Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

Emerging Challenges in Primary Care: Update 2013

Faculty

• Jan Basile, MD
  Professor of Medicine
  Seinsheimer Cardiovascular Health Program
  Division of General Internal Medicine
  Medical University of South Carolina
  Ralph H. Johnson VA Medical Center
  Charleston, SC

• Peter P. Toth, MD, PhD, FAAFP, FICA, FAHA, FNLA, FCCP, FACC
  Director of Preventive Cardiology
  CGH Medical Center
  Professor of Clinical Family and Community Medicine
  University of Illinois School of Medicine
  Professor of Clinical Medicine
  Michigan State University
  Sterling, IL
Faculty Disclosure

- Jan Basile, MD
  - Speaker – Boehringer Ingelheim, Daiichi Sankyo, Forest Labs, Takeda
  - Consultant - Forest Labs, Takeda

- Peter P. Toth, MD, PhD, FAAFP, FICA, FAHA, FNLA, FCCP, FACC
  - Speaker’s Bureau – Abbvie, AstraZeneca, Amarin, Genzyme, Kowa, Merck
  - Consultant - Amgen, AstraZeneca, Atherotech, Diadexus, Kowa, Liposcience, Merck

Learning Objectives

1. Describe The Importance Of Reducing LDL-C As The Primary Target Of Lipid-lowering Therapy
2. Discuss The Role Of Specific Statin Strategies Used In Clinical Trials To Reduce LDL-C
3. Recognize The Role Of Residual Risk and non-HDL-C as A Secondary Target Of Therapy
4. Define The Role Of New Agents That Potentiate The Role Of Statin-based Therapy For Difficult-to-treat Patients
Pre-Test Question 1

On a scale of 1 to 5, please rate how confident you are in treating the dyslipidemic patient.

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident

Pre-Test Question 2

Clinical Studies suggest that our ability to reduce cardiac events when using statin-based therapy correlates best with:

1. The duration of time they have been used
2. The amount of Ldl-C reduction achieved
3. Both of the above
4. Neither of the above
Which of the following are the 2 best tests to target in reducing cardiovascular disease in those with dyslipidemia?

1. HDL-C and Triglycerides
2. Total Cholesterol and LDL-Particle #
3. Total Cholesterol and Apolipoprotein B
4. LDL-C and Apolipoprotein B
5. LDL-C and non-HDL-C

The major reason that statin-based clinical trials achieving effective LDL-C reduction have not shown additional benefit from adding niacin or fibrates is:

1. These drugs are not effective as monotherapy so why think they would work on top of statin therapy
2. They were studied in the wrong patient populations
3. These drugs have been shown to have an off-target effect that negates the effects of statins.
4. These drugs have been found to be effective when added to statin-based therapy for outcome improvement and the premise of the question is wrong.
Which of the following is not true about heterozygote familial hypercholesterolemia?

1. It occurs in 1 in 500 of the population
2. Patients have the normal number of LDL receptors
3. There is a 2-fold increase in plasma LDL-C
4. Heart attacks begin at age 35

Lipid Therapy Made Simple

• LDL-C
  - Statins
  - Resins
  - Ezetimibe
  - Sterols/Stanols

• TG/HDL
  - Fibrates
  - Niacin
  - Fish Oil
### NCEP ATP III Treatment Recommendations

<table>
<thead>
<tr>
<th>TLC</th>
<th>Integral part of CHD risk management</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>Primary target of lipid-modifying therapy</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>A secondary target of therapy in patients with hypertriglyceridemia (≥200 mg/dL)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>No treatment goals are identified for HDL-C</td>
</tr>
<tr>
<td></td>
<td>- Low HDL-C (&lt;40 mg/dL) as a positive CHD risk factor</td>
</tr>
<tr>
<td></td>
<td>- High HDL-C (≥60 mg/dL) as a negative CHD risk factor</td>
</tr>
<tr>
<td></td>
<td>However, TLC and pharmacologic therapies that raise HDL-C are encouraged</td>
</tr>
<tr>
<td>TG</td>
<td>No treatment goals are identified for TG</td>
</tr>
<tr>
<td></td>
<td>- Borderline high TG (150–199 mg/dL), emphasize TLC</td>
</tr>
<tr>
<td></td>
<td>- High TG (200–499 mg/dL), address non–HDL-C</td>
</tr>
</tbody>
</table>

*Except in cases of very high TG (≥500 mg/dL), in which reduction of TG to <500 mg/dL takes priority.

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; TLC = therapeutic lifestyle change; TG = triglycerides.


### LDL-C Remains the Primary Target of Therapy

- Multiple lines of evidence (animal studies, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia, and controlled trials) indicate a strong causal relationship between elevated LDL-C and CHD.¹

- All major US guidelines, including the NCEP, AHA/ACC, and ADA, list LDL-C as the primary modifiable lipid risk factor.¹–⁴

NCEP = National Cholesterol Education Program; AHA = American Heart Association; ACC = American College of Cardiology; ADA = American Diabetes Association.

