Triglycerides and Risk for Atherothrombosis

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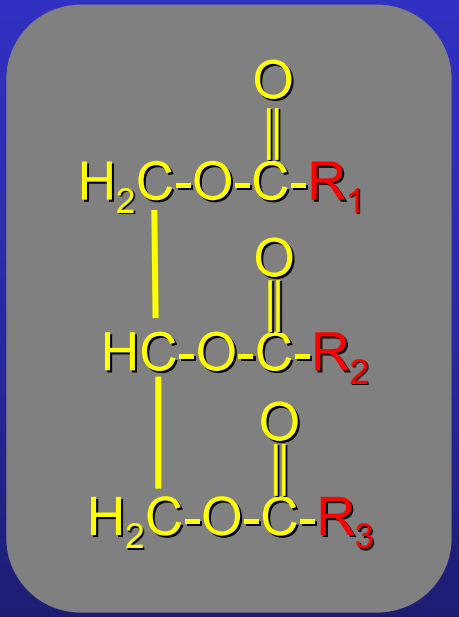
Fredrickson-Levy-Lees Classification of Hyperlipoproteinemia

Phenotype	Occurrence	Lipoprotein Present in Excess	Chol	Trig
I	Rare	Chylomicrons	250-400	>2500
IIA	Common	LDL	>250	<150
IIB	Most common	LDL,VLDL	>250	150-400
III	Rare	VLDL remnants	375-500	600-800
IV	Common	VLDL	225-275	375-500
V	Rare	Chylomicrons, VLDL	350-400	1700-2500

Pharmacotherapy 4th Edition.p. 353

Triglycerides - Triacylglycerol

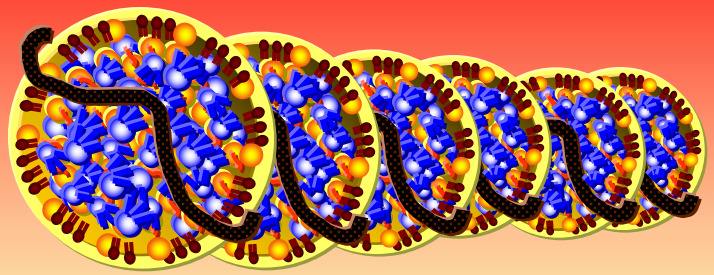
- Triglycerides are water-insoluble lipids consisting of three fatty acids linked to one glycerol molecule.
  - They represent a concentrated source of metabolic energy contributing 9 kcal/gm.
- TG are transported as core constituents of all lipoproteins, but the greatest concentration is in TG-rich chylomicra and VLDL particles



R = Fatty acid chain

Rafai, N et al. Handbook of Lipoprotein Testing AACC Press Washington DC 2nd Ed 2000

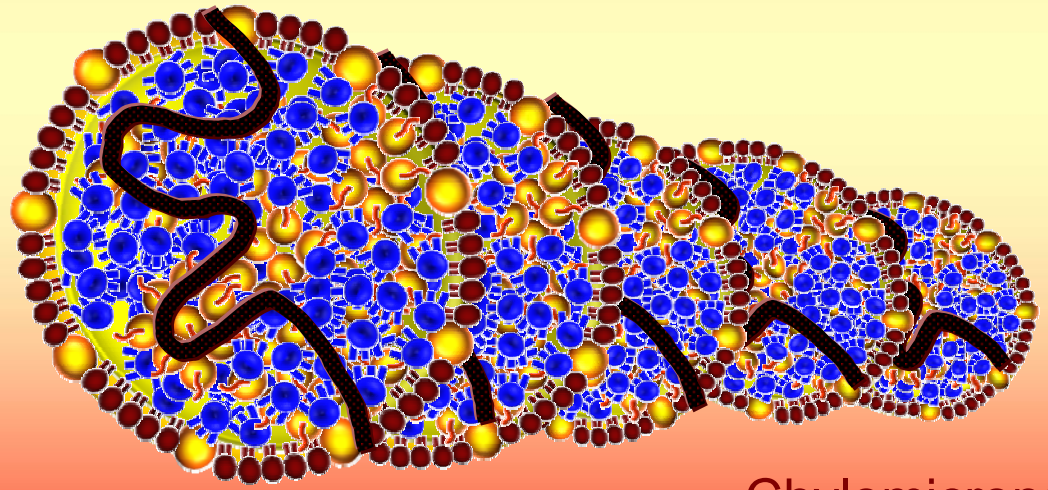
TG-trafficking Lipoproteins



Large Small

VLDLs

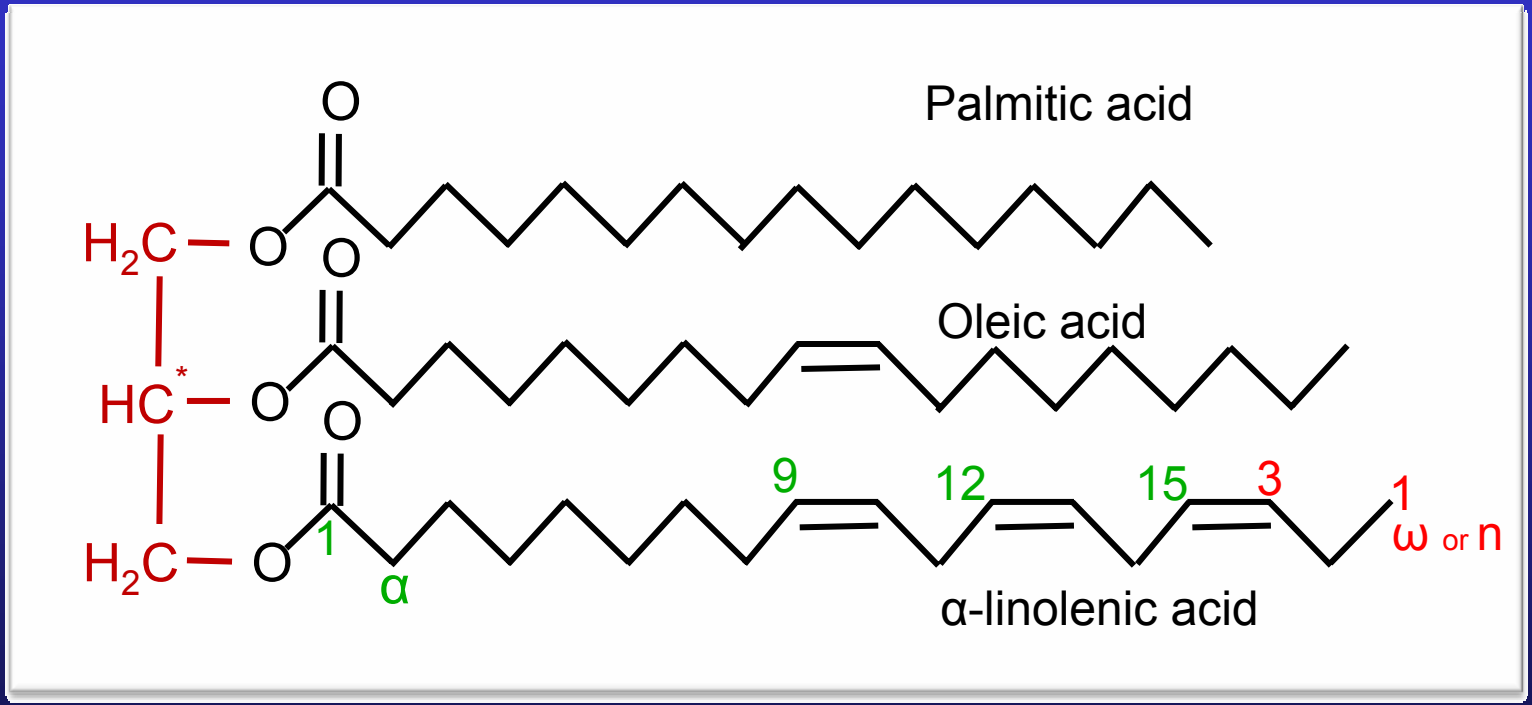
Serum Triglycerides refers to the triacylglycerol (TG) concentration trafficked in all of the **lipoproteins** found in a deciliter of plasma



Chylomicrons

Normally the vast majority of TG are trafficked within chylomicrons and VLDLs

Triacylglycerol - Triglyceride



Palmitic acid, oleic acid, alpha-linolenic acid
Chemical formula: $C_{55}H_{98}O_6$

National Cholesterol Education Program
Adult Treatment Panel III NCEP-ATP III
Risk of Triglycerides

- Several causes underlie elevated Triglycerides in the general population
  - Overweight and obesity
  - Physical inactivity
  - Cigarette smoking
  - Excess alcohol intake
  - Very high carbohydrate diets (>60% of energy)
  - Other disease (diabetes, renal failure, nephrosis)
  - Drugs: steroids, protease inhibitors, estrogen, etc
  - Genetic factors

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Elevations of Triglycerides

In persons with none of these factors, serum triglyceride levels typically are less than 100 mg/dL.

As some of these triglyceride-raising factors develop, levels commonly rise into the range of 150 to 199 mg/dL. Although several factors can elevate triglycerides most common are overweight/obesity and physical inactivity

When triglyceride rise to ≥200 mg/dL, genetic influences play an increasing role as well.

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Risk of Triglycerides

Risk Classification of Serum Triglycerides

Normal <150 mg/dL

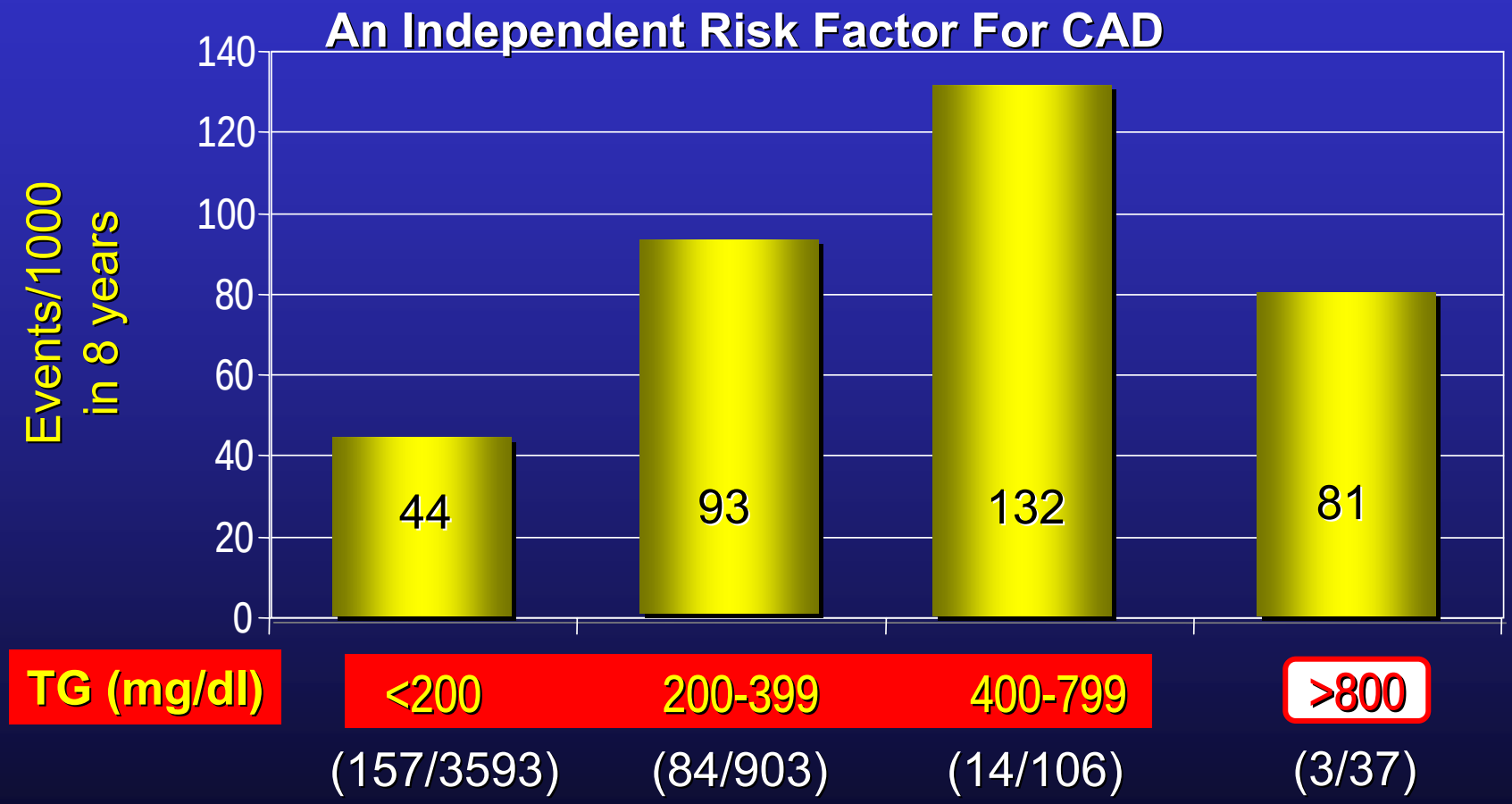
Borderline high 150–199 mg/dL

High 200–499 mg/dL

Very high ≥500 mg/dL

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

PROspective CArdiovascular Munster Study (PROCAM): Hypertriglyceridemia



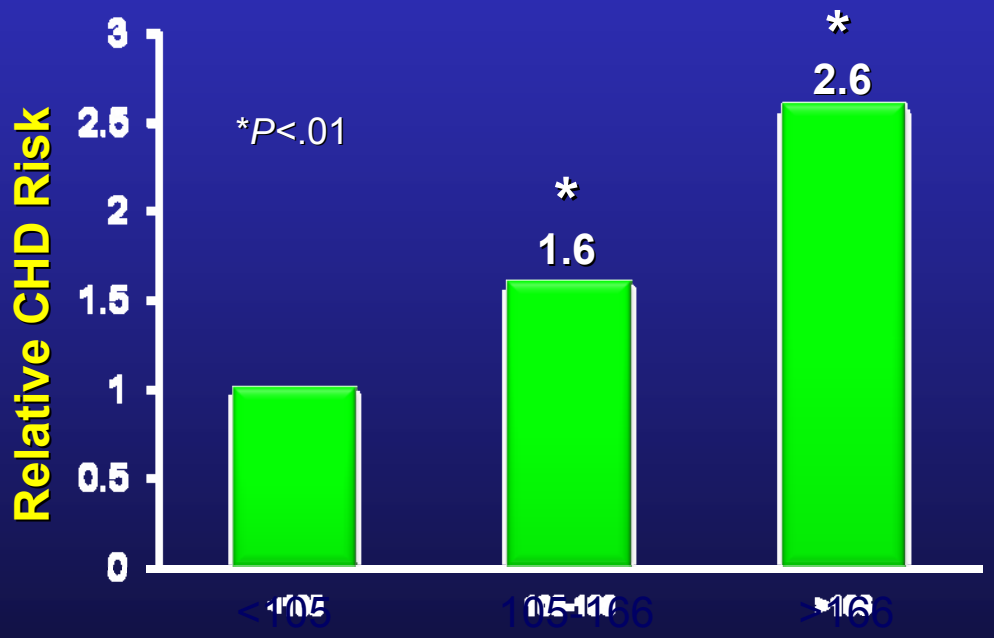
Assman, G et al., Am J Cardiol 1992;70:733-737

PRospective CArdiovascular Münster Study (PROCAM) Risk of CHD by Triglyceride Level

8-Year Follow-Up

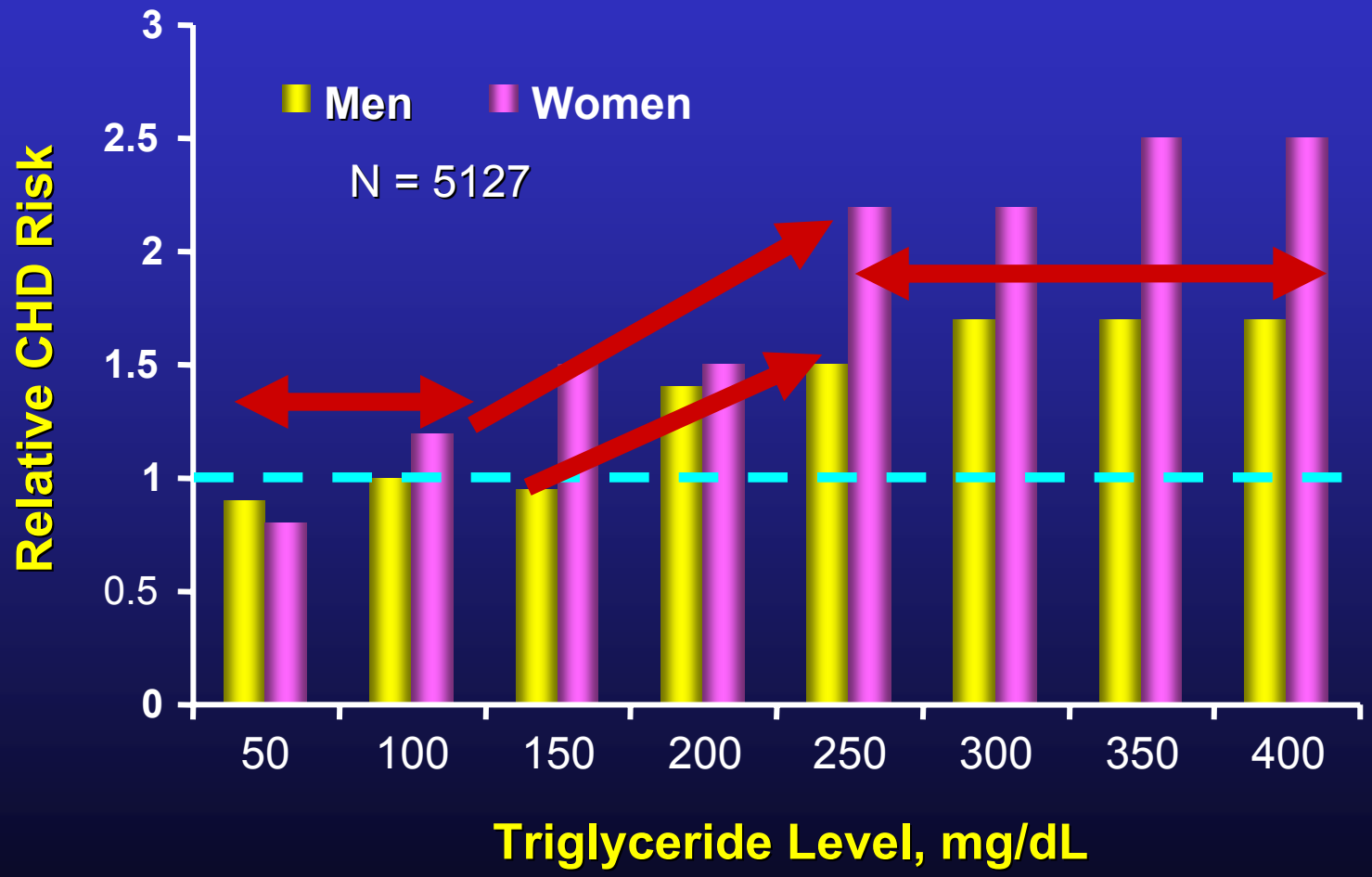
N = 4639 men with no history of MI or stroke

- Elevated triglyceride levels significantly increase CHD risk
- Significant correlation remains between triglyceride level and CHD risk after adjustment for LDL-C and HDL-C
- 6-fold increased CHD risk in patients with triglycerides >200 mg/dL and LDL-C:HDL-C >5



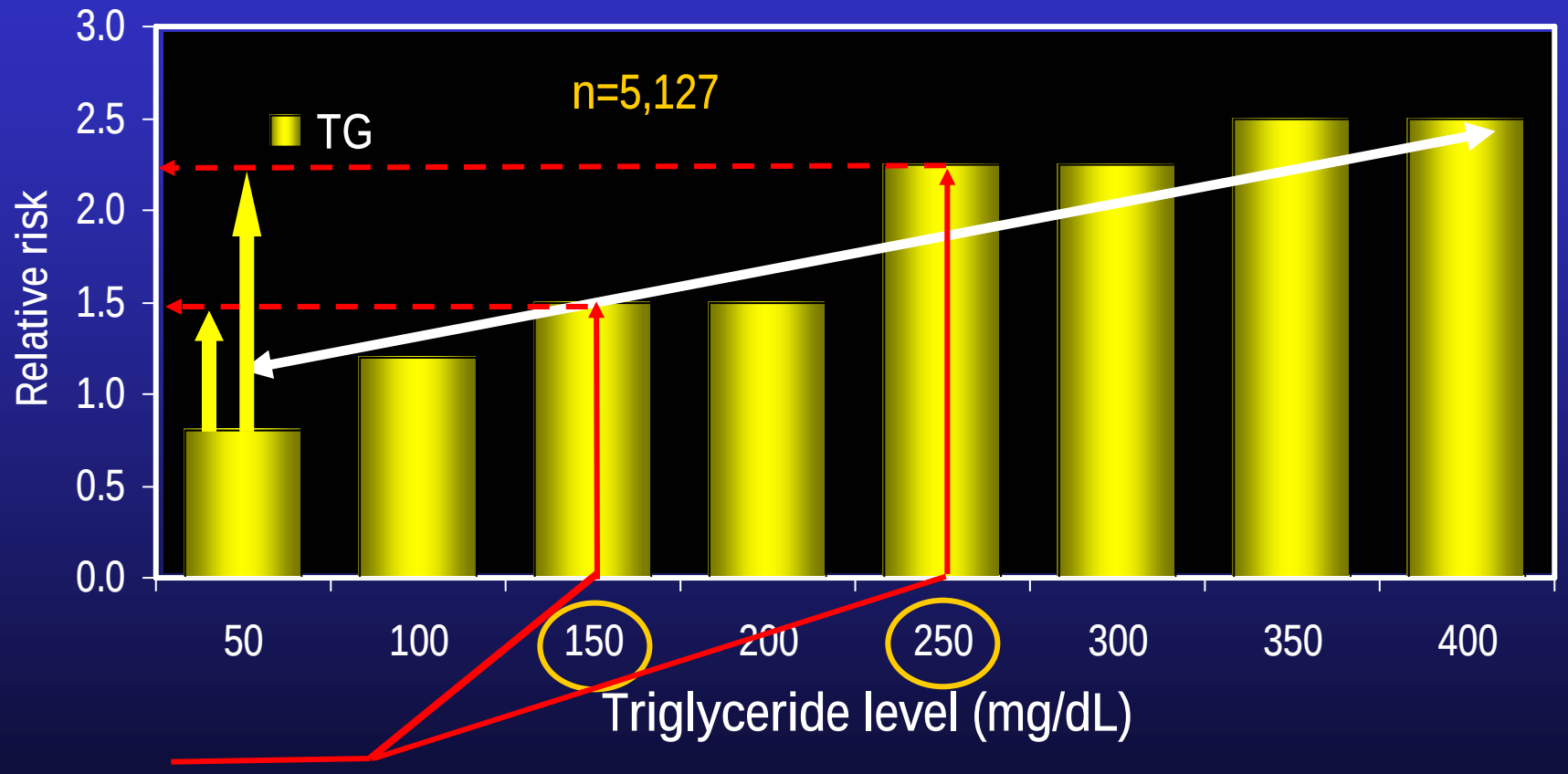
Assmann, et al. Am J Cardiol. 1996;77:1179-1184.

