Treatment of Hypertension

‘ *Metabolic Risk Management* ’

The Metabolic Syndrome in Hypertension

An ESH Position Statement

*Redon J et al. J. Hypertens 2008;26:1891*

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*Director of Cardiology Department, Asklepeion Hospital, Athens, Greece*
1990

4.9% DM Prevalence

11.1 % Obesity

No data available

Less than 4%

4%-6%

Above 6%

2000

7.3% DM Prevalence

19.8 % Obesity

*Includes women with a history of gestational diabetes.

Percentage of the US Population With $\geq 2$ Risk Factors*

Risk Factors: High BP, High Cholesterol, Diabetes,† Obesity, Smoking

1991

2003

Percentage of Population With $\geq 2$ Risk Factors

- <22%
- 22.0% to 24.9%
- 25.0% to 29.9%
- $\geq$30%
- NA

*Risk factors are self-reported. †Diabetes is a CHD risk equivalent.

The Metabolic Syndrome

- Reduced glucose tolerance
- Hyperinsulinemia
- Hypertension
- Visceral obesity
- Hemostatic disorders
- Lipid disorders
  - Triglycerides elevated
  - LDL-cholesterol normal or moderately elevated
  - HDL-C diminished
## Definitions of Metabolic Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Principal criteria</th>
<th>Abdominal obesity</th>
<th>Glucose (mg/dl)</th>
<th>HDL (mg/dl)</th>
<th>Trigl (mg/dl)</th>
<th>BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO</strong></td>
<td>DM, GI or IR</td>
<td>BMI (\geq 30 \text{ k/m}^2)</td>
<td>M (\geq 0.9)</td>
<td>W (\geq 0.85)</td>
<td>(\geq 150)</td>
<td>(\geq 140/90^*)</td>
</tr>
<tr>
<td><strong>EGIR</strong></td>
<td>IR or FI &gt;P75</td>
<td>BMI (\geq 30 \text{ k/m}^2)</td>
<td>M (\geq 102)</td>
<td>W (\geq 88)</td>
<td>(\geq 110^*)</td>
<td>40</td>
</tr>
<tr>
<td><strong>ATPIII</strong></td>
<td></td>
<td>(M \geq 102 \text{ cm})</td>
<td>(W \geq 88 \text{ cm})</td>
<td>(\geq 110^*)</td>
<td>(M \leq 40)</td>
<td>(W \leq 50)</td>
</tr>
<tr>
<td><strong>IDF</strong></td>
<td>Central obesity</td>
<td>M (\geq 94 \text{ cm})</td>
<td>W (\geq 80 \text{ cm})</td>
<td>(\geq 100^*)</td>
<td>(M \leq 40)</td>
<td>(W \leq 50^*)</td>
</tr>
<tr>
<td><strong>AHA</strong></td>
<td></td>
<td>M (\geq 94 \text{ cm})</td>
<td>W (\geq 80 \text{ cm})</td>
<td>(\geq 100^*)</td>
<td>(M \leq 40)</td>
<td>(W \leq 50^*)</td>
</tr>
</tbody>
</table>

*Principal + 2 criteria or 3 criteria

*or treatment for
Mechanisms of the Metabolic Syndrome

- Abdominal obesity
- Insulin resistance
- Genetics
- Diet
- Physical exercise
- Fetal programming

Infections

Insulin

Leptin
FFAs
Angiotensin II
IL-6, TNFα

Adiponectin

Drugs

Abdominal obesity
Insulin Resistance and Hypertension

Genetic factors

Environmental factors
- Diet
- Exercise

Acquired factors
- Central adipose
- Ectopic lipids

Inflammation/Oxidative stress

↑ RAAS

Hyperinsulinemia

↑ SNS

Vascular dysfunction
- ↑ VSMC proliferation
- ↑ Arterial stiffness
- ↑ Vascular tone
- ↑ Vasodilation

Hypertension

Sodium retention
Prevalence of the Metabolic Syndrome in PAMELA

Mancia et al., Hypertension 2006; 49: 40-47
Prevalence of Various Components of MS + in Subjects from PAMELA

Mancia et al., Hypertension 2006; 49: 40-47
## Impact of Lifestyle Habits on the Prevalence of the MS among Greek Adults from the ATTICA Study

