Updates on Dyslipidemia Management in Diabetes: From Guidelines to Novel Therapies

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Introduction/Background

A recent NHANES (National Health and Nutrition Examination Survey) study in the United States with data from 1999 to 2016 identified the ASCVD (atherosclerotic cardiovascular disease) rates in those with metabolic syndrome (MetS) and type 2 diabetes (T2DM)[6].

- 35% in the high-risk ASCVD group (defined by >20% 10-year risk) had MetS.
- T2DM was present in 42% of the high-risk group.
- The prevalence of ASCVD was ~20% in the T2DM group.

Diabetic dyslipidemia is a condition in people with type 2 diabetes that lowers HDL and raises TG and LDL, thus increasing the risk of heart disease and stroke.

In a cross-sectional study completed in Jordan among people with T2DM, 91.4% had dyslipidemia with low HDL-C in 66.2% and high LDL-C in 62.1%[7].

Objectives

This poster provides an update on dyslipidemia management recommendations related to diabetes and cardiovascular risk reduction. To accomplish this, we will:

- Provide a review of novel antilipidemic agents (e.g., inclisiran, alirocumab, evolocumab, bempedoic acid, evinacumab, and icosapent ethyl);
- Summarize results from the available cardiovascular outcome trials (CVOTs), as some of these agents have been approved for treating established ASCVD in addition to LDL-C reduction.

Methodology: Clinical Guidelines & Novel Therapies

American Diabetes Association Standards of Care, 2023[8]

- ***Primary Prevention***: *For people with diabetes aged 40–75 years without ASCVD, use moderate-intensity statin therapy in addition to lifestyle therapy. (A)*
- ***Secondary Prevention***: *For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. (A)*
- ***Treatment of Other Lipoprotein Fractions or Targets***: *In individuals with ASCVD or other CV risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. (A)*

Guideline on the Management of Blood Cholesterol: Executive Summary, 2018[9]

Recommendations for Patients With Diabetes Mellitus
Referenced studies that support recommendations are summarized in Online Data Supplements 11 and 12

COR	LOE	Recommendations
I	A	1. In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.[S4.3-1-S4.3-9]
IIa	B-NR	2. In adults 40 to 75 years of age with diabetes mellitus and an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it is reasonable to assess the 10-year risk of a first ASCVD event by using the race and sex-specific PCE to help stratify ASCVD risk.[S4.3-1-S4.3-9-11]

Recommendations for Patients With Diabetes Mellitus (Continued)

COR	LOE	Recommendations
IIa	B-R	3. In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.[S4.3-1-S4.3-13]
IIa	B-NR	4. In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy.[S4.3-5,S4.3-8,S4.3-13]

Novel Therapies

Agent	Mechanism of Action	Indication
lomitapide (Juxtapid)	Binds and inhibits ***MTP*** (microsomal triglyceride transfer protein) → prevents the formation of apoB-containing lipoproteins (VLDL)	HoFH (homozygous familial hypercholesterolemia)
evinacumab-dgnb (Evkeeza)	Blocks the function of angiopoietin-like 3 (***ANGPTL-3***), which is an inhibitor of lipoprotein lipase and endothelial lipase	HoFH
bempedoic acid (Nexletol)	Prevents cholesterol synthesis in the liver by inhibiting ***ACL*** or ***ATP-CL*** (adenosine triphosphate-citrate lyase)	ASCVD, established HeFH
inclisiran (Leqvio)	Antilipemic small interfering ribonucleic acid (siRNA) agent • In the liver, utilizing RNA interfering method to ***directly breakdown mRNA for PCSK-9*** → increases LDL-C receptor recycling and expression → increases LDL-C uptake → reducing LDL-C levels	Secondary prevention of CV events HeFH (heterozygous familial hypercholesterolemia)
alirocumab (Praluent) **evolocumab** (Repatha) PCSK-9 Inhibitors	PCSK-9 breaks down hepatic LDL-C receptors (upregulated in the presence of statins) • Inhibiting this enzyme → ***allows more efficient hepatic uptake of LDL-C*** → reducing LDL-C levels by more than 50%	alirocumab - HLP or established ASCVD: 75 mg SC once every 2 weeks or 300 mg SC every 4 weeks evolocumab - HLP or established ASCVD: 140 mg SC once every 2 weeks or 420 mg monthly

