Μείωση των κλασσικών παραγόντων κινδύνου για τη πρόληψη της καρδιαγγειακής νόσου. Υπάρχει καμπύλη J?

Κώστας Τσιούφης
Πρόεδρος Ελληνικής Καρδιολογικής (2017-18)
President of European Society of Hypertension (2017-19)
Δήλωση σύγκρουσης συμφερόντων

- Καμία σύγκρουση συμφερόντων για τη συγκεκριμένη ομιλία

+ Έχω λάβει υποστήριξη συμμετοχής σε συνέδρια ή ερευνητική υποστήριξη ή τιμητική αμοιβή ομιλίας από Medtronic, St. Jude Medical, Bayer, Novartis, Astra-Zeneca, Boehringer In, Pfizer, Chiesi, Pharmanel, Sanofi, Vianex, Win-Medica, Elpen, Menarini
The first ESC Atlas statistics publication

- CVD statistics from across the 56 ESC National Cardiac Societies
- Identifies healthcare inequalities and gaps in Europe
- Atlas fact:
  CVD accounts for >50% of all deaths in many middle income countries compared with <30% in the high income countries of Western Europe

Timmis A. et al, European Heart Journal (2017) 0, 1-72
Two types of risk-outcome relationships exist in CV medicine

Linear and J Relationships of Risk Factors and Mortality

34 prospective studies, pooling findings from more than 1 million individuals and almost 100,000 deaths

Some J-Curves in the Literature

Patients with CHD

What are the etiologies for the J-Curves?

Simpson’s Paradox

Simpson's paradox for continuous data: a positive trend appears for two separate groups (blue and red), a negative trend (black, dashed) appears when the data are combined.

Edward H. Simpson 1951
Outline of presentation

- The risk-outcome J-curves in Cardiology
  
  *Obesity*
  
  *Physical inactivity*
  
  *Hypertension*
  
  *High LDL levels*
Obesity and life expectancy

*Sudden death is more common in those who are naturally fat than in the lean.*

Hippocrates

Obesity in adulthood is associated

with a decrease in life expectancy of

about 7 years

“ If past obesity trends continue unchecked, the negative effects on the health of the US population will increasingly outweigh the positive effects gained from declining smoking rates”

Peeters A. Ann Intern Med 2003
Stewart ST. NEJM 2009
BMI and all-cause/CV mortality and hospitalization risk in CHF patients

- Meta-analysis of 6 studies
- N=22,807 patients with CHF
- Mean follow-up: 2.85 years

- Compared to normal BMI, risk for CV mortality and hospitalization was:
  - Highest in patients with low BMI
  - Lowest in overweight patients
  - Increasing degree of obesity failed to have a significant effect
  - Severely obese patients had a rising risk for hospitalization

Sharma A et al. Am J Cardiol 2015
Obesity paradox and the effect of fitness
Implementing the fat and fit hypothesis

- **Fitness alters the relationship between adiposity and prognosis in both CHD and HF**

- In 2066 patients with systolic HF:
  - In preserved fitness \((\text{VO}_2 > 14 \text{ml/Kg/min})\) overall prognosis was good regardless of BMI.
  - In low fitness \((\text{VO}_2 < 14 \text{ml/Kg/min})\) progressively worse survival was noted with BMI of 30.0 or greater, 25.0 to 29.9, and 18.5 to 24.9

From paradox to paradigm

- In Health
  - Primary prevention: Avoid overweight to avoid disease incidence

- In CV Disease
  - Secondary prevention: Overweight may improve survival in patients with existing CV disease

Doehner W et al. Eur Heart J 2015
Outline of presentation

- The risk-outcome J-curves in Cardiology
  - Obesity
  - Physical activity
  - Hypertension
  - High LDL levels
Physical activity: A cardioprotective “vascular conditioning”

- Physical Inactivity accounts for 12.2% of the population-attributable risk AMI and 6% of CAD cases with an estimated 0.68-year reduction in life expectancy.

- Physical activity should include at least:
  - 30 minutes of moderate-intensity PA 5 days/week,
  - 20 minutes of vigorous aerobic exercise 3 days a week or combinations,
  - in addition to 2–3 days/week of resistance and flexibility exercise.

- The Exercise in Medicine campaign calls for “prescribe” exercise at appropriate “dosages.”

