Management of The Patients with Hypertension and High Risk Cardiovascular Disease

Songsak Kiatchoosakun, MD.
Cardiology, Medicine
Khon Kaen University
CVD and Hypertension: Worldwide Morbidity and Mortality

- Cardiovascular disease accounted for 16.6 million deaths in 2000
  - 7.3 million ischemic heart disease deaths
  - 5.4 million stroke deaths
- High blood pressure is associated with an estimated 7.1 million deaths
- Estimated 690 million persons have hypertension; most remain untreated or uncontrolled
Effect of Systolic BP and Diastolic BP on CHD Mortality

CHD Death Rate per 10,000 Person-Years

: MRFIT Study (N=316,099)*

*Men aged 35-57 years followed for a mean of 12 years.
# Classification of Hypertension

## Definitions and Classification of Blood Pressure (BP) Levels (mmHg)

( European Society of Cardiology 2007)

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimal</strong></td>
<td>&lt;120</td>
<td>and &lt;80</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>120-129</td>
<td>and/or 80-84</td>
</tr>
<tr>
<td><strong>High normal</strong></td>
<td>130-139</td>
<td>and/or 85-89</td>
</tr>
<tr>
<td><strong>Grade 1 hypertension</strong></td>
<td>140-159</td>
<td>and/or 90-99</td>
</tr>
<tr>
<td><strong>Grade 2 hypertension</strong></td>
<td>160-179</td>
<td>and/or 100-109</td>
</tr>
<tr>
<td><strong>Grade 3 hypertension</strong></td>
<td>≥ 180</td>
<td>and/or ≥ 110</td>
</tr>
<tr>
<td><strong>Isolated systolic hypertension</strong></td>
<td>≥ 140</td>
<td>and &lt;90</td>
</tr>
</tbody>
</table>
Assessment of Patient with HT

- Establishing blood pressure levels
- Identifying secondary causes of hypertension
- Evaluating the overall cardiovascular risk
  - Other risk factors
  - Target organ damage
  - Concomitant diseases
Sir, your blood pressure is OK.
Secondary Cause of Hypertension

Sings suggesting secondary hypertension

- Features of Cushing syndrome
- Skin stigmata of neurofibromatosis (pheochromocytoma)
- Palpation of enlarged kidneys (polycystic kidney)
- Auscultation of abdominal murmurs (renovascular hypertension)
- Diminished and delayed femoral pulses and reduced femoral BP (aortic coarctation, aortic disease)
Total Cardiovascular Risk

♦ Concepts

♦ Small number of patients have hypertension alone

♦ Blood pressure and metabolic risk factors potential each other and leading to greater cardiovascular risk

♦ Goals for treatment and treatment strategies are different between high risk and low risk patients
Patients With Hypertension Are Likely To Have Additional CV Risk Factors

The Threat of Global CV Risk

Risk shown above is compared with risk for a 40-year-old male nonsmoker with TC 4.7 mmol/L (185 mg/dL), SBP 120 mm Hg, and no glucose intolerance, who is ECG-LVH negative and whose probability of developing CVD is 15/1000 (1.5%) in 8 years.

Factors Influencing Prognosis (1)

Risk factors

- Systolic and diastolic BP levels and pulse pressure (in elderly)
- Age (M > 55 years; W > 65 years)
- Smoking
- Dyslipidemia
  - TC > 5.0 mmol/l (190 mg/dl) or:
  - LDL – C >3.0 mmol/l (115 mg/dl) or:
  - HDL – C: M < 1.0 mmol/l (40 mg/dl), W <1.2 mmol/l (46 mg/dl) or:
  - TG > 1.7 mmol/l (150 mg/dl)
- Fasting plasma glucose 5.6 – 6.9 mmol/l (102 -125 mg /dl)
- Abdominal obesity (waist circumference > 102 cm (M), >88 cm (W)
- Family history of premature CV disease (M at age <55 years; W at age <65 years)
Factors Influencing Prognosis (2)

Sub-clinical organ damage

- LVH by ECG or Echocardiography (LVMI M ≥ 125 g/m², w ≥ 110 g/m²)
- Carotid wall thickening (IMT > 0.9 mm) or plaque
- Ankle/brachial BP index <0.9
- Slight increase in plasma creatinine:
  M: 115 – 113 umol/l (1.3 – 1.5 mg/dl)
  W: 107 – 124 umol/l (1.2 – 1.4 mg/dl)
- Low estimated glomerular filtration rate⁺ (60 ml/min/1.73 m²) or creatinine clearance (< 60 ml/min)
- Microalbuminuria 30 – 300 mg/24 h or albumin – creatinine ratio: ≥ 22 (M); or ≥ 31 (W) mg/g creatinine

