Dyslipidemia Treatment in 2016
Novel Agents
Combination Therapies
Statin Intolerance
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Update on Dyslipidemia Therapy in 2016

- High potency statins were the sole focus of the 2013 guidelines due to lack of RCT for other therapies
- HDL has lost ground as a therapeutic target but remains a critical marker of CVD risk
- CETP is almost out (waiting for anacetrapib REVEAL study) since ACCELERATE/evacetrapib was halted
- Residual risk is well defined
- Statin intolerance is now well defined (Gauss 2/3 studies)
- Combination therapy with niacin/fibrates is out
- Combination therapy with ezetimibe, BAS and PCSK9 is recommended
RESIDUAL RISK

• DESPITE MAXIMAL STATIN THERAPIES IN CLINICAL TRIALS
• Risk of CV mortality and MACE CV events are not eliminated (but certainly better than placebo or less potent therapy) estimated 60% residual risk
• Even after controlling for other risk factors – there is a need to further reduce dyslipidemia dependent risk of CV events
• Over the last decade research into add on therapies or alternative therapies has become the “HOLY GRAIL” of risk reduction in Dyslipidemia
<table>
<thead>
<tr>
<th>Category</th>
<th>LDL Reduction (%)</th>
<th>N</th>
<th>Trial</th>
<th>Patients Experiencing Major Coronary Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>-36%</td>
<td>4,444</td>
<td>4S</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>-25%</td>
<td>9,014</td>
<td>LIPID</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>-28%</td>
<td>4,159</td>
<td>CARE</td>
<td>75%</td>
</tr>
<tr>
<td>High Risk</td>
<td>-29%</td>
<td>20,536</td>
<td>HPS</td>
<td>73%</td>
</tr>
<tr>
<td>Primary</td>
<td>-26%</td>
<td>6,595</td>
<td>WOS</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>-27%</td>
<td>6,605</td>
<td>AFCAPS/TexCAPS</td>
<td>62%</td>
</tr>
</tbody>
</table>

WHAT ABOUT THOSE PATIENTS WHO DON’T ACHIEVE THEIR TARGET?
Approximately 70% of patients at the highest risk* are not at optional < 70 mg/dL (< 1.8 mmol/L) LDL-C goal†

* Very high risk defined as: CHD plus ≥ 2 major risk factors. Data shown are from a 2006-2007 multinational survey, of which 2,334 patients were considered very high risk. Countries in this analysis included the United States, Canada, Spain, the Netherlands, France, Taiwan, Korea, Brazil, and Mexico.

† National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) US optional goal < 70 mg/dL (1.8 mmol/L)
Number of High Risk US Adults Achieving LDL-C Levels of < 100 mg/dL or LDL-C Levels of < 70 mg/dL, AN EVEN BIGGER PROBLEM FOR HIGH RISK PATIENTS

High-risk patients were defined as patients older than 18 years with a history of CHD or CHD risk equivalent who had the latest complete lipid panel measurement and were treated with statin monotherapy for > 90 days.

EMR = electronic medical record database collected from 40,000 clinicians and 20,000 NP and PA (GE Centricity); Administrative Claims Database of the medical and pharmacy claims for 42MM patients enrolled in a large US managed care plan (Clininformatics DataMart, a product of OptumInsight Life Sciences); NHANES = National Health and Nutrition Examination Survey, a national public health survey conducted by the CDC of a nationally representative sample of 5000 individuals each year across a country.

As per NCEP ATP III, the LDL-C goal patients was <100 mg/dL. High-risk patients were also evaluated for the optional goal of LDL-C <70 mg/dL, as per the 2004 update to the NCEP ATP III Guidelines.

Residual CV risk remains even at lower LDL-C levels

Despite lipid lowering therapy, patients still have residual CV risk. Therefore, these cardiovascular patients must be closely monitored.
HOW DOES THIS HAPPEN & DOES IT MATTER?

- UNTREATED (Not following Guidelines?)
- SUBOPTIMALLY TREATED
- UNABLE TO LOWER WITH STATIN (FAMILIAL HYPERLIPIDEMIA)
- TREATMENT DISCONTINUED / STATIN INTOLERANCE
- WHEN SUB OPTIMAL LDL IS PRESENT RISK CLEARLY INCREASES!!!
Residual Risk Should we use ALTERNATE non LDL Therapy?

- Not taking a statin or unable to take a statin (non adherence/intolerance) therefore becomes a major cause of residual risk as the patient is unable to take the most effective therapy in CV risk prevention.
- Can we lower risk by non LDL targeted therapy in combination or alone?
- Raising HDL – niacin, fibrates, CETP
- Lowering TG- fibrates
- Inflammation – methotrexate
- PCSk9 inhibition
Residual Risk & LDL Targets

• Combination therapy implies need for ADDITIONAL effectiveness
• Or should we just lower LDL even more :-
  • Statin Combination with Ezetemibe
  • Profound LDL lowering with PCSk9

• WHAT IS THE EVIDENCE BASE ?
Low HDL-C Increases CVD Risk Even if LDL-C Levels Are Very Well Controlled

<table>
<thead>
<tr>
<th>HDL-C Quintiles, a mg/dL</th>
<th>Hazard Ratio vs. Q1 b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>0.85</td>
</tr>
<tr>
<td>Q3</td>
<td>0.57</td>
</tr>
<tr>
<td>Q4</td>
<td>0.55</td>
</tr>
<tr>
<td>Q5</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Patients With LDL-C ≤70 mg/dL On Statin a,b

- <37
- 37 to <42
- 42 to <47
- 47 to <55
- ≥55

Similar Inverse Relationship also seen in:

*On-treatment level (3 months statin therapy); N=2,661
Mean LDL-C, 58 mg/dl; mean TG, 126 mg/dl; *P=.03 for differences among quartiles of HDL-C

## Lipid Effects of CETP-Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Change from Baseline</th>
<th>CETP Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDL-C</td>
<td>Apo A-I</td>
</tr>
<tr>
<td>Dalcetrapib&lt;sup&gt;1&lt;/sup&gt; 600 mg/day</td>
<td>↑31%</td>
<td>↑14%</td>
</tr>
<tr>
<td>Anacetrapib&lt;sup&gt;2&lt;/sup&gt; 100 mg/day</td>
<td>↑138%</td>
<td>↑45%</td>
</tr>
<tr>
<td>Evacetrapib&lt;sup&gt;3&lt;/sup&gt; 100 mg/day</td>
<td>↑79%</td>
<td>(↑36%&lt;sup&gt;4&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>

- Changes added to background statin therapy
- (Anacetrapib partitions to adipocytes and has est. T<sub>1/2</sub> > 1 year)<sup>5</sup>

<sup>1</sup>Stein EA. Am J Cardiol. 2009 (12 Weeks);  
<sup>2</sup>Cannon CP. N Engl J Med. 2010 (24 Weeks);  
<sup>3</sup>Nicholls S. JAMA. 2011 (12 weeks; changes with atorva 20 mg/day);  
<sup>4</sup>Suico JG, et al. J Pharm Pharmacol. 2014 (2 weeks, no statin);  

ND = no data
ACCELERATE TRIAL

(Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High-Risk for Vascular Outcomes)

- N=12,000 with:
  - ACS (30-365 days earlier), or
  - CVA, or PAD, or
  - T2DM with CAD
- Background LDL-C lowering with statin
- Randomized to evacetrapib 130 mg/day (new formulation) vs. placebo
- Scheduled follow-up: 4 years (started October 2012, estimated completion July 2016)
- Primary outcome: composite endpoint of CV death, nonfatal MI, CVA, hospitalization for unstable angina, or coronary revascularization

CETP Inhibitor Development

- Torcetrapib: ~80% increase in HDL-C
- Evacetrapib: ~80% increase in HDL-C
- Anacetrapib: ~140% increase in HDL-C
- Dalcetrapib: ~30% increase in HDL-C

- Torcetrapib and Evacetrapib: X (stop development)
- Anacetrapib: no X (continue development)
- Dalcetrapib: X (stop development)

- ↑CVD (25%) but OK HDL function (off-target effect?)
- *No ↓CVD, but OK HDL function +/- anti athero?


*Dalcetrapib development stopped May 7, 2012 due to lack of efficacy in the Dal-OUTcomes CVD endpoint trial.*
HPS-3/TIMI-55/REVEAL: CVD Endpoint Trial of Anacetrapib
(Randomized EVevaluation of the Effects of Anacetrapib through Lipid-modification)

- N=30,624, prior CVD; recruiting in North America, Europe, and Asia
- Background LDL-C lowering with atorvastatin
- Randomized to anacetrapib 100 mg/day vs. placebo
- Scheduled follow-up: 4 years (started 6/2011, estimated completion 1/2017)
- Primary outcome: major coronary event defined as CV death, MI, or coronary revascularization procedure

http://www.revealtrial.org;
WHAT ABOUT COMBINATION WITH FIBRATES AND NIACIN?
ACCORD Lipid

- Primary Outcome: First occurrence of nonfatal MI, nonfatal stroke, or CV death
- 5518 pts T2DM treated with simvastatin randomized to fenofibrate or placebo
- The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

Combination Therapy – Statins and Niacin

AIM HIGH Primary Endpoint
(death from CAD, nonfatal MI, stroke, hospitalization for ACS, sx-driven coronary or cerebral revascularization)

Event Rate (%)

- Niacin + Statin: 16.4%
- Placebo + Statin: 16.2%

P = .79 by log-rank test

Combination Therapy – Statins and Niacin

HPS2-THRIVE Primary End Point
(nonfatal MI, death from coronary causes, stroke, or arterial revascularization)

Event Rate (%)

- Placebo: 15.0%
- Niacin-laropiprant: 14.5%

P = .29 by log-rank test

Fenofibrates

Niacin (HDL Hypothesis)

Statins for Secondary Prevention

Statins for Primary Prevention
### Patient Populations with HIGH Unmet Need for Additional LDL-C Lowering

<table>
<thead>
<tr>
<th>FH Population in EU</th>
<th>High / Very High CV Risk Population</th>
<th>Statin-Intolerant Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Genetic disorder</td>
<td>• Previous MI/stroke / CVD or multiple CV risk factors incl. T2DM</td>
<td>• 10-15% on high-intensity statins show intolerance⁶</td>
</tr>
<tr>
<td>• High risk of early CHD</td>
<td>• Difficult to achieve LDL-C goals, despite current therapies⁵</td>
<td>• Many discontinue due to muscle pain and/or weakness</td>
</tr>
<tr>
<td>• HeFH prevalence 1:200 to 1:250¹²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Untreated LDL-C of 200-400 mg/dL³</td>
<td><strong>20% with CHD not at goal (&lt;100 mg/dL [2.6 mmol/L])</strong></td>
<td></td>
</tr>
<tr>
<td>79% with HeFH not at goal (&lt;100 mg/dL [2.6 mmol/L])⁴</td>
<td><strong>59% at very high CV risk not at goal (&lt;70 mg/dL [1.8 mmol/L])</strong></td>
<td>Nearly all patients who need considerable LDL-C reductions will not reach goal</td>
</tr>
</tbody>
</table>

