Newer Concepts in Lipid Management: Beyond Statin Therapy

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MedNet21

THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER

Objectives

- Understand guidelines and approach for management of dyslipidemias
- Review treatment options beyond statins
- Share clinical pearls of hyperlipidemia management

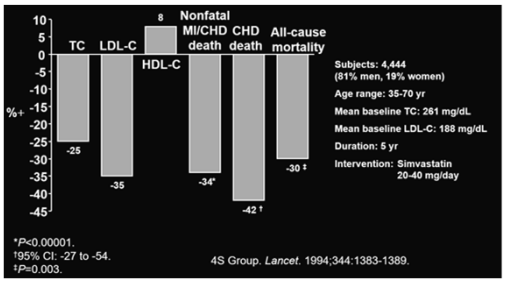
Case: 56 Year Old Female Executive

- Presents with resting persistent angina associated with anterior T wave inversions and elevated HS-troponin levels
- Heart cath: 95% LAD stenosis, 50% RCA lesion and serial 25-50% stenoses in the LCX; EF 35%
- Receives a drug eluting stent in the LAD
- No h/o DM or htn, although BP measured 145/96
- Father died of MI age 54
- Non-smoker
- Mild central obesity (waist circumference of 36)

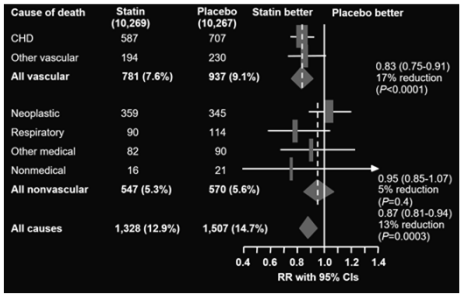
Case: 56 Year Old Female Executive

- Lipids drawn at presentation
  - Cholesterol 230 LDL 160 HDL 30 TG 180
- Discharged on ASA, Ticagrelor, B blocker, ACE inhibitor and Atorvastatin 80 mg daily and referred to cardiac rehab
- 3 months later
  - Cholesterol 140, LDL 83, HDL 32, TG 165

4S: Effect of LDL-C Lowering on Coronary Events in Men and Women

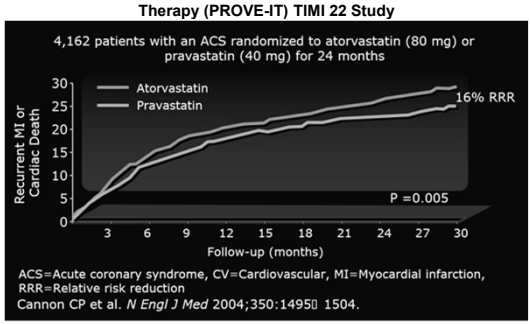


Heart Protection Study: Effects of Simvastatin on Cause-Specific Mortality



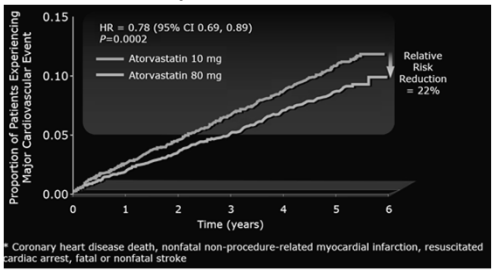
HPS Collaborative Group. *Lancet*. 2002;360:7-22.

Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) TIMI 22 Study



Treating to New Targets (TNT): Primary Efficacy Outcome Measure

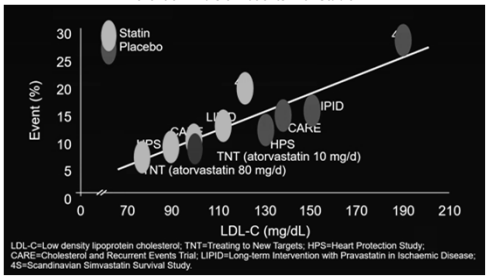
First Major Cardiovascular Event*



LaRosa et al. *N Engl J Med* 2005;352:1425-35

HMG-CoA Reductase Inhibitor: Secondary Prevention

Relationship between LDL Levels and Event Rates in Secondary Prevention Trials of Patients with Stable CHD