Rike maximal for concentric LVH (left ventricular hypertrophy): increased LVMI (left ventricular mass index) with a wall thickness/radius ratio > 0.42.
Factors Influencing Prognosis (3)

Established CV or Renal Disease

- Cerebrovascular disease
- Heart disease: CAD, CHF
- Renal disease: diabetic nephropathy; renal impairment (creatinine; M > 133, W > 1 24 mmol/l); proteinuria (> 300 mg/24 h)
- Peripheral artery disease
- Advanced retinopathy: haemorrhages or exudates, papilledema
Diagnostic Evaluation
Blood Test

- FBS
- Lipid panel
- Renal function
- Electrolyte
Waist Circumference
Electrocardiography
Proteinuria
Echocardiography: LV Hypertrophy
Carotid Plaque
## Total Cardiovascular Risk

<table>
<thead>
<tr>
<th>Other risk factors, OD or Disease</th>
<th>Normal SBP 120–129 or DBP 80–84</th>
<th>High normal SBP 130–139 or DBP 85–89</th>
<th>Grade 1 HT SBP 140–159 or DBP 90–99</th>
<th>Grade 2 HT SBP 160–179 or DBP 100–109</th>
<th>Grade 3 HT SBP ≥ 180 or DBP ≥ 110</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other risk factors</td>
<td>Average risk</td>
<td>Average risk</td>
<td>Low added risk</td>
<td>Moderate added risk</td>
<td>High added risk</td>
</tr>
<tr>
<td>1–2 risk factors</td>
<td>Low added risk</td>
<td>Low added risk</td>
<td>Moderate added risk</td>
<td>Moderate added risk</td>
<td>Very high added risk</td>
</tr>
<tr>
<td>3 or more risk factors, MS, OD or Diabetes</td>
<td>Moderate added risk</td>
<td>High added risk</td>
<td>High added risk</td>
<td>High added risk</td>
<td>Very high added risk</td>
</tr>
<tr>
<td>Established CV or renal disease</td>
<td>Very high added risk</td>
<td>Very high added risk</td>
<td>Very high added risk</td>
<td>Very high added risk</td>
<td>Very high added risk</td>
</tr>
</tbody>
</table>
High/Very High Risk Subjects

- BP $\geq 180$ mmHg systolic and/or $\geq 110$ mmHg diastolic
- Systolic BP $> 160$ mmHg with low diastolic BP ($< 70$ mmHg)
- Diabetes mellitus
- Metabolic syndrome
- $\geq 3$ cardiovascular risk factors
- One or more of the following sub-clinical organ damages:
  - LV hypertrophy
  - Carotid plaque detected by ultrasound
  - Renal impairment/micro-albuminuria or proteinuria
- Established cardiovascular or renal disease
Goals of Treatment

- Primary goal is to achieve maximum reduction in the long term total risk of cardiovascular disease.
- BP should be reduced to at least below 140/90 mmHg.
- Target BP should be at least <130/80 mmHg in diabetics and in high or very high risk patients such as stroke, myocardial infarction, renal dysfunction, proteinuria.
- In order to more easily achieve goal BP, antihypertensive treatment should be initiated before significant cardiovascular damage develops.
Treatment Strategies

- Lifestyle changes
- Smoking cessation
- Moderation of alcohol consumption
- Sodium restriction
- Other dietary changes
- Weight reduction
- Physical exercise
Antihypertensive Therapy

- Five major classes
  - Diuretics
  - Beta-blocker
  - ACE inhibition
  - Angiotensin receptor antagonist
  - Calcium antagonist
Systematic overviews showed that reductions in blood pressure of about 10-12 mm Hg systolic and 5-6 mm Hg diastolic conferred relative reductions in stroke risk of 38% and in risk of coronary heart disease of 16% within just a few years of beginning treatment.

Clinical Research Questions in Hypertension

Is blood pressure lowering beneficial?

