Management of Dyslipidemia: An Update

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Sergio Fazio, MD, PhD
Cornelius Vanderbilt Chair of Cardiovascular Medicine
Professor of Medicine, Pathology, Immunology, and Microbiology
Chief, Section of Cardiovascular Disease Prevention
Vanderbilt University Medical Center
Nashville, Tennessee

Disclosures

Consulting: Kowa, Merck, Pfizer, Genzyme, Roche, Takeda, Amarin, Lupin, Aegerion, Genentech

Research: ISIS, Merck, Pfizer, NIH
Many Ways to Get in Trouble

Cardiovascular Risk

- Overweight/Obesity
- Genetics
- Insulin Resistance Syndrome
- Age

Abnormal Lipid Metabolism
- LDL
- ApoB
- HDL
- Triglycerides

Lipids
BP
Glucose

Smoking,
Physical Inactivity,
Unhealthy Eating

Hypertension

Age, Race, Gender,
Family History

Inflammation,
Hypercoagulation

Case

- 64 yo AA woman, BMI 34, diabetic, hypertensive, with mild renal insufficiency, CABG at 52, recent stent.
- On atorvastatin 40 mg
- Fasting lipid profile: TC 199, TG 325, LDL 103, HDL 31.
CVD Prevention Is Based on Systemic Maneuvers

- Lifestyle changes
- Blood pressure control
- Diabetes treatment
- Inhibition of platelet aggregation
- Lipid Management

The Lipid Drugs

Ordered according to clinical trial evidence of CV benefits

- Statins (currently 7 available)
- Omega 3 fats (supplements and 2 Rx strength)
- Cholesterol Absorption Inhibitors (1 available)
- Bile Acid-Binding Resins (3 available)
- Fibrates (2 available)
- Niacin (immediate, slow, and extended release)

The Lipid Drugs

Ordered according to LDL lowering effects

- Statins (currently 7 available)
- Cholesterol Absorption Inhibitors (1 available)
- Bile Acid-Binding Resins (3 available)
- Omega 3 fats (supplements and 2 Rx strength)
- Niacin (immediate, slow, and extended release)
- Fibrates (2 available)
The Lipid Drugs

Ordered according to HDL raising effects

- Niacin (immediate, slow, and extended release)
- Fibrates (2 available)
- Statins (currently 7 available)
- Cholesterol Absorption Inhibitors (1 available)
- Omega 3 fats (supplements and 2 Rx strength)
- Bile Acid-Binding Resins (3 available)

The Lipid Drugs

Ordered according to TG lowering effects

- Fibrates (2 available)
- Omega 3 fats (supplements and 2 Rx strength)
- Niacin (immediate, slow, and extended release)
- Statins (currently 7 available)
- Cholesterol Absorption Inhibitors (1 available)
- Bile Acid-Binding Resins (3 available)
ADA and ACC Consensus Statement on Lipoprotein Management in High-Risk Patients

TREATMENT GOALS

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
<th>ApoB (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 70</td>
<td>&lt; 100</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>&lt; 130</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

Very high-risk patients:
1) Known CVD
2) Diabetes + CVD risk factor

High-risk patients:
1) Two or more CVD risk factors
2) Diabetes


The Lipoproteins

- Fasting plasma apoB is mostly associated with LDL
- Non-HDL cholesterol mostly includes LDL
- Triglycerides are associated only with atherogenic lipoproteins
LDL-C Reduction and Atheroma Burden

**IVUS trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Atheroma Volume Δ%</th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMELOT</td>
<td>Placebo</td>
<td>-0.6</td>
<td></td>
<td>-1.2</td>
</tr>
<tr>
<td>REVERSAL</td>
<td>Atorvastin</td>
<td>1.8</td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>REVERSAL</td>
<td>Pravastin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTEROID</td>
<td>Rosuvastatin</td>
<td>-1.2</td>
<td></td>
<td>-0.6</td>
</tr>
</tbody>
</table>

- $r^2 = 0.97$
- $P < 0.001$

**SATURN Trial: Maximum Dose Atorvastatin or Rosuvastatin**

- Subjects with CAD, on A-80 or R-40 for 104 weeks
- IVUS at baseline and end of study
- Treatment LDL 70 (A) and 62 (R), HDL 48 (A) and 50 (R), TG<130 in both
- Two thirds of subjects showed regression
- PAV -0.99% (A) and -1.22% (R)

NEJM, 2011; 365: 2078-87
LDL Reduction and Atheroma Burden

- LDL lowering below 70 mg/dl causes arrest of plaque progression but only minimal plaque regression.
- Regression of plaque is likely dependent on activation of specific targets related to cholesterol efflux and inflammatory response.