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

LaRosa JC et al. *NEJM.* 2005;352:1425-1435

History of Lipid Management: Guidelines

ATP 1 → ATP II → ATP III → ACC/AHA

2018
AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA
Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

AHA/ACC Statin Benefit Groups

Secondary prevention	LDL > 190 mg/dL
Diabetes Mellitus	Primary prevention

Intensity of Statin Therapy

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)-80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20–40 mg‡‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

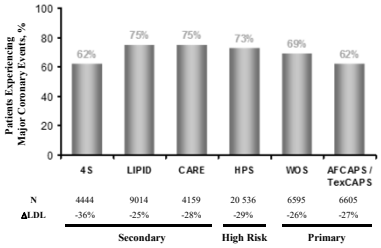
*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only; down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Helping Cardiovascular Professionals Learn, Advance, Heal.

2013 ACC/AHA Blood Cholesterol Guidelines

American Heart Association.

Residual Cardiovascular Risk in Major Statin Trials



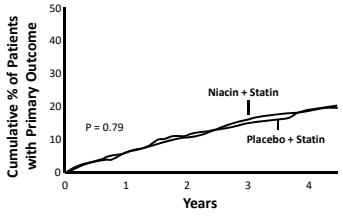
Libby PJ, et al. *J Am Coll Cardiol*, 2005:46:1225-1228.

Niacin

- Lipid Effects:
  - ↓ LDL 5-25%
  - ↓ TRG 20-50%
  - ↑ HDL 15-35%
- Side Effects:
  - Flushing
  - Hyperglycemia
  - Hyperuricemia
- Contraindications
  - Chronic liver disease
  - Severe gout

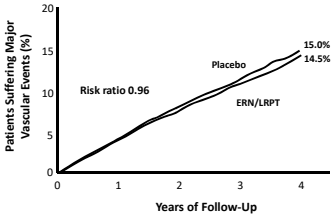
- Dose:
  - Niaspan: 500 mg, 750 mg
  - Generic: 500 mg, 750 mg, 1000 mg

AIM-HIGH: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy.



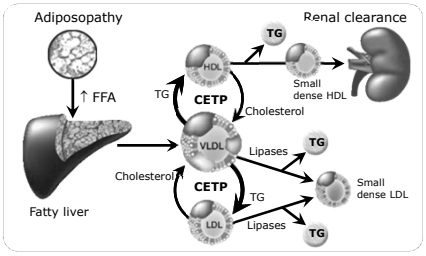
N Engl J Med 2011;365:2255–2267

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



N Engl J Med 2014; 371:203-212

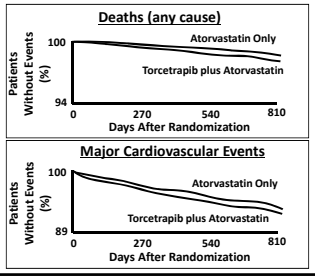
The Role of Cholesterol Ester Transfer Protein and the Dyslipidemia Found with Metabolic Syndrome



Bays H. *Expert Rev Cardiovasc Ther* 2004;2:89-105

Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE)

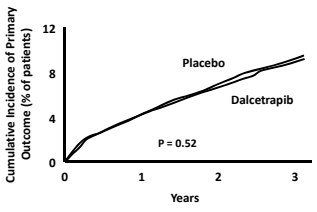
- 15,000 patients on Atorvastatin with CAD or DM
- Increase of HDL cholesterol by 72.1% on torcetrapib
- Decrease of LDL cholesterol by 25% on torcetrapib
- Systolic BP increased by 6 mm Hg on torcetrapib
- Greater number of events in those on Torcetrapib



Barter PJ et al. N Engl J Med 2007;357:2109-2122.

Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome: Dal-outcomes Trial

- 15,000 patients
- Mean HDL cholesterol level was 42 mg per deciliter
- Mean low-density lipoprotein (LDL) cholesterol level was 76 mg per deciliter
- HDL cholesterol levels increased from baseline by 4 to 11% in the placebo group and by 31 to 40% in the dalcetrapib group.



