Evolving Pipeline of Lipid Altering Agents

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Disclosure

Dr. Koren is an employee of a company that receives study grants and consulting fees from manufacturers of PCSK9 inhibitors and other treatments for lipid disorders.

Dr. Koren enjoys sardines for breakfast and unseasoned pretzels…. so his opinions should be taken with a grain of salt.
“IT’S TOUGH TO MAKE PREDICTIONS, ESPECIALLY ABOUT THE FUTURE.”

– Yogi Berra
Lipid Treatment Predictions Circa 10 Years Ago:

- Aggressive use of the well tolerated statin class has achieved the greatest part of clinical gains related to LDL-C lowering.
- HDL and TG treatments represent the next productive next steps.
- Like hypertension, combination lipid therapy will become standard first line therapy.
- Reducing LDL-C to very low levels won’t occur for most patients and may raise risks.
Things I’ve learned over 10 years

• Statins represent the most successful class of preventative therapy ever, but they have tolerability and efficacy limits.

• Raising blood levels of HDL-C doesn’t improve clinical outcomes.

• Cells need cholesterol, but not necessarily LDL-C, to function. Patients without PCSK9 live normal lives with very low LDL-C and CV risk.

• To ensure appropriate cytosolic cholesterol levels, cells produce cholesterol de novo, and deploy extensive feedback mechanisms to maintain levels including genetic activation.
Outline
Evolving Pipeline of Lipid Agents

• Lipid problems and cardiovascular risk
• HDL/ Apo A1 treatment approach
• LDL-C treatment approach
• Statins/ Statin Intolerance
• Niche Treatments
• Predictions
In the statin era, cardiovascular disease death rates have declined but the burden remains high

Data from the National Institutes of Health…

- Between 2000 and 2010, US death rates attributable to CVD and CHD have been reduced by 26% and 34%, respectively.

Paradigm Shift?

• Clinicians treat lipid problems to reduce cardiovascular risk.

• Until recently, favorable changes in lipids were assumed to result in improved outcomes, particularly for LDL-C cholesterol.

• Recent events challenge this paradigm.
On June 28th 2016, drug developers and investors received shocking news.

Esperion Therapeutics Inc Sinks After FDA Says, "Ask Us in 2019"

The FDA leaves the biotech hanging.

• Company shares slumped 27 percent after saying its experimental drug may not win approval based on its ability to reduce LDL-C (20-39%), raising concerns it may take 6 more years to reach the U.S. market.

• Company must show that bempedoic acid prevents heart attacks, strokes and death from cardiovascular disease, a trial that won’t be done until 2021.
Paradigm Shift?

• The FDA decision on bempedoic acid probably signals the end of the prior lipid treatment development era as we have known it.

• Future lipid treatments will not likely receive approval based on their lipid effects alone.
Recent Lipid Trials that Failed to Show Primary Endpoint Benefits Despite “Favorable” Lipid Changes

Niacin: AIM HIGH; HPS THRIVE
Fenofibrate: FIELD; ACCORD
CETP inhibitors:
  ILLUMINATE (torcetrapib)
dal-OUTCOMES (dalcetripib)
ACCELERATE (evacetrapib)
HDL/ CETP: Strike One!
Torcetrapib Effect on Coronary Events

HDL/ CETP: Strike Two!
Dalcetrapib Did Not Reduce CVD Events

*Death from CHD, major nonfatal coronary events (acute MI, hospitalization for UA with objective evidence of acute myocardial ischemia, or cardiac arrest with resuscitation), or stroke of presumed atherothrombotic cause

CETP Inhibitors – Strike Three?
Evacetrapib Fails

Nicholls SJ, et al. Joint ACC/JAMA Late-Breaking Clinical Trials. Presented at: American College of Cardiology Scientific Session; April 2-4, 2016; Chicago
Has HDL treatment struck out?

• REVEAL Study using anacetrapib remains unreported.