- Cost-effective nonphysician health coaches, pedometers/accelerometers, mobile applications, and social media provide increasing physical activity awareness, motivation, and monitoring of exercise progress.
Extreme exercise: marathon

Acute Trop-I, BNP elevations and deterioration of RV indexes
Measurements: Before, Finish line, 24-hours later

25 marathon runners
Age: 39 years (48% males)

Table 2. Biochemical data at baseline, immediately after the marathon, and 24 h later

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Immediately Postmarathon</th>
<th>24 h Postmarathon</th>
<th>Greatest Change in Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP, pg/ml</td>
<td>15.5 ± 11.3</td>
<td>18.7 ± 15.3</td>
<td>44.8 ± 31.2</td>
<td>28.5 ± 35.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>15.4 ± 3.1</td>
<td>24.0 ± 4.8</td>
<td>17.0 ± 3.3</td>
<td>8.4 ± 5.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>0.5 ± 0.1</td>
<td>1.2 ± 0.2</td>
<td>0.8 ± 0.1</td>
<td>0.3 ± 0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum sodium, mmol/l</td>
<td>140.3 ± 3.4</td>
<td>141.3 ± 3.3</td>
<td>141.2 ± 2.2</td>
<td>0.4 ± 4.3</td>
<td>0.69</td>
</tr>
<tr>
<td>Serum potassium, mmol/l</td>
<td>4.3 ± 0.2</td>
<td>5.5 ± 0.6</td>
<td>4.3 ± 0.4</td>
<td>1.3 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood glucose, mg/dl</td>
<td>91.3 ± 11.7</td>
<td>108.3 ± 26.9</td>
<td>91.3 ± 16.7</td>
<td>17.0 ± 24.5</td>
<td>0.004</td>
</tr>
<tr>
<td>CK, UI</td>
<td>186.4 ± 132.7</td>
<td>675 ± 497.7</td>
<td>1,984 ± 2,031.0</td>
<td>1,822 ± 1,976.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CK-MB, UI</td>
<td>2.4 ± 1.6</td>
<td>10.1 ± 5.1</td>
<td>16.4 ± 98</td>
<td>13.8 ± 9.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac troponin I, ng/ml</td>
<td>0.05 ± 0.003</td>
<td>0.2 ± 0.3</td>
<td>0.1 ± 0.2</td>
<td>0.2 ± 0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Aldolase, UI</td>
<td>5.5 ± 1.7</td>
<td>15.2 ± 5.0</td>
<td>13.4 ± 7.5</td>
<td>9.3 ± 4.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 3. Cardiovascular magnetic resonance imaging data before and after marathon

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Postmarathon</th>
<th>Change in Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>57.7 ± 4.1</td>
<td>58.7 ± 4.3</td>
<td>1.0 ± 4.9</td>
<td>0.32</td>
</tr>
<tr>
<td>LVESD index, mm/m²</td>
<td>79.1 ± 13.7</td>
<td>78.8 ± 11.5</td>
<td>0.3 ± 1.7</td>
<td>0.08</td>
</tr>
<tr>
<td>LVESS index, mm/m²</td>
<td>33.5 ± 6.7</td>
<td>32.6 ± 6.0</td>
<td>0.9 ± 1.0</td>
<td>0.36</td>
</tr>
<tr>
<td>LAV volume index, mm/m²</td>
<td>48.0 ± 9.4</td>
<td>49.8 ± 9.8</td>
<td>1.8 ± 10.2</td>
<td>0.38</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>53.6 ± 7.1</td>
<td>45.5 ± 8.5</td>
<td>8.1 ± 7.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RVEDV index, mm/m²</td>
<td>101.7 ± 17.8</td>
<td>104.2 ± 19.7</td>
<td>2.5 ± 14.3</td>
<td>0.40</td>
</tr>
<tr>
<td>RVESS index, mm/m²</td>
<td>47.4 ± 11.2</td>
<td>57.0 ± 14.5</td>
<td>9.6 ± 11.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RA volume index, mm/m²</td>
<td>46.7 ± 14.4</td>
<td>57.0 ± 14.5</td>
<td>10.3 ± 11.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Potential mechanisms

Increase of wall tension
Dilation of right chambers
No ischemia/infarct

Exercise and AF

Prospective observational study of older men and women (mean age 73 years) reported that moderate intensity PA such as walking reduced the risk for AF by about one-third.

Mechanism:
1. Derangement of autonomic tone
2. Acute myo-injury (?)

Mozaffarian D et al. Circulation 2008;118:800
Can too much exercise be dangerous?