1. NCEP ATP III. Circulation. 2002;106:3143-3421;
### Risk Reduction in Heart Disease Events with Statins is a Function of Time and LDL-C Reduction

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>LDL-C reduction (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 - 27</td>
</tr>
<tr>
<td></td>
<td>30 - 54</td>
</tr>
<tr>
<td></td>
<td>≥ 54</td>
</tr>
<tr>
<td>1–2 years</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>33</td>
</tr>
<tr>
<td>3–5 years</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>50</td>
</tr>
<tr>
<td>6+ years</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>52</td>
</tr>
</tbody>
</table>

*Meta-analysis of 49 randomized statin clinical trials

Percent reduction in major coronary events

Adapted from Law MR et al. BMJ 2003;326:1423

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### Statin Evidence: Landmark Statin Trials

The Greater the Risk The Greater the Benefit

**LDL-C, mmol/L (mg/dL)**

<table>
<thead>
<tr>
<th>Study</th>
<th>LDL-C (mg/dL)</th>
<th>% with CHD event</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFCAPS-P</td>
<td>4.9 (190)</td>
<td>15</td>
</tr>
<tr>
<td>4S-P</td>
<td>5.4 (210)</td>
<td>20</td>
</tr>
<tr>
<td>WOSCOPS-P</td>
<td>4.4 (170)</td>
<td>10</td>
</tr>
<tr>
<td>WOSCOPS-S</td>
<td>3.9 (150)</td>
<td>5</td>
</tr>
<tr>
<td>CARE-P</td>
<td>3.1 (130)</td>
<td>2</td>
</tr>
<tr>
<td>LIPID-P</td>
<td>2.8 (110)</td>
<td>5</td>
</tr>
<tr>
<td>ASCOT-P*</td>
<td>3.4 (140)</td>
<td>10</td>
</tr>
<tr>
<td>ASCOT-S*</td>
<td>2.3 (90)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Extrapolated to 5 years

Adapted from Kastelein JP. Atherosclerosis. 1999;143(suppl 1):S17-S21.
**LDL-C Goals for High-Risk Patients Have Become More Intensive Over Time**

- As part of therapeutic lifestyle changes, including diet, LDL-C treatment goals for high-risk patients have been lowered over time.

<table>
<thead>
<tr>
<th>Year</th>
<th>ATP I</th>
<th>ATP II</th>
<th>ATP III</th>
<th>2004 Update</th>
<th>2006</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>Goal: &lt;130 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
</tr>
<tr>
<td>1993</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
</tr>
<tr>
<td>2001</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
</tr>
<tr>
<td>2004</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
</tr>
<tr>
<td>2006</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
</tr>
<tr>
<td>2010</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
<td>Goal: &lt;100 mg/dL</td>
</tr>
</tbody>
</table>

**Definition of high-risk or highest-risk patient:**

- ATP I: definite CHD or 2 other CHD risk factors
- ATP II: prior CHD or other atherosclerotic disease
- ATP III and the 2004 update: CHD or CHD risk equivalents
- 2º AHA/ACC 2006: established coronary and other atherosclerotic disease
- ADA 2010: overt CVD

Factors that place a patient at very high risk are multiple components of the metabolic syndrome, established CVD, plus any of the following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (e.g., cigarette smoking), multiple components of the metabolic syndrome (especially TG ≥200 mg/dL + non-HDL-C ≥130 mg/dL, with HDL-C <40 mg/dL), and recent acute coronary syndromes.

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**RECENT INSIGHTS FROM CHOLESTEROL TREATMENT TRIALISTS COLLABORATION**
Relation Between Proportional Reduction in Incidence of Major CVD Events & Mean Absolute LDL-C
Reduction at Year 1*

*Meta-analysis of 14 statin trials (CTT collaborators)


Meta-analysis : For Every 40 mg/dl LDL-C reduction, 22% Reduction in CV Events
statin vs no statin: more vs less statin


N= 170,000
Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

CTTT 2010 Meta-analysis: No Evidence of Threshold-ALL BENEFIT Regardless of Baseline LDL-C

<table>
<thead>
<tr>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td>More vs less statin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>704 (4.0%)</td>
<td>0.91 (0.67-1.24)</td>
</tr>
<tr>
<td>2 to &lt;2.5 mmol/L</td>
<td>1374 (14.8%)</td>
<td>0.72 (0.64-0.81)</td>
</tr>
<tr>
<td>2.5 to &lt;3 mmol/L</td>
<td>1249 (15.0%)</td>
<td>0.81 (0.67-0.99)</td>
</tr>
<tr>
<td>3 to &lt;3.5 mmol/L</td>
<td>631 (8.3%)</td>
<td>0.61 (0.46-0.81)</td>
</tr>
<tr>
<td>3.5 mmol/L</td>
<td>398 (7.8%)</td>
<td>0.64 (0.47-0.86)</td>
</tr>
<tr>
<td>Total</td>
<td>4416 (5.3%)</td>
<td>0.72 (0.66-0.78)</td>
</tr>
</tbody>
</table>

Statin vs control:

<table>
<thead>
<tr>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mmol/L</td>
<td>266 (2.9%)</td>
<td>0.87 (0.60-1.28)</td>
</tr>
<tr>
<td>2 to &lt;2.5 mmol/L</td>
<td>412 (7.9%)</td>
<td>0.72 (0.63-0.82)</td>
</tr>
<tr>
<td>2.5 to &lt;3 mmol/L</td>
<td>1202 (3.2%)</td>
<td>0.69 (0.62-0.77)</td>
</tr>
<tr>
<td>3 to &lt;3.5 mmol/L</td>
<td>1821 (3.6%)</td>
<td>0.70 (0.61-0.80)</td>
</tr>
<tr>
<td>3.5 mmol/L</td>
<td>5336 (7.8%)</td>
<td>0.80 (0.72-0.88)</td>
</tr>
<tr>
<td>Total</td>
<td>8934 (5.6%)</td>
<td>0.79 (0.77-0.81)</td>
</tr>
</tbody>
</table>

All trials combined:

<table>
<thead>
<tr>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mmol/L</td>
<td>1012 (4.8%)</td>
<td>0.78 (0.61-0.99)</td>
</tr>
<tr>
<td>2 to &lt;2.5 mmol/L</td>
<td>1279 (4.2%)</td>
<td>0.72 (0.63-0.81)</td>
</tr>
<tr>
<td>2.5 to &lt;3 mmol/L</td>
<td>2225 (4.0%)</td>
<td>0.72 (0.63-0.82)</td>
</tr>
<tr>
<td>3 to &lt;3.5 mmol/L</td>
<td>2454 (4.0%)</td>
<td>0.76 (0.70-0.82)</td>
</tr>
<tr>
<td>3.5 mmol/L</td>
<td>5266 (9.9%)</td>
<td>0.80 (0.72-0.88)</td>
</tr>
<tr>
<td>Total</td>
<td>13350 (6.0%)</td>
<td>0.78 (0.76-0.80)</td>
</tr>
</tbody>
</table>

CTTC Group Meta-analysis of 27 Trials:

Statins Benefit ALL Regardless of Baseline 5-year Major Vascular Event (MVE) risk (<5% to >30%)

In a Managed Care Database, a Large Percentage of High-Risk Patients Did Not Achieve LDL-C <100 mg/dL or <70 mg/dL

Patients Achieving LDL-C Levels, %

<table>
<thead>
<tr>
<th>Year</th>
<th>LDL-C &lt;100 mg/dL</th>
<th>LDL-C &lt;70 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>11%</td>
<td>50%</td>
</tr>
<tr>
<td>2005</td>
<td>13%</td>
<td>49%</td>
</tr>
<tr>
<td>2006</td>
<td>16%</td>
<td>49%</td>
</tr>
<tr>
<td>2007</td>
<td>15%</td>
<td>51%</td>
</tr>
<tr>
<td>2008</td>
<td>16%</td>
<td>51%</td>
</tr>
</tbody>
</table>

N=178,027, 2004; N=220,084, 2005; N=227,517, 2006; N=166,497, 2007; N=168,790, 2008 (Jan–Aug)

Adapted from cohort study using linked population-based administration data from Ontario, Canada (N=85,020).

Nonadherence to Statin Treatment Happens Early: Selected Data From a Cohort of N=85,020

Adherence continues to drop over time, particularly when treating the asymptomatic patient

At 6 months, 50% of patients have stopped therapy

Adapted from cohort study using linked population-based administration data from Ontario, Canada (N=85,020).

Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

**Options for Achieving Optimal LDL-C**

- Highly efficacious statins help achieve ATP III goals at a low starting dose\(^1\)-\(^3\)
- For patients who do not achieve goals on initial therapy\(^1\),\(^4\)
  - Double the dose of current statin therapy
  - Switch to a more efficacious statin
  - Add ezetimibe or bile acid resin
  - Administer combination therapy

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**Statin and Complementary GI-Acting Drugs vs Statin Titration**

<table>
<thead>
<tr>
<th>% Reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin at starting dose</td>
</tr>
<tr>
<td>5–6%</td>
</tr>
</tbody>
</table>

**3-STEP TITRATION**

<table>
<thead>
<tr>
<th>% Reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin at starting dose</td>
</tr>
<tr>
<td>5–6%</td>
</tr>
</tbody>
</table>

**1-STEP COADMINISTRATION**

**Bile Acid Sequestrants plus Statins**

- **Cholestyramine**
  - Dose: 4 g
  - Amount: 24 g/day

- **Colestipol**
  - Dose: 5 g
  - Amount: 30 g/day

- **Colesevelam**
  - Dose: 0.625 g
  - Amount: 3.8 g/day

**Ezetimibe: Efficacy Dose–Response Study**

- **Placebo**
  - (n=52)
  - Change in LDL-C: -4.3%

- **Ezetimibe**
  - 0.25 mg (n=47)
    - Change: -9.9%
  - 1 mg (n=49)
    - Change: -12.6%
  - 5 mg (n=49)
    - Change: -16.4%
  - 10 mg (n=46)
    - Change: -18.7%

* *p<0.05 vs placebo.*

IMPROVE-IT
(IMPproved Reduction of Outcomes : Vytorin Efficacy International Trial)

