SMART Approach

Diabetic Dyslipidemia: A Precision Framework for Risk-Based Lipid Management

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1. Overview

Substantial heterogeneity in cardiovascular risk persists among individuals with diabetes, reflecting discordance between traditional lipid measures, risk estimation, and underlying cardiometabolic phenotypes. Current guidelines emphasize risk-based treatment using LDL-C and non-HDL-C thresholds and tools such as PREVENT but provide limited operational guidance when risk estimates and clinical features are incongruent. We present a practical framework, the SMART approach, to support individualized lipid management in diabetes. This approach integrates quantitative risk estimation with selective refinement using diabetes-specific risk enhancers, biomarkers, and imaging when appropriate. Treatment is aligned with atherogenic burden and clinical context using a stepwise escalation strategy prioritizing LDL-directed therapy while incorporating targeted management of hypertriglyceridemia and special clinical scenarios across diverse clinical settings. By formalizing decision-making under conditions of uncertainty, this approach translates guideline principles into actionable, individualized care pathways.

2. Background

Diabetic dyslipidemia is the most common form of atherogenic dyslipidemia and a major contributor to atherosclerotic cardiovascular disease (ASCVD). It is characterized by elevated triglycerides (TGs), reduced HDL-C, increased non-HDL-C, and an excess of TG-rich, cholesterol-depleted apolipoprotein B (ApoB)-containing lipoproteins. This pattern often persists despite controlled LDL-C, reflecting an increased atherogenic particle burden not fully captured by LDL-C alone.

Diabetes is associated with systemic metabolic dysfunction, driven largely by insulin resistance and relative insulin deficiency, ultimately resulting in lipid abnormalities, hyperglycemia, and other complications that contribute to broader cardiometabolic risk. Accordingly, diabetic dyslipidemia should not be managed in isolation: interventions that improve metabolic health also improve the lipid phenotype, whereas lipid-lowering alone does not correct the underlying dysfunction and may worsen glycemic control.[1] In addition, therapies such as GLP-1 receptor agonists and SGLT2 inhibitors improve glycemic control and reduce cardiovascular risk through mechanisms beyond conventional lipid, glycemic, and insulin resistance pathways.[2-4] Nonetheless, targeting diabetic dyslipidemia remains a foundational component of cardiovascular risk reduction within the broader cardiometabolic context.

Contemporary guidelines from the American Diabetes Association (ADA) and the ACC/AHA emphasize risk-based lipid management, LDL-C and non-HDL-C thresholds, and use of risk equations such as Predicting Risk of Events via Novel Tools (PREVENT) to guide therapy.[5-7] Diabetes is no longer considered a risk equivalent but rather a risk modifier. PREVENT incorporates diabetes diagnosis and kidney function (eGFR) and may incorporate measures of glycemic burden (HbA1c) and albuminuria (UACR) when entered as optional predictors; however, even with these variables, PREVENT does not fully capture the heterogeneity of diabetes-related cardiovascular risk. As a result, applying these recommendations in practice remains challenging, particularly in patients with discordant profiles or at

Abbreviations: ABI, ankle–brachial index; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); non-HDL-C, non-high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; PREVENT-ASCVD, Predicting Risk of Events via Novel Tools–ASCVD; SGLT2, sodium-glucose cotransporter 2; TG, triglyceride; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UACR, urine albumin to creatinine ratio.

