Assessing and managing patients. Are they all the same?

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Ain Shams University

Case Presentation

• Mr. MW is a 54 year old male.
• He is presenting to the outpatient clinic for a regular check up.
• He is a smoker.
• Type II DM for 2 years.
Clinical Examination

- No signs of pallor, jaundice, or cyanosis.
- Height 175 cm, weight 81 kg, BMI of 27 kg/m²,
- Waist circumference: 95 cm, hip Circumference: 101 cm, waist hip ratio: 0.95.
- BP 160/100 mmHg in both upper limbs
- Pulse 80 bpm, felt peripherally.
- Otherwise there were no abnormal findings

WHO Report: Causes of Global Mortality

Death Rates From Ischemic Heart Disease In Egypt is the Highest Compared to Other Countries In Africa And Middle East
Q: Is this patient considered hypertensive?

**Definition and Classification of office hypertension**

Hypertension is defined as values \( \geq 140 \text{ mmHg} \) SBP and/or \( \geq 90 \text{ mmHg} \) DBP, based on the evidence from RCTs that in patients with these BP values treatment-induced BP reductions are beneficial.

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal</td>
<td>120–129</td>
<td>and/or 80–84</td>
</tr>
<tr>
<td>High normal</td>
<td>130–139</td>
<td>and/or 85–89</td>
</tr>
<tr>
<td>Grade 1 hypertension</td>
<td>140–159</td>
<td>and/or 90–99</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>160–179</td>
<td>and/or 100–109</td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>( \geq 180 )</td>
<td>and/or ( \geq 110 )</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>( \geq 140 )</td>
<td>and &lt;90</td>
</tr>
</tbody>
</table>

*The blood pressure (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.*
**New Definitions of hypertension:**

**AHA:** 130/80 mmHg is the new national BP target

<table>
<thead>
<tr>
<th>SBP</th>
<th>DBP</th>
<th>2017 ACC/AHA</th>
<th>JNC7</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>&lt;80</td>
<td>Normal BP</td>
<td></td>
</tr>
<tr>
<td>120–129</td>
<td>&lt;80</td>
<td>Elevated BP</td>
<td></td>
</tr>
<tr>
<td>130–139</td>
<td>80–89</td>
<td>Stage 1 hypertension</td>
<td>Pre-hypertension</td>
</tr>
<tr>
<td>140–159</td>
<td>90–99</td>
<td>Stage 2 hypertension</td>
<td>Stage 1 hypertension</td>
</tr>
<tr>
<td>≥160</td>
<td>≥100</td>
<td>Stage 2 hypertension</td>
<td>Stage 2 hypertension</td>
</tr>
</tbody>
</table>

- Redefinition of stage 1 hypertension from ≥140 mmHg SBP or ≥90 mmHg diastolic blood pressure (DBP) to ≥130 mmHg SBP or ≥80 mmHg DBP
- 45.6% of US population now defined as hypertensive – an increase of 13.7%
- Changes are heavily influenced by SPRINT and ACCORD trials

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**Q. What investigations would you request?**
ESC/ESH 2013 Hypertension Guidelines: Investigations

**Laboratory Investigations Revealed:**

- FBG 132 mg/dl, PP 189 mg/dl, HbA1c 7.3%

- Creatinine 1.5 mg/dl, Urinary Albumin 168 mg

- K+ 4.1

- Hgb 14.6 g/dl

- Cholesterol 150, TG 140, LDL 115, HDL 45

- ECG: no LVH
Q. According to the European Hypertension Society risk stratification, what is the level of risk for Mr. MW?
ESC/ESH 2013, Stratification of total CV risk

<table>
<thead>
<tr>
<th>Other risk factors, asymptomatic organ damage or disease</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High normal SBP 130–139 or DBP 85–89</td>
</tr>
<tr>
<td>No other RF</td>
<td>Low risk</td>
</tr>
<tr>
<td>1–2 RF</td>
<td>Low risk</td>
</tr>
<tr>
<td>≥3 RF</td>
<td>Low to moderate risk</td>
</tr>
<tr>
<td>O/E, CKD stage 3 or diabetes</td>
<td>Moderate to high risk</td>
</tr>
<tr>
<td>Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs</td>
<td>Very high risk</td>
</tr>
</tbody>
</table>