- 18,000 patients
- Post ACS
- Simvastatin 40 mg vs. Simvastatin 40 mg/Ezetimibe
- Primary Endpoint: Composite of Death, MI, Rehospitalization for ACS, or Revascularization occurring 30 days or more after the initial event
- 2013: Anticipated Completion Date

Plant Sterols/Stanols:

- Average diet supplies ~ 300 mg per day
- Supplements usually from soybean and tall pine tree oil
- Studies show: LDL-C lowering about 9–13%
- Lowering greater in elderly
  - Additive to statin therapy
  - Used in various population groups
- Well-tolerated
- Recommended dose is 2,000 mg/day

Lichtenstein AH et al. Circulation 2001;103:1177-1179
Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

Plant Sterol and Stanol Products

- 400 mg
- 700 mg
- 850 mg
- 1000 mg
- 2000 mg per day

STATINS AND RISK FOR DIABETES MELLITUS
Do Lipid-lowering Drugs Increase the Risk of Diabetes?

- It has been known for some time that Niacin is associated with insulin resistance and new-onset diabetes.

Statins and Risk of Incident Diabetes: a Collaborative Meta-analysis of Randomized Statin Trials

13 randomized trials, 91,140 patients of whom 4,278 (2,226 assigned statins and 2,052 assigned placebo) developed diabetes during a mean FU of 4 yrs.

The association between statins and risk of diabetes mellitus was stronger in trials with older participants, but baseline BMI and percentage change in LDL concentration did not seem to be important factors.

Sattar et al. Lancet 2010; 375:735-742
**Statins and Risk of Incident Diabetes: Intensive vs Moderate Statin Therapy**

Meta-analysis of 5 randomized trials; 32,752 non diabetic patients followed for a mean FU of 4.9 yrs.

- **Incident Diabetes**
  - Intensive
    - 1449 (8.8%) pts developed incident diabetes
  - Moderate
    - 1300 (8.0%) pts developed incident diabetes

- The Odds of developing diabetes was comparable between simvastatin 80 mg and atorvastatin 80 mg (p=0.56), in contrast, there was a significant benefit of atorvastatin in preventing CV events compared to simvastatin (p<0.001)

- **The risk of new-onset diabetes was not comparable to the benefit of cardiovascular event reduction**

- Preiss et al. JAMA 2011; 305:2556-2564

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**New-Onset Diabetes on Atorvastatin 80 mg Occurs More Often in Patients With Features of the Metabolic Syndrome CV Events Reduced Despite Developing Chemical Diabetes**

- **A-TNT Trial**
  - Fasting glucose > 120 mg/dL: HR=0.794, (95% CI: 0.656-0.977)
  - Triglycerides > 150 mg/dL: HR=0.782, (0.690-0.887)
  - BMI > 30 kg/m²: HR=0.903, (0.794-1.027)
  - History of Hypertension: HR=2.426, (1.300-4.505)

- **B-IDEAL Trial**
  - Fasting glucose > 120 mg/dL: HR=0.723, (0.620-0.843)
  - Triglycerides > 150 mg/dL: HR=0.767, (0.669-0.879)
  - BMI > 30 kg/m²: HR=0.917, (0.794-1.056)
  - History of Hypertension: HR=1.380, (1.210-1.568)

- **C-SPARCL Trial**
  - Fasting glucose > 120 mg/dL: HR=0.361, (0.259-0.501)
  - Triglycerides > 150 mg/dL: HR=0.311, (0.239-0.398)
  - BMI > 30 kg/m²: HR=0.597, (0.501-0.710)
  - History of Hypertension: HR=0.920, (0.754-1.118)

**Figure Legend:** Incident Diabetes According to Baseline Clinical Predictors

Incident diabetes in (A) the TNT (Treating to New Targets) trial, (B) the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial, and (C) the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial according to baseline clinical predictors. BMI = body mass index; HR = hazard ratio.

LEARNING OBJECTIVES

1. Describe The Importance Of Reducing LDL-C As The Primary Target Of Lipid-lowering Therapy
2. Discuss The Role Of Specific Statin Strategies Used In Clinical Trials To Reduce LDL-C
3. Recognize The Role Of Residual Risk and non-HDL-C as A Secondary Target Of Therapy
4. Define The Role Of New Agents That Potentiate The Role Of Statin-based Therapy For Difficult-to-treat Patients

NON-HDL-C: THE NEGLECTED TARGET OF THERAPY IN PATIENTS WITH BASELINE TRIGLYCERIDES ≥ 200 mg/dL
Non–HDL-C Is a Risk Factor and Secondary Target for CHD

- Non–HDL-C = total cholesterol – HDL-C
  - Measures the cholesterol content of all ApoB-containing lipoproteins
  - These include VLDL, IDL, LDL, Lp(a), and chylomicron remnants
- Multiple prospective cohort studies have shown that non–HDL-C may be superior to LDL-C for CV risk assessment.
- When TG levels are ≥200 mg/dL, the relationship between LDL-C and CHD risk becomes discordant, and non–HDL-C better represents the concentration of all atherogenic lipoproteins than does LDL-C alone.
- Predictive value of non–HDL-C levels for CHD is generally similar to LDL particle number.