Risk of CHD by Triglyceride Level
The Framingham Heart Study



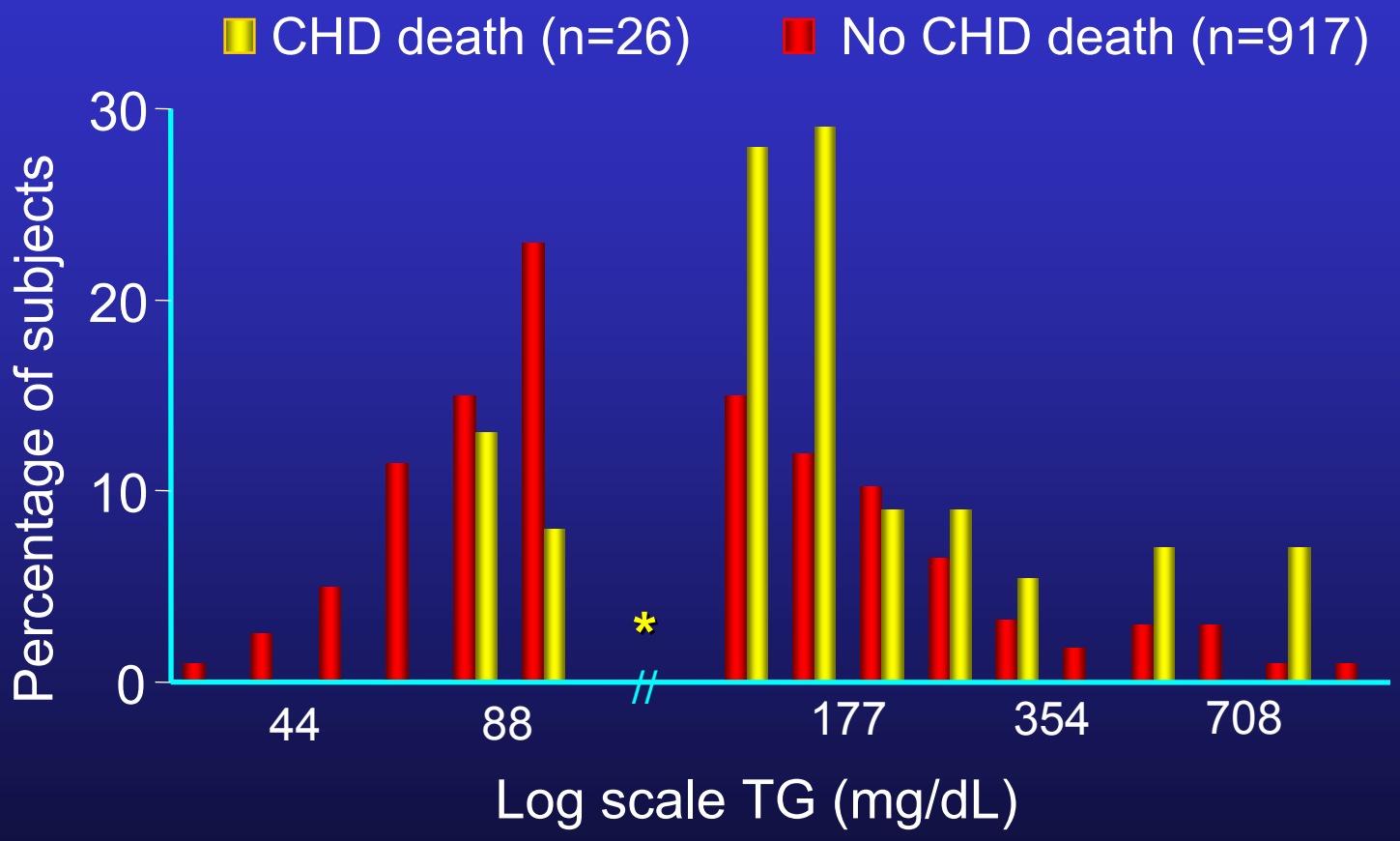
Castelli WP. *Am J Cardiol.* 1992;70:3H-9H.

Risk of CHD by Triglyceride Level: The Framingham Heart Study Women



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

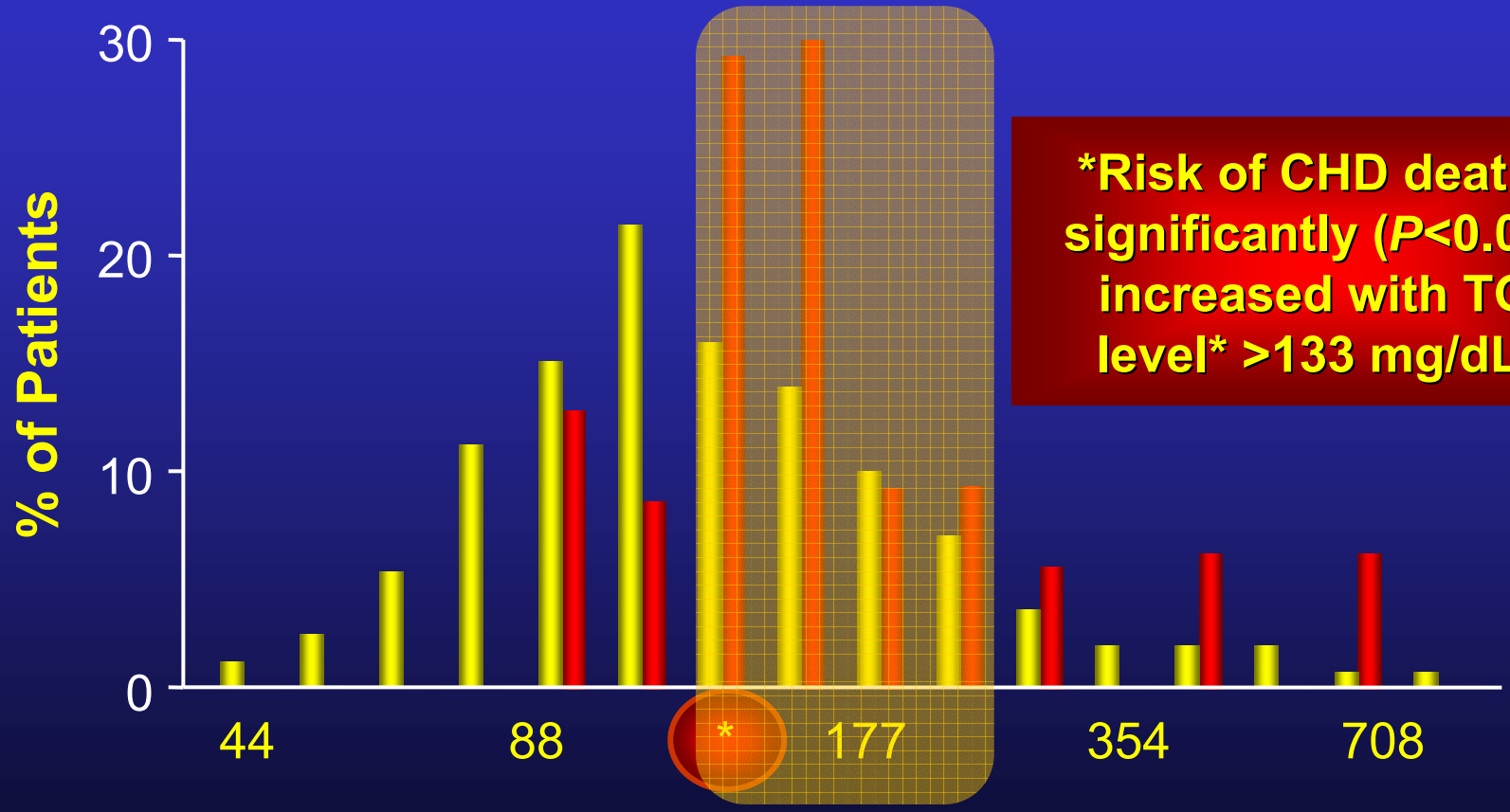
Hypertriglyceridemia as a Risk Factor for CHD in Men With IGT or Diabetes



*Risk of CHD death **significantly (*P*<0.01) increased** in subjects with triglyceride level above this point.

Fontbonne A et al. *Diabetologia*. 1989;32:300-304.

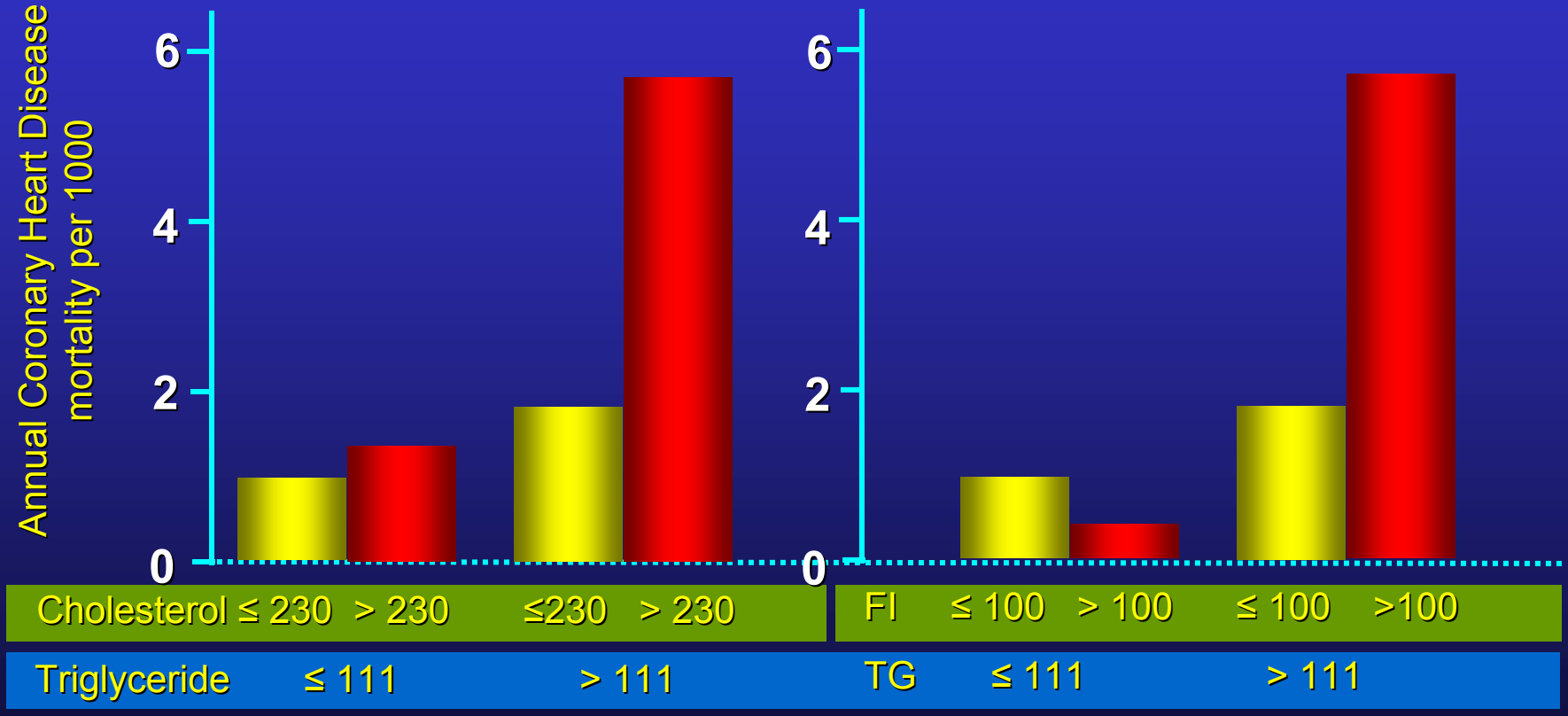
Paris Prospective Study: 11 Year Follow-up Hypertriglyceridemia as a Risk Factor for CHD in Male Patients with Diabetes or IFG



***Risk of CHD death significantly (*P*<0.01) increased with TG level* >133 mg/dL.**

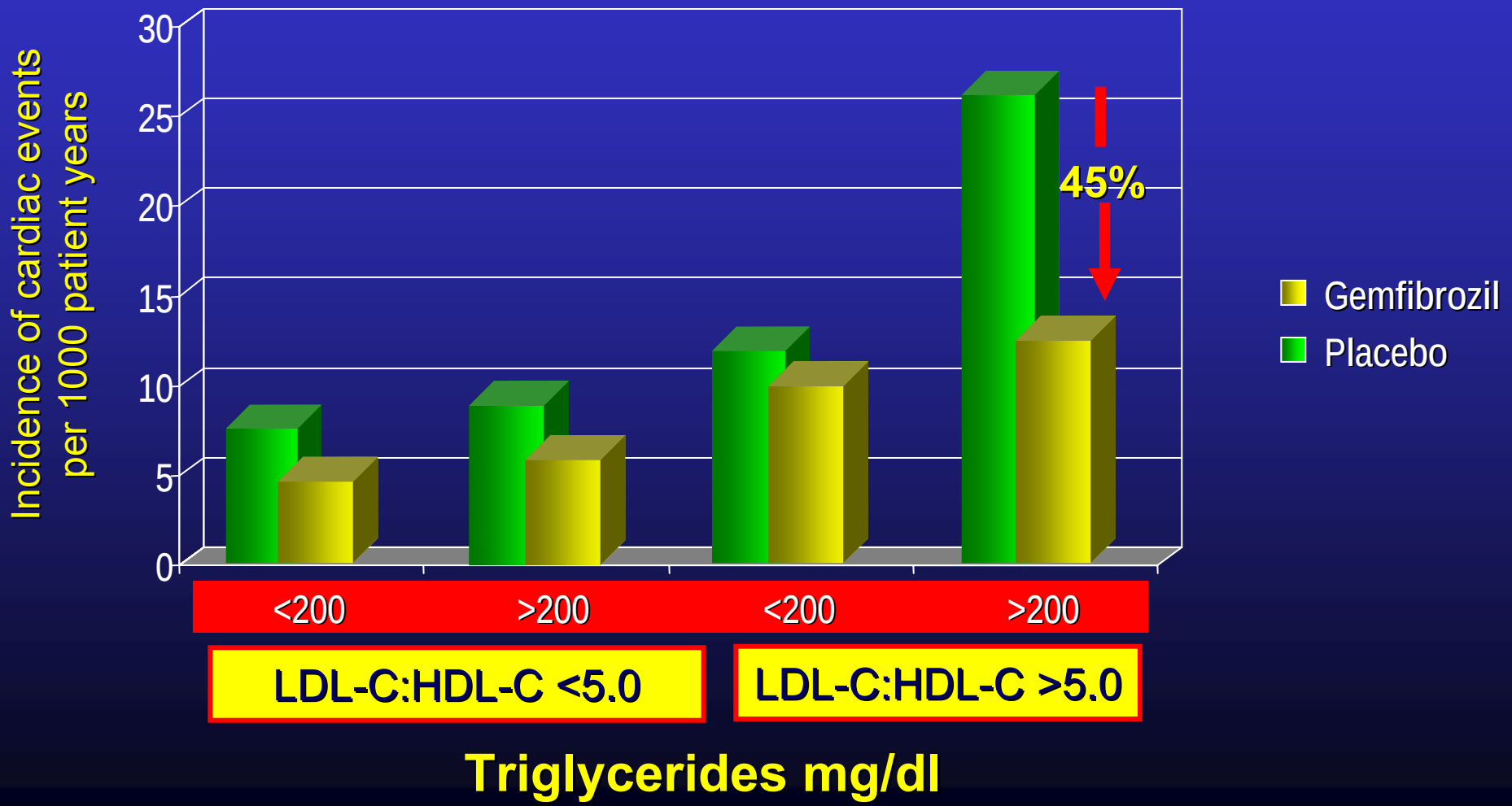
Fontbonne et al. *Diabetologia.* 1989;32:300.

Paris Prospective Study: 11 Year Follow-up Hypertriglyceridemia as a Risk Factor for CHD in Male Patients with Diabetes or IFG



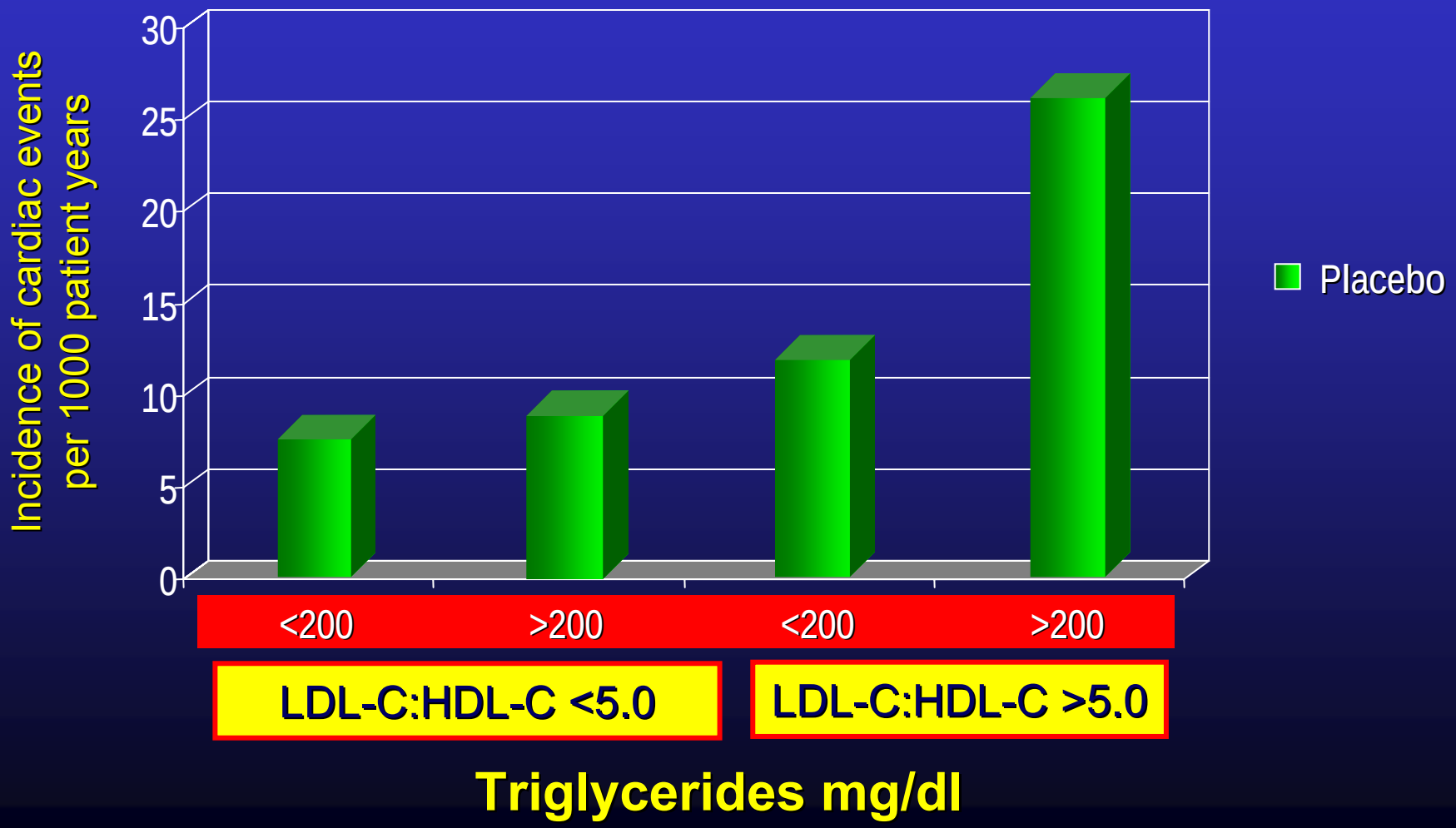
Fontbonne et al. *Diabetologia.* 1989;32:300.

