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WHO - global burden of disease for the year 2002. Causes for total mortality for age and gender

Today, about 300 million people are at high-risk of cardiovascular disease:

In 2020, about 600 million people will be at high-risk to experience major cardiovascular events: about 1.5 billion with hypertension.

Volpe M, 2006
Projected Global and European deaths due to CVD in 2030. Data extracted from WHO

<table>
<thead>
<tr>
<th>Disease</th>
<th>World (total deaths 67.8 million)</th>
<th></th>
<th>Europe (total deaths 9.5 million)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Million</td>
<td>Percentage of total deaths (%)</td>
<td>Million</td>
<td>Percentage of total deaths (%)</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>9.6</td>
<td>14.1</td>
<td>2.1</td>
<td>22.6</td>
</tr>
<tr>
<td>Hypertensive Heart Disease</td>
<td>1.5</td>
<td>2.2</td>
<td>0.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>8.2</td>
<td>12.1</td>
<td>1.4</td>
<td>14.9</td>
</tr>
<tr>
<td><strong>Total CVD</strong></td>
<td><strong>23.6</strong></td>
<td><strong>34.8</strong></td>
<td><strong>4.7</strong></td>
<td><strong>49.7</strong></td>
</tr>
</tbody>
</table>

World Health Organization Projections
Accessed on 04/05/2009
Diagnostic and Interventional Procedures in Italy (1/3)
Diagnostic and Interventional Procedures in Italy (2/3)
Total health care costs in the EU

Bridging science and health policy in cardiovascular disease: focus on lipid management
A Report from a Session held during the 7th International Symposium on Multiple Risk Factors in CV Diseases: Prevention and Intervention - Health Policy, in Venice, Italy, on 25 October, 2008
Derived from Atherosclerosis Supplements 10 (2009) 3-21
Investing in General Practice

The New General Medical Services Contract
Coronary Heart Disease - Indicator 8
% of patients whose last measured total cholesterol is 5mmol/l or less in the last 15 mths
Results from the British Regional Heart Study comparing the impact of modest population-wide and high-risk strategies on CHD risk.
Cardiovascular Disease Risk Factors Overlap

*Chart is not to scale; illustrates overlapping of risk factors*
Multiple Independent Risk Factors Management (Silo Approach)

Integrated Identification and management of Risk Factors contributing to CVD Risk (Global Approach)

Traditional CVD Perspective

New CVD Risk Perspective

New Targets and Goals for Therapy

Reduction of Total CVD Risk

Integrated Guidelines for Global CV Reduction

Prevalence of cardiovascular Risk Factors in Italian hypertensive patients included in population and clinical surveys

Global cardiovascular risk stratification according to ESH/ESC guidelines, in Italian hypertensive patients included in population and clinical surveys

Reference group: female aged 50 years, TC=4 mmol/L, HDL=1.6 mmol/L, non smoker, no diabetes, at SBP levels of 110, 120, 130, 140, 150, 160, 170 & 180 mmHg

Reference group: male age 60 yrs & HDL=1mmol/L

Reference group: male age 60 yrs & diabetes

Reference group: male age 60 yrs

Derived from Anderson et al., Am Heart J 1991;121-293-8.
Risk of acute myocardial infarction associated with exposure to multiple risk factors

Physicians Often Underestimate Their Patients' CVD Risk

Comparison of actual versus perceived 10-year risk among 80 Swedish GPs asked to estimate the risk of a number of given patient profiles.

- **Man 61 years**
  - Smoker
  - LDL cholesterol: 6.3 mmol/L (244 mg/dL)
  - Total cholesterol: 8.2 mmol/L (317 mg/dL)
  - Framingham calculated risk: 33%
  - Perceived risk: 10%

- **Woman 66 years**
  - Diabetic
  - LDL cholesterol: 4.6 mmol/L (178 mg/dL)
  - Total cholesterol: 6.9 mmol/L (267 mg/dL)
  - Framingham calculated risk: 27%
  - Perceived risk: 10%

- **Woman 51 years**
  - Smoker
  - LDL cholesterol: 4.1 mmol/L (166 mg/dL)
  - Total cholesterol: 6.5 mmol/L (255 mg/dL)
  - Framingham calculated risk: 14%
  - Perceived risk: 5%

A new strategy for defining therapeutic goals in hypertension: different options

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<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>High added risk</td>
<td>Low added risk</td>
<td>Moderate added risk</td>
<td>High added risk</td>
</tr>
<tr>
<td>1–2 risk factors</td>
<td>Low added risk</td>
<td>Low added risk</td>
<td>Moderate added risk</td>
<td>Moderate added risk</td>
<td>Very high added risk</td>
<td></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>
<td></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>
<td></td>
</tr>
</tbody>
</table>
Even Mild Elevations in Blood Pressure and Cholesterol Increases Total CVD Risk

Death per 10,000 Patients - Years

Neaton et al. Arch Intern Med. 1992;152:56-64
Participants and endpoints

- 600,000 participants, 10 year follow-up
  - 500,000 Asia
  - 100,000 Australia-New Zealand

- 7,000 cardiovascular deaths
  - 2,200 deaths from IHD
  - 2,800 deaths from stroke
  - 5,000 CVD deaths in Asia
  - 2,000 CVD deaths in Australasia (ANZ)

- 4,000 non-fatal events
  - 1,000 myocardial infarctions
  - 3,000 strokes
Epidemiologically-predicted effects of reducing blood pressure and cholesterol

- **10 mmHg systolic (60-69 years)**
  - 22% reduction in coronary disease
  - 38% reduction in stroke

- **1 mmol/l cholesterol**
  - 32% reduction in coronary disease
  - 22% reduction in ischemic stroke

- **Both (10 mmHg plus 1 mmol/l)**
  - 47% reduction in coronary disease
  - 51% reduction in stroke

AP Cohort Study Collaboration. Circulation 2005;112:3384-90
Trends of Risk of Stroke according to initial risk in three visits over six months

Patients Score ≤6

Patients Score >6 e ≤15

Patients Score >15

* p<0.0001 vs visit 1; # p<0.0001 vs visit 2

Low, moderate and high risk of stroke in the overall patient population and in various subgroups according to the stroke risk scoring algorithm.

Framingham Heart Study evaluated 10 CV biomarkers in more than 3,000 people who were followed for about 10 years. Several biomarkers were found to be significant predictors of death (C-reactive protein, BNP, urinary albumin, renin and homocysteine) or CV events (BNP and urinary albumin). When biomarkers were combined into a 'multimarker' score, individuals with high scores had a 4-fold higher risk of death and a 2-fold higher risk of MACE than people with low scores. However, the multimarker score was associated with only a moderate increase in the AUC compared with a risk score based on conventional risk factors alone.

The addition of multimarker scores to conventional risk factors resulted in only small increases in the ability to classify risk, as measured by the C statistic.

For assessing risk in individuals, the use of the 10 contemporary biomarkers adds only moderately to standard risk factors.

Search for new CV Biomarkers

Information complexity increases from genome to transcriptome to proteome. Estimated number of entities (e.g., polypeptides) of each type of molecule in a typical cell.

