Η θέση του σταθερού συνδυασμού αμλοδιπίνης / ατορβαστάτινης στη συνολική μείωση του καρδιαγγειακού κινδύνου

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ΓΝΜ¨ΕΛΕΝΑ ΒΕΝΙΖΕΛΟΥ¨
Δήλωση σύγκρουσης συμφερόντων

Τιμητική αμοιβή από τις εταιρείες

Novartis, Bayer, Menarini, Win Medica
Comparison of leading causes of deaths, Global, 2000 and 2012

- Ischaemic heart disease
- Stroke
- COPD
- Lower respiratory infections
- Trachea, bronchus, lung cancers
- HIV/AIDS
- Diarrhoeal diseases
- Diabetes mellitus
- Road injury
- Hypertensive heart disease
- Prematurity
- Tuberculosis

Deaths (million)

Word Health Organization 2014
Most >35 years have ≥1 CV risk factors

- 1 in 3 hypercholesterolemia
- 1 in 3 obese
- 1 in 3 hypertension
- 1 in 5 smoke
- 1 in 10 diabetes

AHA. Heart Disease and Stroke Statistics–2005 Update.
Cardiovascular Disease Risk Factors Overlap

Lancet. 2005;365:434-41
Atherothrombosis: Significantly Shortens Life Expectancy

Analysis of data from the Framingham Heart Study:
Average remaining life expectancy for males aged 60 years

- Healthy: 9.2 years
- History of any cardiovascular disease*: 7.7 years
- History of acute MI: 12.0 years
- History of stroke: 12.0 years

*Including coronary heart disease, cerebrovascular accident, congestive heart failure and intermittent claudication

Multifactorial Approach for an Effective Macrovascular Disease Prevention

- Ρύθμιση ΑΠ
- Ρύθμιση λιπιδίων
- Ρύθμιση σακχάρου
- Αντιθρομβωτική αγωγή
- Δίαιτα και Φυσική άσκηση κάπνισμα
Factors—other than office BP—influencing prognosis; used for stratification of total CV risk

Dyslipidaemia

TC > 4.9 mmol/L (190 mg/dL), and/or

LDL- C > 3.0 mmol/L (115 mg/dL), and/or

HDL- C: men <1.0 mmol/L (40 mg/dL),

women <1.2 mmol/L (46 mg/dL), and/or

TGL >1.7 mmol/L (150 mg/dL)

2013 ESH Guidelines for the Management of Hypertension.
Dyslipidemia and the risk of Hypertension

- 3110 men followed for 14 years in Physicians’ Health Study
- Baseline lipids analyzed by quintiles

Baseline

- LDL Chol: HTN Risk by 39%
- Tot Chol: HTN Risk by 23%
- HDL Chol: HTN Risk by 32%

Halperin et al Hypertens 2006: 47:45
Most patients have overlapping CV Risk Factors

Multiple Comorbidities Increases Risk 400% to 700%

Of all hypertensives
- 65% have dyslipidaemia
- 16% have type 2 diabetes
- 45% are overweight/obese

Of all dyslipidaemics
- 48% have hypertension
- 14% have type 2 diabetes
- 35% are overweight/obese

Of all type 2 diabetes
- 60% have hypertension
- 60% have hyperlipidemia
- 90% are overweight/obese
A SBP < 140 mmHg recommended/considered, regardless the level of risk

- Low/moderate risk (IB)

- Diabetes (IA)

- Diabetic/nondiabetic CKD (IIaB)

- Patients with CHD/previous stroke or TIA (IIaB)

  Elderly A SBP = 140 – 150 mmHg

A DBP < 90 mmHg recommended

  Diabetic Patients A DBP < 85 mmHg recommende
Current Antihypertensive Therapy Reduces CV Events

Average Reduction in Events, %

- Stroke: 30%–40%
- Major CV Events: 20%–30%
- CV Death: 30%–40%
- CHF: 50%

Recommendations for lipid analysis as treatment targets in the prevention of CVD

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C is recommended as target for treatment.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>TC should be considered as treatment target if other analyses are not available.</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>TG should be analysed during the treatment of dyslipidaemias with high TG levels.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Non-HDL-C should be considered as a secondary target in combined hyperlipidaemias, diabetes, the MetS or CKD.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Apo B should be considered as a secondary treatment target.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>HDL-C is not recommended as a target for treatment.</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>The ratios apo B/apo A 1 and non-HLD-C/HDL-C are not recommended as targets for treatment.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
• Strongly associated with atherosclerosis and CHD events

• 10% increase results in a 20% increase in CHD risk

• Risk associated with LDL-C is increased by other risk factors:
  ◆ low HDL-cholesterol
  ◆ smoking
  ◆ hypertension
  ◆ Diabetes
## Recommendations for the pharmacological treatment of hypercholesterolaemia

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
Meta-analyses based on data from

22 trials of statin therapy versus control (n=134,537) and

5 trials of more-intensive versus less-intensive statin therapy (n=39,612)

Overall, each 1 mmol/L reduction in LDL-C with statin therapy reduced major coronary events or coronary revascularisation each by 24%, and stroke by 15%.

Proportional reductions in these outcomes were similar in men and women.

Lancet Published Online January 9, 2015
Σε υπερτασικούς ασθενείς μετρίου και υψηλού κκ κινδύνου συνιστάται η χορήγηση στατινών με στόχο τιμή LDL- C < 115 mg/dL

Ι - Α

Εάν υπάρχει στεφανιαία νόσος ( δευτερογενής πρόληψη ) ο στόχος για την LDL- C < 70 mg/dl

Ι - Α

2013 ESH Guidelines for the Management of Hypertension
Majority of Hypertensive Patients Have LDL-C 100 mg/dL or Greater

Only 14.3% of hypertensive have LDL-C <100 mg/dL

Source: NHANES III Phase 2 Morning Fasting Subset. 2000 Census Data.
(Unweighted N = 7697; Weighted Sample = 200,948,641)
Of 136,905 patients hospitalized with CAD, more than 75% had LDL levels below 130 mg/dl
Multiple CV Risk Management Results in Dramatic Reductions in CVD

10% Reduction in BP + 10% Reduction in LDL-C = 45% Reduction in CVD

"Attention should be moved from knowing one’s BP and cholesterol concentrations to knowing one’s absolute CV risk and its determinants."

Lipid-lowering and antihypertensive therapies improve endothelial function

In clinical practice, most patients are undertreated.