Dyslipidemia in Familial Hypercholesterolemia

PATIENTS WITH VERY HIGH BASELINE AND HYPORESPONDERS TO STATINS = UNABLE TO ACHIEVE TARGET WITH STATIN THERAPY
## Familial Hypercholesterolemia Phenotypes

<table>
<thead>
<tr>
<th>FH Heterozygotes</th>
<th>FH Homozygotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ 1 in 200 to 1:500 persons worldwide&lt;sup&gt;1,4&lt;/sup&gt;</td>
<td>~ 1 in 1,000,000 persons worldwide&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 mutated allele&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2 mutated alleles&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>TC: 350 to 500 mg/dL&lt;sup&gt;3&lt;/sup&gt;</td>
<td>TC: &gt; 500 to &gt; 1,000 mg/dL&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>LDL-C: 200–400 mg/dL&lt;sup&gt;1,2&lt;/sup&gt;</strong></td>
<td><strong>LDL-C: &gt; 600 mg/dL&lt;sup&gt;2&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>Half the number of LDLR expressed&lt;sup&gt;3&lt;/sup&gt;</td>
<td>LDLR activity absent or dysfunctional&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

TC = total cholesterol

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Despite Maximal Treatment, A Low Percentage of Patients with HeFH Achieve LDL-C < 100 mg/dL

In a Randomized Global Clinical Trial of HeFH Patients, A Low Percentage Achieved LDL-C Levels of < 100 mg/dL on Maximal Treatment*

In Netherlands Estimates of HeFH Patients On Maximal Lipid Lowering Therapy Achieving LDL-C < 100 mg/dL**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Statin 1</th>
<th>Statin 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;130 mg/dL</td>
<td></td>
<td>blue</td>
<td>red</td>
</tr>
<tr>
<td>&lt;100 mg/dL</td>
<td></td>
<td>n = 103</td>
<td>p &lt; 0.05, n = 103</td>
</tr>
<tr>
<td>&gt;100 mg/dL</td>
<td></td>
<td>n = 37</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
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</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg/dL</td>
<td></td>
<td>blue</td>
<td>red</td>
</tr>
<tr>
<td>&gt;100 mg/dL</td>
<td></td>
<td>n = 67</td>
<td></td>
</tr>
</tbody>
</table>

* NCEP Adult Treatment Panel III Risk Category: Medium Risk: <130 mg/dL (3.4 mmol/L); ≥ 2 risk factors, 10-year risk of coronary artery disease ≤ 20%; High Risk: <100 mg/dL (2.6 mmol/L); coronary artery disease or its risk equivalents (atherosclerosis, diabetes, or 10-year risk > 20%). 18 week RCT, double-blind parallel group where heterozygous (He) FH patients initiated statin treatment at 20 mg with forced titration to 40 and 80 mg in 1999-2000. N = 623 randomized; p Values were obtained from a logistic regression model. Global population consisted of 31% US patients.

** Adults with HeFH were part of a cross-sectional study. 96% were on statin treatment where 34% were on maximum dose. N = 1249 met inclusion criteria. n = 304 patients on maximal therapy. Maximum lipid-lowering therapy was defined as maximum statin doses in combination with ezetimibe. Using outpatient visits to Lipid Clinics after February 2006.

Mean Calculated LDL-C Levels
Pool of FH I and II Studies (Alirocumab 75/150 mg q2w)

- ΔW24: -56.1 (2.1)%
- ΔW52: -58.4 (2.5)%
- ΔW78: -56.1 (2.6)%

Per-protocol
Week 12 Dose Increase (41.8%)

All % Changes
P < .0001 Versus Placebo

Reduction in LDL-C Level from Baseline at Week 12
According to Mutation Status for Heterozygous FH Patients

According to Mutation Status for Heterozygous FH Patients

- **APOB** defective
  - Alirocumab 75 mg Q2W: -48.9% (SE: 0.2)
  - Alirocumab 150 mg Q2W: -47.3% (SE: 1.5)
  - Control: -43.2% (SE: 3.1)

- **LDLR** defective
  - Alirocumab 75 mg Q2W: -56.7% (SE: 47.3)
  - Alirocumab 150 mg Q2W: -61.6% (SE: 56.7)
  - Control: -53.3% (SE: 61.6)

- **LDLR** negative
  - Alirocumab 75 mg Q2W: -93.4% (SE: 93.4)
  - Alirocumab 150 mg Q2W: -43.2% (SE: 43.2)
  - Control: -56.4% (SE: 56.4)

- **PCSK9 GOF**
  - Alirocumab 75 mg Q2W: -93.4% (SE: 93.4)
  - Alirocumab 150 mg Q2W: -43.2% (SE: 43.2)
  - Control: -56.4% (SE: 56.4)

- No known mutation
  - Alirocumab 75 mg Q2W: -93.4% (SE: 93.4)
  - Alirocumab 150 mg Q2W: -43.2% (SE: 43.2)
  - Control: -56.4% (SE: 56.4)

SE, standard error

Poster number 1293M-05
FOR THE HIGH RISK PATIENT SHOULD WE NOW GO EVEN LOWER WITH LDL? AND HOW COULD WE ACHIEVE THIS GOAL?
Cholesterol Trialist Collaboration
Meta-Analysis of Dyslipidemia Trials

Every 1 mmol LDL reduction = 20% event rate reduction

CTT Collaborators. Lancet. 2005; 366:1267-78
### Percent Reduction vs. Treat-to-Target