- Helsinki Heart Trial - Triglyceride, HDL-C and Risk for CAD



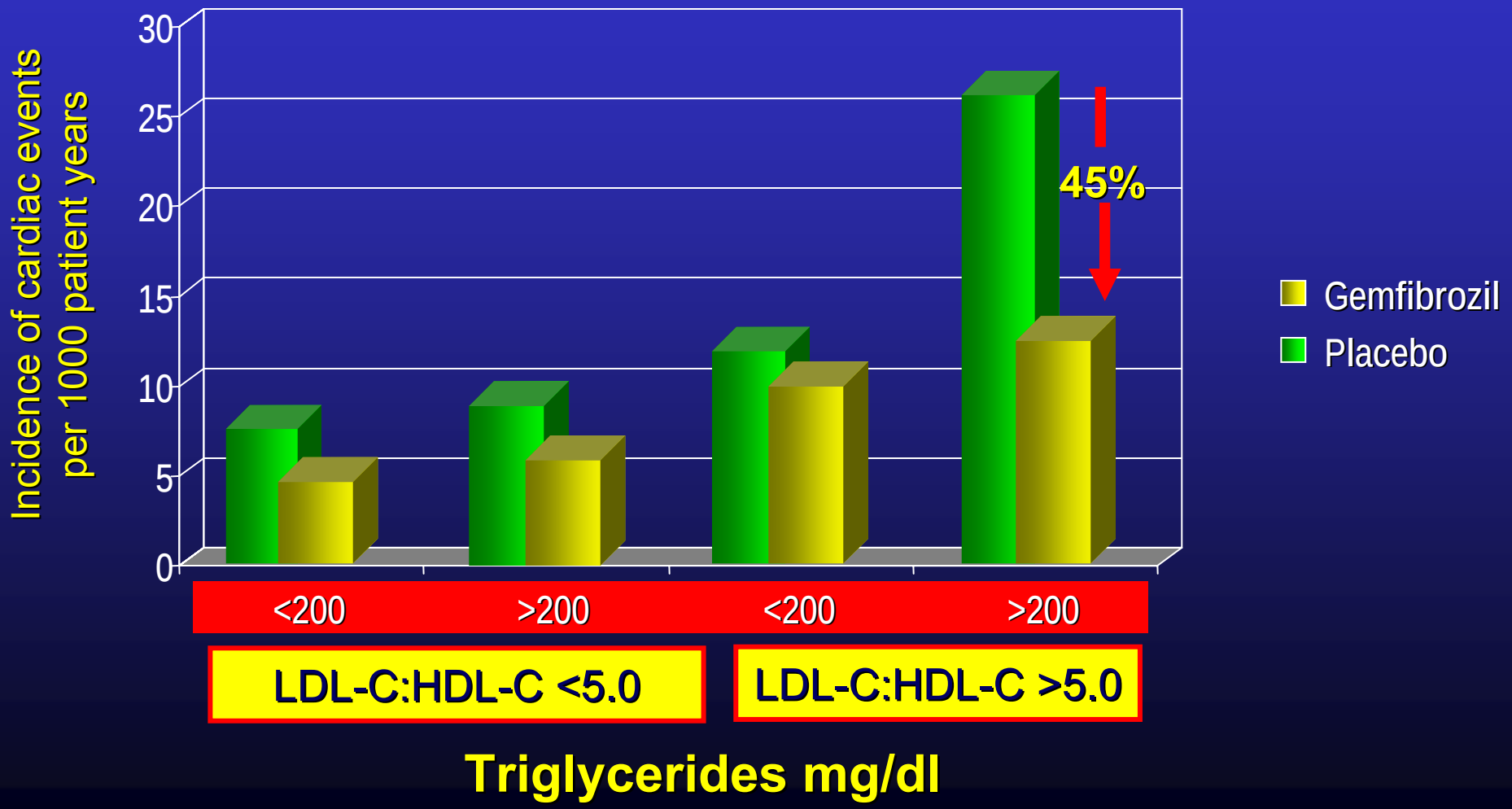
Circulation 1992;85:37-46

- Helsinki Heart Trial - Triglyceride, HDL-C and Risk for CAD



Circulation 1992;85:37-46

- Helsinki Heart Trial - Effects of Gemfibrozil



Circulation 1992;85:37-46

The Baltimore Coronary Observational Long-Term Study

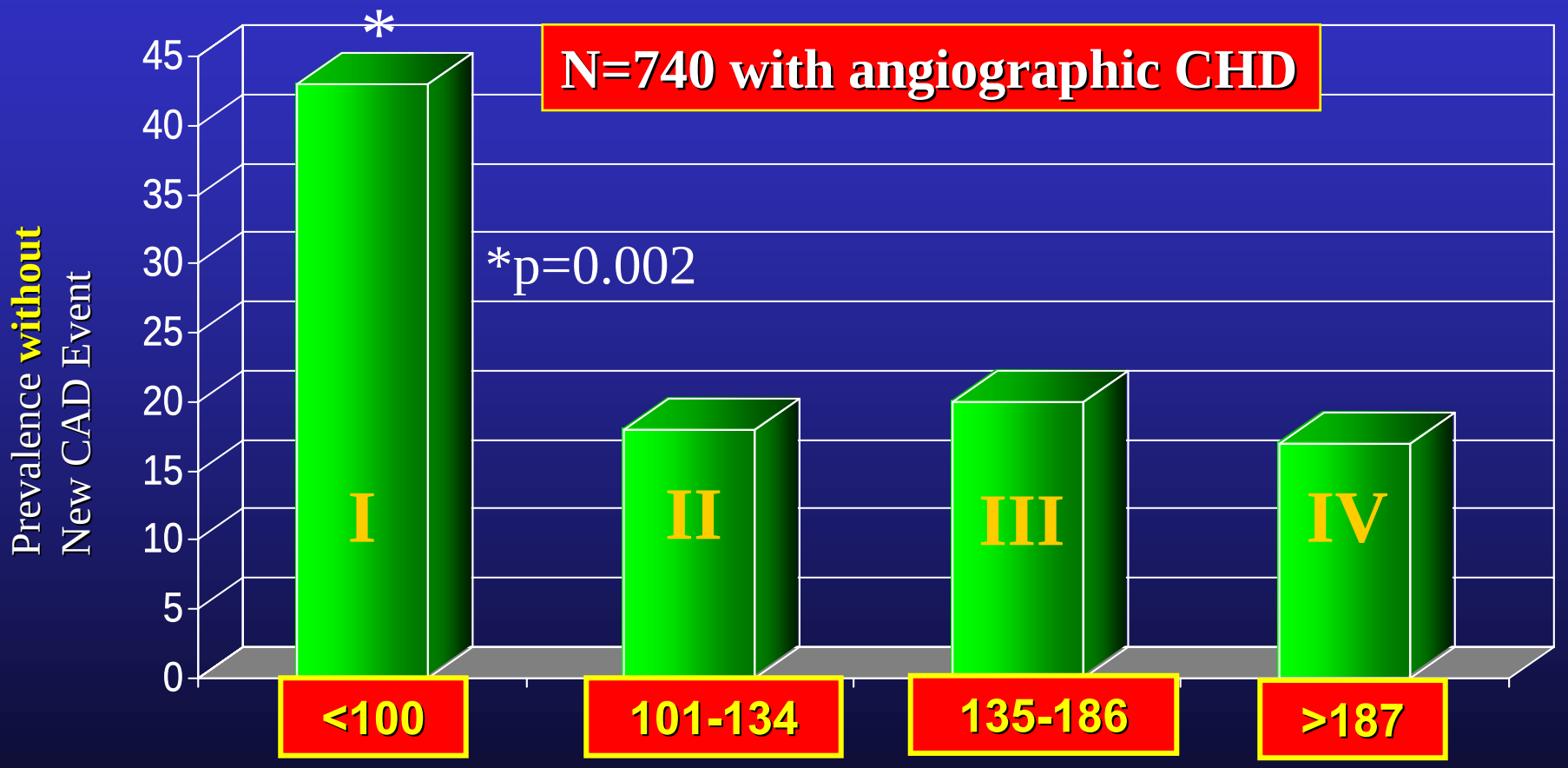
N=740 with angiographic CHD at baseline

What is the prevalence without new CAD event after 18 years

According to standard baseline risk factors

Miller, M J Am Coll Cardiol 1998;31:1252-7

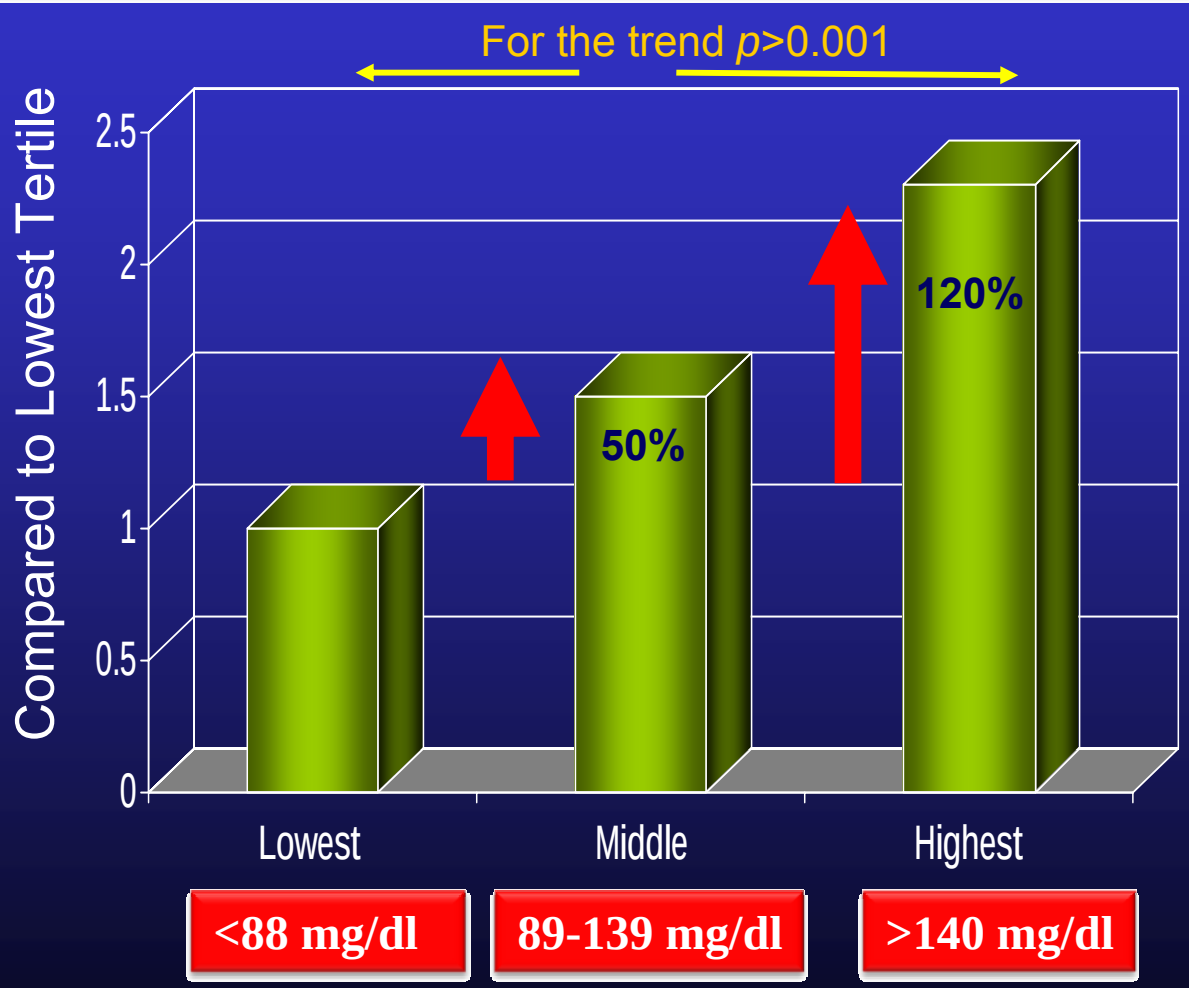
The Baltimore Coronary Observational Long-Term Study



Miller, M J Am Coll Cardiol 1998;31:1252-7

The Copenhagen Male Study

2906 men free of CVD 8 year follow up 229 men had first CHD event

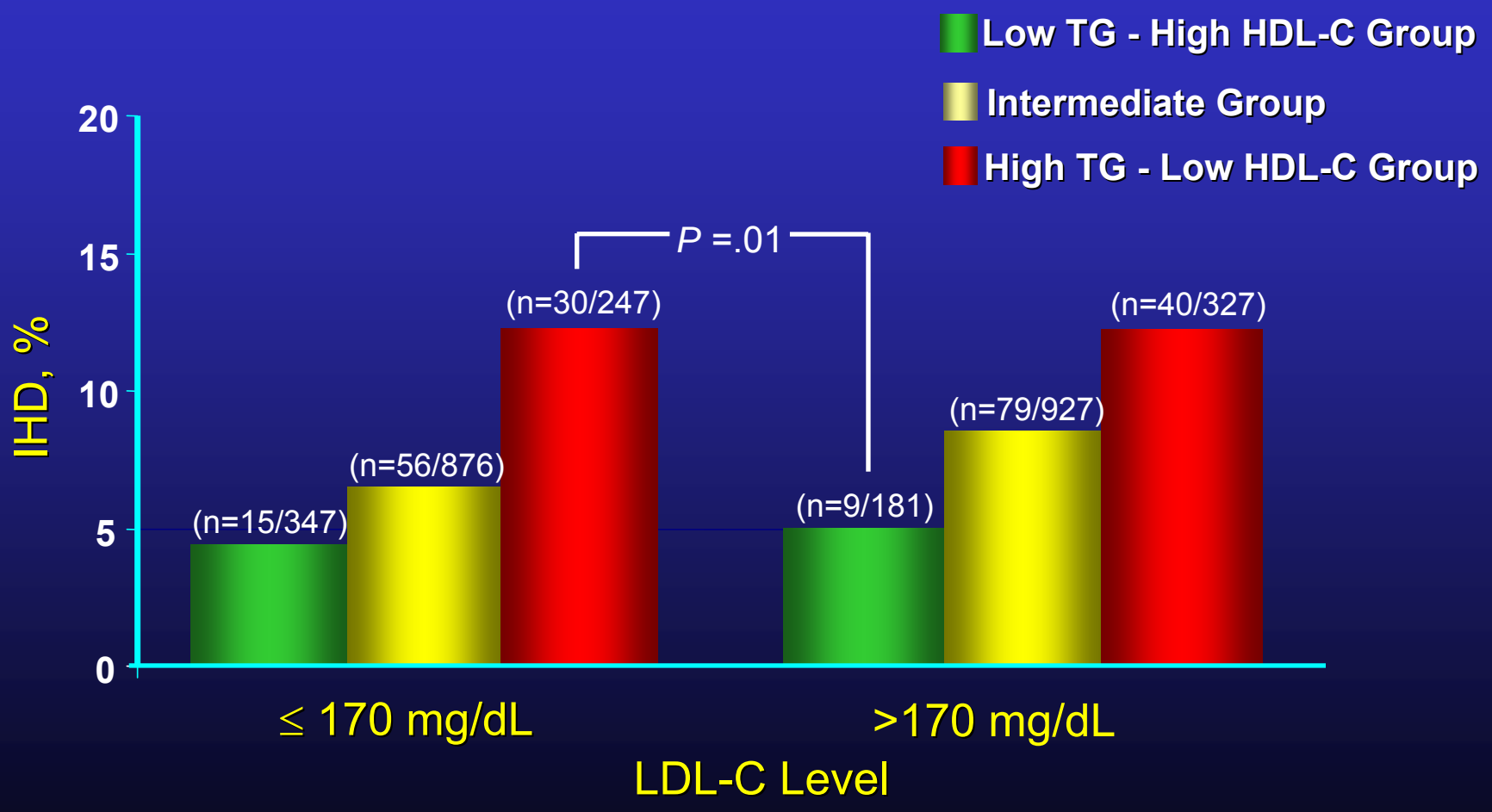


Adjusted for

- Age
- Body mass index
- Alcohol use
- Smoking
- Physical activity
- Hypertension
- Type 2 diabetes
- Social class
- LDL-C
- HDL-C

Circulation 1998;97:1029-36

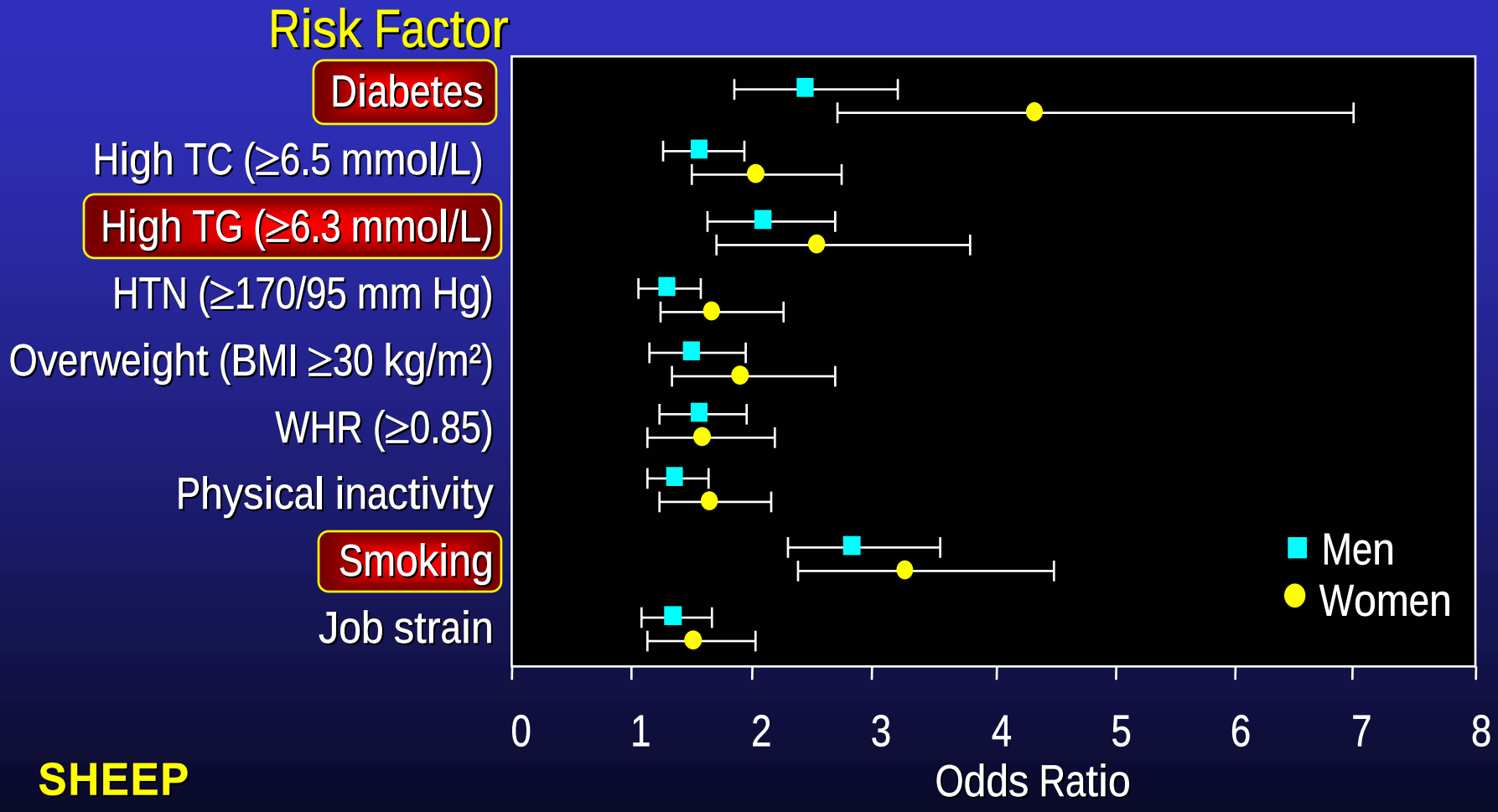
Copenhagen Male Study
Combination of High Triglyceride and Low HDL



Jeppesen, et al. *Arch Int Med.* 2001;161:361.

