



CARDIOVASCULAR & METABOLIC HEALTH FOUNDATION



Reducing Residual Cardiovascular Risk

Risk Reduction Through Aggressive Management of TG and HDL-C



CARDIOVASCULAR & METABOLIC HEALTH FOUNDATION



The Cardiovascular & Metabolic Health Foundation (CMH)

- Is a not-for-profit, 501(c)(3) organization, founded and directed by clinicians
- Is funded by multiple industry sources via educational grants to ensure fair balance
- Provides educational programs to healthcare practitioners to:
 - Enhance the understanding of cardiovascular and metabolic diseases
 - Promote the use of current treatment guidelines and recommendations
 - Offer practical strategies for clinical practice and patient education
 - Improve practice patterns and patient outcomes

Learning Objectives

- Explain why a patient with LDL-C at goal may still have significant cardiovascular risk
- Explain the importance of measuring non-HDL-C and treating it to goals described in clinical treatment guidelines
- Describe how multiple lipid risk factors contribute to a patient's total risk profile
- Identify patients who may need additional therapeutic intervention with fibrates or niacin in order to reduce residual CHD risk
- Identify treatment options that address elevated TG and low HDL-C levels
- Describe strategies to improve patient compliance and adherence to lipid therapy

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ACTION Objectives

- For patients at LDL-C goal who have great residual cardiovascular risk, reduce this risk by treating:
 - Elevated non-HDL-C
 - Elevated TG
 - Low HDL-C
- Calculate and treat non-HDL-C to goal for patients with elevated TG (≥ 200 mg/dL)
- Use combination therapy to provide optimal therapeutic benefit
- Teach patients about secondary lipid targets and their importance

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Patient Profile: Emma F.

Current Visit

Patient:

- 50 y/o white female who started treatment for dyslipidemia 2 mos ago

History:

- No prior CVD
- Perimenopausal
- Smokes ½ PPD
- Does not drink alcohol
- Mother had CHD <65 y/o

Physical Exam:

- Height: 5'6"
- Weight: 192 lbs
- Waist: 37"
- BMI: 31 kg/m²
- BP: 132/82 mm Hg

	Before Rosuvastatin	After Rosuvastatin
TC	332 mg/dL	220 mg/dL
LDL-C	224 mg/dL	122 mg/dL
HDL-C	38 mg/dL	39 mg/dL
TG	344 mg/dL	289 mg/dL
Non-HDL-C	294 mg/dL	181 mg/dL
Fasting glucose	98 mg/dL	97 mg/dL

Risk Assessment:

- Framingham risk score: 15%
- LDL-C goal <130 mg/dL (3 RFs)
- Non-HDL-C goal <160 mg/dL

Current Treatment:

- TLC
- Rosuvastatin 10 mg/d

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In Your Opinion, What Would Be the Most Reasonable Approach to a Patient Like Emma F.?

1. Treatment is working; reinforce adherence
2. Watch lipid parameters other than LDL-C; request follow-up visit. Additional treatment not currently warranted
3. Additional pharmacologic treatment options should be discussed or initiated at this visit

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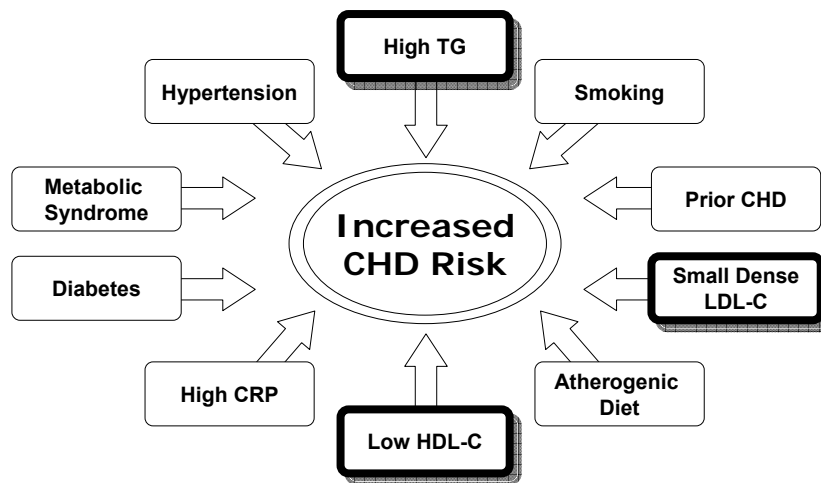


What Is Residual Cardiovascular Risk?

ACTION: Address Residual CV Risk in Patients Who Are Already at LDL-C Goal



Multiple Lipid and Nonlipid Risk Factors Contribute to CHD Risk

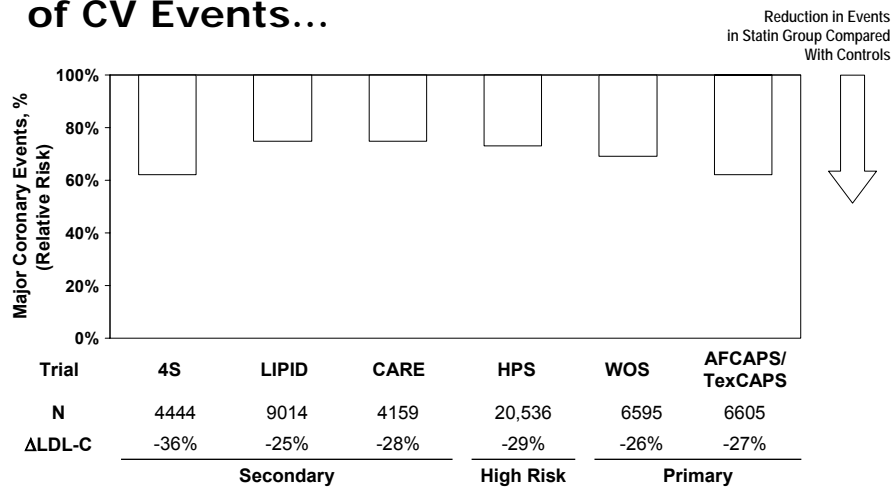


What Is Residual Cardiovascular Risk?