**Distribution of the components of the MS in the population study by sex**

<table>
<thead>
<tr>
<th>Component</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (&gt;102 or 88 cm)</td>
<td>359 (31.8)</td>
<td>343 (29.7)</td>
</tr>
<tr>
<td>TG levels &gt;150 mg/dL</td>
<td>320 (28.4)</td>
<td>146 (12.7) *</td>
</tr>
<tr>
<td>HDL &lt; 40 mg/dL</td>
<td>424 (37.6)</td>
<td>432 (37.4)</td>
</tr>
<tr>
<td>Blood pressure &gt;130/85 mm Hg</td>
<td>494 (43.7)</td>
<td>403 (34.9) *</td>
</tr>
<tr>
<td>Fasting blood glucose`&gt;110 mg/dL</td>
<td>160 (14.2)</td>
<td>89 (7.7) *</td>
</tr>
</tbody>
</table>

Panagiotakos D. et al. Am Heart J 2004
From individual RF and the metabolic syndrome to global cardiometabolic risk

8331 hypertensives, >54 yrs, from Primary Care
ATPIII criteria

Number of Metabolic Syndrome components and organ damage

$p<0.001$ for both

Kaplan-Meier Survival Curves for CV Death and All Cause Death in Subjects Without and With Metabolic Syndrome

**All cause death**

- Proportional survival (%)
- Survival time (years)
- p < 0.0001

**Cardiovascular death**

- Proportional survival (%)
- Survival time (years)
- p < 0.0001

Mancia et al., Hypertension 2007; 49: 40-47
ESH/ESC Guidelines
Stratification of CV Risk in Four Categories

<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>Low 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>

Cardiovascular event rate in 10 years
Risk for cardiovascular death in 10 years (SCORE)
ESH/ESC Guidelines and Search for Subclinical Organ Damage (OD)

**Routine**
- ➤ SCr (> 1.4-1.5 mg/dl)
- ➣ eCrCl / GFR
- MA / Proteinuria
- EKG †

**Recommended**
- LVH (Echo)
- Concentric LVH
- LA enlargement
- CA thickening / plaques
- Ankle/Brachial ratio
- Arterial stiffening (PWV)*

* Search for multiorgan D
* OD (MA / EKG / echo) to be assessed also during treatment

- Depending on availability / also shown by high SBP / low DBP
- LVH / MI-ischemia / Arrhythmias
What Do You Want Your Levels To Be?

- Blood pressure
- LDL cholesterol
- Haemoglobin A1c
Goals of hypertension treatment in the Metabolic Syndrome

- Threshold to define: 130/85 mmHg
- BP $\geq 140/90$ mmHg ($\geq 130/80$ mmHg if diabetes) requires antihypertensive treatment
- Goal: $<130/80$ mmHg
**Lipid Targets Continue to Evolve: Treatment Goals and New Therapeutic Options**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>NCEP ATP III LDL-C Goal (mg/dL)</th>
<th>NCEP ATP III Update LDL-C Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk*: CHD† or CHD risk equivalents‡</td>
<td></td>
<td>&lt;70</td>
</tr>
<tr>
<td>High risk: CHD† or CHD risk equivalents‡, 10-year risk&gt;20%</td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Moderately high risk: 2+ risk factors, 10-year risk 10% to 20%</td>
<td></td>
<td>&lt;130</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors, 10-year risk &lt;10%</td>
<td>&lt;130</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Lower risk: 0-1 risk factor</td>
<td>&lt;160</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>

<v> NCEP ATP III Update: In moderate- or high-risk patients, lipid-lowering therapy should result in at least a 30% to 40% reduction in LDL-C.</v>

<v> Identify major risk factors (exclusive of LDL-C) that may modify lipid goals</v>

*For example, patients with established CVD plus multiple major risk factors (especially diabetes) have an optional goal of <70 mg/dL; †CHD includes history of MI, stable or unstable angina, coronary artery procedures, or evidence of clinically significant myocardial ischemia; ‡CHD risk equivalent includes diabetes, noncoronary forms of atherosclerotic disease, and 2+ risk factors with 10-year risk of CHD >20%.