BP = Blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

Egypt is a very high risk country
### Total Cardiovascular Risk

#### Risk categories

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Subjects with any of the following:</th>
</tr>
</thead>
</table>
| **Very high-risk** | • Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous MI, ACS, coronary revascularisation (PCI, CABG) and other arterial revascularization procedures, stroke and TIA, and PAD. Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.  
  • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.  
  • Severe CKD (GFR <30 mL/min/1.73 m2).  
  • A calculated SCORE ≥10% for 10-year risk of fatal CVD. |
| **High-risk** | Subjects with:  
  • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg.  
  • Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk).  
  • Moderate CKD (GFR 30–59 mL/min/1.73 m2).  
  • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD. |
| **Moderate-risk** | SCORE is ≥1% and <5% for 10-year risk of fatal CVD. |
| **Low-risk** | SCORE <1% for 10-year risk of fatal CVD. |
Q. Does this patient need Statin Therapy?

<table>
<thead>
<tr>
<th>Lipid lowering recommendations to reduce CV risk in diabetic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid lowering agents (principally statins)</strong> are recommended to reduce CV risk in all patients with type 2 or type 1 DM above the age of 40 years.</td>
</tr>
<tr>
<td>Lipid lowering agents (principally statins) may be considered also in individuals below 40 years of age if at significantly elevated risk, based on the presence of micro-vascular complications or of multiple CV risk factors.</td>
</tr>
</tbody>
</table>
| In DM patients at very high-risk (see table 5), a LDL-C target <1.8 mmol/L (<70 mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL), is recommended.  
In DM patients with high-risk (see table 5), LDL-C target <2.6 mmol/L (<100mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) is recommended. |

Q. What Type of Statin should we prescribe this patient?

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors/10-year risk</th>
<th>Treatment goals</th>
</tr>
</thead>
</table>
| Extreme risk       | – Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL  
|                    | – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH  
|                    | – History of premature ASCVD (<55 male, <65 female)                                                                                                                                                                      | LDL-C (mg/dL)   |
|                    |                                                                                                                                                                                                                         | <55             | <80             | <70             |
| Very high risk     | – Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%  
|                    | – DM or stage 3 or 4 CKD with 1 or more risk factor(s)  
|                    | – HeFH                                                                                                                                                                                                                  | LDL-C (mg/dL)   |
|                    |                                                                                                                                                                                                                         | <70             | <100            | <80             |
| High risk          | ≥2 risk factors and 10-year risk 10%-20%  
|                    | – DM or stage 3 or 4 CKD with no other risk factors                                                                                                                                                                       | LDL-C (mg/dL)   |
|                    |                                                                                                                                                                                                                         | <100            | <130            | <90             |
| Moderate risk      | ≤2 risk factors and 10-year risk <10%                                                                                                                                                                                     | LDL-C (mg/dL)   |
|                    |                                                                                                                                                                                                                         | <100            | <130            | <90             |
| Low risk           | 0 risk factors                                                                                                                                                                                                         | LDL-C (mg/dL)   |
|                    |                                                                                                                                                                                                                         | <130            | <160            | NR              |

AACE 2017 Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AND AMERICAN COLLEGE OF ENDOCRINOLOGY
GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION
OF CARDIOVASCULAR DISEASE
### Statins types

**High, Moderate, and Low intensity** *

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Atorvastatin (40†)–80 mg</td>
<td>• Atorvastatin 10 (20 ) mg • <strong>Rosuvastatin (5) 10 mg</strong> • Simvastatin 20–40 mg‡ • Pravastatin 40 (80 ) mg • Lovastatin 40 mg • Fluvastatin XL 80 mg • Fluvastatin 40 mg BID • Pitavastatin 2–4 mg</td>
<td>• Simvastatin 10 mg • Pravastatin 10–20 mg • Lovastatin 20 mg • Fluvastatin 20–40 mg • Pitavastatin 1 m</td>
</tr>
<tr>
<td>• <strong>Rosuvastatin 20 (40) mg</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Daily dose lowers LDL-C, on average, by approximately ≥50%**
- **Daily dose lowers LDL-C, on average, by approximately 30% to <50%**
- **Daily dose lowers LDL-C, on average, by <30%**