Effect of three preventive strategies on deaths from coronary heart disease over 10 years in Canadians aged 20-74

<table>
<thead>
<tr>
<th>Strategy</th>
<th>No (%) of population treated</th>
<th>&lt;0.1% (% of risk group treated)</th>
<th>0.1-0.99%</th>
<th>1-10%</th>
<th>&gt;10%</th>
<th>No of deaths avoided*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population health (Rose)</td>
<td>12 300 000 (100)</td>
<td>55.1 (100.0)</td>
<td>20.2 (100.0)</td>
<td>20.4 (100.0)</td>
<td>4.4 (100.0)</td>
<td>5 160 (42)</td>
</tr>
<tr>
<td>High baseline risk</td>
<td>1 590 000 (12.9)</td>
<td>0.1 (0.0)</td>
<td>2.2 (1.4)</td>
<td>64.0 (40.5)</td>
<td>33.8 (100.0)</td>
<td>35 800 (290)</td>
</tr>
<tr>
<td>Single risk factor</td>
<td>1 370 000 (11.1)</td>
<td>4.0 (0.8)</td>
<td>27.4 (15.1)</td>
<td>54.0 (29.5)</td>
<td>14.7 (37.5)</td>
<td>15 500 (125)</td>
</tr>
</tbody>
</table>

*Assuming 100% community effectiveness for the single risk factor and high baseline risk strategies and a 2% total cholesterol reduction for the Rose strategy.

Projected number of patients at risk of hospitalisation for CVD due to high levels of cholesterol. This number is forecasted to increase by more than 50% over the next 30 years. Calculation based on RGS and Ministry of Health data.
Potential gain in terms of hospitalisation reduction under the assumption of a fully compliant population at risk.
Use of the IMPACT mortality model to explain the fall in CHD deaths in England & Wales 1981-2000

Bridging science and health policy in cardiovascular disease: focus on lipid management
A Report from a Session held during the 7th International Symposium on Multiple Risk Factors in CV Diseases: Prevention and Intervention - Health Policy, in Venice, Italy, on 25 October, 2008
Derived from Atherosclerosis Supplements 10 (2009) 3-21
Cost Estimation of CV Prevention

• In Italy, nowadays the effective gross cost of the only intra-hospital phase of acute myocardial infarction could be estimated around €6000 per patient (€720 000 000 per year).

• A 25% increase of this condition (without considering the costs related to rehabilitation, leave of absence from work, drug therapies, after-discharge diagnostic tests, jobs and working days lost) will lead to an estimated cost of more than €1 000 000 000 per year.

• In the US, in 2006, the cost of cardiovascular disease was $US368 billion, covering two-thirds of the overall in-hospital medical assistance cost.

• An increase of 25% in the next 15 years would probably imply an additional cost of more than $US500 billion.

Call-To-Action: Suggested Interventions (1/3)

1. To sustain and support health policies designed to promote or improve prevention of CV diseases in Italy.

2. To support and implement initiatives to quit smoking.

3. To identify training and educational strategies aimed at preventing CV diseases.

4. To increase awareness of the importance of medical management of total (or global) CV risk.

5. Use detection of potential indicators of high CV risk (family history, high blood pressure, cholesterol, blood glucose or other modifiable risk factors) as a starting point to perform the total CV risk stratification.

Call-To-Action: Suggested Interventions (2/3)

6. Assessing the global (or total) cardiovascular risk and projecting the estimate of CV risk over time.

7. Discuss the importance of cardiovascular risk assessment and prevention of CV benefits with patients.

8. Starting diagnostic and therapeutic interventions early.

9. Promote the use of recommendations for CV prevention, which should be simple, integrated and shared by the various scientific societies.

10. Promoting the role of General Practitioners (GPs).

Call-To-Action: Suggested Interventions (3/3)

11. Providing cultural and scientific support to multidisciplinary professional activities of all health professionals involved in preventing CV diseases.

12. Identifying and supporting initiatives by industries, or public and private associations, which may have impact on CV disease prevention.


14. Harmonizing the initiatives and sanitary policies in terms of CV prevention in association with the EU.

15. Identifying annual or periodic objectives, clearly specified, realistic and achievable, using criteria of periodic verification of the attained results.

Attività Diagnostica ed Interventistica 2009
UOS Emodinamica - UOC Cardiologia
Azienda Ospedaliera Sant’Andrea
Direttore: Prof. Massimo Volpe

<table>
<thead>
<tr>
<th>Totale Esami</th>
<th>Esami CVG</th>
<th>Altri Esami</th>
</tr>
</thead>
<tbody>
<tr>
<td>1166</td>
<td>1121</td>
<td>5</td>
</tr>
</tbody>
</table>
Registro Nazionale GISE
Aprile 2008

Totale Esami: 67.319
Esami CVG: 54.182
Altri Esami: 6.266
Attività Diagnostica ed Interventistica 2009
UOS Emodinamica - UOC Cardiologia
Azienda Ospedaliera Sant’Andrea
Direttore: Prof. Massimo Volpe

- **Totale Angioplastiche**: 526
- **Procedure Multivaso**: 174
- **PTCA Primarie**: 97
- **PTCA Rescue**: 4
Registro Nazionale GISE
Aprile 2008

Totale Angioplastiche

- Procedure Multivaso: 7,570
- PTCA Primarie: 5,226
- PTCA Rescue: 609

- Totale: 26,797
Registro Nazionale GISE
Aprile 2008

PTCA con stent: 24.696
PTCA con 1 DES: 13.559
Totale BMS: 16.643
Totale DES: 24.726
Cost effectiveness of statins according to analysis of major trials
Lack of public awareness of cholesterol as a CHD risk factor

Physicians believe their patients know cholesterol is associated with CVD

Only half the public is aware (after prompting) that high cholesterol increases CHD risk

- Smoking: 70%
- High blood pressure: 65%
- Obesity/been overweight: 62%
- Stress: 58%
- High cholesterol: 51%
- Drinking alcohol: 40%

Base: All GPs (N=754)

Base: all 40–70 year olds surveyed across France, Germany, Italy, Sweden and the UK (n=5104)
CVD events and incidence by 10-year risk classes in men ages 35 to 69 in Italy

A key strategic challenge—and opportunity—for medical care and public health is to achieve a progressive steady increase in the proportion of the population at low risk. This is essential for the conquest (i.e., ending) of the CVD epidemic.”

Jeremiah Stamler
Suggested interventions to reduce CVD burden in Italy

1. Sustain and support health policies designed to promote or improve prevention of CVD in Italy
2. Support and implement initiatives to quit smoking
3. Identify training and educational strategies aimed at preventing CVD
4. Increase awareness of the importance of medical management of total (global) CV risk
5. Use detection of potential indicators of high CVD risk (such as family history, high BP, cholesterol levels, or other modifiable risk factors) as a starting point to perform a total CV risk stratification
6. Assess the total (global) CV risk and project an estimate of CV risk over time
7. Discuss the importance of CV risk assessment and prevention of CV benefits with patients
8. Start diagnostic and therapeutic interventions early
9. Promote the use of recommendations for CV prevention, which should be simple, integrated, and shared by the various scientific societies
10. Promote the role of general practitioners
11. Provide cultural and scientific support to multidisciplinary professional activities of all health professionals involved in preventing CVD
12. Identify and support initiatives by industries or public and private associations, which may have an impact on CVD prevention
13. Develop documents for CV prevention
14. Harmonise and sanitise the initiatives and policies in terms of CV prevention in association with the EU
15. Identify annual or periodic objectives that are clearly specified, realistic, and achievable using criteria of verification the attained results
Aspirational and achievable goals to improve the health of all nations within the EU

- Evaluate the economic burden of CVD by including indirect costs and informal costs linked to patients’ relatives
- Focus attention on stroke prevention as well as CHD
- Consider joint government initiatives
- Re-evaluate farming policy and food subsidies related to unhealthy foods
- Increase funding of primary prevention strategies
- Evaluate potential impact of financial incentives to patients
- Assess the impact of further reducing statin costs
- Improve patient adherence/persistence with lipid-lowering therapies
- Improve public awareness of CVD
- Coordinate the knowledge and efforts of health economists, medical professionals, and biologists to change public policy on CVD prevention
2008 White Paper for Implementing Strategies and Interventions for Cardiovascular Prevention in Italy

• **Chairman:** Prof. Massimo Volpe, President SIPREC, Chair and Division of Cardiology, II Faculty of Medicine, University of Rome “La Sapienza”, Sant’Andrea Hospital, Rome, Italy.