- Statin trials show many patients at LDL-C goal have high “residual” CHD risk¹
- Statins reduce risk by 25% to 35% compared with controls, but many patients still have events due to residual risk²⁻⁴
- More intensive treatment is needed in addition to statin monotherapy to effectively reduce residual risk

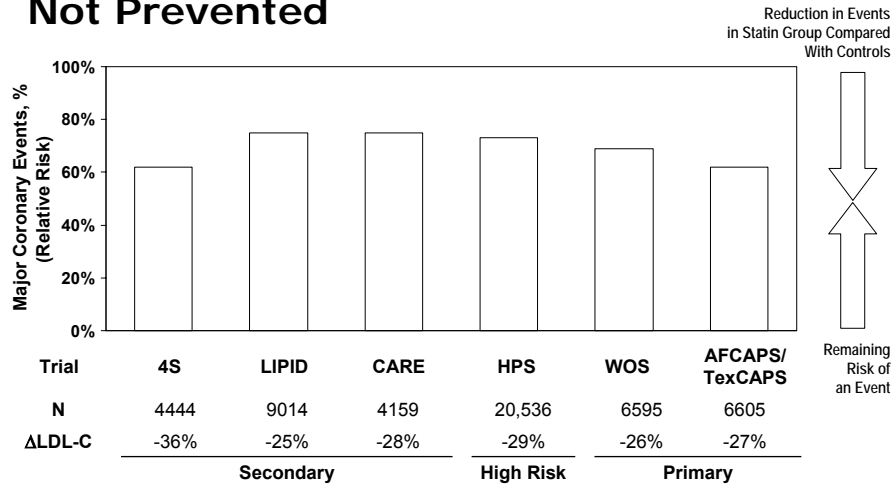
1. Davidson MH. *Am J Cardiol.* 2005;96:3K-13K. 2. Pedersen TR, et al. *Diab Vasc Dis Res.* 2006;3:S1-S12.
 3. Baigent C, et al. *Lancet.* 2005;366:1267-1278. 4. LaRosa JC, et al. *JAMA.* 1999;282:2340-2346.

Major Statin Trials Show Reduced Risk of CV Events...



Adapted from Libby PJ, et al. *J Am Coll Cardiol.* 2005;46:1225-1228.

...But the Majority of Events Were Not Prevented



Adapted from Libby PJ, et al. *J Am Coll Cardiol.* 2005;46:1225-1228.

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Role of Non-HDL-C in Residual Cardiovascular Risk

*ACTION: Measure and Use Non-HDL-C
as a Secondary Treatment Target,
Especially in Patients With ↑ TG*

Non-HDL-C Provides a Treatment Target Option for Patients With Hypertriglyceridemia

- Serum TG elevations are a marker for atherogenic remnant lipoproteins, or remnant lipoproteins
- In patients with ↑ TG:
 - Non-HDL-C better represents the concentrations of all atherogenic lipoproteins than LDL-C does alone
 - Non-HDL-C represents LDL-C + VLDL-C
 - Non-HDL-C is a surrogate marker for apolipoprotein B, the major apolipoprotein of all atherogenic lipoproteins
- Non-HDL-C is a secondary target of therapy for patients with TG ≥200 mg/dL
- Combination therapy is often required to achieve non-HDL-C goals

Adapted from: National Cholesterol Education Program. *Circulation*. 2002;106:3143-3421.

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Calculating Non-HDL-C and Determining its Goal

Calculate and record non-HDL-C:

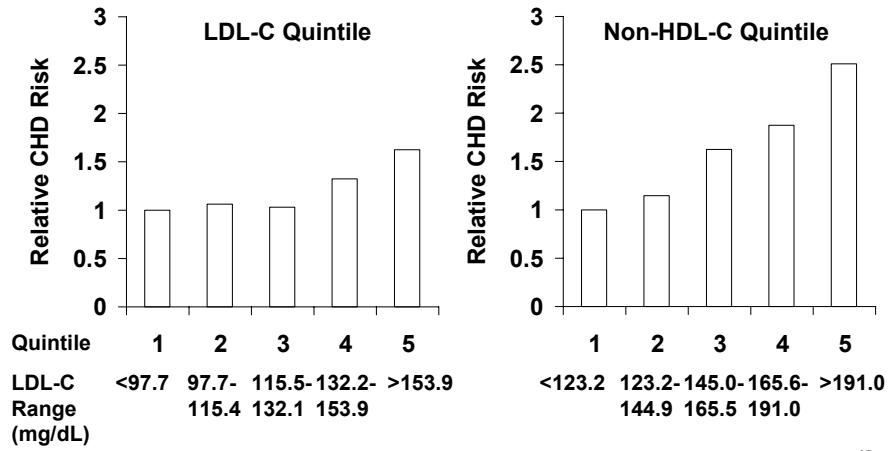
$$\text{Non-HDL-C} = \text{TC} - \text{HDL-C}$$

Determine non-HDL-C goal:

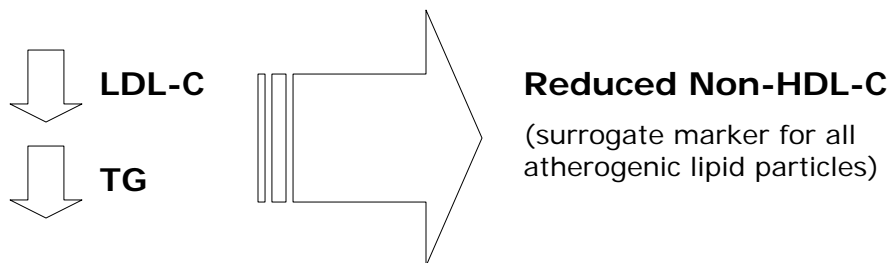
$$\text{Non-HDL-C Goal} = \text{LDL-C Goal} + 30 \text{ mg/dL}$$

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497. 14

Non-HDL-C Is Superior to LDL-C in Predicting CVD Risk in Women



Treatment of Non-HDL-C: What Moves it Toward Goal?