Suboptimal number of antihypertensive medications*

<table>
<thead>
<tr>
<th>Antihypertensive medications (n)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

Only 1 in 3 patients receive lipid-lowering therapy†

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥130 (n = 49,925)</td>
<td>34.7</td>
</tr>
<tr>
<td>&lt;130 (n = 37,906)</td>
<td>27.4</td>
</tr>
</tbody>
</table>

*Framingham Heart Study, N = 4919 treated patients
†87,831 patients with ≥2 risk factors (≥45 years [men], ≥55 years [women], hypertension, HDL-C <40 mg/dL, total-C ≥200 mg/dL, obesity)

Most Patients Diagnosed With Hypertension and Dyslipidemia Were Not at Both Goals

In a managed care population, the vast majority of patients diagnosed with hypertension and dyslipidemia (n = 154,235) were not at both goals.

More than 90% were not at both goals

Less than 10% were at both goals

As the number of CV risk factors increased, the rate of goal attainment decreased.

CV = cardiovascular.

Poor adherence and poor persistence... “contribute to the lack of adequate control in more than two thirds of patients with hypertension”

Συμμόρφωση: Αυστηρή τήρηση των οδηγιών στη λήψη της θεραπευτικής αγωγής και το προτεινόμενο δασολογικό σχήμα

Παραμονή στη θεραπεία: Αποφυγή περιοδικής ή μόνιμης διακοπής της αγωγής χωρίς συνεννόηση με το θεράποντα ιατρό

Arch Intern Med. 1997;157:2413-2446
22% of U.S. patients take less of the medication than is prescribed

Persistence with antihypertensive treatment significantly reduces long-term CV risk

- **242,594 patients** newly treated for hypertension during 2000-2001
- No history of cardiovascular (CV) disease
- Mean follow-up: 6 years
- Analysis of hospitalisation for coronary or cerebrovascular disease

*Corrao et al. J Hypertens 2011;29:610-8*
Πτωχή συμμόρφωση στη θεραπεία

- Μακρά διάρκεια θεραπείας
- Ανεπιθύμητες ενέργειες
- Περίπλοκα φαρμακευτικά σχήματα
- Μη κατανόηση της σπουδαιότητας της θεραπείας
- Οικονομικό κόστος

Στρατηγικές βελτίωσης της συμμόρφωσης στην θεραπεία

- Ιατρός
- Ασθενής Ενημέρωση
- Κοινωνική υποστήριξη
- Πρακτικές συμβουλές
- Ο σταθερός συνδυασμός βελτιώνει τη συμμόρφωση
Η συμμόρφωση μειώνεται όσο αυξάνει ο αριθμός των φαρμάκων


CI = διάστημα εμπιστοσύνης, LLT = αντιλιπιδαιμική θεραπευτική αγωγή
Αναδρομική μελέτη σε ομάδα του πληθυσμού MCO. n=8.406 ασθενείς με υπέρταση στους οποίους προστέθηκε αντιυπερτασική αγωγή και LLT σε υφιστάμενα συνταγογραφούμενα φάρμακα σε χρονικό διάστημα 90 ημερών.
Συμμόρφωση με τη συγχορηγούμενη θεραπευτική αγωγή: επαρκή αντιυπερτασικά και αντιλιπιδαιμικά συνταγογραφούμενα φάρμακα για την κάλυψη ≥80% των ημερών ανά περίοδο 91 ημερών

<table>
<thead>
<tr>
<th>Αριθμός υφιστάμενων Rx φαρμάκων</th>
<th>Μη προσαρμοσμένος λόγος πιθανοτήτων για τη συμμόρφωση (&gt;80%) με αντιυπερτασική αγωγή και LLT (95% CI, τιμή p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1,73 (1,56–1,90, p&lt;0,001)</td>
</tr>
<tr>
<td>1</td>
<td>1,25 (1,13-1,39, p&lt;0,001)</td>
</tr>
<tr>
<td>2</td>
<td>0,96 (0,86–1,06, p=0,41)</td>
</tr>
<tr>
<td>3–5</td>
<td>0,87 (0,79-0,94, p&lt;0,001)</td>
</tr>
<tr>
<td>≥ 6</td>
<td>0,65 (0,59-0,71, p&lt;0,001)</td>
</tr>
</tbody>
</table>

CI = διάστημα εμπιστοσύνης, LLT = αντιλιπιδαιμική θεραπευτική αγωγή
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Minimizing the total number of daily doses has been found to be more important in promoting adherence than minimizing the total number of medications.

Only 1 in 3 patients adherent to preventive therapy after 6 months

N = 8406 managed-care enrollees receiving antihypertensive and lipid-lowering medications

Concomitant antihypertensive and lipid-lowering therapy ↓ pill burden and may ↑ adherence.

Retrospective, database-based study of members of a national commercial pharmacy benefit manager (N=3942).

Αρτηριακή Υπέρταση και Υπερλιπιδαιμία:
Μια νέα θεραπευτική πρόταση

Σταθερός Συνδυασμός

Αμλοδιπίνης – Ατορβαστατίνης
A single-pill combination therapy targeting hypertension and dyslipidemia could:

- Streamline co-treatment of these 2 CV risk factors by treating a patient’s overall risk of cardiovascular disease
- Lower prescription costs
- Reduce a patient’s pill burden and improve patient adherence

A single-pill combination therapy has been developed that contains:

- The calcium channel blocker (CCB) amlodipine besylate
- The HMG CoA-reductase inhibitor atorvastatin calcium

Clinical Benefit of Multiple Risk Factor Management Is Not Unique to ASCOT: The New Standard of Care

**ASCOT**
- Low-to moderate-risk patients with hypertension and ≥3 additional CV risk factors (amlodipine treatment compared with atenolol)
- Addition of atorvastatin to BP treatment resulted in
  - 36% RRR in nonfatal MI and fatal CHD (P=.0005)
  - 27% RRR in fatal and nonfatal stroke (P=.0236)

**VALUE**
- Amlodipine-based therapy resulted in improved cardiac outcomes in high-risk patients with hypertension over valsartan-based therapy
- Amlodipine treatment resulted in benefits for fatal and nonfatal MI (HR=1.19; 95% CI, 1.02-1.38; P=.02) compared to valsartan treatment

**CARDS**
- High-risk patients with diabetes and high prevalence of hypertension
- Atorvastatin 10 mg resulted in
  - 37% RRR of major CV events (P=.001)
  - 48% RRR of stroke

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ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; MI = myocardial infarction; CHD = cardiovascular heart disease; CV = cardiovascular.

Sever PS, Dahlöf B. American College of Cardiology 2005 Scientific Sessions; March 6-9, 2005; Orlando, FL.
ASCOT-LLA: 36% RRR in Nonfatal MI and Fatal CHD When Atorvastatin Added to BP Treatment

Originally planned length of trial: 5 years
Actual length of trial: median 3.3 years

Proportion of Patients (%)

Atorvastatin 10 mg (n=5168)
Placebo (n=5137)

HR=0.64 (0.50-0.83)

RRR=relative risk reduction.

