UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

LDL Limbo: How Low Should We Go?

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Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Hayam Giravi, PharmD:**
    - None
  - **CE mentor(s), Hanna Raber, PharmD, BCACP, TTS:**
    - None
- Off-Label Uses of Medications
  - None

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Learning Objectives – Pharmacists

At the conclusion of this activity, participants should be able to successfully:

1) Interpret relevant primary literature and treatment recommendations included in the 2018 ACC/AHA and the 2022 ACC ECDP to evaluate LDL goals.
2) Compare and contrast the indications, mechanism of action, and dosing of nonstatin therapies.
3) Identify when to add nonstatin therapy based on patient specific factors in both primary and secondary prevention.

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Learning Objectives – Technicians

At the conclusion of this activity, participants should be able to successfully:

1) Summarize the relevance of hyperlipidemia and the importance of implementing therapy.
2) Compare and contrast storage requirements for nonstatin therapies.
3) Discuss financial concerns and resources available for nonstatin therapies.

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Abbreviations

- ABI: ankle-brachial index
- ACS: acute coronary syndrome
- ASCVD: atherosclerotic cardiovascular disease
- BPH: benign prostatic hyperplasia
- CK: creatine kinase
- CKD: chronic kidney disease
- CV: cardiovascular
- eGFR: estimated glomerular filtration rate
- HeFH: heterozygous familial hypercholesterolemia
- HDL-C: high-density lipoprotein cholesterol
- HoFH: homozygous familial hypercholesterolemia
- LDL-C: low-density lipoprotein cholesterol
- MI: myocardial infarction
- PAD: peripheral artery disease
- PAP: patient assistance program
- PCI: percutaneous coronary intervention
- UA: unstable angina
- siRNA: small interfering ribonucleic acid

Background

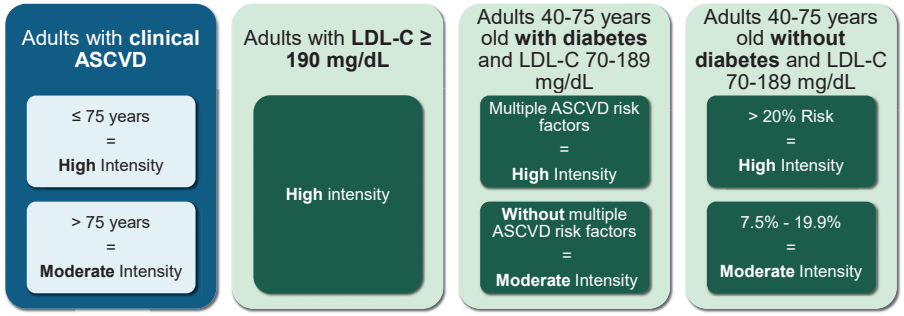
Guidelines and Recommendations

- 2018 AHA/ACC Multisociety Guideline on the Management of Blood Cholesterol
- 2019 ESC/EAS Guidelines for the Management of Dyslipidemias
- 2020 AACE/ACE Guidelines for the Management of Dyslipidemia and Prevention of Cardiovascular Disease
- 2021 ACC Expert Consensus Decision Pathway (ECDP) on the Management of ASCVD Risk Reduction in Patients with Persistent Hypertriglyceridemia
- 2022 USPSTF: Recommendations on Statin Use for the Primary Prevention of Cardiovascular Disease in Adults
- 2022 ACC ECDP on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

Dyslipidemia and ASCVD[9]

Risk Factors	Prevalence	↑ LDL-C = ↑ Risk
• Obesity • Poor diet • Lack of exercise • Smoking • Alcohol • Age • Genetics	• ~ **2 in 5** adults in the US have high cholesterol	• **Heart disease** • **Stroke**

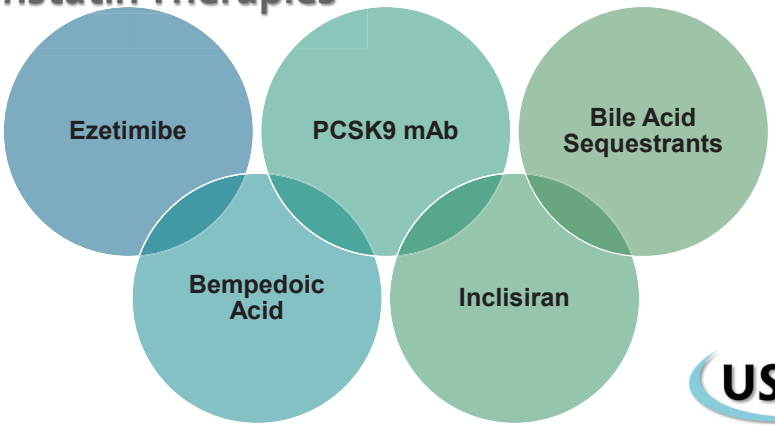
Patient Management Groups[1]



2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies[2]

1) In what **patient populations** and **situations** should newer nonstatin therapies be considered?
2) Which treatment options should be considered in patients who are **truly statin intolerant**?
3) If newer nonstatin therapies are to be added, **which therapies should be considered and in what order** to maximize patient benefit and preference?