Does it matter how elevated blood pressure is lowered?
Hypertension Treatment Significantly Reduced Mortality and Morbidity

VA Cooperative Study Group – Estimated Cumulative Incidence of All Morbid Events Over 5 Years

- 380 male patients
- diastolic blood pressure (BP) averaging 90 - 114 mmHg

Active Treatment Groups - Diuretic-based regimen and hydralazine

Control - Placebo

37% risk reduction

SHEP Trial: Endpoints

Active Therapy (diuretic, beta-blocker vs Placebo)

Relative Risk (95% CI)

-37%  -25%  -54%  -32%  -13%

P-NS

In hypertension, beta blockers and diuretics have proven risk reduction in cardiovascular morbidity and mortality vs. placebo (STOP, HEP, MRC).

Hypertension guidelines recommend beta blockers or diuretics as one of the initial treatments for hypertension.

*JNC-VII Guideline*
Diuretic / Beta-blocker

- The benefits of diuretic therapy on coronary artery disease were less than expected.
- Metabolic side effects of diuretic/beta-blocker mitigated the beneficial effect of blood pressure reduction.
- The beneficial effect of new treatment may beyond the blood pressure lowering effect.
Renin-Angiotensin-Aldosterone (RAAS) and Hypertension

Angiotensinogen

Angiotensin I

Angiotensin Converting Enzyme

Angiotensin II

AT I receptor

Vasoconstriction

Sodium Retention

Increase blood pressure

Increase blood pressure

Renin
Manipulation of Ang II generation

Angiotensinogen (Liver)

Angiotensin I

Bradykinin

ACE-inhibitor

Angiotensin II

Peptides

AT$_1$

AT$_2$

ACE Inhibition

- Blood pressure lowering
- Beyond blood pressure
  - Anti-atherosclerotic effects
  - Improvement in vascular endothelial function
  - LV hypertrophy reduction
  - Reduce new onset of diabetes

Reduce cardiovascular complications of hypertension
The Heart Outcomes Prevention Evaluation Study: HOPE Study

**Aim:** Effect of Ramipril (up to 10mg/d) vs placebo on CV death, MI or stroke (primary)

**Design:** Randomized double blind, Wide entry criteria, large, simple trial

**Size:** 9541 patients followed for 4 to 6 years

HOPE Study Population: “Typical” Office Practice Patients

- Patients did not have clinical of heart failure
- 47% of had high blood pressure
- Patients were 55 years or older

- CV events
  - 11% had previous stroke
  - 52% had previous MI
- Vascular disease
  - 80% had history of CAD
  - 42% had history of PVD
- Diabetes
  - 39% had diabetes + 1 or more CVD risk factors

HOPE: Primary Outcome
Reductions in MI, Stroke, or Cardiovascular Death

Note: Trial halted early due to the highly significant risk reductions seen with Ramipril
HOPE Study: Results (contd.)

-26% CV death
-20% MI
-32% Stroke
-15% Revasc
-37% Cardiac arrest
-23% Heart failure
-16% Total mortality
-34% Type 2 diabetes

HOPE: Dose-dependent Effects of Ramipril on LV Mass and Function

Mean baseline LVEF 58% in all groups

- Placebo (n = 151)
- Ramipril 2.5 mg (n = 149)
- Ramipril 10 mg (n = 146)

Δ LV mass (g)

- Placebo: 8.21
- Ramipril 2.5 mg: 7.86
- Ramipril 10 mg: 5.31

Δ LV end systolic volume (mL)

- Placebo: 2.9
- Ramipril 2.5 mg: -1.9

P Trend = 0.03

P Trend = 0.001

HOPE: Conclusions

- In people with high risk for CVD, addition of ramipril to other effective therapies prevents:
  - CV death, strokes and MI
  - Total mortality
  - Revascularization

- The benefit is beyond the effect on BP (3/2 mmHg)
HOPE-TOO: Primary Outcome (CV death, MI, Stroke)

RRR = 17%
P = 0.0002

HOPE-TOO: Additional Reduction in New-onset Diabetes

Placebo

Ramipril

New-onset diabetes (% HOPE-TOO patients)

RRR 31%
P = 0.0006

SECURE: Dose-dependent Effect of Ramipril on Carotid Atherosclerosis


Slope of the mean maximum carotid-intima thickness (mm/y)

Placebo

Ramipril 2.5 mg

Ramipril 10 mg

0.025

0.020

0.015

0.010

0.005

0.000

P = 0.028

NS

37% Reduction

0.022

0.018

0.014

ACE Inhibitor Evidence: Post MI with HF

SAVE
Radionuclide EF < 40%

AIRE
Clinical and/or radiographic signs of HF

TRACE
Echocardiogram EF < 35%

OR: 0.74 (0.66–0.83)
26 % reduction

ACE-I=Angiotensin converting enzyme inhibitors, LVSD=Left ventricular systolic dysfunction, MI=Myocardial infarction, OR=Odds ratio

Comparison of ACE Inhibitors and Calcium Antagonist


ACE inhibitors based therapy may reduce risk of CAD and heart failure.