Stockholm HEart Epidemiology Program

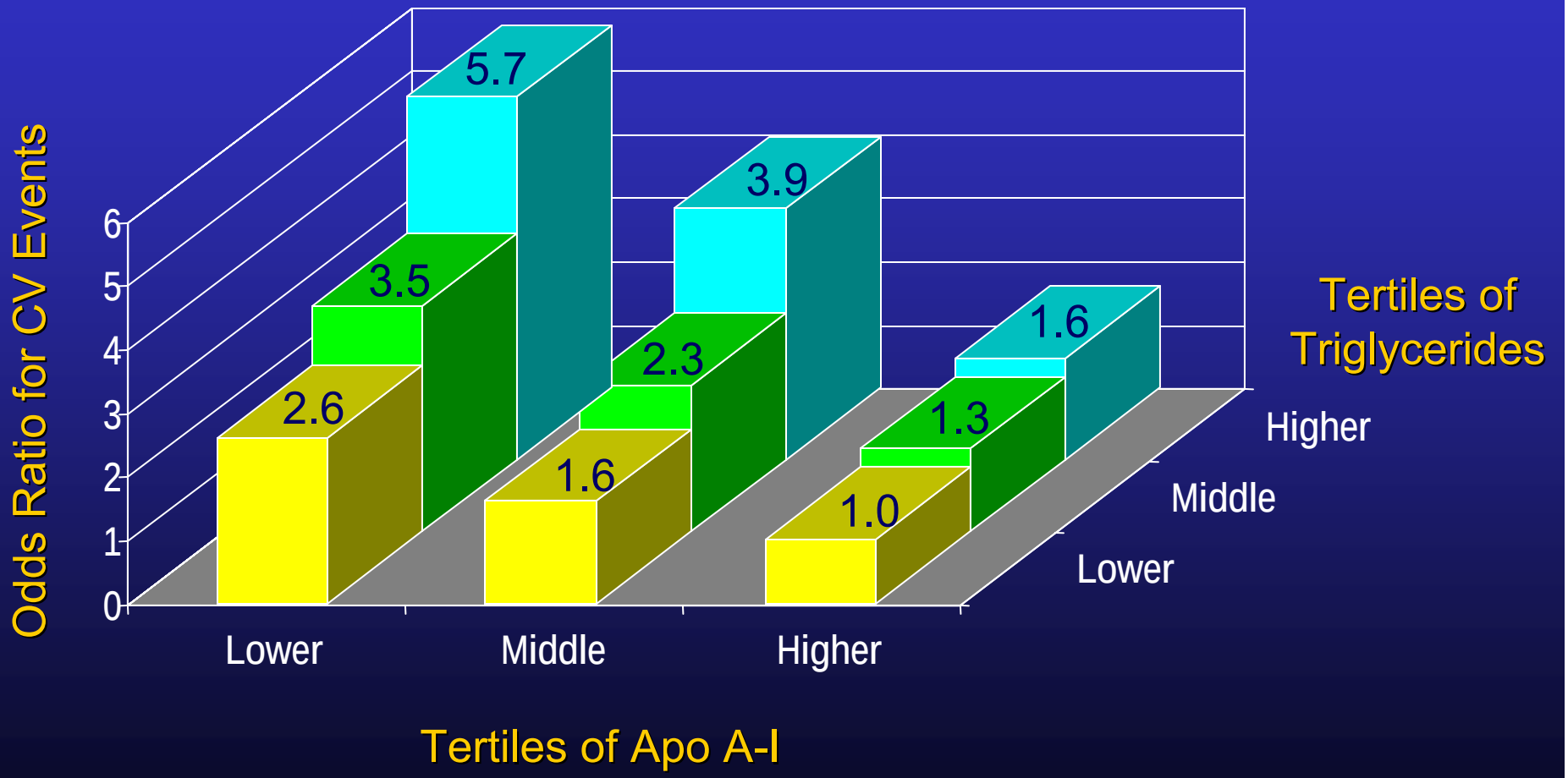
Risk Factors for Nonfatal MI in Men and Women



SHEEP

Reuterwall C et al. *J Intern Med*. 1999;246:161-174.

CAD Risk in European Concerted Action on Thrombosis (ECAT)-Angina Pectoris Study



Thromb Haemost 2000;84:955-960

Applying Clinical Trial Results To The General Population

- 4 Primary Prevention Trials
  - LRC-CPPT, Helsinki, WOSCOPS, AFCAPS-TexCAPS
  - 19-37% reductions in risk of first coronary event
  - Inclusion criteria: high risk lipid profiles
    - Only AFCAPS included women

- Framingham Heart Study included 2498 men and 2870 women age 34-75, free of CHD
  - Only **60%** of these men and **20%** of the women had cholesterol elevations which would have qualified them for the above studies.

Arch Intern Med 2001;161:949-954

Framingham Heart Study

40% of presumably healthy men and **80% of women** aged 30-74 in Framingham Heart Study had lipid profiles that were not considered serious enough to study in any primary coronary prevention clinical trials to date.

In general subjects with desirable or average cholesterol and lower, average or high HDL-C have not been included in clinical trials

Lloyd-Jones D, et al. Arch Intern Med 2001;161:949-954

Framingham Heart Study

In other words, **40%** of presumably healthy men and **80% of women** in Framingham Heart Study had lipid profiles that were not considered serious enough to study in any primary coronary prevention clinical trials to date.

Unfortunately, a large number of these “ineligible” patients with minor lipid abnormalities went on to develop CHD events.

Arch Intern Med 2001;161:949-954

Framingham Heart Study

Unfortunately, many (11% of the 2498 men and 4.7% of 2870 women) of these "ineligible" patients with minor LDL-C abnormalities went on to develop CHD events.

Arch Intern Med 2001;161:949-954

Framingham Heart Study

- Among subjects in Framingham who developed incident CHD during a 12 year follow-up:
  - The **MAJORITY (66%) of the women**
  - **25% of the men**

Did not have an elevated LDL-C that would have qualified for any primary prevention lipid trial ever done

Arch Intern Med 2001;161:949-954

Framingham Heart Study

What was the most common lipid abnormality in these patients who developed CHD ?

Isolated hypertriglyceridemia
(>200 mg /dl)

Elevated TG and low HDL-C

Arch Intern Med 2001;161:949-954

Applying Trials To The General Population

This landmark study shows us that there is no cutoff cholesterol number below which coronary heart disease cannot develop.

Therefore, many men and **most** women with heart disease have lipid problems other than high total or LDL cholesterol that put them at risk for heart disease.

Edward F Gibbons MD

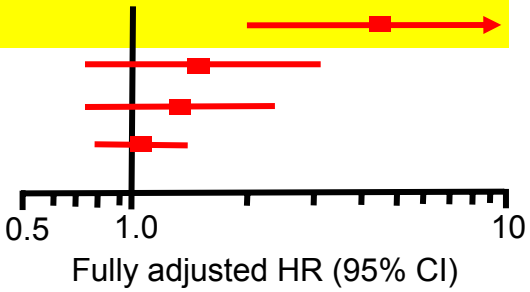
Editor of New England Journal Medicine Heart Watch

June 2001 Vol 5 #5 p3

Women's Health Study
Fasting versus Nonfasting Triglycerides

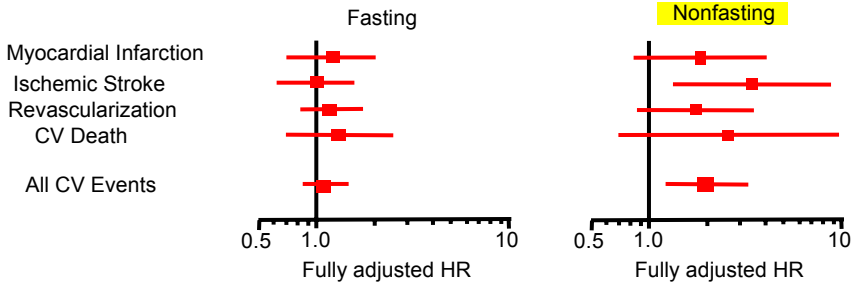
Association of TG with Future CV Events Stratified by Time from Last meal

Time from last meal, hrs	# patients	# Events	Hazard ratio (95% CI)
2 - < 4	2707	08	4.48 (1.08-10.15)
4 - 8	2504	02	1.50 (0.72-3.13)
8 - 12	4846	177	1.31 (0.73-2.36)
≥ 12	15272	600	1.04 (0.70-1.36)

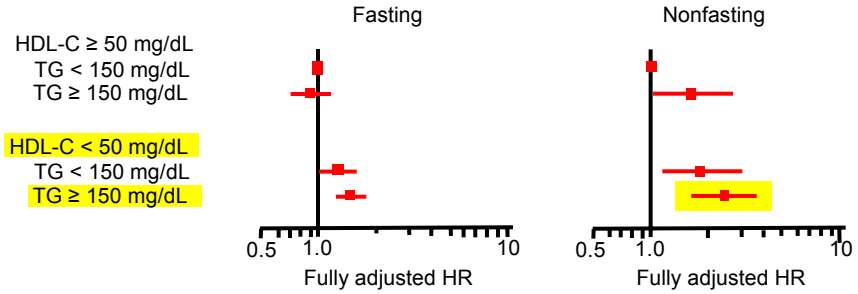


HR for highest (> 147) vs lowest tertiles (≤ 90) of TG levels adjusted for age, BP, smoking, hormone use, tertiles of total and HDL-C, DM, BMI & hs-CRP

Association of TG with Individual CV Endpoints according to fasting status



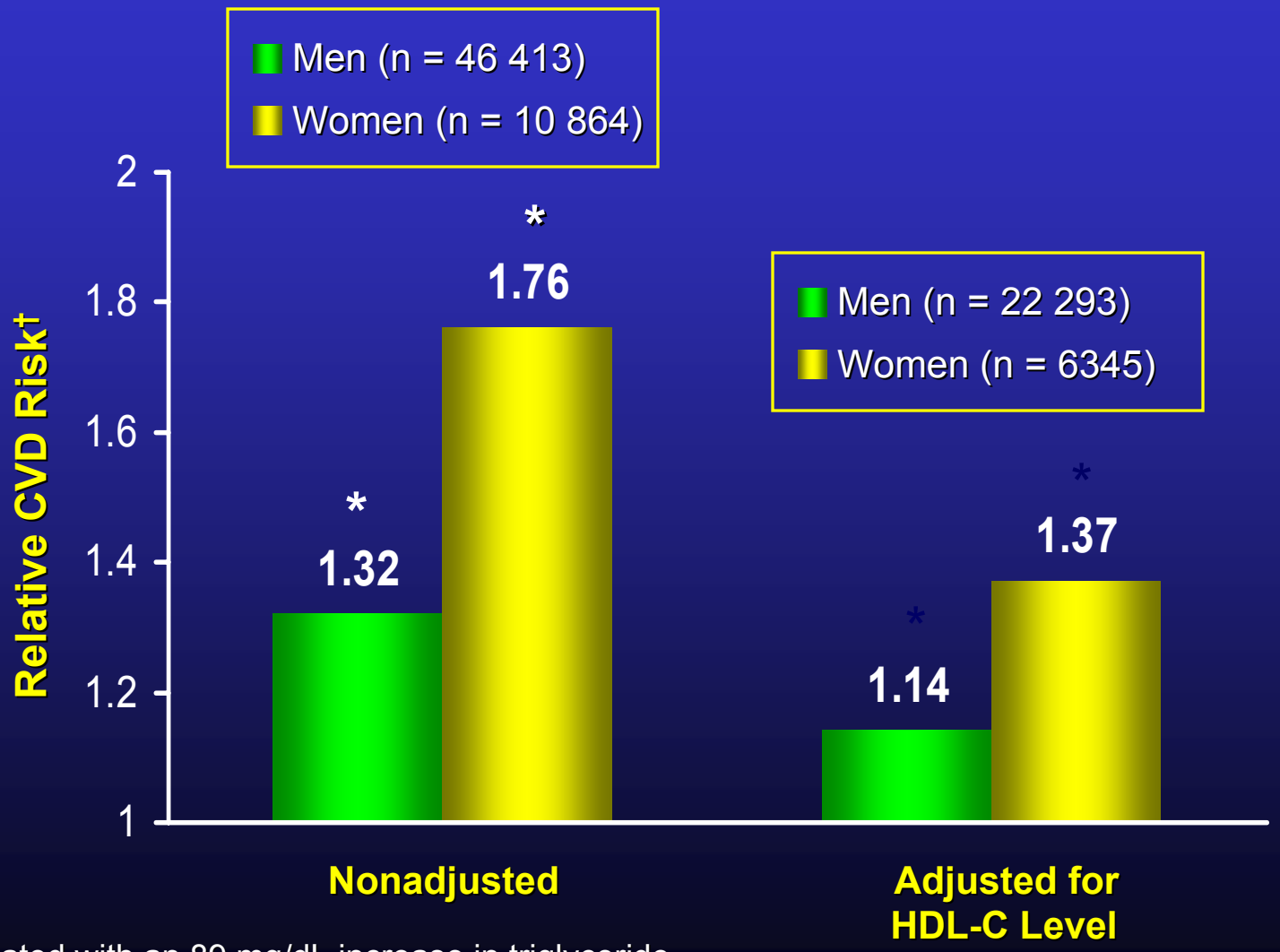
Association of High vs Low TG levels with future CV events stratified by HDL-C level



HR using TG levels < 150 and HDL-C levels ≥ 50 mg/dL adjusted for age, BP, smoking, hormone use, tertiles of total and HDL-C, DM, BMI & hs-CRP

Bansal, S et al. JAMA. 2007;298:309-316

Triglyceride Level Is Independent CVD Risk Factor Meta-Analysis of 17 Studies



†Associated with an 89 mg/dL increase in triglyceride

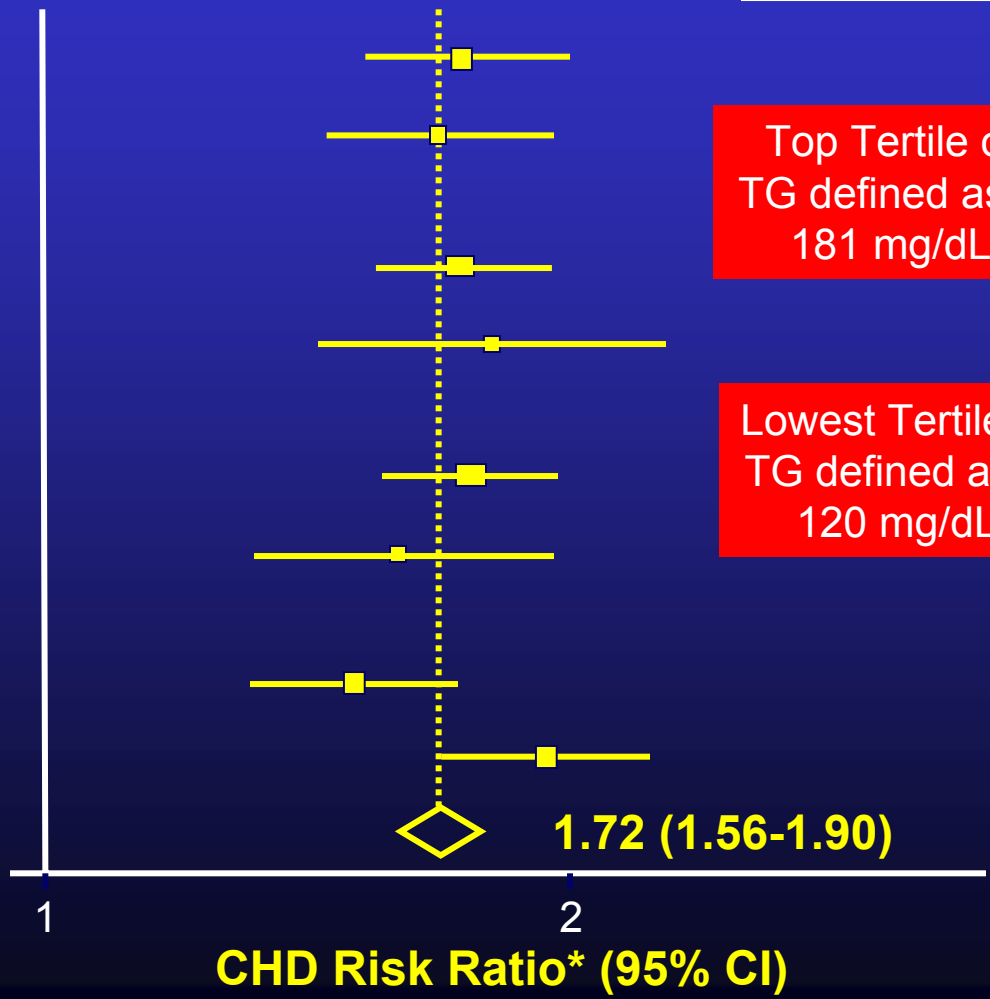
*P<.05

Austin MA, et al. *Am J Cardiol.* 1998;81:7B-12B.

Triglyceride Level Is Significant CVD Risk Factor
Recent Meta-Analysis of 29 Studies

Groups	CHD Cases
Duration of follow-up	
≥10 years	5902
<10 years	4256
Sex	
Male	7728
Female	1994
Fasting status	
Fasting	7484
Nonfasting	2674
Adjusted for HDL	
Yes	4469
No	5689

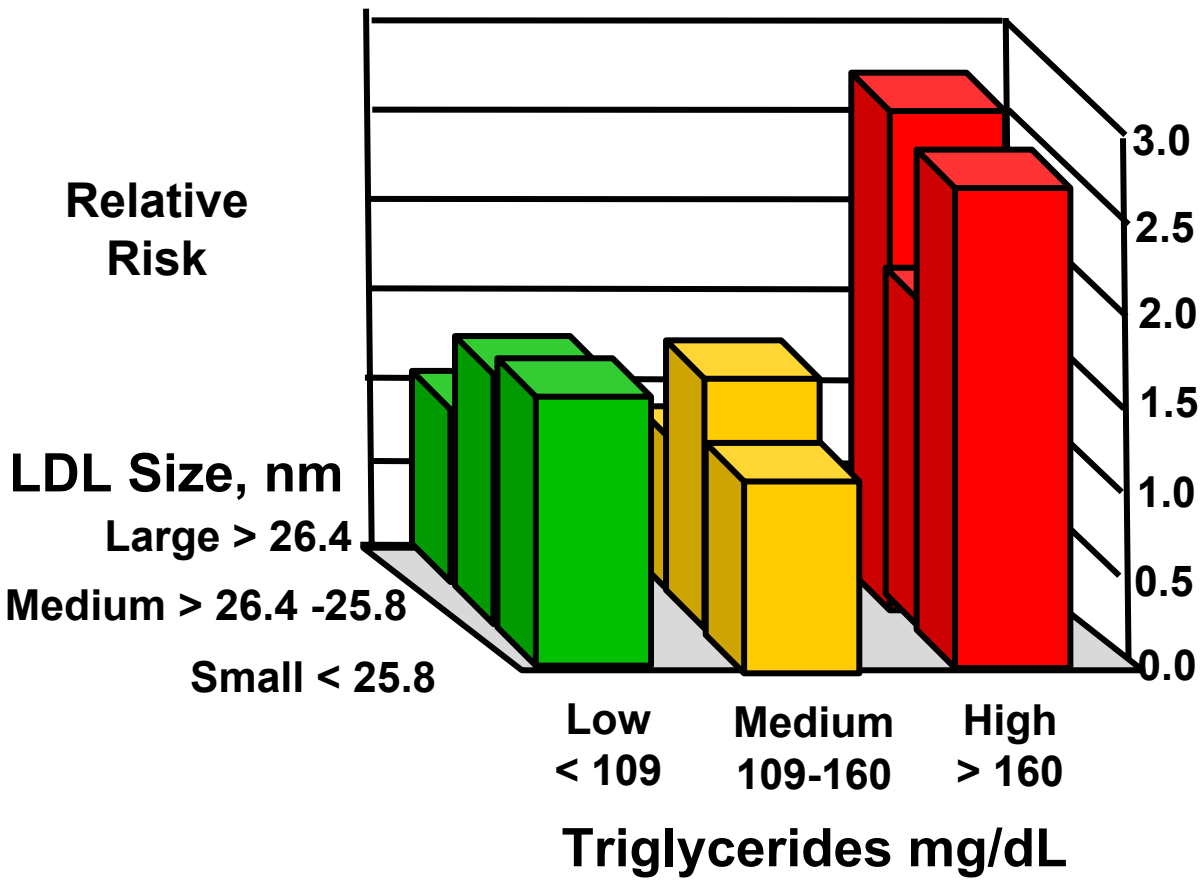
N = 262 525



*Individuals in top versus bottom third of usual log- triglyceride values, adjusted for at least age, sex, smoking status, lipid concentrations, and blood pressure (most)

Sarwar N, et al. *Circulation.* 2007;115:450-458.