In healthy persons, while “more is not always better,”
it is not clear whether “more is actually worse.”
The Cardiac “overuse injury” hypothesis

Extreme exercise efforts (eg, marathon)
- ↑Catecholamine
- ↑O₂ Demand
- ↑↑Preload and ↑afterload
- ↑Troponin, ↑CK-MB, ↑BNP

Chronic training
- LV dilatation
- LV hypertrophy
- ↑LV mass

Immediate effects
- Right heart strain
- RA/RV dilatation
- RV hypokinesia
- Diastolic dysfunction

Long-term effects
- ↑Cardiac chamber sizes
- Patchy areas of fibrosis
- ↑Atrial arrhythmias
- ↑Ventricular arrhythmias
- ↑Incidence of SCD

Subacute effects
- Cardiac fibrosis

Outline of presentation

- The risk-outcome J-curves in Cardiology
  - Obesity
  - Physical inactivity
  - Hypertension
  - High LDL levels
Are we all Hypertensive?
And if so, why?

1. Genetics
2. Obesity
3. Immobility
4. Alcohol
5. Nutrition

What is a Normal Blood Pressure?
The Yanomani Indians

Yanomani Indios: 95/61 mmHg
2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension

Authors/Task Force Members: Bryan Williams (ESC Chairperson) (UK)*, Giuseppe Mancia (ESH Chairperson) (Italy)*, Wilko Spiering (The Netherlands), Enrico Agabiti Rosei (Italy), Michel Azizi (France), Michel Burnier (Switzerland), Denis L. Clement (Belgium), Antonio Coca (Spain), Giovanni de Simone (Italy), Anna Dominiczak (UK), Thomas Kahan (Sweden), Felix Mahfoud (Germany), Josep Redon (Spain), Luis Ruliope (Spain), Alberto Zanchetti (Italy)†, Mary Kerins (Ireland), Sverre E. Kjeldsen (Norway). Reinhold Kreutz (Germany), Stephane Laurent (France), Gregory Y.H. Lip (UK), Richard McManus (UK), Krzysztof Narkiewicz (Poland), Frank Ruschitzka (Switzerland), Roland E. Schmieder (Germany), Evgeny Shlyakhto (Russia), Costas Tsioufis (Greece), Victor Aboyans (France), and Ileana Desormais (France)
Classification of office BP and definitions of hypertension grade

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt; 120</td>
<td>and</td>
</tr>
<tr>
<td>Normal</td>
<td>120–129</td>
<td>80–84</td>
</tr>
<tr>
<td>High normal</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Grade 1 hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>≥ 180</td>
<td>≥ 110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥ 140</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>
### ACC/AHA HTN Guidelines 2017

**Categories of BP in Adults***

<table>
<thead>
<tr>
<th>BP Category</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Elevated</td>
<td>120–129 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>130–139 mm Hg</td>
<td>80–89 mm Hg</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥140 mm Hg</td>
<td>≥90 mm Hg</td>
</tr>
<tr>
<td>Age group</td>
<td>Office SBP treatment target ranges (mmHg)</td>
<td>Diastolic treatment target range (mmHg)</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>+ Diabetes</td>
</tr>
<tr>
<td>18–65 years</td>
<td>Target to 130 or lower if tolerated</td>
<td>Target to 130 or lower if tolerated</td>
</tr>
<tr>
<td></td>
<td>Not &lt; 120</td>
<td>Not &lt; 120</td>
</tr>
<tr>
<td>65–79 years</td>
<td>Target to &lt; 140 to 130</td>
<td>Target to &lt; 140 to 130</td>
</tr>
<tr>
<td></td>
<td>if tolerated</td>
<td>if tolerated</td>
</tr>
<tr>
<td>≥ 80 years</td>
<td>Target to &lt; 140 to 130</td>
<td>Target to &lt; 140 to 130</td>
</tr>
<tr>
<td></td>
<td>if tolerated</td>
<td>if tolerated</td>
</tr>
<tr>
<td>Diastolic</td>
<td>&lt; 80 to 70</td>
<td>&lt; 80 to 70</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>target range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Relationships of mortality and morbidity outcome reductions and increase in discontinuations for adverse events to the extent of SBP and DBP reductions
How old would you be if you didn’t know how old you are?

