Baptist Health
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Lipid Management: Statins and Alternatives

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February 28, 2025

No Relevant Disclosures

Hyperlipidemia

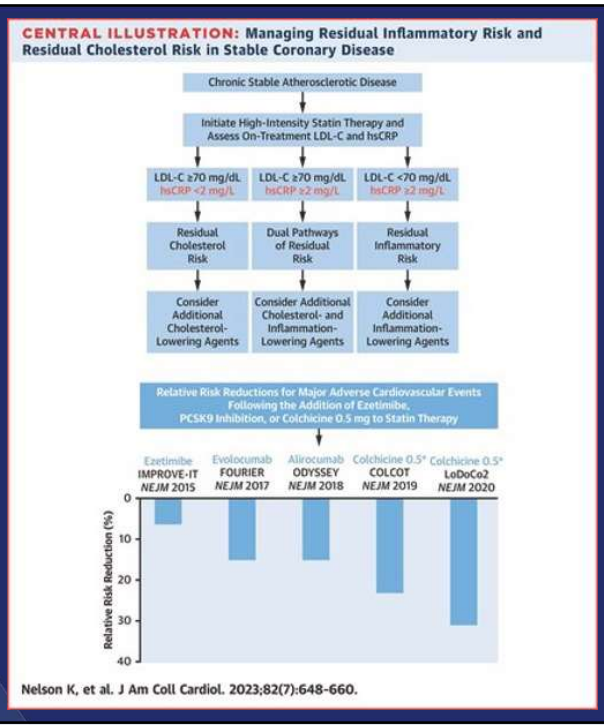
- Definition: Hyperlipidemia is a condition characterized by elevated levels of lipids (cholesterol, triglycerides, glycoproteins) in the blood.
- Importance: Major risk factor for atherosclerosis, cardiovascular disease (CVD), and stroke.
- “Old” Therapies: Statins, fibrates, niacin, bile acid sequestrants, and lifestyle modifications.

Limitations of Current Therapies

- Statins: Intolerance in some patients, residual cardiovascular risk.
- Fibrates/Niacin: Limited efficacy, side effects (e.g., flushing, myopathy).
- Lifestyle Changes: Difficult to sustain long-term.
- Unmet Needs: Better LDL-C reduction, triglyceride management, and HDL-C modulation.

Benefits of New Lipid Therapies

- Improved Efficacy: Greater LDL-C and triglyceride reduction.
- Reduced Side Effects: Better tolerability compared to statins.
- Personalized Medicine: Tailored treatments based on genetic and metabolic profiles.
- Cardiovascular Risk Reduction: Lower incidence of heart attacks and strokes.