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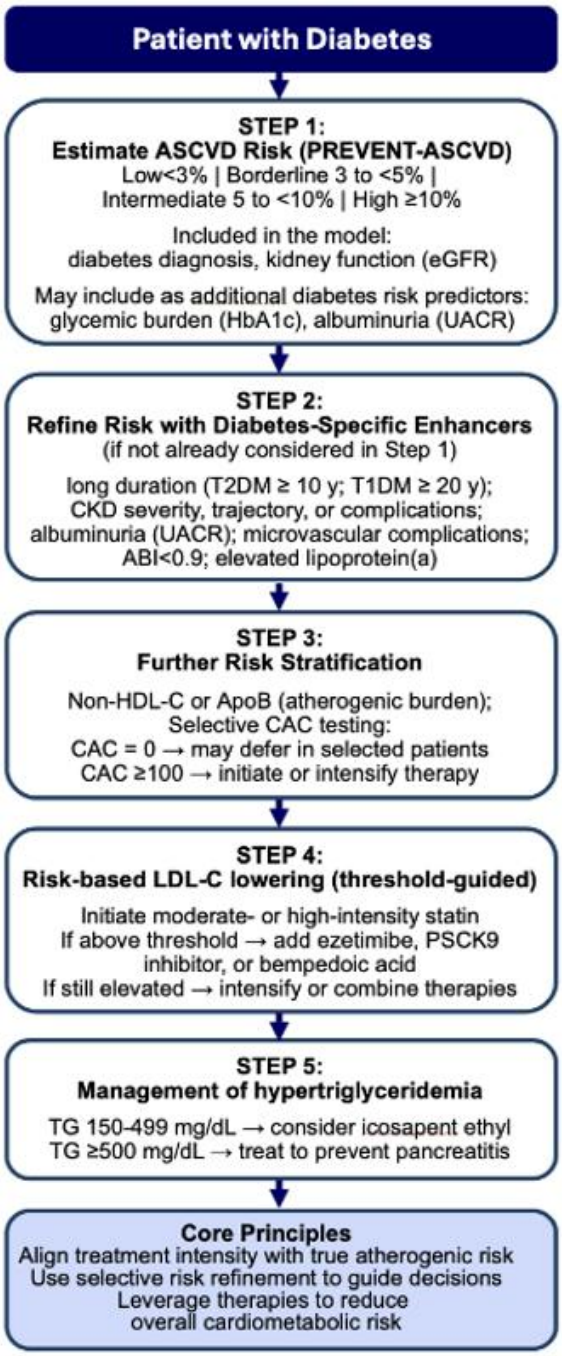
borderline or intermediate risk, where guidance on intensification and refinement is limited.

Figure 1. SMART Framework for Lipid Management in Diabetes



Stepwise framework integrating PREVENT-ASCVD risk estimation, selective refinement with diabetes-specific enhancers and biomarkers, and risk-based escalation of lipid-lowering therapy. Interpret PREVENT estimates in clinical context; prioritize LDL-directed therapy, followed by triglyceride management and special clinical scenarios.

This SMART approach builds on existing guidelines by providing a structured framework for individualizing lipid management, particularly in situations of clinical uncertainty. Rather than introducing new risk constructs, it translates guideline recommendations into actionable clinical decisions when risk estimates, lipid measures, and clinical phenotypes are discordant. This approach prioritizes atherogenic burden as the primary determinant of treatment intensity, selectively incorporates risk refinement tools, and applies pragmatic, stepwise treatment strategies (**Figure 1**). By integrating guideline-based care with a precision-oriented clinical perspective, it aims to improve consistency and effectiveness of lipid management while preserving flexibility for patient-specific decision making (**Tables 1–4**).

3. Guideline Recommendations

Contemporary lipid management is guided by ADA and ACC/AHA recommendations emphasizing risk-based, individualized treatment[5,6], categorizing patients as low (<3%), borderline (3–<5%), intermediate (5–<10%), or high (≥10%) risk. Guidelines recommend statin therapy based on ASCVD risk, with most adults with diabetes aged 40–75 years meeting criteria for at least moderate-intensity statin therapy based on estimated risk and clinical factors, and escalation to high-intensity therapy for those at higher risk or with additional risk enhancers.[5,6] Recent updates reestablish numeric LDL-C and non–HDL-C thresholds to guide treatment intensity and escalation (**Table 1**), allowing therapy to align more directly with atherogenic burden.

For patients with LDL-C remaining above threshold despite maximally tolerated statin therapy, stepwise escalation to non-statin therapy is recommended; options include ezetimibe, bempedoic acid, or a PCSK9 inhibitor, selected based on the degree of LDL-C lowering needed, risk level, and patient preference (**Table 2, Table 3**). These recommendations are emphasized in higher-risk populations.