*Used in the and RCTs Reviewed by the Expert Panel

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**CHD Events Are Reduced Proportional to LDL-C**

\[
y = 0.1629x - 4.6776 \\
R^2 = 0.9029 \\
P < 0.0001
\]

Efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia

996 patients with hypercholesterolemia (LDL-C between 130 and 220 mg/dL), and coronary heart disease (CHD), atherosclerosis, or a CHD-risk equivalent.

Patient demographics and baseline characteristics (randomized population)

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin 10 mg (n = 504)</th>
<th>Atorvastatin 20 mg (n = 492)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>60.2 (10.4)</td>
<td>60.7 (10.6)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>273 (54.2)</td>
<td>285 (57.9)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>29.7 (5.6)</td>
<td>29.7 (5.9)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>376 (74.6)</td>
<td>380 (77.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>96 (19.4)</td>
<td>90 (18.3)</td>
</tr>
<tr>
<td>Black</td>
<td>23 (4.6)</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (1.2)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Renal function, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>292 (57.9)</td>
<td>271 (55.1)</td>
</tr>
<tr>
<td>Mild impairment</td>
<td>177 (35.1)</td>
<td>190 (38.6)</td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>35 (6.9)</td>
<td>29 (5.9)</td>
</tr>
<tr>
<td>Metabolic syndrome¹, n (%)</td>
<td>254 (50.4)</td>
<td>237 (48.2)</td>
</tr>
<tr>
<td>Diabetes (type 1 or 2), n (%)</td>
<td>256 (50.8)</td>
<td>250 (50.8)</td>
</tr>
<tr>
<td>CHD or CHD-risk equivalent, n (%)</td>
<td>431 (85.5)</td>
<td>407 (82.7)</td>
</tr>
<tr>
<td>Patients without CHD or a CHD-risk equivalent, n (%)</td>
<td>72 (14.3)</td>
<td>85 (17.3)</td>
</tr>
</tbody>
</table>

Michael B Clearfield, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia – Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). Trials. 2006; 7: 35.
Rosuvastatin 10 mg was significantly more effective at reducing the primary efficacy variable, LDL-C level, than Atorvastatin 20 mg after 6 weeks of treatment.

<table>
<thead>
<tr>
<th>Lipids/lipoproteins</th>
<th>Rosuvastatin 10 mg (n = 493)</th>
<th>Atorvastatin 20 mg (n = 481)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline level, mg/dL</td>
<td>Mean LSM percentage change (SE)</td>
<td>Mean baseline level, mg/dL</td>
<td>Mean LSM percentage change (SE)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>165.1</td>
<td>-44.6 (0.6)</td>
<td>164.9</td>
</tr>
<tr>
<td>TC</td>
<td>250.9</td>
<td>-30.8 (0.5)</td>
<td>250.9</td>
</tr>
<tr>
<td>HDL-C</td>
<td>50.3</td>
<td>6.4</td>
<td>50.2</td>
</tr>
<tr>
<td>TG</td>
<td>178.1</td>
<td>-19.1 (1.2)</td>
<td>180.3</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>200.6</td>
<td>-40.1 (0.6)</td>
<td>200.9</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>3.5</td>
<td>-47.6 (0.7)</td>
<td>3.5</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>5.3</td>
<td>-34.5 (0.5)</td>
<td>5.6</td>
</tr>
<tr>
<td>Non-HDL-C/HDL-C</td>
<td>4.3</td>
<td>-33.6 (0.5)</td>
<td>4.3</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>32.6</td>
<td>2.1 (3.8)</td>
<td>27.0</td>
</tr>
<tr>
<td>ApoB</td>
<td>157.4</td>
<td>-35.2 (0.6)</td>
<td>155.4</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>160.5</td>
<td>-37.6 (0.7)</td>
<td>159.6</td>
</tr>
<tr>
<td>ApoB/ApoA-I</td>
<td>1.0</td>
<td>-37.6 (0.7)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* p value obtained from analysis of variance comparing rosuvastatin 10 mg with atorvastatin for LSM percentage change in lipid and lipoproteins.