Relative risk

- 0.5
- 1.0
- 2.0

Favor ACEI  Favor calcium antagonist

- Stroke
- Coronary heart disease
- Heart failure
- Total mortality
A Comparison of Outcomes with Angiotensin-Converting–Enzyme Inhibitors and Diuretics for Hypertension in the Elderly

<table>
<thead>
<tr>
<th>End Point</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>ACE Inhibitors Superior</th>
<th>Diuretics Superior</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cardiovascular events or death from any cause</td>
<td>0.89 (0.79–1.00)</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cardiovascular event or death from any cause</td>
<td>0.89 (0.79–1.01)</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.90 (0.75–1.09)</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Manipulation of Ang II generation

Angiotensinogen (Liver)

Angiotensin I

Angiotensin II

ARB
AT₁ receptor blocker

AT₁
AT₂

The Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE Study)

- 9,193 hypertensive patients with LVH, aged 55-80 years
- Mean 4.8-year follow-up
- 44,119 patient-years of follow-up
- 945 study sites in 7 countries

LIFE: Primary Composite Endpoint

Composite of CV death, stroke and MI

Adjusted Risk Reduction 13.0%, p=0.021
Unadjusted Risk Reduction 14.6%, p=0.009

Fatal and non-fatal stroke

Adjusted Risk Reduction  24.9%, p=0.001
Unadjusted Risk Reduction 25.8%, p=0.0006

LIFE: Myocardial Infarction and CV Mortality

Fatal and non-fatal MI

Cardiovascular mortality

Adjusted RR 11.4%, p=0.206
Unadjusted RR 13.3%, p=0.136

Adjusted RR -7.3%, p=0.491
Unadjusted RR -5.0%, p=0.628

Results from ASCOT-BPLA: Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm
ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial

Study 1: ASCOT-LLA
- Double-blind, randomized, placebo-controlled trial of a lipid-lowering agent in a sample of the total ASCOT patient population

Study 2: ASCOT-BPLA
- Prospective, randomized, open, blinded endpoint (PROBE) design comparing two antihypertensive regimens in the total ASCOT patient population

### ASCOT-BPLA: Study design

**Design:** Double-blind, placebo controlled, randomized

**Population:** N = 19,257 with hypertension and ≥3 other CV risk factors

**Treatment:**
- Amlodipine 5–10 mg ± perindopril 4–8 mg prn (n = 9639)
- Atenolol 50–100 mg ± bendroflumethiazide 1.25–2.5 mg/potassium prn (n = 9618)

**Primary outcome:** Nonfatal MI (including silent MI) and fatal CHD

**Secondary outcome:** All-cause mortality, stroke, nonfatal MI (excluding silent MI), all coronary events, CV events/procedures, CV mortality, fatal/nonfatal HF
**ASCOT-BPLA: Reduction in Primary Outcome (nonfatal MI and fatal CHD)**

Proportion of events (%)

Time since randomization (years)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine-based regimen</td>
<td>9639</td>
<td>9475</td>
<td>9337</td>
<td>9168</td>
<td>8966</td>
<td>7863</td>
<td></td>
</tr>
<tr>
<td>Atenolol-based regimen</td>
<td>9618</td>
<td>9470</td>
<td>9290</td>
<td>9083</td>
<td>8858</td>
<td>7743</td>
<td></td>
</tr>
</tbody>
</table>

HR = 0.90 (95% CI, 0.79–1.02)
RRR = 10%
P = 0.1052

*Atenolol 50–100 mg ± bendroflumethiazide 1.25–2.5 mg/potassium prn
†Amlodipine 5–10 mg ± perindopril 4–8 mg prn

ASCOT-BPLA: Reduction in Fatal and Nonfatal stroke

Number at risk
Amlodipine-based regimen  9639  9483  9331  9156  8972  7863
(327 events)
Atenolol-based regimen  9618  9461  9274  9059  8843  7720
(422 events)

HR = 0.77 (95% CI, 0.66–0.89)
RRR = 23%
P = 0.0003

*Atenolol 50–100 mg ± bendroflumethiazide 1.25–2.5 mg/potassium prn
†Amlodipine 5–10 mg ± perindopril 4–8 mg prn

ASCOT-BPLA: Overall Results

- Study stopped prematurely after 5.5-year median follow-up because of higher death rate in assigned atenolol-based-regimen group.