• **List of Societies and Organizations participating in this Document:** Associazione Nazionale Cardiologi Extraospedalieri (ANCE); Associazione Regionale Cardiologi Ambulatoriali (ARCA); European Society for Cardiovascular Prevention (ESOCAP); Federazione delle Società Medico-Scientifiche Italiane (FISM); Federazione degli Ordini dei Farmacisti Italiani (FOFI); Fondazione Lorenzini; Federazione Nazionale Collegi Infermieri Professionali; Assistenti Sanitari e Vigilatrici d’Infanzia (IPASVI); Società Italiana di Diabetologia (SID); Società Italiana Ipertensione Arteriosa (SIIA); Società Italiana di Medicina Interna (SIMI); Società Italiana per la Prevenzione Cardiovascolare (SIPREC); Società Italiana per lo Studio dell’Aterosclerosi (SISA); Società Italiana per lo Studio dell’Emostasi e della Trombosi (SISET); Società Italiana di Terapia Clinica e Sperimentale (SITECS).

## Global Burden of CV Disease

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>1990 Millions</th>
<th>1990 (%)</th>
<th>2020 Millions</th>
<th>2020 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>6.2</td>
<td>12.4</td>
<td>11.1</td>
<td>16.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.3</td>
<td>8.5</td>
<td>7.7</td>
<td>11.3</td>
</tr>
<tr>
<td>Other CVD</td>
<td>2.6</td>
<td>5.1</td>
<td>6.0</td>
<td>8.8</td>
</tr>
<tr>
<td><strong>TOTAL CVD</strong></td>
<td><strong>13.1</strong></td>
<td><strong>26.0</strong></td>
<td><strong>24.8</strong></td>
<td><strong>36.3</strong></td>
</tr>
</tbody>
</table>
Rationale of a Document for Cardiovascular Prevention (1/3)

• The present Document for improving strategies and interventions for cardiovascular prevention in Italy represents the collaborative work of several scientific societies that recognize their own role and mission in the field of prevention of cardiovascular diseases.

• It originates from the need, felt in many European and non-European countries, as well as at the level of the EU, to rapidly promote strategies and interventions to better prevent cardiovascular diseases.

• The main reason for producing this Document is represented by the growing clinical and socioeconomic impact that cardiovascular diseases will have in Italy in the next few years. This, in fact, will bring serious problems regarding the ability to sustain the entire national healthcare system in Italy.

The Document **reviews some of the major data available** on projections of cardiovascular diseases and their social and economic burden.

It is conceived as a **starting point**, proposing general and specific interventions, addressed to decision-makers, stakeholders, institutions, citizens, physicians, healthcare workers, organizations and industries.

The major purpose is the development of a ‘**call-to-action**’, aimed at reducing the incidence of cardiovascular diseases and their impact on the healthcare system, even within a relatively short/medium term (3 to 10 yrs).

Rationale of a Document for Cardiovascular Prevention (3/3)

- In the last 3 decades, remarkable progress has been achieved, particularly in Western Countries, including Italy, in terms of knowledge of cardiovascular diseases and clinical management of cardiovascular risk factors, mostly cigarette smoking, arterial hypertension, hypercholesterolemia and diabetes.

- However, the level of prevention of cardiovascular diseases that has been possible to achieve today remains largely unsatisfactory.

- Poor control of major, traditional cardiovascular risk factors in the principal scientific reports (in Italy only 22% of individuals with arterial hypertension achieve blood pressure values within normal limits, the mean value of cholesterol is 203 mg/dL, and adult smokers exceed 20%)

- The progressively growing incidence of obesity and diabetes in adults and young people, and the persistently high individual attitudes to sedentary lifestyle and inappropriate dietary habits, seriously threaten to endanger any perspective of reduction in the incidence of cardiovascular diseases.

Projection of the Burden of Coronary Disease

- On the basis of the WHO MONICA (MONItoring Trends and Determinants in CArdiovascular Disease Project), the number of coronary events has increased from about 354 000 to 368 000 (an increase of about +5%) in the period from 1990 to 2000.

- Although mortality rate due to acute myocardial infarction is reduced, data derived from a recent analysis performed by the WHO indicate that a conservative estimation of the increase of acute myocardial infarction events will be 25% by 2030, involving an older and more complex (with major comorbidities) population.

CV Prevention: Past, Present, and Perspective

• Although a significant reduction of the incidence of cardiovascular events may represent a realistically achievable objective for healthcare policies and interventions, if such an inadequate level of cardiovascular prevention should persist in the near future, it is reasonable to predict an unavoidable acceleration of the tendency to increase cardiovascular disease incidence, also in consideration of the current demographic and socio-economical condition.

• The continuous, progressive and considerable increase in the incidence of cardiovascular diseases, mostly myocardial infarction and ischaemic stroke, is a matter of great and growing concern in regulators and professionals involved in maintaining and promoting public health, both at individual and at society levels, not only in Western countries, but also in all those nations with emergent economies, in which the phenomenon is progressively assuming huge proportions.
Costs and Sustainability of Global Burden of CV disease

- The complexity of these data should generate concern and should raise the threshold of attention for the potential impact that they could have on the capacity to sustain the whole healthcare system in the near future, especially when considering that structures specifically dedicated to cardiovascular disease care and currently available for acute patients (coronary care units, stroke unit, intensive care units, specialized hospitals, rehabilitation units, specialized outpatient clinics) could quickly become insufficient to manage the growing number of patients requiring long, intensive care and assistance.

- At the same time, costs for medical care could further increase, mostly in relation to the continuous evolution of the available medical treatments.

- Thus, it could be difficult to sustain such an advanced medical assistance, both in terms of economic costs of drugs and therapeutic devices, and in terms of diagnostic and interventional technologies, follow-up programme, etc.
Main Objectives of the Consensus Document (1/2)


2. Increasing awareness of physicians, healthcare operators and citizens about the relationship between cardiovascular risk factors and major cardiovascular events (mostly myocardial infarction and ischaemic stroke), and about the possibility to reduce risk.

3. Promoting the development of more effective interventions for the control of global cardiovascular risk.
Main Objectives of the Consensus Document (2/2)

4. Planning and developing a specific and programmatic document ('call-to-action') aimed at increasing and promoting the physician’s role in short- to medium-term programs, and reducing the incidence of major cardiovascular events.

5. Integrating and improving, when applicable, the use of tools for estimating cardiovascular risk in Italy.

6. Contributing to the creation and improvement of information in national registers and databases on cardiovascular diseases in Italy.
Methodology and Synthesis of Programmatic Action (1/2)

- Scientific societies participating in this initiative share common purpose and constitute a task force for elaborating programmatic consensus document, defined as a White Paper, identifying objectives and instruments for assessing the efficiency of the interventions over time and the verification of results.

