Dyslipidemia: targeting the management of cardiovascular risk factors

M. Leon Sanz (ES)
Dyslipidemia: Targeting the management of cardiovascular risk factors

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Department of Medicine
Medical School
Complutense University
Madrid, Spain
Cholesterol Battle
Clinical manifestations of Dyslipidemia

- initially asymptomatic
- skin abnormalities
- pancreatitis
- clinical manifestations of atherosclerosis
Cardiovascular diseases and diabetes, death rates per 100 000 population, age standardized
Males, 2008

Death rates per 100 000 population

- ≤200
- 201–300
- 301–400
- 401–500
- >500
- Data not available
- Not applicable

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Data Source: World Health Organization
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization
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Major Clinical Manifestations of Atherothrombosis

Ischemic stroke

Myocardial infarction

Transient ischemic attack

Angina:
- Stable
- Unstable

Peripheral arterial disease:
- Intermittent claudication
- Rest Pain
- Gangrene
- Necrosis

Adapted from: Drouet L. *Cerebrovasc Dis* 2002; 13(suppl 1): 1–6.
Symptomatic Polyvascular Disease

Reduction of Atherothrombosis for Continued Health (REACH) Registry

One-Year CV Event Rates as a Function of Number of Symptomatic Disease Locations

Steg, Ph G. JAMA 2007; 297:1197–1206
Individual risk assessment and management of risk factors
Lifetime Risk Factors Exposure
## Lifetime Risk of Death from Cardiovascular Disease at 55 Years of Age

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Optimal</th>
<th>Suboptimal</th>
<th>Elevated</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>&lt; 180 mg/dl, &lt; 4.7 mmol/l</td>
<td>180-199 mg/dl, 4.7-5.2 mmol/l</td>
<td>200-239 mg/dl, 5.2-6.2 mmol/l</td>
<td>&gt; 240 mg/dl, 6.21 mmol/l</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td>&lt; 120, &lt; 80</td>
<td>120-139, 80-89</td>
<td>140-159, 90-99</td>
<td>&gt; 160, &gt; 100</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Smoking</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

17 cohort studies involving a total of 257,384 black men and women and white men and women
Lifetime Risk of Death from Cardiovascular Disease at 55 Years of Age

Men

Women

10 year risk of fatal CVD in **low** risk regions of Europe

<table>
<thead>
<tr>
<th>Region</th>
<th>Belgium</th>
<th>France</th>
<th>Greece</th>
<th>Italy</th>
<th>Luxembourg</th>
<th>Portugal</th>
<th>Switzerland</th>
<th>Spain</th>
</tr>
</thead>
</table>

### 10 year risk of fatal CVD in low risk regions of Europe

#### Women

<table>
<thead>
<tr>
<th>Non-smoker</th>
<th>180</th>
<th>160</th>
<th>140</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Age 60</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Age 55</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Age 50</td>
<td>7</td>
<td>10</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Age 40</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>

#### Men

<table>
<thead>
<tr>
<th>Non-smoker</th>
<th>180</th>
<th>160</th>
<th>140</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65</td>
<td>8</td>
<td>10</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Age 60</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Age 55</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Age 50</td>
<td>7</td>
<td>10</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Age 40</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>

### SCORE

- **15% and over**
- **10% - 14%**
- **5% - 9%**
- **3% - 4%**
- **2%**
- **1%**
- **< 1%**

### Systolic Blood Pressure (mmHg)

<table>
<thead>
<tr>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>160</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>140</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>120</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

### Cholesterol (mmol/L)

- 150
- 200
- 250
- 300
- mg/dl

<table>
<thead>
<tr>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>160</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>140</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>120</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
10 year risk of fatal CVD in high risk regions of Europe
# Online versions

Use the European (English) version for low or high risk, or access the national version in your language.