Hypertriglyceridemia is addressed separately, distinguishing therapies for ASCVD risk reduction versus pancreatitis prevention. Icosapent ethyl can be considered for selected patients with persistent TG elevation despite statin therapy[8], while fibrates or prescription omega-3 fatty acids are reserved for more severe hyper-triglyceridemia. Across these scenarios, non-HDL-C serves as a secondary treatment threshold, and ApoB is a selective tool for refining risk, particularly in patients with elevated TGs or discordant lipid profiles.

Although guidelines provide a framework for risk stratification and treatment escalation, they offer limited operational guidance in patients with discordant risk and lipid profiles, which often characterize diabetic dyslipidemia.

Table 1. Risk-Based Lipid Thresholds and Initial Therapy in Adults with Diabetes

Population	Clinical Context (including diabetes-specific risk enhancers)*	LDL-C Threshold†	Non–HDL-C Threshold†	Recommended Approach
Ages 20–39	***Included in calculator:*** diabetes diagnosis, kidney function (eGFR), albuminuria (UACR), & current glycemic burden (HbA1c) ***Not included in calculator:*** Long diabetes duration (≥10y T2DM or ≥20y T1DM), retinopathy, neuropathy, or ABI <0.9	<100 mg/dL	<130 mg/dL	Consider initiation of moderate-intensity statin after shared decision-making
Age 40–75	No ASCVD or major risk enhancers	<100 mg/dL	<130 mg/dL	Initiate moderate-intensity statin
Age 40–75	Multiple risk enhancers or PREVENT ≥10%	<70 mg/dL	<100 mg/dL	Initiate high-intensity statin; add ezetimibe if above threshold or a PCSK9 mAb
Age >75	Assess comorbidities and functional status	<100 mg/dL	<130 mg/dL	Continue or consider statin after shared decision-making
ASCVD	Established ASCVD (secondary prevention)	<55 mg/dL	<85 mg/dL	Initiate high-intensity statin; add ezetimibe or a PCSK9 mAb
Statin intolerance	Partial or complete	Individualized	Individualized	Use highest tolerated statin; add non-statin therapies as needed

Abbreviations: ABI, ankle–brachial index; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non–high-density lipoprotein cholesterol; UACR, urine albumin to creatinine ratio.

*ASCVD risk categories are based on PREVENT-ASCVD estimates (low <3%, borderline 3–<5%, intermediate 5–<10%, high ≥10%) and should be interpreted with diabetes-specific risk enhancers: albuminuria (UACR), eGFR <60 mL/min/1.73 m^2, long duration (≥10y T2DM or ≥20y T1DM), retinopathy, neuropathy, or ABI <0.9. Because PREVENT may not fully capture risk heterogeneity in diabetes, clinical factors not explicitly or consistently incorporated in the model (e.g., disease duration, microvascular complications, clinical phenotype) refine risk and guide treatment intensity.

†Thresholds guide treatment intensity and escalation and are not fixed treatment goals.

‡The 2026 ACC/AHA guideline distinguishes ASCVD at very high risk (LDL-C <55 mg/dL; non–HDL-C <85 mg/dL) from ASCVD not at very high risk (LDL-C <70 mg/dL; non–HDL-C <100 mg/dL). The majority of patients with diabetes and established ASCVD will qualify as very high risk; clinicians should assess each patient individually.

4. How We Manage Diabetic Dyslipidemia

Management of diabetic dyslipidemia requires individualized interpretation of risk, lipid measures, and clinical context. This SMART approach provides a structured, stepwise framework integrating risk assessment with selective refinement and pragmatic therapy escalation (**Figure 1**).

