Residual Risk and Novel Lipid-lowering therapy:

What’s new? What works?

Vinaya Simha, M.D.

Endocrine University, March 5th 2019
Learning Objectives

1. Appreciate the limitations of current lipid-lowering therapies to fully address CVD risk
2. Understand the physiological basis of new treatment options for hypercholesterolemia
3. Understand the physiological basis for new therapies targeting triglyceride and HDL
4. Critically examine the role of novel lipid lowering therapies to reduce CVD risk
Lipid lowering therapy: WHY????

There’s no such thing as a sudden heart attack.
It requires years of preparation.

Cardiovascular disease is leading cause of death
Long pre-clinical period, opportunity for prevention
CHD risk reduction in Statin trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relative Risk Reduction in Major Coronary Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>34%</td>
</tr>
<tr>
<td>CARE</td>
<td>24%</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>31%</td>
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<tr>
<td>LIPID</td>
<td>24%</td>
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<tr>
<td>AFCAPS</td>
<td>40%</td>
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<tr>
<td>HPS</td>
<td>27%</td>
</tr>
<tr>
<td>PROSPER</td>
<td>19%</td>
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<tr>
<td>ASCOT</td>
<td>36%</td>
</tr>
</tbody>
</table>
Residual risk after statin therapy

How do we address Residual CV risk?

- More aggressive LDL cholesterol reduction
  - Statin add-on: Ezetimibe
  - PCSK9 inhibitors
  - Others: Mipomersen, Lomitapide, ATP Citrate Lyase inhibitor

- Reduction of other atherogenic lipid particles
  - Triglyceride rich lipoprotein reduction with
    - Anti Apo CIII
    - Anti ANGPTL3

- HDL targeted therapies
  - CETP inhibition
  - Recombinant HDL infusion
  - Apo A1 mimetics and modulators
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IMPROVE IT trial

- 18,144 patients
- High risk post ACS
- Simva 40 mg vs Simva 40 mg + Ezetimibe 10 mg
- Multi center 9 year study (7 year follow up)
- Median LDLc: 69.5 vs 53.7 mg/dL

Results:
- Primary Outcome: HR = 0.93 (0.88 – 0.98)
- Greater benefit in DM: 0.86 (0.78 – 0.94)
- ARR = 2%
Primary Endpoint — ITT

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

In DM: HR = 0.856 (0.779-0.939)

7-year event rates
Should Ezetimibe be used for CV risk reduction?

• Guidelines do recommend addition of ‘proven’ non-statin therapies under ‘select’ conditions

• IMPROVE-IT shows modest benefit in high risk patients for secondary prevention, especially those with diabetes

• No safety concerns with ezetimibe therapy

• FDA has not approved an application for ‘expanded indication’ of Ezetimibe in high risk patients
2018 Lipid Treatment guidelines

In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy.

- Very-high risk: Multiple ASCVD events OR one ASCVD + Multiple high risk conditions
- Reasonable to first add Ezetimibe
- Reasonable to add PCSK9i if LDLc still > 70
  - Long term (> 3y) safety and cost effectiveness (at mid 2018 prices) of PCSK9i therapy is uncertain
I'm going to switch you to a new medication that does more advertising.
PCSK9 inhibitors

Humanized monoclonal antibodies against PCSK9
- Heterozygous Familial Hypercholesterolemia
- Established cardiovascular disease who need additional LDL-C reduction

Alirocumab
75-150 mg
SC q 2 week

Evelocumab
140 mg
SC q 2 week

$14,000 - $16,000/y

$5,000 - $6,000/y
Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

ODYSSSEY LONG TERM: Efficacy

- LDL chol ↓ 62%
- 80% achieved LDL < 70 mg/dL
- Non HDL chol and Apo B ↓ 52%
- Lp (a) ↓ 30%
- Triglycerides ↓ 15%
- HDL chol ↑ 4%
ODYSSEY LONG TERM: Safety

- No difference in overall rate of adverse events
  - Total, serious or leading to drug discontinuation
- Specific adverse events slightly higher
  - Injection site reactions (5.9% vs 4.2%)
  - Myalgia (5.4% vs 2.9%)
  - Neurocognitive events (1.2% vs 0.5%)
- No increase in new Diabetes or worsening
- No change in liver or muscle enzymes
- No increase in AE in those with LDL < 25 mg/dL
Alirocumab Pooled data: Safety in patients with very low LDL cholesterol

• Pooled data from 14 trials
• ≈ 4000 patient-year exposure to Alirocumab
• 25% had LDL-C < 25 mg/dL
• 10% had LDL-C < 15 mg/dL
• Higher incidence of cataracts in those with LDL-C < 25 compared to > 25 mg/dL
• No difference in: Neurological/Neurocognitive events, Diabetes or other adverse effects

Robinson et al. JACC Feb 7, 2017
968 patients with CHD
Monthly Evolocumab 420 mg
76 weeks
LDLc: 93 vs 36.6 mg/dL
Greater plaque regression
Evolocumab and clinical outcomes in patients with CVD

