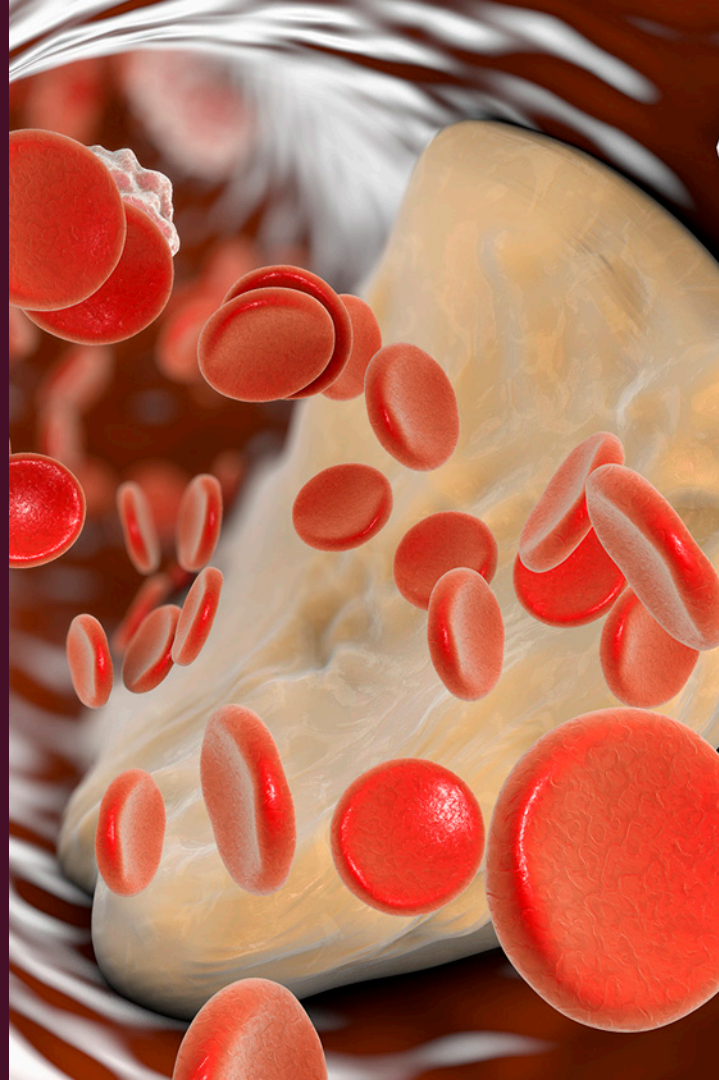
Who Gains the Most from Intensive Dyslipidemia Therapy?

Om P. Ganda, MD



Om Ganda Disclosures

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  Boehringer-Ingelheim / Eli Lilly
- Editorial Board

  Dynamed Plus
- No Stocks or Options in any Pharma/Biotech

ACC/AHA Lipid Guidelines: Secondary ASCVD Prevention

Very High Risk for Future ASCVD Events

≥ 2 Major ASCVD Events

- Recent acute coronary syndrome (within the past 12 months)
- History of myocardial infarction (other than recent acute coronary syndrome event listed above)
- History of ischemic stroke
- Symptomatic peripheral arterial disease (history of claudication with ankle-brachial index <0.85 or previous revascularization or amputation)

? LP(a)
? TG or TRL-C

1 Major and ≥ 2 High-Risk Conditions

- Age ≥65 years
- HeFH
- History of prior CABG or PCI outside of the major ASCVD event(s)
- DM
- Hypertension
- CKD (eGFR 15-59 mL/min/1.73 m^2)
- Current smoking
- Persistently elevated LDL-C ≥100 mg/dL despite maximally tolerated statin therapy and ezetimibe
- History of congestive heart failure

Grundy SM, et al. *Circulation*. 2018;online.

ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	• Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL • Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH • History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	• Established or recent hospitalization for ACS, coronary, carotid, or peripheral vascular disease, 10-year risk >20% • DM or stage 3 or 4 CKD with 1 or more risk factor(s) • HeFH	<70	<100	<80
High risk	• ≥2 risk factors and 10-year risk 10%-20% • DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Jellinger P, et al. *Endocr Practice*. 2017;23:479-97.