It is recommended to use **statin therapy in hypertensive patients** at moderate to high CV risk targeting a low density lipoprotein Cholesterol value < 3.0 mmol/L (115 mg/dL).
**VALUE: Outcome and SBP Differences at Specific Time Points – Primary Endpoint (morbidity and mortality)**

<table>
<thead>
<tr>
<th>Time interval (months)</th>
<th>ΔSBP mmHg</th>
<th>Primary endpoint Odds Ratios and 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall study</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>3–6</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>6–12</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>12–24</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>24–36</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>36–48</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Study end</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

N = 15,245

Favours valsartan
Favours amlodipine

Julius et al. Lancet June 2004;363
CARDS Trial Stopped Early Because Atorvastatin 10 mg Was Associated With Significant CV Event Reduction in Patients With Type 2 Diabetes

Primary end point = composite of acute CHD events (MI including silent MI, unstable angina, acute CHD death, resuscitated cardiac arrest), coronary revascularisation, or stroke.

Trial was stopped nearly 2 years early because of significant reductions in CV events.

Median duration of follow-up = 3.9 years.

Gemini: More than 55% of patients achieved both BP and LDL-C goals

Amlodipine/Atorvastatin Gemini Study
N = 1220, 14 weeks with amlodipine/atorvastatin single-pill therapy

Combining multiple risk interventions into a single-pill (amlodipine/atorvastatin) helps patients to attain recommended target levels for blood pressure and lipids.

The JEWEL Programme

JEWEI I
- UK
- Canada

JEWEI II
- Italy, Ireland, Belgium, Spain
- Greece, Switzerland, Austria
- Portugal, Finland, Hungary, Slovenia
**Inclusion criteria:**
- Male or female aged 18–80 years
- Diagnosis of concurrent hypertension (uncontrolled) and dyslipideamia (controlled or uncontrolled)
- Untreated, or if treated on stable medication
- BP above target, LDL-C must be above target or (if on treatment), at or above target

**Exclusion criteria:**
- Adequately controlled BP at baseline
- Currently receiving treatment with:
  - Amlodipine and atorvastatin
  - Atorvastatin 80 mg but with a LDL-C ≥2.6 mmol/L (100 mg/dL)
- Treated with amlodipine 10 mg or another CCB at maximum dose
• **Primary efficacy analysis:**
  - The percentage of patients reaching BP and LDL-C targets as defined by their governing guidelines

• **Secondary efficacy analyses:**
  - Changes from baseline in SBP, DBP, LDL-C, TC, TG, HDL-C, HDL-C/LDL-C ratio and TC/HDL-C ratio
  - Safety and tolerability

• **Additional analyses:**
  - Assess reduction of CV risk as determined by ESC SCORE method (in appropriate study countries)
### JEWEL I and II: Mean Baseline Blood Pressure and Lipid Levels

<table>
<thead>
<tr>
<th></th>
<th>JEWEL I</th>
<th>JEWEL II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>n = 1138</td>
<td>n = 1107</td>
</tr>
<tr>
<td><strong>Blood Pressure, mm Hg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>152.3</td>
<td>152.3</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>89.0</td>
<td>91.4</td>
</tr>
<tr>
<td><strong>Lipids, mmol/L (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.22 (201.9)</td>
<td>5.72 (221.2)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.99 (115.6)</td>
<td>3.49 (135.0)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.88 (72.7)</td>
<td>1.77 (68.5)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.37 (53.0)</td>
<td>1.43 (55.3)</td>
</tr>
</tbody>
</table>
Patients Achieving Country-specific BP and LDL-C goals

Amlodipine/atorvastatin
All doses

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

Patients (%) reaching both BP and LDL-C country specific goals (+/- CI)

JEWEL I
(n=1135)

JEWEL II
(n=1084)

JEWEL I
(n=476)

JEWEL II
(n=478)

62.9% ± 5%
50.6% ± 5%
59% ± 5%
51.9% ± 5%

Common goals defined as: LDL-C <3.0 mmol/L (116.0 mg/mL)
SBP <140 and DBP <90 mm Hg; Patients with diabetes: SBP <130 and DBP <80 mm Hg

Mean Change in Blood Pressure and LDL-C

Mean change (±CI) in BP (mm Hg)

JEWEL I: SBP -19.3, DBP -10.2
JEWEL II: SBP -20.4, DBP -12.2

Mean change (±CI) in LDL-C (mmol/L)

JEWEL I: -0.85 mmol/L (-32.9 mg/dL)
JEWEL II: -0.95 mmol/L (36.7 mg/dL)


Amlodipine/atorvastatin
5/10 mg or 10/10 mg
### JEWEL I & II:
### Adverse Events (≥ 2%): All Cause

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>JEWEL I (N = 1138)</th>
<th>JEWEL II (N = 1107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Oedema</td>
<td>120 (10.5)</td>
<td>126 (11.4)</td>
</tr>
<tr>
<td>Joint Swelling</td>
<td>56 (4.9)</td>
<td>9 (0.8)</td>
</tr>
<tr>
<td>Diabetic Neuropathy</td>
<td>51 (4.5)</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>45 (4.0)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>46 (4.0)</td>
<td>18 (1.6)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>41 (3.6)</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>35 (3.1)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>30 (2.6)</td>
<td>7 (0.6)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>28 (2.5)</td>
<td>13 (1.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26 (2.3)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 (2.2)</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>30 (1.8)</td>
<td>11 (1.0)</td>
</tr>
<tr>
<td>Abnormal Liver Function Tests</td>
<td>7 (0.6)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Influenza</td>
<td>0</td>
<td>23 (2.1)</td>
</tr>
</tbody>
</table>
JEWEL I & II ESC SCORE: Ten-Year Fatal CVD Risk

- **Baseline**
  - UK
  - Austria
  - Finland
  - Ireland
  - Canada
  - Slovenia
  - Switzerland
  - Hungary
  - Italy
  - Belgium
  - Portugal
  - Greece
  - Spain

- **Endpoint**
  - Greece: 17% reduction

Amlodipine/atorvastatin: All doses

- **Legend**:
  - Red: Baseline
  - Green: Endpoint

Country scores range from 1.0 to 8.0, with Greece showing a significant decrease of 17% compared to the baseline.
Λευκός άνδρας ευρωπαίος, 57 ετών, καπνιστής, μη διαβητικός

**Baseline**

- **ΑΠ**: 150/95 mm Hg
- **ΤC**: 240 mg/dL
- **LDL-C**: 140 mg/dL
- **HDL-C**: 50 mg/dL
- **ΔΜΣ**: 29 Kg*/m²
- **ESC SCORE** (10-year risk of CVD death): 13%

*16-weeks: AML 5 mg/ATV 10 mg*

**Endpoint**

- **ΑΠ**: 130/70 mm Hg
- **ΤC**: 175 mg/dL
- **LDL-C**: 107 mg/dL
- **HDL-C**: 49 mg/dL
- **ΔΜΣ**: 29 Kg*/m²
- **ESC SCORE** (10-year risk of CVD death): 5%
Conclusions

- Single-pill amlodipine/atorvastatin therapy was effective and well-tolerated in the treatment of hypertensive patients with additional risk factors.