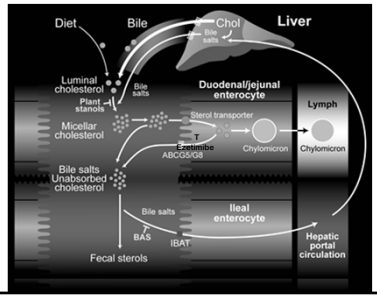
Schwartz GG et al. N Engl J Med 2012;367:2089-2099.

Cholesterol Absorption Inhibitors

Ezetimibe

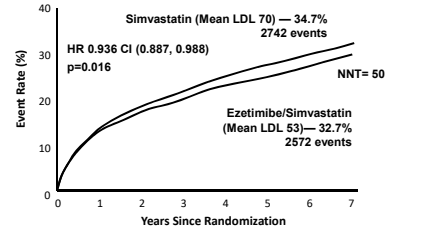
- Lipid Effects:
  - ↓ LDL 18% alone
  - No change TRG
  - No change HDL
- Dose:
  - 10 mg tablet
- Side Effects:
  - URI
  - GI distress

Intestinal-Acting Agents



IMProved **R**eduction of **O**utcomes: **V**ytorin **E**fficacy **I**nternational **T**rial (IMPROVE-IT)

Effect of the Addition of Ezetimibe to Simvastatin Compared to Simvastatin Monotherapy.



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

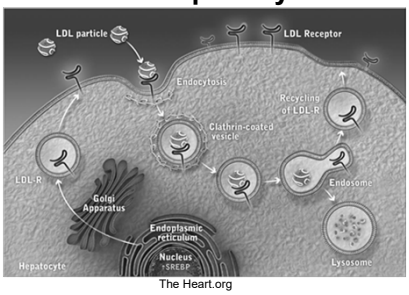
Cannon CP et al. N Engl J Med 2015;372:2387-2397

Proprotein Convertase Subtilisin-Kexin Type 9 (PCSK9)

- In 2006, it was reported that a loss of function mutation in the gene encoding PCSK9 was associated with significantly lower long-term plasma levels of LDL cholesterol (1)
- A substantial (47 to 88%) lower risk of coronary heart disease was observed over a period of 15 years in middle-aged persons with such genetic polymorphisms.
- Additional genetic studies indicated that PCSK9 activity was a major determinant of plasma levels of LDL cholesterol in humans (2)
- Opened the door for drug development to synthesize inhibitors against PCSK9

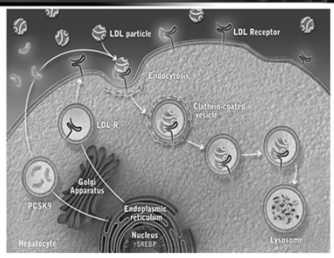
(1) NEJM 2006;354:1264-72 (2) Am J Hum Genet 2006;78:410-22

LDL Receptor Cycle



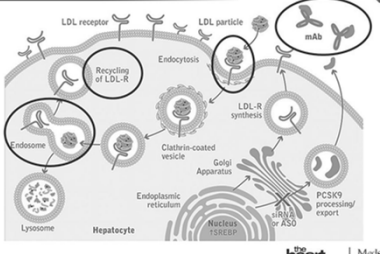
The Heart.org

The Role of PCSK9 in the Regulation of LDLR Expression



The Heart.org

PCSK9 Inhibition Using Monoclonal Antibodies



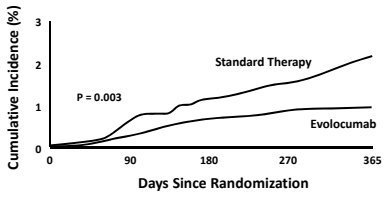
Lambert G, et al. *J. Lipid Res.* 2012;53:2515-2524.[16]

PSCK9 Inhibitors

Alirocumab and Evolocumab

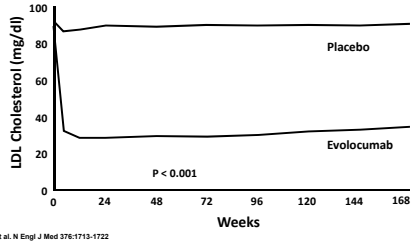
- Lipid Effect:
  - ↓ LDL up to 65%
  - Favorable: Lp(a), HDL, TRG
- Dose:
  - Alirocumab: 75 mg, 150 mg
  - Evolocumab: 140 mg
  - Dosed q2-4 weeks
- Side Effect:
  - Injection site reaction
  - Nasopharyngitis
  - Diarrhea

