

Lipid Disorders in Diabetes: Contemporary Management of Hyperlipidemia and Complex Dyslipidemias

Reframing Lipid Management Beyond Traditional Targets

Practical, guideline-based management for the primary care provider

Includes:

- ADA lipid targets & treatment choices
- Nonstatin therapies & evidence
- Persistent hypertriglyceridemia
- FH & Lp(a) pearls
- 12 interactive cases

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Disclosures: Kiniksa Pharmaceuticals.

Learning objectives

What a primary care team should be able to do after this session

By the end, you should be able to...

- Apply contemporary LDL-C targets for diabetes (primary vs secondary prevention).
- Start and optimize statins; monitor response and safety efficiently.
- Select nonstatin therapies (ezetimibe, PCSK9 mAbs, inclisiran, bempedoic acid) using evidence and patient factors.
- Manage persistent hypertriglyceridemia and recognize pancreatitis-risk thresholds.
- Recognize complex dyslipidemias (FH, Lp[a], mixed dyslipidemia) and know when to refer.
- Work through 12 diabetes-centered cases with practical “next steps.”

Clinical reality check: For many patients with T2D, lifetime ASCVD risk is high—so small LDL reductions accrue major benefit over time. Focus on: adherence, intensification when above threshold, and addressing triglyceride-driven risk when present.

Diabetic dyslipidemia: the typical pattern

Why LDL alone can miss residual risk

Common lipid features in insulin resistance / T2D

- ↑ Triglycerides and remnant lipoproteins (VLDL remnants).
- ↓ HDL-C.
- Small, dense LDL particles → higher ApoB particle number for a given LDL-C.
- Non-HDL-C and ApoB often better reflect atherogenic burden.

Typical in T2D



Implication: treat LDL aggressively + address TG-driven / ApoB burden

Practical tip: In TG ≥ 200 or metabolic syndrome, consider tracking non-HDL-C or ApoB to better reflect atherogenic particle burden (especially when LDL-C is “near goal”).

LDL-C targets in diabetes: keep it simple

Know your local guideline, but align on intensity + thresholds

Commonly used targets (mg/dL)

Population	Typical LDL-C goal	Notes
Diabetes, primary prevention	<70	ADA recommends treating to target; statins first-choice
Diabetes + ASCVD (secondary prevention)	<55	ADA target; add nonstatins if needed
ESC (T2D very high CV risk)	<55 and $\geq 50\%$ reduction	Risk-stratified targets; often more aggressive
ACC/AHA (ASCVD)	Threshold ≥ 70 to add nonstatins	Ezetimibe then PCSK9i based on risk

Operational approach for primary care: Start high-intensity statin when risk is high, then add ezetimibe if LDL remains above goal/threshold; escalate to PCSK9 mAb or inclisiran (or bempedoic acid if statin-intolerant) when additional LDL lowering is needed.

Statins in diabetes: baseline playbook

Start, intensify, and monitor efficiently

Who gets what?

- Age 40–75 with diabetes: at least moderate-intensity statin.
- Higher-risk diabetes (multiple ASCVD risk factors or age 50–75): reasonable to use high-intensity statin (aim $\geq 50\%$ LDL reduction).
- Any diabetes + ASCVD: high-intensity statin unless contraindicated.
- Age >75: continuation is reasonable; initiation/modification should follow individualized risk–benefit discussion.

Monitoring & documentation

- Baseline: fasting or nonfasting lipid panel, ALT (as indicated), assess secondary causes.
- Recheck lipids 4–12 weeks after start or dose change; then at least annually.
- Document: baseline LDL, % change, adherence, side effects, and plan for escalation if above goal.

Pearl: The “best” statin is the one the patient will reliably take. When symptoms arise, pause–evaluate–rechallenge rather than abandoning therapy.

When LDL is still above goal: nonstatin options

Choose based on required LDL lowering, evidence, and patient factors

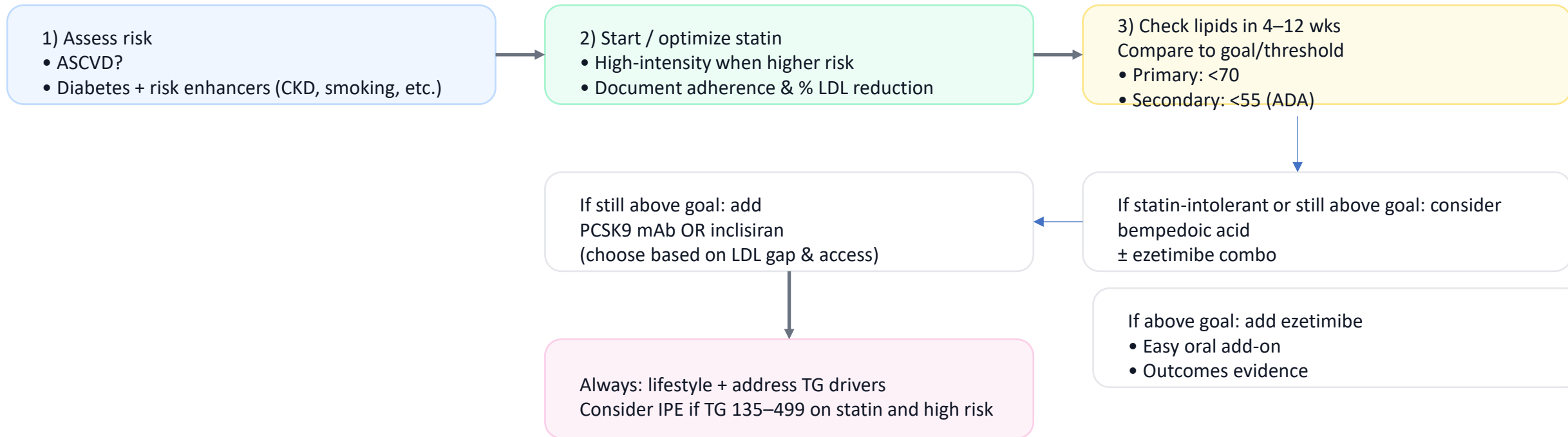
At-a-glance (approximate LDL-C lowering)

Therapy	LDL-C lowering (approx.)	Evidence / pearls
Ezetimibe	15–25%	Outcomes benefit post-ACS (IMPROVE-IT). Oral, well tolerated.
PCSK9 mAb (alirocumab, evolocumab)	~50–60%	Outcomes benefit in ASCVD (FOURIER, ODYSSEY). Injectable q2–4w.
Inclisiran	~50%	LDL lowering with twice-yearly dosing after loading; outcomes trial ongoing. Useful for adherence.
Bempedoic acid	~17–20%	Outcomes benefit in statin-intolerant (CLEAR Outcomes). Oral; consider uric acid/gout history.