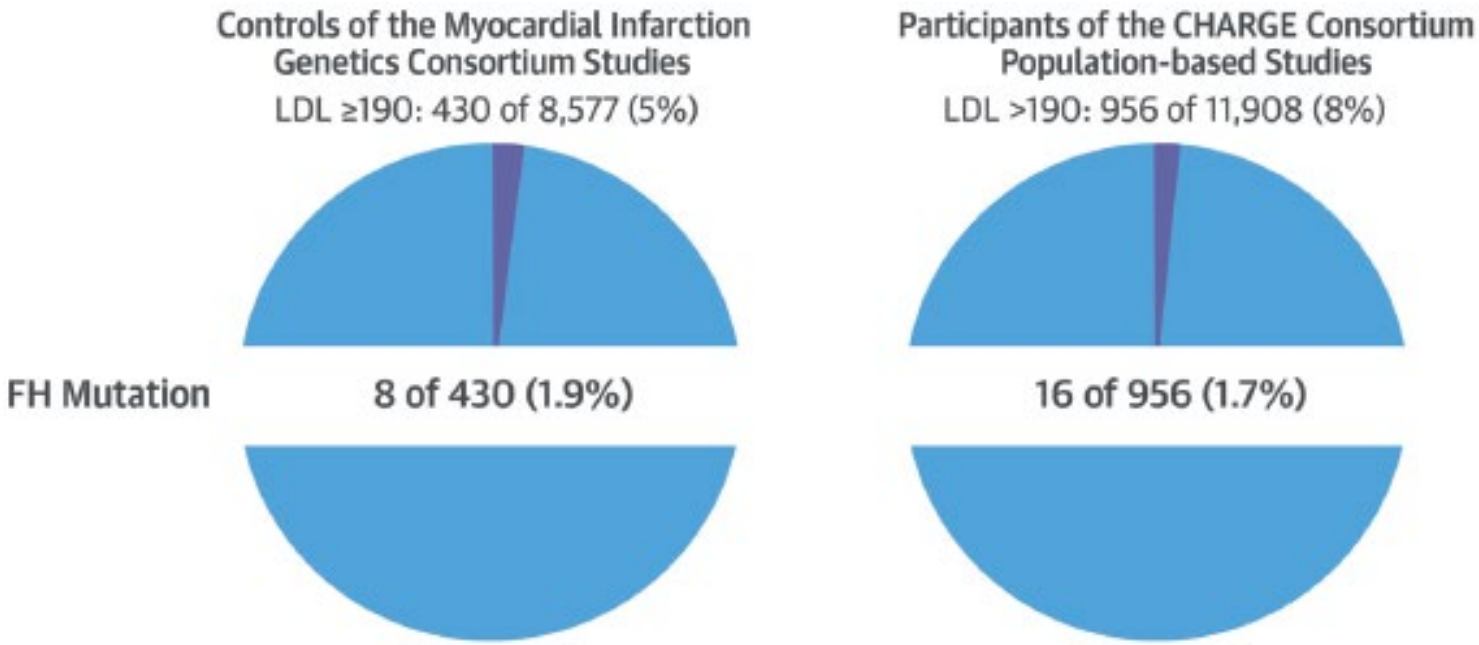
2019 ESC/EAS Guidelines

If 2nd ASCVD event in < 2.0 years, on maximally tolerated statin:

Consider LDL-C goal of < 40, non-HDL-C < 75, and apo-B < 65 mg/dL

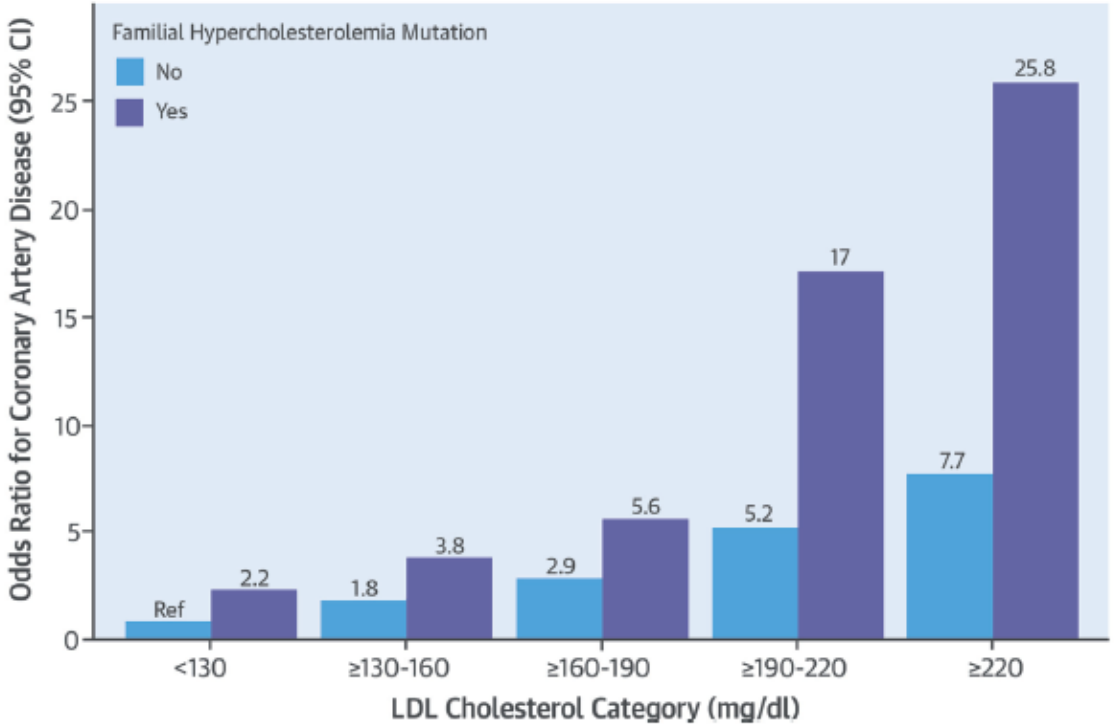
Eur Heart J. 2020;41:111-88.

Fine-tuning the Risk Level: FH Mutations Among Those with LDL-C ≥ 190 mg/dL



Khera AV, et al. *J Am Coll Cardiol*. 2016;67(22):2578-89.

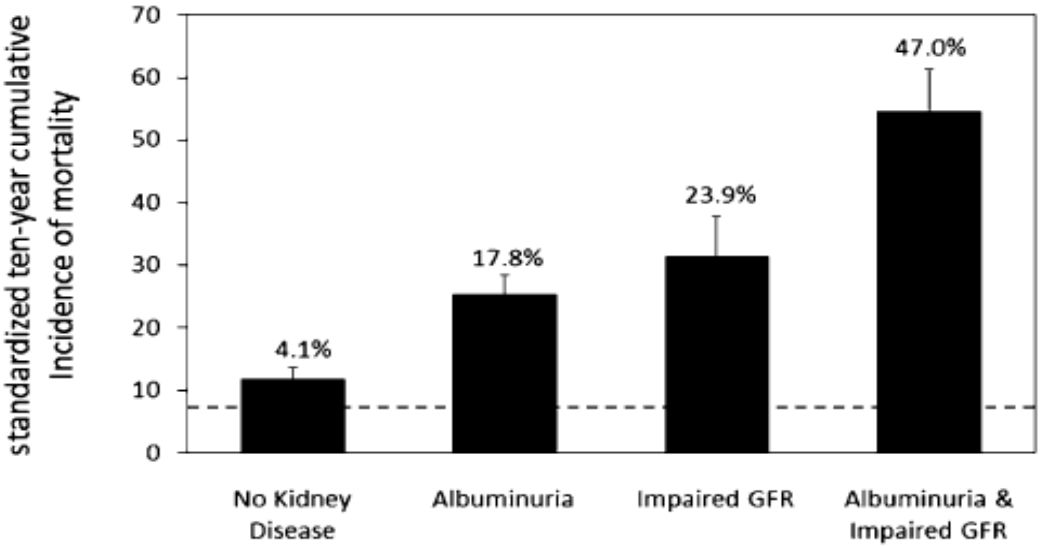
FH Mutation Status and CAD by LDL-C



Khera AV, et al. *J Am Coll Cardiol*. 2016;67(22):2578-89.