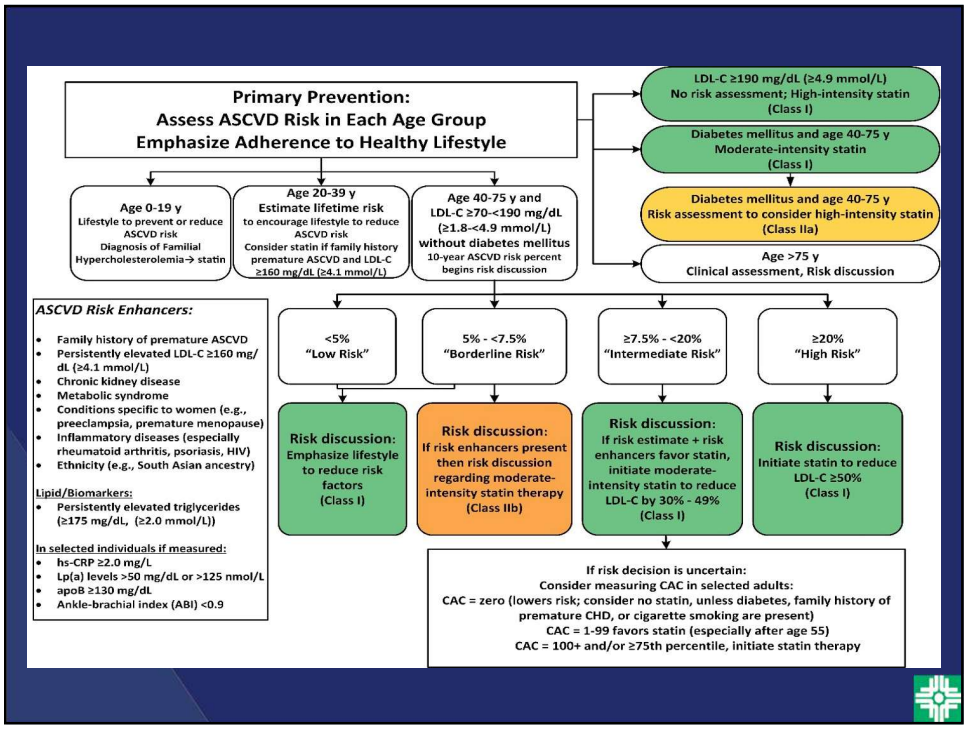


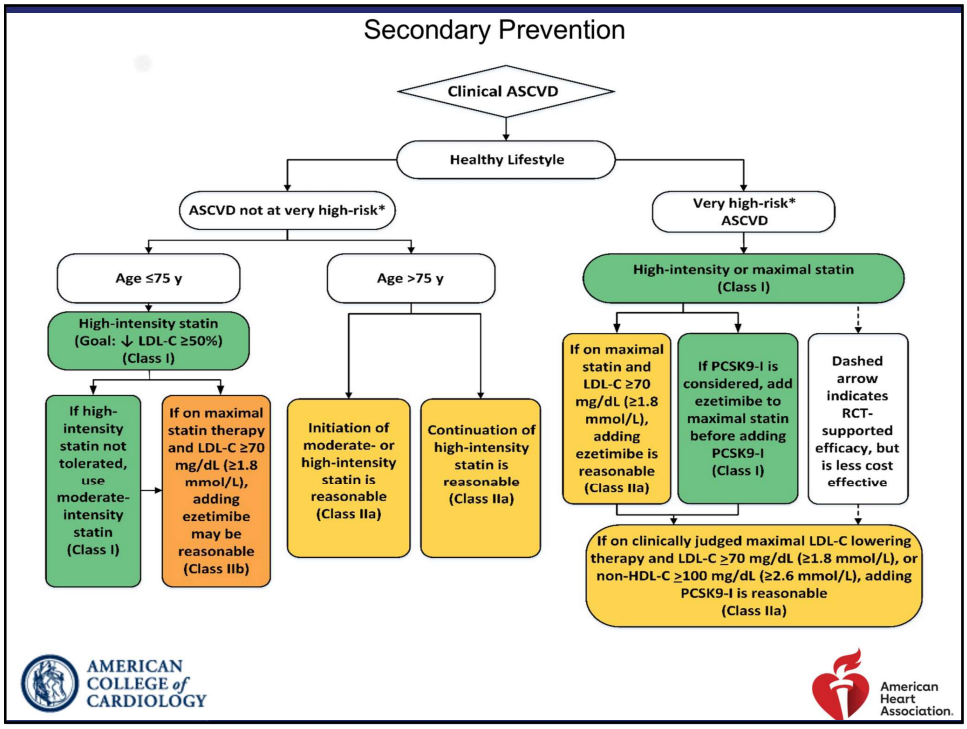
Challenges of New Lipid Therapies

- Cost: High price of biologics (e.g., PCSK9 inhibitors, siRNA therapies).
- Access: Limited availability in low-resource settings.
- Long-Term Safety: Need for more data on novel therapies.
- Patient Adherence: Ensuring compliance with new treatment regimens.

Statins

- High Intensity Statins: Rosuvastatin, Atorvastatin
  - Indicated for all patients with known vascular disease and/or diabetes.
- Medium Intensity Statins: Simvastatin, Pravastatin
- ACC/AHA (2018): Recommend statins for primary prevention in adults with:
  - LDL ≥190 mg/dL.
  - Diabetes + LDL 70–189 mg/dL.
  - 10-year CVD risk ≥7.5% (using pooled cohort equations).


Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk
to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy


Secondary Prevention
Clinical ASCVD
Healthy Lifestyle
ASCVD not at very high-risk*
Very high-risk* ASCVD
Age ≤75 y
Age >75 y
High-intensity or maximal statin
(Class I)
High-intensity statin
(Goal: ↓ LDL-C ≥50%)
(Class I)
If high-intensity statin not tolerated, use moderate-intensity statin
(Class I)
If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable
(Class IIb)
Initiation of moderate- or high-intensity statin is reasonable
(Class IIa)
Continuation of high-intensity statin is reasonable
(Class IIa)
If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable
(Class IIa)
If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I
(Class I)
Dashed arrow indicates RCT-supported efficacy, but is less cost effective
If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable
(Class IIa)
AMERICAN COLLEGE of CARDIOLOGY
American Heart Association.

Statin CV Mortality Trials

- **4S (Scandinavian Simvastatin Survival Study) 1994**: One of the 1st major trials to demonstrate a mortality benefit of statins. Simvastatin **reduced total mortality by 30%** and **coronary mortality by 42%** in patients with angina or prior MI.
- **WOSCOPS. (West of Scotland Coronary Prevention Study) 1995**: Pravastatin reduced the risk of non-fatal myocardial infarction or death from coronary heart disease by **31%** in men with hypercholesterolemia and no history of myocardial infarction. **PRIMARY PREVENTION**
- **CARE (Cholesterol And Recurrent Events) 1996**: Pravastatin reduced the risk of fatal coronary events or nonfatal myocardial infarction by **24%** in patients with a history of myocardial infarction and average cholesterol levels.
- **LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) 1998**: Pravastatin reduced mortality from coronary heart disease by **24%** in patients with a history of myocardial infarction or unstable angina and a broad range of initial cholesterol levels.
- **AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) 1998**: Lovastatin reduced the risk of first acute major coronary events by **37%** in men and women with average cholesterol levels but below-average HDL cholesterol levels. **PRIMARY PREVENTION**

Statin CV Mortality Trials (Continued)

