Perindopril 4 to 8 mg: Role in the modern Management of Hypertension

Bangladesh Society of Medicine
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Modification in Hypertension recommendations

« Old » ABCD algorithm in hypertension

The British Hypertension Society recommendations for combining Blood Pressure Lowering drugs

1. Younger (e.g. <55yr) and Non-Black
   - Step 1: A (or B*)
   - Step 2: A (or B*) +
   - Step 3: A (or B*) + C +
   - Step 4: Add: either α-blocker or spironolactone or other diuretic

2. Older (e.g. ≥55yr) or Black
   - Step 1: C or D
   - Step 2: C or D
   - Step 3: C or D

A: ACE Inhibitor or angiotensin receptor blocker
B: β-blocker
C: Calcium Channel Blocker
D: Diuretic (thiazide)

* Combination therapy involving B and D may induce more new onset diabetes compared with other combination therapies.

New ACD algorithm in hypertension

Modification in Hypertension recommendations

BHS/NICE-2006 hypertension guidelines

- **< 55 yrs**
  - ACEi*
  - ACEi* + CCB
  - ACEi + CCB + Diuretics
  - Consider 4th line drug
    - α-blocker
    - further diuretic therapy
    - β-blocker
    - Consider seeking specialist advice

- **≥ 55 yrs** or any age if black
  - CCB or Diuretics
  - ACEi* + Diuretics
  - ACEi + CCB + Diuretics
  - (consider ARB if ACEi intolerant)
New BHS/NICE guidelines: Press coverage

**THE TIMES**
“β-blockers are to be phased out for 1.5m patients”

**REUTERS**
“UK recommends new drugs for high blood pressure”

**Herald Sun**
“Studies showed β-blockers raise the risks of strokes, heart attacks and diabetes”

**THE AUSTRALIAN**
“Blood pressure rethink as Britain bars β-blockers”

**The Daily Telegraph**
“Doctors advised to curb β-blockers”
“New UK guidelines omit β-blockers for routine use”

**theguardian**
“We will be saving thousands of people from dying from strokes and heart attacks”
19 257 hypertensive patients without cardiac disease treated with Amlodipine + Perindopril 4 to 8 mg

• Hypertension at baseline BP $\geq 160/100$ mm Hg untreated or $\geq 140/90$ mm Hg treated with one or more drugs

• Patients aged 40-79 years

• Patients with 3 or more risk factors for a future cardiovascular event

  Male
  Age $> 55$ years
  LVH
  NIDDM
  Smoking
  ECG abnormalities

  History of cerebrovascular event
  History of early CHD in first degree relative
  Plasma TC/ HDL ratio $\geq 6$
  Peripheral vascular disease
  Microalbuminuria/ proteinuria
19,000 patients

- amlodipine alone 15%
- patients with β-blockers alone. 9%
- patients with Coversyl + amlodipine: 70%

SBP and DBP by time

Anglo-Scandinavian Cardiac Outcomes Trial

BP (mm Hg)

- β-blocker + diuretic
- Amlodipine + Perindopril

Time (y)

0 1 2 3 4 5 6

60 70 80 90 100 110 120 130 140 150 160 170 180

77.4 79.2 136.1 137.7

94.5 94.8 163.9 164.1
All-cause mortality: -11%
Fatal and nonfatal strokes: -23%
Cardiovascular mortality: -24%
HR = 0.76 (0.65, 0.90)
RRR = 24%
p = 0.001
New onset of diabetes: -30%
In patients with no diabetes at inclusion

Elliott WJ, Meyer PM. Lancet. 2007;369:201-207
Gupta A. Oral communication. ESC 2006
Number of events avoided with Perindopril / amlodipine

1,000,000 HT patients uncontrolled switched to Perindopril / amlodipine instead of beta blocker + diuretic

-26,400 CV events and procedures

-23,800 NOD

-11,000 Coronary events

-10,000 Stroke

-9,000 Cardiovascular mortality
Total CV events and procedures among sub-groups

amlodipine + Perindopril

- Diabetes
- Non diabetes
- Current smoker
- Non current smoker
- Obese
- Non obese
- Older (> 60 years)
- Younger (≤ 60 years)
- Female
- Male
- LVH according to the ECG or ECHO
- NO LVH according to the ECG or ECHO
- Previous vascular disease
- No previous vascular disease
- Renal dysfunction
- No renal dysfunction
- With metabolic syndrome
- Without metabolic syndrome

Total CV events and procedures
Perindopril = clinical value and life saving benefits in Modern Management of Hypertension
No ACEi or ARBs demonstrated superiority versus comparator, mainly diuretics +/- beta-blockers (or CCB) in hypertension on total and cardiovascular mortality.

- **ALLHAT**
  - Lisinopril
  - Enalapril

- **TOMHS**
  - Enalapril or lisinopril

- **ANBP2**
  - Lisinopril
  - Enalapril

- **CAPPP**
  - Captopril

- **INVEST**
  - Trandolapril
  - Ramipril
  - Losartan

- **LIFE**
  - No results
How to explain such a reduction in clinical outcome?