Sequencing (common): Statin → add ezetimibe → add PCSK9 mAb or inclisiran (or bempedoic acid if statin-intolerant) based on how far from goal the patient is.

Practical algorithm: diabetes-focused LDL optimization

A usable pathway for primary care



Primary care goal: close the “intensification gap.” Many high-risk diabetes patients remain above LDL targets for years. Build a repeatable follow-up loop: start → recheck → add-on → recheck.

Evidence snapshots (headline trials)

Know the “why” behind the add-ons

IMPROVE-IT (ezetimibe)

Post-ACS

Ezetimibe + statin improved outcomes vs statin alone

CLEAR Outcomes (bempedoic acid)

Statin-intolerant population

Reduced MACE vs placebo

REDUCE-IT (icosapent ethyl)

TG elevation on statin; included diabetes cohort

Reduced ischemic events vs placebo

FOURIER / ODYSSEY (PCSK9 mAbs)

ASCVD on statin

Lower LDL substantially and reduce CV events

ORION-10/11 (inclisiran)

LDL lowering ~50% with q6 month dosing after loading

Outcomes trial ongoing

PROMINENT (pemafibrate)

T2D + high TG, low HDL

Lowered TG but did NOT reduce CV events

Statin-associated symptoms: a pragmatic approach

Keep patients on proven therapy whenever possible

Stepwise workflow

1) Clarify symptoms: onset, pattern, CK if severe; check thyroid, vitamin D, drug interactions

2) Discontinue /rechallenge stop briefly, then restart a different statin or lower dose

3) Alternative dosing: intermittent (e.g., 2–3×/week rosuvastatin) if needed

4) If truly intolerant: ezetimibe ± bempedoic acid; consider PCSK9 mAb or inclisiran

5) Document carefully for coverage: failed statins, doses, symptoms, and response

Persistent hypertriglyceridemia in diabetes

Two goals: pancreatitis prevention and ASCVD risk reduction

Thresholds & priorities (mg/dL)

TG category	Typical range	Primary priority
Mild–moderate	150–499	Lifestyle + address secondary causes; statin for ASCVD risk
Severe	≥500	Pancreatitis risk ↑ → urgent lifestyle + consider TG-lowering meds
Very severe	≥1,000	High pancreatitis risk → very-low-fat diet + fibrate/omega-3; evaluate secondary causes

Secondary causes to hunt (especially in diabetes)

- Poor glycemic control / insulin deficiency
- Alcohol, excess refined carbs, weight gain
- Hypothyroidism, CKD/nephrotic syndrome
- Medications (estrogens, steroids, antipsychotics, HIV meds, etc.)

ASCVD risk reduction option

If TG persist 135–499 on statin in high-risk patients (ASCVD or diabetes + risk factors), consider icosapent ethyl (EPA) based on REDUCE-IT.

ApoB and non-HDL-C: helpful in diabetes

Use when TG are elevated or LDL-C underestimates risk

When to consider ApoB or non-HDL-C

- TG \geq 200 mg/dL (metabolic syndrome / insulin resistance).
- Discordance: LDL-C “near goal” but persistent high TG or suspected high particle burden.
- Diabetes + CKD or inflammatory states where remnant lipoproteins are common.
- As a secondary target in some international guidelines (e.g., ESC uses non-HDL-C goals in diabetes).

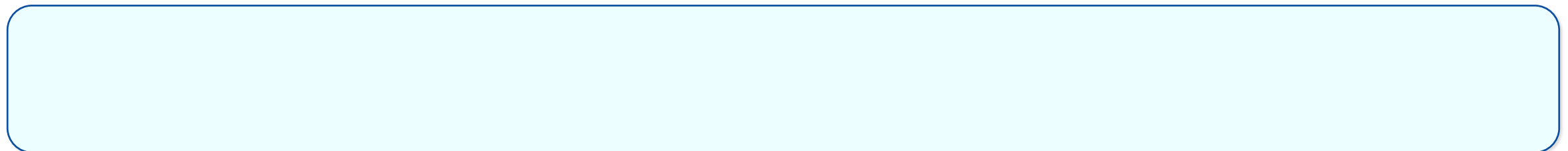
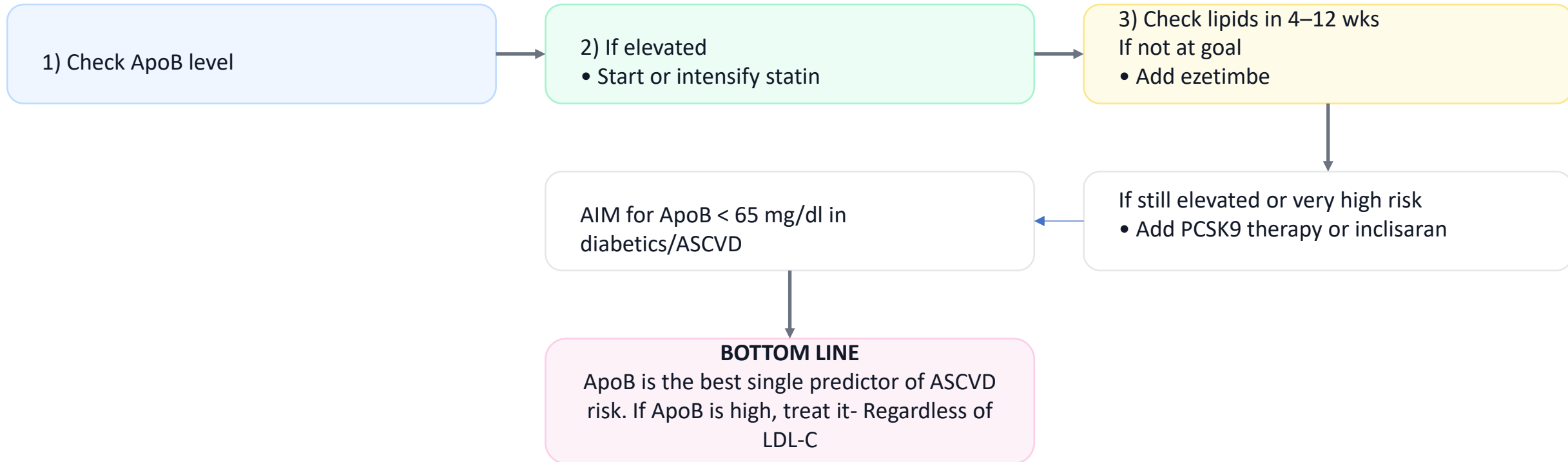
Simple math: non-HDL-C = Total cholesterol – HDL-C. It captures LDL + VLDL remnants (atherogenic when TG are high).

