

# Hypertriglyceridemia

How low to go and how to go low ?

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## INTRODUCTION

### ATHEROSCLEROSIS

is the most common underlying cause of cardiovascular disease. It is due a complex interplay between lipoproteins, white blood cells (macrophages), the immune system and the natural elements of the arterial wall.

## LIPOPROTEIENS

- Lipoproteins are the particles that transport cholesterol and triglycerides in the blood stream.
- Lipoproteins that are directly involved in atherosclerosis are termed *atherogenic*.
- Most of these lipoproteins carry cholesterol and other types of fats such as triglycerides.

- **Low Density Lipoprotein Cholesterol ( LDL-C )** has become a primary goal of therapy in cardiovascular treatment and prevention. Recommendations regarding diet and drug therapy to lower cholesterol are most often based on the LDL-C number.

*However, LDL is not the only lipoprotein involved in atherosclerotic heart disease.*

\* Triglyceride-rich very low-density lipoprotein (**VLDL**) and the so-called remnant lipoproteins are also atherogenic.

\* This is of particular importance when the LDL level is not elevated and **Triglyceride** level are high .. which is quite common, among people with :

*abdominal obesity or metabolic syndrome.*

*Who are at high risk of CVD*

## **Hypertriglyceridemia**

## TG Levels ... What Is Considered High ?

	NCEP ATP III <sup>a</sup>		The Endocrine Society 2010 <sup>b</sup>
Normal	< 150 mg/dL	Normal	< 150 mg/dL
Borderline-high TGs	150-199 mg/dL	Mild hypertriglyceridemia	
High TGs	200-499 mg/dL	Moderate hypertriglyceridemia	200 - 999 mg/dL
Very high TGs	≥ 500 mg/dL	Severe hypertriglyceridemia	1000-1999 mg/dL
		Very severe hypertriglyceridemia	≥ 2000 mg/dL

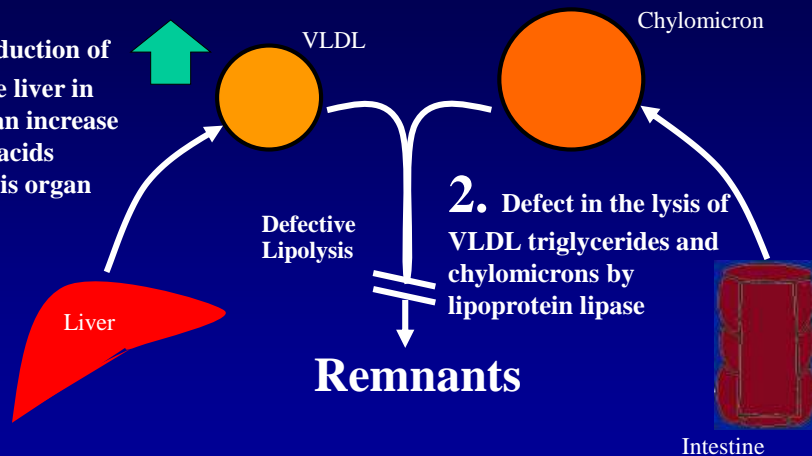
- Risk of pancreatitis<sup>c</sup>
  - Risk is greater when TG ≥ 1000 mg/dL
  - Caution with TG 500 mg/dL owing to wide variances in daily TG levels