Nonstatin Therapies



Ezetimibe (Zetia®)[2,3]

Mechanism of action

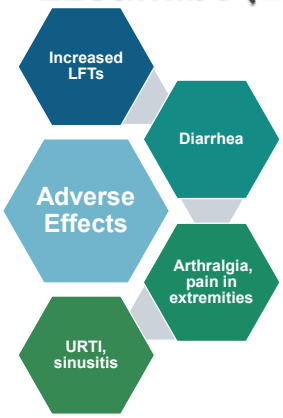
Inhibits absorption of cholesterol in the small intestine via NPC1L1

- ↓ **cholesterol delivery** to the liver
- ↓ **hepatic cholesterol stores**
- ↑ **clearance** of cholesterol from blood

Indication

- Primary HLD
- HoFH
- Homozygous sitosterolemia

Ezetimibe (Zetia®)[2,3]



Warnings/ Precautions

- Moderate or severe hepatic impairment (Child-Pugh class B & C): **use is not recommended**

Monitoring

- **Lipid levels** within **4 to 12 weeks of initiation** and every 3 to 12 months thereafter
- Signs or symptoms of myopathy / CPK
- **Baseline LFTs** and as clinically indicated

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Ezetimibe (Zetia®)[2,3]

LDL-C % ↓	• Monotherapy: **18%** • Ezetimibe + Statin: **25%**
Cost	• **~$2** per tablet
CV Outcomes Trial	• **IMPROVE-IT** (2015)

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IMPROVE-IT (2015)[4]

Study Design	Randomized, double-blind trial
Population	• 18,144 patients • Recent **ACS** (within 10 days) • LDL-C **50 - 100 mg/dL** on therapy *or* **50 to 125 mg/dL** if not on therapy
Interventions	• **Ezetimibe 10 mg + simvastatin 40 mg** (n = 9,067) • Simvastatin 40 mg + placebo (n = 9,077)
1° Endpoint	• CV death, nonfatal MI or stroke, UA requiring rehospitalization, or coronary revascularization

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IMPROVE-IT (2015)[4]

Baseline Mean LDL-C	Ezetimibe + Simvastatin	Simvastatin Monotherapy	Ezetimibe LDL % ↓
93.8 mg/dL	53.7 mg/dL	69.5 mg/dL	~24%

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IMPROVE-IT (2015)[4]

Primary Outcome	Simvastatin Monotherapy (n=9077)	Simvastatin + Ezetimibe (n=9067)	Hazard Ratio (95% CI)	P	NNT
Death from CV causes, major coronary event, or nonfatal stroke	2742 **(34.7%)**	2572 **(32.7%)**	0.936 (0.89 – 0.99)	0.016	**50** over **7 years**

Results of IMPROVE-IT indicate that in patients post ACS, **ezetimibe 10 mg/simvastatin 40 mg is superior to simvastatin 40 mg alone in reducing CV events.**

PCSK9 Monoclonal Antibodies[2,3]

Medications: alirocumab (Praluent®) & evolocumab (Repatha®)

Mechanism of action: Binds to PCSK9 which results in an ↑ of LDL receptors available to remove circulating LDL-C

Indication

- Primary HLD
- Secondary prevention
- HoFH

Dosage & Administration

- Subcutaneous injections (eg, thigh, abdomen, or upper arm)

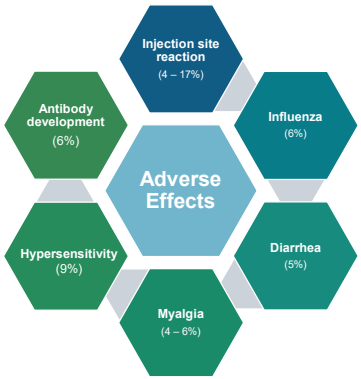
Storage

- Refrigerated; can be kept at room temperature for up to 30 days

PCSK9 mAb Dosing[2,3]

1° HLD or 2° Prevention	Alirocumab (Praluent®)	Evolocumab (Repatha®)
Biweekly	Initial: 75 mg **every 2 weeks** Maximum dose: 150 mg every 2 weeks	140 mg **every 2 weeks**
Monthly	300 mg **every 4 weeks**	420 mg **every 4 weeks**

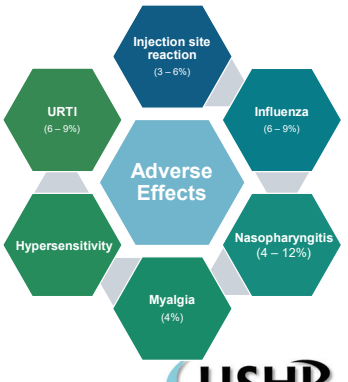
Alirocumab (Praluent®)[2,3]



Monitoring

- **Lipid levels** within 4 to 12 weeks of initiation and every 3 to 12 months thereafter
- **Hypersensitivity reactions**

Evolocumab (Repatha®)[2,3]



PCSK9 Monoclonal Antibodies[2,3]

LDL-C % ↓	• Alirocumab: **45 – 58%** • Evolocumab: **58 – 64%**
Cost	• **~$600** per month
CV Outcomes Trial	• **FOURIER** (2017) • **ODYSSEY Outcomes** (2018)

FOURIER (2017)[5]

Study Design	**Randomized, double-blind trial**
Population	• 27,564 patients • **ASCVD** (prior MI, stroke, or PAD) • LDL-C **≥ 70 mg/dL** or non-HDL-C **≥ 100 mg/dL** • On maximally tolerated statin therapy
Interventions	• **Evolocumab** 140 mg every 2 weeks or 420 mg every 4 weeks (n = 13,784) • **Placebo** (n = 13,780)
1° Endpoint	CV death, MI, stroke, hospitalization for UA, or coronary revascularization

FOURIER (2017)[5]

Baseline Median LDL-C	After Treatment	Least-squares Mean LDL % ↓
92 mg/dL (IQR 80 – 109)	**30 mg/dL** (IQR 19 – 46)	**59%**

FOURIER (2017)[5]

Primary Outcome	Evolocumab (n=13,784)	Placebo (n=13,780)	Hazard Ratio (95% CI)	P-Value	NNT
CV death, MI, stroke, hospitalization for UA, or coronary revascularization	1344 (**9.8%**)	1563 (**11.3%**)	0.85 (0.79 – 0.92)	<0.001	**67** over **2.2 years**