- **HPS (Heart Protection Study) 2002:** Simvastatin reduced the risk of major vascular events by about **24%** in a wide range of high-risk individuals, including those with diabetes, peripheral artery disease, and cerebrovascular disease, regardless of their initial cholesterol levels.
- **PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) 2004**: Compared high-dose atorvastatin with standard-dose pravastatin in patients with acute coronary syndrome and found that the more intensive lipid-lowering strategy resulted in a **16%** reduction in the risk of death or major cardiovascular events.
- **TNT (Treating to New Targets) 2005**: High-dose atorvastatin was more effective than low-dose atorvastatin in reducing the risk of major cardiovascular events in patients with stable coronary heart disease.
- **JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) 2008:** Rosuvastatin significantly reduced the incidence of major cardiovascular events in individuals with normal to low levels of LDL cholesterol but elevated levels of high-sensitivity C-reactive protein, a marker of inflammation. **PRIMARY PREVENTION**
- **HOPE-3 (Heart Outcomes Prevention Evaluation-3) 2016:** Patients without CVD but with risk factors (e.g., hypertension, low HDL, smoking). Rosuvastatin 10 mg showed a **24%** reduction in cardiovascular death, MI, or stroke. Greatest benefit in those with higher baseline LDL or hs-CRP. Supported statins in intermediate-risk primary prevention. **PRIMARY PREVENTION**

Statin: Muscle Pain

- **PRIMO (Prediction of Muscular Risk in Observational Conditions, 2005)**
  - Design: Observational study of 7,924 French patients on high-dose statins (atorvastatin 40–80 mg, simvastatin 40–80 mg, fluvastatin 80 mg)
    - 10.5% reported muscle-related symptoms (pain, weakness, cramps). First large study quantifying SAMS prevalence in real-world settings.
- **STOMP (Effect of Statins on Muscle Performance, 2013)**
  - Design: RCT of 420 statin-naïve adults randomized to atorvastatin 80 mg/day or placebo for 6 months.
    - No significant difference in objectively measured muscle strength or endurance.
    - 9.4% of statin users reported muscle pain vs. 4.6% on placebo. Suggests statins cause muscle pain in some patients, but no measurable muscle dysfunction in most.
- **JUPITER Trial (2008) Subanalysis**
  - Population: 17,802 participants on rosuvastatin 20 mg vs. placebo.
  - Myalgia: 16.0% (statin) vs. 15.4% (placebo) – no significant difference. Clinically significant myopathy: 0.1% in both groups.
  - Significance: High-quality RCTs often report similar rates of muscle pain in statin and placebo arms, highlighting the "nocebo effect."
- **HPS (Heart Protection Study, 2002)**
  - Population: 20,536 high-risk patients on simvastatin 40 mg vs. placebo.
  - Muscle pain: 32.9% (statin) vs. 33.2% (placebo). Rhabdomyolysis 0.05% in both groups. No significant difference.

Statin: Muscle Pain/Myopathy Genetics

- **SEARCH Trial (2010)**
  - Design: Genome-wide study of **simvastatin** 80 mg users.
  - Findings:
  - SLCO1B1*5 variant (common in Europeans) increases simvastatin-induced myopathy risk (OR = 4.5 per allele).
  - Explains ~60% of myopathy cases at high doses.
  - Significance: Genetic testing for SLCO1B1 may help identify high-risk patients.
- **GoDARTS Study (2011)**
- Population: 1,498 patients on **simvastatin**.
- SLCO1B1*5 carriers had 2–3x higher risk of myopathy.
- Implication: Supports personalized statin dosing based on genetics.

Statin: Rechallenge and "Nocebo Effect"

- **SAMSON Trial (2020)**
  - Design: N-of-1 self-blinded trial in 60 patients with prior statin intolerance.
  - Findings:
    - 90% of muscle symptoms recurred during placebo phases.
    - Only 50% of symptoms were statin-specific.
    - Significance: Demonstrates strong nocebo effect in statin intolerance.
- **ASCOT-LLA (2003) Reanalysis**
  - Population: 10,305 hypertensive patients on atorvastatin 10 mg vs. placebo.
  - Muscle-related discontinuations: 1.3% (statin) vs. 1.0% (placebo).
  - Implication: Small absolute risk increase in discontinuation due to SAMS.

Statin Muscle Pain: Take Home Messages

- Incidence of Severe Myopathy:
  - Rhabdomyolysis: 0.01–0.1% (highest with simvastatin 80 mg + CYP3A4 inhibitors).
  - FDA withdrew approval for simvastatin 80 mg in 2011 due to elevated risk.
    - Risk Factors:
      - High-dose statins (e.g., simvastatin 80 mg, atorvastatin 80 mg).
      - Advanced age, female sex, Asian ancestry.
      - Comorbidities: Hypothyroidism, CKD, diabetes.
      - Drug interactions (e.g., fibrates, amiodarone, CYP3A4 inhibitors).
- Nocebo Effect:
  - Up to 50% of SAMS may be due to expectations rather than pharmacological effects.
- Management
  - ACC/AHA (2018):
    - Rechallenge with a lower dose or alternate statin (e.g., rosuvastatin 5 mg, pravastatin).
    - Consider non-statin therapies (e.g., ezetimibe, PCSK9 inhibitors) if intolerance persists.