Physicians Health Study

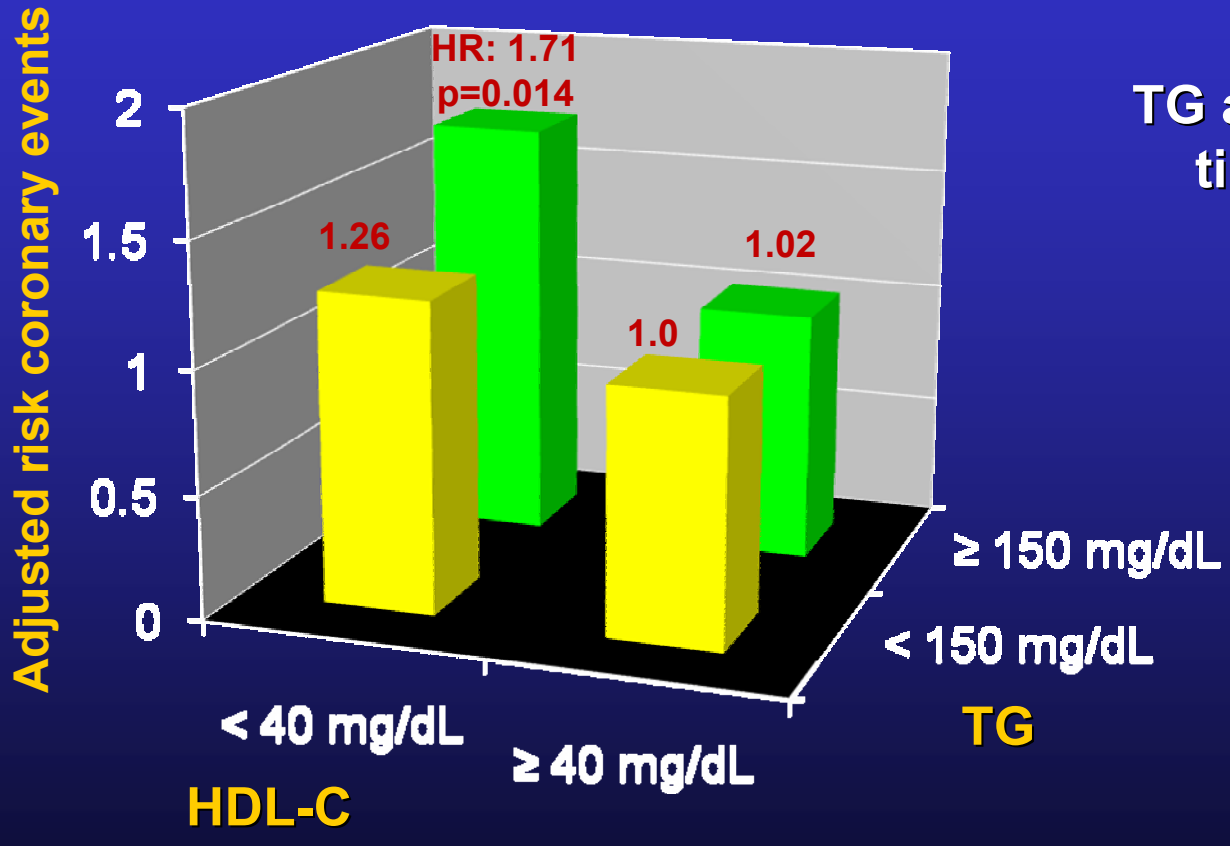


This figure demonstrates that the association between small LDL size and MI arises only from the association between small LDL size and high triglyceride concentration.

High triglyceride concentration is independently related to MI regardless of LDL size.

Sacks F & Campos H. **The J Clin Endo & Metab 88(10):4525–4532**

Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS)



TG and HDL-C values at time of registration

Adjusted for age, gender, smoking, diabetes and HTN

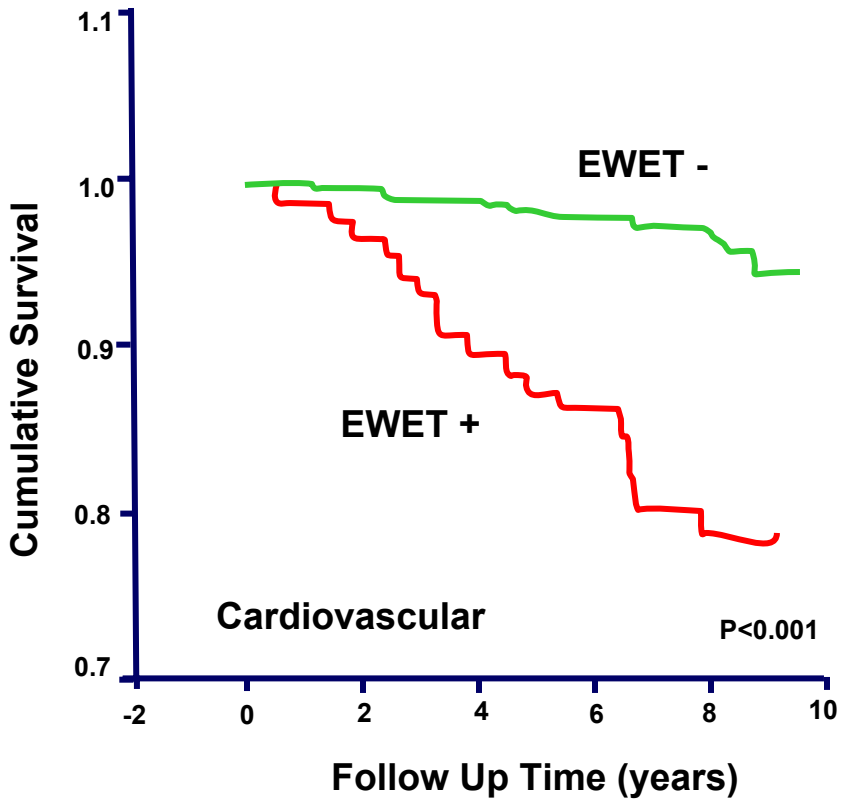
Saito Y et al. Atherosclerosis 2008;

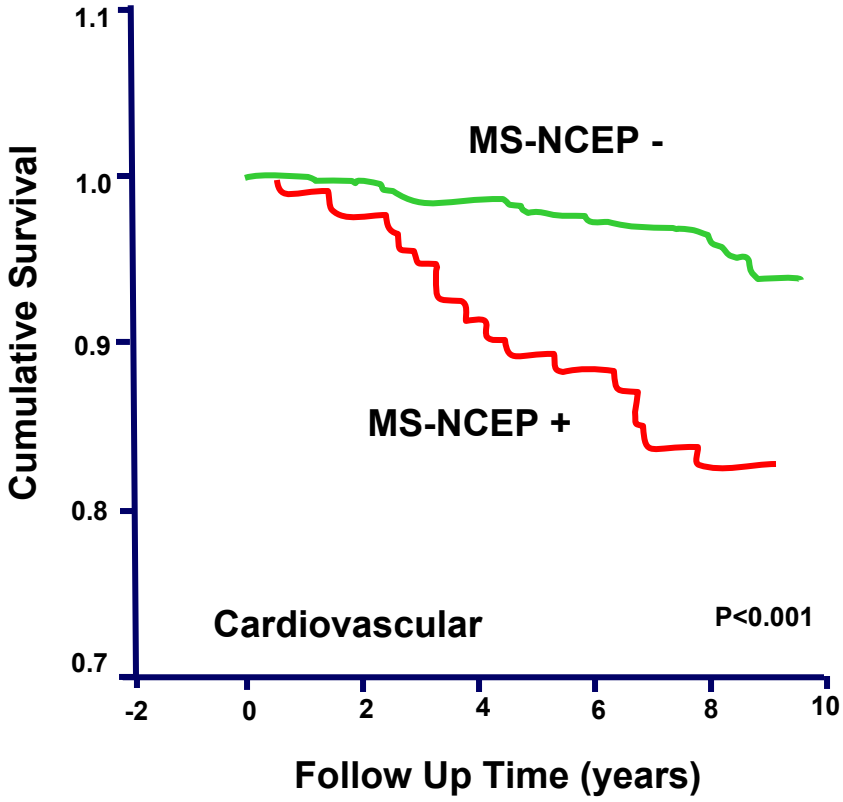
Enlarged Waist Combined With Elevated Triglyceride Is a Strong Predictor of Accelerated Atherogenesis and Related Cardiovascular Mortality in Postmenopausal Women (EWET)

- ***Conclusions:*** The combined presence of EWET may be the best indicator of cardiovascular risk in postmenopausal women.
  - The TG value of concern is 128 mg/dL
- Other components of the MS-NCEP add little medical value to screening in general practices.

***Circulation*.2005;111:1883-1890**

Enlarged Waist Combined With Elevated Triglyceride (EWET)

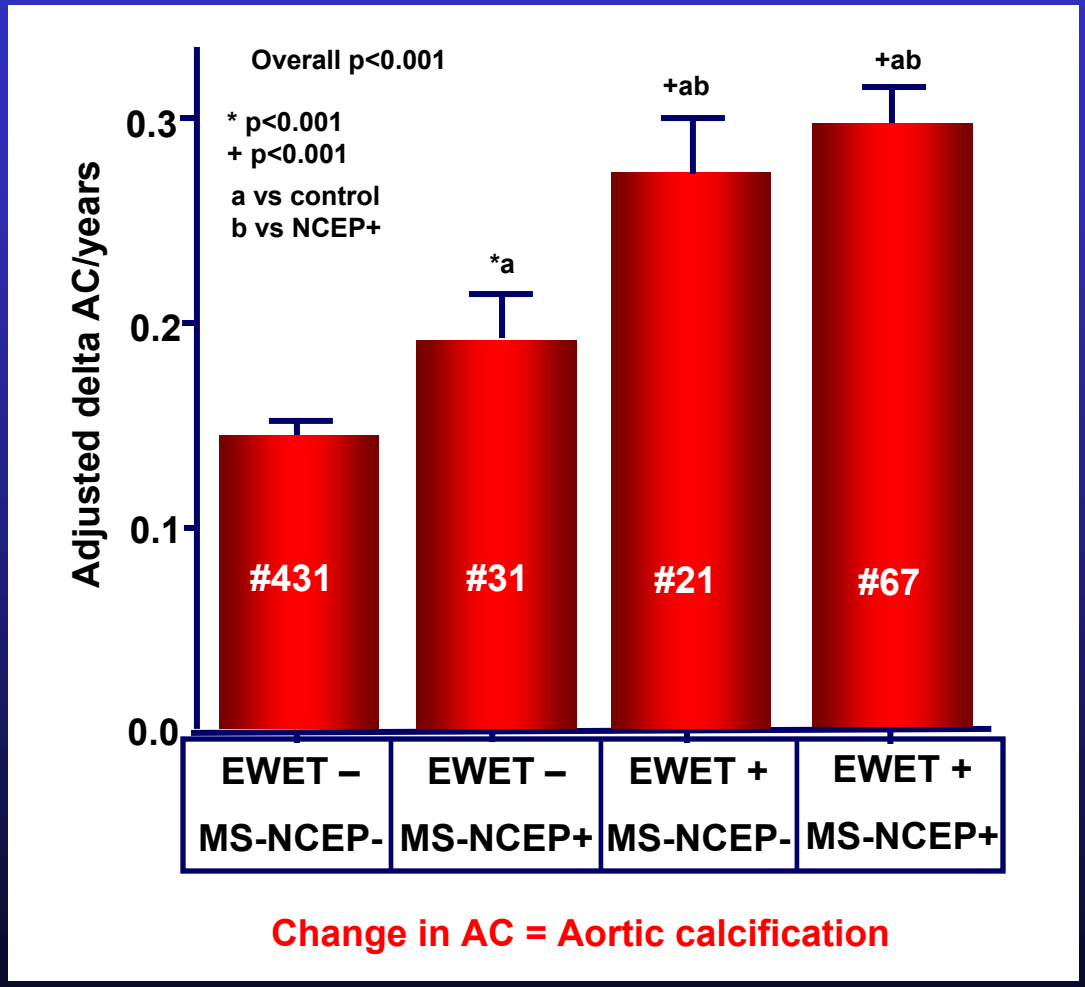




Kaplan-Meier curves indicating cardiovascular event rates in women with (n=88) or without (n=469) EWET or with (n=100) or without (n=433) MS-NCEP

Circulation.2005;111:1883-1890

Enlarged Waist Combined With Elevated Triglyceride (EWET)



Change in AC = Aortic calcification

Annual progression rate of Aortic Calcification during 8.5 year observation period in postmenopausal women with MS-NCEP, EWET, or both diagnostic criteria

Results shown are mean +/- SEM obtained after adjustment for age, smoking and LDL-C at baseline

Circulation.2005;111:1883-1890

Enlarged Waist Combined With Elevated Triglyceride (EWET): LDL Particle Data

	EWET* (+)	EWET* (-)	*P*-Value
LDL-C (mg/dL)	148	144	NS
Apo B (mg/dL)	112	99	*P*<.001
sdLDL-C† (mg/dL)	22	5	*P*<.001
sdLDL† (% of total LDL-C)	16	4	*P*<.001
Mean LDL particle size (nm)	26.1	26.9	*P*<.001

N = 105 men and 155 women
*EWET defined WC ≥90 cm and TG ≥180 mg/dL for men and WC ≥88 cm and TG ≥150 mg/dL for women
†sdLDL: small, dense LDL

Gazi IF, et al. *Lipids.* 2006;41:647-654.

Enlarged Waist Combined With Elevated Triglyceride (EWET) Editorial

- There is a growing consensus about the importance of triglycerides, particularly in women, and we have shown in the same national US sample that triglyceride level was the single most predictive component of the MS-NCEP for CVD in multivariate analysis.

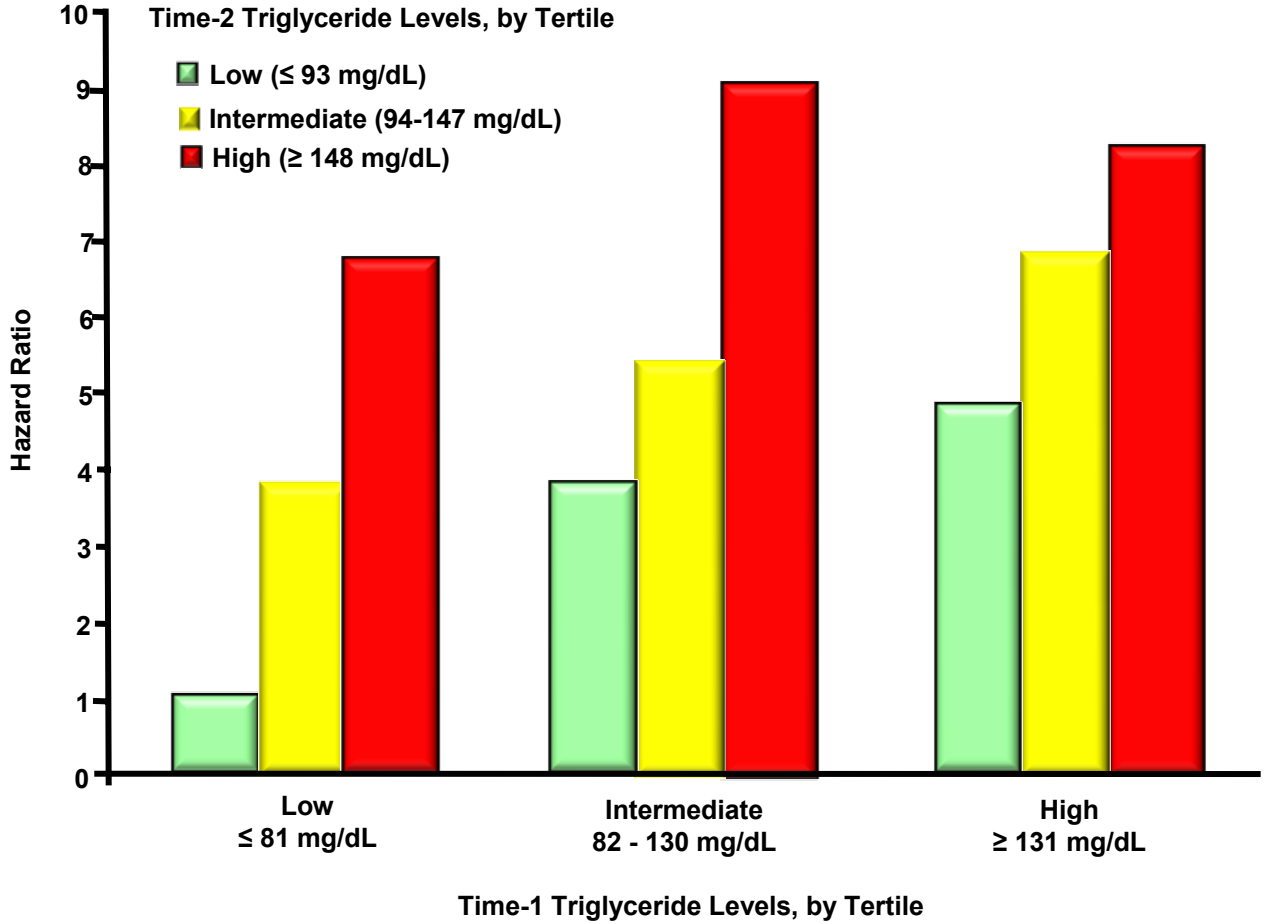
Michael Criqui Editorial *Circulation*.2005;111:1869-1870

MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)

- Patients: 13 953 apparently healthy, untreated, young men (age 26 to 45 years) with triglyceride levels less than 300 mg/dL.
- Measurements: Two triglyceride measurements (at enrollment [time 1] and 5 years later [time 2]), lifestyle variables, and incident cases of angiography-proven CHD.

Tirosh A et al. Ann Intern Med. 2007;147:377-385.

MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)



For 13 953 apparently healthy young adult men (mean age, 32 years; range, 26 to 45 years), 2 measurements of fasting serum triglycerides and lifestyle variables were obtained 5 years apart and followed for incident cases of angiography proven CHD.

The effect of baseline triglyceride levels (time 1) and changes (between time 1 and time 2) in triglyceride levels on CHD risk were estimated.

Tirosh A et al. Ann Intern Med. 2007;147:377-385.

MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)

Hazard ratios for CHD, by Quintile of Time-1 Triglyceride Level

Variable	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P value for trend
Range of TG Level mg/dL	30 - 66	67- 90	91 - 119	120 - 163	164 - 299	
Follow-up, person-years	29,578	28,212	28,169	29,627	29,810	
Incident cases of CHD	8	13	37	42	70	<0.001
Acquired risk ratio (95% CI)						
Age	1.00 (reference)	1.43 (0.70-2.94)	4.48 (1.97-8.85)	5.10 (2.19-10.6)	7.06 (3.72-14.8)	<0.001
Age and BMI	1.00 (reference)	1.26 (0.63-2.78)	4.17 (1.90-8.11)	4.03 (2.20-9.41)	6.22 (3.19-12.6)	<0.001
Age, BMI & HDL-C	1.00 (reference)	1.12 (0.59-2.34)	3.70 (1.81-7.57)	3.84 (1.86-8.29)	5.15 (2.84-10.0)	<0.001
Age, BMI, HDL-C & Family Hx CHD	1.00 (reference)	1.13 (0.62-2.41)	3.78 (1.96-7.60)	3.96 (1.91-8.35)	5.29 (2.93-10.1)	<0.001
Multivariate *	1.00 (reference)	1.04 (0.56-2.30)	2.93 (1.65-6.39)	3.18 (1.72-7.24)	4.05 (2.68-8.61)	<0.001

Tirosh A et al. Ann Intern Med. 2007;147:377-385.

MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)

- The results suggest that information on triglyceride levels at 2 time points 5 years apart are clinically relevant for assessing the risk for CHD.
- Among young men with triglyceride levels lower than 300 mg/dL who were not receiving lipid-lowering therapy, changes in triglyceride levels were statistically significantly associated with alterations in BMI, physical activity, and the habit of eating breakfast.
- These findings corroborate triglycerides as a sensitive marker of lifestyle changes.
  - However, a substantial proportion of the CHD risk remained attributable to changes in triglyceride levels during the subsequent 5.5 years of follow-up, independent of the associated alterations in BMI and lifestyle habits, suggesting an independent cumulative effect.

Tirosh A et al. Ann Intern Med. 2007;147:377-385.

MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)

- In the group where there was a decrease in triglyceride levels between time 1 and time 2
  - The high/low group was associated with reduced BMI and
  - A diminished proportion of smoking, and
  - An increase in physical activity and eating breakfast, all of which are related to adopting a healthier lifestyle.
- Thus, triglycerides might be a valuable biomarker of lifestyle (and/or weight) changes.

Tirosh A et al. Ann Intern Med. 2007;147:377-385.

MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)

- Conclusions: Two triglyceride measurements obtained 5 years apart may assist in assessing CHD risk in young men.
- A decrease in initially elevated triglyceride levels is associated with a decrease in CHD risk compared with stable high triglyceride levels.
  - However, this risk remains higher than in those with persistently low triglyceride levels.

Tirosh A et al. Ann Intern Med. 2007;147:377-385.