How it changes management

If ApoB/non-HDL are high: intensify LDL-lowering (statin + add-ons) and address TG drivers (glycemic control, weight, alcohol, meds).

Practical algorithm: ApoB

A usable pathway for primary care



Complex dyslipidemias to recognize (and refer)

Lp(a), familial hypercholesterolemia, and special situations

Lipoprotein(a) [Lp(a)]

- Heritable ASCVD risk factor; not captured by LDL-C alone.
- Many guidelines recommend measuring at least once in adulthood.
- High Lp(a) is a “risk-enhancing factor” → favor aggressive LDL lowering.
- Therapies: focus on LDL reduction (statin + ezetimibe + PCSK9i). Dedicated Lp(a) drugs are under study.

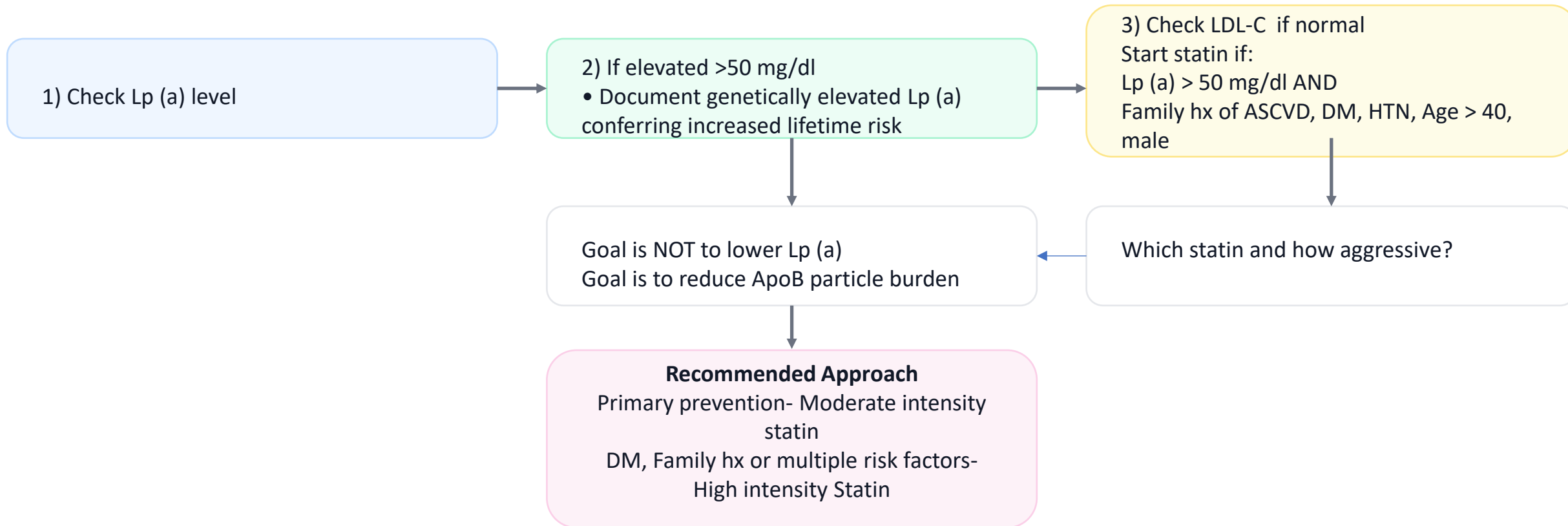
Familial hypercholesterolemia (FH)

- Suspect when LDL ≥ 190 mg/dL, premature ASCVD, or family history.
- Treat promptly (high-intensity statin + early add-ons); refer for advanced therapies.
- Cascade screening of relatives is key to prevention.

Referral triggers: LDL ≥ 190 with poor response to therapy; suspected FH; recurrent events despite LDL < 70 ; TG $\geq 1,000$; complex intolerance; pregnancy planning; or clinician uncertainty about advanced agents.

Practical algorithm: Lipoprotein a / Lp(a)

A usable pathway for primary care



Lp (a) is an independent, genetically mediated ASCVD risk enhancer.
Normal LDL-C does NOT neutralize Lp (a) risk
Should be measured once lifetime in patients

Statins can raise Lp (a) 5-10% but not clinically relevant Demonstrated in Fourier and Odyssey

Diabetes and Lifetime ASCVD Risk

Discussion Points

- Diabetes accelerates atherosclerosis via ApoB excess and inflammation (ApoB biology: Sniderman, Lancet 2019).
- ASCVD risk begins years before clinical diagnosis (population risk: Emerging Risk Factors Collaboration, Lancet 2010).
- Higher baseline absolute risk → greater absolute benefit from LDL lowering (CTT Collaboration, Lancet 2015).
- Cumulative LDL exposure drives lifetime events (FERENCE et al., JACC 2017).