- Group receiving amlodipine-based regimen had nonsignificant 10% reduction in primary outcome (nonfatal MI plus fatal CHD) and significant reductions in nearly all secondary CV endpoints and new-onset diabetes.

ASCOT-BPLA: Summary

- Newer antihypertensive drug regimens should be considered in preference to older beta-blocker ± diuretic therapies
- Amlodipine ± perindopril showed reductions in:
  - Major CV events 16%
  - New-onset diabetes 30%
  - Stroke 23%
  - Mortality 11%
- ASCOT results support the use of newer drugs, in multi-drug combinations, to modify risk factors and/or metabolic disturbances, especially in patients with complicated hypertension

New Onset Diabetes: Impact of Blood Pressure Lowering Drugs
Cardiovascular Events in Treated Hypertensive Subjects

Rate of events (per 100 patient years)

A - without diabetes
B - new onset diabetes
C - previously known diabetes

Total number of CV events - 63

Verdecchia, Hypertens 2004;43:963-968
### Risk of DM among 3804 Hypertensive Patients with Various Antihypertensive Medications

<table>
<thead>
<tr>
<th>Rx</th>
<th>Hazard Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0</td>
</tr>
<tr>
<td>ACEI</td>
<td>0.9</td>
</tr>
<tr>
<td>B-Blocker</td>
<td>1.25**</td>
</tr>
<tr>
<td>CCB</td>
<td>1.17</td>
</tr>
<tr>
<td>Thiazides</td>
<td>0.95</td>
</tr>
</tbody>
</table>

* adjusted for age, race, BMI, CV risk factors, etc.  
** significant difference

Pharmacological Therapy in Hypertension

Choice of antihypertensive drugs

- The main benefits of antihypertensive therapy are due to lowering blood pressure
- Beta-blockers especially in combination with thiazide diuretic, should not be used in patients with metabolic syndrome or at high risk of diabetes

ESC guideline 2007
British Hypertension Society Guideline 2006

Age < 55
ACEI or ARB
Add CCB
ACEI or ARB + CCB + Diuretic
Add beta-blocker or alpha-blocker

Age > 55 or black
CCB or Diuretic
Add ACEI or ARB
# Conditions Favoring use of Some Antihypertensive Drugs versus Others

<table>
<thead>
<tr>
<th>Thiazide diuretics</th>
<th>Beta-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Isolated systolic HT</td>
<td>- Angina pectoris</td>
</tr>
<tr>
<td>- Heart failure</td>
<td>- Post-myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>- Heart failure</td>
</tr>
<tr>
<td></td>
<td>- Tachyarrhythmias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACE inhibitors</th>
<th>Angiotensin receptor antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Heart failure</td>
<td>- Heart failure</td>
</tr>
<tr>
<td>- LV dysfunction</td>
<td>- Post-myocardial infarction</td>
</tr>
<tr>
<td>- Post-myocardial infarction</td>
<td>- Diabetic nephropathy</td>
</tr>
<tr>
<td>- Diabetic nephropathy</td>
<td>- Proteinuria</td>
</tr>
<tr>
<td>- Non-diabetic nephropathy</td>
<td>- LV hypertrophy</td>
</tr>
<tr>
<td>- LV hypertrophy</td>
<td>- Atrial fibrillation</td>
</tr>
<tr>
<td>- Carotid atherosclerosis</td>
<td>- Metabolic syndrome</td>
</tr>
<tr>
<td>- Proteinuria/Microalbuminuria</td>
<td>- ACEI-induced cough</td>
</tr>
<tr>
<td>- Metabolic syndrome</td>
<td></td>
</tr>
</tbody>
</table>
### Conditions Favoring use of Some Antihypertensive Drugs versus Others

<table>
<thead>
<tr>
<th>Calcium antagonists (dihydropyridines)</th>
<th>Calcium antagonists (verapamil/diltiazem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Isolated systolic hypertension</td>
<td>- Angina pectoris</td>
</tr>
<tr>
<td>(elderly)</td>
<td>- Carotid atherosclerosis</td>
</tr>
<tr>
<td>- Angina pectoris</td>
<td>- Supraventricular tachycardia</td>
</tr>
<tr>
<td>- LV hypertrophy</td>
<td></td>
</tr>
<tr>
<td>- Carotid/Coronary Atherosclerosis</td>
<td></td>
</tr>
<tr>
<td>- Pregnancy</td>
<td></td>
</tr>
<tr>
<td>- Hypertension in blacks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diuretics (anti-aldosterone)</th>
<th>Loop diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Heart failure</td>
<td>- End stage renal disease</td>
</tr>
<tr>
<td>- Post-myocardial infarction</td>
<td>- Heart failure</td>
</tr>
</tbody>
</table>
Thank You for Your Attention
VALUE