Reduce risk by ensuring patients (especially those with TG ≥200 mg/dL) meet their non-HDL-C goal



Role of TG in Cardiovascular Risk

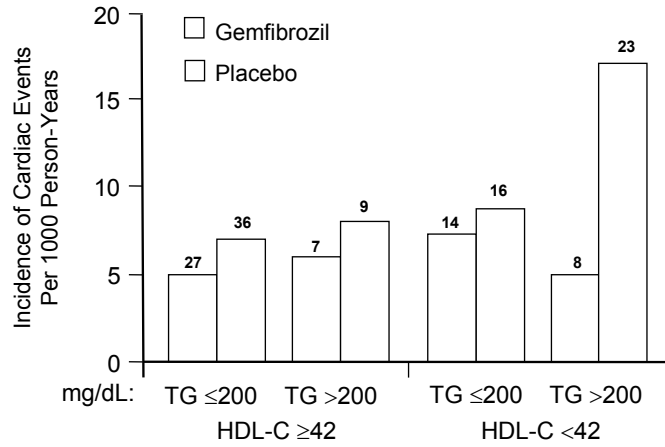
ACTION: Lower TG to Reduce Residual CV Risk in Patients at LDL-C Goal



Classification of TG by ATP III

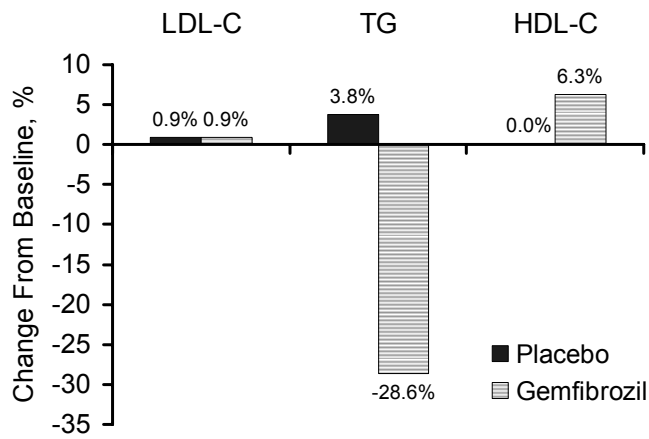
Classification	TG Level (mg/dL)
Normal	<150
Borderline high	150-199
High	200-499
Very high	≥500

HHS: Incidence of CHD Events by Baseline TG and HDL-C



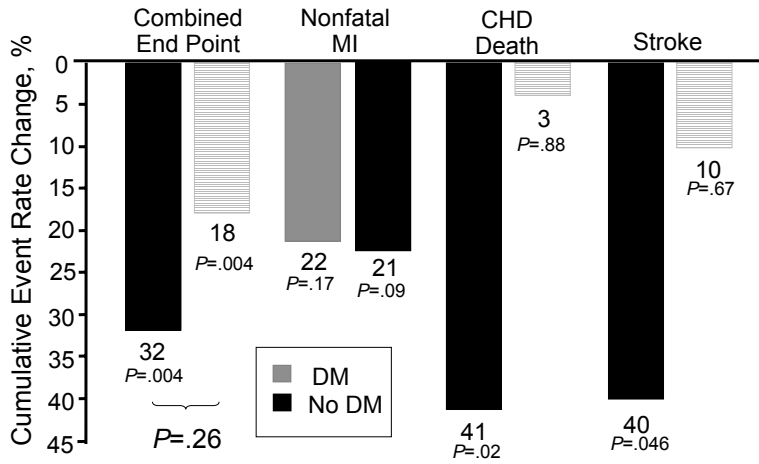
Numbers above bars = number of events.
Manninen V, et al. *Circulation*. 1992;85:37-45.

VA-HIT: Change in Lipoproteins From Baseline



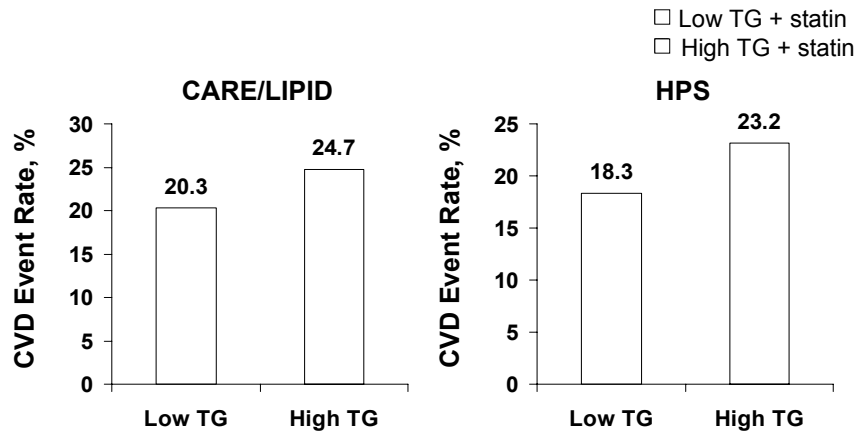
Rubins HB, et al. *N Engl J Med*. 1999;341:410-418.

VA-HIT: CVD Risk Reduction in Diabetics Compared With Nondiabetics



Rubins HB, et al. *Arch Intern Med.* 2002;162:2597-2604.

Statins Reduce But Do Not Eliminate the Excess CVD Risk Associated With High TG



HPS Collaborative Group. *Lancet.* 2002;360:7-22.
Sacks FM, et al. *Circulation.* 2000;102:1893-1900.