• Why Absolute Benefit Is Greater in Diabetes

Feature	Non-Diabetes	Diabetes
Plaque initiation	Later adulthood	Early adulthood
ApoB exposure	Lower	Higher
Duration of exposure	Shorter	Longer
Lifetime ASCVD risk	Moderate	High

References: Ference BA et al. J Am Coll Cardiol. 2017, Sniderman AD et al. Lancet. 2019, emerging Risk Factors Collaboration. Lancet. 2010,

LDL-C Lowering: Biology Drives Outcomes

Discussion Points

LDL Reduction	Relative Risk Reduction	Trial Anchor
~20 mg/dL	≈10–12%	IMPROVE-IT
~39 mg/dL	≈20–25%	CTT Meta-analysis
~50–60%	≈25–30%	FOURIER / ODYSSEY

Trial	Population	LDL Reduction	Outcome Effect
IMPROVE-IT	Post-ACS	15–20 mg/dL ↓	↓ CV events
FOURIER	ASCVD	≈59% ↓	↓ MI, stroke
ODYSSEY	Post-ACS	≈62% ↓	↓ MACE, mortality

LDL-C Reduction vs ASCVD Benefit

- LDL lowering reduces ASCVD events in a dose–response fashion across therapies (CTT Collaboration, Lancet 2015).
- Adding ezetimibe to statin improves outcomes after ACS (IMPROVE-IT, NEJM 2015).
- PCSK9 inhibition further reduces MI/stroke when LDL is lowered to very low levels (FOURIER, NEJM 2017; ODYSSEY OUTCOMES, NEJM 2018).
- No lower LDL-C safety threshold signal in major outcome trials (FOURIER; ODYSSEY OUTCOMES).

Landmark LDL Outcome Trials

Key Clinical Trials

CTT Collaboration. Lancet. 2015.
FOURIER Trial. NEJM. 2017.
ODYSSEY OUTCOMES. NEJM. 2018

Residual Risk in Diabetes Despite LDL Control

Discussion Points

- Residual events persist even with intensive LDL lowering (FOURIER; ODYSSEY OUTCOMES).
- ApoB/remnant-rich phenotypes contribute when TG are elevated (risk marker data: Toth et al., JACC 2020).
- Lp(a) is an independent risk factor; PCSK9 trials show modest Lp(a) reduction with event benefit (FOURIER Lp[a] analyses; Circulation 2019).
- Clinical implication: layered therapy beyond statins in selected high-risk patients (ACC/ADA pathways).

• Residual Risk Stack

Layer	Driver	Marker	Therapy
Primary	LDL burden	LDL-C / ApoB	Statin, ezetimibe, PCSK9
Secondary	Remnants	TG / non-HDL	Lifestyle, EPA
Tertiary	Lp(a)	Lp(a)	Aggressive LDL lowering
Quaternary	Inflammation	hsCRP	Risk factor control

References: Silverman MG et al. JAMA. 2016, Toth PP et al. J Am Coll Cardiol. 2020., 'Donoghue ML et al. Circulation. 2019.

Case Studies

Case 1: New T2D, mixed dyslipidemia (primary prevention)

Patient snapshot

42M • T2D x 3y • Smoker • HTN controlled
Meds: metformin; no lipid meds
Labs: LDL 128, TG 210, HDL 36, non-HDL 170
A1c 8.2% • BMI 33 • No ASCVD, CKD, or albuminuria

Questions

- What LDL target do you use?
- Which statin intensity is most appropriate?
- How do you approach TG 210 in diabetes?

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- A) < 130 mg/dl
- B) < 100 mg/dl
- C) < 70 mg/dl
- D) < 55 mg/dl

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Questions

- What LDL target do you use?
- **Which statin intensity is most appropriate?**
- **How do you approach TG 210 in diabetes?**

Case 1: Suggested approach

Management plan

- Primary prevention LDL goal: <70 mg/dL (ADA). Start statin + lifestyle.
- Given multiple risk factors (smoking/HTN/obesity), choose high-intensity statin to aim ≥50% LDL reduction.
- Address secondary causes: glycemic optimization, weight loss, alcohol review, meds; statin first.
- If TG remain 135–499 on statin and overall CV risk is high, consider icosapent ethyl (4 g/day) for ASCVD risk reduction (REDUCE-IT population included diabetes).

Teaching points

- Use non-HDL-C (or ApoB) as a secondary marker when TG are elevated.
- Recheck lipids 4–12 weeks after starting/changing therapy.

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Follow-up loop: confirm adherence → repeat lipid panel (4–12 wks after change) → escalate if still above goal → document response and tolerance.

Case 2: Secondary prevention: LDL above goal on max statin

Patient snapshot

58F • T2D • NSTEMI 2 years ago (PCI) • Former smoker

Meds: atorvastatin 80 mg, metformin, SGLT2i, ACEi

Labs: LDL 92, TG 155, HDL 41

No statin symptoms; adherent

Questions

- What is the LDL goal for secondary prevention in diabetes?
- What is the next add-on therapy?
- What if LDL is still above goal after the add-on?

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- What is the LDL goal for secondary prevention in diabetes?
- **What is the next add-on therapy?**
- **What if LDL is still above goal after the add-on?**

Case 2: Suggested approach

Management plan

- Secondary prevention LDL goal: <55 mg/dL (ADA). Consider even more aggressive thresholds in very-high-risk frameworks (ESC).
- Add ezetimibe first (outcomes benefit in IMPROVE-IT).
- If still above goal, add PCSK9 monoclonal antibody (FOURIER/ODYSSEY OUTCOMES) or consider inclisiran for adherence/administration preferences (outcome trial ongoing).

Teaching points

- In chronic coronary disease, intensify when LDL \geq 70 mg/dL despite statin; add ezetimibe and/or PCSK9i per guideline context.

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Case 3: Diabetes + CKD: high risk primary prevention

Patient snapshot

64M • T2D • CKD stage 3b (eGFR 32) • Albuminuria

Meds: simvastatin 20 mg, insulin, ARB

Labs: LDL 110, TG 160, HDL 38

BP 132/76 • No known ASCVD

Questions

- How do you risk-stratify?
- What are your next medication changes?
- Any dosing/safety considerations?

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- How do you risk-stratify?
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- B) Moderate Risk
- C) High/ Very High Risk
- D) No Significant Risk

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Questions

- How do you risk-stratify?
- **What are your next medication changes?**
- **Any dosing/safety considerations?**

Case 3: Suggested approach

Management plan

- Diabetes + CKD (and albuminuria) = high/very-high ASCVD risk in most frameworks; use LDL <70 mg/dL (ADA primary prevention target) and often <55 mg/dL in very-high-risk (ESC).
- Switch to a high-intensity statin (e.g., atorvastatin or rosuvastatin as appropriate) and recheck in 4–12 weeks.
- If not at goal, add ezetimibe; consider PCSK9i/inclisiran for larger LDL reductions.
- With CKD: review statin/fibrate dosing and drug–drug interactions; monitor for myopathy, especially with simvastatin and interacting meds.