TARGETS IN HYPERTENSION AND DIABETES MELLITUS

- Aggressive EARLY attainment of known risk factors for CV/renal risk (BP <130, glucose-HbA1c<7%, lipids-<70?) reduce risk.
- Once established nephropathy (eGFR <60 ml/min)-BP <140 is appropriate to reduce risk-pending ACCORD)-Proteinuria>300 mg/day BP should be <130
2007 ESH/ESC Guidelines
Lifestyle Changes in MS

- Modest ↓ of caloric intake
  - ↓ Saturated fat < 7%
  - ↓ Transfatty acids
  - ↓ Cholesterol <200 mg
  - ↓ Simple carbohydrates 50%
  - ↑ Fruit / vegetables
  - ↑ Whole grain

- ↑ Physical exercise
  - 30 min daily of moderate exercise

At least 7-10% ↓ BW in 6-12 months

Marked reduction (~60%) of NOD
Marked reduction (~40-50%) of MS prevalence
Exercise Capacity and Mortality in Black and White Men, in Diabetics, Prehypertensives, and High Risk

**RR of all cause mortality in individuals with no CVD**

Relative Risk

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>ALL</th>
<th>African-American</th>
<th>Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
</tr>
<tr>
<td>0.4</td>
<td>0.51</td>
<td>0.52</td>
<td>0.50</td>
</tr>
<tr>
<td>0.6</td>
<td>0.27</td>
<td>0.23</td>
<td>0.23</td>
</tr>
<tr>
<td>0.8</td>
<td>0.52</td>
<td>0.52</td>
<td>0.50</td>
</tr>
<tr>
<td>1.0</td>
<td>0.23</td>
<td>0.23</td>
<td>0.30</td>
</tr>
</tbody>
</table>


Exercise capacity and Mortality in Hypertensive Men With and Without Cardiovascular Risk Factors

* p<0.007
† p=0.016

* Different from the very-low-fit (≤ 5 Mets) with no risk factors
† Different from the low-fit (5.1 to 7 METs) with risk factors

Diuretics
ACE-inhibitors
Calcium antagonists
Angiotensin receptor antagonists
Beta-blockers
Ideal Antihypertensive in the Patient With Metabolic Syndrome

- Does not worsen Insulin resistance

- Does not cause - Hyperglycemia
  - New-onset diabetes
  - Dyslipidemia

- Protects kidney and heart
What are the effects of antihypertensive drugs on insulin sensitivity?

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Insulin sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>↓ (except celiprolol, carvedilol, nebivolol)</td>
</tr>
<tr>
<td>B-blockers</td>
<td>↓ (Diltiazem ↓ or ~)</td>
</tr>
<tr>
<td>CCB’s</td>
<td>↑</td>
</tr>
<tr>
<td>ACE-I</td>
<td>↑</td>
</tr>
<tr>
<td>ARB’s</td>
<td>↑</td>
</tr>
</tbody>
</table>
Results of a Meta-analysis for Incident Diabetes - Twenty-two Clinical Trials of 143,153 Hypertensive Patients

ARBl 0.57 (0.46-0.72) p < 0.0001
ACE inhibitor 0.67 (0.56-0.80) p < 0.0001
CCB 0.75 (0.62-0.90) p = 0.002
Placebo 0.77 (0.63-0.94) p = 0.009
Beta-blocker 0.90 (0.75-1.09) p = 0.30
Diuretic Referent

Odds ratio of incident diabetes

Incoherence = 0.000017
2007 ESH/ESC Guidelines
Monotherapy versus Combination Therapy Strategies

If goal BP not achieved

Choose between

Mild BP elevation
Low/moderate CV risk
Conventional BP target

Single agent
at low dose

Previous agent
at full dose

Switch to different agent
at low dose

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

Two-drug combination
at low dose

If goal BP not achieved

Two-to-three drug combination at full dose

Full dose monotherapy

Previous combination
at full dose

Add a third drug
at low dose

Two-three drug combination
at full doses

If goal BP not achieved

If goal BP not achieved

If goal BP not achieved

Low/moderate CV risk

Conventional BP target

Mild BP elevation

Marked BP elevation

Add a third drug
at low dose

Two-three drug combination
at full doses

Lower BP target
2007 ESH/ESC Guidelines
Combinations between Some Classes of Antihypertensive Drugs

- Thiazide diuretics
- ACE inhibitors
- AT_{1} receptor antagonists
- Calcium antagonists
- β-blockers
- α-blockers

- Pronounced antihypertensive effect
- CV protection
- Optimal tolerability
“BB, especially in combination with a diuretic, should not be used in patients with metabolic syndrome or at high risk of diabetes.”
STARLET Trial: Low Versus High Diuretic Dose

Post hoc evaluation of dose titration is clinically relevant, although confounded by requirement for dose titration to achieve better BP control.