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Role of Low HDL-C in Residual Cardiovascular Risk

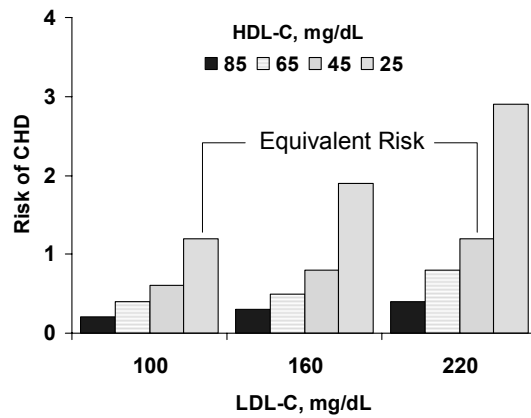
ACTION: Raising HDL-C Can Improve Patient Risk Profiles



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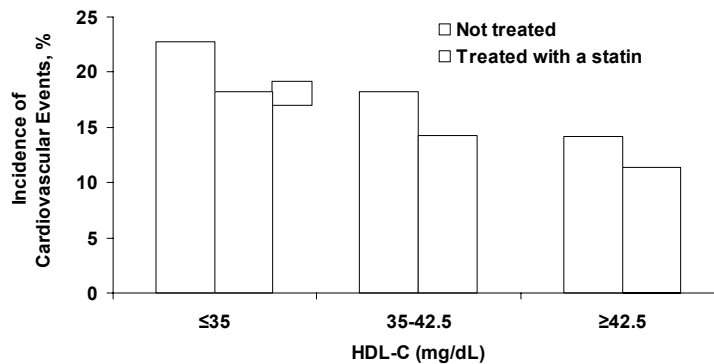


HDL-C Is a Modifier of Risk at All Levels of LDL-C: the Framingham Study*



*Men 50 to 70 years of age.
Castelli WP, et al. *JAMA*. 1986;256:2835-2838.
Castelli WP. *Can J Cardiol*. 1988;4(suppl A):5A-10A.

Low HDL-C Is a Risk Factor in Statin-Treated Patients: A Meta-Analysis of 14 Trials



Baigent C, et al. *Lancet*. 2005;366:1267-1278; Pedersen TR, et al. *Diab Vasc Dis Res*. 2006;3:S1-S12.

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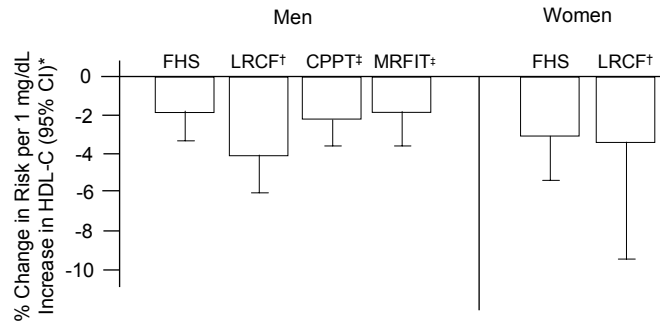
Low HDL-C Is an Independent Risk Factor for CHD

- Strong evidence links low HDL-C to increased CHD morbidity and mortality¹⁻³
- ATP III guidelines define low HDL-C as <40 mg/dL¹
- Presence of high HDL-C (≥ 60 mg/dL) reduces the total number of risk factors in ATP III risk assessment¹

1. National Cholesterol Education Program. *Circulation*. 2002;106:3143-3421. 2. Gordon DJ et al. *Circulation*. 1989;79:8-15.
3. Wilson PWF, et al. *Circulation*. 1998;97:1837-47.

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Reduction in CHD Risk Per 1-mg/dL Increase in HDL-C



*Adjusted for age, BP, smoking, BMI, and LDL-C. [†]Only fatal outcomes were documented. [‡]Only included patients in the control group.

FHS = Framingham Heart Study; LRCF = Lipid Research Clinics Prevalence Mortality Follow-up Study; CPPT = Coronary Primary Prevention Trial; MRFIT = Multiple Risk Factor Intervention Trial.

Gordon DJ, et al. *Circulation*. 1989;79:8-15.

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Knowledge in Practice:

Case Presentations

ACTION: Apply Knowledge of Lipid Parameters Beyond LDL-C and How They Relate to Real Patients and Their Individual Risk Profiles

Who Is the Patient With High “Residual Risk”?

- Mixed dyslipidemia (↑LDL-C, ↑TG, or ↓HDL-C)
- CHD or CHD risk equivalent
- Obese patients
- Metabolic syndrome
- Type 2 diabetes

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Case Presentation: Maria S.

Current Visit

Patient:

- 64 y/o Hispanic female with T2DM and mixed dyslipidemia

History:

- ↑ TG
- Does not smoke or drink alcohol
- Stable T2DM, 2 y
- Gout

Physical Exam:

- Height: 5'1"
- Weight: 174 lbs
- Waist: 39"
- BMI: 33 kg/m²
- BP: 125/80 mm Hg

	Before Simvastatin (mg/dL)	After Simvastatin (mg/dL)
TC	240	198
LDL-C	115	88
HDL-C	39	40
TG	432	350
Non-HDL-C	201	158
Fasting glucose	107	105
HbA1C	6.5	6.5

Risk Assessment:

- LDL-C goal: <100 mg/dL
- Non-HDL-C goal: <130 mg/dL

Current Treatment:

- ASA
- Metformin 500 mg BID
- Lisinopril 10 mg/d
- Simvastatin 40 mg/d ³⁰

Maria S.: Since she is already at her LDL-C goal, but still has an elevated non-HDL-C level, which lipid would you target?

1. TC
2. LDL-C
3. TG
4. HDL-C
5. None

	Current Labs (mg/dL)
TC	198
LDL-C	88
HDL-C	40
TG	350
Non-HDL-C	158
Fasting glucose	105
HbA1c (%)	6.5

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Case Presentation: Doug E.