Teaching points

- Non-HDL-C and ApoB can help when TG are elevated (common in CKD/T2D).

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Labs: LDL 110, TG 160, HDL 38
BP 132/76 • No known ASCVD

Follow-up loop: confirm adherence → repeat lipid panel (4–12 wks after change) → escalate if still above goal → document response and tolerance.

Case 4: Statin-associated muscle symptoms / “statin intolerance”

Patient snapshot

52F • T2D • No ASCVD • Strong family history (father MI at 54)

Reports myalgias on atorvastatin and rosuvastatin; stopped both

Labs: LDL 160, TG 140, HDL 46

CK normal; hypothyroidism treated

Questions

- How do you confirm/manage SAMS (statin-associated muscle symptoms)?
- What nonstatin options fit here?
- What evidence supports bempedoic acid in statin-intolerant patients?

Case 4: Statin-associated muscle symptoms / “statin intolerance”

Patient snapshot

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Questions

- How do you confirm/manage SAMS (statin-associated muscle symptoms)?
- **What nonstatin options fit here?**
- What evidence supports bempedoic acid in statin-intolerant patients?

Case 4: Suggested approach

Management plan

- Rule out secondary causes and the “nocebo” effect; try statin rechallenge with a different statin, lower dose, or intermittent dosing.
- If truly intolerant: start ezetimibe and consider bempedoic acid (or fixed-dose bempedoic acid/ezetimibe); consider PCSK9 mAb or inclisiran for larger LDL reductions.
- CLEAR Outcomes showed bempedoic acid reduced major adverse cardiovascular events in statin-intolerant patients.

Teaching points

- Document the exact statin, dose, timing, symptoms, and rechallenge outcomes—this helps coverage decisions for nonstatins.

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Reports myalgias on atorvastatin and rosuvastatin; stopped both
Labs: LDL 160, TG 140, HDL 46
CK normal; hypothyroidism treated

Follow-up loop: confirm adherence → repeat lipid panel (4–12 wks after change) → escalate if still above goal → document response and tolerance.

Case 5: Possible heterozygous familial hypercholesterolemia (HeFH)

Patient snapshot

39M • T2D • LDL persistently >190 mg/dL

Current LDL 205, TG 120, HDL 44

Family history: mother stroke at 52; Uncle MI at 49

Tendon xanthomas? none noted; never on lipid meds

Questions

- What makes you suspect FH?
- What is the initial treatment plan?
- When do you refer and what family actions are needed?

Case 5: Possible heterozygous familial hypercholesterolemia (HeFH)

Patient snapshot

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Family history: mother stroke at 52; Uncle MI at 49

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Questions

- What makes you suspect FH?
- A) Family history of MI
- B) T2D with TG 120
- C) LDL > 190 mg/dl
- D) HDL 44 mg/dl

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Questions

- What makes you suspect FH?
- **What is the initial treatment plan?**
- **When do you refer and what family actions are needed?**

Case 5: Suggested approach

Management plan

- LDL \geq 190 mg/dL, premature ASCVD family history \rightarrow evaluate for FH (clinical criteria \pm genetic testing).
- Start high-intensity statin now; add ezetimibe early if not at goal; consider PCSK9 inhibitor if LDL remains markedly elevated.
- Refer to lipid specialist if FH suspected, LDL remains >100 – 130 despite therapy, or for complex access/therapy decisions. Recommend cascade screening for first-degree relatives.

Teaching points

- Consider secondary causes (hypothyroid, nephrotic syndrome, cholestasis) but treat promptly while evaluating.

39M • T2D • LDL persistently >190 mg/dL
Current LDL 205, TG 120, HDL 44
Family history: mother stroke at 52; uncle MI at 49
Tendon xanthomas? none noted; never on lipid meds

Follow-up loop: confirm adherence \rightarrow repeat lipid panel (4–12 wks after change) \rightarrow escalate if still above goal \rightarrow document response and tolerance.

Case 6: Severe hypertriglyceridemia (pancreatitis prevention first)

Patient snapshot

47F • T2D • TG 980 mg/dL (fasting) • LDL 82
A1c 10.5% • Drinks alcohol most evenings
Meds: metformin; stopped statin “years ago”
No pancreatitis history (yet)

Questions

- What are the immediate priorities?
- What work-up for secondary causes is needed?
- Which meds/diet changes do you start today?

Case 6: Suggested approach

Management plan

- Priority is pancreatitis risk reduction: treat TG ≥ 500 mg/dL (especially $\geq 1,000$) urgently.
- Address secondary causes: alcohol cessation, optimize glycemic control, review meds, evaluate for hypothyroidism and nephrotic syndrome.
- Implement very-low-fat diet short term; start fibrate (renal-adjusted) and/or prescription omega-3; restart statin once TG trending down and ASCVD risk addressed.
- Recheck fasting TG soon (e.g., 4–12 weeks or sooner if very high) and reinforce lifestyle changes.

Teaching points

- If TG remain very high or pancreatitis occurs, consider urgent specialty referral.

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A1c 10.5% • Drinks alcohol most evenings
Meds: metformin; stopped statin “years ago”
No pancreatitis history (yet)

Follow-up loop: confirm adherence → repeat lipid panel (4–12 wks after change) → escalate if still above goal → document response and tolerance.

Case 7: High Lp(a) in a patient with ASCVD

Patient snapshot

67M • T2D • PAD + carotid stenosis • On rosuvastatin 40 + ezetimibe

LDL 68, TG 130, HDL 43

Lp(a) 180 nmol/L (or >50 mg/dL equivalent threshold)

Asks: “What can we do about Lp(a)?”

Questions

- How do you interpret Lp(a) and why measure it?
- What changes today?
- What should you tell family members?

Case 7: Suggested approach

Management plan

- Lp(a) is a heritable, independent ASCVD risk factor; many guidelines recommend at least once-in-a-lifetime measurement.
- Main action is intensifying overall risk reduction: drive LDL lower (diabetes secondary prevention target <55; consider PCSK9 mAb to lower LDL and modestly lower Lp(a)).
- Recommend cascade screening for first-degree relatives (Lp[a] and standard lipids). Consider clinical trial referral when available.