2-hour OGTT change in blood glucose from Baseline to Study End (mean ± SD)

Bakris GL et.al. Diabetes Care 2006;29:2592-2597
Summary

Routine treatment of type 2 diabetic patients with perindopril-indapamide resulted in:

- 14% reduction in total mortality
- 18% reduction in cardiovascular death
- 9% reduction in major vascular events
- 14% reduction in total coronary events
- 21% reduction in total renal events

Benefits appeared to be similar in all major subgroups. Treatment was very well tolerated, with few side effects and adherence similar to that with placebo.

Lancet 2nd September 2007
Lipid Lowering Agents

- All hypertensive patients with established cardiovascular disease or with type 2 diabetes should be considered for statin therapy aiming at serum total and LDL cholesterol levels of, respectively, <4.5 mmol/L (175 mg/dL) and <2.5 mmol/L (100 mg/dL) and lower, if possible.

- Hypertensive patients without overt cardiovascular disease but with high cardiovascular risk (≥20% risk of events in 10 years) should also be considered for statin treatment even if their baseline total and LDL serum cholesterol levels are not elevated.
HYPERTENSION AND DYSLIPIDEMIA

- If TGs remain elevated (200-499 mg/dL) after the LDL-C target is achieved, then the patient should be treated with TG lowering drugs (e.g. fibrate or niacin).
- If TG exceed 500 mg/dL, the patient should be treated with TG lowering drugs and a very low fat diet (< 15% of total daily calories) in order to reduce the risk of CV events and pancreatitis.
- When serum TG do not normalize additional intervention with orlistat or high dose fish oil can be considered.
Many Patients Newly Treated for Hypertension Do Not Receive Concomitant Statin Therapy Within 1 Year

- Orange: Already on statin therapy
- Yellow: Prescribed concomitant statin therapy in year 1
- Blue: Did not receive statin therapy during first year of AH therapy

<table>
<thead>
<tr>
<th>Hypertensive Patient Groups</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia n=43,825</td>
<td>53.3%</td>
</tr>
<tr>
<td>No CHD but ≥3 CHD risk factors n=15,701</td>
<td>53.7%</td>
</tr>
<tr>
<td>Diabetes n=17,567</td>
<td>61.0%</td>
</tr>
</tbody>
</table>
ASCOT-LLA: SBP and LDL-C Changes

SBP

Atorvastatin
Placebo

Final mean BP: Atorvastatin 138/80 mm Hg
Placebo 138/80 mm Hg

LDL-C

Years

ASCOT lipids results presentation. Available at:
ASCOT-LLA: Reductions in Nonfatal MI and Stroke

100% Were Treated Hypertensive Patients With Additional Risk Factors and Without CHD

![Graph showing cumulative incidence of Nonfatal MI and Stroke with Atorvastatin vs Placebo]

- **Nonfatal MI**
  - Atorvastatin 10 mg (n=5168) with a 45% reduction
  - Placebo (n=5137)

- **Stroke**
  - Atorvastatin vs Placebo with a 26% reduction

*Although the reduction of fatal and nonfatal stroke did not reach a predefined significance level (P=.01), a favorable trend was observed.*

RRR=relative risk reduction.

*Please consult speaker for full prescribing information.*
JEWEL I, JEWEL II Trial: Patients Achieving Country-specific BP and LDL-C goals

Amlodipine/atorvastatin
All doses

62.9%  
50.6%

Amlodipine/atorvastatin
5/10 mg or 10/10 mg

59.0%  
51.9%

## Blood-pressure reductions in the statin arms vs placebo

<table>
<thead>
<tr>
<th>Statin treatment</th>
<th>Reduction in SBP (mm Hg)</th>
<th>P</th>
<th>Reduction in DBP (mm Hg)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>2.2</td>
<td>0.02</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>1.5</td>
<td>0.20</td>
<td>2.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>2.9</td>
<td>0.009</td>
<td>3.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Excluding those with high blood pressure or taking hypertensive medication at baseline**

