You Can IMPROVE-IT: Focus on Statin Therapy

Problems and Solutions

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May 2, 2015
Disclosure of Conflicts

I have received travel grants and honoraria from sanofi-aventis, Pfizer, Servier, Merck, Procter & Gamble, Biovail, AstraZeneca, Medtronic, Novartis, Boehringer-Ingelheim and Merck/Frosst/Schering.

I have been the Primary Investigator of studies sponsored by Pfizer, Boehringer-Ingelheim, sanofi-aventis, and currently, BMS.
Objectives

- To convince you that you should focus on maximizing statin doses not LDL-levels
- To discuss why the results of the IMPROVE-IT trial are exciting
- To discuss best available evidence about the statin side effects
- How to deal with “statin intolerance”
- Choosing Wisely Canada recommendations
What Was The Problem With The Recommendation of An LDL Target?

- On the one hand it encouraged combination therapy in patients who did not achieve an LDL<2 on max. doses of potent statins – a practice that has not been shown to improve outcomes c/w statins alone (niacin, fibrates). Ezetrol is now the only exception.

- On the other hand an LDL target of 2 encouraged the use of lower doses of statins in patients with low baseline lipids who could achieve that target with lower doses. They would still benefit more from higher statin doses/lower LDL levels.
Paradigm Shift in the 2013 Guidelines

- Focus on statin doses – eliminated lipid (LDL) targets altogether
- Identified 4 groups that benefit from statins
- Acknowledged that non-statins are unproven
- In primary prevention recommends statin therapy for >7.5% risk based on 2 meta-analysis
- Exemptions are CHF and dialysis, and no evidence for primary prev. >75 years of age
Four Groups That Benefit From Statins

- 1. Individuals with clinical ASCVD
- 2. Individuals with primary elevations of LDL–C $\geq 190$ mg/dL (5 mM/l)
- 3. Individuals 40 - 75 years of age with diabetes with LDL-C 70-189 mg/dL (1.8-5 mM/l)
- 4. Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher
What Is The Problem With These Guidelines?

- To treat essentially everyone with an LDL>1.8 is… hmm problematic… people focus on costs not benefits.
- There is clear resistance/fear in the public and in the medical community from using high doses of statins – there will be a lot of negotiations in the implementation.
- The “Pooled Cohort Equations” risk assessment is new and less well validated than FRS – just stick to the one you’ve been doing so far – doesn’t matter which risk assessment you’re using.
Evidence Gaps – The “Known Unknowns”

■ 1. Outcomes of RCTs to evaluate statins for the primary prevention of ASCVD in adults >75 yo.

■ 2. Outcomes of RCTs to evaluate alternate treatment strategies for ASCVD risk reduction. These RCTs may compare titration to specific cholesterol or apolipoprotein goals versus fixed-dose statin therapy in high-risk patients.

■ 3. RCTs to determine what to do to reduce risk in statin-intolerant patients – PCSK9-I studies!
Evidence Gaps -2

4. Evaluation of the incidence, pathophysiology, clinical course, and clinical outcomes of new-onset diabetes associated with statin therapy.

5. Outcomes of RCTs of new lipid-modifying agents to determine the incremental event reduction benefits when added to statin therapy.

The first such study published after the Gdlines were published was IMPROVE-IT.
IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome
**IMPROVE-IT:** First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):

- Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?

- “Is (Even) Lower (Even) Better?”
  
  (estimated mean LDL-C ~1.3 vs. 1.7 mmol/L)

- Safety of ezetimibe

*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

#### 1 Yr Mean

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>1.81</td>
<td>3.75</td>
<td>1.55</td>
<td>1.24</td>
<td>3.8 mg/dl</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>1.38</td>
<td>3.25</td>
<td>1.36</td>
<td>1.26</td>
<td>3.3 mg/dl</td>
</tr>
</tbody>
</table>

Δ in mmol/L: -0.43, -0.50, -0.19, +0.2, -0.5 mg/dl

**Median Time avg**

1.8 vs. 1.4 mmol/L
Primary Endpoint — ITT

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

- Simva — 34.7%
  - 2742 events
  - HR 0.936 CI (0.887, 0.988)
  - p=0.016
  - 2% absolute, 6% relative benefit

- EZ/Simva — 32.7%
  - 2572 events
  - NNT= 50

7-year event rates
Simva* EZ/Simva* p-value

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Simva (%)</th>
<th>EZ/Simva (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary CVD/MI/UA/Cor Revasc/CVA</td>
<td>34.7</td>
<td>32.7</td>
<td>0.016</td>
</tr>
<tr>
<td>Secondary #1 All D/MI/UA/Cor Revasc/CVA</td>
<td>40.3</td>
<td>38.7</td>
<td>0.034</td>
</tr>
<tr>
<td>Secondary #2 CHD/MI/Urgent Cor Revasc</td>
<td>18.9</td>
<td>17.5</td>
<td>0.016</td>
</tr>
<tr>
<td>Secondary #3 CVD/MI/UA/All Revasc/CVA</td>
<td>36.2</td>
<td>34.5</td>
<td>0.035</td>
</tr>
</tbody>
</table>

UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)
CV Death, Non-fatal MI, or Non-fatal Stroke

- Simva — 22.2%
- EZ/Simva — 20.4%

HR 0.90 CI (0.84, 0.97)
p = 0.003
NNT = 56

7-year event rates

Event Rate (%) vs. Time since randomization (years)

Simva — 22.2%
1704 events

EZ/Simva — 20.4%
1544 events

7-year event rates
No statistically significant differences in cancer or muscle- or gallbladder-related events

<table>
<thead>
<tr>
<th>Event</th>
<th>Simva n=9077</th>
<th>EZ/Simva n=9067</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT and/or AST ≥3x ULN</td>
<td>2.3%</td>
<td>2.5%</td>
<td>0.43</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1.5%</td>
<td>1.5%</td>
<td>0.96</td>
</tr>
<tr>
<td>Gallbladder-related AEs</td>
<td>3.5%</td>
<td>3.1%</td>
<td>0.10</td>
</tr>
<tr>
<td>Rhabdomyolysis*</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.37</td>
</tr>
<tr>
<td>Myopathy*</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.32</td>
</tr>
<tr>
<td>Rhabdo, myopathy, myalgia with CK elevation*</td>
<td>0.6%</td>
<td>0.6%</td>
<td>0.64</td>
</tr>
<tr>
<td>Cancer* (7-yr KM %)</td>
<td>10.2%</td>
<td>10.2%</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* Adjudicated by Clinical Events Committee  % = n/N for the trial duration
Conclusions

IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- **YES:** Non-statin lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better (achieved mean LDL-C 1.37 vs. 1.81 mmol/L at 1 year)
- **YES:** Confirms ezetimibe safety profile

- **Reaffirms the LDL hypothesis,** that reducing LDL-C prevents cardiovascular events
- Results could be considered for future guidelines
Best Available Evidence About Statin Side-Effects

Myopathy

- Rhabdo is dose-dependent, incidence 0.04-0.2%; mortality 0.15/million prescriptions
- Less severe myopathy is 0.1-1%
- Mech: statins may provoke cellular oxidative stress leading to impairments in mitochondrial function and Ca homeostasis and myotoxicity
- Decreased skeletal muscle Co-Q content has been found as well c/w placebo treated pts
Myopathy - 2

- Muscle cramping is rather neurogenic but there was a 16% increased risk in statin-treated pts.
- The fact that many pts tolerate some statins and not others, suggests multiple mechanisms.
- Grading system of myopathy: myalgia, myositis, rhabdo and hyperCKemia (mild 1: <5x, 2: 5-10x, mod: 10-50x, severe >50x ULN)
CNS

- Cognitive dysfunction, memory loss, confusion have been suggested, FDA warning was issued but this has been reversible and inconsistently seen in studies – insufficient evidence of causality, even in pts w/ Alzheimer’s.
- Fatigue, headache, dizziness – may be more frequent with simva vs. prava, no data on others.
- Psychiatric complications – no increased risk in a study of 46,000 pts.
- ICH – meta of 180,000 pts did not show a higher risk; significantly lower isch. stroke + mortality!
Ophthalmological - Cataracts

- Several studies suggested a higher risk of cataracts in statin users; a case-control study of 48,000 pts reported that more pts were on statins among those w/ cataract surgery than those w/o cataract or cataract surgery.

- However, after adjusting for risk factors and CAD, statins were found to be protective of cataracts, and shorter (<5 yrs) use was a/w ↑ risk of cataract sx.

- A recent propensity-matched analysis found an ↑ risk in those w/o comorbidities leading to cataracts.
Liver Enzymes

- The mechanism is not well understood and in practice, fatty liver may complicate the assoc’n
- Incidence: 1.2/100,000 pts taking statins, dose-related, see TNT 0.2% vs. 1.2%/yr/10,000 pts
- The majority are reversible, but reproducible pattern on re-challenge; jaundice/hepatitis: 1/17,434 users
- A few isolated cases of death have been reported
- Routine screening for liver enzyme elevations is no longer recommended
- Compensated liver dx is not a contraindication
Renal Function

- Controversial topic
- Several major studies (incl. Tonelli et al.) showed no harm, even CV and renal benefit in pre-dialysis
- However, a retrospective analysis of 2 million pts found a 34% ↑ risk of AKI within 120 days after starting high-potency statin therapy
- Microalbuminuria d/t statins is well known but not believed to be indicative of renal dysfunction
Statin-Induced Diabetes

- Increased incidence of DM has been a/w niacin, β-blockers, thiazides, protease inhibitors, glucocorticoids, and now, statins
- In JUPITER pts with >1 RF for DM (metabolic sy, ↑BMI, ↑FBG, ↑HbA1c) had an 28% ↑ incidence (~2% or 31-34/1000 person-years)
- Pts w/o any of these RFs were not at ↑risk
- The benefits of statins clearly outweigh the risks
- Several other studies did not find an ↑ risk or even found that statins provided protection from DM
Cancer