Michael B. Clearfield, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia – Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). Trials. 2006; 7: 35.

Significantly more patients achieved LDL-C goals with Rosuvastatin than with Atorvastatin:

- Significantly more patients achieved NCEP ATP III LDL-C goal with rosuvastatin than with atorvastatin:
  - 68.8% vs. 62.5%, p < 0.05

- Significantly more patients achieved 2003 European LDL-C goals with rosuvastatin than with atorvastatin:
  - 68.0% vs. 63.3%, p < 0.05.

LDL-C Treatment by NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) is < 100 mg/dL; 2003 European goal is < 2.5 mmol/L for patients with atherosclerotic disease, type 2 diabetes, or at high risk of cardiovascular events, as assessed by a Systematic COronary Risk Evaluation (SCORE) risk ≥ 5% or 3.0 mmol/L for all other patients.

Michael B. Clearfield, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia – Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). Trials. 2006; 7: 35.
Recent Coronary IVUS Progression Trials

But as the efficacy improves, does this affect safety?

Nissen SE, Nicholls S et al. JAMA 2006;295:1555-1565
Rosuvastatin Benefit:Risk – Liver Effects
ALT >3 x ULN: Frequency by LDL-C Reduction

Persistent elevation is elevation to >3 x ULN on 2 successive occasions

Brewer HB. Am J Cardiol 2003;92(Suppl):23K–29K

Rosuvastatin Benefit:Risk - Muscle Effects
CK >10 x ULN: Frequency by LDL-C Reduction

Brewer HB. Am J Cardiol 2003;92(Suppl):23K–29K
Long Term Treatment (5 years) with Rosuvastatin lead to a low NNT Compare to other medications such as Asprin

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>All</th>
<th>FRS≤10</th>
<th>FRS&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>25</td>
<td>47</td>
<td>17</td>
</tr>
<tr>
<td>Primary Endpoint, Mortality</td>
<td>20</td>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td>MI, Stroke, CABG/PTCA, Death</td>
<td>20</td>
<td>37</td>
<td>14</td>
</tr>
<tr>
<td>MI, Stroke, Death</td>
<td>29</td>
<td>60</td>
<td>20</td>
</tr>
</tbody>
</table>

Benchmarks:
- Statins for hyperlipidemia: 5-year NNT: 40-60
- Diuretics: 5-year NNT: 80-100
- Beta-blockers: 5-year NNT: 120-160
- Aspirin Men: 5-year NNT: 220-270
- Aspirin Women: 5-year NNT: 280-330

Q. In our patient, what would be your anti-HTN drug of choice?

A. RAAS inhibitor.

B. CCBs.

C. Beta Blockers.

D. Alpha Blockers.
**ESH / ESC Guidelines 2013: Drugs to be preferred in specific conditions**

### Asymptomatic Organ Damage

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preferred Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular hypertrophy</td>
<td>ACE inhibitor, Calcium antagonist, ARB</td>
</tr>
<tr>
<td>Asymptomatic atherosclerosis</td>
<td>Calcium antagonist, ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>ACE inhibitor, ARB</td>
</tr>
</tbody>
</table>

### Clinical Event

<table>
<thead>
<tr>
<th>Event</th>
<th>Preferred Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stroke</td>
<td>Any agent effectively lowering BP</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>BB, ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>BB, Calcium antagonist</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonist,</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>BB</td>
</tr>
<tr>
<td>Atrial fibrillation, prevention</td>
<td>Consider ARB, ACE inhibitor, BB</td>
</tr>
<tr>
<td>Atrial fibrillation, rate control</td>
<td>BB, non-dihydropiridine calcium antagonist</td>
</tr>
<tr>
<td>ESRD/proteinuria</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>ACE inhibitor, Calcium antagonist</td>
</tr>
</tbody>
</table>