<table>
<thead>
<tr>
<th>Clinical risk categories</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those with clinical ASCVD</td>
<td>High-intensity statin therapy. If 50% reduction is not reached drug combination may be considered.</td>
</tr>
<tr>
<td>Diabetes mellitus (Type I or Type II) without ASCVD but with LDL-C between 1.8 and 4.9 mmol/L</td>
<td>Diabetes with high risk: High-intensity statin therapy. Diabetes with low risk: Moderate-intensity statin therapy. High-intensity statin therapy aimed at achieving at least 50% reduction of LDL-C.</td>
</tr>
<tr>
<td>Those with primary elevation of LDL-cholesterol (LDL-C) &gt; 4.9 mmol/L</td>
<td>Moderate-to-high-intensity statin therapy if ASCVD risk &gt; 7.5%. If risk 5–7.5% risk of CVD event: Reasonable to consider moderate-intensity statin therapy.</td>
</tr>
</tbody>
</table>

If none of the above but with estimated 10-year ASCVD risk of 7.5% or more using a pooled populations risk calculator, If risk-based assessment treatment decision uncertain assessment of 1 or more of family history, hs-C-reactive protein, CAC Score or ABPM may be considered (Class IIb, Level E), contribution of ApoB, CKD, microalbuminuria or cardio-respiratory fitness is uncertain (Level N) and CIMT is not recommended for routine assessment of individual patients (Level N).

**ESC/EAS (2011) Guidelines for the management of dyslipidaemias**

<table>
<thead>
<tr>
<th>Clinical risk categories</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those with CVD</td>
<td>LDL-C &lt; 1.8 mmol/L or 50% reduction in LDL-C</td>
</tr>
<tr>
<td>Diabetes mellitus (Type I) or Type I with target organ damage</td>
<td>LDL-C &lt; 1.8 mmol/L or 50% reduction in LDL-C</td>
</tr>
<tr>
<td>Familial dyslipidaemia (FH or FCH or chylomiconaemia)</td>
<td>LDL-C &lt; 2.5 mmol/L or maximal reduction in LDL-C with any possible drug combination plus LDL apheresis</td>
</tr>
</tbody>
</table>

If none of the above estimate 10-year risk of a first fatal atherosclerotic CV event (SCORE), with a SCORE > 10% considered, very high risk, SCORE 5–10% considered high risk and SCORE 1–5% moderate risk. Above risk can be modified if additional information is available on: ↑ TGs, social deprivation, central obesity, ↑ Lipoprotein(a), familial hypercholesterolaemia, subclinical atherosclerosis, CKD, family history of premature CVD (x 1.7 – women, x 2 – men), very high HDL-C, family history of longevity.

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Residual Risk Despite Statin Therapy in TNT effect of additional Risk Factors

The TNT study was a prospective, double-blind, parallel-group trial done at 256 sites in 14 countries between April, 1998, and August, 2004, with a median follow-up of 4.9 years. 10,001 patients were enrolled aged 35-75 years with clinically evident coronary heart disease. Our analysis includes 5584 patients with metabolic syndrome based on the 2005 NCEP ATP III criteria. Patients were randomly assigned to receive either atorvastatin 10 mg per day (n=2820) or 80 mg per day (n=2764). The primary outcome measure was time to first major cardiovascular event, defined as death from coronary heart disease, non-fatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or non-fatal stroke.

ESC / EAS Guidelines Risk Based Targets

**Very High Risk**
- SCORE ≥ 10%
- Documented CVD
- DM + ≥ 1 FR and/or TOD*
- Severe CKD (< 30)

**High Risk**
- SCORE 10 - 5%
- DM 0 FR
- Markedly elevated RF
- Moderate CKD (30-60)

**Moderate Risk**
- SCORE 5 - 1%

**Low Risk**
- SCORE < 1%

* TOD= target organ damage (such as microalbuminuria 30-300 mg/24h)

IMPROVE IT - LOWER IS BETTER REAFFIRMED

• Combination STATIN (simvastatin 40 mg with Ezetimibe 10 mg)

• REVISITED AGAIN IN IMPROVE IT IN HIGH and VERY HIGH RISK ASCVD AND ACS PATIENTS

• ACHIEVED LOWER LDL 53 MG/DL THAN THE HIGH INTENSITY STATIN 69 MG/DL

• SIGNIFICANT REDUCTION IN 7 POINT MACCE CV OUTCOME OVER 6 YEARS OF STUDY
IMPROVE-IT: LDL-C and Lipid Changes

<table>
<thead>
<tr>
<th></th>
<th>1Yr Mean LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Δ in mg/dL:
- LDL-C: -16.7, -19.3, -16.7, +0.6, -0.5

Median Time avg. 69.5 vs. 53.7 mg/d

Number at risk:
- EZ/Simva: 8990, 8889, 8230, 7701, 7264, 6864, 6583, 6256, 5734, 5354, 4508, 3484, 2608, 1078
- Simva: 9009, 8921, 8306, 7843, 7289, 6939, 6607, 6192, 5684, 5267, 4395, 3387, 2569, 1068

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

HR 0.936 CI (0.89-0.99)
P = 0.016

- Ezetimibe/simvastatin: 32.7%
- Simvastatin: 34.7%

Simvastatin: 2,742 events
Ezetimibe/Simvastatin: 2,572 events
NTT = 50

Reduction in Total (First and Additional Recurrent) Cardiovascular Events with Ezetimibe/Simvastatin Compared with Simvastatin Alone Post Acute Coronary Syndromes in the IMPROVE-IT Trial