- 27,564 patients with ASCVD
- Mean duration of f/u: 2.2 y
- LDLc: 92 vs 30 mg/dL
- ARR: 1.5%, RRR 15%
- No difference in adverse events including neurocognitive effects

Sabatine et al NEJM 2017
Cost effectiveness of PCSK9i therapy
A Highly Durable RNAi Therapeutic Inhibitor of PCSK9

Kevin Fitzgerald, Ph.D., Suellen White, B.S.N., Anna Borodovsky, Ph.D.,

Change in LDL Cholesterol Level in Single-Dose Cohorts

- Placebo (N=6)
- Inclisiran, 25 mg (N=3)
- Inclisiran, 100 mg (N=3)
- Inclisiran, 300 mg (N=3)
- Inclisiran, 500 mg (N=3)
- Inclisiran, 800 mg (N=6)
Antisense oligonucleotide
PCSK9 inhibitors: summary

- Very potent LDL-C reduction with seemingly minimal adverse effects (Neurocognitive)
- Outcome trials have demonstrated clinical efficacy, albeit moderate
- Two PCSK9 monoclonal antibodies approved for use in FH and CHD patients as add-on to statin (and Ezetimibe) therapy
- Questions remain about Cost effectiveness
- RNAi technology has potential for ‘minimally disruptive medication use’
Potential targets for LDL reduction

- ATP Citrate Lyase inhibitor
- MTP inhibitor, *Lomitapide*
- Apo B Anti sense Oligonucleotide, *Mipomersin*
- PCSK9 antibody
- Statin
ATP Citrate Lyase Inhibitor

- ATP Citrate Lyase catalyzes the conversion of Citrate to Oxaloacetate and Acetyl CoA
- Acetyl CoA is the building block for de novo cholesterol and fatty acid biosynthesis
- Phase 1 and Phase 2 studies completed
- Oral, once a day
- 20-40% reduction in LDL-C
- Relatively safe, possible use in statin intolerant individuals
- Additional benefit on glucose and weight
ATP Citrate Lyase inhibition: Metabolic effects

Inhibition of ACL

Acyl-CoA synthetase

Inhibition by ETC-1002-CoA

ATP-citrate lyase

Fatty acid synthesis

Fatty acid oxidation

HMG-CoA reductase

Inhibition by statins

HMG-CoA

Mevalonic acid

Squalene

Lanosterol

Cholesterol synthesis

Cholesterol synthesis

LDL-receptor upregulation

ETC-1002

AMPK activation

Activation by ETC-1002

AMPK

Glucose

Lipids

Inflammation

Blood pressure

Weight gain

LDC-C
Bempedoic Acid

Bempedoic acid is a convenient, complementary, consistent, once-daily, oral LDL-C lowering drug that significantly reduces elevated LDL-C levels in patients with hypercholesterolemia, including patients inadequately treated with current lipid-modifying therapies. Bempedoic acid, a first-in-class, non-statin, targeted therapy, works in the liver to block cholesterol biosynthesis.

In the liver, bempedoic acid is converted to a coenzyme A (CoA) derivative, or ETC-1002-CoA, which directly inhibits ATP citrate lyase (ACL), a key enzyme that supplies substrate for cholesterol and fatty acid synthesis in the liver. Inhibition of ACL by ETC-1002-CoA results in reduced cholesterol synthesis and upregulation of LDL receptor activity in the liver. This promotes the removal of LDL-C from the blood.

To date, Esperion has completed Phase 1 and Phase 2 clinical studies conducted in approximately 1,300 patients and treated over 800 patients with bempedoic acid. The Company is currently evaluating bempedoic acid in four, fully enrolled global pivotal Phase 3 LDL-C lowering efficacy and safety studies consisting of approximately 3,600 patients, a Phase 3 open-label extension study and the CLEAR Outcomes global cardiovascular outcomes trial (CVOT).

Bempedoic Acid Phase 2 Clinical Studies**
Mipomersen: Apo B anti sense oligonucleotide

- 20 base nucleotide which is complementary in sequence to a segment of human Apo B-100
- Mipomersen-mRNA complex targeted by Rnase H
- Decreases synthesis of Apo-B and Apo-B containing particles, including Lp(a)
- Catabolized by endo and exonucleases, no dependence on cytochrome P450 metabolism
- Weekly subcutaneous injections (200 mg)
- Approved by FDA for use in patients with Homozygous Familial Hypercholesterolemia in conjunction with low fat diet and other lipid-lowering therapies through a REMS program
- Adverse effects: Hepatic steatosis, injection site reactions
Lomitapide

- Oral inhibitor of Microsomal Triglyceride Transfer Protein (MTP)
- MTP in the hepatocyte ER initiates Apo B lipidation
- Open-label Phase 3 trial in 29 Ho FH patients for 26 weeks
- 50% LDL reduction (baseline LDL-C = 336)
- Approved for use in Ho FH patients through a REMS program
- Expensive; concern for hepatic steatosis
How do we address Residual CV risk?