What Is Non–HDL-C?

- Non–HDL-C = Total cholesterol – HDL-C
- HDL, LDL, IDL, VLDL, Chylomicron remnants
- VLDL = very low-density lipoprotein
- IDL = intermediate-density lipoprotein
- LDL = low-density lipoprotein
- HDL = high-density lipoprotein
- ApoB = apolipoprotein B
- Lp(a) = lipoprotein(a)
- CV = cardiovascular
- CAD = coronary artery disease

References:
Non–HDL-C is a better Predictor of CHD than LDL-C: The Framingham Heart Study\(^1\)

- A strong positive and graded association between non–HDL-C and CHD risk occurred within all levels of LDL-C that were assessed in this study (LDL-C <130, 130–159, and ≥160 mg/dL).
- Within non–HDL-C levels, no association was found between LDL-C and CHD risk.

\(^2\) Adjusted for Age, Gender, Smoking Status, Systolic blood pressure, and Prevalent Diabetes (at baseline)


Association of LDL-C and Non-HDL-C with Risk of CV Events in 62,154 Patients Treated with Statins

<table>
<thead>
<tr>
<th>Target Level</th>
<th>LDL-C ≥160 mg/dL</th>
<th>LDL-C &lt;160 mg/dL</th>
<th>Non-HDL-C ≥130 mg/dL</th>
<th>Non-HDL-C &lt;130 mg/dL</th>
<th>No. of Major Cardiovascular Events</th>
<th>Total No. of Participants</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥100 mg/dL</td>
<td>1877</td>
<td>467</td>
<td>≥130 mg/dL</td>
<td>10419</td>
<td>1.21 (1.13–1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100 mg/dL</td>
<td>283</td>
<td>23426</td>
<td>&lt;130 mg/dL</td>
<td>1435</td>
<td>1.32 (1.17–1.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 mg/dL</td>
<td>2760</td>
<td>283</td>
<td>≥130 mg/dL</td>
<td>1877</td>
<td>1.00 [Reference]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 mg/dL</td>
<td>2760</td>
<td>23426</td>
<td>&lt;130 mg/dL</td>
<td>467</td>
<td>1.02 (0.92–1.12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HRs were adjusted for sex, age, smoking, diabetes, systolic blood pressure, and trial.

Conclusion: Among statin-treated patients, the ability to reduce future CV events is stronger when reducing non-HDL-C than it is when reducing LDL-C.
Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

### Non-HDL-C Is a Secondary Target for Lipid Lowering in Patients With Elevated Triglycerides (≥200 mg/dL)

- **Non-HDL-C goal:** 30 mg/dL higher than the LDL-C goal

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>LDL-C target (mg/dL)</th>
<th>Non-HDL-C target (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CHD, &lt;2 RF</td>
<td>&lt;160</td>
<td>&lt;190</td>
</tr>
<tr>
<td>No CHD, 2+ RF</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
<tr>
<td>CHD or CHD risk equivalent</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>CHD with diabetes or multiple risk factors for metabolic syndrome or ACS</td>
<td>&lt;70</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>


### Non-HDL-C Goal Attainment in Patients With Hypertriglyceridemia: NEPTUNE II

Percent of patients with triglycerides ≥200 mg/dL (≥2.25 mmol/L) LDL-C treatment goals and combined LDL-C and non–HDL-C treatment goals

![Graph showing non-HDL-C goal attainment](image)

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease.

Case

A 52 year old female with stage 3b CKD presents for a second opinion on if she should be started on lipid-lowering therapy. She has no history of CAD, diabetes, or vascular disease but has had hypertension for 15 years and her BP has recently been well controlled. Her renal function decline has recently stabilized.

Labs: Creat 2.6, eGFR 32 cc/min,
   T-chol 191
   LDL-C 108
   HDL-C 48
   TG 200

Small Group Discussion:

True or False:
Based on a recent clinical trial, statin-based therapy would decrease her risk of developing a major atherosclerotic vascular event?

If so, what would you treat her with?
LIPID LOWERING IN THE SETTING OF CHRONIC KIDNEY DISEASE

Framingham Heart Study:
CKD as Predictor of CVD Death

3a CKD: GFR 45-59 women, 51-64 men
3b CKD: GFR 30-44 women, 30-50 men

No CKD/+CVD
CKD3a/No CVD
CKD3b/No CVD
No CKD/No CVD

Am J Cardiol 2008;102;47
SHARP: Eligibility

- History of chronic kidney disease
  - not on dialysis: elevated creatinine on 2 occasions
    - Men: ≥1.7 mg/dL (150 µmol/L)
    - Women: ≥1.5 mg/dL (130 µmol/L)
  - on dialysis: hemodialysis or peritoneal dialysis
- Age ≥40 years
- No history of myocardial infarction or coronary revascularization
- LDL-lowering treatment not definitely indicated or contraindicated