FOURIER demonstrated that **addition of evolocumab to statin therapy significantly reduced the risk of CV events.**

PCSK9 mAb Coverage

Copay Card	HealthWell Foundation Grant	Amgen Safety Net Foundation	MyPraluent	LIS Program
• **Alirocumab: $25/monthly** • **Evolocumab**: **$5/monthly** • **Commercial** or **private** insurance	• Hypercholesterolemia Grant – **Medicare patients only** • **$2500 annually** to help with prescription copays • Household **income** limit 500% of the Federal Poverty Level (adjusted for household size and high cost of living areas)	• **Evolocumab PAP** • **Income** eligibility requirements • **Uninsured** or your insurance **plan excludes evolocumab** • **Medicare Part D** patients with product coverage who cannot afford their out of pocket costs	• **Alirocumab PAP** • **Uninsured** • **Medicare Part D** that covers alirocumab and patient meets income restrictions • Alirocumab may be free of charge for up to 12 months (requires annual renewal) • Need to have **spent $500 on prescriptions** within the calendar year	• **Limits prescription out-of-pocket costs for eligible Medicare Part D patients** with limited income • **Reduce** Medicare Part D **premiums** • **Lower drug copays**

Bempedoic Acid (Nexletol®)[2,3] approved Feb 2020

Indication

- Adjunct to diet and on maximally tolerated statin therapy
- Adults with **HeFH** or **ASCVD** requiring additional LDL-C lowering

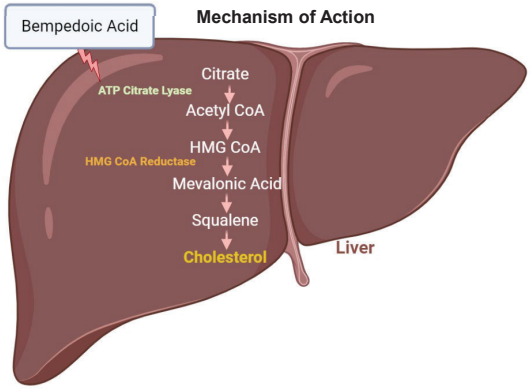
Dosage & Administration

- 180 mg orally once daily

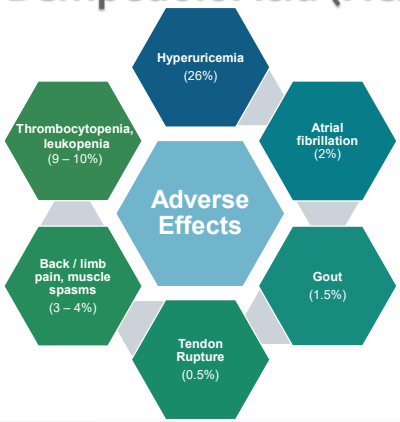
DDIs (avoid use)

- Simvastatin >20 mg
- Pravastatin >40 mg

Mechanism of Action



Bempedoic Acid (Nexletol®)[2,3] approved Feb 2020



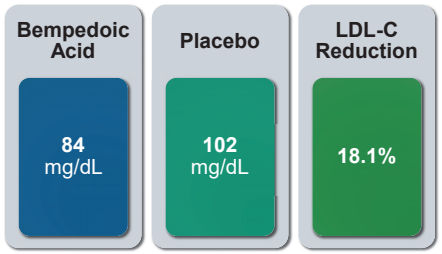
Monitoring

- **Lipid levels** within 8 to 12 weeks of initiation and every 3 to 12 months thereafter
- Signs or symptoms of **hyperuricemia** → assess uric acid levels as clinically indicated
- Signs or symptoms of **tendon rupture or tendinopathy** (joint pain, inflammation, swelling)

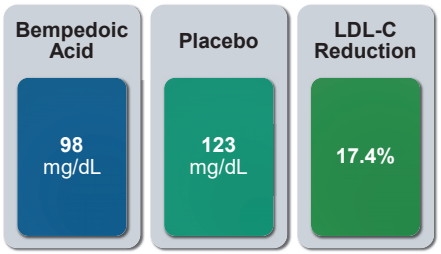
CLEAR Trials[6,7]

Trial (year)	n	Key Inclusion Criteria	Interventions	Key Outcomes
HARMONY (2019)	**2,230**	• **ASCVD** and/or **HeFH** • Maximally tolerated **statin** • Baseline LDL-C **≥ 70 mg/dL**	• BA 180 mg (n=1,488) • Placebo (n=742)	• % change LDL-C at **week 12** • **Adverse events**
WISDOM (2019)	**779**		• BA 180 mg (n=522) • Placebo (n=257)	• % change LDL-C **at week 12**

CLEAR Harmony[6]



CLEAR Wisdom[7]



CLEAR Harmony[6]

Outcome	Bempedoic Acid (n=1487)	Placebo (n=742)	P
Adverse Events	1167 (**78.5%**)	584 (**78.7%**)	0.91
Serious AE	216 (**14.5%**)	104 (**14%**)	0.80
AE leading to discontinuation	162 (**10.9%**)	53 (**7.1%**)	0.005
Myalgia	89 (**6**%)	45 (**6.1**%)	0.92

When added to maximally tolerated statin therapy, **bempedoic acid significantly reduced LDL-C levels by ~16.5% and did not lead to an overall increase in adverse events.**

Bempedoic Acid (Nexletol®)[2,3]

LDL-C % ↓	• **17% to 18%**
Cost	• **~$475** per month
CV Outcomes Trial	• **CLEAR OUTCOMES** (2023)