- This initiative may allow the possibility of sustaining the burden of cardiovascular disease for the national healthcare system in the near future through interventions that may be able to limit the upcoming threat for the public healthcare system, represented by the disease burden and social and economic costs of major cardiovascular events.

- The analysis of the current situation and the projections of economic burden for the national healthcare systems indicate growing difficulties to support needs and expenses for maintaining public health, starting at the beginning of the next decade, as a consequence of the progressive growth and expansion of cardiovascular disease incidence in the general population.

Methodology and Synthesis of Programmatic Action (2/2)

• According to article number 32 of the Fundamental Principles of Italian Constitution "Italian Republic defends health as a fundamental right of the individual and as the interest of the entire population, and guarantees free medical cares to people."

• This initiative is aimed at preserving the right of health in a more modern key of lecture, underlying the driving role of the national healthcare system not only in the presence of disease, but also in preserving a status of wellness in the general population.

• Development of a specific 'call-to-action' aimed at defining integrated strategies for promoting primary and secondary prevention of cardiovascular diseases in Italy.

Central role of intermediate endpoints (disease markers) in the CV continuum and new targets of therapy

Presence of risk factors (BP, cholesterol, smoking, overweight, IGT or metabolic syndrome)

Intermediate Endpoints (Monitored by Biomarkers)

- Arterial stiffness & atherosclerosis
- Endothelial dysfunction
- Vascular inflammation
- LVD or CHF or AF
- LVH
- Microalbuminuria
- Impaired renal function
- New-onset Diabetes mellitus
- Clinical sequelae and events (AMI, stroke, ESRD, death)

Targets and goals of therapy

- PRIMARY PREVENTION
  - Delayed progression
  - Prevented development
- REGRESSION

Volpe M, J Am Soc Nephrol. 2006;17:S36-S43. Modified
Numbers and proportions of patients according to absolute risk threshold and modifiable part of the absolute risk

<table>
<thead>
<tr>
<th>10 year absolute risk*</th>
<th>Modifiable part of absolute risk</th>
<th></th>
<th>Realistic reduction†</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Potential reduction‡</td>
<td>Realistic reduction‡</td>
<td></td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;5%</td>
<td>≥5%</td>
<td>&lt;5%</td>
<td>≥5%</td>
<td></td>
</tr>
<tr>
<td>&lt;20%</td>
<td>111 (38%)</td>
<td>84 (29%)</td>
<td>148 (51%)</td>
<td>47 (16%)</td>
<td>195 (67%)</td>
</tr>
<tr>
<td>≥20%</td>
<td>2 (1%)</td>
<td>96 (33%)</td>
<td>12 (4%)</td>
<td>86 (29%)</td>
<td>98 (33%)</td>
</tr>
<tr>
<td>&lt;40%</td>
<td>113 (39%)</td>
<td>162 (55%)</td>
<td>159 (54%)</td>
<td>116 (40%)</td>
<td>275 (94%)</td>
</tr>
<tr>
<td>≥40%</td>
<td>0 (0%)</td>
<td>18 (6%)</td>
<td>1 (0%)</td>
<td>17 (6%)</td>
<td>18 (6%)</td>
</tr>
<tr>
<td>Total</td>
<td>113 (39%)</td>
<td>180 (61%)</td>
<td>160 (55%)</td>
<td>133 (45%)</td>
<td>293 (100%)</td>
</tr>
</tbody>
</table>

*Based on the Framingham risk equation (based on age, sex, diabetes mellitus, systolic blood pressure, total cholesterol to HDL cholesterol ratio, and smoking); †maximum reduction in 10 year absolute risk by eliminating modifiable risk factors (systolic blood pressure reduction from >120 to 120 mm Hg, total cholesterol to HDL cholesterol reduction from >4 to 4, and smoking cessation if the patient smokes); ‡expected reduction in 10 year absolute risk by lowering the modifiable risk factors according to results from trials (systolic blood pressure reduction by 12 mm Hg, total cholesterol reduction by 20%, HDL increase by 5%, and smoking cessation).
Proven Benefits of Blocking the RAS

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Evidence of Benefit</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension*</td>
<td>↓ mortality</td>
<td>↓ heart failure</td>
</tr>
<tr>
<td>Hypertension/LVH</td>
<td>CV composite EP</td>
<td></td>
</tr>
<tr>
<td>Hypertension, elderly</td>
<td>CV Composite EP</td>
<td>Stroke</td>
</tr>
<tr>
<td>High-risk patients</td>
<td>↓ mortality</td>
<td>↓ heart failure</td>
</tr>
<tr>
<td>CAD without LVD</td>
<td>↓ mortality</td>
<td>↓ heart failure</td>
</tr>
<tr>
<td>Acute MI</td>
<td>↓ mortality</td>
<td>↓ heart failure</td>
</tr>
<tr>
<td>LVD</td>
<td>↓ mortality</td>
<td>↓ heart failure</td>
</tr>
<tr>
<td>Heart failure</td>
<td>↓ mortality</td>
<td>↓ heart failure</td>
</tr>
<tr>
<td>Renal disease</td>
<td>↓ ESRD/mortality</td>
<td>↓ heart failure</td>
</tr>
<tr>
<td>Stroke</td>
<td>↓ mortality</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes +KD</td>
<td>Primary end points</td>
<td></td>
</tr>
</tbody>
</table>

*Hypertension with LVD or DM.
Relative Risk of Stroke

Systolic Blood Pressure Difference Between randomised groups (mmHg)

Coronary Heart Disease

VALUE: Analysis of Results Based on BP Control at 6 Months

**Patients Treated With Valsartan**

- Fatal/Non-fatal cardiac events
- Fatal/Non-fatal stroke
- All-cause death
- Myocardial infarction
- Heart failure hospitalisations

**Patients Treated With Amlodipine**

- Odds Ratio

\[
\begin{array}{cccc}
\text{Hazard Ratio} & 0.4 & 0.6 & 0.8 & 1.0 & 1.2 \\
\text{Controlled patients* (n = 5253)} & (0.66–0.88) & (0.48–0.74) & (0.69–0.91) & (0.66–1.03) & (0.62–0.77) \\
\text{Non-controlled patients (n = 2396)} & (0.66–0.88) & (0.48–0.74) & (0.69–0.91) & (0.66–1.03) & (0.62–0.77) \\
\end{array}
\]

\[
\begin{array}{cccc}
\text{Odds Ratio} & 0.76 & 0.60 & 0.79 & 0.62 \\
\text{Controlled patients* (n = 5502)} & (0.66–0.88) & (0.48–0.74) & (0.69–0.91) & (0.62–0.77) \\
\text{Non-controlled patients (n = 2094)} & (0.66–0.88) & (0.48–0.74) & (0.69–0.91) & (0.62–0.77) \\
\end{array}
\]

\[
\begin{array}{cccc}
\text{Odds Ratio} & 0.73 & 0.50 & 0.79 & 0.64 \\
\text{Controlled patients* (n = 5502)} & (0.63–0.85) & (0.39–0.64) & (0.69–0.92) & (0.52–0.79) \\
\text{Non-controlled patients (n = 2094)} & (0.63–0.85) & (0.39–0.64) & (0.69–0.92) & (0.52–0.79) \\
\end{array}
\]

*SBP < 140 mmHg at 6 months.
**P < 0.01.
VALUE: Outcome and SBP Differences at Specific Time Periods: *Primary Endpoint*

<table>
<thead>
<tr>
<th>Time Interval (months)</th>
<th>Δ SBP mmHg</th>
<th>PRIMARY ENDPOINT Odds Ratios and 95% CIs</th>
</tr>
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<tbody>
<tr>
<td>Overall study</td>
<td>2.2</td>
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<tr>
<td>0–3</td>
<td>3.8</td>
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</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>
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</tr>
<tr>
<td>24–36</td>
<td>1.6</td>
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</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 valsartan

Favours amlodipine

Insight into optimal CVD prevention

• On the basis of the clinical characteristics of the InterHeart population (HT + smoking + HC increase CVD risk 8-times), one can conclude that about 90% of Myocardial Infarction is explained by these RFs.