Teaching points

- Avoid overpromising: dedicated Lp(a)-lowering outcome therapies are in development but not yet routine care.

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LDL 68, TG 130, HDL 43

Lp(a) 180 nmol/L (or >50 mg/dL equivalent threshold)

Asks: "What can we do about Lp(a)?"

Case 8: Older adult (>75): shared decision-making

Patient snapshot

78F • T2D x 15y • No known ASCVD • Frail, falls twice this year

Meds: pravastatin 40 mg, antihypertensives

Labs: LDL 74, TG 140, HDL 52

Concern: pill burden and muscle aches (mild)

Questions

- Continue, intensify, or deprescribe?
- How do you frame benefits vs harms?
- What monitoring makes sense?

Case 8: Suggested approach

Management plan

- ADA: if already on statin at >75, it is reasonable to continue; initiating/modifying should follow individualized risk–benefit discussion.
- Given near-target LDL and frailty/pill burden, continuing current moderate-intensity therapy is often reasonable; consider dose adjustment if symptoms are problematic.
- Focus on adherence, fall risk mitigation, and periodic lipid checks consistent with goals of care.

Teaching points

- Functional status, life expectancy, and patient goals drive decisions more than “one-size” targets.

78F • T2D x 15y • No known ASCVD • Frail, falls twice this year
Meds: pravastatin 40 mg, antihypertensives
Labs: LDL 74, TG 140, HDL 52
Concern: pill burden and muscle aches (mild)

Follow-up loop: confirm adherence → repeat lipid panel (4–12 wks after change) → escalate if still above goal → document response and tolerance.

Case 9: NAFLD / mild transaminase elevation: “Can I take a statin?”

Patient snapshot

61M • T2D • NAFLD on ultrasound • ALT 88 ($\approx 2\times$ ULN)

No decompensated liver disease; drinks rarely

Labs: LDL 140, TG 180, HDL 39

Worried statins will “hurt the liver”

Questions

- Are statins safe in NAFLD with mild LFT elevations?
- How do you counsel and monitor?
- What else helps his lipid profile?

Case 9: Suggested approach

Management plan

- Evidence supports that statins are generally safe in NAFLD and may reduce liver enzyme levels; cardiovascular benefit typically outweighs hepatic risk.
- Start appropriate-intensity statin; check baseline LFTs and recheck if symptoms or clinically indicated (routine repeated LFTs are not required for most).
- Emphasize weight loss, glycemic optimization, and limiting alcohol; consider add-ons (ezetimibe/PCSK9i) if LDL remains above goal.

Teaching points

- Avoid statins only in active liver failure or severe unexplained transaminase elevations—otherwise treat ASCVD risk aggressively.

61M • T2D • NAFLD on ultrasound • ALT 88 ($\approx 2 \times$ ULN)
No decompensated liver disease; drinks rarely
Labs: LDL 140, TG 180, HDL 39
Worried statins will “hurt the liver”

Follow-up loop: confirm adherence → repeat lipid panel (4–12 wks after change) → escalate if still above goal → document response and tolerance.

Case 10: Diabetes + ASCVD with LDL “at goal” (Residual Risk)

Patient snapshot

Patient snapshot

62-year-old male

T2D x 12 years

Prior NSTEMI with PCI (2 years ago)

Medications: rosuvastatin 40 mg, ezetimibe 10 mg,

SGLT2 inhibitor

Labs: LDL-C 64 mg/dL • TG 210 mg/dL • HDL-C 38 mg/dL

Questions

- Is LDL <70 sufficient in secondary prevention diabetes?
- What does elevated TG suggest about residual risk?
- What additional therapy would you consider?

Case 10: Suggested approach

Management plan

- Diabetes + ASCVD = **very high risk**
- ADA secondary prevention target: **LDL <55 mg/dL**
- Elevated TG suggests remnant/ApoB-driven residual risk
- Add **PCSK9 inhibitor**
- Consider **icosapent ethyl** if TG persist 135–499 mg/dL

Teaching points

- LDL-C “at goal” does **not** mean risk elimination in diabetes.

62-year-old male

T2D x 12 years

Prior NSTEMI with PCI (2 years ago)

Medications: rosuvastatin 40 mg, ezetimibe 10 mg, SGLT2 inhibitor

Labs: LDL-C 64 mg/dL • TG 210 mg/dL • HDL-C 38 mg/dL

Follow-up loop: confirm adherence → repeat lipid panel (4–12 wks after change) → escalate if still above goal → document response and tolerance.

CASE 11: Diabetes with TG ~250 — Do I treat this?

Patient snapshot

Patient snapshot

55-year-old female

T2D, obesity, hypertension

Medications: metformin, atorvastatin 40 mg

Labs: LDL-C 78 mg/dL • TG 265 mg/dL • HDL-C 34 mg/dL

Questions

- What is the primary goal at this TG level?
- Are fibrates indicated?
- When does REDUCE-IT apply?

CASE 11: Diabetes with TG ~250 — Do I treat this?

Patient snapshot

Patient snapshot

55-year-old female

T2D, obesity, hypertension

Medications: metformin, atorvastatin 40 mg

Labs: LDL-C 78 mg/dL • TG 265 mg/dL • HDL-C 34 mg/dL

Questions

- What is the primary goal at this TG level?
- A) < 130 mg/dl
- B) < 100 mg/dl
- C) < 150 mg/dl
- D) < 200 mg/dl

CASE 11: Diabetes with TG ~250 — Do I treat this?

Patient snapshot

Patient snapshot

55-year-old female

T2D, obesity, hypertension

Medications: metformin, atorvastatin 40 mg

Labs: LDL-C 78 mg/dL • TG 265 mg/dL • HDL-C 34 mg/dL

Questions

- What is the primary goal at this TG level?
- A) < 130 mg/dl
- B) < 100 mg/dl
- **C) < 150 mg/dl**
- D) < 200 mg/dl

Case 11: Suggested approach

Management plan

- TG 200–499 mg/dL → **ASCVD risk reduction**
- Optimize statin therapy and lifestyle
- Address secondary drivers (glycemia, weight, alcohol)
- Fibrates **do not reduce CV events** (PROMINENT)
- Consider **icosapent ethyl** only if overall CV risk is high when TG > 150 mg/dl

Teaching points

- TG 200–499 are a **risk marker**, not an emergency.
- The recommended triglyceride level is ≥ 150 mg/dl based on the REDUCE-IT Trial

55-year-old female
T2D, obesity, hypertension
Medications: metformin, atorvastatin 40 mg
Labs: LDL-C 78 mg/dL • TG 265 mg/dL • HDL-C 34 mg/dL

Follow-up loop: confirm adherence → repeat lipid panel (4–12 wks after change) → escalate if still above goal → document response and tolerance.