Excess Mortality in Type 2 Diabetes Is Due to Kidney Disease

NHANES III data, n=13,616 (no DM); 1,430 (DM); 10-year follow- up, adjusted for age, sex, and race



Afkarian M, et al. *J Am Soc Nephrol*. 2013;24(2):302-8.

NHANES III: 10-Year All-Cause and CV Mortality

	Number of Events	Standardized Cumulative Incidence, % (95% CI)	Adjusted Difference in Cumulative Incidence, % (95% CI)	
			Model 1	Model 2
All-cause mortality				
None	1027	7.7 (7.0–8.3)	0 (Reference)	0
Diabetes	168	11.5 (7.9–15.2)	3.9 (0.1–7.7)	3.4 (−0.3 to 7.0)
Kidney disease	750	17.2 (14.6–19.7)	9.5 (7.0–12.0)	9.0 (6.6–11.4)
Diabetes and kidney disease	332	31.1 (24.7–37.5)	23.4 (17.0–29.9)	23.4 (17.2–29.6)
Cardiovascular mortality				
None	347	3.4 (3.1–3.7)	0	0
Diabetes	68	6.7 (4.2–9.1)	3.3 (0.7–5.8)	3.0 (0.3–5.6)
Kidney disease	343	9.9 (7.9–11.9)	6.5 (4.5–8.5)	6.1 (4.0–8.1)
Diabetes and kidney disease	155	19.6 (14.7–24.4)	16.1 (11.2–21.0)	16.0 (11.1–20.9)
Noncardiovascular mortality				
None	663	5.7 (5.2–6.3)	0	0
Diabetes	97	7.2 (3.9–10.5)	1.5 (−2.0 to 4.9)	1.1 (−2.1 to 4.2)
Kidney disease	404	11.7 (9.5–13.9)	6.0 (3.9–8.1)	6.0 (4.0–7.9)
Diabetes and kidney disease	174	23.2 (16.5–29.9)	17.5 (10.6–24.3)	18.1 (11.4–24.8)

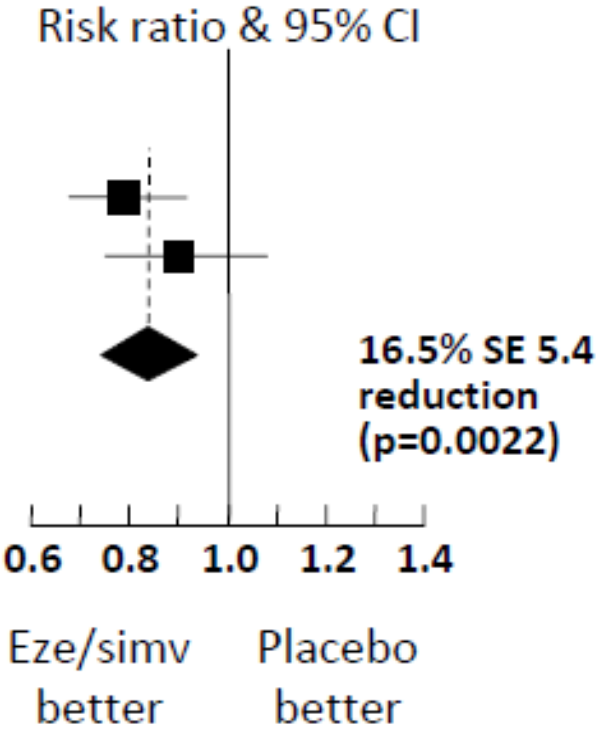
Model 1: adjusted for age, sex, race; Model 2: also adjusted for cholesterol, BP, smoking.

Afkarian M, et al. *J Am Soc Nephrol*. 2013;24(2):302-8.

SHARP: Major Atherosclerotic Events by Renal Status at Randomization

	Eze/simv (n=4650)	Placebo (n=4620)
Non-dialysis (n=6247)	296 (9.5%)	373 (11.9%)
Dialysis (n=3023)	230 (15.0%)	246 (16.5%)
Major atherosclerotic event	**526 (11.3%)**	**619 (13.4%)**

No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)