• You don’t need to think to fancy mechanisms to reduce global cardiovascular risk!
Data Analytics: Antihypertensive Efficacy of Valsartan and Valsartan/HCTZ in Patients with Stage 1-2 Hypertension

ARBSs and the Cardiovascular Continuum

Risk factors
- Diabetes
- Hypertension

Atherosclerosis and LVH

Myocardial infarction

Remodeling

Ventricular dilation

Heart failure

End-stage heart disease

Death

Adapted from Dzau V, Braunwald E. Am Heart J. 1991;121:1244-1263.
What an antihypertensive therapy should take care of?

- Blood Pressure
- Target Organ Damage & relevant Biomarkers (LVH, LVD, MAU, IMT, hsCRP)
- Metabolic Effects
- Diabetes
- Renal Failure
- Stroke
- CHF
- Myocardial Infarction
- Tolerability

mod. Volpe M, 2007
## RAAS and Prevention of CVD and Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Intervention</th>
<th>Diabetes</th>
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</thead>
<tbody>
<tr>
<td>HOPE</td>
<td>High-risk CVD</td>
<td>Ramipril vs CT</td>
<td>↓32%</td>
</tr>
<tr>
<td>CAPPP</td>
<td>Hypertension</td>
<td>Captopril vs CT</td>
<td>↓13%</td>
</tr>
<tr>
<td>LIFE</td>
<td>Hypertension, LVH</td>
<td>Losartan vs atenolol</td>
<td>↓25%</td>
</tr>
<tr>
<td>CHARM</td>
<td>Heart failure</td>
<td>Cande vs CT</td>
<td>↓~20%</td>
</tr>
<tr>
<td>SCOPE</td>
<td>Elderly HT</td>
<td>Candesartan vs CT</td>
<td>↓~20%</td>
</tr>
<tr>
<td>VALUE</td>
<td>High Risk HT</td>
<td>Valsartan vs Amlo</td>
<td>↓~23%</td>
</tr>
</tbody>
</table>
Consider:
- Untreated BP level
- Absence or presence of TOD and risk factors

Choose between

- Single agent at low dose
  - If goal BP not achieved:
    - Previous agent at full dose
    - Switch to different agent at low dose
      - Two- to three-drug combination
      - Full dose monotherapy

- Two-drug combination at low dose
  - Previous combination at full dose
    - Add a third drug at low dose
      - Three-drug combination at effective doses
  - If goal BP not achieved:
    - Previous combination at full dose

Choice between monotherapy and combination therapy. BP, blood pressure; TOD, target organ damage.
Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both

Marc A. Pfeffer, M.D., Ph.D., John J.V. McMurray, M.D., Eric J. Velazquez, M.D., Jean-Lucien Rouleau, M.D., Lars Køber, M.D., Aldo P. Maggioni, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., Frans Van de Werf, M.D., Ph.D., Harvey White, D.Sc., Jeffrey D. Leimberger, Ph.D., Marc Henis, M.D., Susan Edwards, M.S., Steven Zelenkofske, D.O., Mary Ann Sellers, M.S.N., and Robert M. Califf, M.D., for the Valsartan in Acute Myocardial Infarction Trial Investigators*
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Valsartan Group (N=4909)</th>
<th>Valsartan-and-Captopril Group (N=4885)</th>
<th>Captopril Group (N=4909)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>65.0±11.8</td>
<td>64.6±11.9</td>
<td>64.9±11.8</td>
</tr>
<tr>
<td>Race — no. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>4604 (93.8)</td>
<td>4553 (93.2)</td>
<td>4591 (93.5)</td>
</tr>
<tr>
<td>Black</td>
<td>125 (2.5)</td>
<td>137 (2.8)</td>
<td>145 (3.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>44 (0.9)</td>
<td>53 (1.1)</td>
<td>44 (0.9)</td>
</tr>
<tr>
<td>Other</td>
<td>136 (2.8)</td>
<td>142 (2.9)</td>
<td>129 (2.6)</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>1544 (31.5)</td>
<td>1490 (30.5)</td>
<td>1536 (31.3)</td>
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<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Systolic</td>
<td>122.7±16.8</td>
<td>122.5±17.1</td>
<td>122.8±17.0</td>
</tr>
<tr>
<td>Diastolic</td>
<td>72.3±11.3</td>
<td>72.3±11.4</td>
<td>72.4±11.2</td>
</tr>
<tr>
<td>Heart rate — beats/min</td>
<td>76.2±13.0</td>
<td>76.2±12.7</td>
<td>76.2±12.8</td>
</tr>
<tr>
<td>Body-mass index†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>27.34</td>
<td>27.24</td>
<td>27.14</td>
</tr>
<tr>
<td>Left ventricular ejection fraction — %‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killip class — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1294 (26.5)</td>
<td>1381 (28.4)</td>
<td>1424 (29.1)</td>
</tr>
<tr>
<td>II</td>
<td>2401 (49.2)</td>
<td>2329 (47.9)</td>
<td>2346 (48.0)</td>
</tr>
<tr>
<td>III</td>
<td>874 (17.9)</td>
<td>842 (17.3)</td>
<td>813 (16.6)</td>
</tr>
<tr>
<td>IV</td>
<td>313 (6.4)</td>
<td>312 (6.4)</td>
<td>306 (6.3)</td>
</tr>
<tr>
<td>Medical history — no. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
<td>1395 (28.4)</td>
<td>1376 (28.2)</td>
<td>1333 (27.2)</td>
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<tr>
<td>Hypertension</td>
<td>2732 (55.7)</td>
<td>2700 (55.3)</td>
<td>2690 (54.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1134 (23.1)</td>
<td>1146 (23.5)</td>
<td>1120 (22.8)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>759 (15.5)</td>
<td>701 (14.4)</td>
<td>714 (14.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>292 (5.9)</td>
<td>305 (6.2)</td>
<td>298 (6.1)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1556 (31.7)</td>
<td>1546 (31.6)</td>
<td>1562 (31.8)</td>
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<tr>
<td>Coronary-artery bypass grafting</td>
<td>355 (7.2)</td>
<td>327 (6.7)</td>
<td>344 (7.0)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>376 (7.7)</td>
<td>337 (6.9)</td>
<td>354 (7.2)</td>
</tr>
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</table>
A  Death from Any Cause

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>4909</th>
<th>4464</th>
<th>4272</th>
<th>4007</th>
<th>2648</th>
<th>1437</th>
<th>357</th>
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<tbody>
<tr>
<td>Valsartan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valsartan and captopril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Captopril</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Probability of Event vs. Months

- Valsartan
- Valsartan and captopril
- Captopril

VALIANT Trial. NEJM Nov 13, 2003; 349: 1893-906
**B Combined Cardiovascular End Point**