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

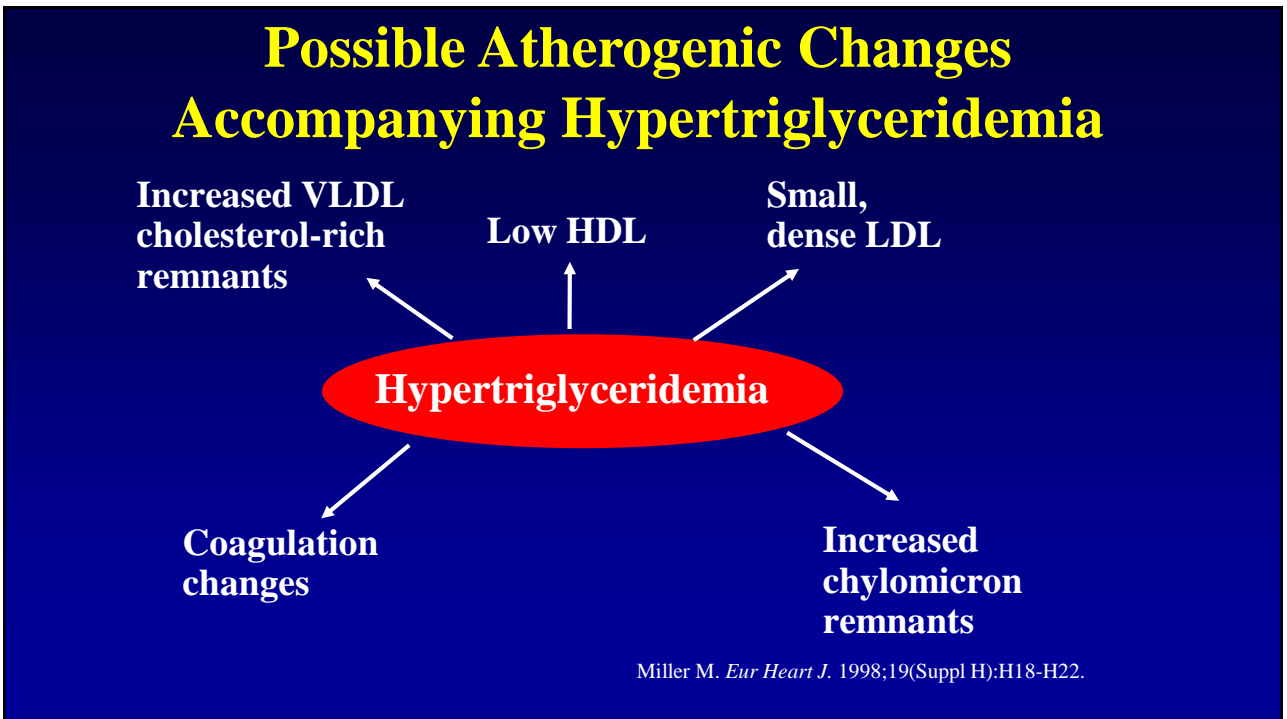
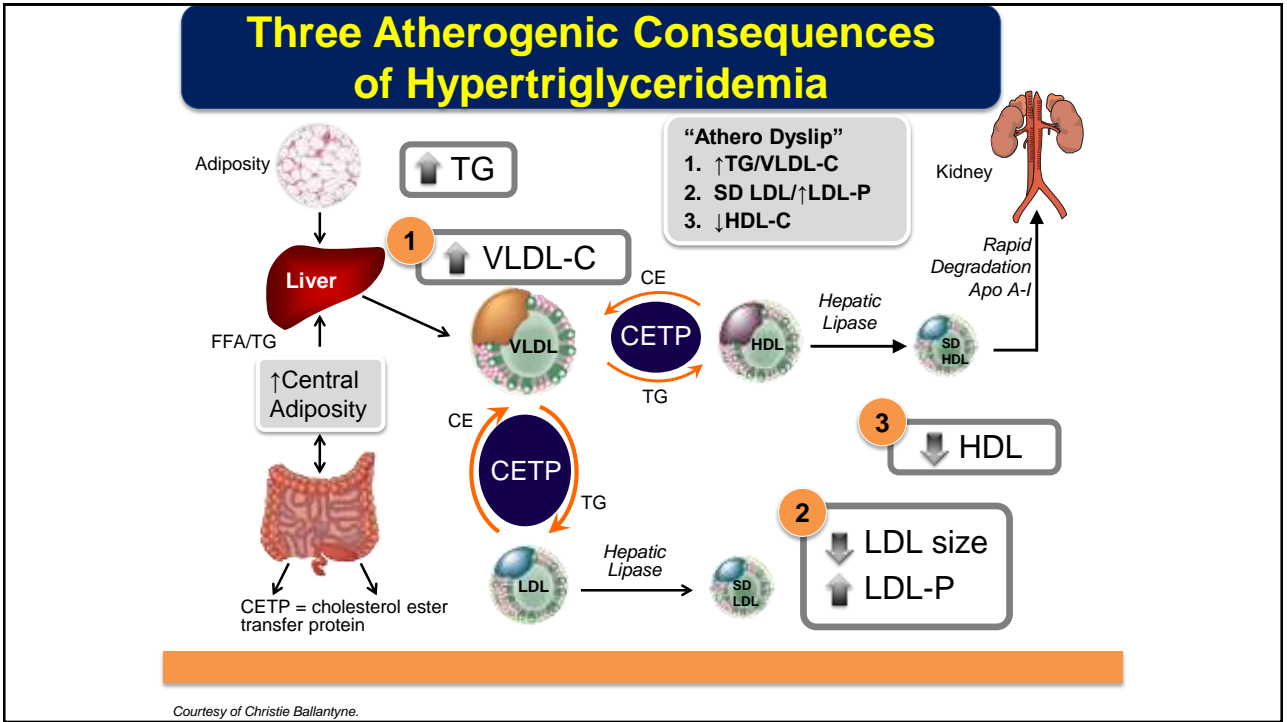
a. NCEP. *Circulation*. 2002;106:3143-3421<sup>[3]</sup>; b. Berglund L, et al. *J Clin Endocrinol Metab*. 2012;97:2969-2989<sup>[4]</sup>; c. Ewald N, et al. *Curr Opin Lipidol*. 2009;20:497-504.<sup>[5]</sup>