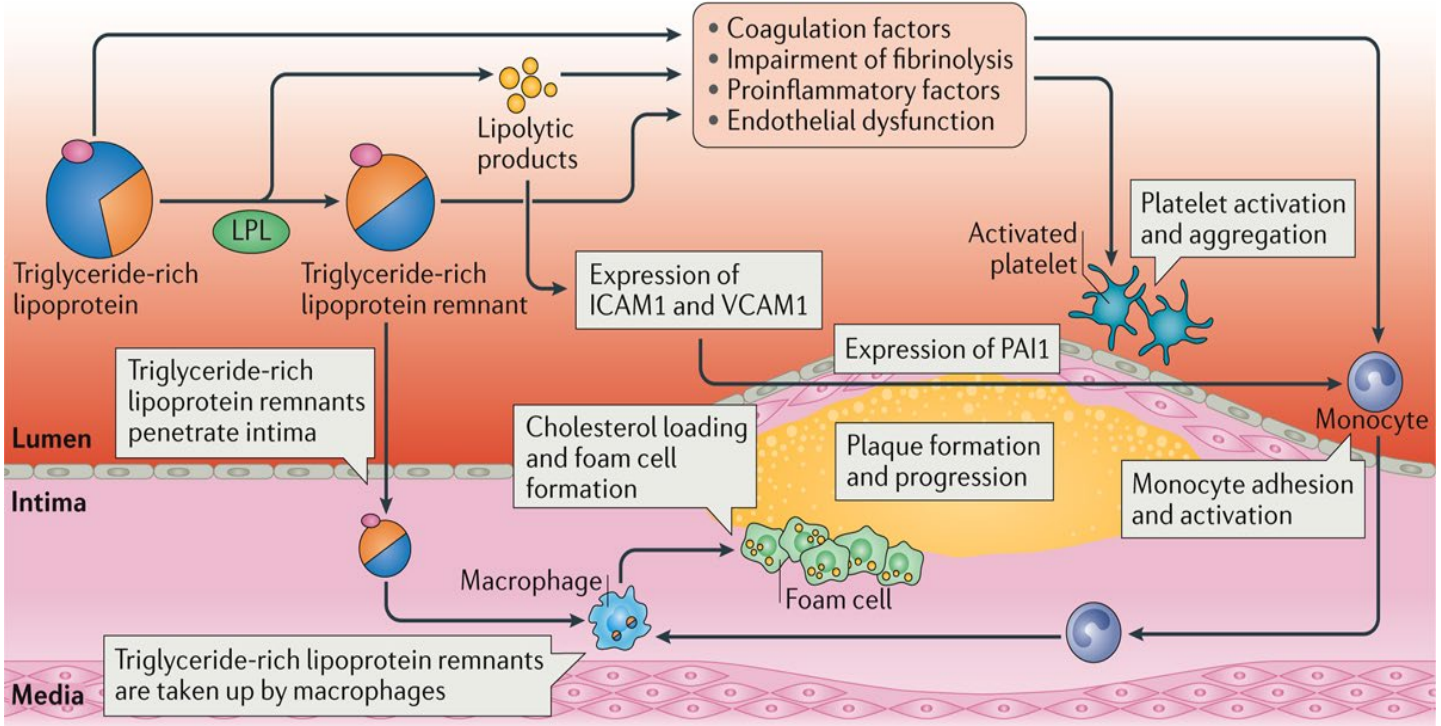


Baigent C, et al. *Lancet.* 2011;377(9784):2181-92.

TG-Rich Lipoproteins (TRLs): Postulated Mechanisms in Atherogenesis

Direct Toxic Effects

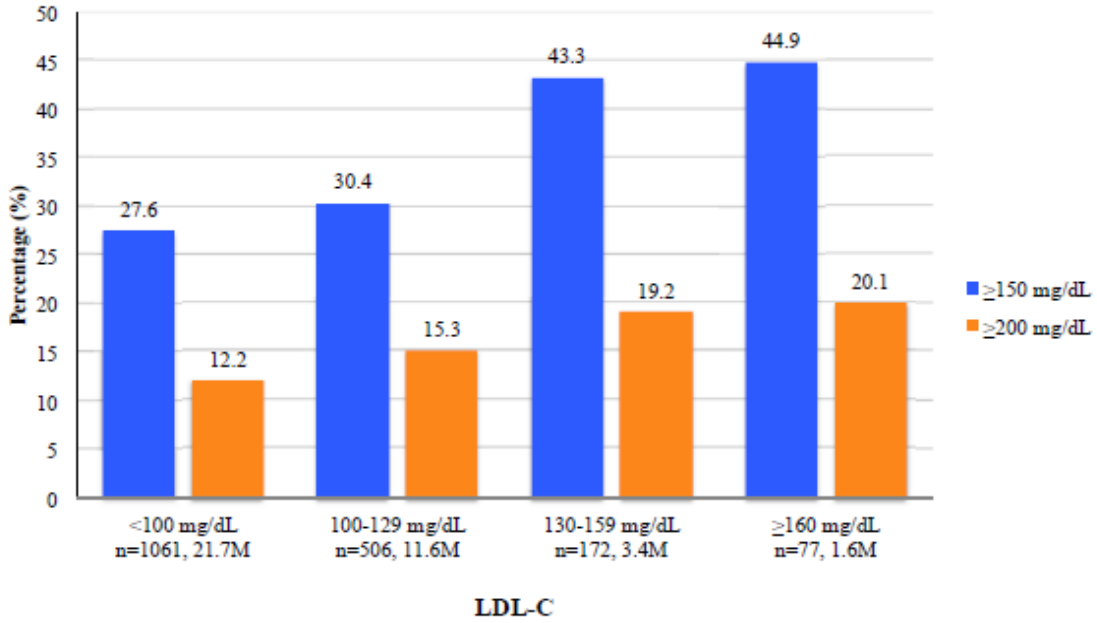
Remnant Cholesterol Entrapment



Reiner Z. *Nate Rev Cardiol.* 2017;14(7):401-11.

Estimated Proportion of Subjects with High TG by LDL-C Category (on Statins)

NHANES 2007-2014; n= 9,593

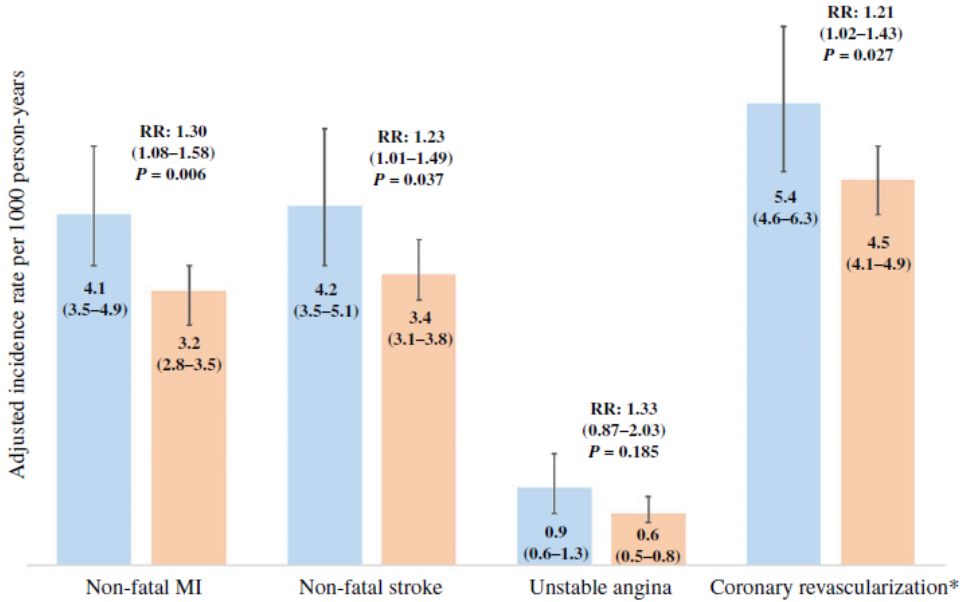


Prevalence even higher in the obese, DM/pre-DM, NW Hispanics

Fan W, et al. *J Clin Lipidol* 2019;13(1):100-8.