SHARP: Baseline characteristics

- Mean age 62, 63% men
- Diabetes 23%
- Dialysis 33%
- eGFR 27 ml/min per 1.73 m² (MDRD) median 25.6
- Lipids:
  - Total Chol 189 mg/dl
  - LDL-C 108 mg/dL
  - HDL-C 43 mg/dL
  - TG 204 mg/dL
- Randomized to Placebo or Simvastatin/ezetimibe 20/10 mg
SHARP: Major Atherosclerotic Events by renal status at randomization

<table>
<thead>
<tr>
<th>Group</th>
<th>Eze/simv (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-dialysis (n=6247)</td>
<td>296 (9.5%)</td>
<td>373 (11.9%)</td>
<td>No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)</td>
</tr>
<tr>
<td>Dialysis (n=3023)</td>
<td>230 (15.0%)</td>
<td>246 (16.5%)</td>
<td>17% SE 5.4 reduction (p=0.0022)</td>
</tr>
<tr>
<td>Any patient</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td>Eze/simv better</td>
</tr>
</tbody>
</table>


Lipid-Lowering Therapy in Persons With CKD: A Systematic Cochrane Review and Meta-analysis

• 18 RCTs, all in adults, were included. 5 involved CKD populations while 13 examined CKD subgroups from general population trials. 16 examined statins and 2 examined statins + ezetimibe.
• Lipid-Lowering Therapy does not improve kidney outcomes but significantly decreases the risk for cardiac mortality, cardiovascular events, and myocardial infarction.
• Rates of adverse events were similar between intervention and comparator groups.
• Conclusion Lipid-lowering therapy decreases cardiac death and atherosclerosis-mediated cardiovascular events in persons with CKD but does not improve kidney outcomes.

Ann Intern Med. 21 August 2012;157(4):251-262
EFFICACY OF NIACIN THERAPY IN PATIENTS ALREADY WELL TREATED WITH A STATIN

Atherothrombosis Intervention in Metabolic Syndrome with low HDL/high triglycerides: Impact on Global Health (AIM HIGH) Results

• 3414 subjects with CVD; mean age 64; 34% with T2DM and 71% with MeS; 94% had prior statin use

• Randomized to simvastatin ± ezetimibe to reduce LDL-C < 80 mg/dL, and then to niacin ER 2 gm (n = 1718) or PBO (n = 1696)

### AIM HIGH: Baseline Lipids (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>On Statin (n=3,196)</th>
<th>Off Statin (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mean)</td>
<td>71</td>
<td>119</td>
</tr>
<tr>
<td>HDL-C (mean)</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Triglycerides (median)</td>
<td>161</td>
<td>215</td>
</tr>
<tr>
<td>Non-HDL (mean)</td>
<td>107</td>
<td>165</td>
</tr>
<tr>
<td>Apo-B (mean)</td>
<td>81</td>
<td>111</td>
</tr>
</tbody>
</table>


### AIM HIGH: HDL-C at Baseline & Follow-up

- **Combination Therapy**
  - Baseline: 25 mg/dL
  - Year 1: 35 mg/dL
  - Year 2: 40 mg/dL
  - Year 3: 45 mg/dL

- **Monotherapy**
  - Baseline: 25 mg/dL
  - Year 1: 30 mg/dL
  - Year 2: 35 mg/dL
  - Year 3: 40 mg/dL

*P < 0.001*

Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

**AIM-HIGH Primary Outcome**

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1696</td>
<td>1718</td>
</tr>
<tr>
<td>1</td>
<td>1581</td>
<td>1606</td>
</tr>
<tr>
<td>2</td>
<td>1381</td>
<td>1366</td>
</tr>
<tr>
<td>3</td>
<td>910</td>
<td>903</td>
</tr>
<tr>
<td>4</td>
<td>436</td>
<td>428</td>
</tr>
</tbody>
</table>

HR 1.02, 95% CI 0.87, 1.21
Log-rank P value = 0.79

**AIM-HIGH CONCLUSIONS**

Among patients with atherosclerotic CV disease and LDL-C levels of less than 70 mg per deciliter (1.81 mmol per liter), there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month f/u period, despite significant improvements in HDL cholesterol and triglyceride levels.

Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

Effect of High Risk Groups on Primary Outcome

<table>
<thead>
<tr>
<th># Pts. with Events (% of Category)</th>
<th>ERN Better</th>
<th>ERN Worse</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-val.**</th>
<th>Int.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG ≥ 198 and HDL &lt; 33 *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>48 (17.0)</td>
<td>54 (22.4)</td>
<td>0.74 (0.50, 1.09)</td>
<td>0.073</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>234 (16.3)</td>
<td>220 (15.1)</td>
<td>1.09 (0.91, 1.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG ≥ 200 and HDL &lt; 32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40 (16.7)</td>
<td>50 (25.0)</td>
<td>0.63 (0.40, 0.98)</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>242 (16.2)</td>
<td>224 (15.0)</td>
<td>1.11 (0.93, 1.33)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Highest tertile of TG and lowest tertile of HDL-C  **Heterogeneity by treatment

HPS2-THRIVE: Randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease.

