Lipid Management

Allison Bigeh, DO, FACC
Assistant Professor, Internal Medicine
Division of Cardiovascular Medicine
The Ohio State University Wexner Medical Center

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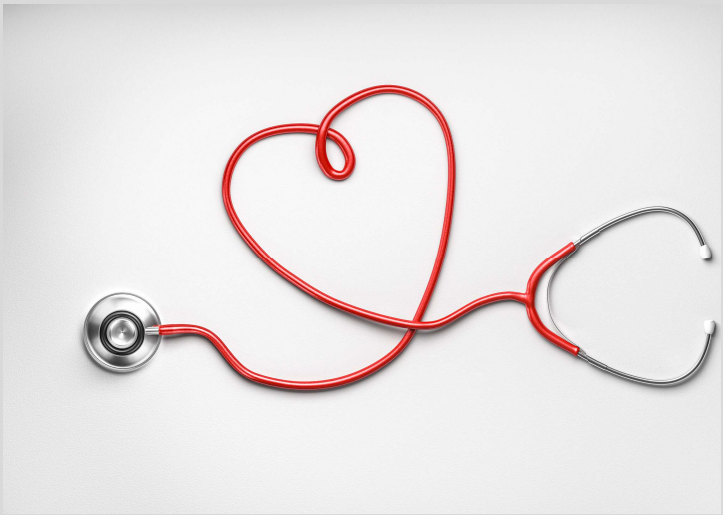
Screening

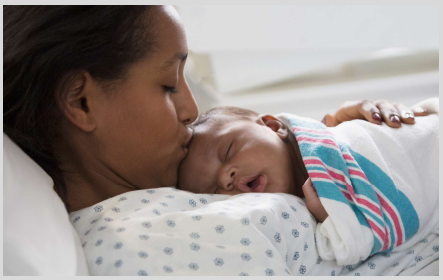
- Nonfasting lipid panel or fasting if elevated ASCVD risk or hyperTG
- Adults
  - Start at 19yo and at least every 5 years thereafter
  - More frequent if additional ASCVD risk factors
- Children
  - Start 9-11yo and again after puberty
  - Start 2yo if family hx premature ASCVD or FH



Blumenthal et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/ ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia. *JACC*. March 2026.

Risk Enhancers

- Premature ASCVD in 1st degree relative (men <55, women <65)
- Ancestry (South Asian, Filipino, Puerto Rican)
- Inflammatory dz (RA, psoriasis, SLE, inflammatory arthritis)
- Lp(a) ≥125 nmol/L
- hsCRP ≥2 mg/L on >1 occurrence (excluding secondary causes)
- OB/GYN (ex: GDM, Pre-E, menopause <40yo)
- CKM syndrome



ApoB

- Measurement of all atherogenic particles
  - 1 ApoB per particle
- Used primarily in adults on lipid lowering therapy at elevated risk
- Guides intensification of Rx once LDL and non-HDL goals achieved

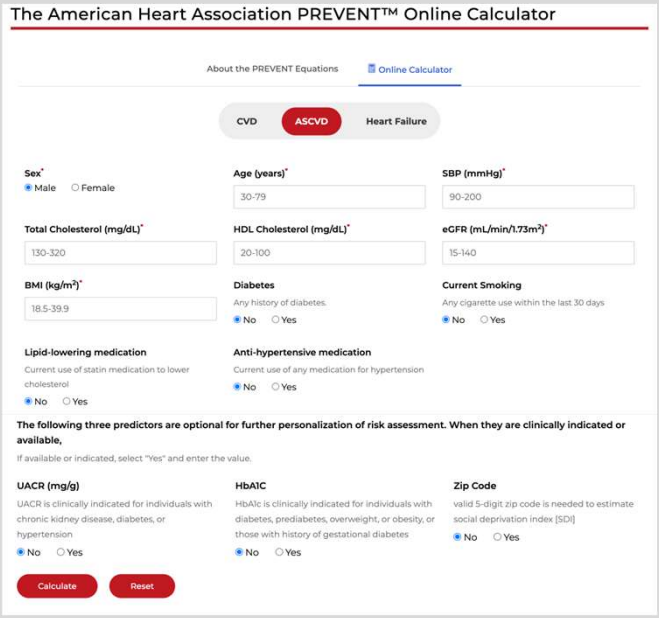
Lp(a)