---

**ESH / ESC Guidelines 2013:**

**Drugs to be preferred in specific conditions**

### Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preferred Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated systolic hypertension</td>
<td>Diuretic, Calcium antagonist</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>ACE inhibitor, ARB, Calcium antagonist</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Methyldopa, BB, Calcium antagonist</td>
</tr>
<tr>
<td>Blacks</td>
<td>Diuretics, Calcium antagonist</td>
</tr>
</tbody>
</table>
ESH / ESC Guidelines 2013:
Possible combinations of classes of antihypertensive drugs


ARBs Mode of Action

- Kinins
  - Degradation of bradykinin
  - Normal ACE activity
- Bradykinin
- Angiotensin II
- Angiotensin
- Production of angiotensin
- ARBs
  - Less constriction
  - Dilatation
- Proapoptotic
- Antigrowth
- Blood pressure, no effect on endothelial continuity
  - No cardioprotection

- eNOs
- BK
- Endothelium
- AT₁
- AT₂
ACEIs Mode of Action

Q. Which ACE inhibitor would you prescribe this patient?
FDA Approved Indication for ACE-I

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>CHF/ Post AMI</th>
<th>LV dysfunction / Post AMI</th>
<th>Prevention of MI, Stroke &amp; CV death in high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>Ramipril</td>
<td>Ramipril</td>
<td>Ramipril</td>
</tr>
<tr>
<td>Captopril</td>
<td>Captopril</td>
<td>Captopril</td>
<td>Perindopril (only CAD patients)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Enalapril</td>
<td>Enalapril</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Lisinopril</td>
<td>Lisinopril</td>
<td></td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Fosinopril</td>
<td>Trandolapril</td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Benazepril</td>
<td>Perindopril</td>
<td></td>
</tr>
</tbody>
</table>

ACE-inhibitors are not the same


Ramipril

Superior Tissue ACE Inhibition

Dzau VJ. Am J Cardiol 1987; 59: 59A-65A
Ramipril Possible Antiatherosclerotic Mechanisms

- Hypertension
- Diabetes
- Smoking
- LDL

Endothelial dysfunction

Improvement

Local Mediators

Ang II

Plaque ACE

Ang II

Growth factors

Proteolysis

Thrombosis

Inflammation

Vasoconstriction

Vascular lesions Remodeling

Plaque rupture

PAI-1

VCAM

ICAM

Cytokines

Endothelin

Bradykinin

NO

Pepine C, Can J Cardiol 14; suppl D (1998)

Evidence of Ramipril in Hypertension
KOENIG Study

Ramipril 2.5mg od reduces BP more than Lisinopril 10mg od

![Graph showing blood pressure comparison between Ramipril 2.5mg, Lisinopril 10mg, and Lisinopril 5mg over 8 weeks of treatment.]

Patients: 140 HTN patient in multi-center, randomised study
Duration: 8 weeks

KOENIG Study

ASTRAL STUDY

- **Study design**: a multi-Centre, non-comparative, open-label, observational study
- **Inclusion criteria**: patients with hypertension not controlled by an ACE inhibitor, a diuretic or any other monotherapy (SBP 169 mmHg - DBP 103 mmHg) 20% with DM
- **Goal**: to evaluate the percentage of hypertensive patients achieving blood pressure goals after eight weeks of treatment with a fixed-dose combination of ramipril/hydrochlorothiazide
- **Number of patients**: 449 (mean age of the patients 55 years), 72% either overweight or obese
- **Outcome**: systolic and diastolic blood pressures significantly changed from baseline: after 8-week treatment –31.7/–17.9 mmHg (p < 0.001), respectively
- **Tolerability**: Few adverse events were reported, with facial edema and dry cough recurring twice in two patients
Ramipril in Prevention of MI, Stroke & CV Deaths in High Risk Patients

Overlap of Vascular Disease in Patients With Atherothrombosis

**Cerebral**
- Ischemic stroke
- Transient ischemic attack

**Coronary**
- Myocardial infarction
- Angina pectoris (stable, unstable)

**Peripheral Arterial Disease**
- Critical limb ischemia, claudication

**CAPRIE Study**

- Cerebral Disease: 25%
- Coronary Disease: 30%
- Peripheral Arterial Disease (PAD): 19%

PAD, peripheral artery disease.