<table>
<thead>
<tr>
<th>Europe low risk (English)</th>
<th>Europe high risk (English)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium, France, Italy, Luxembourg, Switzerland and Portugal</td>
<td>Albania, Algeria, Armenia, Austria, Belarus, Bulgaria, Croatia, Czech Republic, Denmark, Egypt, Estonia, Finland, Georgia, Hungary, Iceland, Ireland, Israel, Latvia, Lebanon, Libya, Lithuania, Former Yugoslav Republic of Macedonia, Moldova, Morocco, Norway, Romania, San Marino, Serbia and Montenegro, Slovakia, Slovenia, The Netherlands, Tunisia, Turkey, Ukraine, United Kingdom</td>
</tr>
</tbody>
</table>

- Bosnia Herzegovina
- Croatia
- Cyprus *
- Czech Republic *
- Estonia
- France
- Germany *
- Greece *
- Poland *
- Romania
- Russian Federation
- Spain *
- Sweden *
- Slovakia *
- Turkey
HeartScore

Your 10-year risk of fatal cardiovascular disease is 19% : High risk

Examination Date  Age  Systolic Blood Pressure  Cholesterol  Smoker
07/08/2008  60  160 mmHg  7 mmol/L (265 mg/dl)  Yes

Modify examination data

Absolute CVD Risk

<table>
<thead>
<tr>
<th></th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>19</td>
</tr>
<tr>
<td>(2)</td>
<td>3</td>
</tr>
</tbody>
</table>

Contribution of risk factors to total risk

- Systolic Blood Pressure (32%)
- Cholesterol (31%)
- Smoker (37%)

Comments:
Please add any information relevant to your patient’s condition. They will be automatically added to the patient’s printout.
0 3 5 140 5 3 0

People who stay healthy tend to have certain characteristics:

0  No tobacco
3  Walk 3 km daily, or 30 mins any moderate activity
5  Portions of fruit and vegetables a day
140 Blood pressure less than 140 mm Hg systolic
5  Total blood cholesterol <5 mmol/l
3  LDL cholesterol <3 mmol/l
0  Avoidance of overweight and diabetes
Treatment of major risk factors (LDL, BP, DM, Smoking) has major impact on outcomes
# Classic Cardiovascular Risk Factors within the Symptomatic REACH Registry Baseline Population

## Risk Factor Prevalence, Symptomatic Population (% of symptomatic population)\(^1\)

<table>
<thead>
<tr>
<th>Region</th>
<th>Diabetes (%)</th>
<th>Hypertension (%)</th>
<th>Hypercholesterolemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>43</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>Latin America</td>
<td>38</td>
<td>77</td>
<td>59</td>
</tr>
<tr>
<td>Western Europe</td>
<td>34</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>26</td>
<td>85</td>
<td>51</td>
</tr>
<tr>
<td>Middle East</td>
<td>49</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Asia</td>
<td>41</td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>Australia</td>
<td>25</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Japan</td>
<td>39</td>
<td>71</td>
<td>45</td>
</tr>
</tbody>
</table>

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Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk

Lancet 2012; 380: 581–90
How well are we managing major risk factors in routine practice?

Levels of prevention

Primary

Reduction of risk factors before occurrence of disease, condition, or injury

Secondary

Tertiary
# EURIKA STUDY

Achievement of goals among patients treated for the main cardiovascular risk factors, by country