Bempedoic Acid Coverage

Copay Card

- **$10/monthly**
- **Commercial** or **private** insurance

HealthWell Foundation Grant

- Hypercholesterolemia Grant – **Medicare patients only**
- **$2500 annually** to help with prescription copays
- Household **income** limit 500% of the Federal Poverty Level (adjusted for household size and high cost of living areas)

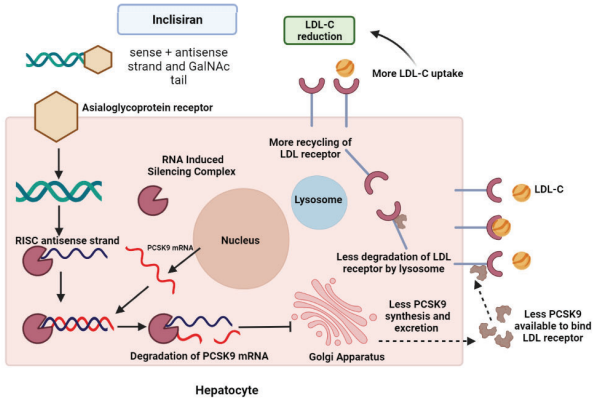
LIS Program

- **Limits prescription out-of-pocket costs for eligible Medicare Part D patients** with limited income
- **Reduce** Medicare Part D **premiums**
- **Lower drug copays**

Inclisiran (Leqvio®)[2,3] approved Dec 2021

Mechanism of Action

- Inclisiran is a siRNA that silences the translation of PCSK9 mRNA
- PCSK9 proteins promote the degradation of LDL-receptors and **inclisiran prevents PCSK9 protein formation intracellularly** → allows for greater uptake of LDL-C into hepatocytes



Inclisiran (Leqvio®)[2,3]

Indication

- Adjunct to diet and maximally tolerated statin therapy
- Adults with **HeFH** or **ASCVD** requiring additional LDL-C lowering

Dosage & Administration

- Subcutaneous injection
- Administered by a **clinician**
- 284 mg per dose

1st dose	2nd dose	Subsequent doses
Day 1	Day 90	Every 6 months

Inclisiran (Leqvio®)[2,3]

Adverse Effects

- Injection site reactions (8%)
- Arthralgia (5%)
- Antibody development (5%)
- Bronchitis (4%)

Monitoring

- Baseline lipid panel
- **Lipid levels** within **4 to 12 weeks of initiation** and every 3 to 12 months thereafter

Inclisiran (Leqvio®)[2,3]

LDL-C % ↓	• **48% to 52%**
Cost	• **~$2,600** per injection
CV Outcomes Trial	• **VICTORION-2P** (expected Oct 2027) • **ORION-4** (expected Jul 2026)

ORION 10 & 11[8]

Trial (year)	n	Key Inclusion Criteria	Key Baseline Characteristics	Interventions	1° Endpoint	Mean LDL-C ↓
ORION-10, ORION-11 (2020)	**3,178**	• **ASCVD** (ORION10) • **ASCVD** with LDL ≥ 70 mg/dL or **ASCVD risk equivalent** with LDL ≥ 100 mg/dL (ORION11) • Maximally tolerated statin therapy or documented statin intolerance +/- additional lipid lowering therapies	• **ASCVD** 94% • **ASCVD-RE** 13% • **HeFH** 1.5% • **LDL-C** 105 mg/dL • **Statin** ~92% • **HI statin** ~73% • **Ezetimibe** ~8%	Inclisiran vs. placebo	• **% change in LDL-C at day 510** (ORION-10) • **% change in LDL-C after day 90 and up to day 540** (ORION-11)	• **52.3%** (ORION-10) • **49.9%** (ORION-11)

Inclisiran **reduced LDL-C by approximately 50%** when compared to placebo **with similar rates of adverse events** reported between groups (with the exception of more injection site reactions reported with inclisiran).

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Inclisiran Coverage

Must be billed under **medical benefit** as it is administered by a clinician

Copay Card	Novartis Patient Assistance Foundation
• **$0**/monthly • **Commercial** or **private** insurance	• **Uninsured** • **Underinsured** • Meet **income** guidelines adjusted for household size

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2022 ACC ECDP on Role of Nonstatin Therapies for LDL-C Lowering

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Clinical ASCVD on Statin Therapy Subgroups[2]

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Clinical ASCVD with Very High Risk on Statin Therapy[2]

Very High Risk

- History of **multiple major** ASCVD events
- History of **1 major ASCVD event** AND **multiple high-risk conditions**

Target LDL-C: **≥ 50 % reduction** from baseline and **< 55 mg/dL**

1st line nonstatin therapies
→ ezetimibe and/or PCSK9 mAb

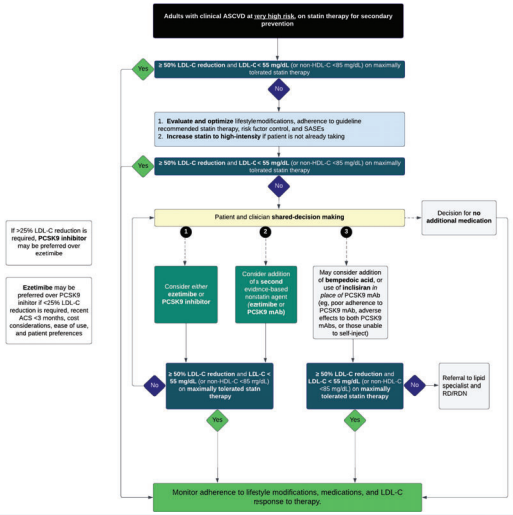
2nd line nonstatin therapies
→ bempedoic acid or inclisiran

Criteria to Define "Very High Risk"[1,2]