Between-group
Simva minus EZ/Simva
LDL-C delta = -16.7 mg/dL

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin Alone</th>
<th>Ezetimibe / Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Events</td>
<td>4983</td>
<td>4562</td>
</tr>
<tr>
<td>Prevented P=.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional Recurrent Events P=.02</td>
<td>2241</td>
<td>1990</td>
</tr>
<tr>
<td>1st Recurrent Event P=.016</td>
<td>2742</td>
<td>2572</td>
</tr>
<tr>
<td>-251 fewer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9% RRR in total events HR 0.91, 95% CI, 0.85-0.97 P=.007 NNT=23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-170 fewer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.4% RRR in 1st events HR 0.936, 95% CI, 0.887-0.988 P=.016 NNT=50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-421 Fewer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12% RRR in additional events HR 0.88, 95% CI 0.79-0.98 P=.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total NF MI (IRR 0.87, 95% CI, 0.85-0.97 P=.004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF stroke (IRR 0.77, P=.005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CHD death, NF MI, urgent revasc events were reduced 15% (IRR 0.85, P=.002)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

THE TREATMENT GAP

• IT IS INSUFFICIENT TO BE COMPLACENT ABOUT JUST BEING ON A STATIN
• THE GOALS FOR TREATMENT HAVE BEEN REEMPHASIZED
• REACHING A GOAL OF LDL LESS THAN 70 HAS AN IMPACT ON ASCVD
• NEED TO RE FOCUS ON ACHIEVING THESE GOALS
• 1 IN 3 DEATHS ARE DUE TO CVD AND 17 MILLION WORLDWIDE – STATINS HAVE IMPACTED THIS SIGNIFICANTLY BUT INCOMPLTELY
Incremental Reduction of LDL New therapeutic strategies

• DOUBLING STATIN DOSE ONLY REDUCES LDL BY ADDITIONAL 6-7% (CEILING EFFECT)

• It was not until 2015 that the ability to improve clinical CV outcomes by adding a non-statin lipid-lowering agent to a statin was confirmed in the IMPROVE IT STUDY

• This finding is particularly important in light of the conservative approach to adding non-statins in 2013 clinical guidelines.

• Moreover, the ability to improve clinical outcomes by incrementally reducing LDL-C levels has raised the expectations for other new classes of drugs, such as PCSK9 inhibitors.
OSLER

• OSLER-1 and -2 4,465 patients randomized open-label treatment with **evolocumab** (140 mg sq every 2 weeks or 420 mg monthly) vs standard therapy

• CV events nearly reduced by 50%

Sabatine MS, et al. NEJM 2015
ODYSSEY Long-Term

- 2,300 patients randomized to 150 mg of alirocumab or placebo as a 1-mL subcutaneous injection every 2 weeks for 78 weeks.

- MACE reduced to 1.7% in the alirocumab group vs 3.3% in the placebo group (p=0.02)
Shift in Distribution of LDL–C in a Population of High–Risk Individuals With Use of PCSK9 Inhibitor

Mean LDL 123

NCEP High-risk Pts in LAPLACE-TIMI 57 Treated with 140mg Q2W Evolocumab
Mean (SD): 47 (30) mg/dL

Population Effect

NCEP High Risk Patients In LAPLACE-TIMI 57 at Baseline mean (SD): 123 (30) mg/dL

Mean LDL 47

NCEP Goal for High-Risk Pts

Effect of PCSK9 MoAb

Physiologic LDL-C

Am Coll Cardiol 2015;65:2638–51
LONG TERM: Most Patients Receiving Alirocumab on Background Statin ± Other LLT Achieved LDL-C Goals

Proportion of patients reaching LDL-C goal at Week 24

Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)
High-risk: <2.6 mmol/L (100 mg/dL)

Placebo

Alirocumab

<1.8 mmol/L (70 mg/dL) regardless of risk

Intent-to-treat (ITT) analysis; LLT = lipid-lowering therapy

LDL Cholesterol Goals
73% ACHIEVED <70 LDL

0

10

20

30

40

50

60

70

80

90

100

Proportion Achieving Goal (%)

Standard of care alone
Evolocumab plus standard of care

P<0.001

P<0.001

26.0

90.2

3.8

73.6

<100

LDL-C Goal (mg/dL) at 12 weeks

<70
Use of COMBINATION OR ALTERNATE THERAPY to address statin intolerance and statin non adherence

CAN STATIN NON ADHERANCE AND INTOLERANCE AND ITS RESULTANT INCREASED CV RISK BE CHANGED?
Adherence to statins after two years, by condition EVEN IN HIGH RISK

Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002;288:462-467
Why don’t patients adhere to their medication therapy?

- Complex therapies
- **Side Effects (WELL PUBLICIZED IN MEDIA)**
- Failure to understand the need for the medication
- High out-of-pocket costs

Non-adherence—Mortality, Hospitalizations, ED Visits

- Non-adherence causes ~30% to 50% of treatment failures and 125,000 deaths annually
- Non-adherence to STATINS increased relative risk for mortality (~12% to 25%)
- Non-adherence to cardioprotective medications increased risk of cardiovascular hospitalizations (10% to 40%) and mortality (50% to 80%)
- Poor adherence to heart failure medications increased the number of cardiovascular-related emergency department (ED) visits

Sources: Ho 2009, Circulation; Edmondson 2013, Br J of Health Psychology; George & Shalansky 2006, Br J Clin Phar
Note the percentage in the placebo arm