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AUS</th>
<th>BEL</th>
<th>FRA</th>
<th>GER</th>
<th>GRE</th>
<th>NOR</th>
<th>RUS</th>
<th>SPA</th>
<th>SWE</th>
<th>SWI</th>
<th>TUR</th>
<th>UK</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension, n</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5559</td>
</tr>
<tr>
<td>Drug treated, %</td>
<td>92.8</td>
<td>96.4</td>
<td>97.2</td>
<td>97.3</td>
<td>97.3</td>
<td>90.1</td>
<td>85.4</td>
<td>92.4</td>
<td>96.3</td>
<td>95.2</td>
<td>94.6</td>
<td>95.5</td>
<td>92.8</td>
</tr>
<tr>
<td>Controlled (SBP &lt;140 mmHg and DBP &lt;90 mmHg), %(^a)</td>
<td>35.9</td>
<td>43.7</td>
<td>45.5</td>
<td>36.3</td>
<td>47.5</td>
<td>34.6</td>
<td>35.9</td>
<td>41.0</td>
<td>33.6</td>
<td>37.4</td>
<td>32.1</td>
<td>42.8</td>
<td>38.8</td>
</tr>
<tr>
<td><strong>Dyslipidaemia, n</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>4407</td>
</tr>
<tr>
<td>Drug treated, %</td>
<td>58.7</td>
<td>75.1</td>
<td>81.2</td>
<td>65.1</td>
<td>80.2</td>
<td>75.5</td>
<td>49.8</td>
<td>81.2</td>
<td>85.9</td>
<td>74.6</td>
<td>80.3</td>
<td>82.6</td>
<td>74.4</td>
</tr>
<tr>
<td>Controlled (TC &lt;5 mmol/L), %(^a)</td>
<td>32.9</td>
<td>54.6</td>
<td>39.9</td>
<td>33.5</td>
<td>39.1</td>
<td>45.8</td>
<td>27.6</td>
<td>32.8</td>
<td>48.0</td>
<td>45.9</td>
<td>30.4</td>
<td>70.8</td>
<td>43.3</td>
</tr>
<tr>
<td>Controlled (TC &lt;5 mmol/L and LDL-c &lt;3 mmol/L), %(^a)</td>
<td>31.9</td>
<td>52.8</td>
<td>37.7</td>
<td>30.4</td>
<td>37.4</td>
<td>41.9</td>
<td>24.3</td>
<td>31.0</td>
<td>45.3</td>
<td>44.6</td>
<td>30.4</td>
<td>68.4</td>
<td>41.2</td>
</tr>
<tr>
<td><strong>Type 2 diabetes, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td>2046</td>
</tr>
<tr>
<td>Drug treated, %</td>
<td>86.3</td>
<td>90.7</td>
<td>93.7</td>
<td>80.9</td>
<td>92.0</td>
<td>82.4</td>
<td>84.2</td>
<td>87.9</td>
<td>83.5</td>
<td>89.8</td>
<td>95.2</td>
<td>77.8</td>
<td>87.2</td>
</tr>
<tr>
<td>Controlled (HbA1c &lt;6.5%), %</td>
<td>39.7</td>
<td>48.4</td>
<td>41.5</td>
<td>40.6</td>
<td>43.8</td>
<td>41.9</td>
<td>26.2</td>
<td>33.7</td>
<td>23.4</td>
<td>41.8</td>
<td>26.0</td>
<td>27.7</td>
<td>36.7</td>
</tr>
<tr>
<td>Controlled (FPG &lt;6.1 mmol/L), %</td>
<td>16.7</td>
<td>19.7</td>
<td>27.4</td>
<td>27.0</td>
<td>15.4</td>
<td>35.9</td>
<td>7.5</td>
<td>13.1</td>
<td>43.1</td>
<td>16.3</td>
<td>6.0</td>
<td>13.4</td>
<td>20.0</td>
</tr>
<tr>
<td>Controlled (HbA1c &lt;6.5% and FPG &lt;6.1 mmol/L), %</td>
<td>7.9</td>
<td>6.4</td>
<td>6.7</td>
<td>11.1</td>
<td>8.0</td>
<td>15.4</td>
<td>3.7</td>
<td>3.1</td>
<td>10.9</td>
<td>8.1</td>
<td>2.5</td>
<td>1.7</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Obesity, n</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3324</td>
</tr>
<tr>
<td>Treatment with lifestyle advice, %</td>
<td>91.7</td>
<td>91.7</td>
<td>98.2</td>
<td>94.6</td>
<td>94.5</td>
<td>86.2</td>
<td>97.7</td>
<td>97.6</td>
<td>72.3</td>
<td>88.6</td>
<td>96.2</td>
<td>94.1</td>
<td>92.2</td>
</tr>
<tr>
<td>Controlled (BMI &lt;30 kg/m(^2)), %</td>
<td>28.0</td>
<td>29.2</td>
<td>19.6</td>
<td>28.8</td>
<td>37.1</td>
<td>26.7</td>
<td>23.3</td>
<td>21.1</td>
<td>23.3</td>
<td>23.8</td>
<td>16.1</td>
<td>12.7</td>
<td>24.7</td>
</tr>
<tr>
<td>Controlled (WC &lt;102/88 cm), %</td>
<td>6.2</td>
<td>12.0</td>
<td>2.9</td>
<td>9.0</td>
<td>7.6</td>
<td>4.9</td>
<td>5.9</td>
<td>11.2</td>
<td>3.6</td>
<td>7.0</td>
<td>2.2</td>
<td>5.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Controlled (BMI &lt;30 kg/m(^2) and WC &lt;102/88 cm), %</td>
<td>3.2</td>
<td>6.0</td>
<td>2.4</td>
<td>5.3</td>
<td>4.1</td>
<td>2.7</td>
<td>0.9</td>
<td>4.1</td>
<td>2.4</td>
<td>3.8</td>
<td>0.4</td>
<td>1.4</td>
<td>3.2</td>
</tr>
</tbody>
</table>
EURIKA STUDY
Achievement of goals among high and low risk patients treated for dyslipidemia

European Heart Journal 2011;32: 2143–2152
EURIKA STUDY
Achievement of goals among high and low risk patients treated for dyslipidemia

European Heart Journal 2011; 32: 2143–2152
How well are we managing major Risk Factors in routine practice?