CASE 12: Younger patient with diabetes and high lifetime risk

Patient snapshot

Patient snapshot

41-year-old male

T2D x 2 years • Smoker

Labs: LDL-C 118 mg/dL • TG 180 mg/dL • HDL-C 36 mg/dL

Questions

- How do guidelines address lifetime risk?
- What statin intensity is appropriate?
- How do you frame this conversation?

Case 12: Suggested approach

Management plan

- Diabetes confers **high lifetime ASCVD risk**
- Start **at least moderate-intensity statin**
- Consider high-intensity statin due to smoking
- Recheck lipids in 4–12 weeks and escalate if above target

Teaching points

- Earlier LDL lowering = **greater lifetime benefit.**

41-year-old male
T2D x 2 years • Smoker
Labs: LDL-C 118 mg/dL • TG 180 mg/dL • HDL-C 36 mg/dL

Follow-up loop: confirm adherence → repeat lipid panel (4–12 wks after change) → escalate if still above goal → document response and tolerance.

Integrated Clinical Escalation Strategy

Discussion Points

- Start with statins: robust event reduction across risk groups (CTT Collaboration, Lancet 2015).
- If LDL remains above goal/threshold: add ezetimibe (IMPROVE-IT, NEJM 2015).
- If still above goal: add PCSK9 therapy for additional event reduction (FOURIER, NEJM 2017; ODYSSEY OUTCOMES, NEJM 2018).
- If statin-intolerant: bempedoic acid reduced MACE (CLEAR Outcomes, NEJM 2023).
- If TG 135–499 and high risk on statin: consider EPA (REDUCE-IT, NEJM 2019).

References IMPROVE-IT. NEJM. 2015, FOURIER. NEJM. 2017, CLEAR Outcomes. NEJM. 2023

Integrated Clinical Escalation Strategy

Summary

- Start with statins: robust event reduction across risk groups (CTT Collaboration, Lancet 2015).
- If LDL remains above goal/threshold: add ezetimibe (IMPROVE-IT, NEJM 2015).
- If still above goal: add PCSK9 therapy for additional event reduction (FOURIER, NEJM 2017; ODYSSEY OUTCOMES, NEJM 2018).
- If statin-intolerant: bempedoic acid reduced MACE (CLEAR Outcomes, NEJM 2023).
- If TG 135–499 and high risk on statin: consider EPA (REDUCE-IT, NEJM 2019).

Clinical Scenario	Primary Focus	Next Step
LDL above goal	LDL burden	Add ezetimibe → PCSK9
LDL at goal, TG elevated	Residual risk	Consider EPA
Family history / early events	Genetic risk	Measure Lp(a)
Recurrent ASCVD events	Global risk	Maximal LDL lowering

Key takeaways (and practical resources)

If you only remember 5 things...

Top 5 takeaways

- Diabetes is a high-lifetime-risk state: treat LDL aggressively and close the intensification gap.
- Know the simple ADA targets: LDL <70 (primary prevention) and <55 (secondary prevention).
- Statin first; add ezetimibe, then PCSK9 mAb or inclisiran when LDL remains above goal/threshold.
- Manage TG with lifestyle + secondary cause review; for TG ≥500 prioritize pancreatitis prevention; consider icosapent ethyl for ASCVD risk reduction in the right population.
- Screen for complex dyslipidemias (FH, Lp[a]) and refer when thresholds or complexity exceed primary care bandwidth.

Clinician-friendly references

ADA 2025 Lipid Management (1-page):

<https://professional.diabetes.org/sites/dpro/files/2025-03/kdbh-lipidmanagement-0225.pdf>

ACC 2022 Nonstatin Pathway (JACC):

<https://www.jacc.org/doi/10.1016/j.jacc.2022.07.006>

ACC 2021 HyperTG Pathway (JACC):

<https://www.jacc.org/doi/10.1016/j.jacc.2021.06.011>

Key trials: IMPROVE-IT, FOURIER, ODYSSEY, CLEAR, REDUCE-IT

Thank You!

Additional Case Studies

Triglycerides: Marker vs Mediator

Discussion Points

- TG elevation is associated with higher risk, but lowering TG alone may not reduce events (PROMINENT, NEJM 2022).
- EPA reduced ischemic events in statin-treated patients with elevated TG (REDUCE-IT, NEJM 2019).
- Fenofibrate did not reduce events overall in T2D when added to statin (ACCORD Lipid, NEJM 2010).
- Therapy selection should be evidence-based: pancreatitis prevention vs ASCVD risk reduction (ACC HyperTG pathway).

• Triglyceride Trials: Mechanistic Contrast

Trial	Therapy	Primary Mechanism	ASCVD Outcome
REDUCE-IT	EPA	Anti-inflammatory / plaque effects	Reduced events
PROMINENT	Pemafibrate	TG lowering	No benefit
ACCORD	Fenofibrate	TG lowering	Neutral

References: Bhatt DL et al. REDUCE-IT. NEJM. 2019, Pradhan AD et al. PROMINENT. NEJM. 2022., CCORD Lipid Trial. NEJM. 2010.

Case: Treat-to-Target vs Thresholds

Question

- Which approach best reflects optimal lipid management in diabetes?
 - A. Strict treat-to-target only, ignoring thresholds
 - B. Threshold-based therapy only, ignoring targets
 - C. Use targets to define risk and thresholds to trigger intensification
 - D. Neither approach is supported by evidence

Discussion points: ADA targets and ACC thresholds converge clinically in high-risk diabetes.

Case: Is TG Lowering Ever Enough?