*Data from CAPRIE study (n=19,185)
Heart Outcomes Prevention Evaluation Study

A large, simple, randomized trial of Ramipril and vitamin E in patients at high risk for cardiovascular events

The New England Journal Of Medicine
Volume 342, January 20, 2000, Number 3: 145-153

Who Were The Participants?

- Mean age 66
- Approximately ¼ female
- 80% had coronary artery disease
- 43% had peripheral vascular disease
- 11% had a stroke
- 38% had diabetes
- 47% had hypertension
- 66% had high cholesterol

What Medications were They Taking?

- Aspirin (or other antiplatelet agents): 76%
- Lipid lowering drugs: 29%
- Beta blockers: 40%
- Diuretics: 15%
- Calcium channel blockers: 47%
- Any anti-ischemic agent: 74%

⇒ Patients were already medically well-managed according to their underlying disease

HOPE Study
Results: Primary endpoints

Ramipril 10mg reduces risk of MI, Stroke & CV deaths early and effect increase by time

Note: Trial halted early due to the highly significant risk reductions seen with Tritace

Ramipril 10mg reduces risk of MI, Stroke & CV deaths early and effect increase by time

Note: Trial halted early due to the highly significant risk reductions seen with Tritace

Micro HOPE Study
Results: Primary endpoints

Ramipril 10mg protection is on top of expected benefits of standard therapies

Ramipril lowered the risk of the combined primary outcome by 25%

Kaplan-Meier survival curves for participants with diabetes

Kaplan-Meier survival curves for participants with diabetes

Gerstein HC et al. MICRO-HOPE, Lancet 2000; 355: 253-59

Lancet 2000; 355: 253-59
Ramipril and Nitric Oxide

Nitric Oxide

- Reduces Oxidation of LDL Cholesterol (major component of plaque)
- Dilates Blood Vessels
- Reduces Release of Superoxide Radicals (Anti-oxidant Effect)
- Reduces multiplication of smooth muscle cells of the artery wall
- Reduces Platelet Stickiness
- Reduces Monocyte Stickiness (prevent Plaque formation)
- Reduces Oxidation of LDL Cholesterol (major component of plaque)
Ramipril Sensitizes Platelets to Nitric Oxide
Implications for Therapy in High-Risk Patients


Study Rationale

• The HOPE (Heart Outcomes Prevention Evaluation) study with Ramipril has proven that ACE inhibitors reduce the risk for cardiovascular events in aging, high-risk populations.
• Furthermore, rates of MI, stroke, cardiac arrest, heart failure, and complications relating to diabetes were also decreased.
• However, the mechanism(s) underlying these beneficial effects have never been delineated.

Study objectives

- Using 2 sequential studies in HOPE (Heart Outcomes Prevention Evaluation) study–type patients, the aims of this study were
  
  - To test the hypothesis that Ramipril improves platelet nitric oxide (NO) responsiveness (i.e. ↓ in platelets aggregation)
  - To explore biochemical and physiological effects of Ramipril in a cohort selected on the basis of platelet NO resistance.

Methods

Study 1 was a double-blind, randomized comparison of Ramipril (10 mg) with placebo in a cohort of patients (n=119) with ischemic heart disease or diabetes plus additional coronary risk factor(s), in which effects on platelet responsiveness to NO were compared.
Methods (cont’d)

Additionally, the effects of Ramipril on **endothelial function** were assessed, using:
- Plasma levels of asymmetric dimethylarginine (ADMA), a marker of endothelial dysfunction
- Augmentation index (AIx), a marker of apparent arterial stiffness

Inclusion criteria were similar to those of the HOPE study

Men and women more than 50 years in age who had histories of:
- Coronary artery disease
- Stroke
- Peripheral vascular disease
- Diabetes plus 1 other risk factor (HTN, elevated total cholesterol level, low high density lipoprotein cholesterol level, cigarette smoking, or documented microalbuminuria).
Methods (cont’d)

**Study 2** was a subsequent short-term evaluation of the effects of Ramipril in a cohort of subjects (n=19) with impaired platelet NO responsiveness in whom additional mechanistic data were sought*.