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events



Sabatine MS et al. N Engl J Med 2015;372:1500-1509

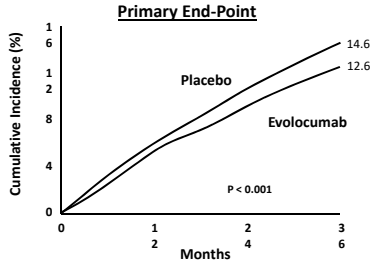
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease



Sabatine MS et al. N Engl J Med 376:1713-1722

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Primary End-Point

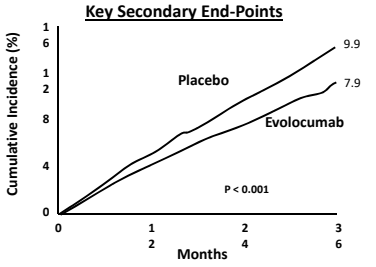


- 27,000+ patients
- LDL above 70 mg/dL despite maximum tolerated lipid lowering therapy

Sabatine MS et al. N Engl J Med 376:1713-1722

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Key Secondary End-Points



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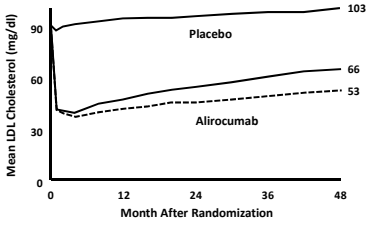
Sabatine MS et al. N Engl J Med 376:1713-1722

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome: LDL levels

Odyssey Outcomes: Randomized controlled double blinded clinical trial comparing alirocumab versus placebo in patients treated with statin therapy whose LDL levels remain above 70

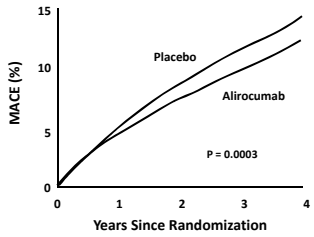


N Engl J Med 2018; 379:2097-2107

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome: MACE outcomes

Odyssey Outcomes: Randomized controlled double blinded clinical trial comparing alirocumab versus placebo in patients treated with statin therapy whose LDL levels remain above 70

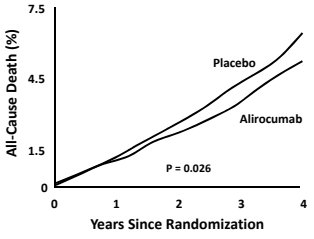
MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization



N Engl J Med 2018; 379:2097-2107

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome: Death rates

Odyssey Outcomes: Randomized controlled double blinded clinical trial comparing alirocumab versus placebo in patients treated with statin therapy whose LDL levels remain above 70



N Engl J Med 2018; 379:2097-2107

Case: 56 Year Old Female Executive

- Lipids drawn at presentation
  - Cholesterol 230 LDL 160 HDL 30 TG 180
- **Discharged on ASA, Ticagrelor, B blocker, ACE inhibitor and Atorvastatin 80 mg daily and referred to cardiac rehab**
- 3 months later
  - Cholesterol 140, LDL 83, HDL 32, TG 165
- After addition of PCSK9 inhibitor Rx, repeat lipid levels
- - Cholesterol 105, LDL 48, HDL 30, TG 135

Newer Concepts in Lipid Management: Beyond Statin Therapy

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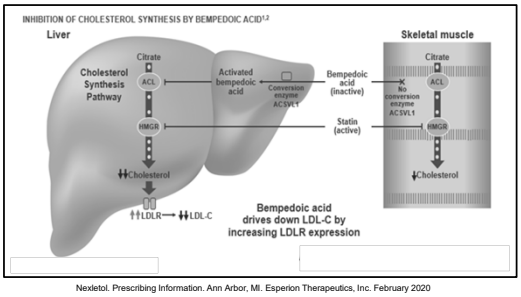
Adenosine Triphosphate Citrate Lyase (ACL) Inhibitor