Incidence Rates of ASCVD Events by TG in Statin-Treated Subjects with DM

n=5,542 (DM), 22,411 (no DM), mean age 64 yr, LDL-C 40-100 (mean 72), TG mean 251 mg/dL; Follow- up, 2000-2016, (mean 5.3 yr); Kaiser database

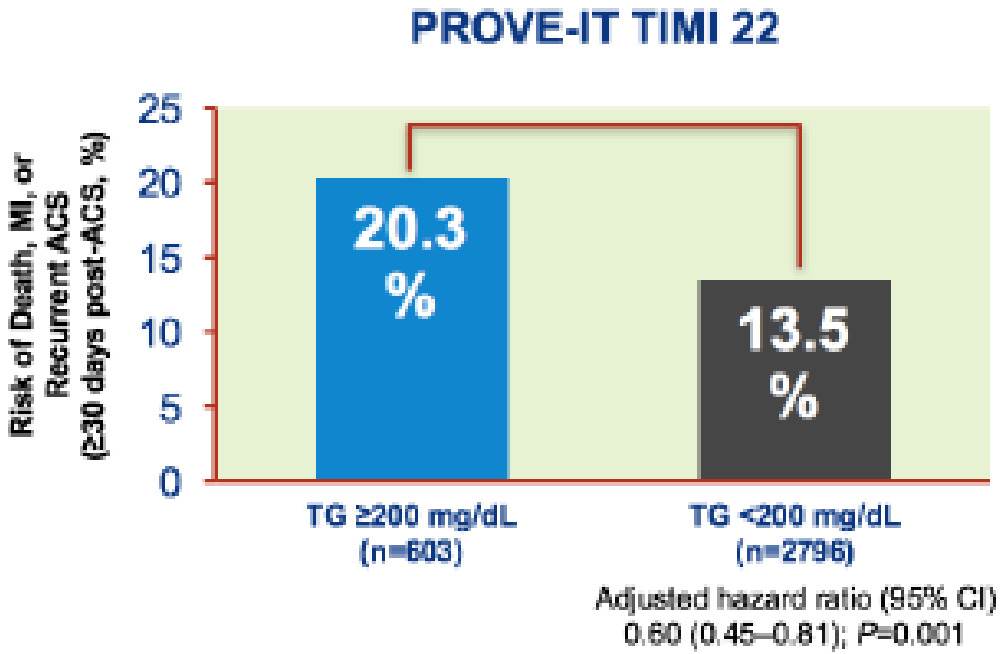


(■) TG 200-499 mg/dL, and (■) TG < 150 mg/dL

Adjusted for age, sex, smoking, A1C, BP, serum creatinine, prior IHD

Nichols GA, et al. *Diabetes Obes Metab.* 2019;21(2):366-71.

Residual Risk Associated with High TG Despite LDL-C < 70 mg/dL on Statin



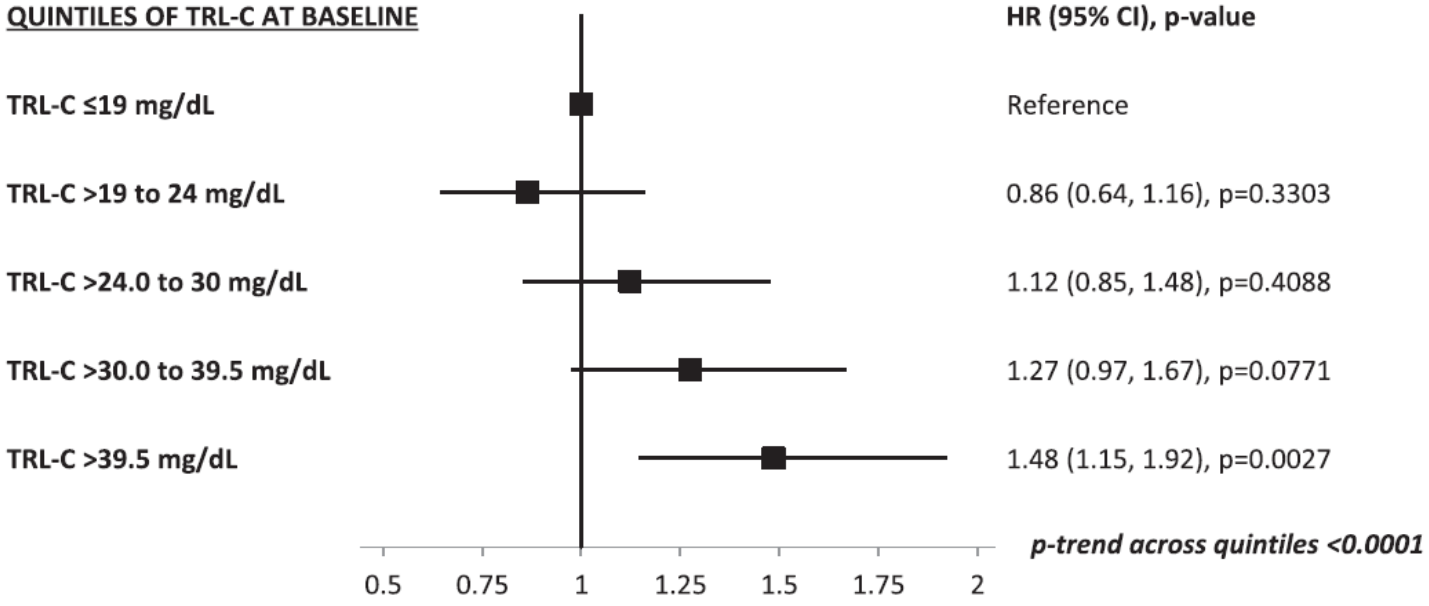
Miller M, et al. *J Am Coll Cardiol*. 2008;51(7):724-30.