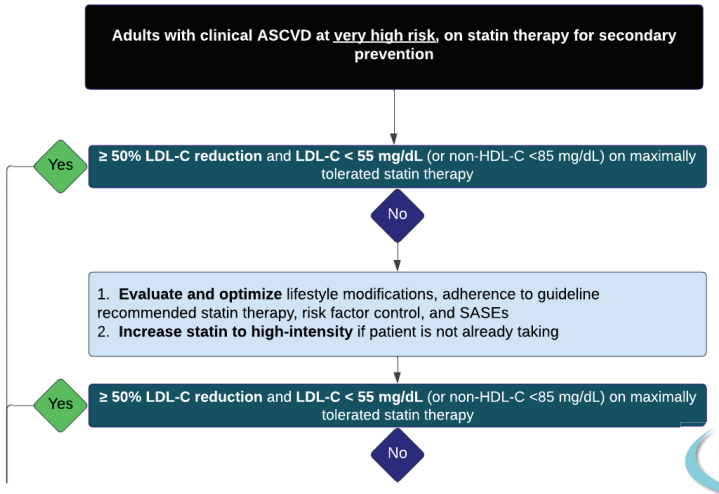
Major ASCVD Events
Recent ACS (within the past 12 months)
History of **myocardial infarction** (other than recent ACS event listed above)
History of **ischemic stroke**
Symptomatic PAD (history of claudication with ABI <0.85 or previous revascularization or amputation)

High-Risk Conditions
Age ≥ **65 years**
HeFH
History of **prior coronary artery bypass surgery** or **PCI** outside of the major ASCVD event(s)
Diabetes
Hypertension
CKD (eGFR 15 – 59 mL/min/1.73)
Current smoking
Persistently elevated LDL-C (LDL-C ≥ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe)
History of **congestive HF**

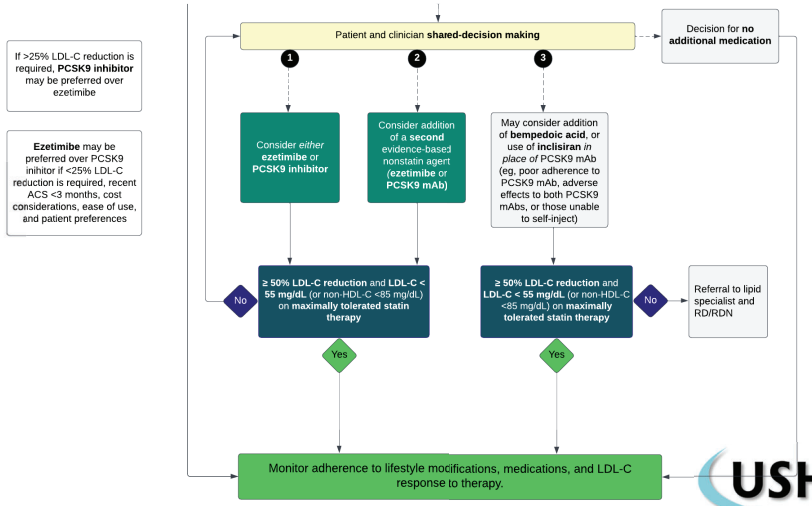
Clinical ASCVD Very High Risk [2]



Clinical ASCVD Very High Risk [2]



Clinical ASCVD Very High Risk [2]



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How Low Should We Go? [4,5,10]

IMPROVE-IT	FOURIER	ODYSSEY OUTCOMES
53.7 mg/dL	30 mg/dL	53 mg/dL

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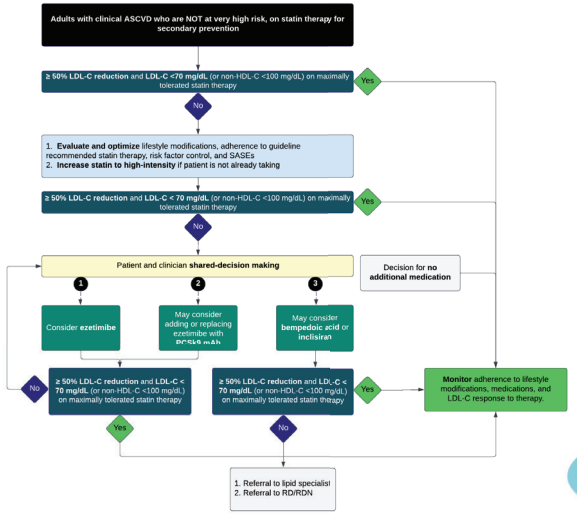
Clinical ASCVD Not at Very High Risk [2]



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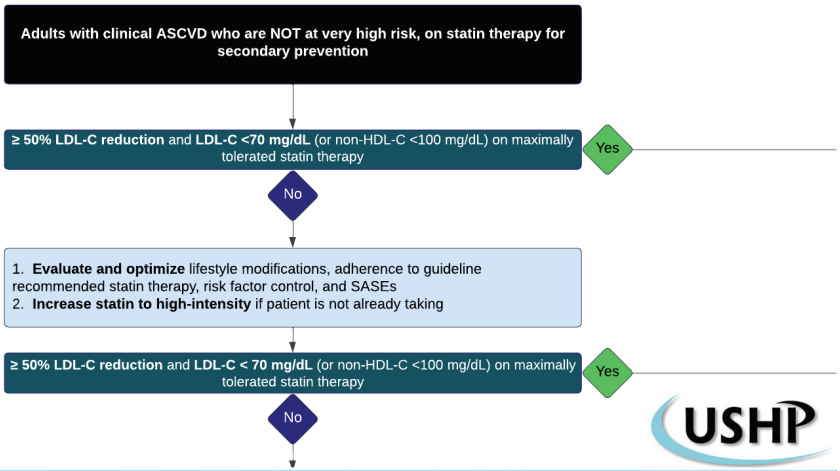
Clinical ASCVD Not at Very High Risk [2]



