Development of statin guidelines and their clinical safety

Dr N SEWGOOLAM
Dept of Endocrinology
Numerous ongoing trials involving statins
Guidelines are continuously changing

National Cholesterol Education Program established a set of guidelines:

ADULT TREATMENT PANAL
(ATP)
Evolution of the NCEP Guidelines

- **1970s**
  - Framingham
  - MRFIT
  - LRC-CPPT
  - Coronary Drug Project
  - Helsinki Heart Study
  - CLAS (angio)

- **1988**
  - Angiographic Trials
    - (FATS, POSCH, SCOR, STARS, Ornish, MARS)
  - Meta-Analyses
    - (Holme, Rossouw)

- **1993**
  - 4S, WOSCOPS, CARE, LIPID,
  - AFCAPS/TexCAPS, VA-HIT, others

- **2001**
  - ATP I
  - ATP II
  - ATP III

- **2004**

The diagram illustrates the evolution of guidelines and their supporting studies, with each stage indicating advances in understanding and treatment of cardiovascular diseases.
### ATP III Treatment Recommendations for CHD and CHD Risk Equivalents

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3.4 mmol/L</td>
<td>Lifestyle and statin</td>
</tr>
<tr>
<td>2.6–3.3 mmol/L</td>
<td>Options: TLC alone, Fibrate, Statin</td>
</tr>
<tr>
<td>&lt; 2.6 mmol/L</td>
<td>No treatment recommended because “no evidence”</td>
</tr>
</tbody>
</table>
Rationale for ATP III’s 2001 Low LDL-C Goal <2.6mmol/L

- Epidemiology and clinical trial evidence included LDL-C levels at least as low as 2.6mmol/L (2001)
- No clinical trial evidence of benefit from achieving very low LDL-C
- Practical goal with standard statin doses
- Safety of high statin doses not documented in large clinical trials
NCEP ATP III Guidelines: Revisions Needed

- Despite NCEP ATP I, II, and III, a large treatment gap still exists.

- There is overwhelming clinical trial evidence demonstrating that patients with CHD or the equivalent benefit from statin treatment regardless of baseline LDL (including patients with LDL <2.6mmol/L).

- A simplified atherosclerosis treatment approach has been proven to dramatically improve treatment rates, long-term patient compliance, and as a result, clinical outcomes.

- The resulting improved statin treatment rates would be expected to translate into tens of thousands of lives saved each and every year.
Post–ATP III Clinical Trials

- **HPS** (simvastatin 40)
- **PROVE IT** (pravastatin 40 vs. atorvastatin 80)
- **PROSPER** (pravastatin 40)
- **ALLHAT-LLT** (pravastatin 40)
- **ASCOT-LLA** (atorvastatin 10)
Heart Protection Study: Design

- 20,536 UK adults (40–80 years)
- High-risk patients: CHD, PVD, diabetes, high BP
- Variable LDL-C at baseline
- Rx: simvastatin 40 mg vs. placebo (also vitamin arm)
- 5-yr study

Heart Protection Study: Results

- **13%** reduction in all-cause mortality
- **24%** reduction in major vascular events
- **27%** reduction in major coronary events
- **25%** reduction in stroke
- **24%** reduction in revascularization

### Heart Protection Study (HPS)

#### Risk ratio and 95% CI

<table>
<thead>
<tr>
<th>Baseline Feature</th>
<th>Statin (10,269)</th>
<th>Placebo (10,267)</th>
<th>Statin better</th>
<th>Statin worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>999</td>
<td>1250</td>
<td>ME</td>
<td></td>
</tr>
<tr>
<td>Other CHD (not MI)</td>
<td>460</td>
<td>591</td>
<td>ME</td>
<td></td>
</tr>
<tr>
<td>No prior CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>172</td>
<td>212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>327</td>
<td>420</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>276</td>
<td>367</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td>24% reduction (2P&lt;0.00001)</td>
<td></td>
</tr>
</tbody>
</table>

Patients 40–80 years old; CAD, CVD, PVD, diabetes or HTN; TC >135

The CHD Risk of HPS and ATP III

### CHD and CHD Risk Equivalent Patients

<table>
<thead>
<tr>
<th>HPS (5-yr risk)</th>
<th>ATP III CHD and Risk Equivalents (10-yr risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>Acute MI                  26–51%</td>
</tr>
<tr>
<td>LDL-C ≥3.4</td>
<td>Revascularization          25–30%</td>
</tr>
<tr>
<td>LDL-C 2.6-3.3</td>
<td>Stable angina              20%</td>
</tr>
<tr>
<td>LDL-C &lt;2.6</td>
<td>Unstable angina            20–26%</td>
</tr>
<tr>
<td></td>
<td>PAD                        20–29%*</td>
</tr>
<tr>
<td></td>
<td>CVA                        14–20%*</td>
</tr>
<tr>
<td></td>
<td>Diabetes                    15–25%*</td>
</tr>
<tr>
<td></td>
<td>10-yr estimated risk       &gt;20%</td>
</tr>
</tbody>
</table>

