A MODERN APPROACH TO DYSLIPIDEMIA

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This review attempts to summarize previous knowledge and to highlight the implications of new developments, including a streamlined classification system for dyslipidemias, the potential value of measuring secondary lipid variables for assessment of ASCVD risk, the role of genetic testing in these disorders, as well as a discussion of the current and emergent treatment options, and their potential role in the management of dyslipidemias.

CLASSIFYING DYSLIPIDEMIAS

The Frederickson (WHO) classification of dyslipidemias was originally described in the 1960s and defined 5 categories of dyslipidemia (types 1-5) based on observable phenotypes and lipoprotein fractionation findings.

Although it was useful in the premolecular era, we believe it is time to dispense with this classification system. Because fractionation methods such as ultracentrifugation are inaccessible for most clinicians, accurate Frederickson phenotyping is not practical. Also, contrary to past beliefs, most Frederickson phenotypes are not monogenic, but rather have a polygenic basis. For these reasons, there is no further need to perpetuate this system as the basis for diagnosis and treatment of dyslipidemias.

Only FCS (former type 1) and familial hypercholesterolemia (FH; a subtype of former type 2A) are caused by rare pathogenic Mendelian variants, although at least one-third of patients with suspected FH have a high polygenic score for LDL-C.

We recommend that the overall lipid disturbance obtained from the routine lipid panel—primary hypercholesterolemia, primary HTG, combined, or other—is a practical starting point for clinical algorithms (Table 1).

Table 1. Biochemical levels for dyslipidemia in adults >18 years of age

	LDL-C	TG	HDL-C
Mild-to-moderate deviation			
Levels	3.4-4.9 mmol/L 130-194 mg/dL	2-9.9 mmol/L 175-885 mg/dL	0.7-0.9mmol/L 25-35 mg/dL
Etiology	Polygenic predisposition plus secondary factors (see Table 7)		
Severe deviation			
Levels	≥ 5.0 mmol/L ≥ 194 mg/dL	≥ 10 mmol/L ≥ 885 mg/dL	< 0.7 mmol/L < 25 mg/dL
Etiology	Monogenic disorders (see Table 4) and/or marked polygenic predisposition plus secondary factors (see Table 7)		

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

CLINICAL CONSEQUENCES

Lipoproteins and ASCVD.

- LDL: A direct causal role in the pathogenesis of ASCVD.
- HDL: A direct role in mediating ASCVD is uncertain.
  - low HDL-C is an independent ASCVD risk factor.
  - TC:HDL-C ratio (mirrored by the apo B:A-I ratio) is more predictive of ASCVD risk than either component, indirectly suggesting a role for low HDL-C in ASCVD.
  - Many individuals with isolated low HDL-C resulting from genetic variants show no increased tendency toward ASCVD.
  - HDL-C-raising therapies have failed to demonstrate ASCVD benefit.
- TG: The role in predisposing to ASCVD risk is less controversial.
  - elevated TG is an independent risk factor for ASCVD; this is especially true for non-fasting TG levels

CLINICAL CONSEQUENCES

Pancreatitis.

There is the causal relationship between severe HTG (TG >885 mg/dL, specially >1770 mg/dl) and the development of acute pancreatitis. Although the underlying pathophysiology is not understood, it could be related to abnormal lipolysis by mislocalized exocrine pancreatic lipase, leading to pancreatic autodigestion and inflammation.

Multisystem involvement.

monogenic dyslipidemias can present with multisystem involvement.

Table 2. Screening for dyslipidemia

	CCS	EAS/ESC	ACC/AHA/NECP/ ATP III	USPSTF	NHLBI/NLA
Males, age (y)	> 40	>40	>20	>35	Age 9-11 and Age 20
Females, age (y)	> 40 (or postmenopausal)	>50 (or postmenopausal)	>20	>45	
Special populations	Screen at time of identification of risk factors	Children with suspected FH		20-35 y (male) 20-45 y (female) if risk factors for ASCVD	>2 if family history of premature ASCVD or FH or ASCVD risk factors
How to screen	Standard fasting or nonfasting lipid profile: TC, LDL-C, HDL-C, non-HDL-C, TG	Standard fasting or nonfasting lipid profile: TC, LDL-C, HDL-C, non-HDL-C, TG	Standard fasting or nonfasting lipid profile: TC, LDL-C, HDL-C, non-HDL-C, TG	Standard fasting or nonfasting lipid profile: TC, LDL-C, HDL-C, non-HDL-C, TG	Standard fasting or nonfasting lipid profile: TC, LDL-C, HDL-C, non-HDL-C, TG
	Lp(a) – once in patient's lifetime, with initial screening	apo B	Optional:		
	Optional: apo B	Lp(a): consider once in patient's lifetime	apo B Lp(a)		

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; apo B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; ATP, Adult Treatment Panel; CCS, Canadian Cardiovascular Society; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FH, familial hypercholesterolemia; Lp(a), lipoprotein(a); NECP, National Cholesterol Education Program; NHLBI, National Heart, Lung, and Blood Institute; NLA, National Lipid Association; USPSTF, US Preventative Services Task Force; TC, total cholesterol; TG, triglyceride.

Monitoring of lipid levels.

There is no consensus on the best approach to monitor lipid profiles in patients before and during treatment.

Generally, lipids should be assessed **at least twice before starting drug** therapy, and then **repeated 8-12 weeks after initiation or dose adjustment**.

For individuals being treated for **secondary prevention of ASCVD** or **higher risk primary prevention** with LDL-C below treatment intensification thresholds, monitoring **annually** is reasonable.

For **low-risk primary ASCVD** prevention individuals with LDL-C levels below treatment intensification thresholds, **less frequent** monitoring (ie, **every 5 years**) may be appropriate.

For biochemical monitoring for adverse effects of statins, we advocate that **ALT and creatine kinase (CK) should be measured before starting treatment** to obtain a baseline as a point of reference should future concerns arise; however, routine monitoring is generally unnecessary.

Statins are **not contraindicated** in individuals with mild baseline elevation in transaminases **(<3× ULN)** or in those with **NAFLD**, and these individuals do not seem to be at increased risk for statin hepatotoxicity. Statins are, however, **contraindicated** in those with **decompensated cirrhosis** or **acute liver failure**. For those individuals with transaminase **elevations >3× ULN**, using a **lower starting dose** of statin and **monitoring transaminases at 4- to 12-week intervals during cautious up-titration** may be reasonable.

If **baseline CK is >5 times ULN**, some would advise **refraining from statin initiation** and considering alternative therapy because CK may rise even higher when a statin is introduced. However, if a patient has no risk factors for myopathy, CK does not need to be routinely monitored.

Table 3. Laboratory assessment of patients with dyslipidemias

Baseline lipid evaluation
- Lipoprotein profile: TC, LDL-C, non-HDL-C and HDL-C, and TG
- Apolipoprotein B is desirable if accessible
- Lipoprotein(a) can be measured once in the patient's lifetime
- Optional/academic interest: lipoprotein particle size, remnant particle assay, cholesterol efflux assay for HDL function, apo A-I to allow calculation of apo B to A-I ratio

Screening for secondary causes
- Diabetes: fasting glucose, glycated hemoglobin
- Hypothyroidism: thyroid stimulating hormone
- Liver disease: transaminases, bilirubin, alkaline phosphatase, gamma glutamyl transferase
- Renal disease: serum creatinine, urinary albumin, albumin to creatinine ratio
- Autoimmune diseases: serum rheumatoid factor, antinuclear antigen, C-reactive protein

Associated abnormalities in monogenic dyslipidemias
- Hematologic: abnormal erythrocyte morphology in low LDL-C states and LCAT deficiency
- Coagulation: prolonged international normalized ratio in low LDL-C states
- Serum fat-soluble vitamin levels: depressed in low LDL-C states
- Serum pancreatic lipase: elevated in hypertriglyceridemia-associated pancreatitis
- Cardiovascular: noninvasive imaging of premature atherosclerosis in coronary, extracranial carotid arteries, and peripheral arteries in several dyslipidemias
- Gastrointestinal and hepatic: abdominal ultrasound for fatty liver in low LDL-C states, hepatosplenomegaly in monogenic chylomicronemia

Diagnostic targeted sequencing panel or targeted exome for dyslipidemia genes
- Causative genes listed in Table 4

Specialized research lipid biochemistry (not essential; confirmatory or for academic interest)
- Serum or plasma plant sterols to confirm sitosterolemia
- Post-heparin plasma lipolytic assay to confirm lipoprotein lipase deficiency
- Serum or plasma lysosomal acid lipase to confirm lysosomal acid lipase deficiency
- Serum cholesterol efflux capacity in HDL-C deficiency states

RARE DYSLIPIDEMIAS

For any patient referred with severe dyslipidemia, rare monogenic causes must be considered and ruled out because these may require specialized diagnosis, intervention, and monitoring.