5-Year CV Event Rates in RCTs by TG Levels in Placebo/Control Group, with or without DM

Trial (s)	n	Mean Duration (Yrs)	Rate /5 years (%)
CTT – meta in DM (14 RCTs)	**~9,350**	**4.3**	
TG < 124 mg/dL			**18.1**
TG > 177 mg/dL			**25.0**
PROVE-IT (LDL< 70 mg/dL)	**4,162**	**2.0**	**2.0 yr event rates**
TG < 150 mg/dL			**11.7**
TG ≥ 150mg/dL			**16.5**
TNT (stable CHD)	**9,901**	**5.0**	
TG 120-150 mg/dL			**10.1**
TG 150-198 mg/dL			**12.4**
ACCORD-Lipid (DM)	**2,753**	**4.7**	
TG < 203 and HDL < 34 mg/dL			**10.8**
TG ≥ 203 and H ≥ 34 mg/dL			**18.4**
REDUCE-IT	**4,090**	**4.9**	
TG < 200 mg/dL			**21.5**
TG ≥ 200 mg/dL			**23.1**

TNT: Major CVE by TRL-C at Baseline

n=9,903; on atorvastatin 10 mg



Vallejo-Vaz AJ, et al. *Circulation* 2018;138(8):770-81.

Multivariate Mendelian Analyses of the Association of TG, LDL-C, Apo-B with Risk of CHD

63 cohort or case-control studies; 186 genetic variants

Analysis	Variables	Odds Ratio for CHD (95% CI)	*P* Value
Association of 10-mg/dL lower ApoB with risk of CHD	ApoB	0.770 (0.760-0.781)	1.42E-170
Association of 10-mg/dL lower LDL-C with risk of CHD	LDL-C	0.846 (0.833-0.858)	8.16E-77
Association of 50-mg/dL lower triglycerides with risk of CHD	Triglycerides	0.815 (0.785-0.846)	1.37E-18
Association of 10-mg/dL lower LDL-C and 50-mg/dL lower triglycerides with risk of CHD included in same model	LDL-C	0.862 (0.849-0.875)	6.92E-65
	Triglycerides	0.876 (0.850-0.902)	1.36E-14
Association of 10-mg/dL lower LDL-C, 50-mg/dL lower triglycerides, and 10-mg/dL lower ApoB with risk of CHD included in same model	ApoB	0.761 (0.723-0.798)	7.51E-20
	LDL-C	1.010 (0.967-1.055)	.19
	Triglycerides	1.014 (0.965-1.065)	.19

Ference BA, et al. *JAMA*. 2019;321(4):364-73.

PROMINENT: Study Design

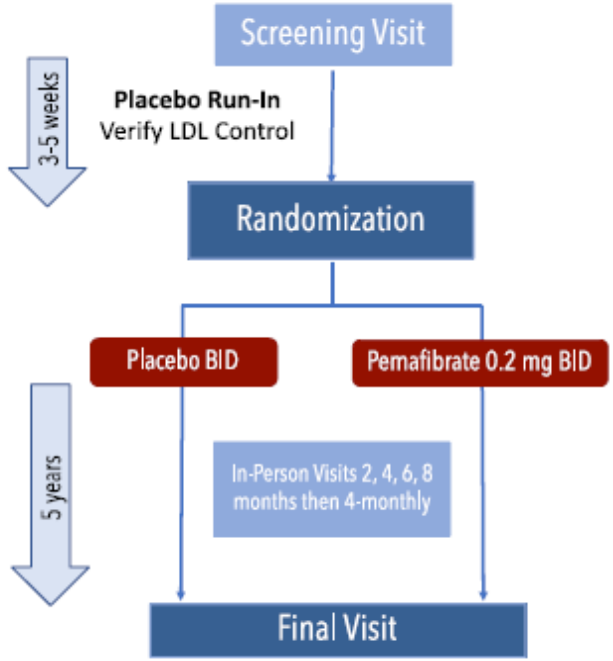
TG 200-499 mg/dl (2.26-5.64 mM) and HDL ≤ 40 mg/dl (1.03 mM)
Moderate-High Intensity Statin Therapy or LDL-C Control
(≤70 mg/dl other therapy or ≤100 mg/dl if statin intolerant)
1/3 Primary Prevention, 2/3 Secondary Prevention

ENDPOINTS

Event Driven: 1092 Primary Endpoints, 200 in ♀

PRIMARY ENDPOINT (MACE+):
Myocardial infarction, ischemic stroke, or unstable angina requiring unplanned revascularization, cardiovascular death.

Secondary/Tertiary Endpoints: all-cause mortality, any coronary revascularization, heart failure, total stroke, retinopathy, nephropathy, glycemic control, PAD, biomarkers, QOL



Pradhan AD, et al. *Am Heart J*. 2018;206:80-93.