Results

Study (Agent)	Median Duration of Follow-Up (Years)	N	CAD or CVD at Baseline	Diabetes at Baseline	Intervention Arm	Results (Number of Patients Meeting End Point*)		Primary or Secondary Composite Outcome			NNT	LDL-C Reduction
						Intervention	Placebo	Measure of Comparison	95% CI	P-value		
Phase 3 HoFH Lomitapide Study[11] (lomitapide; Juxtapid)	78 weeks (full study)	29	-	-	lomitapide 5 – 60 mg/day PO Median dose: 40 mg/day	-	-	-	-	-	-	38% (p < 0.0001) (at Week 78)
ELIPSE HoFH[10] (evinacumab; Evkeeza)	24 weeks (intervention)	65	88% in intervention group	-	IV infusion at a dose of 15 mg/kg every 4 weeks	-	-	-	-	-	-	47.1% relative reduction (p < 0.001)
CLEAR OUTCOMES[5] (bempedoic acid; Nexletol)	3.4	13,970	70% in intervention group	45% in intervention group	180 mg bempadoic acid daily PO	819 (11.7%)	927 (13.3%)	HR 0.87	0.79 – 0.96	0.004	46	-26.1% from baseline – treatment arm (60 months)
ORION-9, 10, 11[1] (inclisiran; Leqvio)	varied	3,660	85% ADCVD**; 45% MI in intervention group	37.5% in intervention group	ORION-9: inclisiran sodium 300 mg SQ monthly	131 (7.4%)	172 (9.4%)	OR 0.75	0.60 – 0.94	0.013	63	Reduced by 1.38 mmol/L (Day 540)
REDUCE-IT[4] (icosapent ethyl; Vascapa)	4.9	8,179	71% in intervention group	58.6% in intervention group	2 g of icosapent ethyl twice daily (total daily dose, 4 g)	705 (17.2%)	901 (22.0%)	HR 0.75	0.68 – 0.83	<0.001	21	Does not raise LDL-C levels; DHA-based formulations do
ODYSSEY OUTCOMES[2] (alirocumab; Praluent)	2.8	18,924	19% MI & 3.2% stroke in intervention group	29% in intervention group	alirocumab 75 mg Q 2weeks SQ	903 (9.5%)	1,052 (11.1%)	HR 0.85	0.78 – 0.93	<0.001	63	49% difference (at 48 months)
FOURIER[3] (evolocumab; Repatha)	2.2	27,564	81% MI & 20% HS* in intervention group	37% in intervention group	evolocumab either 140 mg every 2 weeks or 420 mg monthly SQ	1,344 (9.8%)	1,563 (11.3%)	HR 0.85	0.79 – 0.92	<0.001	67	54% difference (at 168 weeks) (p < 0.001)

*NS = nonhemorrhagic stroke; **ASCVD = Atherosclerotic Cardiovascular Disease

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ODYSSEY OUTCOMES
Primary endpoint: composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization

CLEAR OUTCOMES
Primary efficacy endpoint: a four-component composite of adjudicated major adverse cardiovascular events (MACE), defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization

REDUCE-IT
Primary efficacy endpoint: a composite of cardiovascular death, nonfatal myocardial infarction (including silent myocardial infarction), nonfatal stroke, coronary revascularization, or unstable angina

FOURIER
Primary endpoint: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization

ORION-9, 10, 11
Prespecified exploratory endpoint of major cardiovascular events (MACEs) included non-adjudicated CV death, cardiac arrest, non-fatal myocardial infarction (MI), and fatal and non-fatal stroke

Discussion: What Would DCESs Want To Know Relating to Lipids?

- **Lipid Profile Interpretation And Lipid Goals**: Interpret levels, e.g., TC, LDL-C, HDL-C, TG; explaining each parameter as how each relates to CV risk in people with type 2 diabetes
- **Pharmacotherapies**: Classic lipid-lower agents (e.g., statins, fibrate, fish oil); novel therapies: know the options when a statin is not enough
- **Individualized Treatment Plans**: Recognize lipid management plans need to be tailored to each individual's needs, considered in conjunction with diabetes management, CV risk factors (primary vs. secondary prevention), overall health status, etc
- **Patient Education**: Communicate effectively about the importance of lipid management in overall diabetes management and empathetically empower patients to make informed decisions
- **Collaborative Care**: Work collaboratively with other healthcare providers to deliver comprehensive care to prevent complications

Case Study: Let's Meet Ken

Case:

Assessment & Plan:

Conclusion/Summary

- Effective diabetes management requires strategies beyond just glycemic management, e.g., treating the whole person rather than just managing a chronic condition.
- This poster provides an update on dyslipidemia management recommendations relating to type 2 diabetes and cardiovascular risk reduction.
- A review of novel antilipidemic agents (e.g., inclisiran, alirocumab, evolocumab, bempedoic acid, evinacumab, and icosapent ethyl) beyond statins and their associated CVOTs are included, as some of these agents have been approved for managing established ASCVD (evidence-based practice).
- This poster takes a patient-centered approach where a patient case is included to assist in applying guideline recommendations and implementing a treatment and monitoring plan.

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