Suspicion for a monogenic dyslipidemia is raised by:

- (1) the degree of deviation of the lipid or lipoprotein trait (ie, a more extreme deviation means a monogenic etiology is more likely)
- (2) a younger age at presentation
- (3) the detection of specific clinical features
- (4) a known family history of dyslipidemia and/or early atherosclerosis
- (5) the absence of secondary factors.

Table 4. Monogenic dyslipidemias: molecular genetics

Disorder	Gene/chromosome	Inheritance	MIM reference numbers
Group 1: Monogenic hypercholesterolemia			
Familial hypercholesterolemia	*LDLR*/19q13	ASD	143890, 143890, 606945, 144010,
	APOB/2p24		615558, 107730, 603776, 607786
	PCSK9/1p32		
Autosomal recessive hypercholesterolemia	*LDLRAP1*/1p35	AR	603813, 605747
Sitosterolemia	*ABCG5*/2p21	AR	210250, 605459, 605460
	ABCG8/2p21		
Lysosomal acid lipase deficiency	*LIPA*/10q23	AR	278000, 613497
Group 2: Monogenic hypocholesterolemia			
Abetalipoproteinemia	*MTTP*/4q23	AR	20010, 157147
Hypobetalipoproteinemia	*APOB*/2p24	ASD	144010, 615558, 107730
Chylomicron retention (Anderson) disease	*SAR1B*/5q31	AR	246700, 607690
Familial combined hypolipidemia	*ANGPTL3*/1p31	AR	605019, 604774
PCSK9 deficiency	*PCSK9*/1p32	ASD	605019, 613589, 607786
Group 2A: Monogenic hyperalphalipoproteinemia			
CETP deficiency	*CETP*/16q13	ASD	143470, 118470
Hepatic lipase deficiency	*LIPC*/15q21	AR	614025, 151670
Scavenger receptor B1 deficiency	*SCARB1*/12q24	ASD	610762, 601040
Group 2B: Monogenic hypoalphalipoproteinemia			
Familial hypoalphalipoproteinemia	*APOA1*/11q23	ASD	604091
Tangier disease	*ABCA1*/9q31	ASD	205400
Familial LCAT deficiency	*LCAT*/16q22	AR	245900
Group 3A: Monogenic hypertriglyceridemia			
Familial chylomicronemia syndrome	*LPL*/8p22	AR	609708, 238600
	APOC2/19q13		207750, 608083
	APOA5/11q23		145750, 144650, 606368
	LMF1/16p13		246650, 611761
	GPIHBP1/8q24		612757
Infantile HTG, transient	*GPD1*/12q12	AR	614480
Dysbetalipoproteinemia	*APOE*/19q13	AR[a]	618347
Secondary hereditary dyslipidemias			
Partial lipodystrophies	*LMNA*/1q22	AD	151660
	PPARG/3p25.2	AD	604367
	PLIN1/15p26.1	AD	613877
	CIDEC/3p25.3	AR	615238

Table 5. Monogenic dyslipidemias: clinical features

Condition	Clinical features and comorbidities	Comments
Group 1: Monogenic hypercholesterolemia: severely elevated LDL-C		
Familial hypercholesterolemia	Xanthomas: tendinous (mainly) rarely periosteal, intracranial, peripatellar, digital web spaces	HDL-C can be depressed;
	Xanthelasmas, corneal arcus	Lp(a) can be very elevated;
	Early ASCVD: angina, acute coronary syndrome, myocardial infarction, stroke, transient ischemic attack, peripheral arterial disease, claudication, arterial bruits	Untreated biallelic (ie, homozygous) form can express clinical features in childhood while monoallelic (ie, heterozygous) form expresses clinical features in early adulthood
	Aortic valve disease	
Autosomal recessive hypercholesterolemia	As above	Parents have normal lipids Affected children are indistinguishable from homozygous FH
Sitosterolemia	Xanthomas: tendinous, cutaneous, tuberous	↑ plasma beta-sitosterol, campesterol stigmasterol are diagnostic, as is positive genetic sequencing showing biallelic mutations
	Splenomegaly	
	Early ASCVD: angina, myocardial infarction, stroke, transient ischemic attack, claudication, arterial bruits	
	Hemolysis/ hemolytic anemia	
	Impaired platelet aggregation with easy bruising or bleeding	
Lysosomal acid lipase deficiency	Nausea, vomiting, diarrhea/steatorrhea	↑ TG frequently
	Protuberant abdomen	Transaminase elevations
	Hepatosplenomegaly, hepatic fibrosis, cirrhosis	Lipid infiltration of liver is cholesterol not TG
	Xanthomatous infiltration of adrenal, spleen, lymph nodes, bone marrow, small intestine, lungs, and thymus	Calcified adrenal gland on imaging Aliases: Wolman syndrome in infants and cholesterol ester storage disease (somewhat milder presentation)
Group 2: Monogenic hypocholesterolemia		
Abetalipoproteinemia	Failure to thrive, steatorrhea	Acanthocytosis on peripheral blood smear
	Night blindness, atypical retinitis pigmentosa, retinal degeneration	Complete absence of apo B containing lipoproteins; HDL-C normal
	Osteomalacia, osteoporosis	Undetectable levels of fat-soluble vitamins
	Ataxia, peripheral neuropathy, posterior column signs, deep tendon reflex loss	
Hypobetalipoproteinemia	Biallelic (ie, homozygous) form is clinically identical to abetalipoproteinemia	Monoallelic (ie, heterozygous) form has mainly biochemical features (ie, low but not absent apo B-containing lipoproteins) plus susceptibility to fatty liver (typical hepatosteatosis) and protection from ACSCVD
Chylomicron retention (Anderson) disease	Similar to abetalipoproteinemia Systemic features are less severe; no erythrocyte abnormalities	Distinguished biochemically from abetalipoproteinemia and homozygous hypobetalipoproteinemia by normal TG levels
Familial combined hypolipidemia	No defining clinical features Probable protection from ASCVD	Biallelic form: profound deficiency of all lipoproteins Monoallelic form: normal HDL-C; low apo B-containing lipoproteins
Group 2A: Monogenic hyperalphalipoproteinemia: extremely elevated HDL-C		
CETP deficiency	No defining clinical features	Biallelic form: extreme high HDL-C
	Possible protection from ASCVD, although this is controversial	Monoallelic form: moderately elevated HDL-C
Hepatic lipase deficiency	Associated with acccelerated ASCVD	Increases in both HDL-C and apo B-containing lipoproteins;
	Eruptive or palmar xanthomas sometimes	Managed according to LDL-C targets
SR-B1 deficiency	No defining clinical features	Biallelic form: extremely high HDL-C
	Possible protection from ASCVD, although this is controversial	Monoallelic form: moderately elevated HDL-C

Table 5. Continued

Condition	Clinical features and comorbidities	Comments
Group 2B: Monogenic hypoalphalipoproteinemia: severely depressed HDL-C		
Apolipoprotein A-I deficiency (familial hypoalphalipoproteinemia)	Xanthomatosis: cutaneous, interdigital web spaces	Biallelic form: absent HDL-C and apo A-I
	Predisposition to early ASCVD	Monoallelic form: moderately depressed HDL-C and apo A-I
Tangier disease	Hepatosplenomegaly	Biallelic form: absent HDL-C and apo A-I with clinical features plus stomatocytes on peripheral blood film
	Corneal opacities	Monoallelic form: moderately depressed HDL-C and apo A-I with no clinical features
	Enlarged orange tonsils	
	Dry/brittle skin/hair/nails	
	CE deposition in lymph nodes, bone marrow, liver, spleen, tonsils	
	Demyelinating sensory, autonomic, and motor neuropathies	
	Often premature coronary disease, angina, carotid bruits, claudication	
Familial LCAT deficiency	Corneal lipid deposits and opacities	Low HDL-C, plasma esterified cholesterol, apo A-I and A-II
	Foam cells in bone marrow and renal glomeruli	High plasma free cholesterol, TG,
	Proteinuria, renal failure	Alias: fish eye disease for severe LCAT deficiency
	Anemia	
Group 3A: Monogenic hypertriglyceridemia: severely elevated TG		
Familial chylomicronemia syndrome	Nausea, vomiting, failure to thrive, abdominal pain, pancreatitis risk	Biallelic form is associated with early onset (often childhood)
	Lipemic plasma	Relatives with mono-allelic form express extremely heterogeneous phenotypes ranging from normal TG to severe HTG
	Hepatosplenomegaly, lipemia retinalis, eruptive xanthomas, jaundice	
Infantile HTG, transient	Short stature	Elevated TG ± cholesterol and liver enzymes normalize with age
	Hepatosplenomegaly	High urinary dicarboxylic acid
	Hepatic steatosis/fibrosis	
Dysbetalipoproteinemia	Tuberoeruptive xanthomas, palmar crease xanthomas	Remnant lipoproteins, termed IDL and beta-VLDL, persist abnormally
	Premature atherosclerosis	*APOE* E2/E2 homozygotes are predisposed but expression requires a second genetic abnormality
Secondary dyslipidemias		
Partial lipodystrophies	Distinctive patterns of regional lipoatrophy associated with simultaneous lipohypertrophy in unaffected areas	Elevated TG which can be severe in 10%-20% of cases
	Insulin resistance	
	Recurrent pancreatitis	
Generalized lipodystrophies	Absence of subcutaneous fat in subcutaneous tissues	Elevated TG, which can be severe in majority of cases
	Insulin resistance	Elevated liver enzymes
	Recurrent pancreatitis	
	Hepatosplenomegaly	