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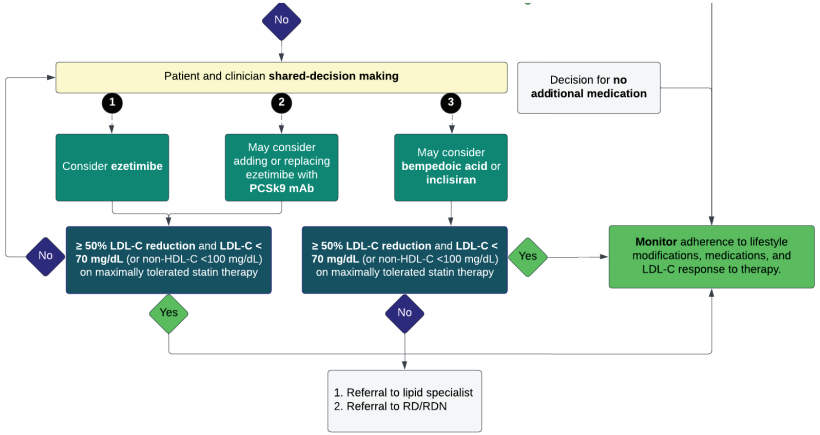
Clinical ASCVD Not at Very High Risk[2]



Clinical ASCVD – Not at Very High Risk[2]

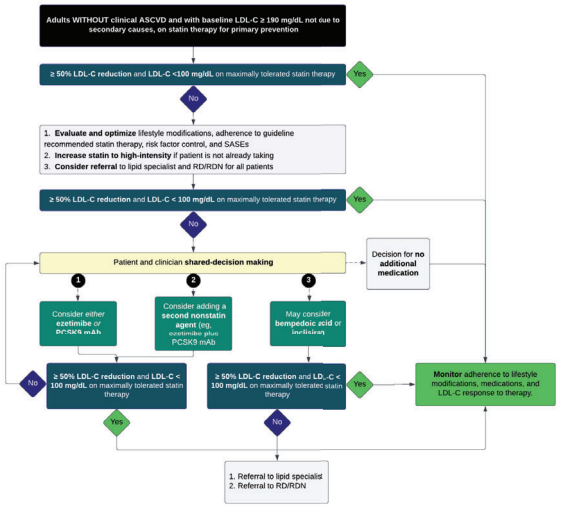
Target LDL-C: **≥ 50 % reduction** from baseline and **< 70 mg/dL**

1st line nonstatin → ezetimibe

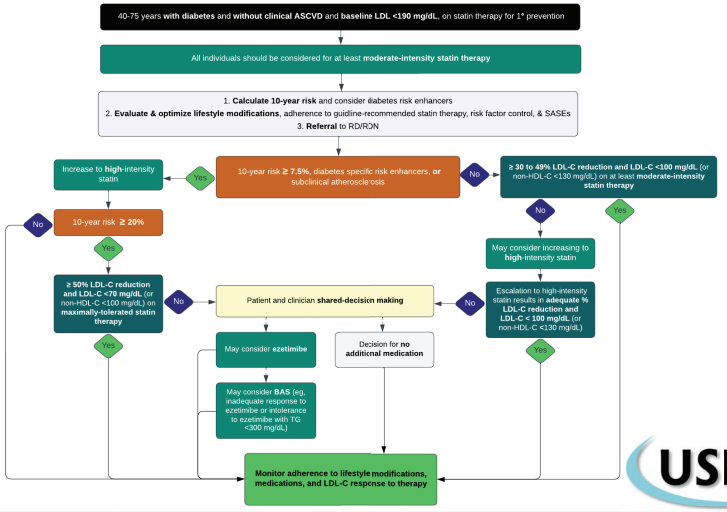
2nd line nonstatin → PCSK9 mAb

3rd line nonstatin → bempedoic acid or inclisiran

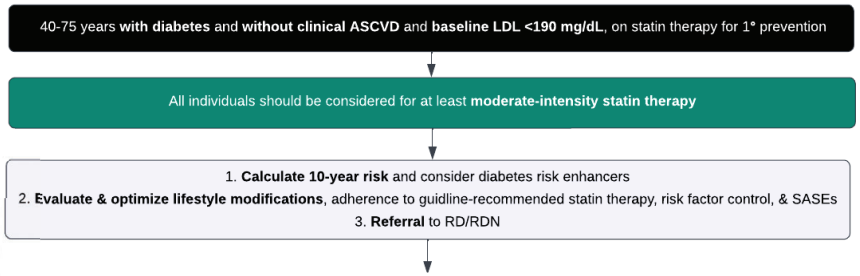
1° Prevention LDL ≥ 190 mg/dL[2]



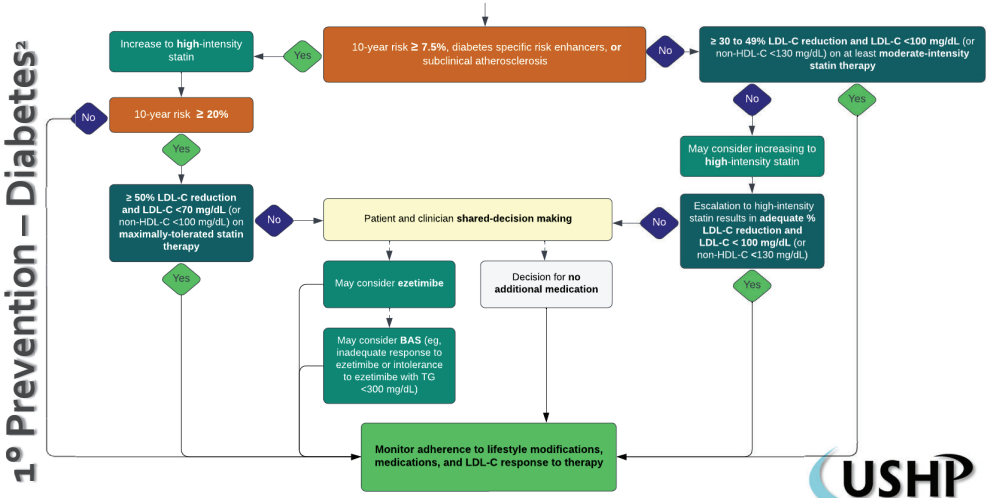
1° Prevention Diabetes[2]