Management begins with estimation of 10-year ASCVD risk using PREVENT-ASCVD[7], which guides statin initiation and intensity (**Table 1**). PREVENT provides a structured estimate of ASCVD risk that incorporates diabetes diagnosis and kidney function (eGFR) into the base model. For further personalization, HbA1c and UACR should also be entered into the calculator as additional diabetes-specific predictors when these data are available. If entered,

Table 2. Adjunctive LDL-Lowering Therapies in Diabetes

Agent	LDL-C Reduction[†]	Mechanism	Key Evidence[‡]	Clinical Use (Preferred Scenarios)
Ezetimibe	~18–25%	Inhibits intestinal cholesterol absorption (NPC1L1)	IMPROVE-IT	Preferred for modest LDL-C gaps; oral, well-tolerated, low cost
PCSK9 monoclonal antibodies (evolocumab, alirocumab)	~50–65%	Increase LDL receptor recycling	FOURIER, ODYSSEY	Preferred for large LDL-C reduction or very high ASCVD risk
Inclisiran	~50%	siRNA inhibition of hepatic PCSK9 synthesis	ORION trials	Consider if adherence or dosing frequency is a concern
Bempedoic acid	~20%	ATP citrate lyase inhibition	CLEAR Outcomes	Useful in statin intolerance
Bile acid sequestrants	~10–25%	Bind intestinal bile acids and increase LDL clearance	Legacy trials	Avoid if TG ≥300 mg/dL; consider when statins not tolerated

Abbreviations: LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA; TG, triglyceride.

[†]Percent LDL-C reductions are approximate and may vary based on baseline therapy and adherence.

[‡]Key evidence: IMPROVE-IT[(12)]; FOURIER[(13)]; ODYSSEY Outcomes[(14)]; ORION[(15)]; CLEAR Outcomes[(16)]

these variables should not be reused as independent risk enhancers.

In patients with borderline or intermediate risk, or when clinical features suggest higher risk than estimated, other risk enhancers not fully captured in the above PREVENT risk estimator should be considered to further refine risk. These diabetes-specific risk enhancers include longer duration of diabetes, UACR, microvascular complications (i.e., retinopathy, neuropathy), abnormal ankle-brachial index (ABI), and chronic kidney disease (CKD) if severity, trajectory, and/or complications are not reflected by the eGFR. Lipoprotein(a) measurement identifies individuals with elevated lifetime risk. In patients with elevated TGs or discordance between LDL-C and clinical phenotype, non-HDL-C or ApoB more directly reflect atherogenic burden and support intensification of therapy.[(9,10)]

When uncertainty persists, coronary artery calcium (CAC) testing is used to refine risk when results may alter management, with higher scores supporting earlier or more intensive therapy,[(11)] CAC is used as a targeted tool when risk and clinical presentation are discordant.

Lipid-lowering therapy uses a statin-first, threshold-guided escalation strategy. If LDL-C remains above threshold on maximally tolerated statin therapy, ezetimibe[(12)], a PCSK9 inhibitor[(13-15)], or other agents[(16)] can be added (**Table 2**, **Table 3**). Bempedoic acid is an alternative in statin intolerance.[(16)] In statin intolerance, partial statin use is prioritized (any statin is better than no statin), with early incorporation of non-statin therapies.

Management of hypertriglyceridemia follows LDL-directed therapy and reflects the underlying clinical objective. In moderate TG elevation, icosapent ethyl is used for ASCVD risk reduction in selected high-risk patients.[(8)] In severe hypertriglyceridemia, treatment focuses on prevention of pancreatitis while maintaining statin therapy (**Table 3**).

Special clinical contexts, including type 1 diabetes, CKD, pregnancy, older age, and elevated lipoprotein(a), require further individualization (**Table 4**). Across all scenarios, the central principle of the SMART approach is alignment of treatment intensity with atherogenic risk through selective refinement and context-specific decision-making.

5. Summary

Atherogenic dyslipidemia is a major driver of ASCVD risk in diabetes but is not fully captured by traditional lipid measures or risk equations. Current guidelines provide a framework for risk-based management but offer limited guidance in patients with discordant risk and lipid profiles. The SMART approach provides a structured framework integrating risk estimation, selective refinement, and

stepwise therapy escalation. By prioritizing atherogenic burden and clinical context, it aligns treatment intensity with patient-specific risk and supports more precise and consistent lipid management in diabetes.