Table 6. Dyslipidemias clinical summary

	Dermatologic	Cardiovascular	Gastrointestinal	Eye	Laboratory findings	Genetic influences	Secondary causes
High cholesterol states	Tendon xanthomas	Premature ASCVD		Xanthelasmas	↑ TC, LDL-C	Single gene, autosomal semidominant:	Hypothyroidism
		Carotid bruits		Corneal arcus		*LDLR*, *APOB*, *PCSK9*	Cholestatic liver disease
		Femoral bruits				Single gene, autosomal recessive: *LDLRAP1*	Nephrotic syndrome
						Other syndromes: Wolman (*LIPA*)	
						Sitosterolemia (*ABCG5/ABCG8*)	
						Polygenic	
High triglyceride states	Eruptive xanthomas	Increased ASCVD risk	Pancreatitis	Lipemia retinalis	↑ TC, TG	Single gene, recessive: *LPL*, *APOC2*, *APOA5*,	Uncontrolled diabetes
	Tuberoeruptive xanthomas[a]		Recurrent abdominal pain			*LMF1*, *GPIHBP1*	Hypothyroidism
	Palmar xanthomas[a]					Single gene, recessive, susceptibility:	Obesity
						APOE	Alcohol
						Polygenic	Medications: OCP, Retinoic acid, BAS, Steroids
Low HDL states		Variably Increased ASCVD risk			↓ HDL-C	Single gene, recessive: *ABCA1*, *APOA1*, *LCAT*	Metabolic syndrome
						Single gene, semidominant: *ABCA1*	Obesity
Combined hyperlipidemia		Increased ASCVD risk			↑ TC, LDL-C, TG (also ↓ HDL-C)	Polygenic	Same as high cholesterol and TG states
Lipoprotein(a)		Increased ASCVD risk			↑ Lp (a)	*LPA* gene size polymorphism and SNPs	None

Table 7. Secondary lifestyle factors and medical conditions associated with dyslipidemia

	Associated primary lipid disturbance		
	↑ LDL-C	↑ TG	↓ HDL-C
Lifestyle			
Obesity	X	X	X
Physical inactivity	X	X	X
Excess alcohol		X	
Smoking			X
Dietary			
High trans fat	X		
High saturated fat	X		
High carbohydrate		X	X
Medical conditions			
Obstructive liver disease	X		
Hypothyroidism	X		
Nephrotic syndrome	X		
Anorexia	X		
Metabolic syndrome		X	X
Insulin resistance		X	X
Diabetes mellitus		X	X
Nonalcoholic fatty liver disease		X	X
Chronic renal failure		X	X
Cushing syndrome		X	X
HIV infection		X	X
Systemic lupus erythematosus		X	X
Lipodystrophy		X	X

ROLE OF GENETIC TESTING

When to consider genetic testing.

Potential benefits of genetic testing include:

- establishing a clear dyslipidemia diagnosis, which eliminates uncertainty for both patient and provider and allows for more personalized management. This includes an improved understanding of overall prognosis and better selection of targeted pharmacological agents.
- Another potential benefit of a genetic diagnosis includes the ability to screen for genetic risk in family members who may be presymptomatic and could benefit from early intervention or increased monitoring.

A reasonable threshold at which to consider genetic testing for FH would be LDL-C >194 mg/dL and for FCS would be TG >885 mg/dL in the absence of secondary causes.

For rare dyslipidemias, this is best decided on a case-by-case basis, and referral to a specialist in genetics of lipid disorders would also be appropriate.

Types of genetic testing.

We recently reviewed genetic testing methods for dyslipidemias, which include single gene sequencing, targeted gene panels, whole exome, and whole genome sequencing .

Gene panels that sequence regions known for dyslipidemia genes, are currently the most common method. Advantages of gene panels include reasonable cost and turnover time. They have limited risk of detecting incidental findings unrelated to dyslipidemia.

A pragmatic approach for now would be to discuss the limitations of such testing with the patient, and in the case of an apparent positive result, to repeat the testing in a clinically accredited laboratory.

HIGH CHOLESTROL STATE

Diagnosis.

An individualized diagnosis of hypercholesterolemia involves first an assessment of cholesterol levels, generally obtained from a **standard lipid profile**, as well as an **assessment of individual risk**, preferably using a validated cardiovascular risk calculator (ie, Framingham risk assessment), SCORE, QRISK, or ACC/AHA to determine the threshold at which cholesterol levels should be clinically addressed.

To diagnose monogenic FH, several clinical scoring systems have been developed. Two of the most widely used are the **Simon Broome Register criteria** and the **Dutch Lipid Network criteria**, both of which use a combination of lipid values (total cholesterol and/ or LDL-C levels); presence of physical stigmata; and personal or family history of premature ASCVD.

Pathogenic DNA variants detected in FH-associated genes is the gold standard method of diagnosis, and can be considered in those whose LDL-C levels are >194 mg/dL.

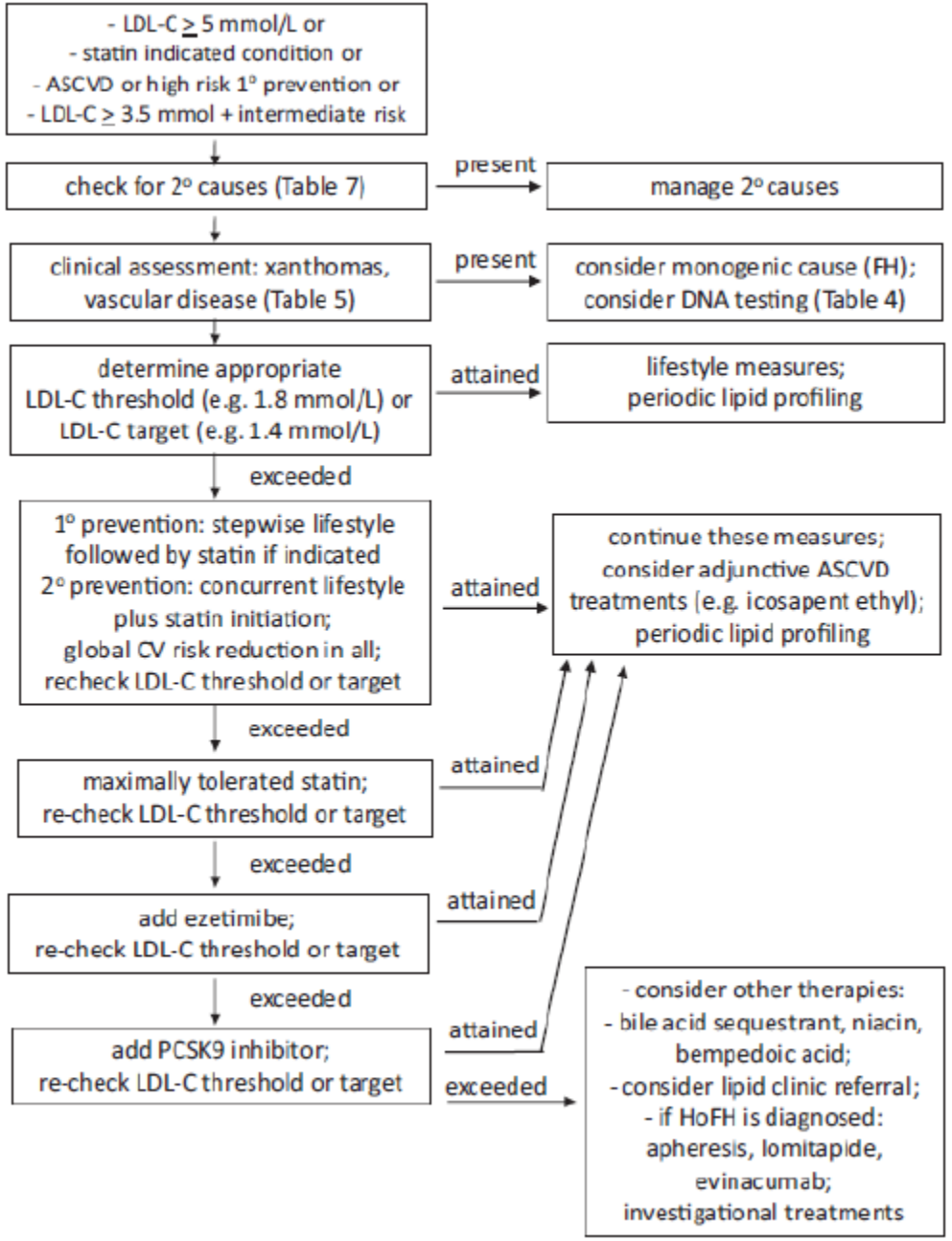

Figure 3. Approach to the patient with high LDL-C.

