Joint Guidelines for the detection and treatment of dyslipidemias.

Controlled Clinical Trials and Cardiovascular Risk

Guy G. De Backer
Ghent University
Ghent, Belgium

ESC Congress – Paris- France – August 27-31 2011
G. De Backer

Declaration of possible conflict of interest regarding this presentation:
speaker fees from Astra-Zeneca advisory boards of Astra-Zeneca, MSD/SP, BMS and Merck
ESC / EAS Guidelines on the management of dyslipidaemias

Controlled Clinical Trials and Cardiovascular Risk

-Strenghts and limitations of grading systems

-Total Cardiovascular Risk as the target of all prevention strategies
Guidelines on Prevention

Research

SCORE
Evidence based reviews

Guidelines

EuroAspire

Audit

Implementation

‘94,’98,’03,’07

PIC
JPC
Nat. Co-ord
Desirable attributes of clinical guidelines

- **Validity**: predicted health benefits achieved
- **Reproducibility**: same evidence produces same guidelines
- **Reliability**: same interpretation in similar clinical circumstances
- **Clinical applicability**: useful in real life
- **Flexibility**: exceptions and patient preferences permitted
- **Clarity**: unambiguous and user-friendly
- **Meticulously documented**: what evidence was collected and how
How to evaluate scientific evidence?

• The quality of the evidence ultimately depends on the question to be answered.

• Quality implies being fit for purpose.
### Table 1: Classes of Recommendations

<table>
<thead>
<tr>
<th>Classes of Recommendations</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence/opinion is in favour of usefulness/efficacy.</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion.</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td>
</tr>
</tbody>
</table>

### Table 2: Level of Evidence

<table>
<thead>
<tr>
<th>Level of Evidence A</th>
<th>Data derived from multiple randomized clinical trials or meta-analyses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Evidence B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies.</td>
</tr>
<tr>
<td>Level of Evidence C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</td>
</tr>
</tbody>
</table>
Multiple risk factor interventions for primary prevention of coronary heart disease (Review)°

• “That this review of the evidence from randomized trials suggests that these interventions may have small effects on levels of the major risk factors but very limited, if any, on reducing mortality and morbidity.”

°Cochrane review 2006
Belgian Heart Disease Prevention Project

part of the WHO European Collaborative Trial of Multifactorial Prevention of CHD

30 industries
N = 19,409
men 40-59 yrs

Intervention
Health Promotion

Control

6 yrs incidence of CHD
BELGIAN HEART DISEASE PREVENTION PROJECT INCIDENCE RESULTS

**TOTAL MORTALITY**

- % over years 1 to 6

**NON-FATAL MYOCARDIAL INFARCTION**

- % over years 1 to 6

**CORONARY MORTALITY AND NON-FATAL MYOCARDIAL INFARCTION**

- % over years 1 to 6

* p<.05
** p<.01

- **INTRODUCTION**
- **CONTROL**
WHO European Collaborative Trial of Multifactorial Prevention of CHD

Lancet 1986,I,869 ; Lancet 1987,I, 685

The difference in risk factor changes between intervention and control groups was related to the changes in CHD incidence; for each of the coronary events groups the relation proved to be strong and significant. The conclusion was:

“that in middle-aged men the lifestyle changes that were advised were effective in terms of CHD prevention to the extent that they are accepted and put into practice.”
In an analysis that set off a fierce debate over the health effects of salt, researchers are saying they found no evidence that small cuts to salt intake reduce the risk of developing heart disease or dying prematurely.

Reuters, London, July 2011

"Cutting down on salt does not reduce your chance of dying."

Cochrane Library’s press release headline

"Now salt is safe to eat – Health fascists proved wrong after lecturing us all for years."

Daily Express
Reduced dietary salt for the prevention of cardiovascular disease (Review)

- 7 RCT’s (3 normotensives, 2 hypertensives, 1 mixed, 1 heart failure)
- 6489 participants
- End of trial SBP was reduced by an average of 1 mm hg in normotensives which would be predicted to reduce CVD mortality by 5%.
- The pooled RR was consistent with a halving of the RR of CV deaths (RR: 0.69 95% CI: 0.45-1.05)

° Cochrane review 2011
Quality of evidence

- Study limitations: non-concealment of allocation
  non-blinding of outcome assessment
  high loss to follow-up

- Inconsistent Findings
- Indirectness of evidence: A vs B derived from A vs control
  and B vs control
- Imprecision: small numbers
- Publication bias
Evidence Recommendation

- Strong evidence of effectiveness does not equal strong recommendation.
- It also depends on the balance of benefits versus harms, inconveniences, costs ...
ESC / EAS Guidelines on the management of dyslipidaemias

Controlled Clinical Trials and Cardiovascular Risk

- Strengths and limitations of grading systems

- Total Cardiovascular Risk as the target of all prevention strategies
Preventive actions should be guided in accordance to the total CV risk level. The higher the total CV risk the stronger should be the measures to be taken to change lifestyles and to a better control of modifiable and causal risk factors.
Preventive actions should be guided in accordance to the total CV risk level.

But

Not in a dichotomous way

High risk is not defined by a magic number!!
Dichotomous approach in medicine

Hypertension versus Normotension
Hypercholesterolemia versus Normal Cholesterol
Type 2 Diabetes versus No Type 2 Diabetes

High Total CV risk versus Low Total CV risk
1) Very high risk
Subjects with any of the following:
• Documented CVD by invasive or non-invasive testing, previous myocardial infarction, ACS, coronary revascularization
• Patients with type 2 diabetes, patients with type 1 diabetes with target organ damage (such as microalbuminuria).
• Patients with moderate to severe CKD (glomerular filtration rate (GFR) <60 ml/min/1.73 m²).
• A calculated 10 year risk SCORE ≥10%.

2) High risk
Subjects with any of the following:
• Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension.
• A calculated SCORE ≥5% and <10% for 10 year risk of fatal CVD.
3) Moderate risk

Subjects are considered to be at moderate risk when their SCORE is \( \geq 1\% \) and <5% at 10 years. Many middle aged subjects belong to this risk category. This risk is further modulated by a family history of premature CAD, abdominal obesity, physical activity pattern, HDL-C, TG, hsCRP, Lp(a), fibrinogen, homocysteine, apo B and social class.

4) Low risk

The low risk category applies to individuals with SCORE of <1%.
## Intervention strategies as a function of total CV risk and LDL-C level

<table>
<thead>
<tr>
<th>Total CV risk (SCORE) %</th>
<th>LDL-C levels</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;70 mg/dL</td>
<td>1.8 mmol/L</td>
<td>2.5 to 4.0 mmol/L</td>
<td>4.0 to 4.9 mmol/L</td>
<td>&gt;4.9 mmol/L</td>
</tr>
<tr>
<td>Class/Level</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
</tr>
<tr>
<td>&lt;1</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
</tr>
<tr>
<td>1 to &lt;5</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
</tr>
<tr>
<td>&gt;5 to &lt;10, or high risk</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
</tr>
<tr>
<td>≥10 or very high risk</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
<td>CR:</td>
</tr>
</tbody>
</table>
Total CV risk estimation models should be considered as tools for encouraging greater equity in the distribution of effective therapies.
The problem in the prevention of CVD is not the need to personalised treatment but the failure to act in those who have the potential to benefit.
Thank You for Your Attention