac dysfunction

**LVH (ECG) and CV Events: Men**

**Myocardial Fibrosis and Stiffness With Hypertrophy and Heart Failure in SHR**
- Myocardial stiffness constant \(kcs\) (left) and fractional area of fibrosis (right) for WKY, SHR-NF and SHR-F.
**LIFE: Fatal/Nonfatal Stroke**

Intention-to-treat

Proportion of patients with first event (%)

Atenolol

Losartan

Adjusted risk reduction 24.9%, \( P = 0.001 \)

Unadjusted risk reduction 25.8%, \( P = 0.0006 \)


**LIFE: Blood Pressure Results – Follow-up**

Systolic

Diet: Losartan 144.1 mmHg

Diastolic

Diet: Losartan 81.3 mmHg

Mean Arterial

Diet: Losartan 80.9 mmHg


**Effect of Losartan and Atenolol on ECG – LVH in the LIFE Study**

Prevalence of LVH (%)

Baseline 6-Months 1-Year 2-Year 3-Year 4-Year 5-Year Last

Cornell Product LVH

\( P = 0.879 \)

\( P = 0.001 \)

\( P = 0.001 \)

\( P = 0.001 \)

\( P = 0.001 \)

\( P = 0.001 \)

\( P = 0.001 \)

Clinical Investigation and Reports. Regression of Electrocardiographic Left Ventricular Hypertrophy by Losartan Versus Atenolol. Circ. 2002;106:844-850

**Regression of Hypertensive LVH: Results of 2000 Meta-Analysis**

Diuretics Beta Blockers ACE Inhibitors Ca²⁺ Blockers AII Receptor Blockers

Regression of Hypertensive LVH: Results of 2000 Meta-Analysis


**Progression From Cardiovascular Risk Factors to Coronary Artery Disease**

Hypertension

Dyslipidemia

Diabetes

Smoking

Injury to endothelium

Endothelial dysfunction

Compensatory responses

Oxidative stress

Inflammation

Cell migration/proliferation

Monocyte/platelet adhesion

Platelet aggregation

Coronary Artery Disease

Changes in Serum hsCRP

Effects of Olmesartan/Medoxomil on Atherosclerosis in Cynomolgus Monkeys

Endothelial Function and ACE Inhibition: TREND Results

ACE Inhibitors and Mortality in Vascular Disease

ONTARGET Non-Inferiority Comparison

Vicious Cycle in Heart Failure
Effect of Captopril on Survival in the Post-Infarct Rat Model

Survival (%)

No MI Small Infarct Moderate Infarct Large Infarct

Untreated Captopril-treated

44/62 45/63 6/13 17/35 3/40 4/37

Adapted from Pfeffer MA et al. Circulation 1987;75 (suppl IV):93–97.

RAAS Blockade Post-MI*

ACEI Inhibition

SAVE, AIRE, and TRACE, long-term meta-analysis
15.6% RR total mortality (ACEI=23.4%, Placebo=29.1%)

Cumulative mortality (%)

0 10 20 30 40

ACEI Placebo

0 12 24 36 48 60

Months

*Patients with left-ventricular dysfunction, heart failure, or both.

Prevention of Myocardial Infarction with ACE Inhibitors

Percentage of Treated Patients with Hypertension at Goal

- Caucasians: 56%
- African-Americans: 45%
- Hispanics: 44%
- Patients >60 years old: 44%
- Patients with diabetes: 25%


TEST YOUR KNOWLEDGE

Case: 71M, CAD, HTN

What are the preferred drugs to manage this patient’s HTN?

1. β blocker, diuretic, ACEI or ARB
2. β blocker, ACE inhibitor and ARB
3. β blocker, diuretic, CCB
4. β blocker, CCB, ACEI or ARB
5. None of the above

ACEI = ACE inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium-channel blocker.

Combination Therapy: A Practical Necessity

- Required in ~ 75% of hypertensives to achieve target BP
- Greater efficacy
- Faster achievement of target BP
- Higher response rates
- May make therapy effective in broader population (races, patient types, co-morbidities)
- Additive antihypertensive effects through complimentary pharmacologic mechanisms
- In some cases, improved side effect profile

BP Control Usually Requires Combination Therapy

Most patients require ≥2 antihypertensives to reach BP goal

Trial/SBP Achieved
UKPDS (144 mmHg)
RENAAL (141 mmHg)
ALLHAT (138 mmHg)
IDNT (138 mmHg)
HOT (138 mmHg)
INVEST (133 mmHg)
AASK (128 mmHg)

Number of BP Medications

1
2
3
4

Rational Use of Antihypertensive Drugs In Combination

Diuretics
Beta Blockers
ACE Inhibitors
ARBs
Calcium Channel Blockers
α₁-Receptor Blockers

BP Reductions With Amlodipine and Benazepril Monotherapies and Combination Therapy

Amlodipine + Olmesartan Combination More Effective Than Monotherapy in Lowering SBP After 8 Weeks

Placebo-Subtracted Incidence of Edema*: Amlodipine 10 mg + Olmesartan Medoxomil

Placebo
Amlodipine 10 mg
Olmesartan 10 mg
Amlodipine 5 mg + Olmesartan 40 mg
Amlodipine 10 mg + Olmesartan 20 mg
Amlodipine 10 mg + Olmesartan 40 mg


Adapted from Chrysant SG et al. Presentation at: ASH Annual Meeting 2007. May 19-22; Chicago, Ill.
Proposed Effect of CCB/ARB Therapy on Peripheral Edema

**Proposed Effect of CCB/ARB Therapy on Peripheral Edema**

- Hypertension
- Arteriole
- Venule
- Calcium channel blocker (CCB)
- Capillary
- Edema
- CCB + ACE Inhibitor
- Capillary pressure
- Less edema

**ACCOMPLISH**

Kaplan Meier for Primary Endpoint

- ACCOMPLISH Kaplan Meier for Primary Endpoint
- Cumulative event rate
- HR (95% CI): 0.80 (0.72, 0.90)
- 20% Risk Reduction
- Time to 1st CV morbidity/mortality (days)
- p = 0.0002

**ACCOMPLISH Primary and Other Endpoints**

- Composite CV mortality/morbidity Primary w/o revascularization
- Hard CV endpoint (CV death, non-fatal MI, non-fatal stroke)
- All cause mortality
- Risk Ratio (95% CI)

**Optimizing Antihypertensive Treatment**

- Emphasis on systolic BP
- Lower BP goals in selected subgroups (CAD)
- Prompt achievement of target BP
- Evidence-based drug selection
- Combination therapy
- RAAS blockade

**Advanced Treatment of Hypertension for the Cardiologist**

- To array a man’s will against his sickness is the supreme art of medicine.”
  --Henry Ward Beecher

- ALAN H. GRADMAN, MD
  JOSEPH A. HILL, MD, PhD