For patients whose **LDL-C levels do not warrant treatment, or if LDL-C cannot be accurately assessed** because of high TG levels, alternative thresholds for clinical action based on **apo B** or **non-HDL-C levels** may be used instead. These alternative measurements may also be used to help guide decisions on treatment intensification.

For those who **exceed their threshold or target on maximally tolerated statin**, adding additional agents, either **ezetimibe** in primary prevention or when LDL-C levels that are close to target, or **PCSK9 inhibitors** in those at higher risk or who require greater LDL-C lowering, should be considered.

The general principle of managing cholesterol is that “lower is better,” with no negative effects seen with even the lowest values of LDL-C obtained from clinical trials. Therefore, there is no need to deintensify treatment in those who attain very low LDL-C levels.

Treatment “targets” vs “thresholds.”

Cholesterol recommendations from major guideline organizations differ in several aspects, despite each committee being composed of lipid experts, and evaluating essentially the same evidence.

A major difference is the LDL-C level at which treatment intensification is recommended:

- Some guideline organizations (ie, EAS/ESC) have opted for a treatment “target,” which varies based on guideline organization
- some for a treatment “intensification threshold” (ie, Canadian Cardiovascular Society).

The difference is subtle but important. A target level implies that maximal benefit is obtained once the target is attained and may lead to providers possibly back-titrating the dose or even deprescribing medication if the attained level is far below the target. However, most clinical trials of cholesterol-lowering agents were performed by selecting patients with LDL-C exceeding a threshold value, and did not aim for a specific target level: some on-treatment patients attained extremely low LDL-C levels and yet continued to show benefit with respect to ASCVD risk reduction.

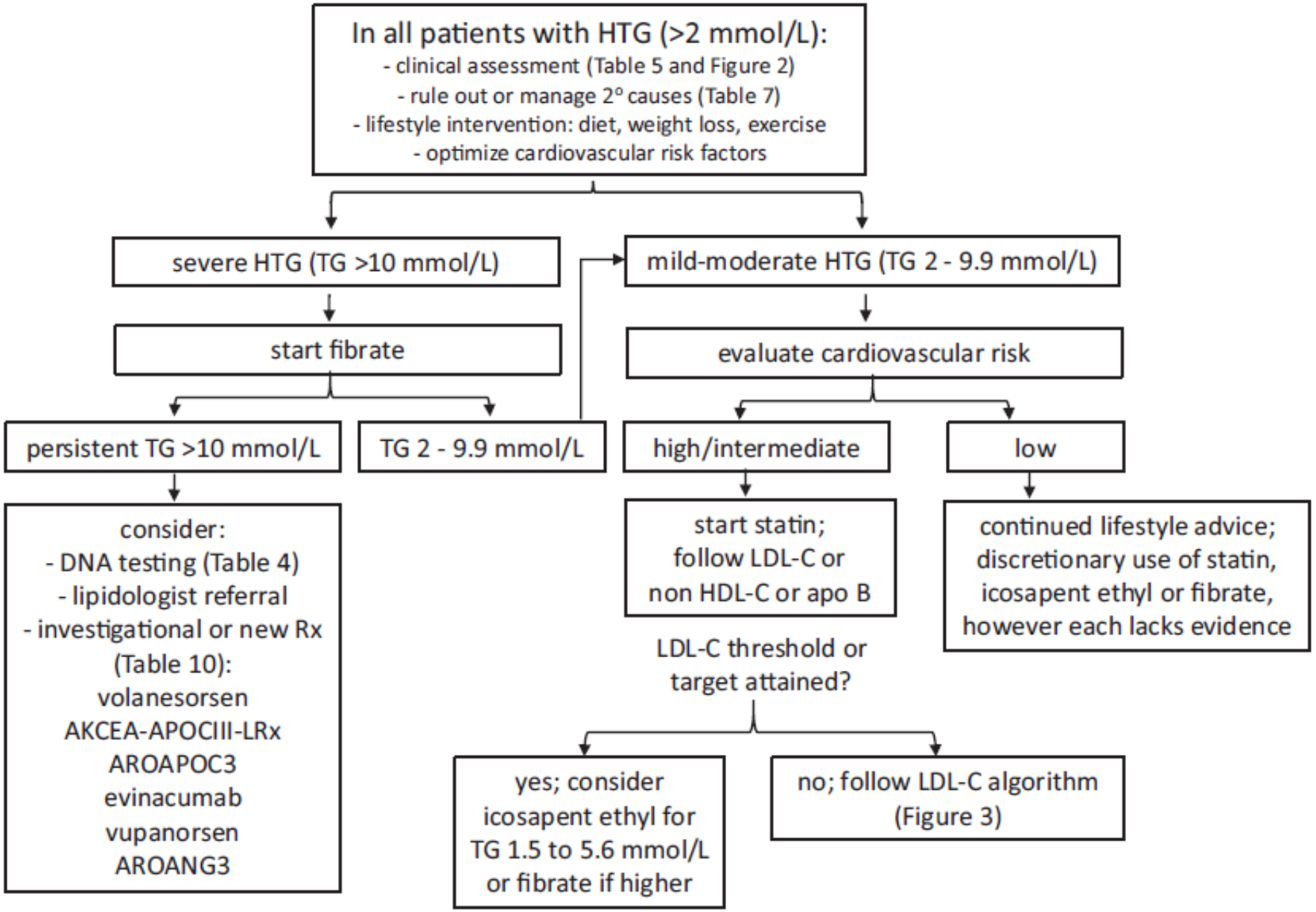

Figure 4. Approach to the patient with high TG.

HIGH TRIGLYCERIDE STATE

In FCS, most standard pharmacologic agents for elevated TG, such as fibrates, niacin, and omega 3 fatty acids, are ineffective in FCS patients, although they are still often tried. For FCS patients who suffer from recurrent episodes of pancreatitis, other investigational options include:

- Drugs targeting apo CIII
  - volanesorsen, which was approved in Europe for the treatment of patients with FCS and recurrent pancreatitis. Volanesorsen was denied approval by FDA because of its tendency to cause thrombocytopenia.

- Therapies targeting ANGPTL3 are in late-stage development and may offer a promising new therapy for individuals with FCS.

Approach to the patient with hypertriglyceridemia-associated pancreatitis.

HTG-associated pancreatitis should generally be managed **supportively** and conservatively, by **withholding oral intake** and administration of **IV fluids** and pain control.

Use of **insulin infusions, heparin, or plasmapheresis**: There is a **lack of definitive evidence to support** any of these approaches as superior to conservative management.

- there is no evidence to suggest that the course of pancreatitis will be altered if TG levels are lowered more rapidly once an episode has been triggered.
- TG levels will rapidly fall following cessation of oral intake, with a half-life of ~30 hours.
- Uncontrolled studies have **failed to show benefit for plasmapheresis in terms of morbidity, mortality, or pancreatitis severity**.
- Similarly, evidence of benefit in terms of outcomes for **insulin infusions** to treat HTG levels in those who without concurrent hyperglycemia is lacking; this treatment would increase the **risk of hypoglycemia**

Hypertriglyceridemia in pregnancy.

Until recently, it was advised that women taking **statins** before pregnancy should stop these when they are trying to conceive or as soon as they are aware of the pregnancy; however, in July 2021, the US FDA **removed this prohibition for women who are at very high ASCVD risk**.

Omega 3 fatty acids are considered **safe** to continue during pregnancy.

Fibrates have not been specifically studied in pregnancy but are not known to be teratogenic in humans. If it is possible for women treated with a fibrate or statin before pregnancy to safely stop these treatments, they should be held before conception. For women who have a **history of pancreatitis with TG >885 mg/dL, reintroduction of a fibrate may be recommended,** especially beyond the first trimester.