Patient:

- 55 y/o white male with recent onset (1-2 y) dyslipidemia, hypertension, and erectile dysfunction

Physical Exam:

- Height: 5'10"
- Weight: 188 lbs
- Waist: 35"
- BMI: 27 kg/m²
- BP: 136/84 mm Hg

History:

- No prior CVD
- Smokes 1 PPD
- Drinks 3-4 beers/wk
- Father had CHD <50 yrs

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Case Presentation: Doug E. (cont'd)

Current Treatment:

- TLC
- HCTZ 25 mg/d
- Sildenafil 50 mg prn
- Atorvastatin 40 mg/d

Risk Assessment:

- Framingham risk score: >30% (5 RFs)
- LDL-C goal: <100 mg/dL

	<i>Current Visit</i>	
	Before Atorvastatin (mg/dL)	After Atorvastatin (mg/dL)
TC	262	168
LDL-C	189	98
HDL-C	29	31
TG	196	182
Fasting glucose	89	88

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Doug E.: To further reduce his risk, which lipid parameter(s) would you recommend for additional intervention?

1. None
2. LDL-C
3. HDL-C
4. Both LDL-C and HDL-C
5. LDL-C, HDL-C, and TG
6. TG and HDL-C

	Current Labs (mg/dL)
TC	178
LDL-C	98
HDL-C	31
TG	182
Fasting glucose	88

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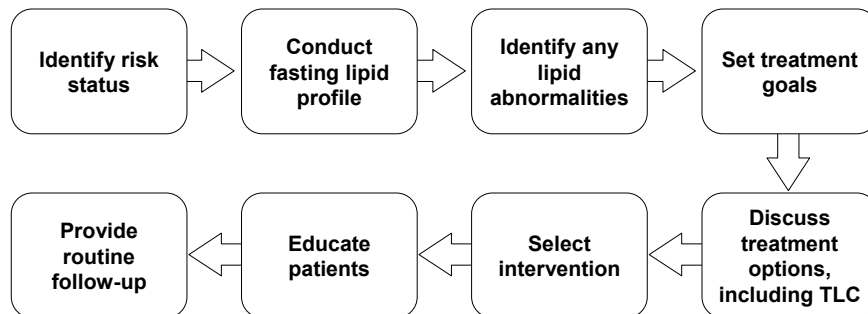


Managing Residual Risk

ACTION: Apply Aggressive Therapeutic Interventions to Targets Beyond LDL-C to Maximize Risk Reduction and Improve Outcomes



Evaluating and Managing Patients With Dyslipidemia



Usual Changes in Lipid Parameters: Pharmacological Options With Effects Beyond LDL-C

	Change in LDL-C (%)	Increase in HDL-C (%)	Decrease in TG (%)
Monotherapy			
Fibrates	↓ 5%-20% ¹	10%-35% ¹	20%-50% ¹
Niacin	↓ 5%-25% ¹	15%-35% ¹	20%-50% ¹
Rx Omega-3 fatty acids	↑ 5%-10% ²	5%-10% ^{2,3}	15%-45% ^{2,3}
Statins	↓ 18%-55% ¹	5%-15% ¹	7%-30% ¹

1. National Cholesterol Education Program. *Circulation*. 2002;106:3143-3421. 2. Pejic RN, et al. *J Am Board Fam Med*. 2006;19:310-316. 3. Omacor (omega-3-acid ethyl esters) [package insert]. Liberty Corner, NJ: Reliant, 2005.

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Evolving Treatment Paradigm

- Statin monotherapy reduces risk, but significant residual risk remains
- Future of therapy is aggressive management of LDL-C, non-HDL-C, TG, and HDL-C
- Combination therapy increasingly important:
 - Addresses multiple risk contributors
 - Effective through multiple mechanisms

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Fibrates Favorably Affect Multiple Parameters

- Fibrates activate the nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPAR α) and:
 - Upregulate genes for apolipoprotein A-I, fatty acid transport protein, fatty acid oxidation, and possibly lipoprotein lipase
 - Downregulate the apolipoprotein C-III gene
 - \uparrow Lipoprotein lipase and \downarrow apolipoprotein C-III, \uparrow VLDL-C catabolism
- Reduce VLDL-C TG formation
- Serum TG lowering and increased synthesis of apolipoproteins raise HDL-C
- Extra-atherogenic, small, dense LDL-C converted to normal-sized LDL-C

National Cholesterol Education Program. *Circulation*. 2002;106:3143-3421.

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Outcomes in Fibrate Trials Involving Patients With Diabetes or Metabolic Syndrome

Trial	N	Major CVD Event Rate		RRR	P
		Control	Drug		
Primary Prevention					
HHS* ¹	292	13.0%	3.9%	71%	<.005
FIELD ^{†2}	7664	10.8%	8.9%	19%	.004
Secondary Prevention					
BIP ^{‡3}	1470	18.4%	14.1%	25%	.03
VA-HIT ^{§4}	769	29.4%	21.2%	32%	.004

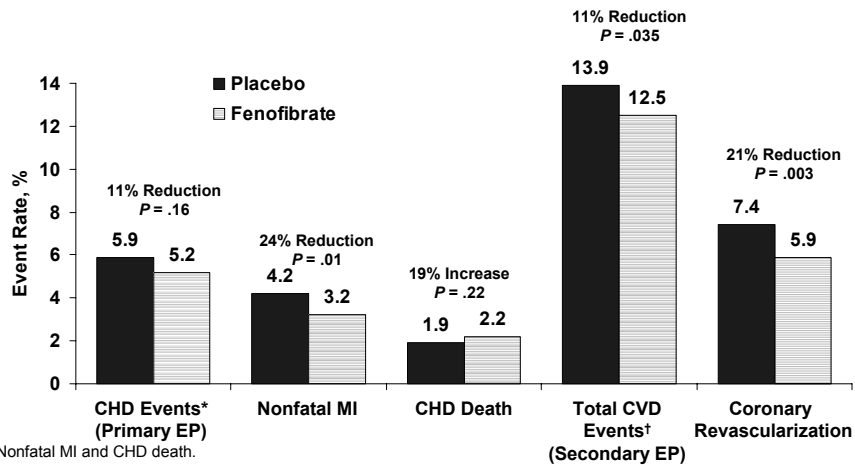
RRR, relative risk reduction.