- LDL-like particle that is genetically determined
- Independent risk factor for ASCVD and aortic stenosis
- ≥ 125 nmol/L (50 mg/dL) considered risk enhancing
- Levels stable over lifetime (except pregnancy)
- Not affected by diet/lifestyle
- Current recommendation: measure once in adults
  - Cascade screening of 1st degree relatives if elevated

Primary Prevention

- Adults 30-79yo and LDL 70-189 mg/dL
  - Health behavior counseling (diet, exercise)
  - Calculate PREVENT-ASCVD
    - Low <3%
    - Borderline 3-<5%
    - Intermediate 5-<10%
    - High ≥10%
    - Calculate 30y risk for 30-59yo (≥10% considered elevated)

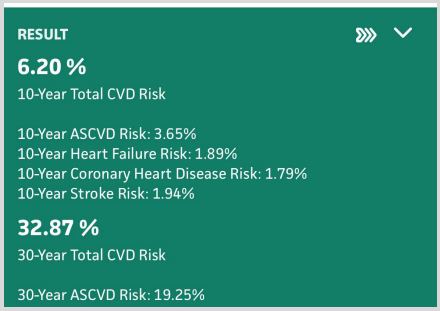
PREVENT-ASCVD



Downloadable Apps

AMERICAN COLLEGE of CARDIOLOGY — CVD Risk Estimator Plus

MD+CALC — MDCalc



Primary Prevention

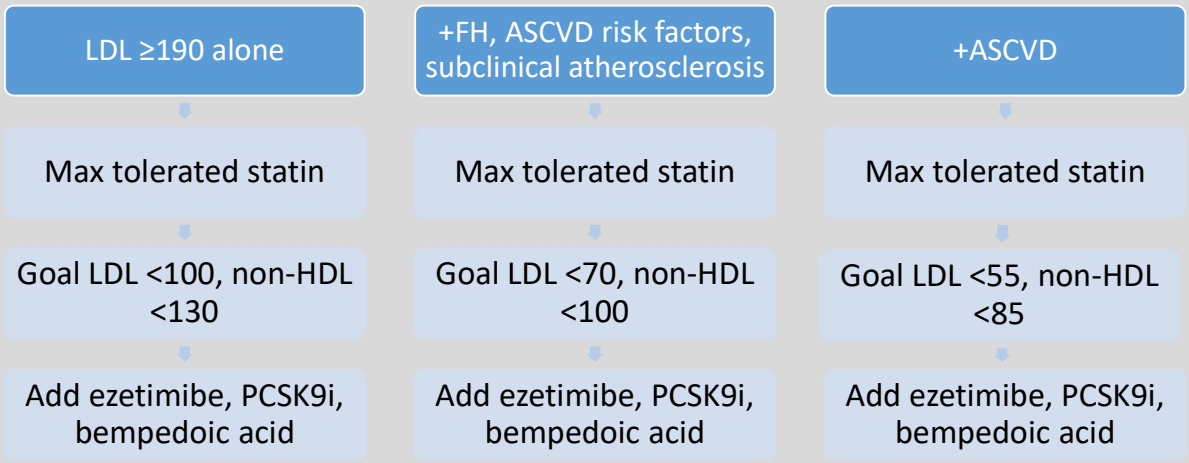
Low 10y risk <3%	Borderline 3-<5%	Intermediate 5- <10%	High ≥10%
LDL ≥160 or 30y ≥10%?	Moderate intensity statin	Moderate-High intensity statin	High intensity statin
Yes	Goal LDL <100 and 30% reduction	Goal LDL <100 and 30-50% reduction	Goal LDL <70 and 50% reduction
Moderate intensity statin	Consider CAC if unsure (CAC>0 favors statin)	Consider CAC if unsure (CAC>0 favors statin)	
Goal LDL <100 and 30% reduction			

No → Lifestyle modification

Severe hypercholesterolemia LDL ≥190

- Exclude secondary causes first
  - Diet (high saturated fat, keto)
  - Hypothyroidism
  - Nephrotic syndrome
  - Pregnancy
  - Meds (ex: steroids)
- Cascade screening of 1st degree relatives
- Consider genetic testing

Severe Hypercholesterolemia LDL ≥190



Primary Prevention

- Adults with Diabetes 40-75yo
  - Moderate intensity statin (goal LDL <100)
  - Multiple RF → high intensity statin (goal LDL <70)
  - TG >150 → consider icosapent ethyl (*after optimizing statin, lifestyle etc)
- 20-39yo with long duration DM → consider statin