Diet is a key component of managing TG levels throughout pregnancy: low glycemic index diet.

For women with resistant HTG, for instance with **TG >1770 mg/dL**, admission to the **hospital**, supportive **fluid replacement**, and temporary **withholding of oral diet** may be advisable.

In **extreme cases of resistant HTG**, **plasmapheresis** may be considered as a last resort, but can be discontinued after delivery.

APPROACH TO ABNORMAL HDL

Although levels of HDL-C were once regarded as reliable predictors of ASCVD risk, current evidence suggests that **there is little to be gained in therapeutically targeting them**.

Individuals with either extremely high or low HDL-C levels show increased mortality compared with those with average HDL-C levels.

A **low HDL-C** is most commonly seen in patients **with elevated TG** levels. In this scenario, diagnosis and management would devolve to the **algorithm for elevated TG and ruling out any secondary factors**. Because genetic determinants of the joint elevated TG and depressed HDL-C phenotype are typically polygenic, **there is no reason for genetic evaluation** in these patients, unless a monogenic cause of severe HTG such as FCS is seriously being considered.

In the second scenario, **HDL-C is low in isolation**, without concomitant deviation in TG levels or indeed any other lipoprotein. This situation can arise from the **same secondary factors that raise TG** levels, so these should be ruled out. In cohort studies of >900 individuals with isolated low HDL-C, we found that overwhelmingly the **genetic basis is polygenic**. A smaller proportion of such patients instead has a single copy of a pathogenic variant in a gene for which 2 copies cause severe monogenic HDL-C deficiency syndromes.

At present, there is no evidence that knowing the precise genetic basis of low HDL-C affects management. Thus, **genetic testing is not recommended**, **unless** the isolated HDL-C deficiency is so extreme that a monogenic condition such as **Tangier disease, apo A-I deficiency, or LCAT deficiency is suspected**.

Rare monogenic HDL-C deficiency states may require specialized attention because of possible systemic involvement. Otherwise, management of a patient with isolated low HDL-C includes prudent **lifestyle** advice and pharmacotherapy that focuses on optimizing management of atherogenic apo B-containing lipoproteins, using **statins** as the first step.

Finally, for patients with extremely elevated HDL-C, we no longer assume that this metabolic state is cardioprotective. In addition to epidemiologic evidence that patients with markedly elevated HDL-C are not protected from ASCVD, families with monogenic disorders of high HDL-C, also have increased ASCVD risk.

Very high HDL-C levels are misleading because the HDL particles are likely poorly functional or even pro-atherogenic. Furthermore, many patients have markedly elevated HDL-C on a polygenic basis.

Secondary causes are most frequently **oral estrogen** replacement therapy in postmenopausal females, and also excessive **alcohol** consumption, which in some patients results only in increased HDL-C without any collateral effect on the TG metabolic axis. Our approach with such patients is to **disregard the elevated HDL-C and focus on the atherogenic lipoprotein species.**

COMBINED HYPERLIPIDEMIA

CHL is a complex phenotype that is often associated with early ASCVD. Terms such as “combined dyslipidemia” or “mixed dyslipidemia” are also sometimes used to describe CHL.

We suggest that the term “familial combined hyperlipidemia” is misleading because the adjective “familial” gives the impression that this lipid trait is monogenic, like FH. But genetic studies have never identified any single gene determinants of CHL.

Management of CHL patients begins with **ruling out secondary factors**, expanding the lipid profile with **apoB** and **possible Lp(a)** determination, and **assessment of ASCVD risk**.

Genetic analysis is not generally helpful because the CHL is **polygenic** and there is no evidence at present that this information is clinically actionable.

Treatment includes **correcting secondary factors**, lifestyle modification with weight loss, improved diet, and alcohol restriction, and medication, guided by the algorithms for the individual lipid perturbations. Typically, statin and/or ezetimibe are used first, and TG-lowering therapies such as icosapent ethyl or fibrates can be added if significant residual HTG remains.

ELEVATED Lp(a)

Lp(a) structure, function, and genetics.

Lp(a) is a distinct lipoprotein that shares structural similarity to LDL, with a single apo B-100 molecule on its surface. Unlike LDL, however, Lp(a) has a unique polymorphic apo(a) glycoprotein tail covalently linked to the apo B-100 via disulfide bridging.

The apo(a) tail contains 5 cysteine-rich domains, with the fourth being structurally **similar to plasminogen**, an antithrombotic plasma protein.

There is a strong association between Lp(a) levels and risk for ASCVD. Because apo(a) shares structural similarity with plasminogen, it is hypothesized that the apo(a) itself plays a direct role in atherogenesis and/or thrombosis.

Role of Lp(a) in ASCVD.

There is a strong association between Lp(a) levels and risk for ASCVD. Because apo(a) shares structural similarity with plasminogen, it is hypothesized that the apo(a) itself plays a direct role in atherogenesis and/or thrombosis.

Proposed mechanisms for the prothrombotic effect of Lp(a) include **competitive inhibition of plasminogen** leading to a decrease in fibrinolysis. Lp(a) particles also **interact with endothelial macrophages**, **generating foam cells and atherosclerotic plaques**, as well as potentially **enhancing oxidation of LDL**.

Because circulating Lp(a) is thought to remain relatively stable throughout life, once a baseline level is obtained, further monitoring is not required.

A high level of Lp(a) is considered to be ≥125 nmol/L (≥50 mg/dL).

Investigations and measurement.

There is no consensus regarding screening individuals for Lp(a) levels.

- Some guideline committees, such as the European Atherosclerosis Society/European Society of Cardiology and Canadian Cardiovascular Society, suggest measuring Lp(a) once as an adult for risk stratification.
- Other societies, such as the National Lipid Association, suggest screening only in high-risk situations, such as in individuals with a personal or family history of premature ASCVD, or those with known FH.

At high concentrations, Lp(a) can interfere with LDL determination as a substantial portion of measured LDL-C may be contained within Lp(a) particles; therefore, measurement of Lp(a) may also be warranted in anyone who presents with **LDL-C levels >194** mg/dL or **reduced responsiveness to statins**.

Management.

Pharmacologic treatments targeting Lp(a) are currently in development, with an **antisense oligonucleotide against Lp(a)** demonstrating up to an **80% lowering**. *Ongoing outcome studies* will establish *if there is a role for this agent to treat elevated Lp(a) in ASCVD prevention*. Until this is clarified, **management of other ASCVD risk factors** should be the **mainstay of treatment** for individuals with elevated Lp(a).

More aggressive LDL-C lowering than would otherwise be recommended based on cardiovascular risk assessment may be warranted in those with elevated Lp(a).

Of currently approved lipid agents, **statins can elevate Lp(a) levels**, but are nonetheless **considered first-line treatment in patients with high Lp(a)** because of their general benefit with respect to elevated ASCVD risk.

Ezetimibe has a **neutral effect on Lp(a)**, whereas **niacin lowers Lp(a).**

In a meta-analysis that included 6566 individuals, **PCSK9 inhibitors lowered Lp(a)** by 26%, although Lp(a) lowering is not currently an approved use for these agents.

MANAGEMENT

General principles for dyslipidemia management.

Clinical practice guidelines recommend LDL-C as the primary target of therapy to reduce ASCVD risk.

Management include:

- life style interventions
- Pharmacological therapy

LDL-C LOWERING AGENTS

Statins.

Statins are oral agents that inhibit HMGCR, thus depleting intracellular cholesterol and upregulating the LDL receptor, which in turn **increases LDL particle catabolism** and lowers plasma LDL-C levels.

Statins also have a **minor effect on reducing secretion of apo B-containing lipoproteins**. This resulting decrease in circulating LDL particles reduces the proportion of plasma cholesterol residing within LDL by 30% to 50% depending on agent, dose, pharmacogenetic factors, and compliance. This in turn **reduces exposure of the arterial wall to the deleterious effects of LDL**.

The definitive meta-analysis of 27 randomized statin trials found that **for each 38.7 mg/dL of LDL-C reduction**, there was a significant **9% reduction in all-cause mortality** and a **21% reduction in major ASCVD events**.

Statins are very widely used, are generally well tolerated, and only very rarely cause severe myopathy or hepatic toxicity.

About **10%** of patients report annoying **myalgia symptoms** (**usually occur within the first 4 to 6 weeks** after statin initiation but **may occur after several years** of treatment) , which can reduce compliance but are **reversible** and **not threatening to health**.

Some of the muscle symptoms reported with statins may be due to a **nocebo effect**.

Of the available statins**, simvastatin** may be **most associated** with SAMS, and **fluvastatin** the **least** . Muscle symptoms seem to be dose dependent but unrelated to the degree of LDL lowering.

With high doses of statins, there is **a small increased risk of developing diabetes** among predisposed individuals who would likely have developed this in any event.