- Use of single-pill amlodipine/atorvastatin therapy may help physicians to improve the management of total CV risk in patients requiring BP- and lipid-lowering therapy by:
  - Targeting two modifiable risk factors simultaneously
  - Reducing calculated CV Risk
  - Simplifying treatment which may lead to improved medication adherence
ΕΝΔΕΙΞΕΙΣ

Πρωτοβάθμια φροντίδα

Ασθενείς με ήπια και μέτρια ΑΥ και οριακές η αυξημένες τιμές λιπιδίων
Ασθενείς με ΑΥ και μεταβολικό σύνδρομο
Ασθενείς με ΑΥ και ΣΔ

Δευτερογενή πρόληψη

Ασθενείς με στεφανιαία νόσο και ΑΥ σε συνδυασμό με β – blocker
Ασθενείς με στεφανιαία νόσο και σταθερή στηθάγχη με η χωρίς ΑΥ σε συνδυασμό με β – blocker
Οικονομικό κόστος

ΕΛΕΥΘΕΡΟΙ ΣΥΝΔΥΑΣΜΟΙ

- Αμλοδιπίνη 5mg
- Ατορβαστατίνη 10mg  
  26,31 euro

- Αμλοδιπίνη 10mg
- Ατορβαστατίνη 10mg  
  30,06 euro

Σταθερός συνδυασμός
Αμλοδιπίνης/Ατορβαστατίνης 5/10 mg  
7,71 euro

Σταθερός συνδυασμός
Αμλοδιπίνης/Ατορβαστατίνης 10/10 mg  
7,99 euro
Multiple Risk Factor Management Results in Greater CVD Risk Reduction

“Likelihood of a Major Cardiovascular Event in the **Next 10 Years** in 100 People Like You”

Cardiovascular Events Expected Without Drug Therapy

Williams B. J Am Coll Cardiol. 2005;45:813-827
Multiple Risk Factor Management Results in Greater CVD Risk Reduction

“Likelihood of a Major Cardiovascular Event in the Next 10 Years in 100 People Like You”

Cardiovascular Events Prevented by Antihypertensive Therapy

Williams B. J Am Coll Cardiol. 2005;45:813-827
Multiple Risk Factor Management Results in Greater CVD Risk Reduction

“Likelihood of a Major Cardiovascular Event in the Next 10 Years in 100 People Like You”

Events Prevented by Antihypertensive Therapy

Events Prevented by Adding Statin Therapy

Williams B. J Am Coll Cardiol. 2005;45:813-827
Optimising Hypertension Management by Addition of Statin Therapy May Reduce CV Events by Half

“Likelihood of a Major Cardiovascular Event in the Next 10 Years in 100 People Like You”

Multiple Risk Factor Management Results in Greater CVD Risk Reduction

Events Prevented by Antihypertensive Therapy

Events Prevented by Adding Statin Therapy

Η συνύπαρξη αρτηριακής υπέρτασης και δυσλιπιδαιμίας είναι συχνό φαινόμενο, με τη παρουσία του να αυξάνει το καρδιαγγειακό κίνδυνο. Η παράλληλη αντιμετώπιση των δυο παραγόντων κίνδυνου και η επίτευξη των θεραπευτικών στόχων μειώνει την επίπτωση των καρδιαγγειακών συμβαμάτων.

Η επιλογή σύγχρονης αντιυπερτασικής αγωγής σε συνδυασμό με στατίνες έχει δώσει ευεργετικά αποτελέσματα.

Ο σταθερός συνδυασμός amlodipine/atorvastatin είναι ασφαλής και αποτελεσματικός στη ρύθμιση της αρτηριακής πίεσης και της υπερλιπιδαιμίας σε υψηλό ποσοστό ασθενών, με τη χορήγηση του να μειώνει σημαντικά την νοσηρότητα και τη θνησιμότητα.

Η επιλογή του βελτιώνει τη συμμόρφωση και παραμονή των ασθενών στη θεραπεία, ενώ παράλληλα μειώνει το οικονομικό κόστος.
High-risk patients with high BP will not have their CVD risk optimally reduced by BP control alone

Early intervention reduces events

Statin therapy reduces the risk of CHD and stroke in people with hypertension
  - Benefit is additive to the benefits of BP lowering – even when BP is controlled
  - Benefit occurs early and occurs irrespective of baseline cholesterol
Cholesterol and CHD: Seven Countries Study

**TC mg/dL (mmol/L)**

- Northern Europe
- United States
- Southern Europe, Inland
- Southern Europe, Mediterranean
- Siberia
- Japan

**CHD mortality rates (%)**

- United States: 3.25, 4.50, 5.80, 7.10, 8.40
- Southern Europe, Inland: 3.90, 5.15, 6.45, 7.75, 9.05
- Southern Europe, Mediterranean: 4.50, 5.80, 7.10, 8.40, 9.70
- Siberia: 6.45, 7.75, 9.05
- Japan: 5.15, 6.45, 7.75, 9.05

Effective Blood Pressure Control Reduces Cardiovascular Morbidity and Mortality

Event reduction in patients on active antihypertensive treatment vs. placebo or no treatment

CHD: coronary heart disease; CV: cardiovascular
Prevalence of Selected Risk Factors Among Subjects With Metabolic Syndrome

Effects of Increasing TC Levels on the Risk for CHD in the Presence of Other Risk Factors

- Low HDL
- Smoking
- Hyperglycemia
- Hypertension
- No Other Risk Factors

Schaefer EJ, adapted from the Framingham Heart Study
Hypertension Is the Gateway to CV Risk Management

- **Prevalent**
  - Hypertension is the most prevalent CV risk factor

- **Potentially predictive**
  - Almost all patients with CV risk factors have hypertension

- **Early marker**
  - Frequently the first diagnosed risk factor

- **BP easily measured**
What is metabolic syndrome?