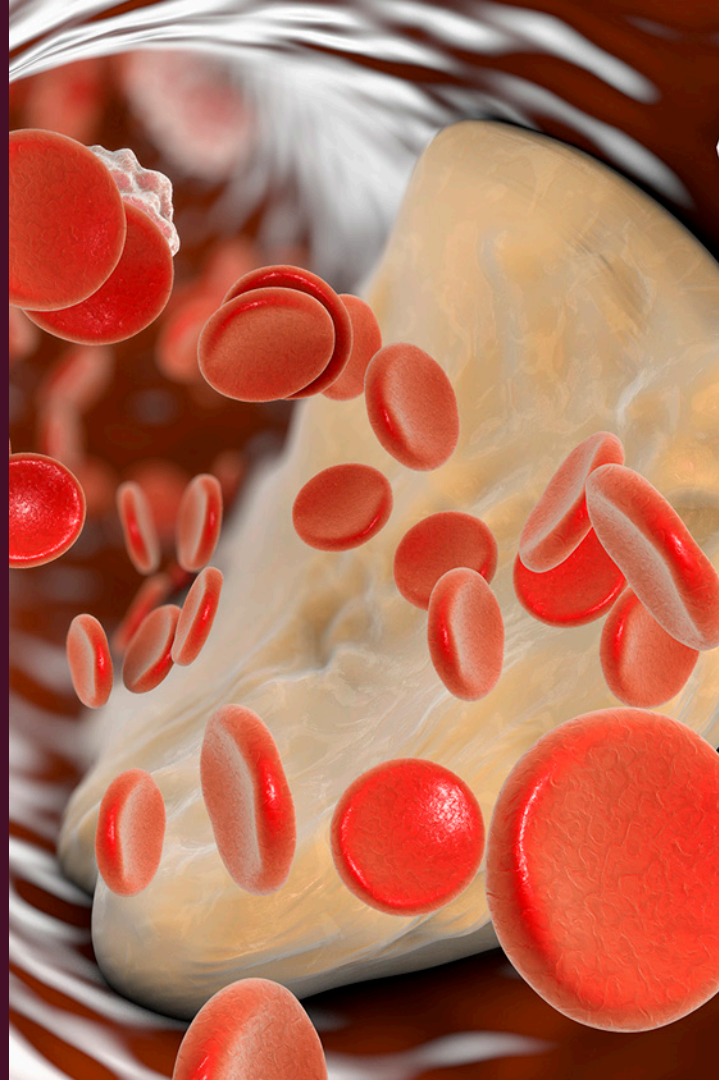
NCT 03071692

Conclusion

More to learn about TG, TRL-C, and ASCVD risk

Options for Dyslipidemia Therapies in 2020

Yehuda Handelsman, MD, FACP, FNLA, FASPC, MACE
Chair



Statins: Starting Doses and Dosage Ranges

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Statins			
Lovastatin	20 mg	10–80 mg	Oral
Pravastatin	40 mg	10–80 mg	Oral
Simvastatin	20–40 mg	5–80 mg[a]	Oral
Fluvastatin	40 mg	20–80 mg	Oral
Atorvastatin	10–20 mg	10–80 mg	Oral
Rosuvastatin	10 mg	5–40 mg	Oral
Pitavastatin	2 mg	2–4 mg	Oral

[a] Simvastatin, 80 mg, not approved for therapy unless individual has been on treatment for more than 1 year without myopathy.

Crestor (rosuvastatin calcium); [PI]; 2016; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Lescol (fluvastatin sodium) [PI]; 2012 Lipitor (atorvastatin calcium) [PI]; 2015; Livalo (pitavastatin) [PI]; 2013; ; Mevacor (lovastatin) [PI]; 2014; Pravachol (pravastatin sodium) [PI]; 2016; Zocor (simvastatin) [PI]; 2015.

Representative Statin Effects on Lipids After 6 Weeks of Treatment in Men and Women With LDL-C ≥160 mg/dL and ≤250 mg/dL (N=2431)

Statin	Dosage range, daily (mg/dL)	TC	LDL-C	HDL-C	TG
Lovastatin	20-80	↓ 21 to ↓ 36	↓ 29 to ↓ 48	↑ 4.6 to ↑ 8.0	↓ 12 to ↓ 13
Pravastatin	10-40	↓ 15 to ↓ 22	↓ 20 to ↓30	↑ 3.2 to ↑ 5.6	↑ 8 to ↓ 13
Simvastatin	10-80[a]	↓ 20 to ↓ 33	↓ 28 to ↓ 46	↑ 5.2 to ↑ 6.8	↓ 12 to ↓ 18
Fluvastatin	20-40	↓ 13 to ↓ 19	↓ 17 to ↓ 23	↑ 0.9 to ↓ 3.0	↓ 5 to ↓ 13
Atorvastatin	10-80	↓ 27 to ↓ 39	↓ 37 to ↓ 51	↑ 2.1 to ↑ 5.7	↓ 20 to ↓ 28
Rosuvastatin	10-40	↓ 33 to ↓ 40	↓ 45 to ↓ 55	↑ 7.7 to ↑ 9.6	↓ 20 to ↓ 26

- The lipid-lowering effects of various statins in these studies are representative of those seen in other controlled trials, with one exception: pravastatin had a slightly greater TG-lowering effect in the CARE, WOSCOPS, and LIPID trials.
- Lovastatin and fluvastatin data are from the 8-week CURVES trial, a comparison of the effects of lovastatin, fluvastatin, atorvastatin, simvastatin, and pravastatin in men and women with LDL-C 192-244 mg/dL (N=534). However, these data overall do not represent head-to-head analyses

[a] Not to be used at dosages of 80 mg unless individual has been on treatment for more than 12 months.

Jellinger PS, et al. *Endocr Pract.* 2017 Apr;23(Suppl 2):1-87.

CARE = Cholesterol and Recurrent Events; CURVES = Comparative Dose Efficacy of Atorvastatin, Simvastatin, Pravastatin, Lovastatin, and Fluvastatin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease; TC = total cholesterol; TG = triglycerides; WOSCOPS = West of Scotland Coronary Prevention Study.

See notes for references.

PCSK9 Inhibitors: Starting Doses and Dosage Ranges

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
PCSK9 Inhibitors			
Alirocumab	75 mg every 2 weeks	75–150 mg every 2 weeks	SQ
Evolocumab	140 mg every 2 weeks or 420 mg once monthly	Not applicable	SQ

Abbreviations: PCSK9 = proprotein convertase subtilisin/kexin type 9; SQ = subcutaneous injection.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Praluent (alirocumab) [PI] 2015; Repatha (evolocumab) [PI]; 2016.