Statin: Memory Issues

- **Randomized Trials**
  - **Heart Protection Study (HPS, 2002)**
    - No difference in cognitive decline, dementia, or memory-related adverse events between statin and placebo groups.
  - **PROSPER Trial (2002):** Elderly patients.
    - No significant effect on cognitive function (assessed via Mini-Mental State Examination) over 3.2 years.
  - **JUPITER Trial (2008)**
    - No increase in reported memory loss or confusion in the statin group.
  - **ALLHAT-LLT (2002)**
    - No difference in cognitive outcomes after 4.8 years.
- **Observational Studies and Meta-Analyses:**
  - **Cochrane Review (2021)**
    - Analyzed 36 RCTs (83,000+ participants) and found no evidence that statins worsen cognition or increase dementia risk.
  - Long-Term Observational Studies
    - Some studies (e.g., Kuan et al., 2022) suggest statins may reduce dementia risk by improving vascular health, though results are mixed
- ACC/AHA (2018): No recommendation to avoid statins due to cognitive concerns; benefits outweigh risks.
- National Lipid Association (2022): Concludes **statins do not cause dementia and may protect against vascular cognitive impairment.**

Statin Diabetes Risk

- Statins **ARE** associated with a modest increase in the likelihood of developing diabetes especially in patient with risk factors for diabetes (obesity, metabolic syndrome)
  - **JUPITER Trial (2008)**
    - Rosuvastatin 20 mg 27% increased risk of physician-reported diabetes in the statin group (p=0.01).
    - Absolute risk: 3.0% (statin) vs. 2.4% (placebo) over 1.9 years.
  - **Meta-Analysis by Sattar et al. (2010, Lancet)**
    - Data: 13 statin trials (91,140 participants)
    - 9% increased risk of diabetes (odds ratio [OR] 1.09).
    - Higher risk with intensive statin therapy (OR 1.12).
    - Risk factors: Older age, higher BMI, fasting glucose ≥100 mg/dL.
- **HPS (Heart Protection Study, 2002)** Simvastatin 40 mg vs. placebo.
  - 15% increased risk of diabetes (non-significant trend).
- **PROVE-IT TIMI 22 (2004)**
  - 34% higher risk of new-onset diabetes with atorvastatin (p=0.04).
- **WOSCOPS** (pravastatin 40 mg) showed a 30% **reduced** diabetes risk.
- **ASCOT-LLA** (atorvastatin 10 mg) showed a 15% increased risk.

Statin Diabetes Risk

- Mechanism:
  - Impaired Insulin Secretion:
    - Statins may reduce pancreatic β-cell function by inhibiting isoprenoid synthesis, which is critical for insulin signaling.
  - Insulin Resistance:
    - Statins decrease adipocyte GLUT4 expression and increase hepatic glucose production.
  - Genetic Factors:
    - Variants in HMGCR (the statin target gene) and KCNJ11 (involved in insulin secretion) may modulate diabetes risk.
- Guidelines and Recommendations
  - **ADA (American Diabetes Association, 2023):**
    - Statins are recommended for CVD prevention in diabetes patients.
    - Monitor HbA1c and glucose in high-risk individuals starting statins.
  - **ACC/AHA (2018):**
    - The cardiovascular benefits of statins "overwhelm" the small diabetes risk.
    - Prioritize statins in patients with diabetes risk factors but avoid withholding therapy
- **For every 255 patients treated with statins for 4 years, 1 additional case of diabetes occurs, while 5.4 cardiovascular events are prevented (CTTC meta-analysis, 2022).**
- High-risk patients (e.g., prior CVD) benefit significantly, but debate about primary prevention in low-risk individuals with metabolic syndrome.

Ezetimibe

- Works in the small intestine to prevent cholesterol absorption.
- **ENHANCE Trial** (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression)
  - The combination of ezetimibe and simvastatin significantly reduced LDL cholesterol levels more than simvastatin alone. However, there was no significant difference in the progression of carotid intimal media thickness between the two groups
- **IMPROVE-IT Trial** (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)
  - The combination of ezetimibe and simvastatin led to a significant reduction in LDL cholesterol levels and a modest but statistically significant reduction in the risk of major cardiovascular events

Ezetimibe

- SHARP Trial (Study of Heart and Renal Protection)
  - The combination of ezetimibe and simvastatin significantly reduced the risk of major atherosclerotic events (e.g., myocardial infarction, coronary death, ischemic stroke, or any revascularization procedure) in patients with CKD compared to placebo.
- SEAS Trial (Simvastatin and Ezetimibe in Aortic Stenosis)
  - The SEAS trial found that while the combination therapy significantly reduced LDL cholesterol levels, it did not reduce the overall risk of aortic valve replacement or major cardiovascular events. However, there was a reduction in ischemic cardiovascular events, suggesting a potential benefit in reducing atherosclerosis-related outcomes.

Ezetimibe Monotherapy

- Ezetimibe monotherapy reduces LDL-C by ~15–20%, making it less potent than statins (which typically lower LDL-C by 30–50%) or PCSK9 inhibitors (50+%).
- **GAUSS-3 Trial (2016)**
  - In patients with statin intolerance ezetimibe monotherapy vs. evolocumab (a PCSK9 inhibitor).
  - Ezetimibe reduced LDL-C by 16.7%, while evolocumab reduced LDL-C by 54.5%.
  - Confirmed ezetimibe's modest efficacy but better tolerability in statin-intolerant patients.
- ACC/AHA (2018): Ezetimibe monotherapy is a second-line option for LDL-C lowering if statins are contraindicated or not tolerated.
- ESC/EAS (2019): Recommends ezetimibe as add-on therapy but acknowledges its role in monotherapy for specific populations.