• TA-8995, “best in class” CETP?
  – TULIP study: 10 mg TA-8995 lowered LDL-C by 45% and increased HDL-C by 179%; 10 mg of TA-8995 with statin therapy reduced LDL-C by an additional 48%.

AMGEN was impressed enough to take another swing…. They bought Dezima Pharma for $300 million.

Apolipoprotein A-1 Mimetics

- Epidemiologically, apolipoprotein A-1 (ApoA-1) levels are inversely associated with cardiovascular (CV) events.
- Human carriers of the ApoA-1 Milano variant have a reduced incidence of CV disease.
- ETC-216 / MDCO-216, a complex of dimeric ApoA-1 Milano and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, is being developed to reduce plaque burden and CV events.
- Regression of atherosclerotic plaque was observed using intravascular ultrasound with ETC-216/ MDCO-216.
- Early studies also show enhanced cholesterol efflux associated with ETC-216/ MDCO-216 which may distinguish it from the CETP inhibitors and niacin.
Cholesterol Efflux Capacity and ASCVD Events: Dallas Heart Study

ASCVD Events:
- MI
- Stroke
- PCI/ CABG
- CV Death

132 events over 9.4 years (median)

Log rank $p=0.002$

MDCO-216 and ABCA1-mediated efflux: change from baseline

D.G. Kallend et al. Eur Heart J Cardiovasc Pharmacother 2015;ehjcvp.pv041; ABCA1- ATP-binding cassette transporter protein
© The Author 2015. Published by Oxford University Press on behalf of the European Society of Cardiology.
# HDL/ Apo A1 Mimetics

Adapted from *Nature Reviews Drug Discovery* 13, 445–464

<table>
<thead>
<tr>
<th>Drug (developer)</th>
<th>Properties</th>
<th>Development status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anacetrapib (Merck)</td>
<td>A potent CETP inhibitor</td>
<td>In Phase III trials</td>
</tr>
<tr>
<td>Evacetrapib (Eli Lilly)</td>
<td>A potent CETP inhibitor</td>
<td>Failed in Phase III trials</td>
</tr>
<tr>
<td>Dalcetrapib (Hoffman La Roche)</td>
<td>A CETP inhibitor</td>
<td>Failed in a Phase III trials</td>
</tr>
<tr>
<td>Torcetrapib (Pfizer)</td>
<td>A CETP inhibitor</td>
<td>Failed in a Phase III trials</td>
</tr>
<tr>
<td>Apabetalone RVX-208 (Resverlogix)</td>
<td>An oral APOA1 transcriptional upregulator</td>
<td>ASSURE IVUS study failed; Phase III trials ongoing</td>
</tr>
<tr>
<td>CER-001 (Cerenis)</td>
<td>HDL mimetic from recombinant ApoA1 produced in mammalian cell expression systems complexed with phospholipids</td>
<td>Successful IVUS study; CARAT study ongoing</td>
</tr>
<tr>
<td>CSL112 (CSL Behring)</td>
<td>A HDL mimetic manufactured from purified, authentic human plasma APOA1 reconstituted with phospholipids</td>
<td>Phase II trials ongoing</td>
</tr>
<tr>
<td>Recombinant ApoA1 Milano/ MDCO-216 (The Medicines Company)</td>
<td>Naturally occurring mutated variant of the APOA1 protein associated with a low frequency of cardiovascular disease</td>
<td>Phase 2 IVUS trials ongoing</td>
</tr>
<tr>
<td>APP018/ D-4F (Bruin Pharma/ Novartis)</td>
<td>An oral APOA1 mimetic peptide; IV form also synthesized</td>
<td>Negative Phase 1 trials; No current development reported</td>
</tr>
<tr>
<td>Delipidated HDL</td>
<td>Lipid-poor HDL produced by selective delipidation of HDL can then be used for autologous reinfusion (apheresis)</td>
<td>Negative small IVUS trials; No current development reported</td>
</tr>
<tr>
<td>ACP-501 (AlphaCore Pharma/ MedImmune)</td>
<td>Recombinant human LCAT</td>
<td>Successful Phase I trial; Phase 2 studies; Possible orphan drug for LCAT deficiency</td>
</tr>
</tbody>
</table>

APOA1, apolipoprotein A1; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; LCAT, lecithin–cholesterol acyltransferase.
While hope springs eternal, HDL treatments won’t play out by next spring

Another bold prediction:

Neither will Tebow
Speaking of HOPE ....
Where there’s statins, there’s hope.
Speaking of HOPE .... Where there’s statins, there’s hope.