Question

- A patient with diabetes has LDL-C 62 mg/dL and TG 310 mg/dL on statin therapy. Which statement is most accurate?
- A. TG lowering alone will reliably reduce ASCVD risk
- B. Fibrates should be added to reduce cardiovascular events
- C. EPA may reduce ASCVD risk; TG lowering alone is insufficient
- D. No additional therapy is indicated once LDL-C <70 mg/dL

Discussion points: REDUCE-IT vs PROMINENT highlights mechanism over magnitude of TG lowering.

Case: How Low Is Too Low?

Question

- In a high-risk patient with diabetes and ASCVD, achieved LDL-C is 18 mg/dL on statin + PCSK9 inhibitor. What is the most appropriate interpretation?
- A. LDL-C should be increased due to bleeding and neurocognitive risk
- B. LDL-C should be maintained; trials show continued benefit without safety signal
- C. PCSK9 therapy should be discontinued once LDL-C <25 mg/dL
- D. Outcomes data do not apply at LDL-C levels this low.

Discussion points: FOURIER and ODYSSEY OUTCOMES showed no lower LDL-C safety threshold.

Case: Are We Overtreating LDL in Diabetes?

Patient snapshot

62-year-old man with T2D, no prior MI, LDL-C 68 mg/dL on high-intensity statin.

Questions

- Is further LDL lowering necessary?

Case: Are We Overtreating LDL in Diabetes?

Discussion

- Diabetes confers higher lifetime ApoB exposure and absolute ASCVD risk.
- Meta-analyses show linear benefit with lower LDL and no safety signal at very low levels.
- Clinical takeaway: lower LDL is justified when risk is high and therapy is tolerated.

Patient Snapshot

62-year-old man with T2D, no prior MI, LDL-C 68 mg/dL on high-intensity statin.

Discussion points:

Diabetes is associated with higher ApoB burden and absolute ASCVD risk. Meta-analyses show linear benefit from LDL lowering with no safety signal at very low LDL levels.

Question

- What is the most appropriate interpretation of his LDL level?
 - A. LDL is low enough; further therapy offers no benefit
 - B. Diabetes confers higher lifetime ASCVD risk; lower LDL may still provide benefit
 - C. LDL targets only apply in secondary prevention
 - D. Statins should be de-escalated at LDL <70 mg/dL

Case: ADA Targets vs ACC Thresholds

Patient snapshot

58-year-old woman with T2D and prior NSTEMI, LDL-C 72 mg/dL on statin.

Questions

- Question: Should treatment follow ADA targets or ACC thresholds?

Case: ADA Targets vs ACC Thresholds

Discussion

- Discussion: ADA treat-to-target and ACC threshold approaches are complementary.
- Discussion: Both frameworks support intensification at this LDL level in secondary prevention.

Patient Snapshot

58-year-old woman with T2D and prior NSTEMI, LDL-C 72 mg/dL on statin.

Question

- How should LDL goals be applied in this patient?
 - A. Follow ACC thresholds only and avoid treat-to-target approaches
 - B. Follow ADA targets only and ignore ACC guidance
 - C. Recognize ADA targets and ACC thresholds as complementary frameworks
 - D. No further intensification is indicated

Discussion points:

ADA treat-to-target and ACC escalation thresholds converge clinically, both supporting intensification in secondary prevention diabetes.

Case: Inclisiran Without Outcomes Data

Patient snapshot

65-year-old man with ASCVD and poor adherence to oral therapy.

Questions

- Question: Is inclisiran appropriate without completed outcomes trials?

Case: Inclisiran Without Outcomes Data

Discussion

- Discussion: LDL lowering is the proven mechanism of benefit across lipid trials.
- Discussion: Inclisiran offers durable LDL reduction with improved adherence.
- Discussion: Outcomes trials (ORION-4, VICTORION-2P) are ongoing.

Patient Snapshot

65-year-old man with ASCVD and poor adherence to oral therapy.

Question

- What best justifies inclisiran use?
 - A. Proven superiority over PCSK9 monoclonal antibodies
 - B. Unique triglyceride-lowering properties
 - C. Durable LDL lowering with improved adherence
 - D. Established cardiovascular outcomes benefit

Discussion points:

LDL lowering is the proven mechanism of ASCVD risk reduction. Inclisiran provides sustained LDL reduction and adherence advantages; outcomes trials are ongoing.

Case: EPA vs Fibrates

Patient snapshot

60-year-old woman with T2D, TG 220 mg/dL on statin therapy.

Questions

- Question: Why consider EPA but not a fibrate?

Case: EPA vs Fibrates

Discussion

- Discussion: PROMINENT showed TG lowering alone does not reduce ASCVD events.
- Discussion: REDUCE-IT demonstrated event reduction with EPA, likely via pleiotropic effects.
- Discussion: Use EPA selectively in REDUCE-IT–eligible patients.

Patient Snapshot

60-year-old woman with T2D, TG 220 mg/dL on statin therapy.

Question

- Which statement best explains therapy selection?
 - A. Fibrates reduce ASCVD events in diabetes
 - B. Triglyceride lowering alone guarantees risk reduction
 - C. EPA reduces events through pleiotropic effects beyond TG lowering
 - D. No additional therapy is indicated at this TG level

Discussion points:

PROMINENT showed TG lowering alone does not reduce events. REDUCE-IT demonstrated event reduction with EPA, likely via anti-inflammatory and plaque-stabilizing effects.

Case: Statins in NAFLD

Patient snapshot

61-year-old man with T2D and NAFLD, ALT $\sim 2\times$ ULN, LDL-C 142 mg/dL.

Questions

- Question: Are statins safe in this setting?

Case: Statins in NAFLD

Discussion

- Discussion: Statins are safe in NAFLD and may improve liver enzymes.
- Discussion: Cardiovascular benefit outweighs hepatic risk unless active liver failure is present.

Patient Snapshot

61-year-old man with T2D and NAFLD, ALT ~2× ULN, LDL-C 142 mg/dL.

Question

- What is the best management approach?
 - A. Avoid statins due to liver disease
 - B. Use statins cautiously only if ALT normalizes
 - C. Initiate statin therapy; cardiovascular benefit outweighs hepatic risk
 - D. Use fibrates instead of statins

Discussion points:

Statins are safe in NAFLD and may improve liver enzymes. Cardiovascular benefit outweighs hepatic risk unless active liver failure is present.