Secondary Prevention

- **"At Very High Risk":** ≥2 Major Events or 1 Major + ≥2 High Risk Conditions
- Major
  - ACS <1y, Hx MI, Hx ischemic CVA, Symptomatic PAD
- High Risk
  - Age ≥65yo
  - Prior CABG/PCI
  - Smoker
  - Diabetes
  - CHF
  - HTN
  - LDL >100 despite statin + zetia

Secondary Prevention

Not Very High Risk	Very High Risk
High intensity statin	High intensity statin
Goal ≥50% LDL reduction, LDL <70, and non-HDL <100	Goal ≥50% LDL reduction, LDL <55, and non-HDL <85
Add ezetimibe, PCSK9i, bempedoic acid	Add ezetimibe, PCSK9i, bempedoic acid

Subclinical Atherosclerosis

- CAC score should <u>not</u> be done on patients taking lipid lowering therapy (increases CAC volume)

CAC 1-99 and <75th percentile	CAC ≥100-299 or ≥75th percentile	CAC ≥300-999	CAC ≥1000
Moderate intensity statin	Statin	Statin	Statin
≥30% LDL reduction, LDL <100	≥50% LDL reduction, LDL <70	≥50% LDL reduction, LDL <70	≥50% LDL reduction, LDL <55
	Consider ASA 81mg	Consider ASA 81mg	Consider ASA 81mg

Hypertriglyceridemia

- Exclude secondary causes!
- Optimize diet, exercise, ETOH intake, weight management
- Adults with ASCVD + TG ≥150
  - Maximize statin/LLT → Get LDL and non-HDL to goal **FIRST**
  - May consider icosapent ethyl
- Adults with fasting TG ≥500
  - Estimate 10y PREVENT-ASCVD→ maximize statin/LLT →LDL to goal first
  - Consider fibrate or prescription omega-3 FA

When to Refer to Lipid Specialist

Diagnosed or suspected FH
ASCVD or high risk
ASCVD on complex med regimens (HIV, transplants, cancer)
FH, ASCVD, TG >400 considering or are pregnant, breastfeeding
Severe HyperTG after secondary causes ruled out
Patients with inherited HLD needing genetic testing
Candidates for advanced therapies (evinacumab, lomitapide, apheresis, olezarsen)

Antihyperlipidemics

Kelly M. Bartsch, PharmD, BCPS, CLS, AACC
Specialty Practice Pharmacist, Ambulatory Care
The Ohio State University Wexner Medical Center

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LDL Lowering Therapies

Oral Therapies

- HMG-CoA Reductase inhibitors
- Cholesterol absorption inhibitors
- ATP-Citrate Lyase inhibitors
- Bile Acid Sequestrants (not addressed here)

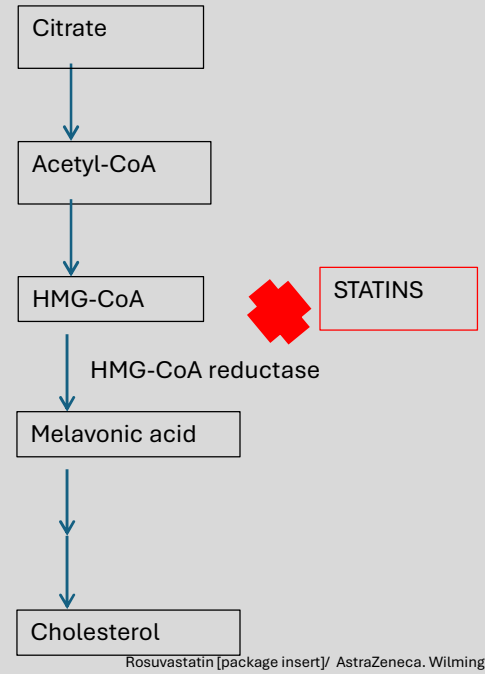
Injectable Therapies

- PCSK9 mAb
- PCSK9 siRNA

- Note: additional therapies available for HoFH patients include lomitapide and evinacumab

HMG-CoA Reductase Inhibitors

Statins



- Dosing + Effects:
  - Potency varies by statin and dose
    - High intensity: >50% ↓LDL-C
    - May also decrease TRG and HDL
    - Small increase in Lp(a)
  - PO formulations
  - Once daily administration*
  - Newer agents can be taken at any time of day
- Pleiotropic effects
- Adverse Effects: Myalgias
  - More likely with lipophilic statins: atorva-, lova-, simva-
- Contraindications:
  - Acute liver failure, decompensated cirrhosis, lactation, severe underlying neuromuscular disease
- Drug interactions

*exception: fluvastatin

Rosuvastatin [package insert]/ AstraZeneca. Wilmington, DE. 11/2018. Graphic original.