Valsartan

Antihypertensive Long-Term Use Evaluation
VALUE: Patient Population

- Treated or untreated hypertensive patients
  - entry criteria for untreated hypertension: 160–210 mmHg systolic, 95–105 mmHg diastolic
  - Age ≥50 years, male or female
  - High-risk for cardiac events
    - one or more defined risk factors or diseases

**VALUE: Primary Composite Cardiac Endpoint**

- **Valsartan-based regimen**
- **Amlodipine-based regimen**

**Proportion of Patients With First Event (%)**

- **HR = 1.03; 95% CI = 0.94–1.14; P = 0.49**

**Number at risk**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Valsartan</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7649</td>
<td>7596</td>
</tr>
<tr>
<td>6</td>
<td>7459</td>
<td>7469</td>
</tr>
<tr>
<td>12</td>
<td>7407</td>
<td>7424</td>
</tr>
<tr>
<td>18</td>
<td>7250</td>
<td>7267</td>
</tr>
<tr>
<td>24</td>
<td>7085</td>
<td>7117</td>
</tr>
<tr>
<td>30</td>
<td>6906</td>
<td>6955</td>
</tr>
<tr>
<td>36</td>
<td>6732</td>
<td>6772</td>
</tr>
<tr>
<td>42</td>
<td>6536</td>
<td>6576</td>
</tr>
<tr>
<td>48</td>
<td>6349</td>
<td>6391</td>
</tr>
<tr>
<td>54</td>
<td>5911</td>
<td>5959</td>
</tr>
<tr>
<td>60</td>
<td>3765</td>
<td>3725</td>
</tr>
<tr>
<td>66</td>
<td>1474</td>
<td>1474</td>
</tr>
</tbody>
</table>

HOPE (Heart Outcomes Prevention Evaluation) Study

- Patients $\geq 55$ years with a history of
  - CAD or stroke or peripheral artery disease
  - Diabetes plus at least one other CV risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking or microalbuminuria)
- Patients did not have heart failure or LV dysfunction
- 9297 patients received ramipril or placebo
- Treatment duration: 4.5 years
Dyslipidemia Is More Common in Patients With Hypertension

*Hypertension defined as BP ≥ 150/≥ 95 mm Hg


*Hypertension defined as BP ≥ 150/≥ 95 mm Hg

Monotherapy versus Combination Therapy Strategies

Choose between

If goal BP not achieved

ESC guideline 2007

Mild BP elevation
Low/moderate CV risk
Conventional BP target

Marked BP elevation
High/very high CV risk
Lower BP target

Single agent at low dose

Two-drug combination at low dose

If goal BP not achieved

Previous agent at full dose
Switch to different agent at low dose

Previous combination at full dose
Add a third drug at low dose

Two-to three-drug combination at full dose
Mono-therapy

If goal BP not achieved

Two-three drug combination at full dose
Possible Combinations Between Some Classes of Antihypertensive Drugs
**VALUE: Incidence of New-onset Diabetes**

New-Onset Diabetes (% of patients in treatment group)

- Valsartan-based Regimen (n = 7649)
  - 13.1%
- Amlodipine-based Regimen (n = 7596)
  - 16.4%

23% Risk Reduction With Valsartan

$P < 0.0001$

Cardiovascular (CV) disease continues to be the chief cause of mortality and morbidity worldwide. Most of this is due to coronary heart disease (CHD).

Multiple risk factors have synergistic effects in the pathogenesis of CV disease.

Combination treatment regimens using ≥2 agents are recommended to reach target BP goals.