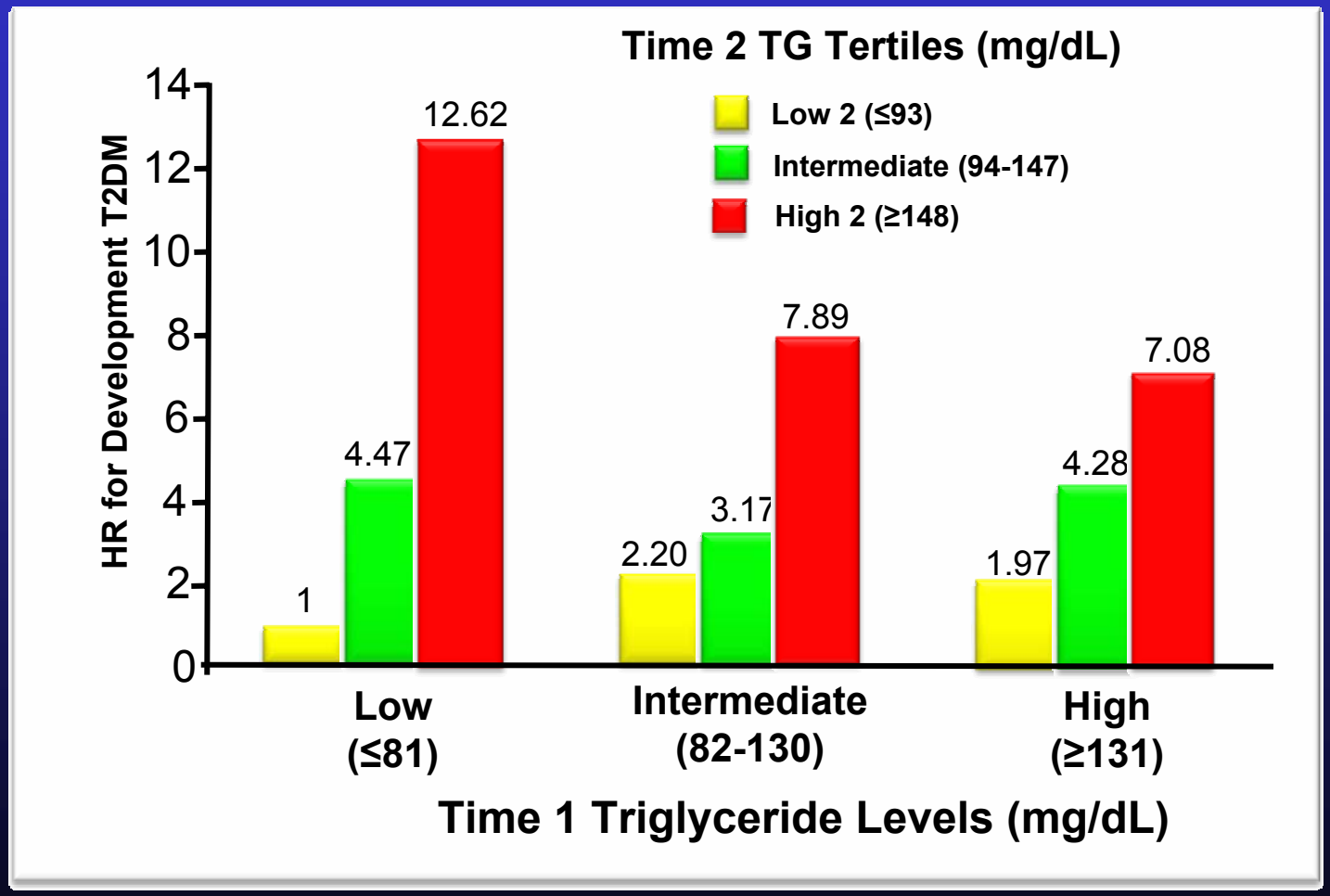
MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)

- Collectively, these findings highlight the predictive value of follow-up triglyceride measurements for CHD risk assessment in apparently healthy young men and may assist in estimating the potential value of lifestyle interventions for the primary prevention of CHD.
- The difference in CHD risk between the high/high and the high/low groups may suggest that decreasing triglyceride levels dramatically affects CHD risk within a relatively short period given the slow progression of CHD.
- In this young age group, high triglyceride levels may identify those exhibiting accelerated atherosclerosis, resulting in clinically significant CHD by the mid-40s.

Tirosh A et al. Ann Intern Med. 2007;147:377-385.

MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)

Association between TG and future morbidity



During 76,742 person-years, 322 cases of diabetes occurred.

Multivariate model showing association of fasting TG obtained 5 years apart and incidence of T2DM

Adjusted for age, BMI, TC/HDL-C. FG, time lapse between time 1 & 2, BP, physical activity, FH of DM, & smoking

Tirosh A et al. Diabetes Care 2008;31:2032-2037

MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)

Multivariate model for comparing HRs for T2DM or CHD associated with fasting 2 TG measurements 5 years apart

	Diabetes		Heart Disease	
	Low Time 2	High Time 2	Low Time 2	High Time 2
Low Time 1	1	7.32 (2.62-20.7)	1	6.76 (1.34-33.92)
High Time 1	1.56 (0.33-7.4)	4.10 (1.93-8.73)	1.56 (0.33-7.4)	8.23 (2.50-27.13)

Model adjusted for age FH of CHD, interval between time 1 & 2, HDL-C, glucose, BP, physical activity and BMI. Also adjusted for changes between time 1 & 2 for smoking and habit if eating breakfast

Tirosh A et al. Diabetes Care 2008;31:2032-2037

MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)

- Circulating triglyceride levels represent a balance between triglyceride synthesis and utilization. These are greatly affected by lifestyle factors (nutritional habits and exercise) and by insulin sensitivity.
- Consistently, an increasing triglyceride level, particularly when accompanied by low HDL, was shown to be a surrogate marker of insulin resistance, a strong predisposing condition for type 2 diabetes.
    - Furthermore, high free fatty acids potentially derived from triglyceride may further deteriorate insulin sensitivity, creating a vicious cycle between triglyceride level and insulin resistance.
- Such a process may have operated to acutely increase diabetes risk when triglyceride levels progressed during follow-up from the lowest to the highest tertile, potentially surpassing the excessive risk associated with persistently elevated triglyceride levels.
- Improving insulin sensitivity and glucose tolerance by pharmacological means decreased circulating free fatty acids or triglyceride levels

Tirosh A et al. Diabetes Care 2008;31:2032-2037

MEtabolic, Lifestyle, And Nutrition Assessment in Young Adults Study (MELANY)

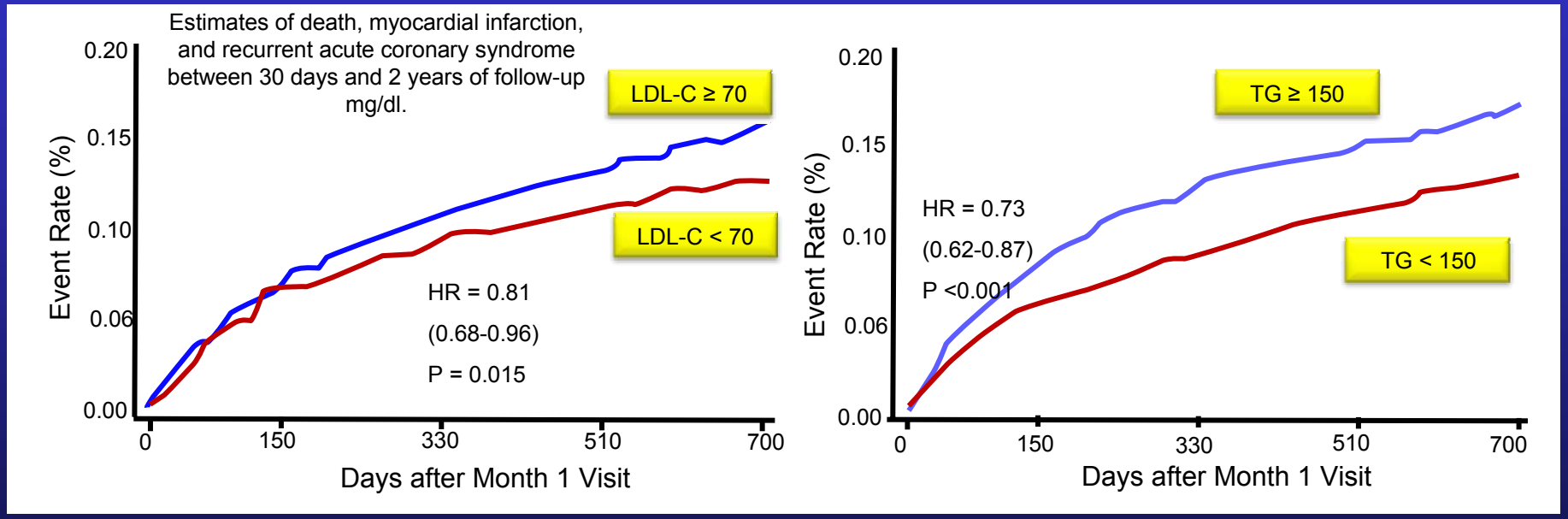
Conclusions

Two measurements of fasting triglyceride levels obtained 5 years apart can assist in identifying apparently healthy young men at increased risk for diabetes, independent of traditional risk factors and of associated changes in BMI and lifestyle parameters.

Tirosh A et al. Diabetes Care 2008;31:2032-2037

PRavastatin Or AtorVastatin Evaluation and Infection Therapy (PROVE IT): Thrombolysis In Myocardial Infarction 22 (TIMI 22)

Impact of Triglycerides Beyond LDL-C



On-treatment TG 150 mg/dL was independently associated with a lower risk of recurrent CHD events, lending support to the concept that achieving low TG may be an additional consideration beyond low LDL-C in patients after ACS.

Miller M et al. J Am Coll Cardiol 2008;51:724–30

PRavastatin Or AtorVastatin Evaluation and Infection Therapy (PROVE IT): Thrombolysis In Myocardial Infarction 22 (TIMI 22)

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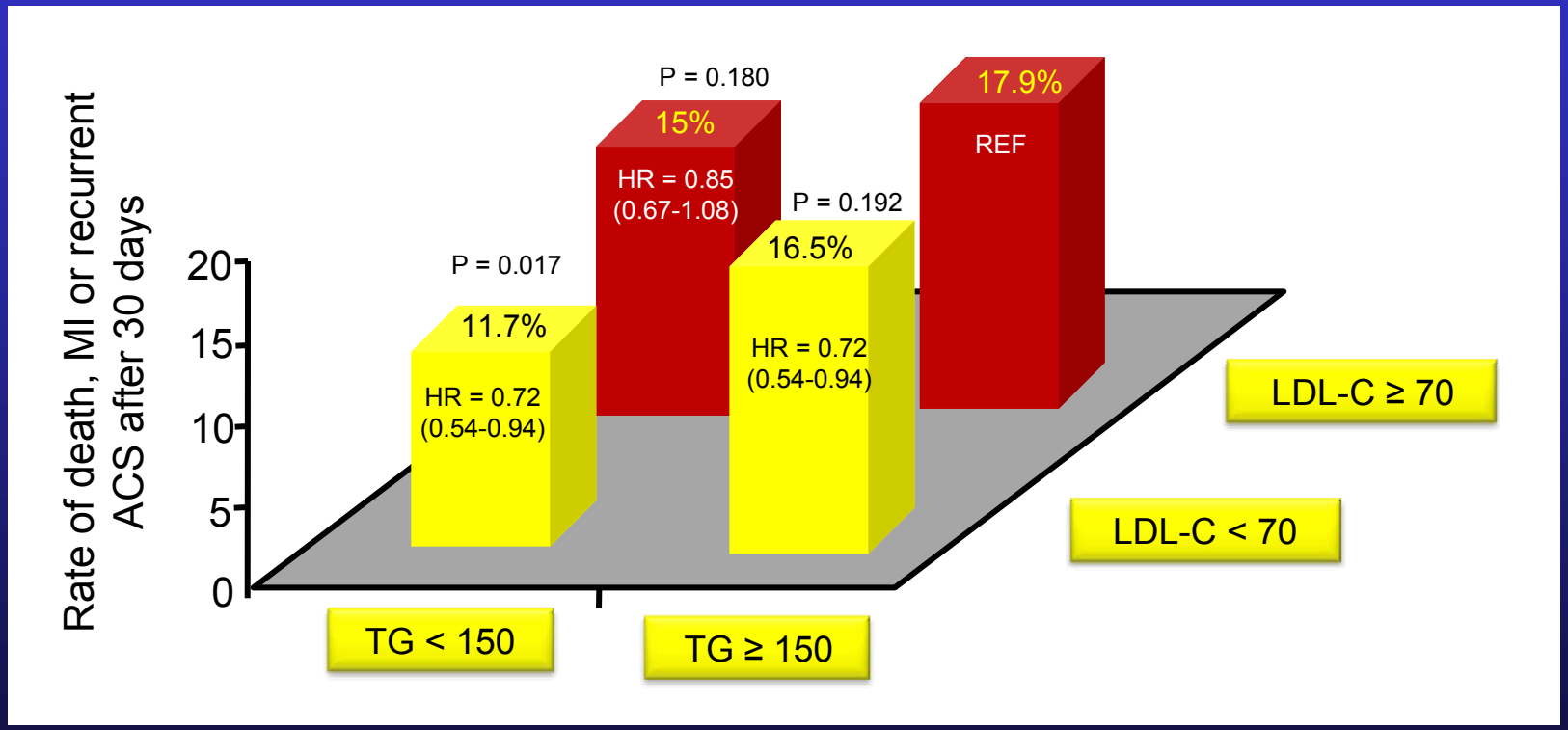
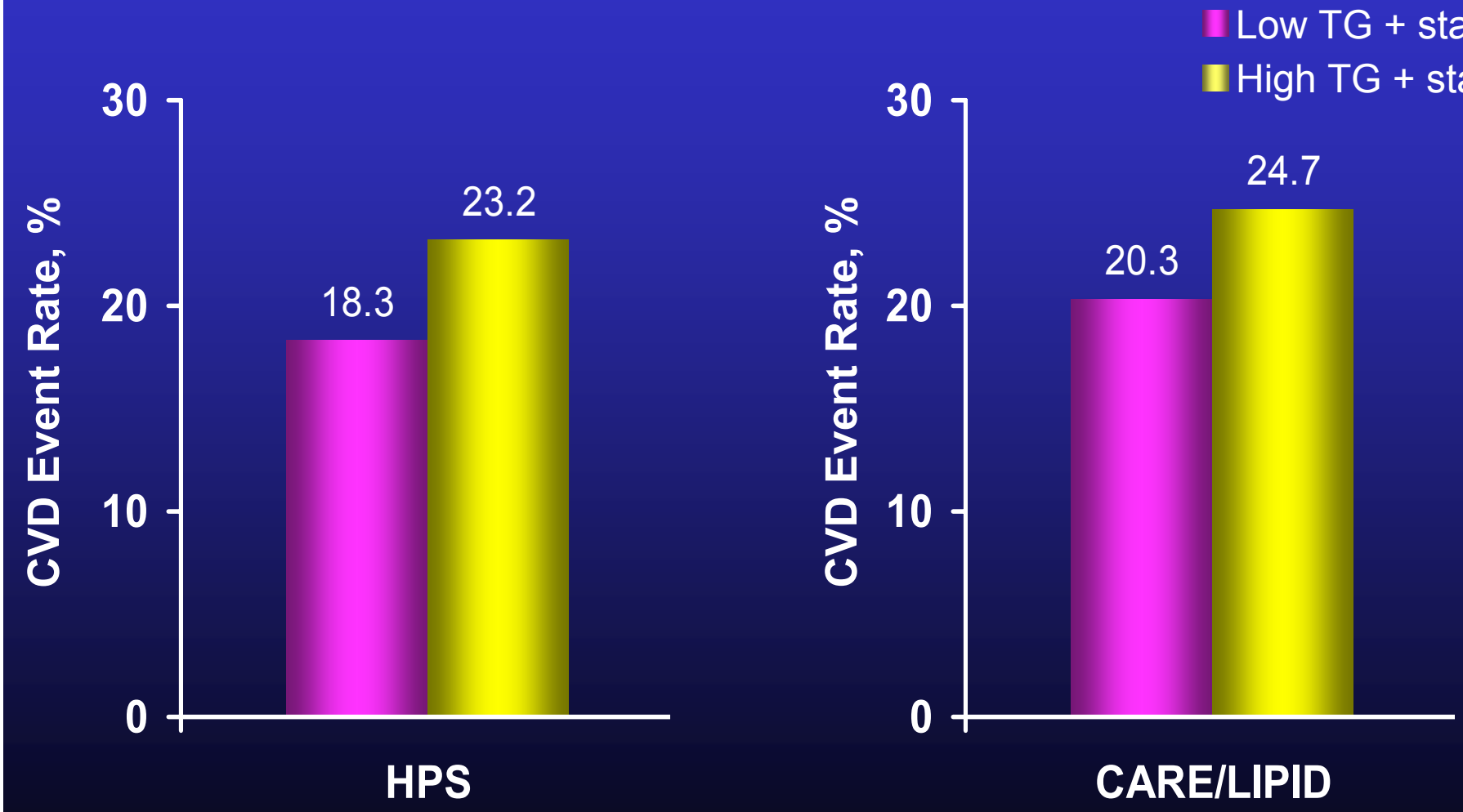


The referent (Ref) group is LDL-C ≥ 70 mg/dl and TG ≥ 150 mg/dl. This model is adjusted for age, gender, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment effect.

Miller M et al. J Am Coll Cardiol 2008;51:724–30

CVD Risk Associated With High Triglyceride Level Remains in Patients Treated With Statins



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

The triglyceride–high-density lipoprotein axis: An important target of therapy?

Philippe O. Szapary, MD, and Daniel J. Rader, MD *Philadelphia, Pa*

Coronary heart disease is the single largest cause of morbidity and mortality in the United States. The link between elevated low-density lipoprotein cholesterol (LDL-C) levels and coronary heart disease (CHD) has been clearly established. However, triglycerides (TG) are increasingly believed to be independently associated with CHD, while high-density lipoprotein cholesterol (HDL-C) is inversely associated with CHD risk. High TG and low HDL often occur together, often with normal levels of LDL-C, and can be described as abnormalities of the TG-HDL axis. This lipid abnormality is a fundamental characteristic of patients with the metabolic syndrome, a condition strongly associated with the development of both type 2 diabetes and CHD. Patients with high TG and low HDL-C should be aggressively treated with therapeutic lifestyle changes. For high-risk patients, lipid-modifying therapy that specifically addresses the TG-HDL axis should also be considered. Current pharmacologic treatment options for such patients include statins, fibrates, niacin, fish oils, and combinations thereof. Several new pharmacologic approaches to treating the TG-HDL axis are currently being investigated. More clinical trial data is needed to test the hypothesis that pharmacologic therapy targeting the TG-HDL axis reduces atherosclerosis and cardiovascular events. (Am Heart J 2004;148:211–21.)

Szapary P & Rader D. Am Heart J 2004;148:211–21

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Coronary heart disease (CHD) is the single largest cause of morbidity and mortality in the United States. The link between elevated cholesterol and CHD has been clearly established, and clinical trials have found that a 1% reduction in serum total cholesterol (TC) reduces CHD risk by 2%. The National Cholesterol Education Program (NCEP) clinical guidelines for the treatment of hypercholesterolemia in adults identify low-density lipoprotein cholesterol (LDL-C) as the primary treatment target.[1] Risk assessment limited to LDL-C, however, fails to capture a significant portion of patients at risk for CHD, and patients effectively treated for elevated LDL-C still experience a significant number of coronary events. Thus increasing attention is being focused on other lipoprotein fractions, such as high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), as additional potential targets of therapy. Elevated serum TG combined with low HDL-C, a condition often associated with smaller, dense LDL particles, is frequently referred to as atherogenic dyslipidemia or the "lipid triad" and is most often seen in the context of the metabolic syndrome. This syndrome represents a cluster of metabolic abnormalities driven by abdominal obesity and insulin resistance, leading to the development of high blood pressure, elevated TG, and depressed HDL-C levels as well as impairments of glucose tolerance.[1] The accumulating evidence suggests that metabolic syndrome is strongly associated with the development of type 2 diabetes and clinical CHD.[2] Since lipoprotein particle size is not routinely obtained in clinical practice, and since elevated TG and depressed HDL-C can occur together, we refer to this dyslipidemia as an abnormality of the TG-HDL axis. Because abnormalities of the TG-HDL often occur in the setting of a "normal" LDL-C, new approaches, not covered in detail in the recent NCEP guidelines, need to be developed in addressing this dyslipidemia. In this review, we focus on the epidemiology and treatment of disorders of the TG-HDL axis, and provide a clinical framework to address this increasingly common dyslipidemia.

Elevated TG and low HDL-C levels as CHD risk factors

There is little doubt that decreased HDL-C is a potent risk factor for CHD, independent of other known risk factors. In fact, both observational studies and controlled clinical trials suggest that each 1% increase in HDL-C is associated with a 2% to 3% reduction in risk of CHD.[3] However, there is more debate as to the independent association of TG levels with CHD risk. Although some epidemiologic studies have not found a consistent association of TG level with CHD mortality,[4] the bulk of the evidence now suggests that elevated fasting TG level is in fact an independent risk factor for CHD. For example, the Copenhagen Male Study, which followed 2906 white men over 8 years, found that fasting serum TG in the upper 2 tertiles was independently associated with incidence of CHD.[5] In this cohort, middle-aged white men with fasting TG ≥142 mg/dL had an adjusted risk ratio for CHD of 2.2 (1.4–

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0002-8703/$ - see front matter

doi:10.1016/j.ahj.2004.05.007

Am Heart J 2004;148:211–21

High TG, low HDL-C and normal levels of LDL-C can be described as abnormalities of the TG-HDL axis.