CARE=Cholesterol and Recurrent Events Trial, 4S=Scandinavian Simvastatin Survival Study, HPS=Heart Protection Study, LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; TNT=Treating to New Targets

Aggressive LDL-C Reduction Eliminates One Third of the Expected CVD Events


HPS WOSCOPS 4S ASCOT CARDS
Reduction in major coronary events vs. placebo (%)

Unmodified Risk

*Includes stroke
†P<0.005
‡P<0.001

Residual CVD Risk in Diabetic Patients on Statin Treatment

<table>
<thead>
<tr>
<th></th>
<th>Event Rate (No Diabetes)</th>
<th>Event Rate (Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On Statin</td>
<td>On Placebo</td>
</tr>
<tr>
<td>HPS* (CHD patients)</td>
<td>19.8%</td>
<td>25.7%</td>
</tr>
<tr>
<td>CARE†</td>
<td>19.4%</td>
<td>24.6%</td>
</tr>
<tr>
<td>LIPID‡</td>
<td>11.7%</td>
<td>15.2%</td>
</tr>
<tr>
<td>PROSPER §</td>
<td>13.1%</td>
<td>16.0%</td>
</tr>
<tr>
<td>ASCOT-LLA‡</td>
<td>4.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>TNT †</td>
<td>7.8%</td>
<td>9.7%</td>
</tr>
</tbody>
</table>


* CHD death, nonfatal MI, stroke, revascularizations
† CHD death, nonfatal MI, CABG, PTCA
‡ CHD death and nonfatal MI
§ CHD death, nonfatal MI, stroke
‖ CHD death, nonfatal MI, revascularized cardiac arrest, stroke (80 mg vs 10 mg atorvastatin)
Current Options for Management of Combined Dyslipidemia

- TLC
- Statin
- Niacin
- Fibrate
- TZD
- Omega-3 fats

Comparison of Lipid Subgroup Analyses in Fibrate Trials

<table>
<thead>
<tr>
<th>Study (Drug)</th>
<th>CVD Reduction (P)</th>
<th>Lipid Subgroup Criteria</th>
<th>CVD Reduction (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helsinki Heart Study (gemfibrozil)</td>
<td>-34% (0.02)</td>
<td>TG ≥ 204 mg/dl</td>
<td>-78% (0.002)</td>
</tr>
<tr>
<td>VA-HIT (Gemfibrozil)</td>
<td>-22% (0.006)</td>
<td>HDL &lt; 42 mg/dl</td>
<td>-28% (&lt;0.05)</td>
</tr>
<tr>
<td>BIP (bezafibrate)</td>
<td>-7.3% (0.24)</td>
<td>TG ≥ 180 mg/dl</td>
<td>-39.5% (0.02)</td>
</tr>
<tr>
<td>FIELD (Fenofibrate)</td>
<td>-11% (0.16)</td>
<td>TG ≥ 200 mg/dl</td>
<td>-27% (0.005)</td>
</tr>
<tr>
<td>ACCORD (Fenofibrate)</td>
<td>-8% (0.32)</td>
<td>HDL-C &lt; 40 mg/dl</td>
<td>-31% (0.03)</td>
</tr>
</tbody>
</table>


*and BMI > 26 kg/m²
**HDL-C < 50 mg/dL in women
FIELD: Overall Outcomes

CHD events (nonfatal MI plus CHD death)

↓ 11% [P=0.16]

Total CHD events (also includes stroke and revascularizations)

↓ 11% [P=0.035]


FIELD: Evidence of Microvascular Improvement

Nontraumatic Amputations

38% Reduction

P=0.01

Progression and Regression of Albuminuria*

14% Reduction

P=0.002

15% Increase

*Progression of albuminuria was defined as the proportion of patients who progressed either from normoalbuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria

Action to Control Cardiovascular Risk in Diabetes (ACCORD)

Description:
- Fenofibrate + simvastatin vs placebo + simvastatin
- Population: Adults with diabetes (N=5,518)
- Primary end point: first occurrence of nonfatal MI, nonfatal stroke, or CHD-related death


ACCORD: Overall Outcomes

No significant changes in primary end point or in mortality

ACCORD: Efficacy in Patients with Dyslipidemia

Primary outcome reached in overall study population and in those with HDL-C <34 mg/dL and TGs>204 mg/dL

Trend towards fewer CHD events seen in patients with low HDL and high TGs at baseline \( (P=0.06) \)


Current Options for Management of Combined Dyslipidemia

- TLC
- Statin
- **Niacin**
- Fibrate
- TZD
- Omega-3 fats
HATS (HDL-C Atherosclerosis Treatment Study) Clinical End Points

Quantitative Coronary Angiography

CVD Events

90% Reduction

*P<.005 versus placebo
Mean dose of simvastatin was 13 mg/day
Mean dose of niacin was 2400 mg/day

AIM HIGH: Effects of Niacin Added to Simvastatin

- 3414 Subjects with CAD
- Simvastatin alone or with ezetimibe ± ER niacin
- On niacin TG 120 mg/dL, HDL 44 mg/dL, LDL 65 mg/dL
- Controls TG 152 mg/dL, HDL 38 mg/dL, LDL 67 mg/dL
- 282 subjects on niacin had primary endpoint (16.4%)
- 274 controls had primary endpoint (16.2%)

NEJM, 2011; 365: 2255-2267
AIM-HIGH—Results
Primary Outcome

1st Endpoint: CHD Death, nonfatal MI, ischemic stroke, high-risk ACS, hospitalization for coronary or cerebrovascular revascularization


Assessing HDL Function

- Cholesterol efflux
- Cholesterol delivery
- Lipid exchange
- Regulation of inflammation
- Control of oxidation
- Regulation of endothelial responses
- Transcriptional endocrine function (miRNA)
Serum Cholesterol Efflux Capacity

\(^3\)H-Cholesterol labeled + ACAT Inhibitor

J774 MACROPHAGES

cAMP + 0.2% BSA

apoB-depleted sera

% FC Efflux


Cholesterol Efflux Capacity in Coronary Artery Disease Patients

• 442 CAD patients and 351 controls
• Serum efflux capacity independent predictor of coronary artery disease status
• Results only partially explained by HDLc levels
• Efflux improved by pioglitazone, not by statins

Does HDL become dysfunctional in CAD or does dysfunctional HDL cause CAD?

- Lack of association between function and HDLc levels suggests that atherosclerosis may modify HDL
- Dysfunctional HDL may be hiding in either the low or high HDLc range
- Dysfunctional HDL may be present in unique patient types

HDL-c is associated with increased CAC in RA subjects with high levels of urinary isoprostanes (n=169)

From Rho et al. *Arthritis Care Research* 2010;62:1473-8
CAD* Risk Reduction with LDL Lowering in ESRD Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D (atorva)</td>
<td>33 (1.91%)</td>
<td>35 (2.02%)</td>
</tr>
<tr>
<td>AURORA (rosuva)</td>
<td>91 (1.97%)</td>
<td>107 (2.33%)</td>
</tr>
<tr>
<td>SHARP (simva/eze)</td>
<td>134 (0.71%)</td>
<td>159 (0.85%)</td>
</tr>
</tbody>
</table>

*Non-fatal myocardial infarction

HDL of Patients on Renal Dialysis Have Impaired Cholesterol Efflux Capacity

JACC 2012
Dialysis Patients Have Dysfunctional HDL Irrespective of HDL-C

From Data in Yamamoto S. et al.

• Supplementation (1 g) reduces CVD rates but does not affect lipid levels
• High-dose therapy (4 g) reduces elevated TG but not proven to affect CVD rates
• No effects on HDL or LDL
• EPA-only formulation claims no LDL raising effects
Case

- 64 yo AA woman, BMI 34, diabetic, hypertensive, with mild renal insufficiency, CABG at 52, recent stent.
- On atorvastatin 40 mg
- Fasting lipid profile: TC 199, TG 325, LDL 103, HDL 31.