Limited outcome data have led to an investigation comparing standard vs newer antihypertensive treatment options.
European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA)

13,655 patients with CAD and presumed normal left ventricular function randomized to perindopril (8 mg) or placebo for 4.2 years

Cardiovascular death (0.86; 0.72-1.03)
Non-fatal MI (0.78; 0.20-0.90)
Cardiac arrest (0.54; 0.20-1.47)
Combined endpoint (0.80; 0.71-0.91)

Favors Perindopril  Favors Placebo

ACE-I=Angiotensin converting enzyme inhibitors, CAD=Coronary artery disease, CV=Cardiovascular, MI=Myocardial infarction
ACE Inhibitor Evidence: CAD

Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial

8,290 patients with stable coronary artery disease and normal left ventricular function randomized to trandolapril (4 mg) or placebo for 4.8 years

*Includes death from cardiovascular causes, myocardial infarction, or coronary revascularization

PEACE Trial Investigators. *NEJM* 2004;351:2058-2068
HOPE-TOO: Rationale

- HOPE-TOO was an extension of the HOPE trial, which examined the effects of ACE inhibition in reducing major CV events in high-risk patients with vascular disease or diabetes.

- HOPE-TOO was designed to assess whether the CV and metabolic benefits of ramipril were sustained over time and occurred in subgroups based on varying risk and concomitant treatment.

HOPE-TOO: Study Design

Heart Outcomes Prevention Evaluation–The Ongoing Outcomes

◆ 4528 HOPE patients at 174 centers who agreed to further follow-up

◆ Blinded treatment ended and patients were advised to use ACEI

◆ 2.6-year post-trial extension

◆ ACEI use during extension
  ♦ HOPE ramipril arm (n = 2317): 72%
  ♦ HOPE placebo arm (n = 2211): 68%
  ♦ >90% of all HOPE-TOO patients used ramipril

## Major CV Events and New Diagnosis of Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of patients (%)</th>
<th>Ramipril (n = 3393)</th>
<th>Placebo (n = 3393)</th>
<th>RR (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, stroke, or CV death</td>
<td></td>
<td>699 (20.6)</td>
<td>820 (24.2)</td>
<td>0.83 (0.75–0.91)</td>
<td>0.0002</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td>485 (14.3)</td>
<td>581 (17.1)</td>
<td>0.81 (0.72–0.92)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>174 (5.1)</td>
<td>215 (6.3)</td>
<td>0.79 (0.65–0.97)</td>
<td>0.023</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td>327 (9.6)</td>
<td>374 (11.0)</td>
<td>0.86 (0.74–1.00)</td>
<td>0.045</td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
<td>767 (22.6)</td>
<td>880 (25.9)</td>
<td>0.84 (0.76–0.92)</td>
<td>0.0003</td>
</tr>
<tr>
<td>New diagnosis of diabetes</td>
<td></td>
<td>152 (7.3)</td>
<td>216 (10.3)</td>
<td>0.69 (0.56–0.85)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

*Calculated by log-rank test and data on all participants in the study extension, censored for period of observation.

HOPE-TOO: Effect of ACEI on Major CV Events and New-onset Diabetes

<table>
<thead>
<tr>
<th>Event*</th>
<th>Ramipril (n = 2317)</th>
<th>Placebo (n = 2211)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, stroke, or CV death</td>
<td>220 (7.9)</td>
<td>225 (8.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>MI</td>
<td>146 (5.1)</td>
<td>169 (6.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>59 (2.0)</td>
<td>56 (1.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>CV death</td>
<td>133 (4.4)</td>
<td>126 (4.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Revascularization</td>
<td>235 (9.1)</td>
<td>259 (10.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>New diagnosis of diabetes</td>
<td>48 (2.7)</td>
<td>70 (4.0)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Event rates were calculated as proportions of events in those study participants who were event-free at the end of the in-trial period.

HOPE-TOO: Additional Reduction in MI

RRR = 19%
P = 0.0007

HOPE-TOO: Sustained Reduction in Stroke

**Main HOPE study ends**

**HOPE-TOO begins**

**RRR = 21%**

**P = 0.023**

HOPE-TOO: Sustained Reduction in CV Death

CV death (% HOPE-TOO patients)

RRR = 14%
P = 0.045

RRR = 14%
P = 0.045

**HOPE-TOO: Study Conclusions**

- The benefits of ramipril were maintained during post-trial follow-up for CV death, stroke, and hospitalization for heart failure.

- Additional reductions in MI, revascularization and new-onset diabetes were also observed despite similar rates of ACEI use in the randomized groups.

- The reduction in CV outcomes demonstrated in the HOPE trial is most likely an underestimate of the full effects of long-term ramipril therapy.

- Subgroup analyses demonstrate the benefits observed are additive to those of other life-saving therapies, and extend to all patients with vascular disease, independent of their baseline risk.