Nexletol (Bempedoic Acid) and Nexlizet (Bempedoic acid/ezetimibe)

- Lipid Effects:
  - ↓ LDL 20-30%
  - Favorable: total cholesterol, ApoB
- Side Effects
  - URI
  - Bronchitis
  - Back pain
- Contraindications
  - History of gout
  - History of tendon rupture

- Dose
  - Bempedoic acid: 180 mg
  - Bempedoic acid/ezetimibe: 180/10 mg

Bempedoic acid: Mechanism of action

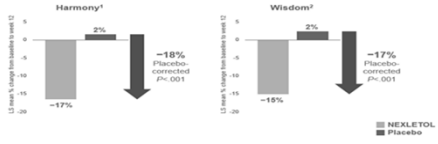


Nexletol. Prescribing Information. Ann Arbor, MI. Esperion Therapeutics, Inc. February 2020

Adenosine Triphosphate Citrate Lyase (ACL) Inhibitor

Nexletol (Bempedoic Acid) and Nexlizet (Bempedoic acid/ezetimibe)

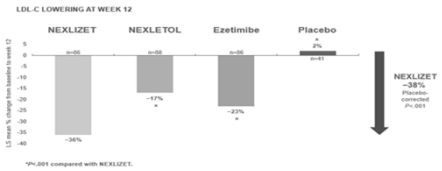
- CLEAR Harmony (n=2230)
  - Adults with ASCVD, HeFH
  - LDL >70 mg/dL
  - Max tolerated statin
- CLEAR Wisdom
  - Adults with ASCVD or HeFF
  - LDL > 100 mg/dL
  - Max tolerated statin



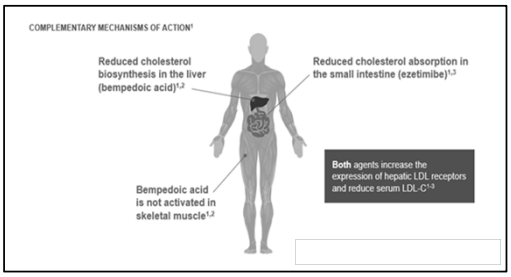
Adenosine Triphosphate Citrate Lyase (ACL) Inhibitor

Nexletol (Bempedoic Acid) and Nexlizet (Bempedoic acid/ezetimibe)

- CLEAR Tranquility
  - Adults with ASCVD or HeFD
  - LDL > 100 mg/dL



Bempedoic acid: Mechanism of action

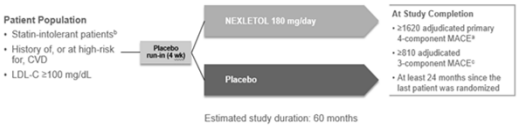


Nexlizet. Prescribing Information. Ann Arbor, MI: Esperion Therapeutics, Inc. February 2020

Adenosine Triphosphate Citrate Lyase (ACL) Inhibitor

Nexletol (Bempedoic Acid) and Nexlizet (Bempedoic acid/ezetimibe)

- CLEAR OUTCOMES
  - Cardiovascular Outcomes Trial in 14000 patients
  - Documented statin intolerance
  - To date: reached 50% of primary MACE endpoints
  - To be completed ~5/2022



Small Interfering Ribonucleic Acid (siRNA)

Leqvio (inclisiran)

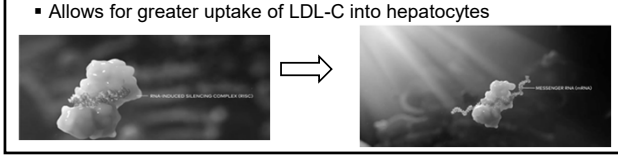
- Newly approved FDA Dec 2021 for HeFH and clinical ASCVD
- Lipid Effect:
  - ↓ LDL 43-52%
  - Reductions: ApoB, LpA, TChol
- Side Effects:
  - Injection Site reactions
  - Arthralgia
  - UTI
  - bronchitis

- Dose
  - 284 mg SubQ injection at baseline, 3 months then every 6 months
  - Given in healthcare office

Small Interfering Ribonucleic Acid (siRNA)

Leqvio (inclisiran)