*CHD death only*
HPS: Reduction in Major Vascular Events According to Baseline LDL-C (mmol/L)

<table>
<thead>
<tr>
<th>LDL-C Level</th>
<th>% Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3.4</td>
<td>-22%</td>
</tr>
<tr>
<td>3.4-2.6</td>
<td>-30%</td>
</tr>
<tr>
<td>&lt;2.6</td>
<td>-22%</td>
</tr>
</tbody>
</table>
Heart Protection Study: Major Findings

- Risk reduction at all LDL-C levels
- Risk reduction at LDL-C <2.6mmol/L
- Older patients benefited
- Patients with diabetes benefited

PROVE IT

- 4162 patients post acute coronary syndrome
- Rx: pravastatin 40 mg vs. atorvastatin 80 mg
- On-Rx LDL-C level: pravastatin 2.5mmol/L, atorvastatin 1.6mmol/L
- 2-yr mean follow-up
- 16% reduction in composite CVD endpoint on atorvastatin compared with pravastatin
Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)

- 5804 subjects (70–82 yrs) at high risk
- Rx: pravastatin 40 mg vs. placebo
- 19% reduction in major coronary events
- 24% reduction in CHD mortality
- 25% reduction in TIAs (no stroke reduction)

**Conclusion:** elderly patients benefit from LDL-C–lowering therapy

ALLHAT Lipid-Lowering Trial

- 10,355 persons ≥55 years and higher risk
- Rx: pravastatin 40 mg (nonblinded) vs. usual care
- High crossover to active treatment (32% of usual-care subjects with CHD at baseline)
- No reduction in major coronary events
- African American subgroup benefited
ASCOT Lipid-Lowering Arm

- 10,305 subjects with hypertension (40–79 yrs)
- Primary prevention in higher-risk subjects
- Mean cholesterol level <6.5mmol/L
- Rx: atorvastatin 10 mg vs. placebo
- Study stopped at 3.3 yr (positive outcome)
- 29% reduction in total coronary events
- 27% reduction in stroke
Rationale for New Therapeutic Option: Very Low LDL-C Goal

<1.8 mmol/L

- HPS results
- PROVE IT results
- Not final word on very low LDL-C goals
  - TNT
  - IDEAL
  - SEARCH
Rationale for new therapeutic option: very low LDL-C goal <1.8mmol/L

- Since the ATP III guidelines were published, however, the results of HPS and PROVE IT have suggested that additional benefit is provided with further reductions in LDL-C below 2.6mmol/L.

- Therefore, a new therapeutic option—an LDL-C goal of <1.8mmol/L—has been introduced
Ongoing trials at that time (2004) were expected to provide more information on the optimal level of LDL-C for risk reduction. Now we have the results:

- Treating to New Targets (TNT),
- Incremental Decrease in Events through Aggressive Lipid Lowering (IDEAL)
- The Study of the Effectiveness of Additional Reductions of Cholesterol and Homocysteine (SEARCH)
- Collaborative atorvastatin diabetes study in pts with T2DM (CARDS)

- The Aggrastat to Zocor Trial (A-to-Z Trial)
To assess efficacy and safety of moderate and intensive statin Rx

Goal was to reduce CVS risk by reducing LDL-C (<2.6mmol/L)

10,001 pts (5006 atorvastatin 10mg / 4995 atorvastatin 80mg)

Stable coronary artery disease

LDL-C <3.4mmol/L
Results
Mean cholesterol levels were 2.6mmol/L with 10mg atorvastatin and 2.0mmol/L with the higher dose

There was no significant difference in overall mortality among the two groups
Endpoint Studies: Treating to New Targets (TNT): *Study Design*

- **Site Selection**
  - November 1997

- **Investigator Meeting**
  - March 1998

- **Recruitment Complete**
  - June 1999

- **Study End**
  - Dec 2004

- **Patients**: 10,000 CAD

- **Drug Treatment**
  - Atorvastatin
    - 10 mg: LDL 2.6mmol/L
    - 80 mg: LDL 2.0mmol

- **Duration**: 5 Years
IDEAL

- 8888 Pts (4439  80mg/d atorvastatin, 4449 20-40mg/d simvastatin)
- Aged aprox 80 yrs with history MI
- Qualified for statin Rx acc to guidelines
- High-dose atorvastatin vs usual dose simvastatin
- The primary endpoint of coronary death or non-fatal AMI occurred in 9.3% atorvastatin group and 10.4% in the simvastatin group
To evaluate the effectiveness of lipid-lowering with atorvastatin for the primary prevention of CVS events in T2DM pts

Follow up 3.9 years

2838 pts (1428 atorvastatin10mg/d, 1410 placebo)

Mean age 62 years with T2DM

Primary endpoint occurred in 5.8% on statin and 9.0% on placebo
A-TO-Z Trial

- Studied an early intensive phase vs a delayed conservative simvastatin Rx strategy in pts with AC
- 40mg/d x 1/12 ffd 80mg/d (n=2265)
- Placebo x 4/12 ffd 20mg/d (n=2232)
- 343 (16.7%) placebo grp reached endpoint
- 309 (14.4%) simvastatin grp (40/80mg)
- Trial did not reach prespecified endpoint
Candidates for Very Low LDL-C
Goal of <1.8mmol/L