## Prevalance of SMS in JUPITER Study

*Adverse Events and Measured Safety Parameters*

<table>
<thead>
<tr>
<th>Event</th>
<th>Rosuvastatin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>1352 (15.2)</td>
<td>1337 (15.5)</td>
<td>0.60</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>1421 (16.0)</td>
<td>1375 (15.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>Myopathy</td>
<td>10 (0.1)</td>
<td>9 (0.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1 (0.01)*</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Incident cancer</td>
<td>298 (3.4)</td>
<td>314 (3.5)</td>
<td>0.51</td>
</tr>
<tr>
<td>Cancer deaths</td>
<td>35 (0.4)</td>
<td>58 (0.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>6 (0.1)</td>
<td>9 (0.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>GFR (mL/min/1.73m² at 12 months)</td>
<td>66.8 (59.1–76.5)</td>
<td>66.6 (58.8–76.2)</td>
<td>0.0</td>
</tr>
<tr>
<td>ALT &gt; 3x ULN</td>
<td>23 (0.3)</td>
<td>17 (0.2)</td>
<td>0.34</td>
</tr>
<tr>
<td>Fasting glucose (24 months)</td>
<td>98 (91–107)</td>
<td>98 (90–106)</td>
<td>0.12</td>
</tr>
<tr>
<td>HbA1c (% at 24 months)</td>
<td>5.9 (5.7–6.1)</td>
<td>5.8 (5.6–6.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Glucosuria (12 months)</td>
<td>36 (0.5)</td>
<td>32 (0.4)</td>
<td>0.64</td>
</tr>
<tr>
<td>Incident diabetes**</td>
<td>270 (3.0)</td>
<td>216 (2.4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Occurred after trial completion, trauma induced. All values are median (interquartile range) or N (%). **Physician reported. JUPITER, Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin.*

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the patient intolerant (defined as the inability to tolerate any dose or increase the dose above the smallest tablet strength) to at least 2 different statins?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, please provide the statins tried and a description of the intolerance:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. For Initial Requests, has the patient achieved less than 50% reduction in LDL-C while on a maximally tolerated lipid lowering regimen?

6. Is the requested medication being prescribed by a specialist in the area of practice related to the patient’s diagnosis (e.g., cardiologist, lipidologist, or endocrinologist) or in consultation with a specialist?

7. Has the patient experienced any of the following cardiovascular events? (check all that apply)
   - Acute coronary syndrome
   - History of myocardial infarction
   - Stable or unstable angina
   - Transient ischemic attack
   - Coronary or other arterial revascularization
   - Stroke
   - Peripheral arterial disease presumed to be of atherosclerotic origin

8. Please list all reasons for selecting the requested medication, dosing schedule and quantity over alternatives (e.g. contraindications, allergies or history of adverse drug reactions to alternatives, lower dose tried.)

9. Please list all medications the patient will use in combination with the requested medication for treatment of this diagnosis.

10. Please list all medications the patient has previously tried and failed for treatment of this diagnosis.
Summary

- SMS is a real phenomenon
  - Major reason for statin non-adherence/discontinuation
  - Contributes to decreased CVD benefit by statins

- Current incidence is ‘too’ high, emphasising the need for ‘elaborate’ selection of SMS patients
  - Characteristic clinical presentation (location/time course)
  - Apply repetitive de/rechallenges with alternative statins

- The unmet need in these SMS patients can be met using non-statin strategies
  - PCSK9-ab offers 50–60% LDL-C reduction with minimal side effects in SMS patients
The GAUSS-3 Trial

Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects-3

Steven E. Nissen MD MACC*
Erik Stroes MD PhD

*Disclosure

Study Sponsor: Amgen
Consulting: Many pharmaceutical companies
Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor tax deduction is received.
Controversy has surrounded the issue of statin-associated muscle symptoms because of large differences in the incidence of this disorder in randomized trials and observational studies.

The GAUSS-3 trial demonstrates that muscle-related intolerance is reproducible during blinded statin rechallenge in a substantial fraction (about 40%) of patients with a history of symptoms.

Accordingly, development of alternative approaches to LDL-C reduction for these patients represents an important medical priority.
Study Design: Two Double-Blind Phases

**Phase A**
- 511 patients enrolled at 53 centers with a history of intolerance to multiple statins due to muscle-related adverse effects.
- 10 weeks: Atorvastatin 20 mg → Placebo
- 10 weeks: Atorvastatin 20 mg → Placebo

**Phase B**
- Patients proceeded to Phase B only if they had *intolerable* muscle symptoms on atorvastatin, but not placebo, or CK ≥ 10 x ULN during prior statin treatment.
- 24 weeks:
  - 2: Monthly SC evolocumab 420 mg
  - 1: Daily oral ezetimibe 10 mg
## Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase A (n=491)</th>
<th>Phase B (n=218)</th>
<th>Ezetimibe (n=73)</th>
<th>Evolocumab (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61</td>
<td>59</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>Male Gender</td>
<td>50%</td>
<td>47%</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>35%</td>
<td>29%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>NCEP-ATP III High Risk</td>
<td>63%</td>
<td>52%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td><strong>Intolerance to ≥ 3 statins</strong></td>
<td><strong>82%</strong></td>
<td><strong>82%</strong></td>
<td><strong>82%</strong></td>
<td><strong>82%</strong></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>301</td>
<td>308</td>
<td>307</td>
<td></td>
</tr>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td><strong>212</strong></td>
<td><strong>222</strong></td>
<td><strong>219</strong></td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>51</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>
Phase A: Study Drug Discontinuation Events

<table>
<thead>
<tr>
<th>Intolerable Muscle Symptoms</th>
<th>N = 491</th>
</tr>
</thead>
<tbody>
<tr>
<td>On atorvastatin, but not placebo</td>
<td>209 (42.6%)*</td>
</tr>
<tr>
<td>On placebo, but not atorvastatin</td>
<td>130 (26.5%)</td>
</tr>
<tr>
<td>On both placebo and atorvastatin</td>
<td>48 (9.8%)</td>
</tr>
<tr>
<td>No symptoms on either treatment</td>
<td>85 (17.3%)</td>
</tr>
<tr>
<td>Did not complete Phase A</td>
<td>20/511</td>
</tr>
<tr>
<td>Bypassed Phase A due to CK elevation ≥ 10 x ULN</td>
<td>19 (3.9%)*</td>
</tr>
</tbody>
</table>