Emerging Therapies for Hyperlipidemia

PCSK9 Inhibitors

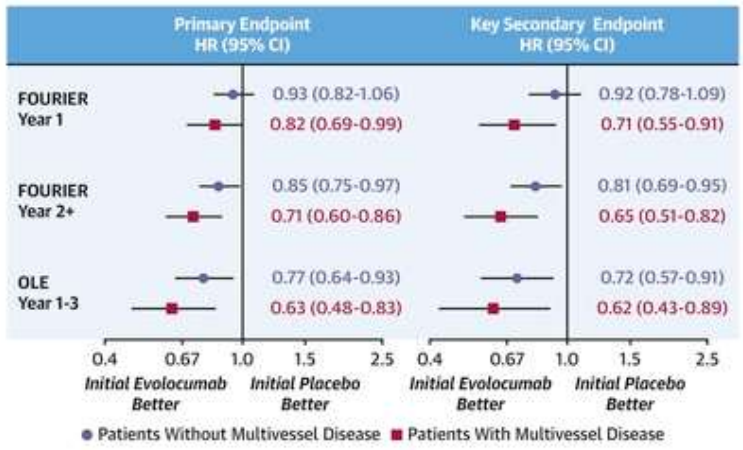
- Mechanism: Monoclonal antibodies that increase LDL receptor availability.
- Examples: Alirocumab, Evolocumab.
- Benefits: Significant LDL-C reduction (50-60%), reduced CVD events.

PCSK9 Cardiovascular Mortality Data

FOURIER Trial (Evolocumab):

- Population: 27,564 patients with atherosclerotic cardiovascular disease (ASCVD).
- Findings:
  - ↓ 59% LDL-C (median LDL: 30 mg/dL)
  - 15% reduction in cardiovascular death, MI, or stroke (primary endpoint).
  - No significant reduction in all-cause mortality (hazard ratio [HR] 1.04, p=0.54).
    - Possible Reason: Shorter follow-up (median 2.2 years) may have limited detection of mortality benefits.

CENTRAL ILLUSTRATION: Effect of Initial Allocation to Evolocumab by Time Period and Multivessel Disease



McClintick DJ, et al. J Am Coll Cardiol. 2024;83(6):652-664.

PCSK9 Cardiovascular Mortality Data

ODYSSEY Outcomes Trial (Alirocumab):

- Population: 18,924 patients with recent acute coronary syndrome (ACS).
- Findings:
  - ↓ 62% LDL-C (median LDL: 25 mg/dL)
  - 15% reduction in major adverse cardiovascular events (MACE).
  - 15% reduction in all-cause mortality (HR 0.85, p=0.026) in prespecified analysis, but this was not the primary endpoint.

PCSK9 Cardiovascular Mortality Data

Meta-Analyses Pooling Data

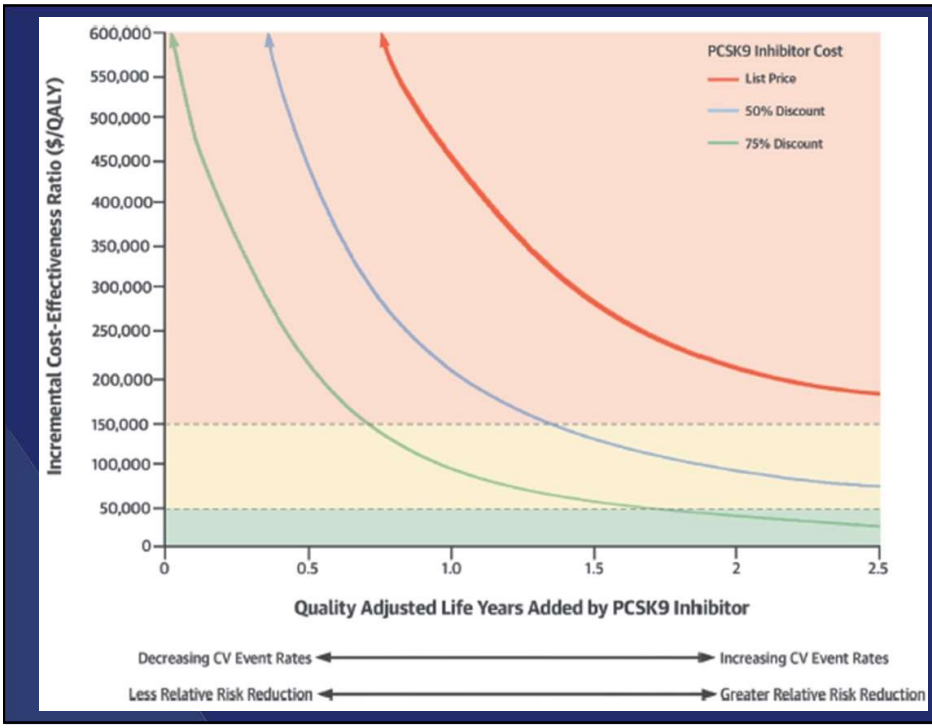
- A 2020 meta-analysis (Nielsen et al., JAMA Cardiology) of 45,539 patients across 3 trials (FOURIER, ODYSSEY, SPIRE) found:
- Reduction in cardiovascular mortality (HR 0.82, 95% CI 0.73–0.93).
- Trend toward reduced all-cause mortality (HR 0.87, 95% CI 0.74–1.02), but not statistically significant.