## Development of Hypertriglyceridemia

1. Overproduction of VLDL by the liver in response to an increase in free fatty acids flowing to this organ

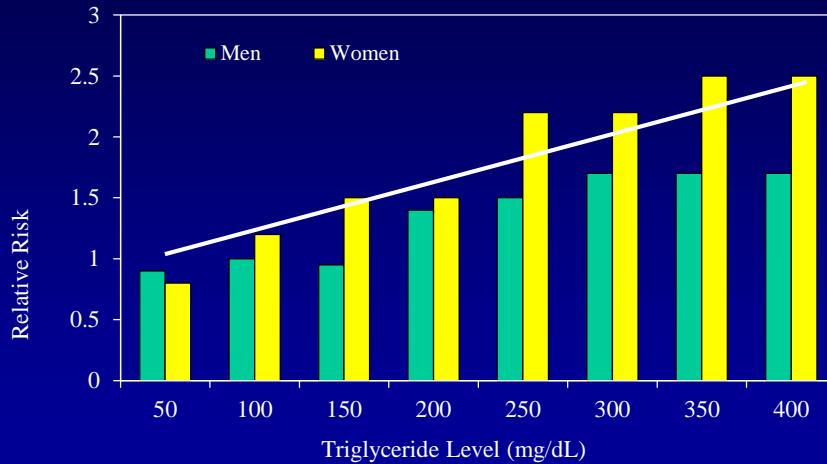


When lipoprotein lipase activity is deficient, triglycerides cannot be converted, hydrolyzed, or broken down, and the metabolism of chylomicron and VLDL remnants may be delayed



## Risk of CHD by Triglyceride Level (The Framingham Heart Study)

N=5127

Castelli WP. *Am J Cardiol.* 1992;70: 3H-9H.

## Meta-analysis of 61 Studies

### TGs Associated With CVD, All-cause Mortality

- Median follow-up of 12 y
- Excluded studies in patients with cancer, diabetes, CVD, dyslipidemia

TG Level, mg/dL	CVD Mortality		All-cause Mortality	
	RR (95% CI)	P Value	RR (95% CI)	P Value
< 90	0.83 (0.75-0.93)	.001	0.94 (0.85-1.03)	.15
90-150	1.00 [referent]		1.00 [referent]	
> 150-200	1.15 (1.03-1.29)	.015	1.09 (1.02-1.17)	.011
> 200	1.25 (1.05-1.50)	.013	1.20 (1.04-1.38)	.011

CI = confidence interval; CVD = cardiovascular disease; RR = risk ratio; TG = triglyceride.