Cholesterol Absorption Inhibitors: Starting Doses, Dosage Ranges, Primary Metabolic Effects, and Main Considerations

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Cholesterol Absorption Inhibitors			
Ezetimibe	10 mg	10 mg	Oral
Combination Therapies (single pill)			
Ezetimibe/simvastatin	10/20 mg	10/10 to 10/80 mg	Oral

Metabolic Effects

- Primarily ↓ LDL-C 10%–18% by inhibiting intestinal absorption of cholesterol and decreasing delivery to the liver, leading to upregulation of hepatic LDL receptors
- ↓ Apo B 11%–16%
- In combination with statins, additional ↓ LDL-C 25%, total ↓ LDL-C 34%–61%
- In combination with fenofibrate, ↓ LDL-C 20%–22% and ↓ apo B 25%–26% without reducing ↑ HDL-C

Main Considerations

- Myopathy/rhabdomyolysis (rare)
- When coadministered with statins or fenofibrate, risks associated with those drugs remain (eg, myopathy/ rhabdomyolysis, cholelithiasis)

Abbreviations: Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Bays HE, et al. *Clin Ther*. (2001) 23:1209–1230; Bays HE, et al. *Clin Ther*. (2004) 26:1758–1773; Bissonnette S, et al. *Can J Cardiol*. (2006)22:1035–1044; Brohet C, et al. *Curr Med Res Opin*. (2005) 21:571–578; Denke M, et al. *Diab Vasc Dis Res*. (2006)3:93–102; Dujovne CA, et al. *Am J Cardiol*. (2002) 90:1092–1097; Farnier M, et al. *Eur Heart J*. 2005;26:897-905; Gagne C, et al. *Am J Cardiol*. 2002;90:1084-1091; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Knopp RH, et al. *Int J Clin Pract*. (2013) 57:363–368; McKenney JM, et al. *J Am Coll Cardiol*. (2006) 47:1584–1587; Zetia (ezetimibe) [PI] 2013.

Bile Acid Sequestrants: Starting Doses, Dosage Ranges, Primary Metabolic Effects, and Main Considerations

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Bile Acid Sequestrants			
Cholestyramine	8–16 g	4–24 g	Oral
Colestipol	2 g	2–16 g	Oral
Colesevelam	3.8 g	3.8–4.5 g	Oral

Metabolic Effects:

- Primarily ↓ LDL-C 15%–25% by binding bile acids and preventing their reabsorption in the ileum (causing hepatic cholesterol depletion and LDL-receptor upregulation)
- Colesevelam ↓ glucose and hemoglobin A1C (~0.5%); FDA-approved to treat T2D

Main Considerations:

- May ↑ serum TG
- Frequent constipation and/or bloating, which can reduce adherence
- Many potential drug interactions (decreased drug absorption), less so with colesevelam (see product labeling)
- May reduce absorption of folic acid and fat-soluble vitamins such as vitamins A, D, and K

Abbreviations: A1C = glycated hemoglobin; FDA = US Food and Drug Administration; LDL-C = low-density lipoprotein cholesterol; T2D = type 2 diabetes; TG = triglycerides.

Colestid (colestipol hydrochloride) [PI]; 2014; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Prevalite (cholestyramine for oral suspension, USP) [PI]; 2015; WelChol (colesevelam hydrochloride) [PI]; 2014; Zieve FJ, et al. *Ther*. (2007) 29:74-839:74–83.

Adenosine Triphosphate-Citrate Lyase (ACL) inhibitor

ACL Inhibitor

Bempedoic acid (Nexletol) 180mg QD

Combination Therapy (single pill)

Bempedoic acid/Ezetimibe (Nexlizet) 180mg/10mg QD

Fenofibrate, Fenofibric Acid, and Fibrates Formulations

Fenofibrate Non-micronized		***All QD***
Fenoglide	Tablet	40, 120
Lipofen	Capsule	50, 150
Lofibra	Tablet	54, 160
Triglide	Tablet	50, 160
Fenofibrate	Tablet	54, 160
Fenofibrate Micronized		***All QD***
Antara	Capsule	43, 130
Tricor	Capsule	67, 200
Lofibra	Capsule	67, 134, 200
Fenofibrate-micronized		67, 134, 20
Fenofibrate Nanocrystal		***QD***
Tricor	Tablet	48, 145

Fenofibric acid		***QD***
Trilipix	Capsule (delayed release)	45, 135
Fibrates	***BID***	
Lopid	Tablet	600
Gemfibrozil	Tablet	600
Atromid-S	Capsule	500, 1000
Clofibrate	Capsule	500, 1000
Bezalip SR	Tablet	400 QD (non US)
Bezafibrate	Tablet	200 TiD (non US)

Omega-3 Fatty Acids: Starting Doses, Dosage Ranges, and Primary Metabolic Effects

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Omega-3-acid ethyl esters (Lovaza)	4 g per day	4 g per day	Oral
Icosapent ethyl (Vascepa)	4 g per day	4 g per day	Oral

Metabolic Effects:

- ↓ TG 27%–45%, TC 7%–10%, VLDL-C 20%–42%, apo B 4%, and non-HDL-C 8%–14% in individuals with severe hypertriglyceridemia most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles. Other potential mechanisms of action include: increased ß-oxidation; inhibition of acyl-CoA; 1,2-diacylglyceral acyltransferase; decreased hepatic lipogenesis; and increased plasma lipoprotein activity
- Icosapent ethyl ↓ LDL-C 5%, whereas, omega-3-acid ethyl esters ↑ LDL-C 45%

Abbreviations: Apo B = apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; TG=triglycerides; VLDL=very low-density lipoprotein.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Lovaza (omega-3-acid ethyl esters) [PI]; 2015; Vascepa (icosapent ethyl) [PI]; 2016.

Niacin: Starting Doses, Dosage Ranges, Primary Metabolic Effects, and Main Considerations

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Niacin (nicotinic acid)			
Immediate-release	250 mg	250–3000 mg	Oral
Extended-release	500 mg	500–2000 mg	Oral

Metabolic Effects:

- ↓ LDL-C 10%–25%, ↓ TG 20%–30%, ↑ HDL-C 10%–35% by decreasing hepatic synthesis of LDL-C and VLDL-C
- ↓ Lipoprotein (a)
- Transforms LDL-C to less-atherogenic form by increasing average particle size and also decreases LDL particle concentration

Main Considerations:

- Potential for frequent skin flushing, pruritus, abdominal discomfort, hepatoxicity (rare but may be severe), nausea, peptic ulcer, atrial fibrillation
- Deleterious effect on serum glucose at higher dosages
- Increases uric acid levels; may lead to gout

Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol.

Guyton JR, et al. *Arch Intern Med.* (2000) 160:1177–1184; Jellinger P, et al. *Endocr Practice.* (2017) 23(4):479–497; Niaspan (niacin extended-release) [PI] 2015.

Options for Dyslipidemia Therapies in 2020

Thank You.

Questions?