Eligibility:
- Men and women
- Aged 50-80 years
- Prior history of: myocardial infarction; ischaemic stroke or TIA; peripheral arterial disease; or diabetes with other CHD
- No contra-indication to study treatments
- No significant liver, kidney or muscle disease
Baseline LIPIDS on statin-based therapy

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) baseline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>128 (22)</td>
<td>3.32 (0.57)</td>
</tr>
<tr>
<td>Direct-LDL</td>
<td>63 (17)</td>
<td>1.64 (0.44)</td>
</tr>
<tr>
<td>HDL</td>
<td>44 (11)</td>
<td>1.14 (0.29)</td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>125 (74)</td>
<td>1.43 (0.84)</td>
</tr>
</tbody>
</table>

*64% fasted for >8 hours

Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

Risk ratio 0.96 (95% CI 0.90 – 1.03)
Logrank P=0.29
Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

### MAJOR VASCULAR EVENTS by low HDL/high triglycerides and prior statin use

<table>
<thead>
<tr>
<th>Low HDL-C, high triglycerides</th>
<th>Risk ratio &amp; 95% CI</th>
<th>Het or trend $\chi^2$ (uncorrected p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0.99</td>
<td>0.00 (p=0.95)</td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>2.88 (p=0.09)</td>
</tr>
</tbody>
</table>

**Prior statin use (years)**

| None                         | 1.00                | 3.5% SE 3.3 reduction   |
| >0 <3                        | 1.00                | 3.5% SE 3.3 reduction   |
| ≥3 <6                        | 1.00                | 3.5% SE 3.3 reduction   |
| ≥ 6                          | 1.00                | 3.5% SE 3.3 reduction   |

**Randomized allocation**

<table>
<thead>
<tr>
<th>ERN/LRPT (12838)</th>
<th>Placebo (12835)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low HDL, high triglycerides</td>
<td>Yes</td>
<td>333 (15.1%)</td>
</tr>
<tr>
<td>No</td>
<td>1363 (12.8%)</td>
<td>1424 (13.3%)</td>
</tr>
</tbody>
</table>

**LEARNING OBJECTIVES**

1. Describe The Importance Of Reducing LDL-C As The Primary Target Of Lipid-lowering Therapy
2. Discuss The Role Of Specific Statin Strategies Used In Clinical Trials To Reduce LDL-C
3. Recognize The Role Of Residual Risk and non-HDL-C as A Secondary Target Of Therapy
4. Define The Role Of New Agents That Potentiate The Role Of Statin-based Therapy For Difficult-to-treat Patients
New Therapies for Familial Hypercholesterolemia:

- Homozygous- Mipomerson - Lomitapide

- Heterozygous- Monclonocal Ab to PCSK9

Familial Hypercholesterolemia

1. Homozygotes occur with a frequency of approximately 1 in 1 million.
2. Serum cholesterol ranges from 650-1000 mg/dL. Homozygotes have near total or total loss of LDL-R functionality.
3. Heart attacks occur in childhood or young adulthood
Mipomersen: mechanism of action

Mipomersen (apoB) antisense strand1,2


Mipomersen crosses the hepatocyte and nuclear membranes to target apoB mRNA1,2

Phase 2: Hypercholesterolemia, Monotherapy
Dose-dependent Reduction of LDL-C

Once Weekly Dosing

Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

Assembly and Secretion of ApoB-100-Containing Lipoproteins in the Liver

Clinical profile of Lomitapide

- **Requirements for administration**
  - Requires adherence to <10% fat diet
  - Titration indices: elevation in ALT and GI AEs
  - Need for supplementation (fat-soluble vitamin malabsorption)

- **Adverse events**
  - 3 of 23 (13%) discontinuation due to GI AEs
  - Weight loss in normal weight/BMI subjects in Phase III study
  - CYP3A4 interactions and requirement for simvastatin and warfarin dose adjustment
  - Phase III study allowed changes in baseline treatment, and medication dose to reduce elevations in AST/ALT
Familial Hypercholesterolemia

1. Heterozygotes occur with a frequency of about 1 in 300 to 500 patients.
2. Heterozygous FH is one of the most commonly occurring congenital metabolic disorders. Serum total cholesterol is elevated in the range of 300-550 mg/dL.
3. Since patients have one normal LDL-R gene, their hepatocytes take up LDL-C at approximately one-half the rate of unaffected patients.

PCSK9

- A Secreted Regulator of Cellular LDL Receptor levels
- Up-regulated by statin therapy
- Gain of function mutations cause high LDL-C
- Loss of function mutations cause low LDL-C
- Therapeutic inhibition lowers LDL-C levels
- Therapeutic inhibition augments statin effects
Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

**PCSK9 Regulates LDLR Turnover Through Increased Intracellular Degradation**

**Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDLR**
**PCS K9 monoclonal antibody REGN727/SAR236553: LDL-C reduction On Top Of Background Atorvastatin**

Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10 and 12 in the mITT population, by treatment group. Week 12 estimation using Last Observation Carried Forward method.