Major Clinical Outcome Trials of RAAS Manipulation

ACE inhibition
Angiotensin receptor blockade

GISSI-3
ISIS-4
AIRE
SAVE
SOLVD-Prevention
TRACE
CHARM-Preserved
OPTIMAAL
VALIANT

HOPE EUROPA

ALLHAT ANBP2 INVEST LIFE

CONSENSUS

SOLVD-Treat
CHARM-Added
CHARM-Alternative
ELITE II
Val-HeFT
ACE Inhibition and Anti-atherosclerotic Effect

(A) Control

(B) Diabetic apoE-deficient mice

(C) Diabetic apoE-deficient mice ACE inhibition treated

Algorithm for the Treatment of Hypertension

Lifestyle Modifications

Not at Goal Blood Pressure (<140/90 mmHg)
(<130/80 mmHg for those with diabetes or chronic kidney disease)

Initial Drug Choices

Without Compelling Indications

Stage 1 Hypertension
(SBP 140–159 or DBP 90–99 mmHg)
Thiazide-type diuretics for most.
May consider ACEI, ARB, BB, CCB, or combination.

Stage 2 Hypertension
(SBP ≥160 or DBP ≥100 mmHg)
2-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB).

With Compelling Indications

Drug(s) for the compelling indications*
Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

Optimize dosages or add additional drugs until goal blood pressure is achieved.
Consider consultation with hypertension specialist.

*Compelling Indications
Heart failure
Post-MI
High coronary artery disease risk
Diabetes
Chronic kidney disease
Recurrent stroke prevention

Chobanian AV et al. JAMA. 2003;289:2560–2572. JNC 7
Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor to Calcium Channel Blocker vs Diuretic

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
ALLHAT: Entry Criteria

- Age >55 years old
- Untreated systolic and/or diastolic hypertension (>140/90 mm Hg but <180/110 mm Hg)
- At least 1 additional risk factor for CV morbidity, including:
  - Old MI or stroke
  - History of revascularization
  - Other documented atherosclerosis
  - Type 2 diabetes mellitus
  - Cigarette smoking
  - Low HDL cholesterol(<35mg/dl)
  - LVH

Cumulative Event Rates for the Primary Outcome (Fatal CHD or Nonfatal MI) by ALLHAT Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/C</td>
<td>0.98 (0.90-1.07)</td>
<td>0.65</td>
</tr>
<tr>
<td>L/C</td>
<td>0.99 (0.91-1.08)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Number at Risk:
- Chlorthalidone: 15,255 14,477 13,820 13,102 11,362 6,340 2,956 209
- Amlodipine: 9,048 8,576 8,218 7,843 6,824 3,870 1,878 215
- Lisinopril: 9,054 8,535 8,123 7,711 6,662 3,832 1,770 195
ACE Inhibitor Recommendations for Secondary Prevention

Use in all patients with LVEF ≤ 40%, and those with diabetes or chronic kidney disease indefinitely, unless contraindicated

Consider for all other patients

Among lower risk patients with normal LVEF where cardiovascular risk factors are well controlled and where revascularization has been performed, their use may be considered optional

ACE=Angiotensin converting enzyme, LVEF= left ventricular ejection fraction
Hypertension and Dyslipidaemia Are Major Risk Factors for CHD

Additive Effect of Cholesterol and SBP on Risk of CHD Death

Neaton JD, Wentworth D. Arch Intern Med. 1992;152:56-64.

*To convert to mmol/L multiply by 0.02586
Diuretic Based Regimens

- Substantially reduce the risk of stroke
- The benefits of diuretic therapy on coronary artery disease were less than expected
- Metabolic side effects of diuretic mitigated the beneficial effect of blood pressure reduction
Major Clinical Outcome Trials of RAAS Manipulation

ACE inhibition
Angiotensin receptor blockade

GISSI-3
ISIS-4

AIRE
SAVE
SOLVD-Prevention
TRACE
CHARM-Preserved
OPTIMAAL
VALIANT

HOPE
EUROPA
PEACE

SOLVD-Treat
CHARM-Added
CHARM-Alternative
ELITE II
Val-HeFT

CONSENSUS

The cardiovascular disease continuum
HOPE: Benefits in All Subgroups

- Younger than 65 years as well as 65 years and older
- With/without diabetes
- With/without evidence of cardiovascular disease
- With/without hypertension
- With/without microalbuminuria
- Whether or not taking aspirin or other antiplatelet agents, beta blockers, lipid-lowering agents or antihypertensive agents

*NEJM 2000; 342: 145-153*