Statin Intolerance

- Ensure true intolerance
  - Rule out or correct secondary causes: thyroid, hypovitaminosis D, new exercise habits, electrolyte imbalances
  - Rule out drug interactions
  - Hold x2 weeks, re-challenge
- Alternate statin
  - Lipophilic: atorvastatin, lovastatin, simvastatin
  - Hydrophilic: rosuvastatin, pravastatin, fluvastatin
  - Pitavastatin
- Start with a lower dose and titrate slowly
  - ADE are typically dose dependent
  - Change goal to max tolerated dose (may not reach initial target dose)

Backes JM, et al. J Clin Lipidol. 2012;6(4):362-7.

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Statin Intolerance

- Intermittent dosing (atorva-/rosuva- only)
  - HD-ROWS (2012) – 23 patients treated for 8 weeks with atorva 10mg daily vs rosuva 80mg weekly
  - No statistically significant difference in LDL lowering found between the groups, both ~29% reduction

Backes JM, et al. J Clin Lipidol. 2012;6(4):362-7.

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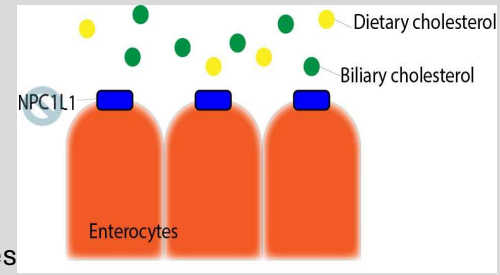
Cholesterol Absorption Inhibitor

Ezetimibe

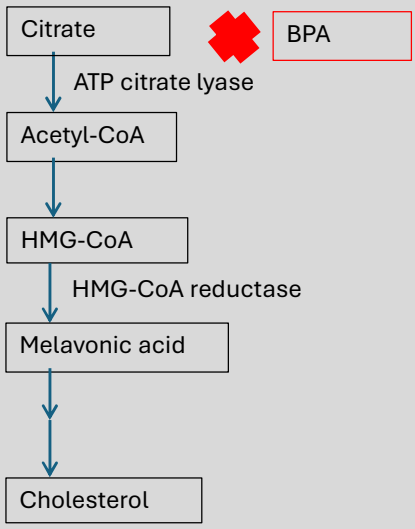


- Major Lipid Effects:
  - ↓ LDL 18% as monotherapy, 25% with statin
  - No significant change in TRG and HDL
- Common Side Effects: URI, arthralgia, GI distress
  - With statin: myalgia, increased hepatic transaminases
- Clinical Trial Data: IMPROVE-IT (2015)
  - Addition of ezetimibe to moderate intensity statin (simvastatin 40mg) in patients with recent ACS
  - Decreased composite endpoint of CV death, nonfatal MI, UA requiring re-hospitalization, revascularization, nonfatal stroke over 6 years
  - Outcome: **HR 0.936** (95% CI 0.89-0.99); NNT 50 over ~5 years
  - Subgroups with most benefit: diabetes (HR 0.85) and those with at least 3 of heart failure, HTN, age >75, diabetes, prior stroke, prior CABG, PAD, eGFR <60, current smoking (NNT 16 over 7 years)
- 1st line therapy for patients with sitosterolemia

Cannon CP, et al. NEJM. 2015;372:2387-97.

ATP Citrate Lyase Inhibitor

Bempadoic Acid

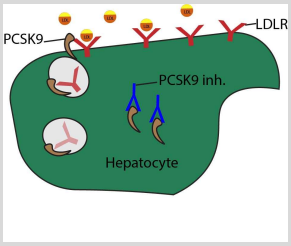


- Approved for: high risk primary prevention, secondary prevention, HeFH
- Dosage: 180mg (1 tablet) daily
- Major Lipid Effects: ↓ LDL up to 20%
- Common Side Effects: anemia, URI, muscle spasm, back pain
- Clinical Pearls:
  - Prodrug activated by very long-chain acyl-CoA synthase
  - Monitor uric acid before and after therapy initiation
  - Use cautiously in patients with a history of tendon rupture or cholelithiasis
  - Not studied in patients with eGFR <30
- Clinical Trial Data: CLEAR-Outcomes (2023)
  - 13,970 patients unable or unwilling to take statin, followed for ~40mo
  - Decreased 4 point MACE vs placebo (**HR 0.87**, CI 0.79-0.96)

Goldberg AC, et al. JAMA 2019;322(18):1780-8.