*Satchel Paige*

>80 years

The most growing and the most heterogeneous POPULATION
The direction of response of body function to any agent depends to a large degree on the initial valuable of that function

*Josef Wilder, 1931*

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**Wilder’s principle: pre-treatment value determines post-treatment response**

Franz H. Messerli¹*, Sripal Bangalore², and Roland E. Schmieder³

Incremental benefit of BP lowering decreases as target BP is lowered
Target BP / Additional considerations

Less than 50% of treated patients currently achieve a target SBP of <140 mmHg

Target BP/Further actions to improve BP control

- Improve patient-Physician relationship
- Single pill combination for most of the patients
- Interventional approach (ie RDN)?
Outline of presentation

• The risk-outcome J-curves in Cardiology

  * Obesity
  * Physical activity
  * Hypertension
  * High LDL levels
### 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients at VERY HIGH CV risk⁴, an LDL-C goal of &lt;1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.</td>
<td>I</td>
<td>B</td>
<td>61, 62, 65, 68, 69, 128</td>
</tr>
<tr>
<td>In patients at HIGH CV risk⁴, an LDL-C goal of &lt;2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.</td>
<td>I</td>
<td>B</td>
<td>65, 129</td>
</tr>
<tr>
<td>In subjects at LOW or MODERATE risk, an LDL-C goal of &lt;3.0 mmol/L (&lt;115 mg/dL) should be considered.</td>
<td>IIa</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>

- The lower, the better?
**LDL Cholesterol**

- **Placebo**
  - 59% mean reduction (95% CI 58-60), P<0.00001
  - Absolute reduction: 56 mg/dl (95% CI 55-57)

- **Evolocumab**
  - (median 30 mg/dl, IQR 19-46 mg/dl)

**Primary Endpoint**

- Hazard ratio 0.65 (95% CI, 0.79-0.92)
  - P<0.0001
  - Placebo: 14.6%
  - Evolocumab: 12.6%
**Primary Efficacy and Endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
<th>HR (95% CI)</th>
<th>Log-rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>903 (9.5)</td>
<td>1052 (11.1)</td>
<td>0.85 (0.78, 0.93)</td>
<td>0.0003</td>
</tr>
<tr>
<td>CHD death</td>
<td>205 (2.2)</td>
<td>222 (2.3)</td>
<td>0.92 (0.76, 1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>626 (6.6)</td>
<td>722 (7.6)</td>
<td>0.86 (0.77, 0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>111 (1.2)</td>
<td>152 (1.6)</td>
<td>0.73 (0.57, 0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>37 (0.4)</td>
<td>60 (0.6)</td>
<td>0.61 (0.41, 0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo

*All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo
Life time exposure to LDL matters? The younger the better?
Lower cumulative exposure LDL can slow plaque progression and delay the onset of myocardial infarction and other acute coronary syndromes.
Life time exposure to LDL matters? The younger the better?
Effect of Primary and Primordial Prevention on Progression of Atherosclerosis and Risk of Acute Cardiovascular Events
Outline of presentation

- The risk-outcome J-curves in Cardiology
  - Obesity
  - Physical activity
  - Hypertension
  - High LDL levels
- Prevention of atherosclerotic CV disease in the future
Primary prevention of atherosclerosis

Once yearly subcutaneous injection (vaccination) of Inclisiran beginning at age 30 will prevent coronary atherosclerosis
Prevention of atherosclerotic CV disease
Addressing the unmeet needs

- Inflammation matters?
- Genetic risk scores matters?
**PCSK9 Inhibition**

Profound LDL reduction, No Anti-inflammatory effects

**Canakinumab**

No LDL reduction, Profound Anti-inflammatory effects

**Primary Endpoint**

![Graph showing primary endpoint comparison between Placebo and Evolocumab.]

Sabatine et al, NEJM 2017

Ridker et al, NEJM 2017
Known Cardiovascular Disease

High Intensity Statin

Residual Cholesterol Risk
- LDL-C >100mg/dL

Residual Inflammatory Risk
- hsCRP >2mg/L

Residual Thrombotic Risk
- No simple biomarker

Residual Triglyceride Risk
- TG >200mg/dL
- HDL <40mg/dL

Residual Lp(a) Risk
- Lp(a) >50mg/dL

Biologic Issue

Critical Biomarker

Potential Intervention
- Targeted LDL / Apo B Reduction
- Targeted Inflammation Reduction
- Targeted Antithrombotic Reduction
- Targeted Triglyceride Reduction
- Targeted Lp(a) Reduction

Randomized Trial Evidence
- IMPROVE-IT
- FOURIER, SPIRE
- ODDYSEY
- CANTOS
- COMPASS
- DAPT
- Ongoing
- Planned

Ridker PM. JACC 2018 (in press)
Precision Medicine is coming and should improve care

Biomarker Driven Therapeutics – Treat the Specific Phenotype

Leopold JA, Loscalzo J. Circ Res 2018;122(9):1302-1315
“Prevention is better than cure”

Hippocrates

Everything in excess is opposed to nature

Hippocrates