- First and only siRNA(small interfering RNA) therapy for LDL-C reduction that selectively targets the liver
- Works as a compliment to statins
- Prevents the formation the PCSK9 protein that promotes the degradation of LDL receptors
- Allows for greater uptake of LDL-C into hepatocytes



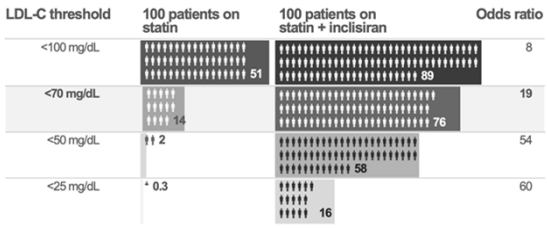
Small Interfering Ribonucleic Acid (siRNA)

Leqvio (inclisiran)

Trial Name	Trial Details
Orion-9	Vs placebo in patients w/ HeFH LDL-C ≥ 100 despite receiving max tolerated dose of statin
Orion-10	Vs placebo in patients w/ ASCVD(CHD, CVD, PAD) and LDL-C ≥ 70 despite receiving max tolerated dose of statin
Orion-11	Vs placebo in patients w/ ASCVD(CHD, CVD, PAD) or ASCVD risk equivalents and LDL-C ≥ 70 despite receiving max tolerated dose of statin

Small Interfering Ribonucleic Acid (siRNA)

Leqvio (inclisiran)



Small Interfering Ribonucleic Acid (siRNA)

Leqvio (inclisiran)

Lipid parameter	Placebo	Inclisiran	P-value
PCSK9	+14.8	-68.2	<0.0001
Total cholesterol	+2.9	-29.5	<0.0001
Non HDL-C	+3.6	-42.8	<0.0001
ApoB	+1.7	-40.2	<0.0001
Lp(a)(day 540)	+0.0	-20.0	<0.0001

Angiopoietin-Like Protein 3 (ANGPTL3) Inhibitor

Evkeeza (Evinacumab)

- Newly FDA Approved Feb 2021 for HoFB
- Lipid Effect:
  - ↓ LDL 47%
  - Reductions: ApoB, Tchol, non-HDL
- Side Effect:
  - Nasopharyngitis
  - Flu like reactions
  - Dizziness
  - Rhinorhea

- Dose:
  - 15 mg/kg infusion once a month
- Other Consideration
  - Cost > $450,000/year
  - Effectiveness outside HoFH not established

Angiopoietin-Like Protein 3 (ANGPTL3) Inhibitor

Evkeeza (Evinacumab)

- ELIPSE HoFH
  - Trial Design
    - Double blind, placebo controlled, phase 3 trial 2:1
    - N=65 with HoFH
    - LDL at baseline: 225
  - Outcomes
    - LDL reduction of 47.1% at week 24
  - Take away: safety and efficacy
    - CV Outcomes data not available

Bile Acid Sequestrants

Colestid (Colestipol) and Welchol (Colesevelem)

- Lipid Effects:
  - ↓ LDL 15-30%
  - ↑ HDL 3-5%
- Side Effects:
  - GI Distress
  - constipation
- Contraindications
  - Dysbetalipoproteinemia
  - TRG >400 mg/dL

- Dose
  - Welchol (colesevelem):
    - 3.75 mg packet
    - 625 mg tablet
  - Colestid (colestipol)
    - 5 g/5 g scoop
    - 5 g packet
    - 1 g tablet

Bile Acid Sequestrants

Colestid (Colestipol) and Welchol (Colesevelem)

- Clinical Trials
  - Trial Design:
    - Meta Analysis of effect of BAS on CVD
  - Outcome
    - Reduced major coronary events and CHD deaths
    - Studies primarily in men without heart disease

- IMPORTANT: Only option in pregnancy

What if Triglycerides are the problem?

- Hypertriglyceridemia increases risk of pancreatitis and CVD
- Contributing factors may include EtOH use, high-fat diet, underlying diabetes or thyroid disease
- For patients >500 mg/dL, goal of therapy is to first reduce to <500 mg/dL

Triglyceride Management

200-499 mg/dL

- Treat LDL goals first, then consider adding drug if needed to reach non-HDL goal for residual risk
- Intensification of statin in combination with fibrate and/or omega-3 fatty acids.