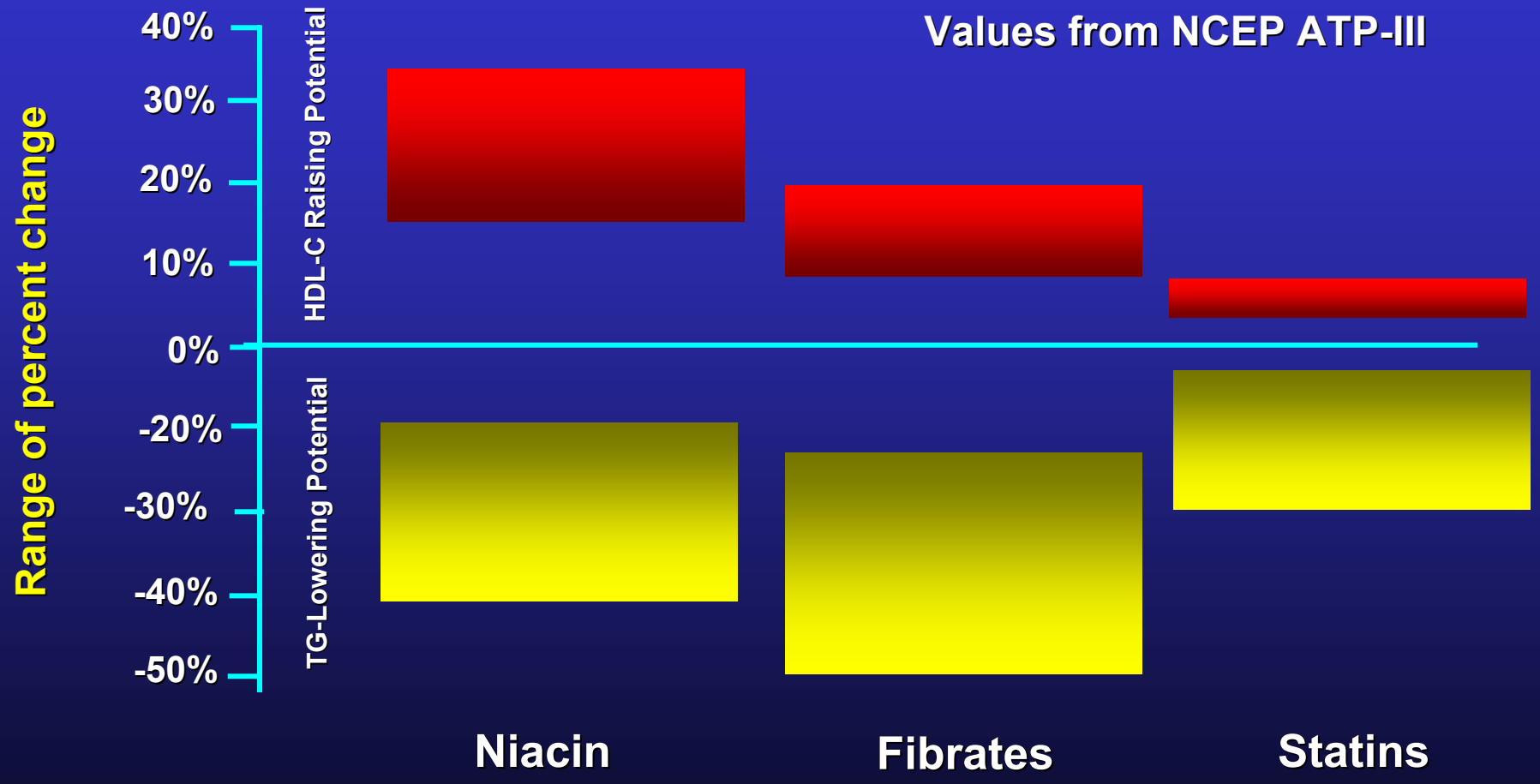
This lipid abnormality is a fundamental characteristic of patients with the metabolic syndrome, a condition strongly associated with the development of both type 2 diabetes and CHD.

Patients with high TG and low HDL-C should be aggressively treated with therapeutic lifestyle changes.

For high-risk patients, lipid-modifying therapy that specifically addresses the TG-HDL axis should also be considered.

Current pharmacologic treatment options for such patients include statins, fibrates, niacin, fish oils, and combinations thereof.

Effect of Drug Therapy on HDL-C and Triglycerides



NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

Triglycerides, ApoAI and HDL-C

- Patients with elevated triglycerides have increased amounts of TG-rich apoB particles (VLDL and IDL and LDL): ApoB levels are ↑
  - CETP exchanges TG for cholesterol between the apoB (VLDL) and apoA (HDL) particles
  - TG-rich HDL particles then become substrates for hepatic lipase in hepatic sinusoids
  - The lipolysis results in a reduction of large and increase in small HDL particles
    - The small HDL (apoA-I) is subject to renal excretion

Triglycerides, ApoAI and HDL-C

Thus, Hypertriglyceridemia will often be associated with decreased HDL-C and ApoA levels and elevated apoB levels or ↑ ApoB/ApoA ratios

- ↑ ApoB is a measure of atherogenic particles
- The reduced apoA is will result in
  - Impaired reverse cholesterol transport
  - Decreased numbers of HDL particles performing other antiatherogenic activities

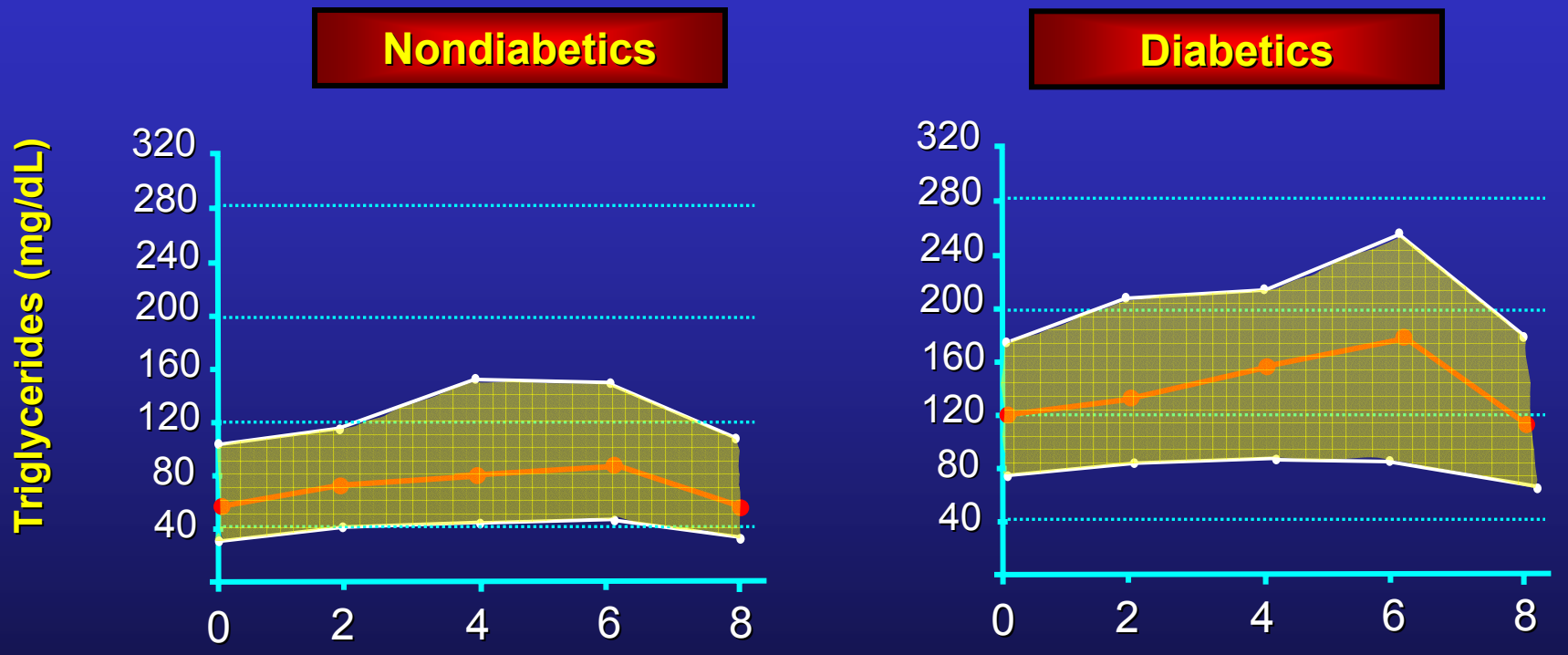
Using The Lipid Profile To More Accurately Predict Risk!

Let's start respecting the forgotten lipid!

- **Start with Triglycerides**

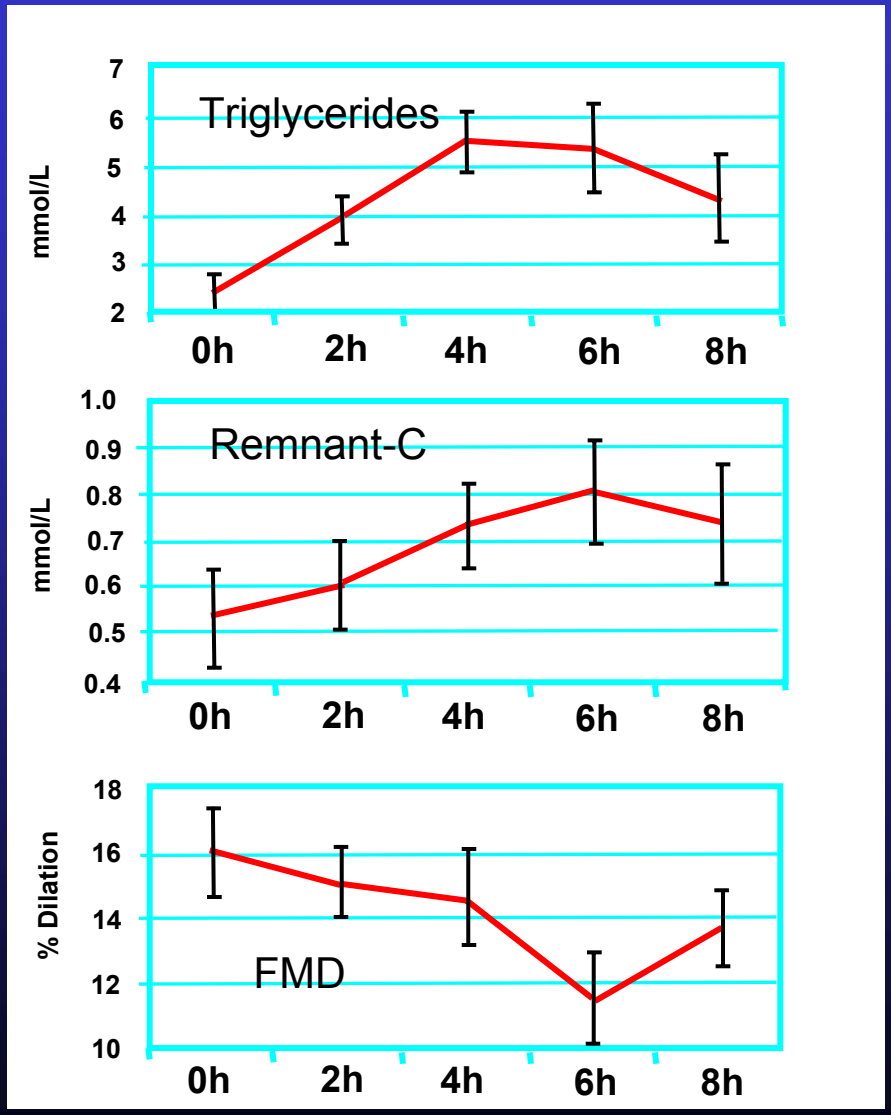
Triglycerides (TG) are how the body transports fatty acids: each molecule carries 3 FA. TG have emerged as a major predictor of heart disease in women.

Oral Triglyceride Tolerance Test



Mohanlal N & Holman R. Diabet Care 2004;27:89-94

Postprandial Change in Lipids and Flow Mediated Dilation after Oral Fat Load



15 moderately overweight & dyslipidemic men with baseline TG of 210 and HDL-C of 39 given an oral fat load

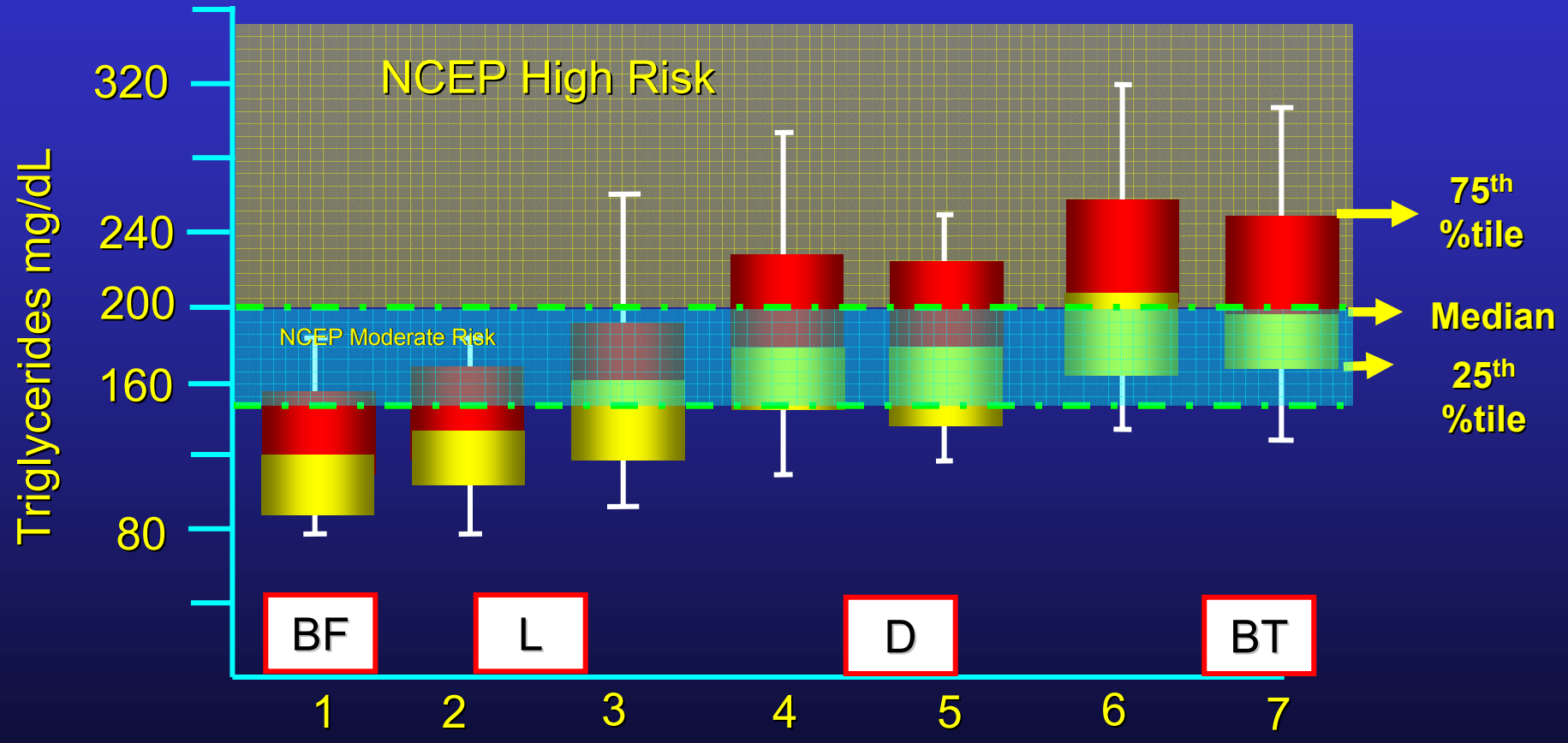
TG & RLP-C increased significantly and continuously up to 4 & 6 hours respectively

FMD revealed decreased vasodilation at 4-6 hours

RLP contribute significantly to impair endothelial dilation

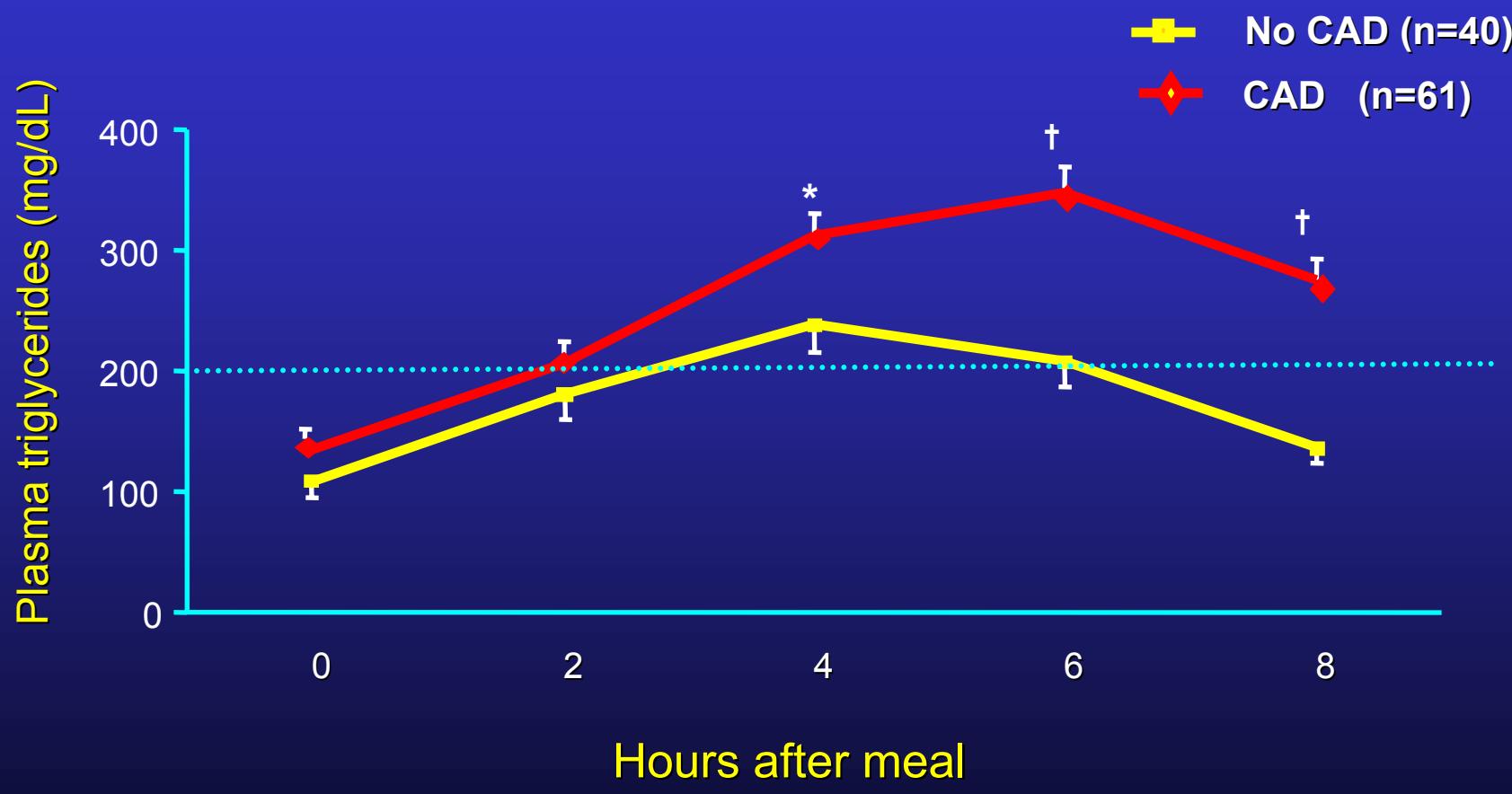
Franco M et al. J Clin Endo & Metab 2004;89:2946-2950

Daytime Triglyceride Profile of Type 2 Diabetics with Normal Fasting Levels



Heine, RJ & Dekker JM. Diabetologia 1997;40:454-462

Postprandial Triglyceride Levels
in Subjects With and Without Coronary Artery Disease

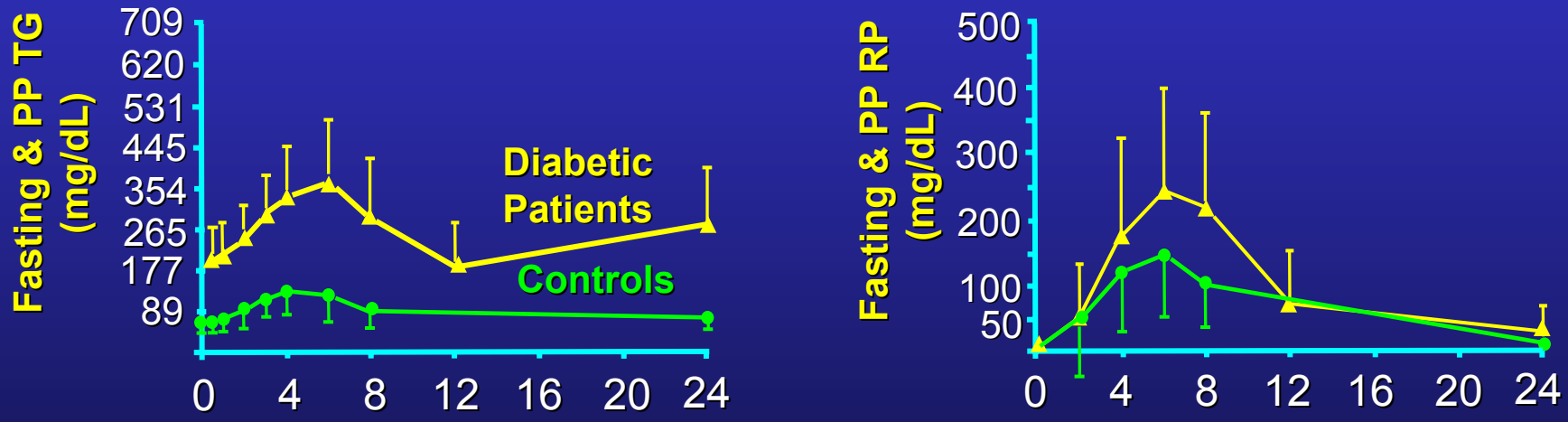


*P=0.025; †$P \leq 0.001$.

Patsch JR et al. *Arterioscler Thromb*. 1992;12:1336-1345.