- **Metabolic syndrome:**
  - a complex disorder consisting of multiple risk factors that promotes cardiovascular disease and overall mortality and morbidity
  - **Obesity and insulin resistance are two of the most important causative factors**
  - Components may have genetic or environmental basis

Patients Achieving Common BP and LDL-C Goals

Amlodipine/atorvastatin
All doses

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

Common goals defined as: LDL-C <3.0 mmol/L (116.0 mg/mL)
SBP <140 and DBP <90 mm Hg; Patients with diabetes: SBP <130 and DBP <80 mm Hg
<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence of metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>20 – 30%&lt;sup&gt;1-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Japan</td>
<td>11.0%&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>France</td>
<td>12.4%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Germany</td>
<td>19.8%&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Italy</td>
<td>14.4%&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Spain</td>
<td>19.5%&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>UK</td>
<td>19.6%&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Greece</td>
<td>20%&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Urban Indians</td>
<td>30 – 40%&lt;sup&gt;10,11&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
JEWEL Programme Design

• Two 16-week, international multi-centre, open label, titration-to-goal trials in a total of 2,245 patients with hypertension and dyslipidaemia

• Initial dose was determined based on each patient’s BP level, LDL-C control and current use of BP and lipid-lowering medications

• Previously treated patients were provided study medication as a substitution or add-on therapy at an appropriate dose

• Eight dosage strengths of Caduet were used in the trials (5/10 mg, 10/10mg, 5/20mg, 5/40mg, 5/80mg, 10/20mg, 10/40mg and 10/80mg)
  – All patients received an increase in dosage as necessary
Hypertension and Additional CV Risk Factors

- **Patient population commonly seen in clinical practice**
  - Hypertensive patients with ≥3 additional CV risk factors
  - Benefits seen even in patients with normal to mildly elevated cholesterol
  - Low-to-moderate risk

- **Amlodipine-based treatment compared with atenolol-based treatment resulted in**
  - Significant benefits in all-cause mortality

- **Atorvastatin added to an amlodipine-based treatment results in significant reductions**
  - Nonfatal MI and fatal CHD (36% RRR)
  - Nonfatal MI (45% RRR)
  - Stroke (27% RRR)

Prevalence of Selected Risk Factors Among Subjects With Metabolic Syndrome

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>80.5</td>
<td>86.5</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>84.2</td>
<td>73.2</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>84.6</td>
<td>86.5</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>82.9</td>
<td>76.7</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>57.6</td>
<td>73.2</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>22.2</td>
<td>62.6</td>
</tr>
</tbody>
</table>

Adjusted Probability of Achieving Adherence

Multivariate Odds Ratios of achieving PDC \( \geq 80\% \) during 6 month follow-up (95% confidence interval)

- **Caduet vs. Amlo + Atorva**: 1.95 (1.80-2.13)**
- **Caduet vs. Amlo + Other Statin**: 3.10 (2.85-3.38)**
- **Caduet vs. Other CCB + Atorva**: 2.05 (1.89-2.24)**
- **Caduet vs. Other CCB + Other Statin**: 2.84 (2.61-3.10)**

*Logistic regression model analysis adjusting for covariates including age, gender, business type, formulary type, baseline AHT, CVD meds, DM med, antidepressant, # of drugs, co-payments, Maintenance Med Refill%*
Correlation Between Serum Cholesterol and CVD Mortality

Multiple Risk Factor Intervention Trial (MRFIT)
N=325,346

Serum Cholesterol Quintile (mg/dL)

Q_1 (<182)
Q_2 (182-202)
Q_3 (203-220)
Q_4 (221-244)
Q_5 (>244)

Untreated Patients

55-57 years
50-54 years
45-49 years
40-44 years
35-39 years

Q = serum cholesterol quintile.

Antiplatelet therapy, particularly low-dose aspirin, should be prescribed to controlled hypertensive patients with previous CV events and considered in hypertensive patients with reduced renal function or a high CV risk.

IIa - B

It is recommended to use statin therapy in hypertensive patients at moderate to high CV risk, targeting a LDL−C cholesterol value <3.0 mmol/L (115 mg/dL).

I – A

When overt CHD is present, LDL-C <1.8 mmol/L (70 mg/dL)

I – A

In hypertensive patients with diabetes, a HbA1c target of <7.0% is recommended with antidiabetic treatment.

I - B

In more fragile elderly patients with a longer diabetes duration, more comorbidities and at high risk, treatment to a HbA1c target of <7.5–8.0% should be considered.

IIa - C
Pleiotropic effects of BP-lowering agents

**ACEIs/ARBs**
- ↓ Fibrinolysis
- ↓ Mononuclear cell migration
- ↓ Collagen matrix formation
- ↑ Endothelial function
- ↑ Plaque stability
- ↑ Arterial compliance
- ↓ Oxidative stress
- ↓ Platelet aggregation
- ↓ Inflammation
- ↓ VSMC proliferation

**CCBs**
- ↑ NO
- ↓ MMP activity
- ↓ Cholesterol deposition in membrane

**Both**

MMP = matrix metalloproteinase

Worldwide blood pressure control in treated hypertensive patients

- Canada: 41.0
- USA: 53.1
- Mexico: 21.8
- England: 29.2
- Greece: 49.5
- Spain: 38.8
- Turkey: 19.8
- Germany: 33.6
- Japan: 55.7
- China: 28.8
- Taiwan: 18.0
- Egypt: 33.5
- South Africa: 47.6
- Italy: 37.5

Long-Term or Secondary Medication Non-Adherence

Παράγοντες που βελτιώνουν την συμμόρφωση στην θεραπεία

Στρατηγικές βελτίωσης της συμμόρφωσης

- Ασθενής Ενημέρωση
- Η χορήγηση σταθερών συνδυασμών βελτιώνει τη συμμόρφωση
- Πρακτικές συμβουλές
- Κοινωνική υποστήριξη
- Ιατρός

JEWEL: Objectives

- Evaluate the utility of **single-pill amlodipine/atorvastatin** in European and Canadian real-world primary care settings

- Assess the efficacy of **amlodipine/atorvastatin** to achieve national lipid and hypertension goals as set out in clinical guidelines

Improving Adherence with fix combination therapy

- Patients need to adhere to their medications in order to effectively treat their CV risk factors
  - Improved adherence when starting 2 medications concurrently
  - Combination therapy reduces pill burden
  - Reduced pill burden improves adherence

single-pill amlodipine/atorvastatin
A single-pill combination therapy targeting hypertension and dyslipidemia could:
- Streamline co-treatment of these 2 CV risk factors by treating a patient’s overall risk of cardiovascular disease
- Lower prescription costs
- Reduce a patient’s pill burden and improve patient adherence

A single-pill combination therapy has been developed that contains:
- The calcium channel blocker (CCB) amlodipine besylate
- The HMG CoA-reductase inhibitor atorvastatin calcium