Table 3. Practical Treatment Strategies for Lipid Management in Diabetes

Clinical Situation	Recommended Action	Clinical Notes[†]
Initial risk assessment (no ASCVD)	Estimate 10-year ASCVD risk using PREVENT; interpret in context of diabetes-specific risk enhancers	Use risk estimate to guide statin initiation and intensity (see **Table 1**)
Diabetes, age 40–75	Initiate statin therapy	Moderate vs high intensity guided by risk and diabetes-specific enhancers
LDL-C above threshold on statin	Add ezetimibe, PCSK9 mAb, or bempedoic acid based on LDL-C gap and preference	Reassess lipid levels before further intensification
Persistent LDL-C elevation on statin + initial non-statin agent	Add PCSK9 mAb or inclisiran; add ezetimibe if not already used	PCSK9 mAb preferred for large LDL-C gaps; inclisiran if adherence is a concern
Statin intolerance	Use highest tolerated statin and add non-statin therapy	Complete intolerance uncommon; consider rechallenge strategies
LDL-C at threshold with concern for residual risk	Measure and address non-HDL-C or ApoB thresholds	Identifies discordance and residual atherogenic particle burden
Uncertain decision after risk assessment	Refine or reclassify PREVENT-estimated risk using diabetes-specific enhancers ± CAC	CAC ≥100 supports treatment escalation
Subclinical atherosclerosis (CAC ≥100)	Initiate or intensify statin therapy	Higher CAC favors earlier and more aggressive therapy
Established ASCVD	Use high-intensity statin and escalate per thresholds (secondary prevention)	Add ezetimibe, PCSK9 inhibitor, or bempedoic acid based on LDL-C gap and patient preference
TG 150–499 mg/dL	Consider icosapent ethyl in high-risk patients	Do not substitute with mixed omega-3 supplements
TG ≥500 mg/dL	Treat secondary causes and add fibrate, prescription omega-3, or ApoC-III or ANGPTL3 inhibitor therapies	Primary goal is prevention of pancreatitis

Abbreviations: ApoB, apolipoprotein B; CAC, coronary artery calcium; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

[†]Reassess lipid levels 4–12 weeks after initiation or modification of therapy.

Table 4. Lipid Management in Special Clinical Situations in Diabetes

Clinical Context	Key Considerations	Recommended Approach	Clinical Notes[†]
CKD (eGFR <60 mL/min/1.73 m²)	Higher ASCVD risk; altered pharmacokinetics	Statin ± ezetimibe; avoid or dose-adjust fibrates if eGFR <30; use statins with low renal clearance (atorvastatin, fluvastatin, pitavastatin)	Monitor renal function and drug interactions
Pregnancy	Statins contraindicated	Discontinue statins; consider bile acid sequestrants if needed	Avoid during breastfeeding unless high-risk scenario
Older adults, age >75	Frailty, comorbidities, polypharmacy	Continue or initiate statin after individualized discussion	Weigh life expectancy and goals of care
Type 1 diabetes (long duration)	Elevated lifetime ASCVD risk	Consider statin with ≥20 years disease duration or complications	Use same thresholds as type 2 diabetes when risk is high
Elevated Lp(a)	Independent ASCVD risk factor	Intensify LDL-C lowering; consider earlier PCSK9 use	No approved Lp(a)-specific therapy currently available
Statin intolerance	Limits standard therapy	Use non-statin therapies and consider rechallenge	Alternate dosing often improves tolerability
Mixed dyslipidemia (elevated TGs)	Residual ASCVD risk	Add icosapent ethyl or fibrate depending on TG level	Avoid bile acid sequestrants if TGs are elevated

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Lp(a), lipoprotein(a); TG, triglyceride.

[†]Management should be individualized with attention to safety, comorbidities, and patient preferences.