- This has come up often and has always been refuted by large studies.
- Potential protective effects have been observed in melanoma, non-Hodgkin’s lymphoma, endometrial cancer, glioma, and hepatocellular cancer in patients with Hep C.
- In breast cancer, there are studies showing both potential benefit and potential harm.
- Most if not all of this is likely just noise.
Diagnosis And Laboratory Monitoring of Statin Intolerance

- Difficult unless it is a/w CK rise
- Re-challenge w/ same or different statin or lower dose is best strategy – often works
- Routine monitoring has not been encouraged recently, not cost-effective – do it for (your) reassurance only or if the patient is worried
- However, symptom-driven monitoring is useful
- A lot of this is mental, a discussion about the R/B ratio may be helpful
“Therapy” of Statin Intolerance

- Very low dose rosuvastatin i.e. 2.5mg twice a week or every other day is a good option
- Gradually increase the dose as tolerated and stop at the highest tolerated dose, just don’t give UP!!
- 60-80% of pts develop intolerance to >1 statin but many cases might be specific to one statin
- Small studies of Vit D, and CoQ10 have been inconclusive
- New lipid lowering drugs are being tested
Conclusions

- The highest dose of potent statins are the most beneficial hence it makes sense to abandon targets (check lipids to prove progress to the pts)
- The relative benefits of statin therapy are very similar in both primary and secondary prevention but the absolute benefits are different – d/w pt!
- Assess, and treat overall risk not LDL-levels only
- Remember, in PP – after smoking cessation and lifestyle - only statins provide further benefit, (ASA’s pluses and minuses are similar) so statins or no statins – that is the question!
Conclusions 2

- Statins are very safe, true side-effects are rare, most studies show a lot of noise.

- However, you have to allow for the possibility of your patient experiencing real SEs – stop, think about the importance of the statin for the pt and re-challenge if all are agreeable; four-fold risk of re-MI in 2 years if statins stopped.

- Non-statin medications do not have proven outcome benefits except for EZE for now.
Choosing Wisely Canada (CWC) and the Canadian Cardiovascular Society

Shortened and modified from the Grand Rounds presentation of Blair O’Neill, MD, FRCPC, FACC
CCS Immediate Past President
Senior Medical Director,
Cardiovascular Health and Stroke Strategic Clinical Network,
Alberta Health Services
Choosing Wisely Canada (CWC)

A campaign to help physicians and patients engage in conversations about the *overuse, waste and harm* associated with unnecessary tests and procedures

Support physician efforts to help patients make smart and effective care choices
Expected Outcomes

1. Ongoing “appropriateness” strategy related to overuse and waste
2. Physician engagement and leadership in use of finite resources
3. Public awareness of why “more is not better”
4. Decreased test, procedure and treatment use, where not needed
CCS 5 Don’ts - #1

1. Don’t perform stress cardiac imaging or advanced non-invasive imaging in the initial evaluation of patients without cardiac symptoms unless high-risk markers are present.

Asymptomatic, low-risk patients account for up to 45% of unnecessary “screening.” Testing should be performed only when the following findings are present: diabetes in patients older than 40-years-old; peripheral arterial disease; or greater than 2 percent yearly risk for coronary heart disease events.

Number of papers reviewed: 140
2. Don’t perform annual stress cardiac imaging or advanced non-invasive imaging as part of routine follow-up in asymptomatic patients.

Performing stress cardiac imaging or advanced non-invasive imaging in patients without symptoms on a serial or scheduled pattern (e.g., every one to two years or at a heart procedure anniversary) rarely results in any meaningful change in patient management. This practice may, in fact, lead to unnecessary invasive procedures and excess radiation exposure without any proven impact on patients’ outcomes. An exception to this rule would be for patients more than five years after a bypass operation.

Number of papers reviewed: 18
CCS 5 Don’ts - #3

3. Don’t perform stress cardiac imaging or advanced non-invasive imaging as a pre-operative assessment in patients scheduled to undergo low-risk non-cardiac surgery.

Non-invasive testing is not useful for patients undergoing low-risk non-cardiac surgery (e.g., cataract removal). These types of tests do not change the patient’s clinical management or outcomes and will result in increased costs.

Number of papers reviewed: 11
4. *Don’t perform echocardiography as routine follow-up for mild, asymptomatic native valve disease in adult patients with no change in signs or symptoms.*

Patients with native valve disease usually have years without symptoms before the onset of deterioration. An echocardiogram is not recommended yearly unless there is a change in clinical status.

Number of papers reviewed: 1,099
CCS 5 Don’ts - #5

5. Don’t order annual electrocardiograms (ECGs) or any other cardiac screening for low-risk patients without symptoms.

Don’t obtain screening ECG testing in individuals who are asymptomatic and at low risk for coronary heart disease. In asymptomatic individuals at low risk for coronary heart disease (10-year risk <10%) screening for coronary heart disease with electrocardiography does not improve patient outcomes.

Number of papers reviewed: 967
Conclusions – Choosing Wisely Canada

• Physicians need to be prudent stewards of our health care resources
• All of us have a role to play in ensuring appropriateness and the highest value for resources spent in our health care system
• If we are not part of the solution, we will become the solution to this problem
Questions?

Thank you!