The efficacy and safety of this combination has been demonstrated in a clinical practice setting, in the US-based GEMINI study\(^1\)
- Furthermore, patients taking the single pill amlodipine/atorvastatin were more likely to be adherent with their antihypertensive and lipid-lowering therapies compared with patients using concomitant CCB and statin therapies\(^2\)

Human LDL incubated with O-hydroxy metabolite of atorvastatin (100 nmol/L), lovastatin (100 nmol/L), and amlodipine (2.5 μmol/L)

TBARS = thiobarbituric acid-reactive substances

*P < 0.0001 vs vehicle treatment

Mason RP et al. *Am J Cardiol.* 2005;96(suppl):11F-23F.
Most >35 years have ≥1 CV risk factors

- 1 in 3 hypercholesterolemia
- 1 in 3 obese
- 1 in 3 hypertension
- 1 in 5 smoke
- 1 in 10 diabetes

AHA. Heart Disease and Stroke Statistics–2005 Update.
Additive effects of statin + CCB on fibrinolytic balance

N = 45 with hypertension, placebo-controlled, crossover trial

\[ \Delta t\text{-PA (U/mL)} \]
- Atorvastatin 20 mg: 0.08 *
- Amlodipine 5 mg: 0.17 †
- Atorvastatin + Amlodipine 20 mg + 5 mg: 0.26

\[ \Delta PAI-1 (U/mL) \]
- Atorvastatin 20 mg: -9.9 *
- Amlodipine 5 mg: -0.5
- Atorvastatin + Amlodipine 20 mg + 5 mg: -10.2 *

\[ t\text{-PA} / PAI-1 \text{ ratio} \]
- Atorvastatin 20 mg: 0.045
- Amlodipine 5 mg: 0.03
- Atorvastatin + Amlodipine 20 mg + 5 mg: 0.06

*P < 0.05 vs placebo
†P < 0.01 vs placebo

MMPs = matrix metalloproteinases

Liao JK. Am J Cardiol. 2005;96(suppl 1):24F-33F.
Pleiotropic effects of BP-lowering agents

**ACEIs/ARBs**
- ↓ Fibrinolysis
- ↓ Mononuclear cell migration
- ↓ Collagen matrix formation
- ↑ Endothelial function
- ↑ Plaque stability
- ↑ Arterial compliance
- ↓ Oxidative stress
- ↓ Platelet aggregation
- ↓ Inflammation
- ↓ VSMC proliferation

**CCBs**
- ↑ NO
- ↓ MMP activity
- ↓ Cholesterol deposition in membrane
- Both
- ↓ AHTN agents

MMP = matrix metalloproteinase

CADUET: Optimising CV Event Reduction by Management of Total CV Risk

- Benefits patients with hypertension plus additional CV risk factors
- Provides in a single pill
  - Proven BP and CV reductions of amlodipine
  - Proven lipid-lowering and CV event reductions of atorvastatin
  - Proven safety and tolerability of both parent compounds
- Easily incorporated into current CV treatment strategies
- May improve adherence rates, resulting in
  - Better rates of goal attainment
  - Reduced risk of suffering a CV event
  - Improved cost-benefit ratio

When patients are asymptomatic . . .

Non-compliance rates increase dramatically to an estimated 75% percent.
Implications: We Need to Address Medication Adherence in Primary Care

4 top reasons for non-adherence

- Cost of medications
- Side effects/fear of side effects
- Forget/can’t keep track of medications/complexity
- Don’t think it works/don’t need it

Key Point: It’s not just about cost. It’s a complex health behavior that is influenced by:

- Socioeconomic factors (age, race, gender, socioeconomic status)
- Patient-related factors (knowledge, attitudes, beliefs, and skills)
- Condition/treatment related factors (disease severity, co-morbidity, regimen complexity, side effects)
- Provider factors (skill, training, resources)
- Setting/policies (access to care, Rx coverage)
Adherence to statins after two years, by condition

Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002;288:462-467
WHO’s Five Dimensions of Adherence

- Social & Economic
- Health Care System
- Therapy Related
- Condition Related
- Patient Related
CV Risk Factor Clustering With Hypertension: Framingham Offspring, Aged 18 to 74 Years

> 50% of Hypertension Occurs in Presence of 2 or More Risk Factors

Men

- 1 RF: 26%
- 2 RFs: 25%
- 3 RFs: 19%
- 4 or More RFs: 8%
- No Additional RFs: 12%

Women

- 1 RF: 27%
- 2 RFs: 24%
- 3 RFs: 17%
- 4 or More RFs: 12%
- No Additional RFs: 20%

RF = risk factor.

Kannel WB. Am J Hypertens. 2000;13:3S-10S.
Most Hypertensive Patients Have Additional Risk Factors:
REACH Registry

N=67,888 patients aged 45 years or older from 44 countries

81.8% patients with atherothrombosis have HTN

90.3% hypertensive patients have ≥3 risk factors

HTN=hypertension; REACH=Reduction of Atherothrombosis for Continued Health.
Risk factors include: treated diabetes mellitus, diabetic nephropathy, asymptomatic carotid stenosis ≥70%, Systolic blood pressure [SBP], ≥150 mm Hg, treated hypercholesterolaemia, current smoking, men ≥55 y, women ≥70 y.

For years, emphasis has been placed on the problem of medication non-adherence:

- $290 billion a year in direct and indirect costs = 13% of total health care spend
- 125,000 deaths that result from not taking medication correctly
- 69% of medication-related hospital admissions due to poor adherence
- 50% of new statin patients will discontinue medication after 6 months
The Cost of Non-Adherence

Patients who were the MOST adherent had **total costs 47% LOWER** than patients who were the LEAST adherent.

Poor medication adherence estimated to cost the US $105.8 billion, or an average of $453 per adult, in 2010.


