CCS Dyslipidemia Guidelines Update: Emerging Evidence and 2015 Draft Recommendations Discussion

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Disclosures

- **Todd Anderson**
  - Advisory board: Merck
  - Clinical Trials: AMGEN, Merck, Pfizer
Approach to Risk Management

Who, how, when to screen

How to evaluate risk

When to initiate what treatment

Monitoring and surveillance
Target Patients for Lipid Screening

Who to screen

- Men age 40 and over
- Women age 40 over, or who are postmenopausal

Consider screening earlier in ethnic groups at increased risk (South Asian or First Nations individuals)

- All patients with any of the following conditions regardless of age:
  - Current cigarette smoking
  - Diabetes
  - Arterial hypertension
  - Family history of premature CVD
  - Family history of hyperlipidemia
  - Erectile dysfunction
  - Chronic kidney disease
  - Inflammatory disease†
  - HIV infection
  - Chronic obstructive pulmonary disease
  - Clinical evidence of atherosclerosis or abdominal aneurysm
  - Clinical manifestation of hyperlipidemia
  - Obesity (body mass index >27)
  - Pregnancy induced hypertension or gestational diabetes
Changes in Postprandial Lipids in Normal Populations

- Langsted A et al., *Circulation* 2008. Fasting and nonfasting lipid levels influence of normal food intake on lipoids, lipoproteins, apolipoproteins and cardiovascular risk prediction
  - Cross-sectional study of fasting versus nonfasting lipid levels in Copenhagen General Population Study and Copenhagen City Heart Study

- Siddhu D and Naugler C. *Arch Int Med* 2012. Fasting time and lipid levels in a community-based population
  - Cross-sectional study of 209180 individuals tested from 1 to 16 hours postprandially

In both studies, NonHDL-C, and apoB varied little between fasting and nonfasting TG levels increased up to 20% (0.3-0.4 mM) and LDL-C was lower by up to 10% (0.2-0.3 mM)
Recommendations and Implications

1. We recommend nonfasting testing can be performed for initial screening and follow up testing of lipid and lipoprotein levels (strong recommendation/high level evidence).

2. We recommend that for individuals with a history of triglyceride levels > 4.5 mM that lipid and lipoprotein levels be measured fasting (weak recommendation/low level evidence).

Implications

• Random nonfasting lipid measurements become the standard for lipid testing. Does not change FRS utility.

• Where nonfasting TG are > 1.5 mM, use NonHDL-C (< 2.6 mM) or apoB (< 0.8 g/L) as primary target (unchanged from 2012 Guidelines)
Approach to Risk Management

Who, how when to screen

How to evaluate risk
Recommendations

• We recommend that a cardiovascular risk assessment be completed every 5 years for men and women age 40 to 75 and the results shared with the patient.

• Options include using the 10 Year Risk provided by the Framingham Model or Cardiovascular Age using the Cardiovascular Life Expectancy Model.

• A risk assessment may also be completed whenever a patient’s expected risk status changes.

• The results should be shared with the patient to support shared decision making and improve the likelihood that they will reach lipid targets.

(Strong Recommendation, High-Quality Evidence)
Approach to Risk Management

- Who, how when to screen
- How to evaluate risk
- When to initiate what treatment
Strong Recommendation, High-Quality Evidence
Treatment based on risk (2)

Intermediate risk patients
Adjusted FRS $\geq 10\% < 20$

- LDL-C $< 3.5$ mmol/L
  - ApoB $< 1.2$ g/L or N-HDL-C $< 4.3$ mmol/L
    - Conditional Recommendation, Moderate-Quality Evidence
  - Optional secondary testing
    - Conditional Recommendation, Moderate-Quality Evidence

- LDL-C $\geq 3.5$ mmol/L
  - ApoB $\geq 1.2$ g/L or N-HDL-C $\geq 4.3$ mmol/L
    - Strong Recommendation, Moderate-Quality Evidence
  - Health behaviour modifications
  - Clinical judgement
    - Patient education/discussion
  - Statin therapy
    - Strong Recommendation, Moderate-Quality Evidence

Conditional Recommendation, Moderate-Quality Evidence

Strong Recommendation, Moderate-Quality Evidence
Treatment based on risk (3)

- **Low risk patients**
  - Adjusted FRS < 10%

  - **LDL-C < 5.0 mmol/L**
    - Health behaviour modifications
    - Adjusted FRS 5-9%
      - Clinical judgement
        - Patient education/discussion
      - Optional secondary testing
  - **LDL-C ≥ 5.0 mmol/L**
    - Statin therapy
      - Clinical judgement
        - Patient education/discussion

*Strong Recommendation, Moderate-Quality Evidence*
Approach to Risk Management

- Who, how when to screen
- How to evaluate risk
- When to initiate what treatment
- Monitoring and surveillance
On-Statin LDL-C Levels and Risk for Major Cardiovascular Events

Meta-analysis of 8 statin trials (n=38,153)

• >40% did not reach LDL-C target (<1.8 mmol/L) on high dose statin

CHD Reduction from Earlier LDL-C Lowering: Lifetime low LDL

Lifetime lower LDL-C due to genetics resulted in a **3-fold greater reduction in the risk of CHD** per unit lower LDL-C than that observed during treatment with a statin started later in life.