*Patients with TG >204 mg/dL and an LDL-C/HDL-C >5 (may or may not have had DM or the MS). [†]Patients with diabetes and no prior CVD; secondary study outcome. [‡]Patients with metabolic syndrome. [§]Patients with diabetes.

1. Manninen V, et al. *Circulation*. 1992;85:37-45; 2. Keech A, et al. *Lancet*. 2005;366:1849-1861. 3. Tenenbaum A, et al. *Arch Intern Med*. 2005;165:1154-1160. 4. Rubins HB, et al. *Arch Intern Med*. 2002;162:2597-2604.

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FIELD: Primary and Secondary End Points



*Nonfatal MI and CHD death.

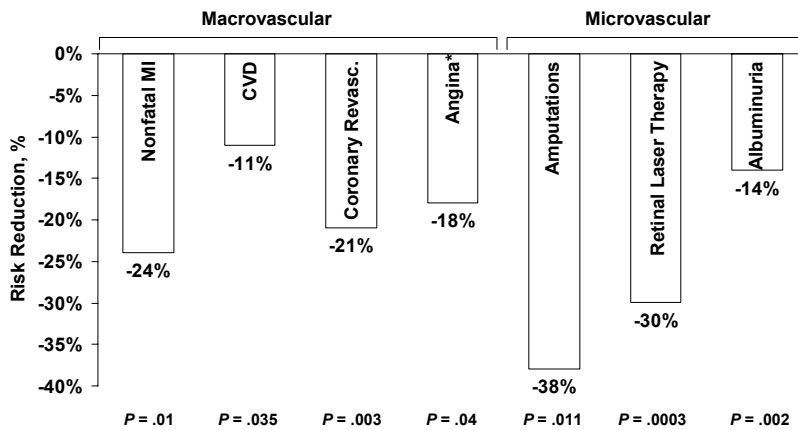
†MI, stroke, CVD death, revascularizations.

Keech A, et al. *Lancet*. 2005;366:1849-1861.

Keech A, et al. *Atheroscler Suppl*. 2006;7:342. Abstract We-S15:2.

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FIELD: Significant Clinical Benefits of Fenofibrate in Patients With Diabetes



*Hospitalizations due to angina.

N = 7664.

Keech A, et al. *Lancet*. 2005;366:1849-1861; Keech A. *Atheroscler Suppl*. 2006;7:342. Abstract We-S15:2.

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Using Fibrates

- Fibrates are generally well tolerated¹
- GI side effects are the most common complaints¹
- Use may potentiate action of oral anticoagulants¹
- Substantial evidence suggests that combination therapy with fenofibrate and a statin has a greater safety profile than gemfibrozil/statin therapy²
 - Gemfibrozil, but not fenofibrate, causes an increase in statin blood levels
 - The rate of rhabdomyolysis with gemfibrozil is 10- to 15-fold higher than for fenofibrate when combined with a statin in the FDA AER database (corrected for number of prescriptions)

1. National Cholesterol Education Program. *Circulation*. 2002;106:3143-3421.
 2. Corsini A, et al. *Am J Cardiol*. 2005;96:44K-49K.

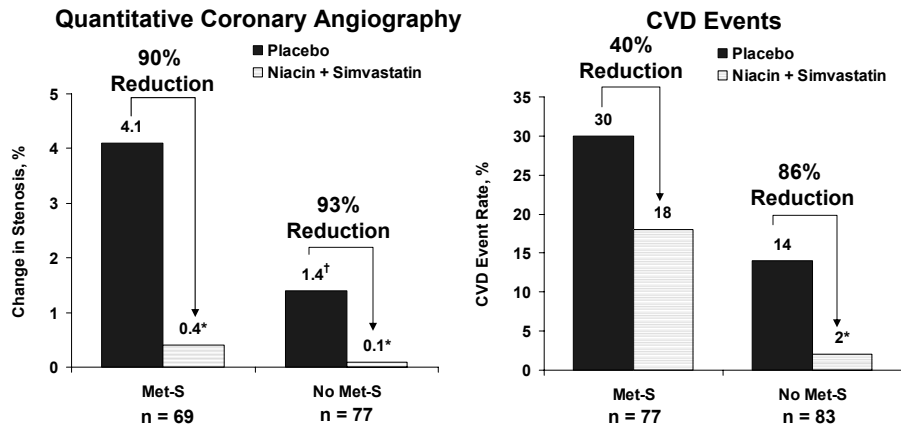
Niacin: Multiple Mechanisms and Clinical Rationale

- Niacin appears to modify lipids by:
 - Inhibiting mobilization of free fatty acids
 - Inhibiting lipoprotein synthesis
 - Decreasing HDL-C catabolism
 - Decreasing VLDL-C production
 - Shifting LDL-C composition from small, denser LDL-C particles to the larger, more buoyant LDL-C particles

Niacin is the most effective HDL-C-raising drug

Adapted from: National Cholesterol Education Program. *Circulation*. 2002;106:3143-3421.

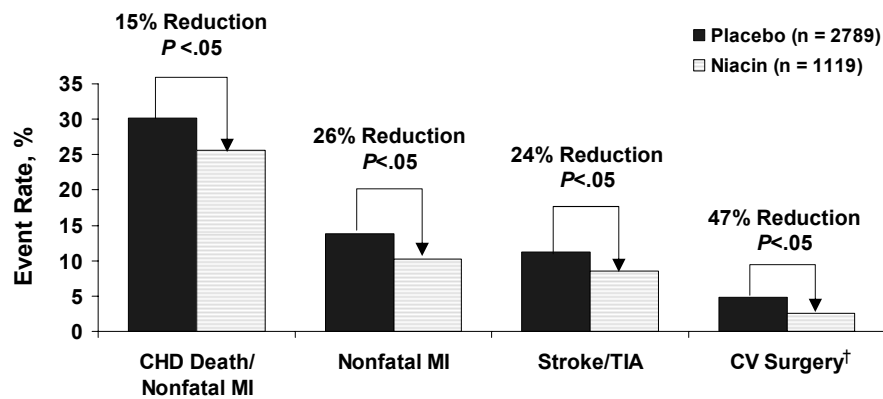
HATS: Clinical End Points in Patients With and Without the Metabolic Syndrome



* $P \leq .05$ vs placebo; [†] $P = .02$ vs Met-S placebo.
Zhao X-O, et al. *J Am Coll Cardiol.* 2002;39(Suppl 1):242A. Abstract 1130-1173.