The Hypertensive Metabolic Phenotype

- Impaired Glucose tolerance
- Decreased HDL-Cholesterol
- Small Dense LDL-Cholesterol
- Increased Visceral Fat
- Insulin Resistance
- Leptin resistance
- Increased Triglycerides
- Hyperuricaemia
- Fatty Liver
- Hypertension

Most patients have overlapping CV Risk Factors

---

**Multiple Comorbidities**

- Increases Risk 400% to 700%

---

**Of all hypertensives**

- 65% have dyslipidaemia
- 16% have type 2 diabetes
- 45% are overweight/obese

---

**Of all dyslipidaemics**

- 48% have hypertension
- 14% have type 2 diabetes
- 35% are overweight/obese

---

**Of all type 2 diabetes**

- 60% have hypertension
- 60% have hyperlipidemia
- 90% are overweight/obese
Global mortality and burden of cardiovascular disease and major risk factors for people aged 30 years

Mortality

16 million

7.8 million

4.3 million

2.3 million

Burden of disease

128 million

59 million

39 million

30 million

- All cardiovascular
- High blood pressure
- High cholesterol
- Overweight and obesity
Endpoints for amlodipine and perindopril versus atenolol and thiazide (ASCOT trial)

- Non-fatal myocardial infarction (excluding silent) and fatal coronary heart disease: -13%
- Total coronary endpoint: -9%
- Total cardiovascular events and procedures: -14%
- All-cause mortality: -16%
- Cardiovascular mortality: -24%
- Fatal and non-fatal stroke: -23%
- Fatal and non-fatal heart failure: -16%
Hypertension as the Gateway to CV Risk

Hypertension is common and clusters with other CV risk factors.

The presence of multiple risk factors amplifies risk of CV events.

Strong evidence (ASCOT, VALUE, CARDs) demonstrates CV risk treatment reduces CV events.

Evaluation of overall CV risk in patients with hypertension critical to optimise management.

Most patients require multiple medications; this decreases adherence and negatively impacts outcomes.
### Outcome and SBP Differences at Specific Time Points – Primary Endpoint

<table>
<thead>
<tr>
<th>Time interval (months)</th>
<th>ΔSBP mmHg</th>
<th>Odds Ratios and 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall study</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>3–6</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>6–12</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>12–24</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>24–36</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>36–48</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Study end</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

**Favours amlodipine**

![Graph showing odds ratios and 95% CIs]

[Julius et al. Lancet June 2004;363](https://doi.org/10.1016/S0140-6736(04)16281-1)
A Broad Approach to Prevention and Treatment of Cardiovascular Disease

Life style intervention

Risk factor modification

Disease intervention/secondary prevention

Physical inactivity
Excessive food intake
Smoking
Stress
Obesity
Hypertension
Diabetes
Dyslipidaemia
Atherosclerosis
Atherosclerosis
Chronic heart failure
Arterial & venous thrombosis/cardiac & cerebral events
Arrhythmia
90% of Hypertensive Individuals have other Cardiovascular Risk factors

10% Reduction in BP + 10% Reduction in Total-C = 45% Reduction in CVD
Lifestyle Modifications to Prevent and Manage Hypertension

- Avoid tobacco
- Reduce weight
- Moderate consumption of:
  - alcohol
  - sodium
  - saturated fat
  - cholesterol
- Increase physical activity
- Maintain adequate intake of dietary:
  - potassium
  - calcium
  - magnesium
- Avoid tobacco

ESH/ESC Guidelines 2013
Statin therapy adherence demonstrated to improve three specific outcomes

West of Scotland Coronary Prevention Study (WOSCOPS). Compliance and adverse event withdrawal: their impact. Eur Heart J 1997;18:1718-1724
Studies have found that increased pharmacy spending (due to increased adherence) resulted in significantly fewer hospitalizations and significantly lower health care costs – these savings are increased for patients over age 65.

**VALUE: SBP and outcome differences during consecutive time periods**

### Valsartan Antihypertensive Long-term Use Evaluation  N = 15,245

<table>
<thead>
<tr>
<th>Time interval (mos)</th>
<th>( \Delta ) SBP (mm Hg)</th>
<th>HF hospitalizations</th>
<th>Stroke</th>
<th>All-cause death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Favors valsartan</td>
<td>Favors amlodipine</td>
<td>Favors valsartan</td>
</tr>
<tr>
<td>All study</td>
<td>2.2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0–3</td>
<td>3.8</td>
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<tr>
<td>3–6</td>
<td>2.3</td>
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<tr>
<td>6–12</td>
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<td>12–24</td>
<td>1.8</td>
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<tr>
<td>24–36</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36–48</td>
<td>1.4</td>
<td></td>
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</tr>
<tr>
<td>Study end</td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cardiovascular Disease Risk Factors Overlap

- High Blood Pressure
- High Cholesterol
- Diabetes
- Smoking
- Obesity

The Cost of Non-Adherence

- Increased hospitalization
- Poor health outcomes
- Increased costs
- Decreased quality of life
- Patient death

It is recommended to use statin therapy in hypertensive patients at moderate to high CV risk, targeting a LDL- C cholesterol value <3.0 mmol/L (115 mg/dL).

When overt CHD is present, LDL- C <1.8 mmol/L (70 mg/dL)

Antiplatelet therapy, particularly low-dose aspirin, should be prescribed to controlled hypertensive patients with previous CV events and considered in hypertensive patients with reduced renal function or a high CV risk.

In hypertensive patients with diabetes, a HbA1c target of <7.0% is recommended with antidiabetic treatment.

In more fragile elderly patients with a longer diabetes duration, more comorbidities and at high risk, treatment to a HbA1c target of <7.5–8.0% should be considered.
Treating hypertension and other risk factors

Risk Factors for Cardiovascular Disease

- **Modifiable**
  - Smoking
  - Dyslipidaemia
  - Raised blood pressure
  - Diabetes mellitus
  - Obesity
  - Dietary factors
  - Lack of exercise

- **Non-modifiable**
  - Personal history of CVD
  - Family history of CVD
  - Age
  - Gender

Global mortality and burden of cardiovascular disease and major risk factors for people aged 30 years

**Mortality**
- 16 million
- 7.8 million
- 4.3 million
- 23 million

**Burden of disease**
- 128 million
- 59 million
- 39 million
- 30 million

- All cardiovascular
- High blood pressure
- High cholesterol
- Overweight and obesity
Relative risk of coronary artery disease by increasing intensity of risk factors in men

10-year probability (%)

- Hypertension only
  - BP = 150-160mm Hg
  - 6%

- Hypertension + hypercholesterolaemia + smoking
  - BP = 150-160mm Hg
  - Chol 240-262 mg/dl and LDL cholesterol of 133 mg/dl
  - 19%

- Hypertension + hypercholesterolaemia + smoking + diabetes + LVH
  - BP = 150-160mm Hg
  - 44%
Complications of Hypertension:

- Ischaemia
- Myocardial infarction
- Cardiac hypertrophy
- Congestive heart failure

- Stroke
- TIA (transient ischaemic attack)
- PRIND (prolonged, reversible, Ischaemic, neurological deficit)

- Nephrosclerosis
- Atrophy of nephrons
- Renal failure

- Retinopathy
- Lesions
- Swelling of optic disc
- Blindness
Hypertension Is the Gateway to CV Risk Management

• Αυξημένη επίπτωση
  – Η ΑΥ είναι ο συχνότερος παράγοντας κινδύνου.