Proof of CVD Benefits

- Statins: yes
- Niacin: not above statin
- Resins: maybe
- Ezetimibe: with simvastatin
- Fibrates: not above statin
- Omega 3 fats: yes, and maybe also above statin
Novel Lipid Drugs

- ApoB Antisense (mipomersen)
- MTP Inhibitors (lomitapide)
- PCSK9 Inhibitors (Phase III, good vibes)
- CETP Inhibitors (Phase III, bad vibes)

Novel Targets for Lipid Management

1. Lowering Levels of Atherogenic Lipoproteins
   A. Blocking Lipoprotein Output
      - MTP Inhibition (Lomitapide)
      - ApoB Blockade (Mipomersen)
   B. Increasing Lipoprotein Clearance (PCSK9 Inhibitors)

2. Raising Levels of Anti-Atherogenic Lipoproteins
   A. Increasing HDL Production, Maturation, Function
      - Increasing apoAI Synthesis
      - Improving LCAT Activity
      - Improving Cellular Cholesterol Extraction
   B. Blocking HDL Cholesterol Exchange (CETP Inhibitors)
VLDL Assembly as Target of Therapy

Cholesterol  Apo B  VLDL
MTP  Triglyceride droplet

LDL Receptor Function and Life Cycle

LDL particle  Endocytosis  Recycling of LDL-R
Golgi Apparatus  Endoplasmic reticulum
Hepatocyte  Nucleus  SREBP  Lysosome
The Role of PCSK9 in the Regulation of LDL Receptor Expression

**PCSK9 Inhibitors Under Development**

<table>
<thead>
<tr>
<th>Company</th>
<th>Agent</th>
<th>Stage</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA-Regeneron</td>
<td>mAB</td>
<td>Phase 2</td>
<td>REGN727 IgG Phase 2 results May 2010, LDL decreased 60%</td>
<td><a href="http://investor.regeneron.com/releasedetail.cfm?ReleaseID=468970">http://investor.regeneron.com/releasedetail.cfm?ReleaseID=468970</a></td>
</tr>
<tr>
<td>Pfizer-Rinat</td>
<td>mAB</td>
<td>Phase 1</td>
<td>RN316 IgG Clinical trial started</td>
<td><a href="http://www.ncbi.nlm.nih.gov/pubmed/19060325">http://www.ncbi.nlm.nih.gov/pubmed/19060325</a></td>
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<tr>
<td>Amgen</td>
<td>mAB</td>
<td>In development</td>
<td>mAb2-IgG Cyno PoC, PNAS May 2009</td>
<td><a href="http://www.ncbi.nlm.nih.gov/pubmed/19506257">http://www.ncbi.nlm.nih.gov/pubmed/19506257</a></td>
</tr>
<tr>
<td>BMS-Ils</td>
<td>ASO</td>
<td>Preclinical</td>
<td>BMS-844421 Phase 1</td>
<td><a href="http://www.isispharm.com/Pipeline/Therapeutic-Areas/Cardiovascular.htm#BMS-PCSK9Rx">http://www.isispharm.com/Pipeline/Therapeutic-Areas/Cardiovascular.htm#BMS-PCSK9Rx</a></td>
</tr>
<tr>
<td>Alnylam/UT-SW</td>
<td>ASO</td>
<td>In development</td>
<td>ALN-PCS, Liposome formula, Cyno PoC, PNAS Aug 2008</td>
<td><a href="http://www.alnylam.com/Programs-and-Pipeline/Programs/Hypercholesterolemia.php">http://www.alnylam.com/Programs-and-Pipeline/Programs/Hypercholesterolemia.php</a></td>
</tr>
<tr>
<td>BMS-Adnexus</td>
<td>Adnectin</td>
<td>Preclinical development</td>
<td>BMS-962476</td>
<td><a href="http://www.adnexusux.com/science_adnectin.html">http://www.adnexusux.com/science_adnectin.html</a></td>
</tr>
</tbody>
</table>