1° Prevention – Diabetes[2]



1° Prevention – Diabetes[2]



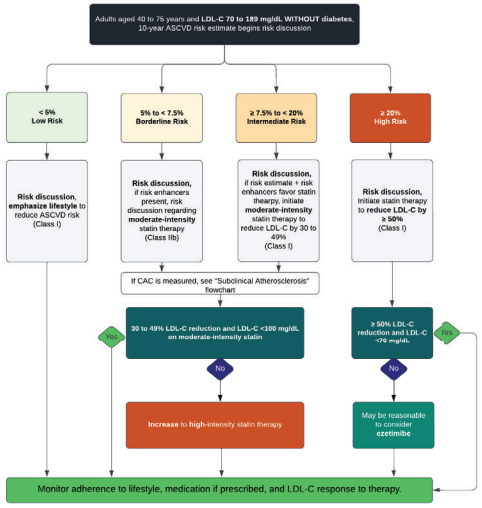
1° Prevention – Diabetes[2]

1st line nonstatin → ezetimibe

2nd line nonstatin → BAS

PCSK9 mAbs, bempedoic acid, and **inclisiran** do not currently have an established, evidence-based role for 1° prevention in patients with diabetes

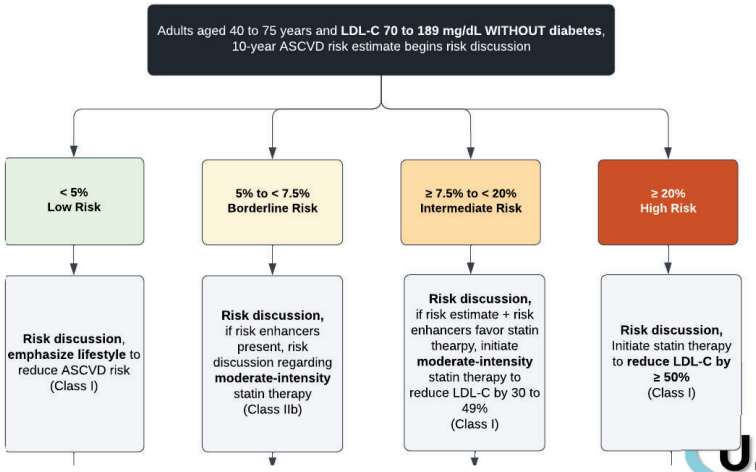
1° Prevention[2] Without diabetes or ASCVD



ASCVD Risk Enhancers

- Family hx of premature ASCVD
- Persistently elevated LDL-C ≥ 160 mg/dL
- CKD
- Metabolic syndrome
- Conditions specific to women (eg, preclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (eg, South Asian ancestry)
- Persistently elevated TG ≥ 175 mg/dL
- hs-CRP ≥ 2.0 mg/dL
- Lp(a) levels >50 mg/dL
- ApoB ≥ 130 mg/dL
- Ankle-brachial index (ABI) <0.9

1º Prevention[2] Without diabetes or ASCVD



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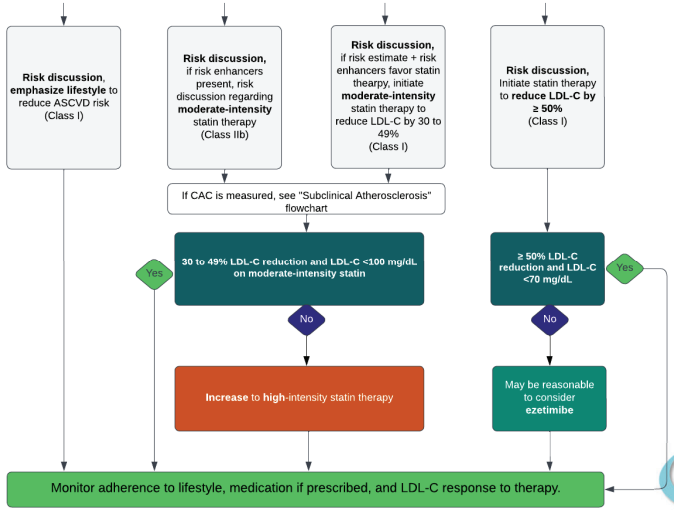
1º Prevention[2] Without diabetes or ASCVD



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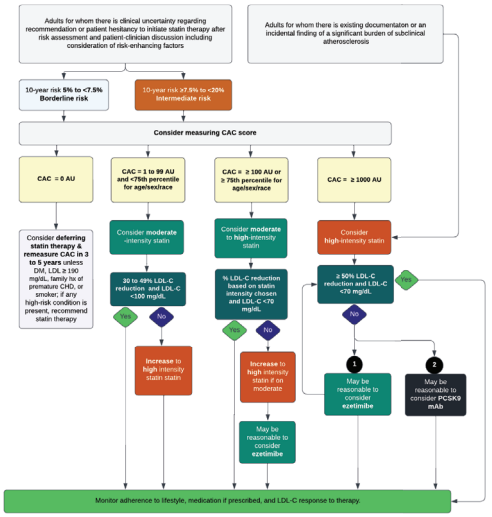
CAC Score[11,12]