Statin Intolerance (SI)

- About 10% of patients with high CV risk decline (or express reluctance) to take statins after experiencing muscle-related symptoms, creating an unmet clinical need.

- SI patients represent a large undertreated group with hypercholesterolemia. LDL-C levels often exceed 160 mg/dl in trials.

- Currently the SI diagnosis is primarily based on subjective patient complaints, since most patients do not have elevations in CK enzymes. Genetic diagnosis may become clinically useful and payer recognized (e.g. SLCO1B1 polymorphisms).

- Conflicting rates of muscle-related symptoms in observational studies and RCTs raise questions about the true incidence of statin intolerance.

- Trials with PCSK9 mAbs have been conducted in patients with a history of intolerance to statins, or effective doses of statins such as GAUSS (1-3) and ODYSSEY Alternative.
GAUSS 3 Study

- Compared evolocumab and ezetimibe and in patients with SI history.
- Differed from earlier SI studies in that treated patients “failed” an atorvastatin challenge with cross-over (N= 492 screened; 218 randomized).
- Evolocumab “beat” ezetimibe in LDL-C lowering. Oral versus percutaneous treatment drop-out rates provides insight to challenge of this population.

JAMA. 2016 Apr 19; 315 (15) 1585-1587.
Other LDL-C Lowering Modalities

## Approaches to Targeting PCSK9

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Agent</th>
<th>Company/Sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td>Alirocumab (Praluent)</td>
<td>Sanofi/Regeneron</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>Evolocumab (Repatha)</td>
<td>Amgen</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>Bococizumab</td>
<td>Pfizer</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>RG7652</td>
<td>Roche/Genentech</td>
<td>2; no recent development</td>
</tr>
<tr>
<td></td>
<td>LGT-209</td>
<td>Novartis</td>
<td>2; no recent development</td>
</tr>
<tr>
<td></td>
<td>LY3015014</td>
<td>Eli Lilly</td>
<td>2; no recent development</td>
</tr>
<tr>
<td></td>
<td>1D05-IgG2, 1B20</td>
<td>Merck</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>J10, J16, J17</td>
<td>Pfizer</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Adnectins</td>
<td>BMS-962476</td>
<td>Bristol-Myers Squibb/Adnexus</td>
<td>1</td>
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<tr>
<td>Mimetic peptides</td>
<td>EGF-AB peptide fragment</td>
<td>Schering-Plough</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>LDLR (H306Y) subfragment</td>
<td>U.S. National Institutes of Health</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>LDLR DNA construct</td>
<td>U.S. National Institutes of Health</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Small-molecule inhibitors</td>
<td>SX-PCK9</td>
<td>Serometrix</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>TBD</td>
<td>Shifa Biomedical</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Antisense oligonucleotides</td>
<td>ISIS 394814</td>
<td>Ionis</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>SPC4061</td>
<td>Santaris-Pharma</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>SPC5011</td>
<td>Santaris-Pharma</td>
<td>1 (terminated)</td>
</tr>
<tr>
<td>RNA interference</td>
<td>ALN-PCS02</td>
<td>Alnylam</td>
<td>2</td>
</tr>
</tbody>
</table>
Structure of Monoclonal Antibody
Antisense Drugs Prevent the Translation of a Specific Targeted Protein

DNA → Transcription → mRNA → Translation → Disease-associated Protein

Antisense Drug (Single stranded, DNA-like) (Oligonucleotide)