PCSK9 Cardiovascular Mortality Data

- Subgroup Insights
  - High-Risk Patients:
    - Patients with baseline LDL-C ≥100 mg/dL or recent ACS showed stronger mortality benefits in post-hoc analyses.
  - Long-Term Follow-Up:
    - Extended follow-up of FOURIER (median 5 years) suggested a 29% reduction in cardiovascular death in patients with multivessel coronary disease.

PCSK9 Cardiovascular Mortality Data

- Limitations
  - Trials were primarily powered for cardiovascular events, not mortality.
  - Absolute mortality benefits are small and may require longer-term data.
  - Cost and accessibility limit widespread use in routine practice.
- Key Takeaway:
  - PCSK9 inhibitors reduce cardiovascular mortality in high-risk patients with ASCVD, but all-cause mortality benefits are less clear and may depend on patient risk profile and treatment duration.
- Ongoing studies (e.g., VESALIUS-CV for evolocumab) aim to clarify long-term mortality effects.



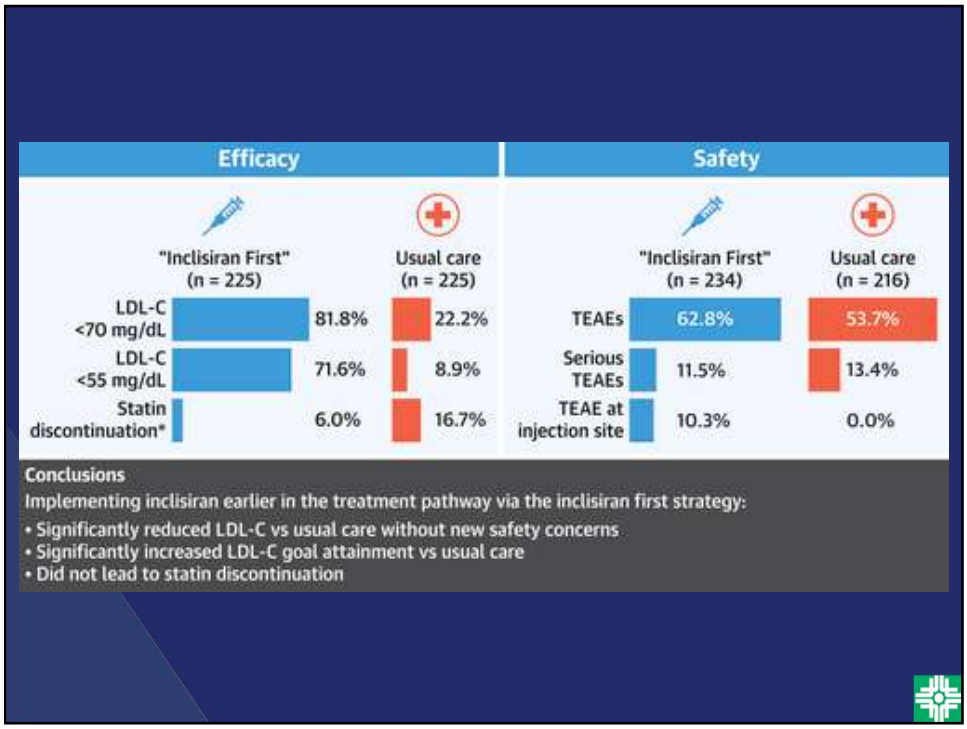
Emerging Therapies for Hyperlipidemia

siRNA Therapeutics (The "Iran" drugs)

- Mechanism: Gene silencing to reduce gene production.
- Small interfering RNA (siRNA) therapies are a revolutionary class of drugs that silence specific genes involved in lipid metabolism
- Example: Inclisiran
- Benefits of siRNA Therapies
  - Durability: Biannual or annual dosing (vs. daily pills or monthly injections).
  - Precision: Gene-specific targeting with minimal off-target effects.
  - Broad Applications: Potential for treating genetic dyslipidemias (e.g., HoFH, familial chylomicronemia).