PCSK9 Inhibitors (aka PCSK9 mAb)

Alirocumab, Evolocumab



- Dosing:
  - Alirocumab: 75mg Q2 weeks, 150mg Q2 weeks, 300mg Q4 weeks
  - Evolocumab: 140mg Q2 weeks, 420mg Q4 weeks (requires 3 injections)
- Indications: ASCVD risk reduction in primary or secondary prevention patients, HeFH, HoFH
- Major Lipid Effects:
  - ↓ LDL by 65% or more
  - Favorable effects on HDL, TRG, and Lp(a) as well
- Common side effects: injection site reaction, hypersensitivity reaction, myalgia
  - Less common: nasopharyngitis, diarrhea, back pain, memory changes

Drug information: "Alirocumb." Drug Monograph. Gold Standard. Published November 14, 2018.
Drug information: "Evolocumab. " Drug Monograph. Gold Standard. Published October 23, 2018.
Graphic original

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PCSK9 inhibitors - Outcomes

	FOURIER	ODYSSEY OUTCOMES
Population	27,564 with ASCVD	18,924 with recent ACS
Duration	2.2 years	2.8 years
Primary endpoint (composite)	CV death, MI, stroke, hospitalization for unstable angina, or cor. revascularization	CHD death, non-fatal MI, fatal or non-fatal ischemic stroke, or UA requiring hospitalization
Treatment vs. placebo	9.8% vs. 11.3%	9.5% vs. 11.1%
Median follow up	2.2 years	2.8 years
HR	0.85 95% CI 0.79-0.92	0.85 95% CI 0.78-0.93
NNT	67	64

Sabatine MS, et al. NEJM 2017; 376:1713-22.
Schwartz GG, et al. NEJM 2018; 379:2097-2107

New kid on the block

- 3rd generation PCSK9i: lerodalcibep-liga
- Approved Dec 2025 for LDL-C reduction in patients with HLD, including HeFH
  - Expected commercial availability by mid-2026
- Dosing: 300mg subQ once monthly
  - Available as autoinjector and prefilled syringe
- Stable at room temperature for 3 months
- ADE: neutralizing antibody development, injection site reaction, nasopharyngitis, peripheral edema
- LIBerate trial series
  - Liberate-CVD: lerodalcibep vs placebo
    - Mean LDL reduction 49.4% at week 52 in the intent-to-treat population
    - ApoB reduced 41.6%
    - Lp(a) reduced 21.6%
  - CVOT trial in process

E Kulg et al. JAMA Cardiology. 2024;9(9):800-7.

siRNA

Inclisiran

- Indications: heterozygous or homozygous familial hypercholesterolemia, hypercholesterolemia as adjunct to diet and exercise
- Dose: SubQ injection at day 0, month 3, then Q6months
  - **Must be injected by a healthcare professional**
- Major Lipid Effects: ↓ LDL by >50%
- Common side effects: injection site reaction, HA
- Clinical Trial Data:
  - ORION 9, 10, and 11
    - Pooled analysis: composite MACE OR 0.74 (CI 0.58-0.94); *not powered for CV outcomes
  - CVOT in progress: ORION-4 (ends 2026), VICTORION-2 Prevent (ends Oct 2027), VICTORION-1 Prevent (ends Apr 2029)

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Which direction do we go after statin?

Ezetimibe	• <25% LDL lowering to reach target • Preference for PO therapy • Access concerns (generic)
PCSK9 mAb	• >50% LDL lowering needed • Lp(a) also elevated • Very high-risk patients (CVOT and safety data)
PCSK9 siRNA	• >50% LDL lowering needed • Concerns with self-injecting (ability or adherence) • Medical benefit billing needed

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What about lipoprotein(a)?