*218 of these 228 eligible patients proceeded to Phase B
LDL-C Values Over Time During Phase B

Percent Change in LDL-C (%)

Weeks Following Randomization in Phase B

Mean reduction 16.7%  
(LDL-C = 181 mg/dL)

Mean reduction 53.0%  
(LDL-C = 104 mg/dL)

Ezetimibe
Achievement of Common LDL-C Target Levels
65% OF TRUE SMS PTS DID ACHIEVE A TARGET

**LDL-C < 70 mg/dL**

- Ezetimibe: 1.4%
- Evolocumab: 29.9%

**LDL-C < 100 mg/dL**

- Ezetimibe: 1.8%
- Evolocumab: 64.1%

P<.001

*not a protocol prespecified analysis*
Phase B: Time to Any Muscle-Related Symptom

Both drugs uncommonly induced muscle symptoms leading to discontinuation (ezetimibe 6.8%, evolocumab 0.7%).

Cumulative Event Probability

Days Following Randomization

Ezetimibe

Evolocumab

HR = 0.68
95% CI, 0.39-1.19

P = .17
Conclusions

- A substantial proportion (42.6%) of patients with a history of muscle-related statin intolerance have symptoms when re-challenged with atorvastatin 20 mg, but not placebo.

- A smaller fraction of patients (26.5%) report muscle-related symptoms when administered placebo, but not atorvastatin.

- In patients with statin-associated muscle symptoms, evolocumab, compared with ezetimibe, produced significantly larger reductions in LDL-C and other atherogenic lipoproteins.

- Both drugs uncommonly induced muscle symptoms leading to discontinuation (ezetimibe 6.8%, evolocumab 0.7%).
## Patient Populations with HIGH Unmet Need for Additional LDL-C Lowering

<table>
<thead>
<tr>
<th>FH Population in EU</th>
<th>High / Very High CV Risk Population</th>
<th>Statin-Intolerant Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Genetic disorder</td>
<td>• Previous MI/stroke / CVD or multiple CV risk factors incl. T2DM</td>
<td>• 10-15% on high-intensity statins show intolerance</td>
</tr>
<tr>
<td>• High risk of early CHD</td>
<td>• Difficult to achieve LDL-C goals, despite current therapies</td>
<td>• Many discontinue due to muscle pain and/or weakness</td>
</tr>
<tr>
<td>• HeFH prevalence 1:200 to 1:250&lt;sup&gt;12&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Untreated LDL-C of 200-400 mg/dL&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>79% with HeFH not at goal (&lt;100 mg/dL [2.6 mmol/L])</strong></td>
<td><strong>Nearly all patients who need considerable LDL-C reductions will not reach goal</strong></td>
</tr>
</tbody>
</table>

<sup>1</sup>Nordestgaard et al. *Eur Heart J* 2013;34:3478-90.  
<sup>4</sup>Pijlman et al. *Atherosclerosis* 2010;209:189-94.  
Lloyd-Jones DM, et al.
2016 Lipid Pathway

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk
A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Endorsed by the National Lipid Association

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Guideline Update 2016

COMBINATION THERAPY

• Incorporates RCT data since 2013 as well as expert consensus
• Clearly addresses benefit in RCT from non statin therapies
• Re assesses the high risk groups that residual risk and further management of dyslipidemia that benefit from PCSK9 and Ezitimibe with no evidence of harm
• Niacin and fibrates as add on therapy remain out - lack of benefit and possible harm
HIGH RISK MARKERS

- The Committee identified several high-risk markers that may be informative, including:
- 10-year ASCVD risk ≥20%;
- Primary LDL-C ≥160 mg /dL at baseline;
- Other major ASCVD risk factor(s) that are poorly controlled
- Family history of premature ASCVD with or without elevated lipoprotein(a)
- Evidence of accelerated subclinical atherosclerosis (e.g., coronary artery calcification)
- Elevated hs-CRP; and other risk-modifying conditions, such as CKD, HIV, and chronic inflammatory disorders.
1-SECONDARY PREVENTION CVD ALREADY ON STATIN

FIGURE 2A | Patients with Stable Clinical ASCVD without Comorbidities, on Statin for Secondary Prevention

Patients with stable clinical ASCVD without comorbidities,* on statin for secondary prevention

Patient has $\geq$50% LDL-C reduction (may consider LDL-C $\leq$100 mg/dL) on maximally tolerated statin†

YES

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.† Consider referral to lipid specialist if statin intolerant.
5. Control other risk factors.

NO

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 4)

Patient has $\geq$50% LDL-C reduction (may consider LDL-C $\leq$100 mg/dL) on maximally tolerated statin†

YES

Decision for no additional medication

Optional non-statin medications to consider

Consider ezetimibe first.§

Consider adding or replacing with PCSK9 inhibitor second.||

NO

Patient has $\geq$50% LDL-C reduction (may consider LDL-C $\leq$100 mg/dL) on maximally tolerated statin/other medications†

YES

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
2-Patient with established ASCVD and Comorbidities SECONDARY PREVENTION OF CVD ON STATIN

ASCVD+DM VERY HIGH RISK= TARGET LDL<70
3-SECONDARY PREVENTION, LDL>190 ON STATIN (LIKELY HEFH)

**FIGURE 2C** | Patients with Clinical ASCVD and Baseline LDL-C ≥ 190 mg/dL Not Due to Secondary Causes, on Statin for Secondary Prevention

Patients with clinical ASCVD and baseline LDL-C ≥ 190 mg/dL not due to secondary causes,* on statin for secondary prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C < 70 mg/dL) on maximally tolerated statin†

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.‡
   - Referral to lipid specialist recommended if statin intolerant.
5. Control other risk factors.
6. Consider referral to lipid specialist and RDN for all patients, especially for homozygous FH.