*To determine whether sensitization of platelets to NO by Ramipril was associated with potentiation of NO responsiveness of platelet soluble guanylate cyclase (sGC)

Results

**In study 1,** Ramipril therapy increased platelet responsiveness to NO relative to the extent of aggregation *(p<0.001)*, but this effect occurred primarily in patients with severely impaired baseline NO responsiveness (n =41).
Results (cont’d)
NO platelet responsiveness

Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Group (n = 57)</th>
<th>Ramipril Group (n = 51)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>1.1 ± 15.5</td>
<td>2.2 ± 8.7</td>
<td>0.63</td>
</tr>
<tr>
<td>ADP-induced aggregation (Ω)</td>
<td>−1.5 ± 2.4</td>
<td>−0.9 ± 2.6</td>
<td>0.22</td>
</tr>
<tr>
<td>Inhibition of aggregation by SNP (%)</td>
<td>1.7 ± 28.2</td>
<td>12.3 ± 36.8</td>
<td>0.10</td>
</tr>
<tr>
<td>AIx (%)</td>
<td>−1.3 ± 8.1</td>
<td>−4.8 ± 10.9</td>
<td>0.02</td>
</tr>
<tr>
<td>MDA (µmol/l)</td>
<td>0.006 ± 0.15</td>
<td>−0.042 ± 0.26</td>
<td>0.25</td>
</tr>
<tr>
<td>ADMA (µmol/l)</td>
<td>6.9 ± 6.1</td>
<td>−15.9 ± 5.9</td>
<td>0.05</td>
</tr>
<tr>
<td>SNP-induced intraplatelet cGMP response (%)</td>
<td>−3.1 ± 42.0</td>
<td>−3.0 ± 41.7</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
ADMA = asymmetric dimethylarginine; ADP = adenosine diphosphate; AIx = augmentation index; cGMP = cyclic guanosine monophosphate; HR = heart rate; MDA = malondialdehyde; SNP = sodium nitroprusside.

The SNP/ADP relationship demonstrated an increase in NO responsiveness in the Ramipril treatment group

Analysis of covariance, p < 0.001
Heterogeneity of Ramipril effect on NO responsiveness (analysis by subgroups)

- NO responsiveness increased markedly after Ramipril therapy in NO-resistant subgroup of patients, compared with the placebo group (p = 0.03)

- In contrast, platelet NO responsiveness was unaltered by Ramipril in the subgroup with normal platelet responses at baseline

At base line, severe platelet NO resistance (SNP responses ≤32%) was present in 41 patients at baseline (23 of whom were randomized to ramipril therapy).

There was no difference in the extent of ADP-induced aggregation between the normal NO responder and impaired NO responder groups.


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NO responsiveness increased markedly after Ramipril therapy in NO-resistant subgroup

Effect of Ramipril on Inhibition of Aggregation According to Baseline SNP Responsiveness

Results (cont’d)
Oxidative Stress and Endothelial Dysfunction

In study 2, Ramipril also improved platelet NO responsiveness (p<0.01), and this improvement was correlated directly with increased NO-stimulated platelet generation of cyclic GMP (p<0.02).

Conclusions

• Ramipril sensitizes platelets to NO in a HOPE-type patient population and that this effect results from sGC-dependent Improvement of platelet NO resistance.

• These findings provide an additional potential basis for the effects of Ramipril in reducing risk for cardiac events.


Take Home Messages

• CVD is the leading cause of death worldwide.

• DM, HTN and Dyslipidemia co exist in most cases.

• BP control should be coupled with risk factor and CVD prevention.

• ACE inhibitors show a mortality benefit outweighing ARBs.

• Ramipril shows a potent anti-HTN effect and also a cardiovascular protective effect.

• Not all statins have proof of cardiovascular event reduction.

• Rosuvastatin has been shown to provide the highest efficacy without affecting safety.
Thank You