- Valsartan
- Valsartan and captopril
- Captopril

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Valsartan</th>
<th>Valsartan and captopril</th>
<th>Captopril</th>
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<tbody>
<tr>
<td>0 months</td>
<td>4909</td>
<td>4885</td>
<td>4909</td>
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<tr>
<td>6 months</td>
<td>3921</td>
<td>3887</td>
<td>3896</td>
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<tr>
<td>12 months</td>
<td>3667</td>
<td>3646</td>
<td>3610</td>
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<tr>
<td>18 months</td>
<td>3391</td>
<td>3391</td>
<td>3355</td>
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<tr>
<td>24 months</td>
<td>2188</td>
<td>2221</td>
<td>2155</td>
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<tr>
<td>30 months</td>
<td>1204</td>
<td>1185</td>
<td>1148</td>
</tr>
<tr>
<td>36 months</td>
<td>290</td>
<td>313</td>
<td>295</td>
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</tbody>
</table>
Framingham Heart Study Lifetime Risk

Adjusted Cumulative Incidence

Men

Women

≥2 Major RFs
1 Major RF
≥ Elevated RF
≥ Not Elevated RF
All Optimal RFs

Men:
- 69% at 80 years
- 50% at 70 years
- 46% at 60 years
- 36% at 50 years
- 5% at 40 years

Women:
- 50% at 80 years
- 39% at 70 years
- 27% at 60 years
- 8% at 50 years

Lloyd-Jones Circ. 2006; 113: 791-798
Burden of Disease and Societal Cost:
Do we need to treat patient A (low-risk)?
Importance of Primary Prevention in Cardiology

- The first clinical presentation of atherosclerosis of the coronary tree is Acute Myocardial Infarction or Sudden Death in about 60% of patients.
- Rheumatic Valvular Disease disappeared.

Murabito, et al. for the Framingham Database. Circulation 2003
Kaplan-Meier curves for CHD events and new-onset diabetes in men with different number of characteristics of the MS at baseline.

A CHD Death or non-fatal MI for different numbers of factors

B Onset of new diabetes by different numbers of factors

Cost-Effectiveness Ratio is improved with the absolute risk approach.
Beyond Hypertension

Toward Guidelines for Cardiovascular Risk Reduction*

Massimo Volpe, Michael H. Alderman, Curt D. Furberg, Rodney Jackson, John B. Kostis, John H. Laragh, Bruce M. Psaty, and Luis M. Ruilope
<table>
<thead>
<tr>
<th>Case</th>
<th>9</th>
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<th>11</th>
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<tbody>
<tr>
<td>Age</td>
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<td>65</td>
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<td>65</td>
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<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>SBP</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>TC</td>
<td>5.0</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
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<tr>
<td>HDL</td>
<td>1.4</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
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<tr>
<td>Smoking</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>5-year CVD risk</td>
<td>3.7%</td>
<td>18.9%</td>
<td>27.6%</td>
<td>37.1%</td>
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<tr>
<td>Gender</td>
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<td>M</td>
<td>M</td>
<td>M</td>
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<tr>
<td>SBP</td>
<td>160</td>
<td>150</td>
<td>130</td>
<td>120</td>
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<tr>
<td>TC</td>
<td>6.0</td>
<td>5.0</td>
<td>6.0</td>
<td>6.0</td>
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<tr>
<td>HDL</td>
<td>0.8</td>
<td>1.2</td>
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<td>0.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5-year CVD risk</td>
<td>18.8%</td>
<td>18.4%</td>
<td>19.1%</td>
<td>18.5%</td>
</tr>
</tbody>
</table>

Conclusions

• Cardiovascular Disease continues to be the leading cause of death and disability worldwide

• Studies show CVD management requires a comprehensive evaluation of multiple risk factors and a patient’s total CVD risk

• It is imperative that we in the medical community improve our approaches to CVD risk management and prevention
Interactions among RFs are multiplicative on CAD and Stroke incidence

- Cardiovascular Disease is a continuum
- Biology does not require thresholds
- Normal limits are a statistical compromise
- High blood pressure and cholesterol levels cause the largest burden of disease in individual within “normal” limits

Volpe M, 2006
Characteristics of patients with a 10 year absolute risk* <20% and a modifiable risk ≥5% (group 1) and of patients with a 10 year absolute risk >20% and a modifiable part ≥5% (group 2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Potential reduction ≥5%†</th>
<th>p Value</th>
<th>Realistic reduction ≥5%‡</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n=84)</td>
<td>Group 2 (n=96)</td>
<td></td>
<td>Group 1 (n=47)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.9 (6.3)</td>
<td>59.1 (6.7)</td>
<td>&lt;0.0001</td>
<td>49.9 (7.0)</td>
</tr>
<tr>
<td>Age categories (years)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;50</td>
<td>44 (52%)</td>
<td>9 (9%)</td>
<td>&lt;0.0001</td>
<td>25 (53%)</td>
</tr>
<tr>
<td>≥50</td>
<td>40 (48%)</td>
<td>87 (91%)</td>
<td></td>
<td>22 (47%)</td>
</tr>
<tr>
<td>Women</td>
<td>52 (62%)</td>
<td>33 (34%)</td>
<td>&lt;0.0001</td>
<td>25 (53%)</td>
</tr>
<tr>
<td>Non-Dutch</td>
<td>54 (64%)</td>
<td>57 (59%)</td>
<td>0.301</td>
<td>25 (53%)</td>
</tr>
<tr>
<td>Smoking§</td>
<td>37 (44%)</td>
<td>45 (47%)</td>
<td>0.409</td>
<td>29 (62%)</td>
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<tr>
<td>Hypercholesterolaemia¶</td>
<td>53 (63%)</td>
<td>75 (78%)</td>
<td>0.020</td>
<td>39 (83%)</td>
</tr>
<tr>
<td>Hypertension¶</td>
<td>50 (60%)</td>
<td>81 (84%)</td>
<td>&lt;0.0001</td>
<td>22 (47%)</td>
</tr>
<tr>
<td>Diabetes mellitus¶</td>
<td>25 (30%)</td>
<td>41 (43%)</td>
<td>0.050</td>
<td>13 (28%)</td>
</tr>
<tr>
<td>Obesity¶</td>
<td>41 (51%)</td>
<td>50 (53%)</td>
<td>0.459</td>
<td>22 (50%)</td>
</tr>
<tr>
<td>Family history of CVDS§</td>
<td>31 (37%)</td>
<td>27 (28%)</td>
<td>0.136</td>
<td>15 (32%)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or number (%).

*Based on the Framingham risk equation (based on age, sex, diabetes mellitus, systolic blood pressure, total cholesterol to HDL cholesterol ratio, and smoking); †maximum reduction in 10 year absolute risk by eliminating modifiable risk factors (systolic blood pressure reduction from >120 to 120 mm Hg, total cholesterol to HDL cholesterol ratio reduction from > 4 to 4, and smoking cessation if the patient smokes); ‡expected reduction in 10 year absolute risk by lowering the modifiable risk factors according to results from trials (systolic blood pressure reduction by 12 mm Hg, total cholesterol reduction by 20%, HDL increase by 5%, and smoking cessation); §based on patients’ self reports; ¶hypercholesterolaemia defined as total cholesterol to HDL cholesterol ratio >4, hypertension defined as systolic blood pressure ≥140 mm Hg, and obesity defined as body mass index ≥30 kg/m².

Integrated Risk Score predicts better than single CV risk factor

Ridker P, Circulation 2003;107:363-6
Going beyond BP control? Add a Statin

• “[...] in my view, statins should and will become routine therapy in people with treated hypertension, especially those at highest CVD risk, because they potently complement the primary objective of antihypertensive therapy - notably, to reduce the risk of coronary heart disease and stroke. This is undoubtedly the most effective way to go beyond blood pressure control.”