<table>
<thead>
<tr>
<th>Statin treatment</th>
<th>Reduction in SBP (mm Hg)</th>
<th>P</th>
<th>Reduction in DBP (mm Hg)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>2.6</td>
<td>0.006</td>
<td>2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>2.2</td>
<td>0.048</td>
<td>2.3</td>
<td>0.006</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>3.0</td>
<td>0.005</td>
<td>2.7</td>
<td>0.002</td>
</tr>
</tbody>
</table>
HYPERTENSION AND OBESITY

Target: reduction of body weight 10-15%

- Psychosocial evaluation
- Behavior modification
- Dietary changes
- Physical activity

Drugs: After 6mos of diet etc if BMI > 25 kg/m² pharmacotherapy can be used

1. Sirbutamine (4.5-6.8 kg/2yrs)
   Contraindicated in CHD, severe HTN
2. Orlistat (same as sirbutamine)
3. Rimonabant
The impact of rimonabant on CVR needs to be assessed in prospective studies due to an increase in the incidence of depression and a small, but significantly greater risk of suicide risk.

### Summary of the Benefits, Adverse Effects and Potential Concerns of Diabetic Drugs

<table>
<thead>
<tr>
<th></th>
<th>Long-term data</th>
<th>Other benefits</th>
<th>HbA&lt;sub&gt;1c&lt;/sub&gt; decrease</th>
<th>Hypoglycaemia risk</th>
<th>Body Weight change</th>
<th>Other Potential concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUs</strong></td>
<td>Proven efficacy/safety</td>
<td>Low cost</td>
<td>0.8-2.0%</td>
<td>YES</td>
<td>Gain</td>
<td>CV events?</td>
</tr>
<tr>
<td><strong>Biguanides</strong> (metformin)</td>
<td>Proven efficacy/safety</td>
<td>Low cost</td>
<td>1.0-1.5%</td>
<td>NO</td>
<td>None or possible loss</td>
<td>Lactic acidosis (very rare)</td>
</tr>
<tr>
<td><strong>Alpha-glucosidase Inhibitors</strong></td>
<td>Limited data</td>
<td>CV benefits?</td>
<td>0.5-0.8%</td>
<td>NO</td>
<td>NO</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Glinides</strong></td>
<td>Limited data</td>
<td>Rapid acting</td>
<td>0.8-1.5%</td>
<td>LOW</td>
<td>Gain</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>TZDs</strong></td>
<td>Improve β-cell function</td>
<td>Lipid profile (pioglitazone)</td>
<td>0.8-1.0%</td>
<td>NO</td>
<td>Gain</td>
<td>Oedema, heart failure, fracture</td>
</tr>
<tr>
<td><strong>GLP-1 agonists</strong></td>
<td>Unknown</td>
<td>Improved β-cell mass?</td>
<td>0.6-1.0%</td>
<td>NO</td>
<td>Loss</td>
<td>Risk of pancreatitis</td>
</tr>
<tr>
<td><strong>Amylin analogues</strong></td>
<td>Unknown</td>
<td>-</td>
<td>~0.6%</td>
<td>NO</td>
<td>Loss</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>DPP-IV inhibitors</strong></td>
<td>Unknown</td>
<td>Improved β-cell mass?</td>
<td>0.05-0.9%</td>
<td>NO</td>
<td>Neutral</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

HbA<sub>1c</sub>, glycated haemoglobin; GI, gastrointestinal; SUs, sulphonylureas; cardiovascular; TZDs, thiazolidinediones; GLP-1, glucagon-like peptide-1; DPP-IV, dipeptidyl peptidase-IV
Management Recommendations for Hypertension and the Metabolic Syndrome

- Threshold: 130/85 mmHg
- Goal: <130/80 mmHg
- Recommended:
  - Non-pharmacological treatment
  - First choice: ACEi or ARB
  - Second choice: CCB or vasodilating β-blockers
- Observations:
  - Thiazide-like diuretics should be avoided in monotherapy or in high dose
  - β-blockers should be avoided if not compelling indications exist
  - Combination of β-blockers of thiazide diuretics should be avoided

Redon et al. J Hypertens 2009