Patient has ≥50% LDL-C reduction (may consider LDL-C < 70 mg/dL) on maximally tolerated statin†

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 4)

Optional non-statin medications to consider

- Consider ezetimibe
  - (or BAS second line). ||
- Consider PCSK9 inhibitor.

Patient has ≥50% LDL-C reduction (may consider LDL-C < 70 mg/dL) on maximally tolerated statin/other medications†

1. Repeat clinician-patient discussion.
2. Add other non-statin medication(s) above.
3. Consider referral to lipid specialist and RDN.

Patient has ≥50% LDL-C reduction (may consider LDL-C < 70 mg/dL) on maximally tolerated statin/other medications†

Referral to lipid specialist and RDN recommended

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
4- PRIMARY PREVENTION & PRIMARY LDL > 190, ON STATIN (LIKELY HEFH)
5-DIABETICS 40-75 , LDL 70-190 , ON STATIN FOR PRIMARY PREVENTION
6-PRIMARY PREVENTION, 40-75 YEARS, LDL 70-190 & CVD RISK >7.5%

**FIGURE 5** | Patients Age 40-75 years without Clinical ASCVD or Diabetes, with LDL-C 70-189 mg/dL and 10-Year ASCVD Risk ≥7.5%, on Statin for Primary Prevention

- **Patients age 40-75 years without clinical ASCVD or diabetes, with LDL-C 70-189 mg/dL and 10-year ASCVD risk ≥7.5%, on statin for primary prevention**
  - On initial high-intensity statin.

- **Patient has 30%-49% LDL-C reduction (may consider LDL-C <100 mg/dL) on moderate intensity statin†**
  - Yes, and without high-risk markers*.
  - No, or with high-risk markers*.

  1. Address statin adherence.
  2. Intensify lifestyle (may consider phytosterols).
  3. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.† Consider referral to lipid specialist if statin intolerant.
  4. Control other risk factors.

- **Patient has 30%-49% LDL-C reduction (may consider LDL-C <100 mg/dL) on moderate intensity statin†**
  - Yes, and without high-risk markers*.
  - No, or with high-risk markers*.

- **Increase to high-intensity statin.**

- **Patient has >50% LDL-C reduction (may consider LDL-C <100 mg/dL) on maximally tolerated statin†**
  - Yes, and without high-risk markers*.
  - No, or with high-risk markers*.

**CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER**

1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4).
2. Potential for drug-drug interactions from addition of non-statin therapy (see Table 4).
3. Patient preference and adherence to medications and lifestyle.

- **Optional non-statin medications to consider**
  - Consider ezetimibe first.
  - NAs second line.†

- **Decision for no additional medication.**

- **Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.**

---

*Abbreviations: ASCVD = atherosclerotic cardiovascular disease. NAs = non-holesterol lactonosterolacetate. LDL-C = low-density lipoprotein cholesterol.*
• Diagnose & manage secondary causes of dyslipidemia
• Optimally manage other ASCVD risk factors
• Implement appropriate nutrition and physical activity

Administer maximally tolerated statin

Lipid blood testing to assess if LDL-C level exceeds “threshold” LDL OF 70 (or 100) treatment level. If so...

Add non-statin therapy

Reassess & Treat to lipid “goals”
“If, after these interventions, the patient still has <50% reduction in LDL-C (and may consider LDL-C ≥70 mg/dL), the patient and clinician should enter into a discussion focused on shared decision making regarding the addition of a non-statin medication to the current regimen.
"In the opinion of the Expert Consensus Writing Committee, in a patient with ASCVD and baseline LDL-C ≥190 mg/dL* with <50% reduction in LDL-C (and may consider LDL-C ≥70 mg/dL) it is reasonable to consider a PCSK9 inhibitor as a first step rather than ezetimibe or BAS given PCSK9 inhibitors’ greater LDL-C lowering efficacy."

*THESE ARE PROBABLE HEFH PTS
Combination Therapy Updates:

- Data indicate that combination therapy with ezetimibe also brings a benefit that is in line with the Cholesterol Treatment Triallists’ (CTT) Collaboration meta-analysis supporting the notion that LDL-C reduction is key to the achieved benefit independent of the approach used.

- **They are recommended as combination therapy with statins in selected patients when a specific goal is not reached with the maximal tolerated dose of a statin.**

- **Patients with dyslipidaemia, particularly those with established CVD, DM or asymptomatic high-risk individuals, may not always reach treatment goals, even with the highest tolerated statin dose.**

- Therefore, combination treatment may be needed. **It must be stressed, however, that the only combination that has evidence of clinical benefit (one large RCT) is that of a statin combined with ezetimibe.**
PCSK9 Inhibitors

• Regarding new therapies, recent data from phase I–III trials show that PCSK9 inhibitors sharply decrease LDL-C by up to 60%, either as monotherapy or in addition to the maximal statin dose.

• Whether this approach results in the predicted reduction in CV events is being addressed in large outcome trials; preliminary evidence suggests that this is the case.
When to consider PCSK9 Inhibitors

1. FH-Het.

2. High risk patients with ASCVD (recurrent ASCVD events).

3. Patients with ASCVD not attaining the goal on maximally tolerated Statin and Ezetimibe.

4. Statin Intolerance.
Thank You