RNase H1 Degrades mRNA → No Translation

No Disease-associated Proteins Produced

Introduction of RNA interference

• RNA interference (RNAi) is a phenomenon leading to post-transcriptional gene silencing (PTGS)
• RNAi is a naturally occurring biological process in which RNA molecules inhibit gene expression, typically by causing destruction of specific mRNA molecules.
• RNAi most likely evolved as a mechanism for cells to eliminate unwanted foreign genes.
Mechanism of RNA Interference

Bumcrot, D et al. Nature Chemical Biology 2, 711-710 (2006); RISC – RNA-induced silencing complexes
Niche Lipids Treatments

- Rare diseases will receive orphan drug status and likely become an exception to the outcomes study rule for lipid drug approvals.
- For example, homozygous hypercholesterolemia treatment won’t require outcomes data.
- Heterozygous hypercholesterolemia may also fall into this category.
- Other rare conditions:
  - Wolman’s disease
  - Cerebrotendinous xanthomatosis
  - Sitosterolemia
  - Refsum’s disease
Familial Chylomicronemia Syndrome (FCS) Pathophysiology

- Chylomicronemia: pathological persistence of chylomicrons in plasma following a fasting period of 10 to 14 hours\(^1,2\)
- In FCS, chylomicronemia is caused by inherited defects in chylomicron processing\(^2\)

Abbreviations: FFA, free fatty acid; TG, triglyceride; VLDL, very low-density lipoprotein.

# Genetics: Known Mutations Responsible for FCS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene product function</th>
<th>Molecular features</th>
<th>% of Monogenic mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LPL</strong></td>
<td>Hydrolysis of TGs and peripheral uptake of FFA</td>
<td>Severely reduced or absent LPL enzyme activity</td>
<td>95%</td>
</tr>
<tr>
<td><strong>APOC2</strong></td>
<td>Required cofactor of LPL</td>
<td>Absent or nonfunctional ApoC-II</td>
<td>2.0%</td>
</tr>
<tr>
<td><strong>GPIHBP1</strong></td>
<td>Stabilizes the binding of chylomicrons near LPL</td>
<td>Absent or defective GPI-HBP1</td>
<td>2.0%</td>
</tr>
<tr>
<td><strong>APOA5</strong></td>
<td>Enhancer of LPL activity</td>
<td>Absent or defective apoA-V</td>
<td>0.6%</td>
</tr>
<tr>
<td><strong>LMF1</strong></td>
<td>Chaperone molecule required for proper LPL folding</td>
<td>Absent or defective LMF1</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Adapted from Brahm, Nat Rev Endocrinol, 2015.

Abbreviations: FFA, free fatty acid; LPL, lipoprotein lipase; TG, triglyceride.

ApoC-III plays key role in determining TG levels

- Potent inhibitor of lipoprotein lipase (LPL) and hepatic uptake of triglyceride rich particles
- Inhibits both LPL-dependent and LPL-independent hepatic clearance of TG-rich lipoprotein remnants
- Volanesorsen is an antisence molecule that blocks ApoC-III

(Somewhat) Bold Predictions

• Except for rare genetic diseases, FDA will require outcomes studies for approval of lipid therapies. Approval based on LDL-C as a surrogate is over.

• Sponsors will launch many outcomes studies in statin intolerant patients once they feel comfortable that payers will accept a definition for this diagnosis. A better biomarker diagnosis will become a priority.

• FOURIER will report results in early 2017. This study and ODYSSEY Outcomes will define lipid therapy for years. If the studies produce robustly positive results, expect a pennant race to LDL of zero.
The future ain't what it used to be.

— Yogi Berra —
QUESTIONS?
Until recently abciximab was the only approved monoclonal antibody used in cardiology
Small interfering mRNA

1. Dicer cleavage of dsRNA
2. Population of siRNAs duplexes produced
3. Single Strand incorporation into RISC
4. Strand unwinding & separation
5. Targeting specific mRNA
6. Slicer mediated cleavage RNA degraded by exonuclease
7. Recycling of siRNA-RISC
8. RDRP amplification of siRNA