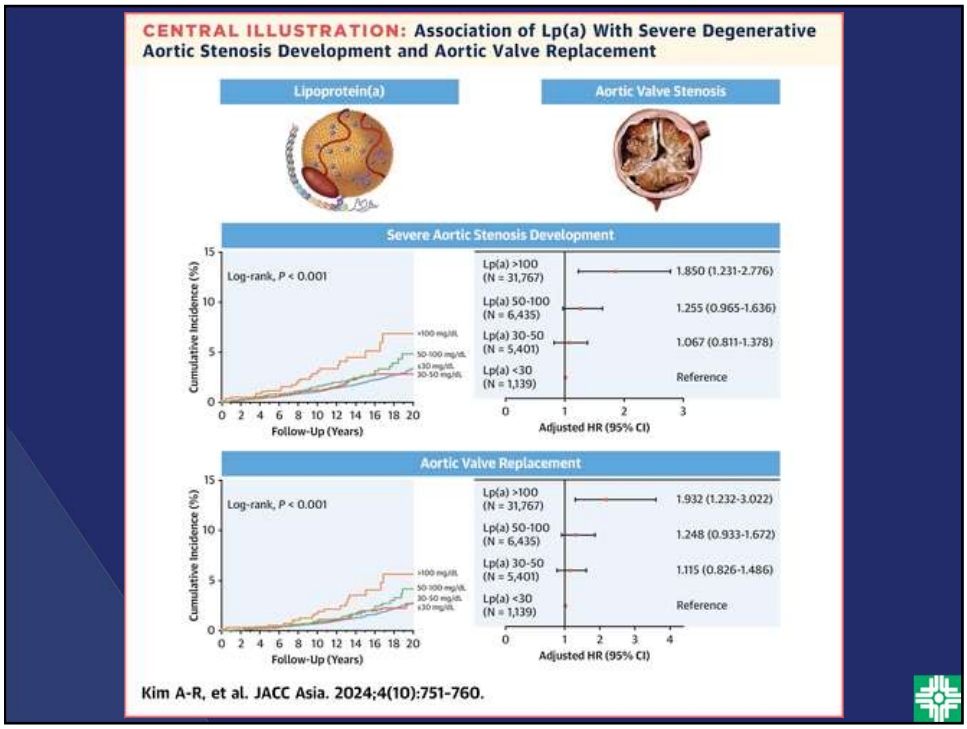
Inclisiran

- Target: PCSK9 gene (reduces LDL-C by increasing hepatic LDL receptor expression).
- Approved for: Adults with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH).
- **ORION-1 (Phase II):**
  - Population: 501 patients with elevated LDL-C despite statins.
  - Results:
    - 50% LDL-C reduction at 6 months.
    - Effects sustained with biannual dosing following initial series of injections at initiation and at 3 months.
- **ORION-9, -10, -11 (Phase III):**
  - Population: ~3,600 patients with ASCVD or HeFH.
  - Results:
    - Consistent LDL-C reduction of ~50% at 17 months.
    - Safe and well-tolerated (mild injection-site reactions).
  - FDA Approval: 2021 (EU: 2020)



Olpasiran

- **Olpasiran**
- Target: Lipoprotein(a) [Lp(a)] gene (reduces Lp(a), a genetic risk factor for CVD)
- Status: Phase III
- Key Trial:
  - - OCEAN(a)-DOSE (Phase II):
    - Population: 281 patients with Lp(a) ≥150 nmol/L
    - Results:
      - Dose-dependent Lp(a) reduction: >90% with highest dose
      - Minimal side effects (mostly mild injection-site reactions)
- Next Step: Phase III OCEAN(a)-OUTCOMES trial (NCT05581303) to assess cardiovascular outcomes



siRNA Drugs: Coming Soon

- **Plozasiran**
- Target: ANGPTL3 gene (reduces triglycerides, LDL-C, and HDL-C).
- Status: Phase III.
  - SHASTA-2 (Phase II):
    - 204 patients with severe hypertriglyceridemia (≥500 mg/dL).
    - 57% reduction in triglycerides.
    - 42% reduction in non-HDL-C
  - MUIR (Phase IIb):
    - 353 patients with mixed hyperlipidemia (LDL-C ≥70 mg/dL + TG ≥150 mg/dL).
    - 44% reduction in LDL-C, 64% reduction in TG, and 35% reduction in Lp(a).
- **Zerlasiran**
- Target: Lp(a) gene.
- Status: Phase II.
  - Phase I/II Trial (2022):
  - Population: 32 patients with Lp(a) ≥150 nmol/L.
  - - 90% Lp(a) reduction at 6 months.
  - - Well-tolerated with no serious adverse events.

siRNA Drugs: Coming Soon

- **Lepodisiran**
- Target: Apolipoprotein C-III (ApoC3) gene (lowers triglycerides)
- Status: Phase II
- Phase I Trial (2023):
- Population: Healthy volunteers and patients with hypertriglyceridemia
- - 94% triglyceride reduction at 28 days
- - Favorable safety profile

Emerging Therapies for Hyperlipidemia

- **ANGPTL3 Inhibitors**
- Mechanism: Reduces LDL-C, HDL-C, and triglycerides
- Example: Evinacumab
- Benefits: Effective in homozygous familial hypercholesterolemia (HoFH)

ANGPTL3 Inhibitors

- **Evinacumab**
- Mechanism: Fully human monoclonal antibody targeting ANGPTL3
- Approved for: Homozygous familial hypercholesterolemia (HoFH) (FDA: 2021). First Therapy specifically approved for HoFH
- Key Trials:
  - Phase II Trial in Refractory Hypercholesterolemia:
    - 272 patients with LDL-C ≥100 mg/dL (including HeFH)
    - 50% LDL-C reduction with monthly intravenous dosing
  - ELIPSE HoFH (Phase III):
    - 65 patients with HoFH (LDL-C ≥70 mg/dL on maximal therapy)
    - 47% reduction in LDL-C at 24 weeks (vs. placebo)
    - Triglycerides reduced by 53%, HDL-C by 25%
    - Well-tolerated; common side effects: nasopharyngitis, flu-like symptoms
- Big Downside: Evinacumab costs ~$450,000/year