- Placebo
- SAR236553 50 mg Q2W
- SAR236553 100 mg Q2W
- SAR236553 200 mg Q4W
- SAR236553 300 mg Q4W
- SAR236553 150 mg Q2W

Injections of 1 ml

**RUTHERFORD: Effect of AMG 145 on Percentage Change in LDL-C From Baseline**

Heterozygous FH

- Placebo (n=56)
- AMG 145 350 mg (n=55)
- AMG 145 420 mg (n=56)

Number of patients:
- Baseline: 56, 56, 55, 55, 54, 56
- 2 weeks: 55, 55, 55, 55, 53, 55
- 4 weeks: 55, 55, 55, 55, 55, 55
- 6 weeks: 55, 55, 55, 55, 55, 55
- 8 weeks: 55, 55, 55, 55, 55, 55
- 12 weeks: 55, 55, 55, 55, 55, 55

p<0.001*  
*p Compared to placebo

Using the Evidence to Improve Clinical Outcomes in the Dyslipidemic Patient

**PCSK9-Directed Therapies in Development**

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug (Alternate Name)</th>
<th>Agent</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi/Regeneron</td>
<td>SAR236553/REGN727</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Agenyen</td>
<td>AMG-145</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Novartis</td>
<td>LGT-209</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Pfizer/Rinat</td>
<td>RN316 (PF-04950615)</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Genentech</td>
<td>MPSK3169A, RG7652</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Alnylam Pharmaceuticals</td>
<td>ALN-PCS02</td>
<td>siRNA oligonucleotide</td>
<td>Hypercholesterolemia</td>
<td>1</td>
</tr>
<tr>
<td>Amgen</td>
<td>AMG-145</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Serometrix</td>
<td>SX-PCK9</td>
<td>Small peptide mimetic</td>
<td>Hypercholesterolemia</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Shifa Biomedical Corp.</td>
<td>TBD</td>
<td>Small molecule PCSK9 modulator</td>
<td>Metabolic disorders</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Adnexus Therapeutics/Bristol-Myers Squibb</td>
<td>BMS-962476</td>
<td>Fusion protein using Adnectin technology</td>
<td>Cardiovascular disease</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Idera Pharmaceuticals</td>
<td>TBD</td>
<td>Antisense oligonucleotide</td>
<td>Hypercholesterolemia</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- Statin therapy is safe with low risk of myopathy, hepatotoxicity
- Statin therapy reduces risk for CVD events at all levels of baseline risk
- Statin therapy modestly increases risk of diabetes mellitus, but benefits outweigh risks
- Statins reduce risk for CV morbidity and mortality equally in diabetics and nondiabetics, and irrespective of baseline LDL-C and risk stratification

CONCLUSIONS

- Non-HDL-C is an important risk factor, and should be treated
- The non-HDL-C target is the LDL-C risk stratified target plus 30 mg/dL
- Non-HDL-C is defined as TC - HDL-C
- Even if LDL-C target is attained, non-HDL-C is an important predictor of residual CV risk

CONCLUSIONS

- Lipid lowering is efficacious in patients with CKD; it does not benefit patients with ESRD
- Niacin does not provide incremental benefit when used as adjuvant therapy in patients already at high-risk goals on a statin.
- A secondary analysis of AIM HIGH suggests that in patients with hypertriglyceridemia and low HDL-C, niacin may provide incremental benefit, though this will have to be tested in a prospective randomized study.
Clinical Studies suggest that our ability to reduce cardiac events when using statin-based therapy correlates best with:

1. The duration of time they have been used
2. The amount of Ldl-C reduction achieved
3. Both of the above
4. Neither of the above

Post-Test Question 1

Which of the following are the 2 best tests to target in reducing cardiovascular disease in those with dyslipidemia?

1. HDL-C and Triglycerides
2. Total Cholesterol and LDL-Particle #
3. Total Cholesterol and Apolipoprotein B
4. LDL-C and Apolipoprotein B
5. LDL-C and non-HDL-C

Post-Test Question 2
The major reason that statin-based clinical trials achieving effective LDL-C reduction have not shown additional benefit from adding niacin or fibrates is:

1. These drugs are not effective as monotherapy so why think they would work on top of statin therapy
2. They were studied in the wrong patient populations
3. These drugs have been shown to have an off-target effect that negates the effects of statins.
4. These drugs have been found to be effective when added to statin-based therapy for outcome improvement and the premise of the question is wrong.

Which of the following is not true about heterozygote familial hypercholesterolemia?

1. It occurs in 1 in 500 of the population
2. Patients have the normal number of LDL receptors
3. There is a 2-fold increase in plasma LDL-C
4. Heart attacks begin at age 35 (ie., premature atherosclerosis)
Post-Test Question 5

**On a scale of 1 to 5, please rate how confident you are in treating the dyslipidemic patient.**

1. Not at all confident  
2. Slightly confident  
3. Moderately confident  
4. Pretty much confident  
5. Very confident

Post-Test Question 6

**Which of the statements below describes your approach to diagnosing and treating patients with dyslipidemia?**

1. I do not manage dyslipidemia, nor do I plan to this year.  
2. I did not manage dyslipidemia before this course, but as a result of attending this course I’m thinking of managing it now.  
3. I do manage patients with dyslipidemia and this course helped me change my treatment methods.  
4. I do manage patients with dyslipidemia and this course confirmed that I don’t need to change my treatment methods.