- Measurement of the **amount of calcium in the walls of the arteries that supply the heart**
- Used for **risk assessment and prediction of future ASCVD events** in patients with no known CAD
- Patient selection for CAC screening:
  - **Adults without ASCVD, diabetes, or LDL-C ≥ 190 mg/dL with borderline to intermediate risk (5% to <20%)** → if decision about statin therapy is uncertain can consider measuring CAC
  - **Not recommended to routinely use in patients with ASCVD risk <5% or in high-risk patients (>20%)**
- Scored using **"Agatston units"**

Agatston Score	Plaque Burden	Probability of Significant CAD
0	**No plaque**	Very low
1 – 99	**Mild** calcification	Mild or minimal coronary artery stenosis
100 – 399	**Moderate** calcification	Nonobstructive CAD likely, although obstructive disease is possible
≥ 400	**Severe** calcification	High likelihood of at least 1 significant coronary artery stenosis

1º Prevention[2] Subclinical Atherosclerosis



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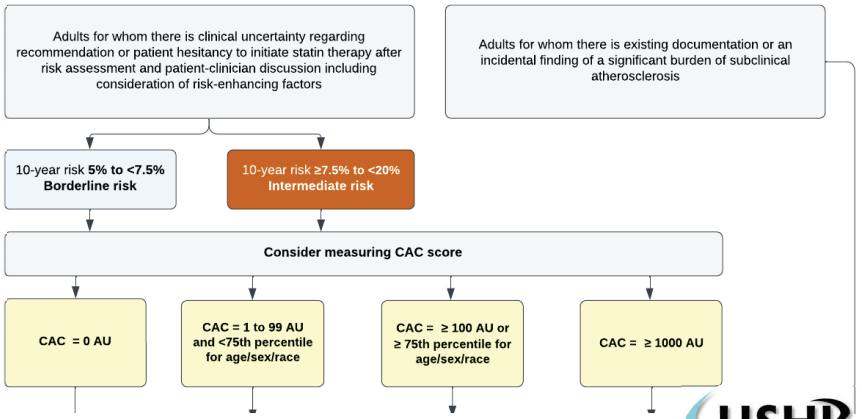
1º Prevention[2] Subclinical Atherosclerosis



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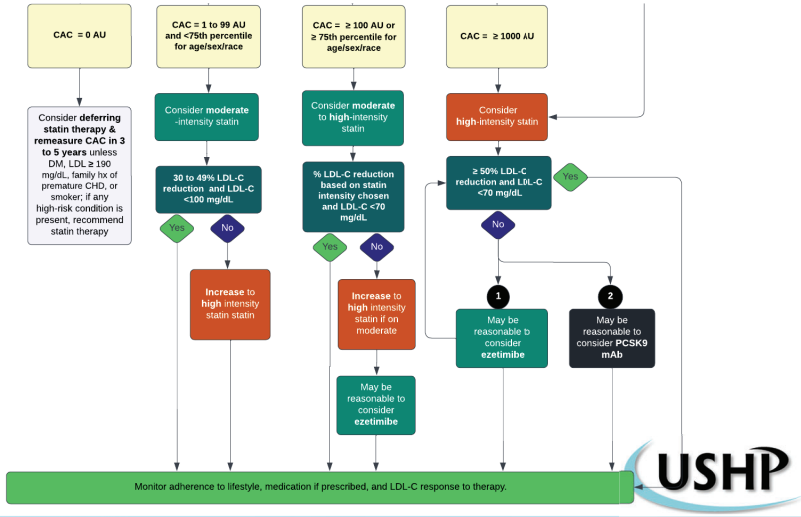
1º Prevention[2] Subclinical Atherosclerosis



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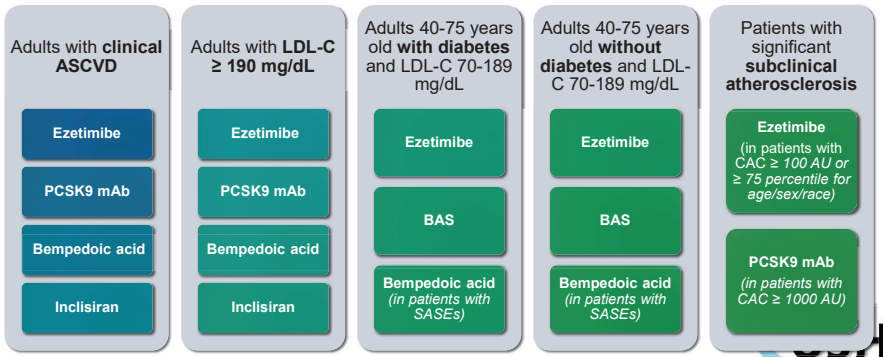
Summary Table of Nonstatin Options



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Clinician-Patient Discussion[2,3]

Drug	LDL-C reduction	Cost	DDI	Other considerations	CV outcomes data
Ezetimibe	18 – 25%	~$10 per month	• Cyclosporine • Fibrates • BAS	• Not recommended in patients with moderate to severe hepatic impairment	**Yes**
PCSK9 mAb	45 – 64%	~$600 per month	• No clinically significant DDI	• Subcutaneous injection at home	**Yes**
Bempedoic Acid	17 – 18%	~$475 per month	• Simvastatin >20 mg daily • Pravastatin >40 mg daily	• Pill burden / compliance • May increase uric acid (eg, avoid in gout) • Avoid in history of tendon rupture or tendon disorders	No (in progress)
Inclisiran	48 – 52%	~$2,600 per injection	• No clinically significant DDI	• Subcutaneous injection by a clinician	No (in progress)

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13) Images created with BioRender.com
14) Flowcharts created in LucidChart