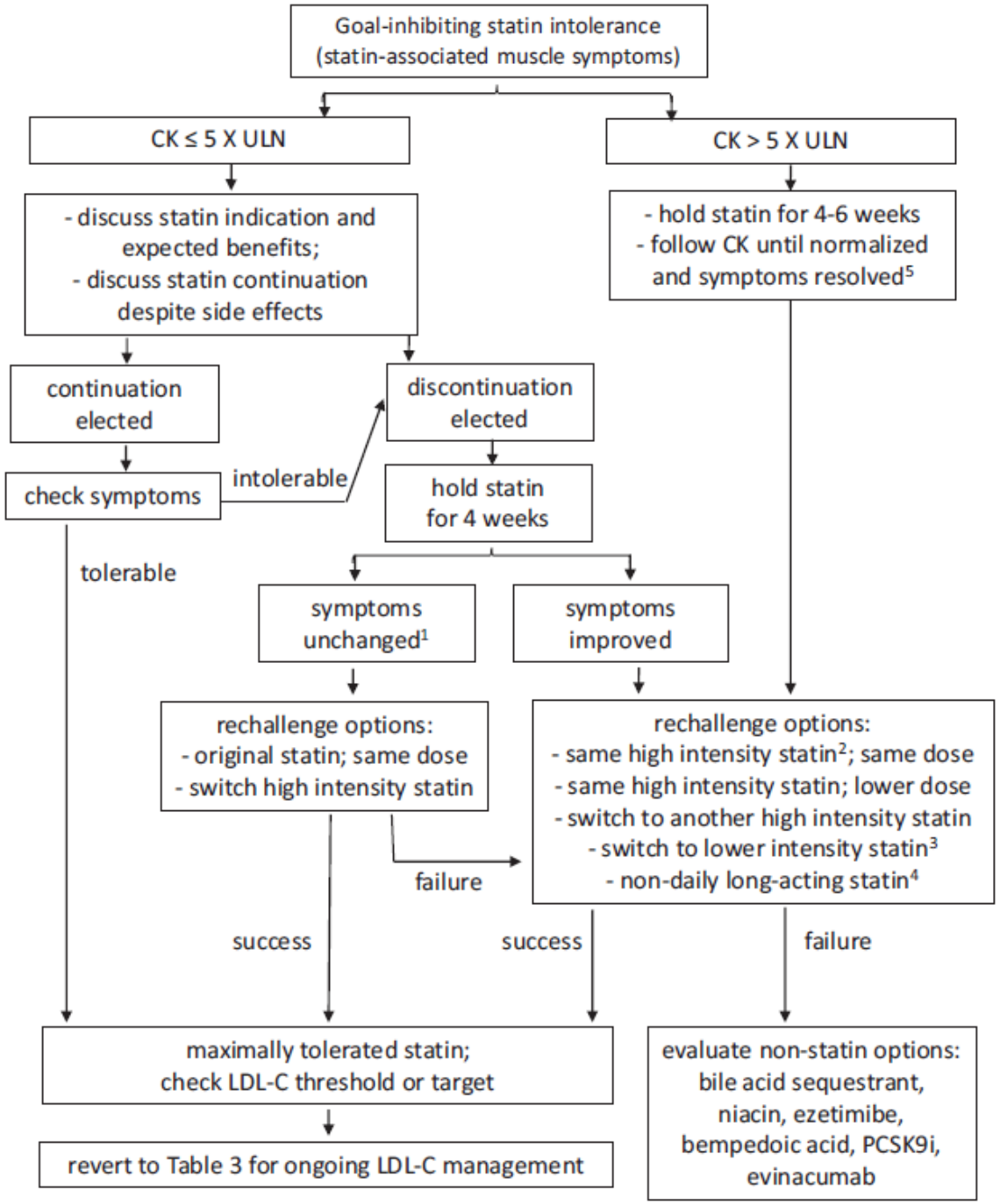

Figure 5. Approach to the patient with statin intolerance.

Cholesterol absorption inhibition.

Ezetimibe

- the only available cholesterol absorption inhibitor, inhibiting Niemann-Pick C1-like protein 1 in the upper small intestine.
- lowers LDL-C levels by 18% to 25%. the ezetimibe-statin combination can lower LDL-C by up to 70%.
- well tolerated with minimal side effects.
- The cardiovascular benefit
- second-line agent in clinical practice guidelines and is often prescribed to statin-intolerant patients.

PCSK9 inhibitors.

Two monoclonal antibodies are currently available for clinical use: **evolocumab** (trade name Repatha; Amgen) and **alirocumab** (trade name Praluent; Sanofi-Regeneron).

These agents are typically administered subcutaneously every 2 weeks, although monthly dosing is available.

Both agents **reduce both LDL-C and ASCVD** events when used in combination with a statin. **Evolocumab** induces **regression and reversal of coronary arterial plaques**.

Indications for PCSK9 inhibitors include patients with FH and patients with ASCVD who are above target LDL-C levels despite statin and/or ezetimibe therapy. These agents are very well tolerated, with only occasional mild injection site reactions, and are worth considering in patients with appropriate clinical indications. However, because of cost considerations, some treatment algorithms suggest that these agents should be considered only after statin and ezetimibe have been tried.

Bile acid sequestrants.

Bile acid sequestrants (BASs), such as cholestyramine, colestipol, and colesevelam, are **orally** administered basic anion-exchange resins that interrupt the enterohepatic recirculation, diverting hepatic cholesterol into bile synthesis and thus depleting intrahepatic cholesterol stores. The resulting **upregulation of the LDL receptor** increases LDL particle catabolism and **decreases LDL-C levels by 15% over statin monotherapy**.

Despite evidence for **reduction of ASCVD** end points and a **long safety record**, **compliance with BASs is poor** because of adverse gastrointestinal effects. Because BASs **raise serum TG**, they must be avoided in individuals with HTG.

BAS **third-line agents** at best for patients who **fail to reach target LDL-C** or who have **statin intolerance**.

Niacin.

Niacin—or nicotinic acid—is a third-line oral agent used in patients with mild-to-moderate dyslipidemia. Niacin 2 to 3 g daily can **lower plasma TG by up to 45**%, **raise plasma HDL-C by up to 25**%, and **reduce plasma LDL-C by up to 20**%.

After almost 6 decades of clinical use, niacin's mechanism of action remains unknown.

Niacin often causes light-headedness, skin flushing, and pruritus. Other adverse effects include elevated liver enzymes, gastrointestinal upset, worsened glucose tolerance, and elevated uric acid. **Adding extended-release niacin to statin therapy did not reduce ASCVD outcomes** in 2 pivotal trials. Thus, niacin is no longer recommended in treatment guidelines and its use has declined.

Lomitapide.

Lomitapide is a daily oral medication that was developed for the treatment of homozygous FH.

Lomitapide lowers LDL-C and TG each by 40% to 50% by **directly inhibiting assembly of apo B-containing lipoproteins** in the liver and intestine. Fatty liver is a mechanism-based adverse effect. However, ~25% of patients in short-term studies developed transaminase elevations and accumulation of hepatic fat, although this became less severe with prolonged treatment.

Fat-soluble vitamin supplements are often included with lomitapide treatment.

Extracorporeal LDL-C removal.

Extracorporeal removal of lipoproteins is achieved through either **weekly or biweekly** nonspecific **serial plasma exchange plasma exchange or plasmapheresis**, or specific targeted approaches to remove LDL or Lp(a) such as size exclusion columns or antibody-based affinity columns.

There are **no randomized ASCVD outcomes trials** with any of these methods, and their use varies widely, mainly to manage the lipid disturbances in severe hypercholesterolemia, especially HoFH or elevated Lp(a).

Untreated HoFH has been associated with premature mortality because patients have virtually no functional LDL receptors to upregulate, and statins have little to no effect. The mainstay of treatment in HoFH is one of several extracorporeal approaches to remove the LDL particles. Future use of apheresis may be reduced by some newer agents.

TG LOWERING AGENTS

Fibric acid derivatives (fibrates).

Fibric acid derivatives or fibrates, such as gemfibrozil, fenofibrate, bezafibrate, and ciprofibrate can **reduce plasma TG by up to 50%,** and can **raise plasma HDL-C by up to 20%.** Fibrates **modulate activity of hepatic PPAR-alpha**, down-regulating apo C-III expression and up-regulating apo A-I, fatty acid oxidation, and LPL activity, thereby increasing fatty oxidation and reducing VLDL production.

Because their **LDL-lowering is modest** and because recent clinical trials show **little to no benefit of fibrates added to statin therapy for ASCVD risk reduction** in patients with normal to mildly increased TG levels, fibrate use is mainly reserved for treatment of patients with severe HTG to reduce risk of acute pancreatitis.