Statin Intolerant Alternative

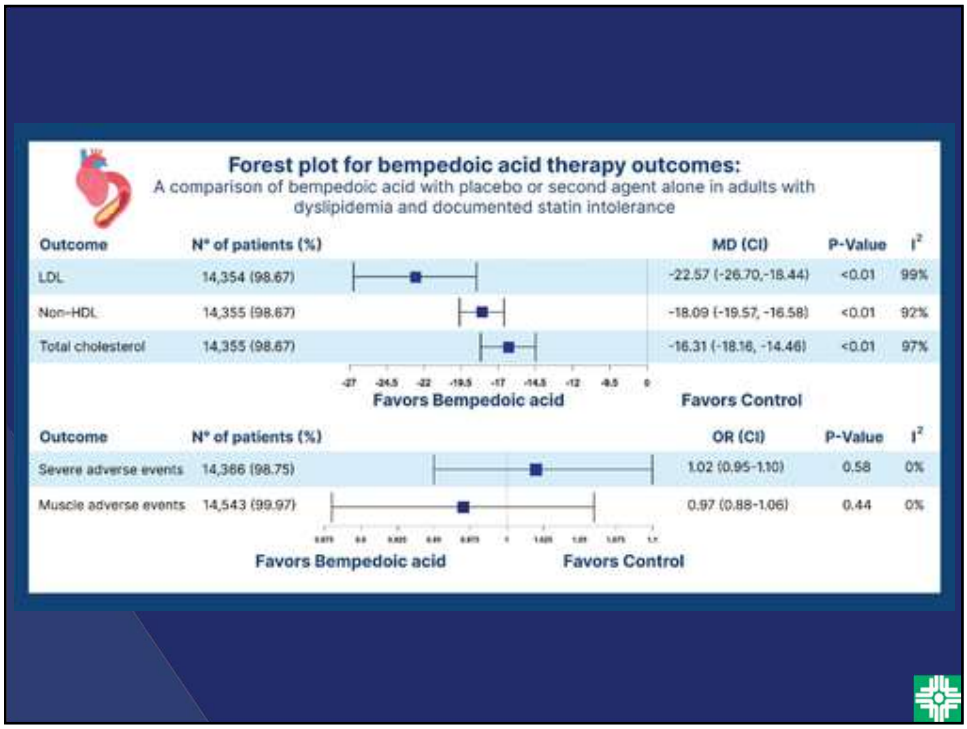
- **Bempedoic Acid**
- Mechanism: ATP-citrate lyase inhibitor, reduces LDL-C
- Benefits: Oral therapy, statin alternative
- ACC/AHA (2022): Bempedoic acid is recommended as a second-line agent for LDL-C lowering in statin-intolerant patients or as adjunctive therapy
- ESC/EAS (2023): Recognizes bempedoic acid for high-risk patients unable to achieve LDL-C goals with statins

Bempedoic Acid

- Phase 3 CLEAR Trials (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen
  - **CLEAR Harmony (2019)**: Confirmed LDL-C lowering and safety in high-risk CAD patients on statins
  - **CLEAR Wisdom (2019)**: Monotherapy in statin intolerant CAD patients. LDL-C reduction: 15.1% vs. placebo. Improved other lipid parameters (non-HDL-C, apoB)
  - **CLEAR Tranquility (2020)**: Bempedoic acid + ezetimibe vs. placebo. LDL-C reduction: 28.5% with combination vs. placebo. Highlighted synergistic effects with ezetimibe.
  - **CLEAR Serenity (2020)**: Hyperlipidemia patients intolerant to statins. LDL-C reduction: 21.4% vs. placebo. Low rates of muscle-related AEs

Bempedoic Acid

- **CLEAR Outcomes (2023)**:
- Population: 13,970 patients with statin intolerance and established or high-risk ASCVD.
- Intervention: Bempedoic acid 180 mg/day vs. placebo for 40 months (median follow-up).
- Primary Endpoint: Composite of cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, or coronary revascularization.
  - Key Results:
  - LDL-C reduction: 21.1% vs. placebo
  - Cardiovascular outcomes:
    - 13% relative risk reduction in the primary endpoint (HR 0.87, 95% CI 0.79–0.96)
    - Significant reductions in non-fatal MI (23%) and coronary revascularization (19%)
- First trial to show cardiovascular event reduction with Bempedoic acid monotherapy in statin-intolerant patients



Novel Approaches in Development

- **CETP Inhibitors**
- Mechanism: Cholesteryl ester transfer protein inhibition to increase HDL-C.
- Example: Obicetrapib (under investigation).

Novel Approaches in Development

- **ApoC-III Inhibitors**
- Mechanism: Reduces triglyceride levels.
- Example: Volanesorsen.

Gene Therapy for Hyperlipidemia

- CRISPR/Cas9 Technology: Editing genes like PCSK9 or LDLR to reduce cholesterol levels
- AAV-Based Gene Therapy: Delivering functional genes to treat genetic dyslipidemias
- Potential: Long-term or permanent solutions for familial hypercholesterolemia

The Future of Lipid Therapy

- Combination Therapies: Using multiple agents for synergistic effects
- Precision Medicine: Genetic testing to guide therapy selection
- Digital Health Tools: Apps and wearables for monitoring lipid levels and adherence
- Research Focus: New targets like Lp(a), inflammation pathways

Thank You