Levels of prevention

Primary
- Reduction of risk factors before occurrence of disease, condition, or injury

Secondary
- Early detection of the potential for development of a disease or condition, or the existence of a disease while asymptomatic

Tertiary
- Treatment of an existing symptomatic disease process to ameliorate its effects, or delay or prevent its progress
For coronary heart disease (A), drugs counted were aspirin, β blockers, ACE inhibitors or ARBs, or statins.

ACE=angiotensin-converting enzyme.
ARB=angiotensin-receptor blocker.

For stroke (B), drugs counted were aspirin, statins, ACE inhibitors or ARBs, or other blood-pressure-lowering drugs (eg, β blockers, diuretics, and calcium-channel blockers).

Lancet 2011; 378:1231–43
Reducing Residual Cardiovascular Risk

Therapies based on LDL-C lowering reduce the risks of CAD

Despite the benefits of LDL-C lowering, 60% to 80% residual risk remains
Modern Strategy for CVD Prevention

Multiple Independent Risk Factors Management (Silo Approach)

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

Reduction of Total CVD Risk

New CVD Risk Perspective

New Targets and Goals for Therapy

Integrated Guidelines for Global CV Reduction

Primary prevention
Secondary treatment

Aspirin → platelets
Statin → lipids
ACE inhibitor → blood pressure
β-Blocker → post MI

↑ Patient affordability
↑ Patient convenience
↑ Patient adherence
↑ Ease of distribution
No solution for obesity, poor nutrition, inactivity

Shotgun approach far from individualized medicine

Wrong message: magic bullet, no lifestyle changes

Aim: tackling low adherence and savings in health programs
There is life out there

There is life beyond statins!
✓ hypertension,
✓ insulin resistance
✓ procoagulable state.
Antisense oligonucleotides for the treatment of dyslipidaemia

Mipomersen

2’ Deoxy
(Supports RNase H Activity)

2’ MOE

<table>
<thead>
<tr>
<th>G</th>
<th>C</th>
<th>C</th>
<th>T</th>
<th>C</th>
<th>A</th>
<th>G</th>
<th>T</th>
<th>C</th>
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</tbody>
</table>

Phosphorothioate Backbone
Figure 3. Mean Percent Change from Baseline to Week 28.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0049006
Inhibitors of the microsomal triglyceride transport protein (MTP)
Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia
a single-arm, open-label, phase 3 study

Lancet 2013; 381:40-46
Lomipatide treatment in FHH
Transaminase levels and percentage of hepatic fat in the liver

A

B

Lancet 2013; 381:40-46
Proprotein convertase subtilisin/kexin type (PCSK9) Antibodies
Change in LDL-C Values among Healthy Volunteers in Single-Dose Studies with PCSK9 Ab (REGN727)

B Subcutaneous Administration

Mean Change from Baseline in LDL Cholesterol (%)

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>11</th>
<th>15</th>
<th>22</th>
<th>29</th>
<th>43</th>
<th>64</th>
<th>85</th>
<th>106</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>7</td>
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### Anti-PCKS9 Agents in Development

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<th>Mechanism of action</th>
<th>Class</th>
<th>Agent</th>
<th>Company</th>
<th>Phase</th>
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<tbody>
<tr>
<td>PCSK9 binding</td>
<td>Human monoclonal antibody</td>
<td>REGN727/ SAR236553</td>
<td>Regeneron/ Sanofi</td>
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<td>SX-PCSK9</td>
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<td>RNA Interference</td>
<td>ALN-PCS02</td>
<td>Alnylam</td>
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CETP Inhibitors

Torcetrapib
- Dose: 60 mg/day
- HDL-C: ↑~61%
- LDL-C: ↓~24%

Dalcetrapib
- Dose: 600 mg/day
- HDL-C: ↑~31%
- LDL-C: ↓~2%

Anacetrapib
- Dose: 100 mg/day
- HDL-C: ↑~138%
- LDL-C: ↓~40%

Evacetrapib
- Dose: 500 mg/day
- HDL-C: ↑~129%
- LDL-C: ↓~36%
Summary

• Risk assessment and risk factor management
• Identifying and managing residual risk
• Polypill: decreasing number of medications
• New molecular therapies for dyslipidemia