Fibrates can also be considered as **add-on therapy** for patients with **high ASCVD risk who may need a second agent because TG remains markedly elevated**. (An ongoing randomized clinical trial of **pemafibrate)**

N-3 (omega-3) fatty acids.

Omega-3 fatty acids such as **eicosapentaenoic acid modestly lower triglyceride** levels by inhibiting de novo lipogenesis through suppression of sterol regulatory element-binding protein genes and by increasing both fatty acid oxidation and triglyceride catabolism through nonspecific activation of peroxisome proliferator activated receptor gene family members.

Omega-3 fatty acid preparations have **inconsistent evidence of reduction of ASCVD risk**.

Current treatment guidelines now advise that **for statin-treated patients with residual HTG up to 500 mg/dL, icosapent ethyl 4 g daily can be added to further reduce risk of ASCVD events**. However, other types of omega-3 preparations, including over-the-counter supplements are explicitly advised against in this context.

ABANDONED TREATMENTS

Table 9. Abandoned treatments for dyslipidemia

Treatment name	Mechanism of action	Year and reason development was abandoned
Mipomersen (trade name Kynamro)	Anti-apo B ASO	2016; adverse effects including skin reactions and hepatotoxicity
Torcetrapib	CETP inhibitor	2006; increased mortality in randomized trials
Evacetrapib	CETP inhibitor	2015; neutral effects in randomized trials
Anacetrapib	CETP inhibitor	2017; no obvious commercial path forward despite positive CV outcomes trial
Alipogene tiparvovec (trade name Glybera)	LPL gene therapy	2017; no obvious commercial path forward
Pradigastat	DGAT inhibitor	2017; adverse gastrointestinal effects

Abbreviations: ASO, antisense oligonucleotide; CETP, cholesterol ester transfer protein; CV, cardiovascular; DGAT, diacylglycerol acyltransferase.

NEW & EMERGING THERAPIES

Bempedoic acid.

Bempedoic acid (Esperion, Ann Arbor, MI) is an oral small molecule that acts in the cholesterol biosynthetic pathway **interfering with ATP-citrate lyase** upstream of HMGCR.

Bempedoic acid 180 mg daily reduces LDL-C by 15% to 20% from baseline either as monotherapy or when taken with background statin therapy.

When **bempedoic acid 180 mg daily and ezetimibe** 10 mg daily were taken together, **LDL-C was reduced by 50%.** Although **serious side effects have not been reported to date**, blinded clinical trial patients randomized to receive bempedoic acid were more likely to discontinue treatment, often because of **headaches.**

Bempedoic acid was approved in 2020 by the **FDA for LDL-C reduction** both as monotherapy 180 mg and in combination with ezetimibe 10 mg.

Potential indications for bempedoic alone and in combination with ezetimibe or PCSK9 inhibitors include **helping patients achieve lower LDL-C than is possible while taking the maximally tolerated statin dose**.

A large **cardiovascular outcome study** of bempedoic acid in patients with statin intolerance has been **initiated**.

Inclisiran.

Inclisiran (trade name Leqvio, Novartis) is a **small interfering RNA (siRNA) against PCSK9 conjugated to triantennary N-acetylgalactosamine (GalNAc)** administered subcutaneously that **reduces LDL cholesterol by 50% to 60%.** Inclisiran's siRNA-based mechanism of inhibiting PCSK9 differs from monoclonal antibodies because **it interferes with intracellular PCSK9 before its secretion**. Also, inclisiran **does not interact directly with LDL particles or LDL receptors**.

Inclisiran is notable for its **long duration of action**, with sustained reductions of both circulating PCSK9 and LDL-C persisting **between 6 and 12 months after a single injection**.

Meta-analysis showed that **inclisiran reduced risk of major ASCVD events**: risk ratio 0.76 (95% CI, 0.61-0.92, $P < 0.01$). Besides an increase in mild injection site reactions, adverse effects were not different between groups.

Inclisiran was approved in the **European Union** in December 2020 and in **Canada** in July 2021 **for use in adults with primary hypercholesterolemia**, either FH or nonfamilial, or with mixed dyslipidemia, as an **adjunct to diet**. A unique but controversial collaboration between the **NHS in the UK** and inclisiran's manufacturer is in the midst of **developing a plan for launching the drug**.

If inclisiran's indication can be expanded to reduction of ASCVD end points, and if cost is reasonable, it will likely be useful in many clinical situations, including in patients with **FH** and/or **established or high ASCVD risk** with recalcitrant LDL-C levels, **statin-intolerant patients**, and **noncompliant patients**.

A large-scale prospective **cardiovascular outcomes** study of inclisiran is currently **ongoing**.

Table 8. Currently available lipid-lowering therapies

Class	Agent	Dose	Mechanism of action	Main indication	Comments
Statin	Lovastatin	20-80 mg/d	Inhibits HMG CoA reductase	ASCVD prevention	↓LDL-C by 25%-40%
	Simvastatin	20-80 mg/d	Inhibits HMG CoA reductase	ASCVD prevention	↓LDL-C by 30%-45%
	Pravastatin	20-80 mg/d	Inhibits HMG CoA reductase	ASCVD prevention	↓LDL-C by 25%-40%
	Fluvastatin	20-80 mg/d	Inhibits HMG CoA reductase	ASCVD prevention	↓LDL-C by 22%-40%
	Atorvastatin	10-80 mg/d	Inhibits HMG CoA reductase	ASCVD prevention	↓LDL-C by 35%-50%
	Rosuvastatin	5-40 mg/d	Inhibits HMG CoA reductase	ASCVD prevention	↓LDL-C by 35%-55%
	Pitavastatin	1-4 mg/d	Inhibits HMG CoA reductase	LDL-C reduction	↓LDL-C by 22%-40%
CAI	Ezetimibe	10 mg/d	Blocks NPC1L1	ASCVD prevention	↓ LDL-C by 18%-25% as monotherapy or added to statin
BAS	Cholestyramine	8-24 g/d	Depletes liver cholesterol	ASCVD prevention	↓ LDL-C by 8%-20% as monotherapy or added to statin
	Colesevelam	0.625-3.75 g/d	Depletes liver cholesterol	LDL-C reduction	↓ LDL-C by 8%-20% as monotherapy or added to statin
PCSK9 MAb	Evolocumab	140 mg every 2 weeks or 420 mg q 4 weeks	Prevents LDLR degradation	ASCVD prevention	↓ LDL-C by 50%-70% as monotherapy or added to statin
	Alirocumab	75 or 150 mg Every 2 weeks	Prevents LDLR degradation	ASCVD prevention	↓ LDL-C by 50%-70% as monotherapy or added to statin
PCSK9 siRNA	Inclisiran	300 mg SC every 3-6 mo	Prevents LDLR degradation	LDL-C reduction	↓LDL-C by 45%-55%
Fibrates	Gemfibrozil	600 mg BID	PPAR-alpha agonist	TG reduction	↓ TG by 20%-40%
	Fenofibrate	145, 160, 200 mg/d	PPAR-alpha agonist	TG reduction	↓ TG by 20%-40%
	Bezafibrate	400 mg/d	PPAR-alpha agonist	TG reduction	↓ TG by 20%-40%
	Pemafibrate	0.1-0.2 mg/d	PPAR-alpha agonist	TG reduction	↓ TG by 20%-40%
EPA	Icosapent ethyl	2 g BID	Highly pleiotropic	ASCVD prevention	↓ TG by 15%-20%
	Epanova	2 g BID	Unknown	TG reduction	↓ TG by 15%-20% Mixture of n-3 FAs
Other	Lomitapide	10-80 mg/d	MTP inhibitor	LDL-C reduction	↓LDL-C by 30%-50% and ↓TG by 15%-40%
	Nicotinic acid	2-3 g/d	Unclear	↓ LDL-C and TG	↓LDL-C by 15%-20% and TG by 20%-30%; no CV benefit; declining use
	Bempedoic acid	180 mg/d	Inhibits ACLY	LDL-C reduction	↓ LDL-C by 15%-20% as monotherapy or added to statin
	BA + ezetimibe	180 mg + 10 mg/d	Inhibits ACLY + blocks NPC1L1	LDL-C reduction	↓LDL-C by 50%

Abbreviations: ACLY, ATP-citrate lyase; ASCVD, atherosclerotic cardiovascular disease; ASO, antisense oligonucleotide; BA, bempedoic acid; BAS, bile acid sequestrant; BID, twice daily; CAI, cholesterol absorption inhibitor; CV, cardiovascular; HMG CoA; 3-hydroxy-3-methylglutaryl-coenzyme A; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; MAb, monoclonal antibody; MTP, microsomal triglyceride transfer protein; NPC1L1, Niemann-Pick C-like transporter; PCSK9, proprotein convertase subtilisin/kexin 9; PPAR, peroxisome proliferator-activated receptor; SC, subcutaneously, siRNA, short interfering ribonucleic acid; TG, triglyceride.