Derived from Williams B. J Am Coll Cardiol 2005;45:813-827
Importance of Relative Risk Reduction in hypertensive patients

Patient A
No Previous CVD
Low CVD risk

Patient B
With Previous CVD
High CVD risk

CVD risk in 5 years (%)

5.8  4.5

20.0  18.5

Hypertension Detection and Follow-Up Program. JAMA 1997;277(2):157-66
Figure 1
10 year risk of fatal CVD in high risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status

European Guidelines on Cardiovascular Prevention
# Illustrating Multiple Risk: Patient Cases

*10-year risk of suffering a heart attack or angina, or dying from heart disease*

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td>160 mmHg</td>
<td>130 mmHg</td>
</tr>
<tr>
<td><strong>LDL-C</strong></td>
<td>4.0 mmol/L (154 mg/dL)</td>
<td>4.0 mmol/L (154 mg/dL)</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td>0.8 mmol/L (31 mg/dL)</td>
<td>0.8 mmol/L (31 mg/dL)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>10-year risk</strong></td>
<td>11%</td>
<td>7%</td>
</tr>
</tbody>
</table>

*Risk calculated based on the Framingham Heart Study Risk Score*
### Illustrating Multiple Risk: Patient Cases

10-year risk of suffering a heart attack or angina, or dying from heart disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
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<td>40</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>SBP</td>
<td>160 mmHg</td>
<td>145 mmHg</td>
</tr>
<tr>
<td>LDL-C</td>
<td>5.0 mmol/L (193 mg/dL)</td>
<td>4.5 mmol/L (173 mg/dL)</td>
</tr>
<tr>
<td>HDL</td>
<td>0.8 mmol/L (31 mg/dL)</td>
<td>0.8 mmol/L (31 mg/dL)</td>
</tr>
<tr>
<td>Smoking</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10-year CVD risk</td>
<td>18%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Risk calculated based on the Framingham Heart Study Risk Score
Illustrating Multiple Risk: Patient Cases

10-year risk of suffering a heart attack or angina, or dying from heart disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>SBP</td>
<td>160 mmHg</td>
<td>145 mmHg</td>
</tr>
<tr>
<td>LDL-C</td>
<td>5.0 mmol/L (193 mg/dL)</td>
<td>4.5 mmol/L (173 mg/dL)</td>
</tr>
<tr>
<td>HDL</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10-year CVD risk</td>
<td>40%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Risk calculated based on the Framingham Heart Study Risk Score
Executive summary

European guidelines on cardiovascular disease prevention in clinical practice

Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts)

Guy De Backer (Chairperson)⁎, Ettore Ambrosioni⁎, Knut Borch-Johnsen⁎⁎, Carlos Brotons⁎, Renata Cifkova⁎, Jean Dallongeville⁎, Shah Ebrahim⁎, Ole Faergeman⁎, Ian Graham⁎, Giuseppe Mancia⁎, Volkert Manger Cats⁎, Kristina Orth-Gomér⁎, Joep Perk⁎, Kalevi Pyörälä⁎, José L. Rodicio⁎, Susana Sans⁎, Vedat Sansoy⁎, Udo Sechtem⁎, Sigmund Silber⁎, Troels Thomsen⁎, David Wood⁎
Calculating Multiple CVD Risk: CVD Risk Score

47-year-old male reporter
non-smoker
does not have diabetes
LDL-C 3.65 mmol/L (141 mg/dL)
HDL-C 0.98 mmol/L (38 mg/dL)
BP 160/100 mg/dL

What is his risk of suffering a heart attack or chest pain, or dying from heart disease in the next 10 years?
Calculating Multiple CVD Risk: CVD Risk Score

39 yr old Female reporter
Smoker
No Diabetes
LDL-C 3.75 mmol/L (145 mg/dL)
HDL-C 1.25 mmol/L (48 mg/dL)
BP 140/90 mmHg

What is her risk of suffering a heart attack or chest pain, or dying from heart disease in the next 10 years?
### 10-Year CHD Risk: 2%

**Risk calculated based on the Framingham Heart Study Risk Score**
Risk At Age 60: 27%
Paradigm shift in CV risk estimation

PAST  →  Relative Risk
       →  Single risk-based approach

PRESENT  →  Absolute Risk
          →  Multifactor Approach
          →  10-years CHD risk estimation

FUTURE  →  Individual CV Risk estimation
         →  Risk composition evaluation
         →  (genetic profile?)

Volpe M, 2004
Riskard 2005. New tools for prediction of cardiovascular disease risk derived from Italian population studies

New Paradigms in Cardiovascular Disease

1. Individual Global Risk replaces Single Risk-based approach
2. Treatment is aimed to reduce Individual Global Risk rather than reducing single Risk
3. Reduction of single or multiple Risk Factors generates a benefit proportional to the level of Risk
4. Combination therapy is most appropriate for these new paradigms
5. Dosages of components in combination therapy may not be sufficient to achieve goal for the Single Risk Factor, but at the same time get the goal for the Single Risk excess.

Volpe M, 2004
Treatment goals in patients with type 2 diabetes:

<table>
<thead>
<tr>
<th>Measure</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA$_{1c}$ (DCCT-standardized)</td>
<td>≤6.1</td>
</tr>
<tr>
<td>Venous plasma glucose</td>
<td></td>
</tr>
<tr>
<td>Fasting/pre-prandial mmol/l</td>
<td>≤6.0</td>
</tr>
<tr>
<td>Fasting/pre-prandial mg/dl</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Self-monitored blood glucose</td>
<td></td>
</tr>
<tr>
<td>Fasting/pre-prandial mmol/l</td>
<td>4.0–5.0</td>
</tr>
<tr>
<td>Fasting/pre-prandial mg/dl</td>
<td>70–90</td>
</tr>
<tr>
<td>Post-prandial mmol/l</td>
<td>4.0–7.5</td>
</tr>
<tr>
<td>Post-prandial mg/dl</td>
<td>70–135</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>≤4.5 (175)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>≤2.5 (100)</td>
</tr>
</tbody>
</table>
Cumulative incidence of CV events in women and men without hypertension, according to blood-pressure Category at the baseline

**Women**

- **High-normal**
- **Normal**
- **Optimal**

**Men**

- **High-normal**
- **Normal**
- **Optimal**

**No. at risk**

<table>
<thead>
<tr>
<th>Category</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimal</strong></td>
<td>1875</td>
<td>1867</td>
<td>1851</td>
<td>1839</td>
<td>1821</td>
<td>1734</td>
<td>887</td>
<td></td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>1126</td>
<td>1115</td>
<td>1097</td>
<td>1084</td>
<td>1061</td>
<td>974</td>
<td>649</td>
<td></td>
</tr>
<tr>
<td><strong>High-normal</strong></td>
<td>891</td>
<td>874</td>
<td>859</td>
<td>840</td>
<td>812</td>
<td>722</td>
<td>520</td>
<td></td>
</tr>
</tbody>
</table>

Vasan RS, *NEJM* 2001
ASCOT-LLA Trial

Cumulative incidence for primary endpoint of non-fatal myocardial infarction and fatal coronary heart disease

-32% reduction

HR=0.64 (0.50–0.83), p=0.0005

Number at risk
Placebo: 5137, 5085, 5042, 5007, 4964, 4603, 3259, 1801
Atorvastatin: 5168, 5134, 5103, 5063, 5035, 4679, 3263, 1801