Why perindopril was the chosen ACEi in ASCOT?
Superior 24-h BP control : T/P ratios

![Graph comparing Trough-to-peak ratio for various medications. The graph shows a comparison between Coversyl 4 to 8 mg, Lisinopril, Ramipril, Enalapril, and Captopril. Coversyl has the highest trough-to-peak ratio, indicating superior 24-hour blood pressure control.]

Leading to better BP control over the 24-h period
Perindopril 4 to 8 mg is very effective in every type of patient.

Perindopril 4 to 8 mg is **very effective** in nonresponders to other ACEIs or ARBs.
Perindopril / amlodipine controls central aortic blood pressure

Although brachial blood pressure is equally controlled,

the central aortic blood pressure with the two regimens is different,

leading to significantly different outcomes (cardiovascular events + procedures + renal impairment, $P<0.01$)

Perindopril has the highest and longest lasting tissue and plasma ACE inhibition

Perindopril has a very high tissue ACE affinity

Highest bradykinin / angiotensin II ratio

Bradykinin/Angiotensin II

- perindopril
- ramipril
- quinapril
- trandolapril
- enalapril
Perindopril decreases angiotensin II, increases bradykinin and NO
Improvement of endothelial dysfunction and prevention of atherosclerosis

Without Perindopril

With Perindopril

atherosclerosis

Normal

Perindopril: Excellent compliance

Cough

Trandolapril\(^1\)
TRACE 12.9%

Captopril\(^2\)
SOLV Dp 6.5%

Enalapril\(^3\)
SOLV Dt 6%

Ramipril\(^4\)
HOPE 5.5%

Coversyl\(^5\)
EUROPA 2.2%
Perindopril = clinical value and life saving benefits in Modern Management of Hypertension and CAD

Perindopril secondary Prevention?
CAD Patients
12,218 coronary artery disease patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>61</td>
</tr>
<tr>
<td>Known CAD (%)</td>
<td>100</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>62</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12</td>
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<tr>
<td>Hypertension (%)</td>
<td>26</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>62</td>
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<tr>
<td>Antiplatelet drugs (%)</td>
<td>91</td>
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<tr>
<td>β-blocker (%)</td>
<td>62</td>
</tr>
<tr>
<td>Lipid-lowering agents (%)</td>
<td>57</td>
</tr>
</tbody>
</table>

Optimal Standard Therapy

Perindopril reduces primary end point (CV death, MI or cardiac arrest) by 20%.

RRR: 20%

$P=0.0003$

Perindopril’s cardioprotection is consistent in high, medium, and low risk level patients.

Annual rate of CV death, non-fatal MI or stroke$^2$

- **EUROPA HIGH RISK**
  - RRR - PEP: -12%
- **EUROPA MEDIUM RISK**
  - RRR - PEP: -32%
- **EUROPA LOWER RISK**
  - RRR - PEP: -17%

**EUROPA TOTAL RISK**
- RRR - PEP: -20%

Source:
Post MI Patients
Perindopril decreases by 22.5% the PEP in patient with previous MI

Reduction in recurrent MI

EUROPA Post-MI
N=7910

- 28%

P<0.001

Non revascularized EUROPA Post-MI
N=4256

- 35%

P<0.001

Acute MI Patients
Perindopril 8 mg significantly reduces combined primary end point: death + heart failure + cardiac remodeling by **22%** ($P<0.001$)

1 252 post-MI elderly patients with preserved LVEF

R Ferrari Hotline I. Oral Communication. ESC Stockholm 2005
Revascularized Patient
Perindopril 8 mg decreases PEP by 17.3% in revascularized patient
Perindopril 8 mg decreases risk of MI by 32% in revascularized patient
Heart Failure Patient
Perindopril 8 mg prevents hospitalization for heart failure
### Perindopril: highest proven efficacy in any antihypertensive class to date!

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>n</th>
<th>Events</th>
<th>Reduction</th>
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</thead>
<tbody>
<tr>
<td>✓2001</td>
<td>PROGRESS</td>
<td>6,000</td>
<td>Stroke</td>
<td>-28%</td>
</tr>
<tr>
<td>✓2003</td>
<td>EUROPA</td>
<td>12,000</td>
<td>CVD+MI+CA</td>
<td>-20%</td>
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<tr>
<td>✓2005</td>
<td>PREAMI</td>
<td>1,000</td>
<td>D+HF+CR</td>
<td>-22%</td>
</tr>
<tr>
<td>✓2005</td>
<td>ASCOT</td>
<td>20,000</td>
<td>CV death</td>
<td>-24%</td>
</tr>
</tbody>
</table>
Perindopril = clinical value and life saving benefits in Modern Management of Hypertension and CAD