Gemcabene.

Gemcabene calcium (Gemphire Therapeutics, Ann Arbor, MI) is an **oral** small molecule, with a symmetrical molecular structure including dicarboxylic acid and 2 terminal gem dimethyl carboxylate moieties.

Gemcabene is being developed as **first-in-class agent**: the 300- and 900- mg daily doses **reduced LDL-C by 23% and 28%,** respectively, over background statin therapy.

If approved, **potential indications for gemcabene** would be **similar to those for bempedoic acid**.

Targeting apolipoprotein C-III: volanesorsen; AKCEA-APOCIII-LRx; AROAPOC3.

Apo C-III is a 79 amino acid protein expressed in the liver and intestine and is a component of TG-rich lipoproteins.

human genetic studies have solidified apo C-III as a treatment target both for both severe and mild-to-moderate HTG to prevent acute pancreatitis and ASCVD, respectively.

The first agent developed to target apo C-III was the **antisense oligonucleotide (ASO) RNA drug volanesorsen** (Waylivra, Akcea Pharmaceuticals).

Two **phase 3** multicenter, randomized, double-blind, placebo controlled clinical trials of volanesorsen have been published:

- APPROACH—A Study of ISIS 304801 in Patients With Familial Chylomicronemia Syndrome (N = 66) and
- COMPASS—A Study of Volanesorsen in Patients With Hypertriglyceridemia (N = 114).

Results were comparable in these 2 studies: at 3 months, patients on volanesorsen **had -77% and -71% decreases in plasma TG levels**, respectively, as well as **favorable changes on the rest of the lipid profile**.

Although not powered to address prophylaxis of acute pancreatitis, reduced frequency of events was observed across the 2 studies in patients receiving volanesorsen.

However, among patients with FCS, volanesorsen was associated with **risk of thrombocytopenia**, which was profound in a few cases. In August 2018, the US **FDA** announced that it **did not approve** volanesorsen. **The European Medicines Agency**, in contrast, has **approved** volanesorsen for **FCS** with some caveats. Thrombocytopenia appears to be a **drug-specific side effect, rather than a class effect** of all agents that target apo C-III.

Development of a next-generation **GalNac-conjugated ASO targeting apo C-III**, namely **AKCEA-APOCIII-LRx**, appears to mitigate thrombocytopenia risk while preserving beneficial effects.

Also, a promising siRNA molecule called AROAPOC3 (Arrowhead Pharmaceuticals) that is currently in **early-phase clinical trials** may avoid this risk while retaining the metabolic benefits of targeting apo C-III.

Targeting ANPTL3: evinacumab, vupanorsen and AROANG3.

ANGPTL3 is a liver-derived protein that broadly regulates lipid metabolism, primarily through **inhibiting plasma lipases**. **Loss-of function mutations** in *ANGPTL3* cause **familial combined hypolipidemia**, in which patients have **pan-hypolipidemia**, along with **reduced ASCVD risk** and no obvious detrimental effects.

This genetic “experiment of nature” supports the idea that knocking down ANGPTL3 will have clinical benefits.

Three approaches to reduce ANGPTL3 levels in early clinical development include:

- the monoclonal antibody **evinacumab** (trade name Evkeeza, Regeneron)
- the ASO **vupanorsen** (IONIS-ANGPTL3-LRx, Akcea and Pfizer)
- the siRNA **AROANG3** (Arrowhead Pharmaceuticals).

Evinacumab (monoclonal Ab) 450 mg given subcutaneously weekly **lowered LDL-C by 56%** over background therapy in patients with severe refractory hypercholesterolemia, with and without FH.

No adverse effects have been noted so far in these small, short-term studies of evinacumab.

Given the paucity of effective treatment options in **homozygous FH**, evinacumab is promising, especially because **frequency of apheresis treatments can likely be reduced**. Evinacumab was **approved** in February 2021 by the US **FDA** as an **adjunct to other LDL-C-lowering therapies** for adult and pediatric patients >12 years with homozygous FH, but not without controversy in light of its hefty price tag. It also received a **positive opinion in 2021 from the European Medicines Agency.**

The efficacy and potential role of evinacumab in **FCS and severe HTG are under evaluation**, but preliminary reports appear **promising**.

Vupanorsen is a GalNac-modified ASO targeting ANGPTL3 which in a dose-ranging study in patients with **mild hypertriglyceridemia and fatty liver showed reductions in plasma TG and LDL** cholesterol of 44% and 7%, respectively, with **no safety signals**.

Early efficacy studies of the **siRNA AROANG3** apparently show **similar efficacy** across the lipoprotein profile.

OTHER TARGETS FOR HYPERTG

Additional potential treatment targets for patients with HTG include apo C-II and ANGPTL4.

Apo C-II is a cofactor for LPL, and **complete deficiency** accounts for **2% to 5% of FCS cases**, with ~20 reported human mutations. This **very rare subgroup** of patients might **theoretically benefit from infusion of an apo C-II** peptide that is under development.

Similar to ANGPTL3, **ANGPTL4 regulates LPL activity**. But targeting ANGPTL4 with a **monoclonal antibody** in preclinical models was associated with **mesenteric adenitis**, which has curbed enthusiasm for pursuing this target in humans.

Lp(a) as a target.

Both **niacin and serial apheresis** treatments were **previously recommended to reduce Lp(a)** but each has significant drawbacks and **neither reduced ASCVD events**.

PCSK9 inhibitors—both monoclonal antibodies and inclisiran— lower Lp(a) by 26%, but this is **insufficient for individuals with very high Lp(a) levels**.

A **GalNAc-linked ASO against Lp(a)** (TQJ230, trade name **pelacarsen**, Novartis) reduces its levels by **80% to 90%** with no effect on other variables; this agent is being evaluated in a large randomized of secondary prevention of ASCVD in individuals with elevated Lp(a) levels.

An **siRNA** compound aimed at reducing apo(a) synthesis (AMG 890, trade name **olpasiran**, Amgen) is also **under investigation**. Depending on results of outcome trials, these agents could be helpful for patients with elevated Lp(a) levels.

HDL as a target.

HDL has been demoted as a therapeutic target based on a preponderance of genetic and clinical trial evidence, although HDL-C levels remain excellent predictors of ASCVD risk. But because of **failure of clinical trials of numerous HDL-raising therapies**, such as **oral inhibitors of CETP and long-acting niacin**, drug development has focused on apo B-containing lipoproteins and remnant particles, rather than HDL-raising.

Similarly, infusion of HDL mimetics or apo A-I peptides has not proven to be beneficial with respect to ASCVD risk reduction, although clinical trials of this approach are ongoing.

It remains possible that **HDL function rather than quantity** will prove to be a clinically relevant target.

In contrast to pursuing HDL-raising for ASCVD protection in the general population, there is ongoing drug development activity for rare patients with monogenic conditions of low to absent HDL-C:

- for patients with **LCAT deficiency**, treatments in development include **enzyme replacement therapy**, liver-directed **gene therapy, engineered cell therapies**, and **infused peptides**.
- Patients with **Tangier disease** likewise represent a priority for development of orphan **treatments targeting ATP binding cassette transporter A1**.
- Similarly, for rare patients with **apo A-I deficiency**, there remain **active drug development programs**, especially for the subgroup of these patients that develops systemic amyloidosis.

ESSENTIAL POINTS

- We suggest a simplified overall approach to classification and management of patients with dyslipidemias: hypercholesterolemia, hypertriglyceridemia, combined dyslipidemia or other.
- Additional tests such as apo B and Lp(a) can help precisely stratify vascular disease risk.
- Genetic testing may be helpful when monogenic dyslipidemias are strongly suspected.
- Hypercholesterolemia from elevated LDL-C is managed according to guidelines using statins, ezetimibe and anti-PSCK9 monoclonal antibodies; inclisiran, bempedoic acid and evinacumab are poised to fill unmet clinical needs.
- Intervention to prevent ASCVD in hypertriglyceridemia is currently limited to icosapent ethyl.
- Severely elevated TG levels can be reduced by fibrates to prevent pancreatitis; new agents targeting apo C-III mRNA will also be helpful for patients.
- Antisense agents and monoclonal antibodies targeting ANGPTL3 can correct several hyperlipidemias.
- Utility of antisense agents targeting Lp(a) will depend on cardiovascular outcome trials.
- Ruling out secondary factors, encouraging a prudent diet, exercise, and weight loss, along with global risk factor control remain the cornerstones of dyslipidemia management.