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Metabolism of Triglyceride Rich Lipoproteins

VLDL/Chylomicrons

Hepatic Uptake and catabolism

LDL

IDL/Remnants

LPL

Apo CIII, ANGPTL3/4

Apo AV

APO

TG

CH
Apo C-III and Triglyceride metabolism

APOC3 regulates TG metabolism by inhibiting an LPL-dependent pathway and one or more LPL-independent pathways.

LPL-dependent pathway

LPL-independent pathway

Hydrolysis

TRL remnant removal

Normal TG levels (<150 mg/dl)

Gaudet NEJM 2014
• ISIS 304801: second generation antisense inhibitor of Apo C-III synthesis
• Phase 2 randomized placebo controlled dose-ranging study
• 85 patients with HTG (250 – 2000 mg/dL) treated for 13 w
• Primary outcome: % change in Apo C-III level
Effects of Anti Apo C-III ASO

↓ Apo C-III by 40-80%

↓ TG by 31-71%

COMPASS study: Abstract NLA 2017

- Multicenter, double blind placebo controlled RCT of Volanesorsen
- 113 patients with fasting TG > 500 mg/dL
- Randomized 2:1 to Volanesorsen 300 mg subq weekly or placebo for 26 weeks
- 72 ± 17% reduction in TG at 3 months (p<0.0001)
- Similar reduction in subset of 7 patients with Familial Chylomicronemia syndrome
- Pancreatitis: 0 vs 6 (p = 0.01)
- Adverse events: Injection site reactions, serum sickness,
APPROACH study: Abstract NLA 2017

• Multicenter, double blind placebo controlled RCT of Volanesorsen

• 66 Familial Chylomicronemia (FCS) patients with fasting TG > 750 mg/dL

• Randomized 1:1 to Volanesorsen 300 mg subq weekly or placebo for 52 weeks

• TG reduction: 77% at 13 weeks, 50% at 52 weeks

• Pancreatitis: No episodes in drug treated patients, decrease in self reported abdominal pain.

• Adverse events: Injection site reactions, Thrombocytopenia (5 early terminations).
In split vote, FDA advisory committee backs Akcea/Ionis’ volanesorsen

by Amirah Al Idrus | May 10, 2018 6:50pm

MEMORANDUM

DATE:        April 13, 2018
FROM:        James P. Smith, MD, MS
             Deputy Director, Division of Metabolism and Endocrinology Products (DMEP)
             Office of Drug Evaluation II / Office of New Drugs
             Center for Drug Evaluation & Research
TO:          Members and Consultants, Endocrinologic & Metabolic Drugs Advisory Committee (EMDAC)
SUBJECT:     EMDAC meeting for volanesorsen (Waylivra)
FDA Rejects Volanesorsen (Waylivra) for Rare Triglyceride Disorder

Megan Brooks
September 04, 2018

The US Food and Drug Administration (FDA) has rejected the new drug application for volanesorsen (Waylivra, Akcea) for the ultrarare lipid disorder familial chylomicronemia syndrome (FCS), the companies have announced.

In a news release, the companies said they received a complete response letter from the FDA but did not divulge the reasons for the rejection or the concerns the FDA had.
Summary: Novel Triglyceride lowering therapy

• Anti Apo CIII and Anti ANGPTL 3/4
• Focused on improving LPL mediated clearance of TG-rich lipoproteins
• ? Possible non LPL mediated uptake of remnant particles
• Useful for reducing risk of pancreatitis in patients with severe HTG
• May reduce CVD risk in patients with mild-moderate HTG
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Novel HDL-based therapies

- Recombinant HDL and Apo A1 Milano infusion
- Oral Apo A1 mimetics
- Apo A1 up-regulators
- CETP inhibitors
  - Torcetrapib: Increased CV mortality in ILLUMINATE trial (? Off target effects)
  - Dalcetrapib: DAL-OUTCOMES stopped prematurely for futility (Lipid changes unimpressive)
  - Evacetrapib: ↓ LDL 35-40%, ↑ HDL 140%; ACCELERATE stopped for futility
  - Anacetrapib: ↓ LDL 30%, ↑ HDL 135%, REVEAL showed moderate benefit, but will not be developed
Lipid lowering medications: Summary

- Statins have helped reduce CVD burden, but residual risk and disease is still enormous
- Role of combination therapy is not clear but high risk patients may benefit. New guidelines suggest LDLc threshold of 70 mg/dL for starting Ezetimibe and PCSK9i
- Mipomersen and Juxtapid are approved for treatment of homozygous FH
- Monoclonal PCSK9 antibodies have shown great promise, and are approved for treatment of heterozygous FH, and those with established CHD and high lipids
- Anti Apo CIII therapy is also promising in patients with elevated triglycerides. Volanesorsen not approved due to thrombocytopenia
- Benefit of HDL modifying therapies is not clear
“Whenever your cholesterol gets too high, a sensor will send out a signal that automatically locks the kitchen door and turns on your treadmill.”
Thank You

Simha.AJ@mayo.edu