Liu J, et al. *Lipids Health Dis.* 2013;12:159.<sup>[1]</sup>

## Secondary Causes of HTG

- **Increase Dietary Carbohydrates and Fats**
- Obesity
- Uncontrolled diabetes
- Hypothyroidism
- Nephrotic syndrome
- Various medications: antiretroviral regimens, some phenothiazines and second-generation antipsychotics, nonselective  $\beta$ -blockers, thiazide diuretics, oral estrogens, glucocorticosteroids, tamoxifen, isotretinoin
- Excessive alcohol consumption
- Pregnancy . Autoimmune Disease ( SLE , ) .

Bays HE. *The Johns Hopkins Textbook on Dyslipidemia*. 2010:245-257.

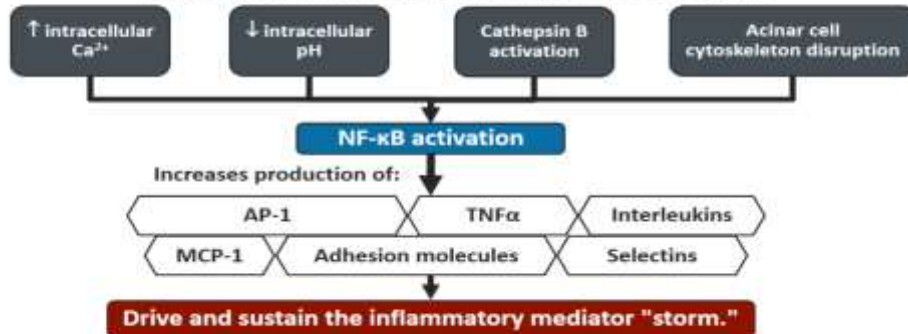
## Beyond CV Risk



## Mechanism of HTG-Induced Pancreatitis

AP develops when intracellular mechanisms to inhibit trypsin activation are overwhelmed by biochemical/structural injury.

Pancreatitis induction depends on a cascade of events.

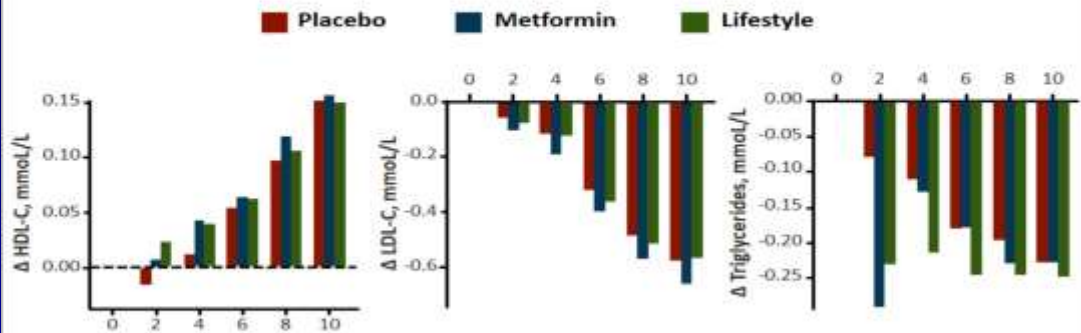


Wang GJ, et al. *World J Gastroenterol.* 2009;15:1427-1430; Felderbauer P, et al. *Basic Clin Pharmacol Toxicol.* 2005;97:342-350; Makhija R, et al. *J Hepatobiliary Pancreat Surg.* 2002;9:401-410.