200-499 mg/dL and T2DM or ASCVD

- Consider icosapent ethyl (Vascepa) due to results of the REDUCE-IT trial

>500 mg/dL

- Primary target of therapy until <500 mg/dL. Recommend very low-fat diet (<15% of calories from fat), weight management & physical activity.
- Medication options include fibrate, omega-3 fatty acids, or statin (if <1000 mg/dL and other statin indication)

Fibric Acid

Tricor/Fibricor/Triglide/Trilipix/Lipofen/Antara (fenofibrate) and Lopid (gemfibrozil)

- Lipid Effect:
  - ↓ LDL 5-20%
  - ↓ TRG 20-50%
  - ↑ 10-20%
- Side Effects
  - Dyspepsia
  - Gallstones
- Contraindicates
  - Severe renal disease
  - Severe hepatic disease

- Dose:
  - Fenofibrate: 48 mg, 54 mg, 120 mg, 145 mg, 160 mg
  - Gemfibrozil: 300 mg, 600 mg
  - Adjustments required for CKD
  - *gemfibrozil preferred with CKD unless concomitant statin

Fibric Acid

Tricor/Fibricor/Triglide/Trilipix/Lipofen/Antara (fenofibrate) and Lopid (gemfibrozil)

- Helsinki Heart Study (HHS)
  - Design:
    - Effects of gemfibrozil on major CVD
    - Middle aged men without ASCVD
    - Primary endpoint: fatal and non fatal MI and cardiac death
  - Outcomes
    - 34% reduction in major coronary events and CHD death
- Veteran Affairs HDL Intervention Trial (VA-HIT)
  - Design
    - Effect of gemfibrozil on major CVD
    - Primary endpoint: non-fatal MI or coronary death
  - Outcomes
    - 22 % of CV risk reduction in patients with CHD

Omega-3 Fatty Acids (DHA, EPA)

Lovaza (Rx) and Over the Counter options

- Lipid Effect:
  - ↓ TRG up to 50%
  - ↑ LDL up to 20%
    - LDL increase due to DHA, EPA does not increase LDL
- Side Effects:
  - GI distress
  - Fishy after taste

- Dose:
  - OTC: vary
  - Lovaza: 1 g capsule

Omega-3 Fatty Acids (EPA only)

Vascepa (Icosapent Ethyl)

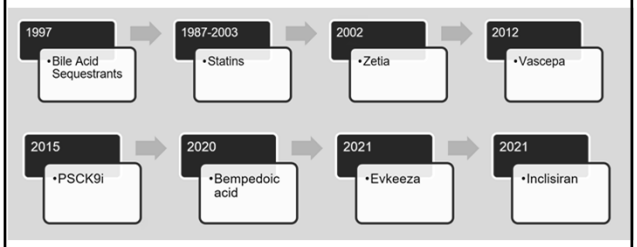
- Lipid Effect:
  - ↓ TRG up to 50%
- Side Effects:
  - GI distress
  - Fishy after taste
- Dose
  - Generic: 0.5 g, 1 g
  - Vascepa: 1 g

Omega-3 Fatty Acids (EPA only)

Vascepa (Icosapent Ethyl)

- REDUCE-IT (2018)
  - Trial Design
    - Randomized, double blind, placebo controlled
    - Patients with TRG 150-499 mg/dL and established ASCVD and T2DM with 1 risk factor
    - Primary endpoint: composite of cardiovascular death, non-fatal MI, nonfatal stroke, coronary revascularization or unstable angina
  - Outcomes
    - Primary endpoint: 17.2% in Vascepa vs 22.0% in placebo
    - Risk of ischemic events despite statin use was lower on Vascepa compared to placebo

History of Lipid Management



Overview: Statin intolerance

If unable to tolerate statin

- Primary prevention
  - PSCK9i
  - Ezetimibe
  - Bempedoic Acid (if LDL > 190 mg/dL)
  - Inclisirin (if LDL > 190 mg/dL)
  - Bile acid sequestrant
  - Niacin
- Secondary Prevention
  - PSCK9i
  - Bempedoic acid
  - Zetia
  - Inclisirin

Thank You

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