- Very high risk patients
  - Established atherosclerotic CVD
    - + multiple risk factors (esp. diabetes)
    - + severe and poorly controlled risk factors (e.g., cigarette smoking)
    - + metabolic syndrome (high TG, low HDL-C)
    - + acute coronary syndromes (PROVE IT)
Implications of Recent LDL-Lowering Trials

- High-risk patients with various LDL-C levels
- Patients with diabetes
- Older patients
- Acute coronary syndromes
- Moderately high risk patients
Implications of Recent LDL-Lowering Trials

- High-risk patients with various LDL-C levels
  - LDL-C $\geq 3.4$ mmol/L: drug + diet
  - LDL-C = 2.6-3.3 mmol/L: LDL-lowering drug preferred (over other options)
  - LDL-C < 1.8 mmol/L
    - Very high risk patients: LDL-C goal < 1.8
    - Other high-risk patients: optional therapies including statins, fibrates, nicotinic acid
What’s New for High-Risk Patients?

- ATP III LDL-C goal: <2.6mmol/L
  - For very high risk: optional goal <1.8mmol/L
  - For LDL-C \( \geq 2.6 \text{mmol/L} \), start LDL-lowering drug simultaneously with lifestyle changes
  - For LDL-C <2.6mmol/L, LDL-lowering drug is a therapeutic option
  - For high TG/low HDL-C, consider fibrate or nicotinic acid in combination with LDL-lowering drug
Hospital admission or outpatient presentation

Antiplatelet
β-Blocker
ACE-I
Statin

Long-term treatment

24 hours
Days
3 months
Years

Discharge
Check lipids
When LDL-lowering drug therapy is employed in high-risk or moderately high risk patients, intensity of therapy should be sufficient to achieve a 30–40% reduction in LDL-C levels.
For people in lower-risk categories, recent clinical trials modify the treatment goals and cutpoints of therapy.

Be aware of the Clinical safety and side effects.
CLINICAL SAFETY OF STATINS

- Approved in 1987 – ability to reduce the risks of vascular death, non-fatal MI, stroke, has been shown by several large randomised trials
- Added benefit with more intensive therapy
- Trend towards using higher doses
- Statins are now recommended in pts with cvs risk even if they have normal lipid levels
THIS CHANGE IS LEADING TO INCREASED STATIN USE AT INCREASED DOSES

HENCE THE SAFETY OF THESE DRUGS IS OF CONSIDERABLE IMPORTANCE !!
Available statins

- Lovastatin (1987)
- Simvastatin (1988)
- Pravastatin (1991)
- Fluvastatin (1994)
- Atorvastatin (1997)
- Rosuvastatin (2003)
- Pitavastatin (2003)
Adverse effects

- Muscle toxicity - myopathy
  - rhabdomyolysis

- Elevation of liver enzymes

ALL statins can cause these adverse effects, but the risk varies and is increased at increased doses
- Risk varies also according to drug interactions related to metabolism via the P450 Cytochrome system

- Some pts with renal impairment, hypothyroidism, serious debility or age >80 yrs are more susceptible esp. to myopathy
In the HPS, at the end, 32.9% on simvastatin and 33.2% on placebo had reported muscle pain at least once.

From trials of pravastatin and atorvastatin: all indicated no myalgia.

In 3 large trials (n=19500) of pravastatin 40mg/d with placebo. There were no reports.

In 2 trials atorvastatin 10mg with placebo, n=13000 in pts with DM and Hpt, there were 3 cases.
To compare the safety and efficacy of 5 statins and their ability to reduce LDL-C to NCEP target levels

- 3916 pt, >18yr with hypercholesterolemia
- No significant safety issues with any of the drugs
- Atorvastatin group featured the best when it came to achieving NCEP goals
Elevation of liver enzymes

- ALT and AST involved
- With std doses no ↑ GGT, ALP, Bilirubin
- Increase in transaminases are usually seen in 1st 6 six months
- Asymptomatic and resolve on stopping Rx
- Statins are not hepatotoxic
- Hepatitis and liver failure have been reported but ? Directly related
- Alcohol: most large randomised studies omitted pts with excessive alcohol intake. **difficult to assess safety**
- Pregnancy: all statins are contraindicated
- Warfarin: statins potentiate the effects of warfarin. Close monitoring is needed
- Renal function: safe to prescribe in moderate renal failure
- Elderly: no dose adjustment required
  **increased risk of myopathy !!**
HIV & Statins

- Use of statins and ARV drugs
- Protease inhibitors have been repeatedly featured
- Shared metabolism with P 450 Cytochrome system (CYP3A4) leads to drug-drug interactions that lead to increased risk of muscle toxicity
References

- Clinical safety of statins. *lancet june 2007*
- NCEP guidelines
- A guide to acronyms for cardiovascular trials. *7th ed AstraZeneca*