- Reminder: considered a risk enhancer when >125 nmol/L
- **No currently approved therapies**
  - Current approach to optimally control other ASCVD risk factors
- Consideration: aspirin
  - Lp(a) has structural similarities to plasminogen making it pro-thrombotic
  - Use depends on overall ASCVD risk, bleeding risk, etc
- Many agents in active clinical trials
  - Lp(a) ASO (Pelacarsen – HORIZON)
  - Lp(a) siRNA (Olpasiran – OCEAN(a); Lepodisiran – ACCLAIM-Lp(a))
  - Lp(a) oral small molecule inhibitor (Muvalaplin - KRAKEN)
  - First studies due to complete in late 2026

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What about triglycerides?

- Primary target of therapy when >500 mg/dL
- For many patients, first line is still statin
- Other therapy options:
  - Omega-3 fatty acids
  - Fibrates
  - APO C-III ASO
  - APO C-III siRNA

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Omega-3 Fatty Acids

- Major Lipid Effects:
  - ↓ TRG up to 60%
  - ↑ LDL up to 20%*
  - *LDL increase due to DHA; EPA does not increase LDL
- Common Side Effects: GI distress, belching, fishy after taste
  - Okay to freeze OTC formulations for increased tolerability
- Contraindications (relative): Symptomatic atrial fibrillation
- Clinical Trial Data: REDUCE-IT (2018)
  - Icosapent ethyl added to pts with TRG 150-499 mg/dL, LDL 41-100 mg/dL AND 45y+ with CVD or 50y+ with DM and at least one RF
  - Decreased composite endpoint of CV death, nonfatal MI, UA requiring re-hospitalization, revascularization, nonfatal stroke

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Fibrates

- Major Lipid Effects:
  - ↓ LDL 5-20%* and TRG 20-50%
  - ↑ HDL 10-20%
  - *LDL may increase in patients with elevated TRG
- Requires dose adjustment in renal disease
  - Fenofibrate: reduce for CrCl <80, contraindicated <30
  - Gemfibrozil: reduce for CrCl <60, contraindicated <30
- Common Side Effects: dyspepsia, gallstones, myopathy
  - Increased myalgia risk in combination with statins
- Contraindications:
  - Absolute: severe renal disease, severe hepatic disease
- Clinical Trial Data: reduced major coronary events and CHD deaths (gemfibrozil)
  - VA-HIT, FIELD

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Misc Drugs

Plozasiran	Olezarsen
• Apo C-III siRNA • Approved for FCS • ADE: hyperglycemia, GI, HA • Q3 month subQ injection • Severe hyperTRG trials: SHASTA	• Apo C-III ASO • Approved for FCS • ADE: hyperglycemia, thrombocytopenia, arthralgias • Qmonth subQ injection • Severe hyperTRG trials: CORE

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Special Populations

- Adults >75yo with estimated life expectancy of at least 2-3 years, moderate-intensity statin *may* be reasonable
  - If decision is uncertain, reasonable to check a CAC and avoid LLT if <10
- In patients with life expectancy <1y, may be reasonable to stop therapy
- Consider a lower starting dose of rosuvastatin in individuals of Chinese, Japanese, or Korean ancestry (particularly women)
- Patients with complex medication regimens should be carefully assessed for drug-drug interactions
  - HIV, cancer, transplant, autoimmune diseases, etc
- Pregnancy
  - Statins – discontinue prior to conception for most, can be considered for patients with ASCVD / FH
  - BAS are safe to use but interfere with absorption of fat-soluble vitamins
  - TG >500 – fibrates after first trimester or omega-3 at any point are reasonable
  - *Most therapies have insufficient data*

Conclusion

- Statins remain the mainstay of therapy for most patients
  - Dose should be maximized to highest tolerated before adding additional therapies in most cases
- Many patients at high or very-high risk will need additional therapies to achieve LDL targets

Population	Second Line	Alternate Options
Primary Prevention – High Risk	Ezetimibe	PCSK9 mAb, bempedoic acid
Severe HLD	Ezetimibe, PCSK9 mAb, bempedoic acid	Refer to lipidologist
Diabetes	Ezetimibe +/- bempedoic acid, PCSK9 mAb	Consider IPE for high ASCVD risk
Secondary Prevention – Not at Very High Risk	Ezetimibe, PCSK9 mAb, bempedoic acid	PCSK9 siRNA
Secondary Prevention – Very High Risk	Ezetimibe and/or PCSK9 mAb	PCSK9 siRNA, bempedoic acid
CAC >300 AU	Ezetimibe, PCSK9 mAb, bempedoic acid	