## MANGEMENT

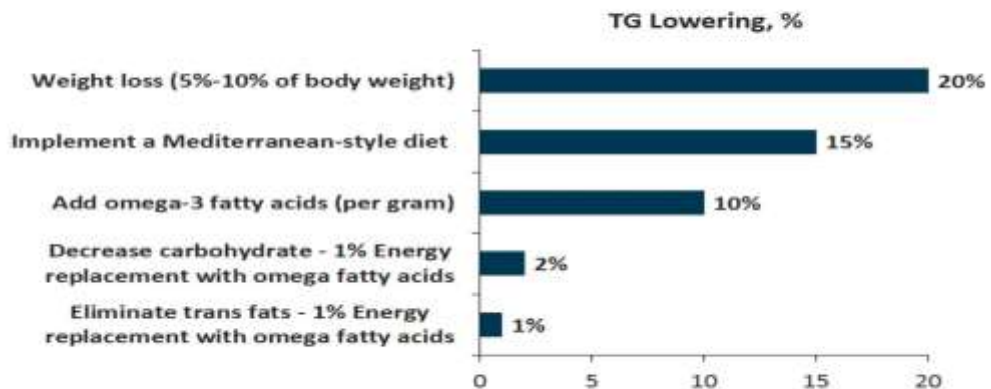


## Managing Hypertriglyceridemia Lifestyle Interventions



Orchard TJ, et al. *Diabet Med.* 2013;30:46-55.<sup>[7]</sup>

## Effects of Nutrition Practices on TG Lowering



Miller M, et al. *Circulation.* 2011;123:2292-2333.<sup>[8]</sup>

## Lipid Effects of Drug Classes in Dyslipidemia and Hypertriglyceridemia

Mixed dyslipidemia	TG	LDL-C	HDL-C
	Range, %		
• Statins	-10 to -37	-26 to -63	+5 to +16
• Omega-3 fatty acids	-19 to -44	-6 to +25	-5 to +7
• Fenofibrate, fenofibric acid, and gemfibrozil	-24 to -36	-5 to -31	+10 to +16
Isolated hypertriglyceridemia	TG	LDL-C	HDL-C
	Range, %		
• Statins	-21 to -52	-27 to -45	+3 to +22
• Omega-3 fatty acids	-26 to -52	+17 to +49	+9 to +14
• Fenofibrate, fenofibric acid, and gemfibrozil	-46 to -62	+3 to +47	+18 to +23

Maki KC, et al. *J Clin Lipidol.* 2012;6:413-426.<sup>[14]</sup>

- **2016 ESC/EAS Guidelines for the management of dyslipidaemias**  
**The Task Force of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)**  
**Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)**

Task Force Members: A L. Catapano\* (Chairperson) (Italy), I Graham\* (Chairperson) (Ireland), G De Backer (Belgium), O Wiklund (Sweden), M. J Chapman (France), H Drexel (Austria), A W. Hoes (The Netherlands), C S. Jennings (UK), U Landmesser (Germany), T R. Pedersen (Norway), Ž Reiner (Croatia), G Riccardi (Italy), M-R Taskinen (Finland), L Tokgozogl (Turkey), W. M. M Verschuren (The Netherlands), Ch Vlachopoulos (Greece), D A. Wood (UK), J L Zamorano (Spain).

Additional Contributor: M T Cooney (Ireland)

## ESC CP Guidelines 2016 – Highlights: Dyslipidaemias

### *Treatment of tryglicerides*

#### 2011 ESC Dyslipidaemias guidelines

Recommendation	Class	Level
Fibrates drug of choice	I	B
Considerd nicotinic acid	IIa	B
Nicotinic acid +laropiprant	IIa	C
Statin+Nicotinic acid	IIa	A
Statin+Fibrate	IIa	C
N-3 fatty acids	IIa	B
Fibrate+n-3 fatty acids	IIb	B

#### 2016 ESC Dyslipidaemias guidelines

Recommendation	Class	Level
Treatment considered in high risk patients and TG >2.3 mmol/L (200 mg/dl)	IIa	B
Statins considered as the first drug of choice for reducing CVD risk in high risk individuals with hypertriglyceridaemia	I	A
In high risk patients with TG >2.3 mmol/L despite treated with statin, fenofibrate considered in combination with statins	IIb	C

## Summary of the efficacy of drug combinations for the management of mixed dyslipidaemias

A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided.

If TG are not controlled by statins or fibrates, prescription of n-3 fatty acids may be considered to decrease TG further, and these combinations are safe and well tolerated.

## **Triglyceride Target Level**

- **The target for triglyceride level is related to the degree of CV risk .**
- **Treatment for high triglyceride should take into account other cholesterol levels and whether triglyceride level consistently high , where the cause must be considered.**
- **Triglycerides add information about the risk , and is indicated for the diagnosis and the choice of treatment .**

**THANK U**