Brautbar A and Ballantyne CM. Nat Rev Cardiol. 2011
PCSK9 Inhibitors - Clinical Trials

Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol

- Jonas S. Stein, M.D., Ph.D., Scott Mathre, M.D., Ph.D.,
- George W. Vencatesan, M.D., Ph.D., Neil Stoff, Ph.D.,
- Douglas Roach, M.D., William R. Smith, M.D.,
- Sharon Utzschneider, M.D., Brian H. Wu, M.D.,
- Maria Gaitanou, M.D.,
- Chele M. Davis, M.D.,
- Richard W. Wu, Ph.D.,
- Yuning Xu, Ph.D.,
- Therese S. Vargren, RN, M.B.A.,
- Elena Guardariano, B.S.,
- and Gail D. Seelig, M.D., Ph.D.

Effect of a monoclonal antibody to PCSK9, REGN727/ SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial

Safety and Efficacy of a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease, SAR236553/REGN727, in Patients With Primary Hypercholesterolaemia Receiving Ongoing Stable Atorvastatin Therapy

- Jaiwan J. McKeown, Prashant G. Michael J. Lopez, MD, CHU, Dea J. Korstanje, MIE
- Caroline Hanley, M.B.B.Ch., Ann-Catherine Filler, MD, Amsterdam, The Netherlands
- Richard P. Valleron, Cleveland Clinic, Ohio, and Paris, France

PCSK9 Inhibition in Subjects on Atorvastatin

- Atorvastatin, 80 mg, plus placebo
- Atorvastatin, 10 mg, plus SAR236553
- Atorvastatin, 80 mg, plus SAR236553

NEJM, Oct 31 2012
### Anacetrapib Effects on LDL-C and HDL-C

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Baseline</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>46</th>
<th>62</th>
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<tbody>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anacetrapib</td>
<td>771</td>
<td>716</td>
<td>687</td>
<td>646</td>
<td>604</td>
<td>568</td>
<td>540</td>
<td>547</td>
<td>607</td>
<td>647</td>
</tr>
<tr>
<td>Placebo</td>
<td>766</td>
<td>759</td>
<td>741</td>
<td>744</td>
<td>736</td>
<td>711</td>
<td>691</td>
<td>666</td>
<td>711</td>
<td>691</td>
</tr>
<tr>
<td><strong>LDL-C (mg/dL) (SE)</strong></td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
<td>160</td>
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<tr>
<td>Anacetrapib</td>
<td>771</td>
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<td>711</td>
<td>691</td>
<td>666</td>
<td>711</td>
<td>691</td>
</tr>
</tbody>
</table>

-39.8% (P<0.001)

### Analysis of Off-target Effects of CETP Inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Torcetrapib</th>
<th>Anacetrapib</th>
<th>Dalcetrapib</th>
<th>Evacetrapib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evidence of increased BP</td>
<td>Yes¹</td>
<td>No²</td>
<td>No³</td>
<td>No⁷</td>
</tr>
<tr>
<td>Preclinical evidence of increased aldosterone production*</td>
<td>Yes³</td>
<td>No⁴</td>
<td>No³</td>
<td>No⁵</td>
</tr>
<tr>
<td>Preclinical evidence of aldosterone synthase (CYP11B2) mRNA induction*</td>
<td>Yes³</td>
<td>?</td>
<td>No³</td>
<td>?</td>
</tr>
<tr>
<td>Preclinical evidence of RAAS-associated gene induction*</td>
<td>Yes⁵</td>
<td>?</td>
<td>No⁵</td>
<td>?</td>
</tr>
<tr>
<td>L-type Ca²⁺ channel activation*</td>
<td>Yes⁶</td>
<td>?</td>
<td>No⁶</td>
<td>?</td>
</tr>
</tbody>
</table>

7. Nicholls et al. JAMA 2011;306:2099-2109
Conclusions

• Lifestyle and pharmacologic interventions reduce short-term risk. Most events cannot be prevented.
• Aggressive LDL reduction halts progression but only induces minimal regression.
• Still uncertain whether TG and HDL modulation provides additional benefits.
• Novel interventions on the horizons for LDL and HDL modulation.