• Προβλέψιμη
  – Σχεδόν όλοι οι ασθενείς με αυξημένο κινδύνο έχουν ΑΥ

• Πρώιμος δείκτης
  – Συχνά είναι ο πρώτος παράγοντας κινδύνου που διαγιγνώσκεται

• Η ΑΠ μετράται εύκολα
Good adherence is associated with lower risk of CHF, CA and cerebrovascular events

Compared with patients with **low (<80%)** adherence, those with **high (≥80%)** adherence showed

- **Relative risk of CHF**
  - **-11%**
  - (RR: 0.89; CI 0.80–0.99)

- **Relative risk of CAD**
  - **-10%**
  - (RR: 0.90; CI 0.84–0.95)

- **Relative risk of CD**
  - **-22%**
  - (RR: 0.78; CI 0.70–0.87)

Adherence calculated using medication possession ratio: total number of days supply of dispensed medication divided by duration of follow up

As Adherence Goes Down, Health Care Costs and Hospitalizations Go Up


![Graph showing the relationship between adherence and health care costs/hospitalization risk for various conditions (Diabetes, Hypertension, Hypercholesterolemia, CHF). The graph illustrates that as adherence decreases, health care costs and hospitalization risk increase.]
Endpoints for amlodipine and perindopril versus atenolol and thiazide (ASCOT trial)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Amlodipine/Perindopril</th>
<th>Atenolol/Thiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal myocardial infarction (excluding silent) and fatal coronary heart disease</td>
<td>-13%</td>
<td>-13%</td>
</tr>
<tr>
<td>Total coronary endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cardiovascular events and procedures</td>
<td>-16%</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>-11%</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td>-24%</td>
</tr>
<tr>
<td>Fatal and non-fatal stroke</td>
<td></td>
<td>-23%</td>
</tr>
<tr>
<td>Fatal and non-fatal heart failure</td>
<td></td>
<td>-16%</td>
</tr>
</tbody>
</table>
Παράγοντες κινδύνου για καρδιαγγειακά νοσήματα

• Τροποποιήσιμοι παράγοντες
  — Κάπνισμα
  — Δυσλιπιδαιμία
  — Αρτηριακή υπέρταση
  — Σακχαρώδης διαβήτης
  — Παχυσαρκία
  — Δίαιτα
  — Έλλειψη άσκησης

• Μη τροποποιήσιμοι παράγοντες
  — Ατομικό ιστορικό κκ νόσου
  — Οικογενειακό ιστορικό κκ νόσου
  — Ηλικία
  — Φύλο

Global mortality and burden of cardiovascular disease and major risk factors for people aged 30 years

**Mortality**

- 16 million total mortality
  - 7.8 million due to high blood pressure
  - 4.3 million due to high cholesterol
  - 2.3 million due to overweight and obesity

**Burden of disease**

- 128 million total burden of disease
  - 59 million due to high blood pressure
  - 39 million due to high cholesterol
  - 30 million due to overweight and obesity
Cardiovascular Disease Risk Factors Overlap

Lancet. 2005;365:434-41
Αρτηριακή υπέρταση

Σακχαρώδης διαβήτης

Υπερλιπιδαιμία

Παχυσαρκία

Κάπνισμα

Cardiovascular Disease Risk Factors Overlap

Synergistic interaction of traditional multiple risk factors on CVD risk

5-year CVD risk per 100 people

SBP (mm Hg)
- 110
- 120
- 130
- 140
- 150
- 160
- 170
- 180

Additive risk factors

TC = total cholesterol

TC = 270 mg/dL

Smoker

HDL = 39 mg/dL

Male

Diabetes

60 years of age

Συμμόρφωση στην κλινική πράξη

• 15% συμμορφώνονται πλήρως στην αγωγή
• 35% έχουν πλημμελή συμμόρφωση
• 50% διακόπτουν τη θεραπεία τον πρώτο χρόνο
• 75% διακόπτουν τη θεραπεία στην πενταετία

Βenedict et al. J Hypertens 2006;24(Suppl 4);
Adherence to statins after two years, by condition

- Acute coronary syndrome: 40%
- Chronic coronary artery disease: 36%
- Primary prevention: 24%

50% of new statin patients will discontinue medication after 6 months

Jackevicius CA, JAMA 2002;288:462-467
Συμμόρφωση στην κλινική πράξη

Κακή συμμόρφωση και μειωμένη παραμονή στη θεραπεία είναι σημαντικά εμπόδια στην αντιμετώπιση των παραγόντων κινδύνου.

Αυξημένη πιθανότητα νοσηλείας για κκ συμβάντα

Κακή ποιότητα ζωής

Οικονομικό κόστος

Αυξημένη θνησιμότητα

63% αύξηση της πιθανότητας θανάτου ή νοσηλείας για πρώτο καρδιαγγειακό επεισόδιο

74% αύξηση του κόστους θεραπείας

Am J Pharm. 2012;4.2:e41–e47.
When patients are asymptomatic . . .

Non-compliance rates increase dramatically to an estimated 75% percent.

Non-Compliance Rates w/Asymptomatic Patients

- 75% Non-Compliant
- 25% Compliant

Am J Pharm. 2012;4.2:e41–e47.
Potential Synergies Between Hypertension, Dyslipidemia, and Atherosclerosis

- Hypertension and dyslipidemia may synergistically accelerate atherogenesis
  - Increased endothelial permeability
  - Increased intimal retention of atherogenic lipoproteins
  - Exacerbation of inflammation
  - Increased free radical production

- BP reduction
  - Improves endothelial function
  - Reduces the retention of atherogenic lipoproteins
  - Reduces inflammation

- Lipid lowering
  - Improves endothelial function
  - Reduces the retention of atherogenic lipoproteins
  - Reduces inflammation
LDL cholesterol and benefit in clinical trials is lower better?

Rosensen RS. Exp Opin Emerg Drugs 2004;9(2):269-279
CARPE Study

Adjusted Probability of Achieving Adherence

Multivariate Odds Ratios of achieving PDC \( \geq 80\% \) during 6 month follow-up
(95% confidence interval)

Fix comb Aml + Atorv vs. Aml + Atorv
1.95 (1.80-2.13)**

Fix comb Aml + Atorv vs. Amlo + Other Statin
3.10 (2.85-3.38)**

Fix comb Aml + Atorv vs. Other CCB + Atorv
2.05 (1.89-2.24)**

Fix comb Aml + Atorv vs. Other CCB + Other Statin
2.84 (2.61-3.10)**

*Logistic regression model analysis adjusting for covariates including age, gender, business type, formulary type, baseline AHT, CVD meds, DM med, antidepressant, # of drugs, co-payments, Maintenance Med Refill%