References

1. Kosmas CE, Silverio D, Sourlas A, Garcia F, Montan PD, Guzman E. Impact of lipid-lowering therapy on glycemic control and the risk for new-onset diabetes mellitus. *Drugs Context*. 2018;7:212562. Epub 20181128. doi: 10.7573/dic.212562. PMID: 30515229; PMCID: PMC6267678.
2. Neuen BL, Fletcher RA, Heath L, Perkovic A, Vaduganathan M, Badve SV, et al. Cardiovascular, kidney, and safety outcomes with GLP-1 receptor agonists alone and in combination with SGLT2 inhibitors in type 2 diabetes: a systematic review and meta-analysis. *Circulation*. 2024;150(22):1781-90. Epub 20240830. doi: 10.1161/CIRCULATIONAHA.124.071689. PMID: 39210781.
3. Nauck MA, Tuttle KR, Tschop MH, Bluher M. Glucagon-like receptor agonists and next-generation incretin-based medications: metabolic, cardiovascular, and renal benefits. *Lancet*. 2026;407(10531):892-908. Epub 20260114. doi: 10.1016/S0140-6736(25)02105-1. PMID: 41547366.
4. Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. *Nat Rev Cardiol*. 2023;20(7):463-74. Epub 20230328. doi: 10.1038/s41569-023-00849-3. PMID: 36977782.
5. American Diabetes Association Professional Practice Committee for D. Standards of Care in Diabetes—2026. *Diabetes care*. 2026;49(1 Suppl 1):S1–S306. doi: doi:10.2337/dc26-SINT.
6. Blumenthal RS, Morris PB, Gaudino M, Johnson HM, Anderson TS, Bittner VA, et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of dyslipidemia: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Journal of the American College of Cardiology*. 2026. 87(19):2624–2757. Epub 20260313. doi: 10.1016/j.jacc.2025.11.016. PMID: 41824590.
7. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, et al. Development and validation of the American Heart Association's PREVENT equations. *Circulation*. 2024;149(6):430–449. Epub 2023 Nov 10. doi:10.1161/CIRCULATIONAHA.123.067626. PMID: 37947085.
8. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *The New England Journal of Medicine*. 2019;380(1):11-22. Epub 20181110. doi: 10.1056/NEJMoa1812792. PMID: 30415628.
9. Johannesen CDL, Mortensen MB, Langsted A, Nordestgaard BG. Apolipoprotein B and non-HDL cholesterol better reflect residual risk than LDL cholesterol in statin-treated patients. *Journal of the American College of Cardiology*. 2021;77(11):1439-50. doi: 10.1016/j.jacc.2021.01.027. PMID: 33736827.
10. Nordestgaard BG, Hegele RA. Residual lipid risk in atherosclerotic cardiovascular disease. *European Heart Journal.* 2026. Epub 20260217. doi: 10.1093/eurheartj/ehag087. PMID: 41701506.
11. Orringer CE, Blaha MJ, Blankstein R, Budoff MJ, Goldberg RB, Gill EA, et al. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. *Journal of Clinical Lipidology.* 2021;15(1):33-60. Epub 20201211. doi: 10.1016/j.jacl.2020.12.005. PMID: 33419719.
12. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *The New England Journal of Medicine*. 2015;372(25):2387-97. Epub 20150603. doi: 10.1056/NEJMoa1410489. PMID: 26039521.
13. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *The New England Journal of Medicine*. 2017;376(18):1713-22. Epub 20170317. doi: 10.1056/NEJMoa1615664. PMID: 28304224.
14. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *The New England Journal of Medicine*. 2018;379(22):2097-107. Epub 20181107. doi: 10.1056/NEJMoa1801174. PMID: 30403574.
15. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *The New England Journal of Medicine*. 2020;382(16):1507-19. Epub 20200318. doi: 10.1056/NEJMoa1912387. PMID: 32187462.
16. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *The New England Journal of Medicine*. 2023;388(15):1353-64. Epub 20230304. doi: 10.1056/NEJMoa2215024. PMID: 36876740.

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