### Meta-Analysis

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Sample Size (N)</th>
<th>OR (95% CI)</th>
<th>CHD RR Per mmol/L LDL reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Studies</td>
<td>312,321</td>
<td>0.46 (0.41-0.51)</td>
<td>54.5%</td>
</tr>
<tr>
<td>Statin Trials</td>
<td>169,138</td>
<td>0.76(0.74-0.78)</td>
<td>24%</td>
</tr>
</tbody>
</table>

Patients stabilized post ACS ≤ 10 days:
LDL-C 1.3 – 3.2 mmol/L (or 1.3 – 2.6 mmol/L if prior lipid-lowering Rx)

N=18,144

Standard Medical & Interventional Therapy

*uptitrated to 80 mg if LDL-C >2.0 mmol/L

Simvastatin 40 mg*

Ezetimibe / Simvastatin 10 / 40 mg*

Duration: Minimum 2 ½-year follow-up (5314 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
LDL-C and Lipid Changes

Median time avg
69.5 vs. 53.7 mg/dL

1.8 vs. 1.4 mmol/L

Number at risk:
EZ/Simva 8990 8889 8230 7701 7264 6864 6583 6256 5734 5354 4508 3484 2608 1078
Simva 9009 8921 8306 7843 7289 6939 6607 6192 5684 5267 4395 3387 2569 1068
Primary Endpoint — ITT (2014)

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)  
p=0.016

Simva — 34.7%  
2742 events

EZ/Simva — 32.7%  
2572 events

NNT= 50

7-year event rates
Outcomes based on Jupiter study
Similar relationships for non-HDL-C and apo B
Ridker et al. EHJ 2016; doi 10-1093
Proposed Recommendations

• We suggest a target LDL-C consistently < 2.0 mmol/L or >50% reduction of LDL-C for individuals in whom treatment is initiated
  – Conditional Recommendation, Moderate-Quality Evidence

• We suggest that apo B < 0.80 g/L or non-HDL-C <2.6 mmol/L be considered as alternative treatment targets for optimal risk reduction
  – Conditional Recommendation, Moderate-Quality Evidence

(unchanged from CCS 2012)
Proposed Recommendations

• To achieve these targets, we recommend the use of maximally tolerated statin therapy
  – Strong Recommendation, High-Quality Evidence
# Summary of treatment target guidelines

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Initiate therapy if</th>
<th>Primary Target LDL-C</th>
<th>Alternate Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Consider treatment in all (Strong, High)</td>
<td>≤ 2 mmol/L or 50% decrease in LDL-C</td>
<td>Apo B ≤ 0.8 g/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non HDL-C ≤ 2.6 mmol/L (Strong, Moderate)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>LDL-C ≥ 3.5 mmol/L (Strong, Moderate)</td>
<td>≤ 2 mmol/L or 50% decrease in LDL-C</td>
<td>Apo B ≤ 0.8 mg/L Non-HDL-C ≤ 2.6 mmol/L</td>
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<tr>
<td></td>
<td>Consider if Apo B ≥ 1.2 g/L or Non-HDL-C ≥ 4.3 mmol/L (Conditional, Moderate)</td>
<td></td>
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<tr>
<td>Low *</td>
<td>LDL-C ≥ 5.0 mmol/L (Strong, Moderate) Familial hypercholesterolemia (Strong, Moderate)</td>
<td>50% reduction in LDL-C</td>
<td></td>
</tr>
</tbody>
</table>

* for those in the 5-9% group, consider yearly calculation of FRS and discussion about risk-benefit ratio of pharmacotherapy at lower levels of LDL-C
Diet recommendations

7447 subjects primary Prevention
Cardiac diet vs Med diet with olive oil or Med diet with nuts
288 events

Estruch et al. NEJM 2013;268:1279
Changes since 2012

• Use of non-fasting lipid determinations
• Expansion of CKD definition for high risk and harmonization with K-DIGO guidelines
• More explicit recommendations for health behaviour changes
• Greater discussion about discussion with patients about their preferences
• Recommendations about non-statin drug use