45

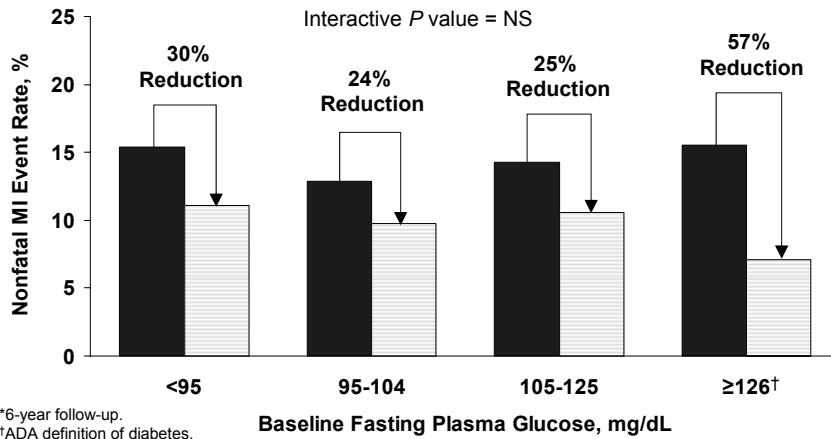
CDP: Macrovascular Outcomes*



*Total follow-up experience (mean, 6.2 years).
[†]15-year incidence.
TI = transient ischemic attack.

CDP Research Group. *JAMA.* 1975;231:360-381. 46

CDP: Reduction in Recurrence of MI * by Baseline Fasting Plasma Glucose



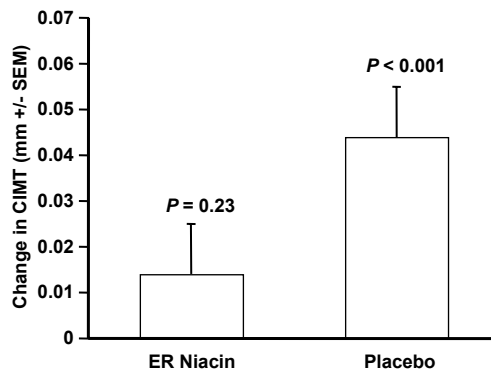
Canner PL, et al. *Am J Cardiol.* 2005;95:254-257.

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ARBITER 2: ER Niacin vs Placebo in Statin-Treated Patients

Primary End Point: Carotid IMT

Δ CIMT at 12 months



■ Placebo vs ER niacin

P = 0.08

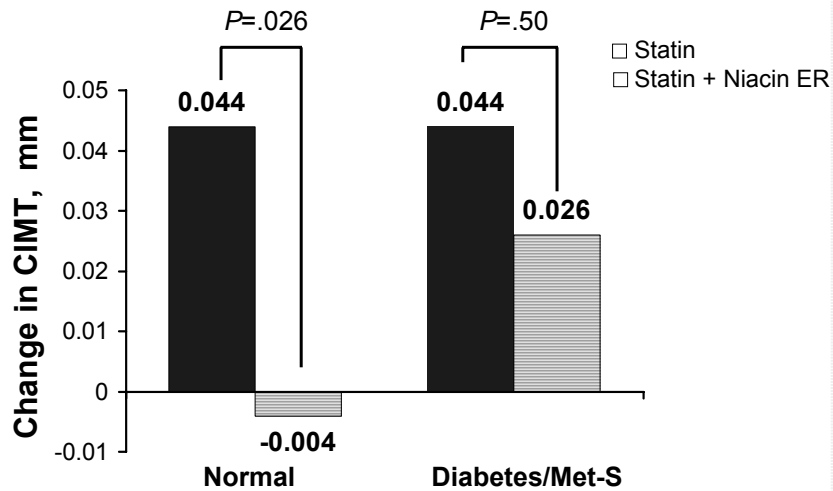
■ Intent-to-treat analysis of placebo vs ER niacin

P = 0.048

Taylor AJ, et al. *Circulation.* 2004;110:3512-3517.

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ARBITER 2: Patients With and Without Diabetes or Metabolic Syndrome (12 Months)



Taylor AJ, et al. *Circulation*. 2004;110:3512-3517.

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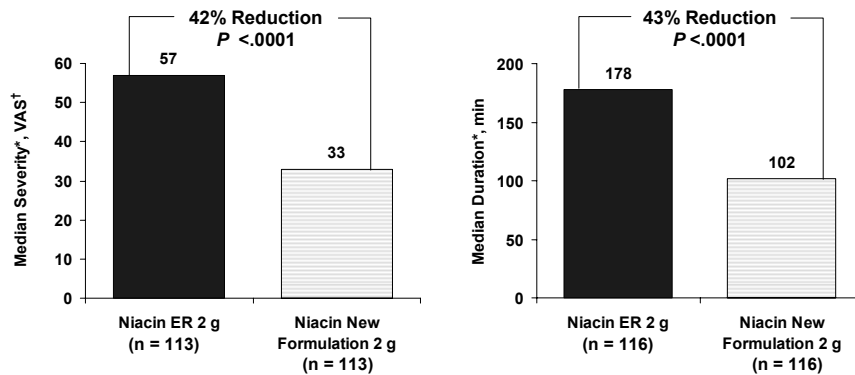
Using Niacin

- Niacin has beneficial effects on all aspects of the lipid profile, making it ideal for treating a wide variety of lipid disorders¹
- Niacin is currently available in multiple formulations (immediate release, extended release, and long acting) that differ in safety and efficacy¹
- Tolerability can be enhanced by¹:
 - Initiating therapy with small doses taken with meals and slowly titrating upward
 - Taking aspirin or other NSAID prior to the morning dose
 - Avoiding taking niacin with alcohol, spicy foods, or hot beverages
 - Avoiding interruptions in niacin therapy
 - Using newer formulation/extended-release niacin instead of immediate-release niacin
 - Educating patients about the possibility of side effects
- Dietary supplement niacin should not be used in place of prescription niacin²

1. McKenney J. *Arch Intern Med*. 2004;164:697-705. 2. Mosca L, et al. *Circulation*. 2004;109:672-693.

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Niacin Formulation May Impact Flushing Profile



No aspirin or other NSAID use permitted.