ASCOT-LLA Trial

Blood Pressure Trends

Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

Peter Gæde, M.D., Pernille Vedel, M.D., Ph.D., Nicolai Larsen, M.D., Ph.D., Gunnar V.H. Jensen, M.D., Ph.D., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.
Percentage of patients in each group who reached the intensive-treatment goals at mean of 7.8 years

<table>
<thead>
<tr>
<th>Goal</th>
<th>Intensive therapy</th>
<th>Conventional therapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycosylated hemoglobin &lt;6.5%</td>
<td>10</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Cholesterol &lt;175 mg/dl</td>
<td>70</td>
<td>50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides &lt;150 mg/dl</td>
<td>50</td>
<td>40</td>
<td>0.19</td>
</tr>
<tr>
<td>Systolic BP &lt;130 mHg</td>
<td>70</td>
<td>60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP &lt;80 mmHg</td>
<td>80</td>
<td>70</td>
<td>0.21</td>
</tr>
</tbody>
</table>

LIFE
Comparable blood-pressure reductions

* Mean BP at last visit

**LIFE**

Fatal/nonfatal stroke

Intention-to-treat

<table>
<thead>
<tr>
<th>Endpoint rate</th>
<th>Study day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0</td>
</tr>
<tr>
<td>0.02</td>
<td>180</td>
</tr>
<tr>
<td>0.03</td>
<td>360</td>
</tr>
<tr>
<td>0.04</td>
<td>540</td>
</tr>
<tr>
<td>0.05</td>
<td>720</td>
</tr>
<tr>
<td>0.06</td>
<td>900</td>
</tr>
<tr>
<td>0.07</td>
<td>1080</td>
</tr>
<tr>
<td>0.08</td>
<td>1260</td>
</tr>
</tbody>
</table>

Adjusted risk reduction 24.9%, \( p=0.001 \)

Unadjusted risk reduction 25.8%, \( p<0.001 \)

Atenolol

Losartan

Study day: 0, 180, 360, 540, 720, 900, 1080, 1260, 1440, 1620, 1800, 1980
### Outcome results in the LIFE trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Losartan better</th>
<th>Atenolol better</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetics</strong> (n=1195)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>-27</td>
<td>00</td>
<td>0.02</td>
</tr>
<tr>
<td>CV deaths</td>
<td>-38</td>
<td>-22</td>
<td>0.02</td>
</tr>
<tr>
<td>Strokes</td>
<td>-19</td>
<td>0.002</td>
<td>0.19</td>
</tr>
<tr>
<td>MI</td>
<td>-40</td>
<td>0.25</td>
<td>0.32</td>
</tr>
<tr>
<td>Total mortality</td>
<td>-42</td>
<td>0.71</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-CV deaths</td>
<td></td>
<td>-40%</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Non-diabetics</strong> (n=7998)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>-11</td>
<td>-11</td>
<td>0.092</td>
</tr>
<tr>
<td>CV deaths</td>
<td>-5</td>
<td>-5</td>
<td>0.67</td>
</tr>
<tr>
<td>Strokes</td>
<td>-26</td>
<td>0.002</td>
<td>0.19</td>
</tr>
<tr>
<td>MI</td>
<td>-3</td>
<td>0.25</td>
<td>0.32</td>
</tr>
<tr>
<td>Total mortality</td>
<td>-14</td>
<td>0.71</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-CV deaths</td>
<td></td>
<td>-40%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Survival in treated hypertension: follow up studies after two decades


- Non-hypertensive men
- Treated hypertensive men

- Probability

- BP at start up: 185/114 mmHg
- BP at the end: 145/89 mmHg
- Follow up: 22 yrs

\[ p = 0.0001 \]
Carta Italiana del Rischio Cardiovascolare
Uomini Diabetici

Volpe M, 2004
Risk Factors for Cardiovascular Disease

Risk Factors You Can Control (Modifiable)

- High blood pressure
- High cholesterol
- Diabetes (High blood sugar)
- Overweight/obesity
- Waist-to-Hip ratio
- Cigarette smoking
- Sedentary lifestyle and poor nutrition

Risk Factors You Cannot Control (Non-Modifiable)

- Age
- Family history of CVD
- Gender

Comprehensive Risk Factor List

- **Major modifiable CV risk factors**
  - Elevated BP, systolic/diastolic
  - Elevated glucose levels (also IGT?)
  - Elevated LDL cholesterol (also low HDL)
  - Smoking

- **Other risk factors**
  - Increased triglyceride levels, Obesity or elevated BW, Dietary factors, Physical inactivity, Stress, Insulin Resistance, Increased CRP, Hyperhomocysteinemia, dysregulation of RAS
  - Left Ventricular Hypertrophy, Augmented IMT or plaques, Peripheral Artery Disease, High Pulse Pressure, Microalbuminuria,
  - Non modifiable risk factors (to be computed for absolute risk)
  - Age, Gender, Race, Family history of CVD

Volpe M, 2003
Most Hypertensive Patients Have Additional Risk Factors

Framingham Offspring (Ages 18-74 years) With Hypertension Are Likely to Have Additional Risk Factors

- **Men**
  - 3 RFs: 26%
  - 2 RFs: 25%
  - 1 RF: 19%
  - No Additional RFs: 30%

- **Women**
  - 3 RFs: 27%
  - 2 RFs: 24%
  - 1 RF: 17%
  - No Additional RFs: 32%

Adapted from Kannel. Am J Hypertens. 2000;13:3S-10S.
## Trends of CV Risk Factors in different world area

<table>
<thead>
<tr>
<th>Population over 60 years</th>
<th>2000</th>
<th>2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>high-income regions</td>
<td>19%</td>
<td>53%</td>
</tr>
<tr>
<td>middle-income regions</td>
<td>8%</td>
<td>21%</td>
</tr>
<tr>
<td>low-income regions</td>
<td>5%</td>
<td>12%</td>
</tr>
</tbody>
</table>
**Insight into Survival in treated Hypertension: follow up studies after two decades**

<table>
<thead>
<tr>
<th></th>
<th>normotensive</th>
<th>hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial BP levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmHg)</td>
<td>145/95</td>
<td>185/114</td>
</tr>
<tr>
<td><strong>Final BP levels</strong></td>
<td>-</td>
<td>145/89</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td>10.3</td>
<td>20.8</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>1.8</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>10.8</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>29.2</td>
<td>37.4</td>
</tr>
</tbody>
</table>

**Hypertension is a gateway to reduce incidence of CVD**

Derived from Andersson O. et al, BMJ 1998;317(18):167-71
Going beyond BP control? 3 options

- Option 1: more aggressive BP lowering strategy
- Option 2: specific properties of drugs
- Option 3: global CV risk control (adding statin + ASA)

Volpe M, 2006
Managing Total CVD Risk

• High-risk patients with high BP may not have their CVD risk optimally reduced by BP control alone

• 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

• Early BP control is important

Volpe M, 2005
Trends of CV Risk Factors in different world area

- RFs in high-income regions
  - Reduced Hypertension
  - Reduced Dyslipidemia
  - Reduced Smoking habits
  - Increased Obesity
  - Increased Diabetes Mellitus
  - Increased Metabolic Syndrome

- RFs in middle-income regions
  - Increased Hypertension
  - Increased Dyslipidemia
  - Increased Smoking habits
  - Increased Obesity
  - Increased Diabetes Mellitus
  - Increased Metabolic Syndrome

Volpe M, 2006

World Health Report 2000

NHANES
EUROASPIRE I
EUROASPIRE II
MONICA