*Of first flushing event in subjects who received at least 1 dose of study medication in at least 2 study periods.

†Visual Analog Scale: 0 = none; 100 = intolerable.

Cefali EA, et al. *Int J Clin Pharmacol Ther.* 2006;44:633-640.

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Omega-3 Fatty Acids: Mechanism of Action and Clinical Rationale

- Reduce hepatic secretion of TG-rich lipoproteins at higher doses (3-4 g/day)¹
- Represent alternatives or complement to fibrates or niacin for treating severe hypertriglyceridemia¹
- Available as fish oil dietary supplements¹ or prescription omega-3 acid ethyl esters²; 12-16 fish oil capsules may be required as a dietary supplement to lower TG

1. National Cholesterol Education Program. *Circulation.* 2002;106:3143-3421.

2. Omacor (omega-3-acid ethyl esters) [package insert]. Liberty Corner, NJ: Reliant, 2005.

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Using Omega-3 Fatty Acids

- Prescription omega-3 fatty acids are indicated for use as an adjunct to diet for reducing very high levels of TG (≥ 500 mg/dL) in adult patients¹
- Potential adverse effects include:
 - Increased LDL-C levels^{1,2}
 - Increased bleeding time¹
 - Fishy burp and aftertaste²
- Patients taking >3 g of omega-3 fatty acids should do so only under a physician's care³

1. Omacor (omega-3-acid ethyl esters) [package insert]. Liberty Corner, NJ: Reliant, 2005. 2. Pejic RN, et al. *J Am Board Fam Med.* 2006;19:310-316. 3. Kris-Etherton PM, et al. *Arterioscler Thromb Vasc Biol.* 2003;23:151-152.

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Selecting Therapies

- Use clinical judgment and patient consultation when selecting therapies to reduce residual risk
- Employ combination therapy to provide additional benefit:
 - Niacin is generally used in patients with low HDL-C levels
 - Fibrates are used more frequently in patients with hypertriglyceridemia
 - Omega-3 fatty acids are generally used in patients with very high TG
- Combination therapy is appropriate in reducing residual risk
- Tailor the drug regimen to the patient's schedule or lifestyle, using once-a-day regimens whenever possible

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Patient Counseling—Promoting Adherence

- Make it clear that a patient’s medications are important and beneficial
- Teach the components of “risk” and what they mean
- Provide clear verbal and written instructions regarding dosing frequency and what to do if a dose is missed
- Review the importance of adherence
- Ask patients about adherence at each visit: “How often do you miss a dose of your medications?”

Adapted from: Spratt KA. *J Am Osteopath Assoc.* 2004;104:S9-S13.

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Emma F., the 50 y/o white female with mixed dyslipidemia who is taking rosuvastatin 10 mg/d, is already at LDL-C goal. What additional pharmacological treatment option(s) would you employ?

1. None
2. Add fenofibrate
3. Add niacin
4. Increase statin dose
5. Add gemfibrozil
6. Add more than 1 of the above

	Current Labs (mg/dL)
TC	220
LDL-C	122
HDL-C	39
TG	289
Non-HDL-C	181
Fasting glucose	97

Current Treatment:

- TLC
- Rosuvastatin 10 mg/d

Risk Assessment:

- Framingham risk score: 15%
- LDL-C goal <130 mg/dL (3 RFs)
- Non-HDL-C goal <160 mg/dL

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Maria S., the 64 y/o Hispanic female with T2DM, mixed dyslipidemia, and gout who is taking simvastatin 40 mg/d, is below her LDL-C target, but above her non-HDL-C target. What treatment would best help her reach her NCEP goal(s)?

1. Increase statin dose
2. Add niacin
3. Add fenofibrate
4. Add ezetimibe
5. Add omega-3 fatty acids
6. No treatment necessary

	Current Labs (mg/dL)
TC	198
LDL-C	88
HDL-C	40
TG	350
Non-HDL-C	158
Fasting glucose	105
HbA1c (%)	6.5

Current Treatment:

- ASA
- Metformin 500 mg BID
- Simvastatin 40 mg/d
- Lisinopril 10 mg/d

Risk Assessment:

- LDL-C goal: <100 mg/dL
- Non-HDL-C goal: <130 mg/dL

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Doug E., a 55 y/o white male with dyslipidemia, hypertension, and erectile dysfunction, is taking atorvastatin 40 mg/d. To further reduce his risk, what additional pharmacological treatment option(s) would you choose for him?

1. Add niacin
2. Add fenofibrate
3. Increase statin dose
4. Add ezetimibe
5. Add bile acid sequestrant
6. Add more than 1 of the above
7. Add none at this time

	Current Labs (mg/dL)
TC	168
LDL-C	98
HDL-C	31
TG	182
Fasting glucose	88

Current Treatment:

- TLC
- HCTZ 20 mg/d
- Sildenafil 50 mg prn
- Atorvastatin 40 mg/d

Risk Assessment:

- Framingham risk score: >30% (5 RFs)
- LDL-C goal: <100 mg/dL

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Conclusions

- Patients on statin therapy at LDL-C goal still have great residual CV risk
- Non-HDL-C is an important treatment target; calculate and achieve goals in patients with TG ≥ 200 mg/dL
- Reduce risk by aggressively treating lipid abnormalities beyond LDL-C, such as elevated TG and low HDL-C
- Therapies in combination with a statin can favorably improve patient risk profiles and reduce residual risk