Postprandial Lipids in Controls and Type 2 Diabetes with Optimal Glucose Control

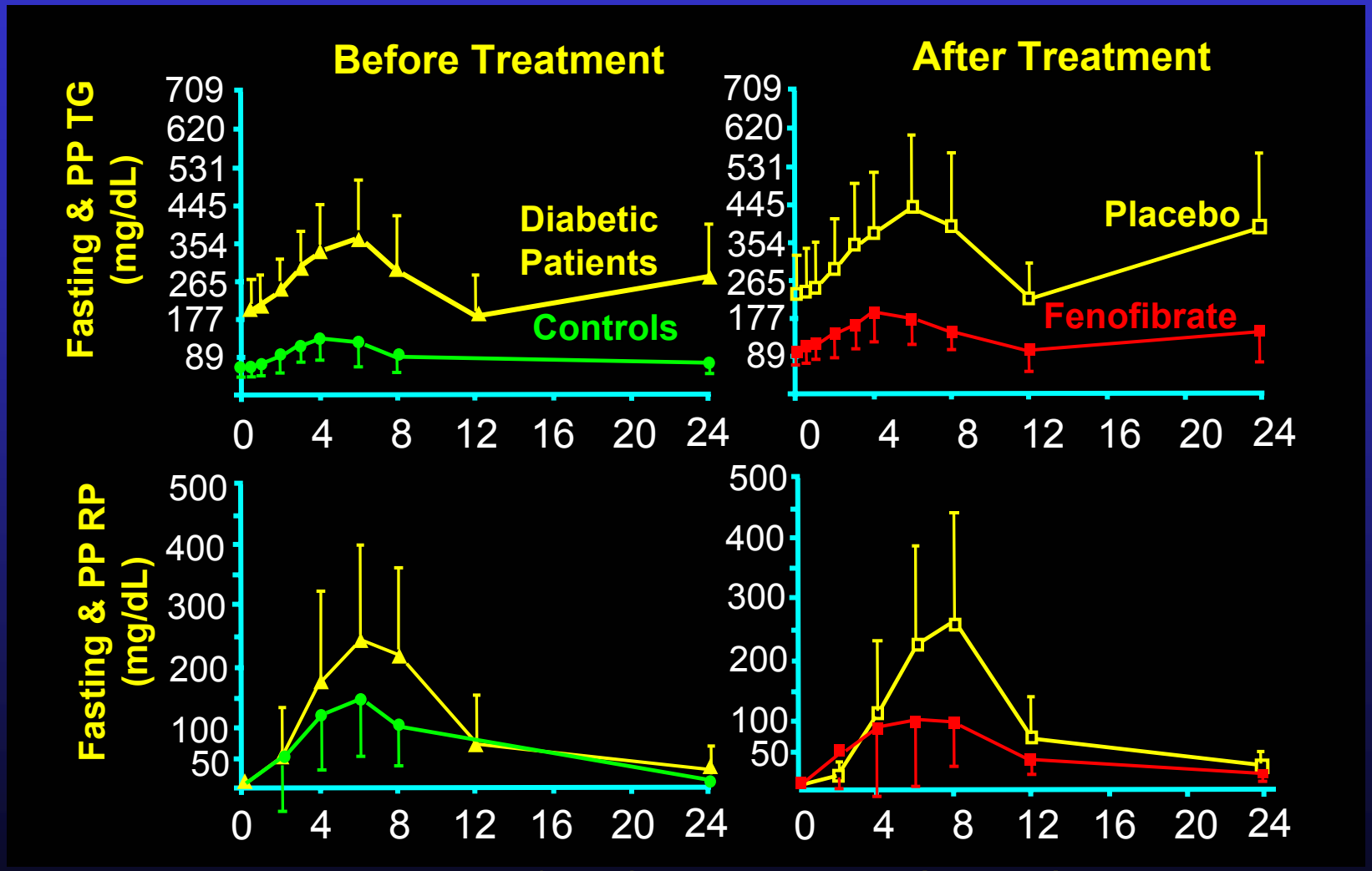
Before Lipid Lowering Treatment



Time After Oral Fat Load (hours)

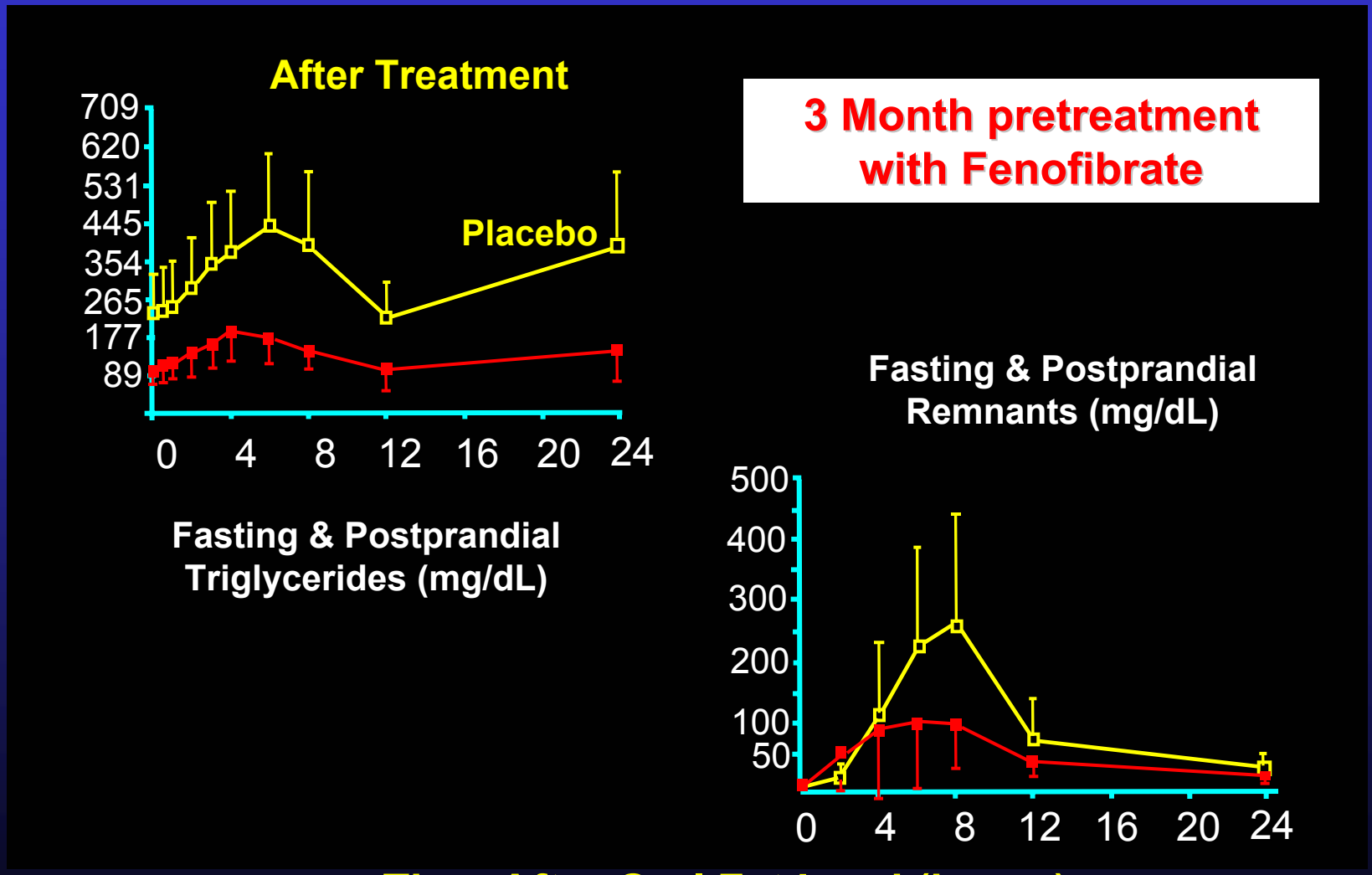
Cavallero et al. Atherosclerosis 2003;166:151-161

Fenofibrate and Postprandial Lipids in Type 2 Diabetes with Optimal Glucose Control



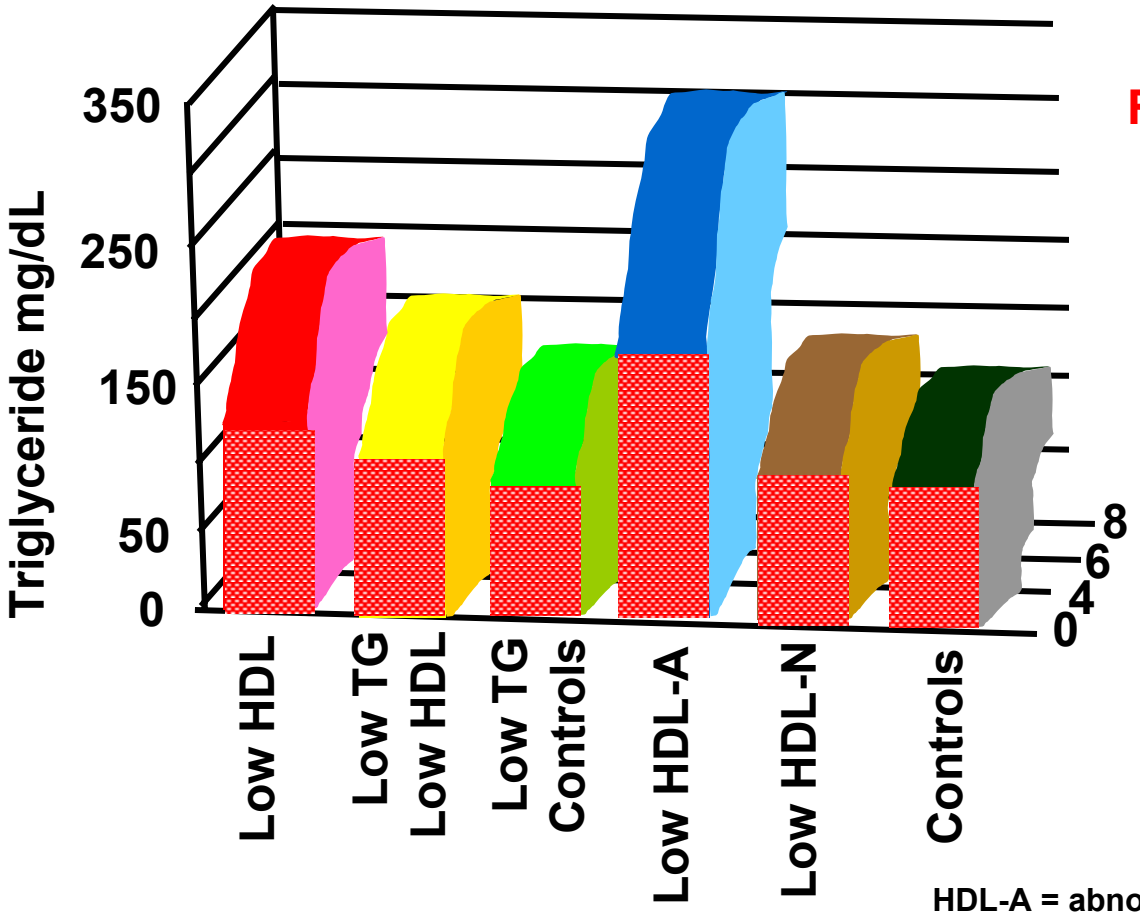
Cavallero et al. Atherosclerosis 2003;166:151-161

Fenofibrate and Postprandial Lipids in Type 2 Diabetes with Optimal Glucose Control



Cavallero et al. Atherosclerosis 2003;166:151-161

HDL-C and Postprandial Lipemia



TG (AUC) in Relation to Time

Low fasting TG defined as < 100

HDL-A = abnormal PP response
HDL-N = normal PP response

Kolovou GD et al. Lipids in Health & Disease 2004;3:18

HDL-C and Postprandial Lipemia

- The delayed TG clearance postprandially seems to **result in low HDL-C levels** even in subjects with low fasting TG
- Fasting TG levels appear to be the **primary determinant** of the magnitude of postprandial lipemia.
  - TG Levels **> 121 mg/dL** are predictable for abnormal response to a fatty meal
- The increase in TG 2-4 hours PP reflects dietary TG absorption
- The return to fasting levels (6-9 hours) is a function of TG clearance

- Suspected factors affecting PP hypertriglyceridemia
  - ApoCIII, Apo E, ApoAI, ApoAIV,
  - Cholesteryl ester transfer protein CETP

} **Polygenic**

Kolovou GD et al. Lipids in Health & Disease 2004;3:18

HDL-C and Postprandial Lipemia

- TG levels 4 hours after the fatty meal
  - The low HDL subjects had a significantly higher ($p<0.006$) TG level compared to controls
- TG levels 6 hours after the fatty meal
  - The low HDL subjects had a significantly higher ($p<0.002$) TG level compared to controls
- TG levels 8 hours after the fatty meal
  - The low HDL subjects had a significantly higher ($p<0.001$) TG level compared to the controls
- Glucose did not show any change postprandially

Kolovou GD et al. Lipids in Health & Disease 2004;3:18

Triglycerides and Atherogenesis

1) Elevated TG are often associated with atherogenic chylomicron remnants

2) Increased hepatic TG result in excess concentration of VLDL particles, VLDL remnants

3) Increased hepatic TG result in excess concentration of LDL particles

4) Increased hepatic TG concentrations result in overproduction of TG rich VLDL particles which become **small, dense LDL particles**

5) Elevated hepatic TG concentrations result reduction of HDL particles overburdened with reverse cholesterol transport: **HDL-C drops**

Triglycerides and Atherogenesis

1) Increased triglycerides are often associated with atherogenic chylomicron and VLDL remnants

2) Increased triglycerides result in increased concentration of LDL particles

3) Increased triglycerides result in promotion of **small, dense LDL particles**

4) Increased triglycerides result in formation of small, cholesterol depleted HDL particles and decreased **HDL-C.**

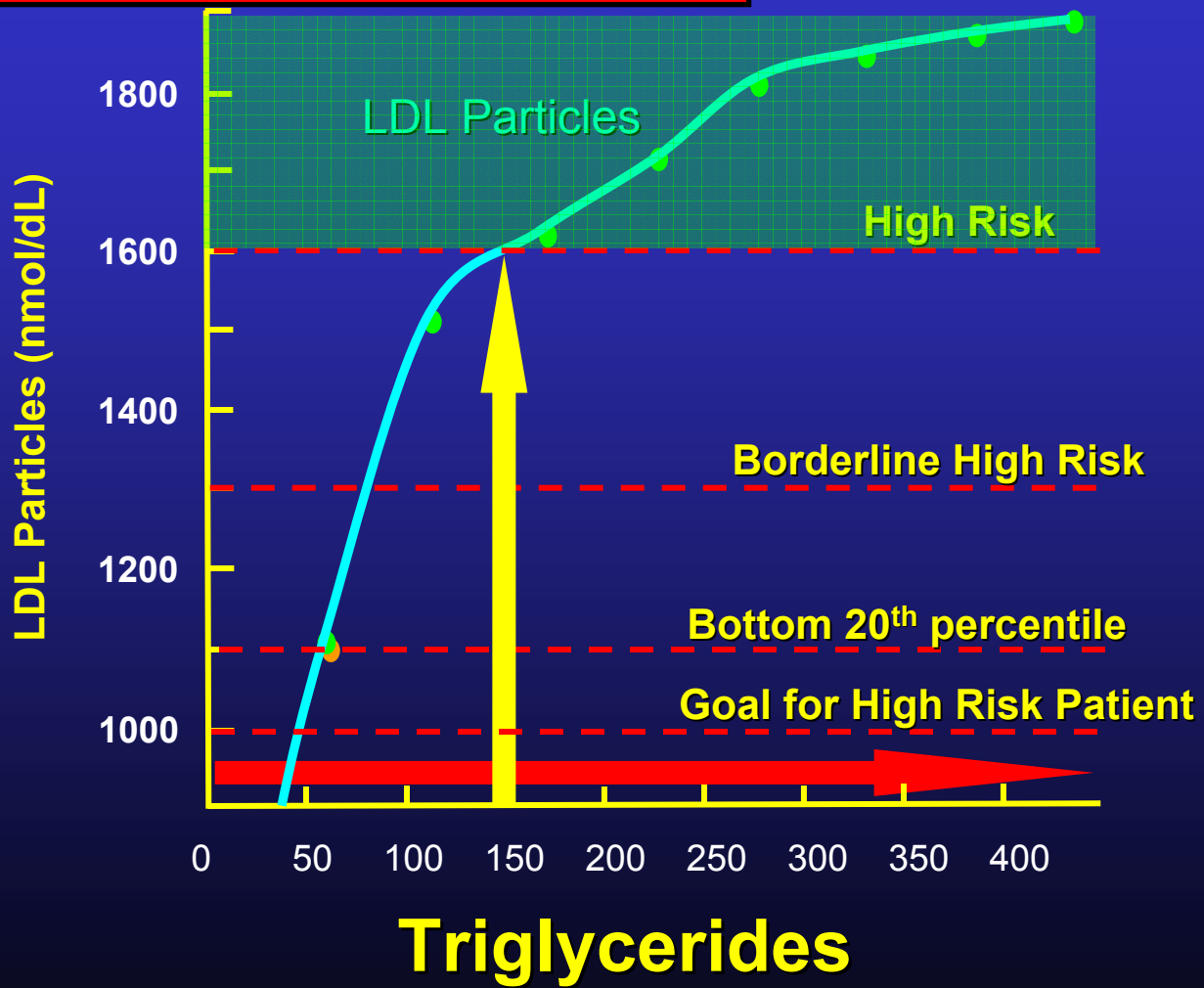
ApoB ↑

ApoA ↓

Framingham Offspring Study

LDL-P (particle #) and TG

As **TG** levels rise so does LDL particle concentration



(n = 3,437)

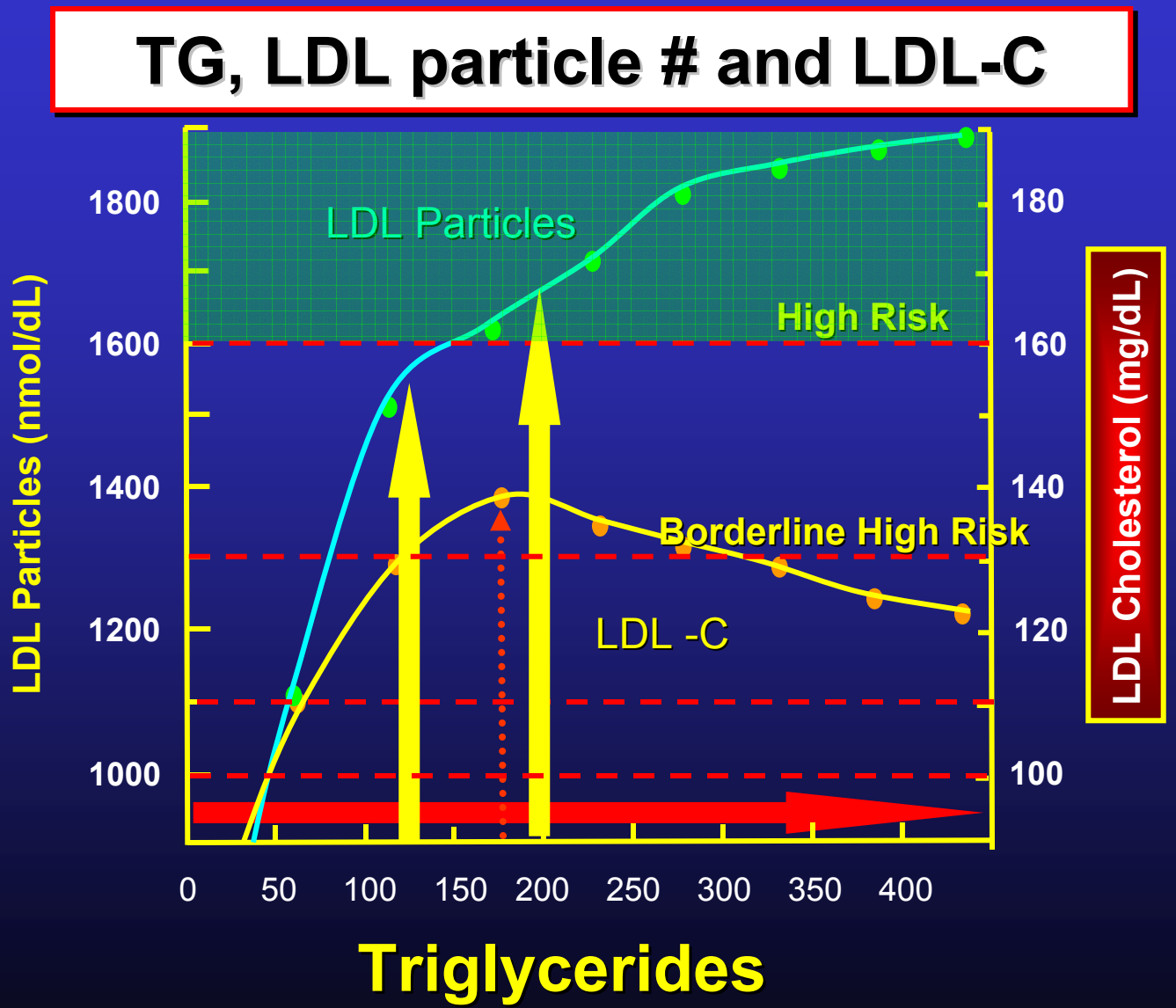
Otvos JD, Cromwell, WC. DALM Scientific Sessions, New York, NY, Sept. 2001

Framingham Offspring Study

As TG rises so does LDL particle concentration

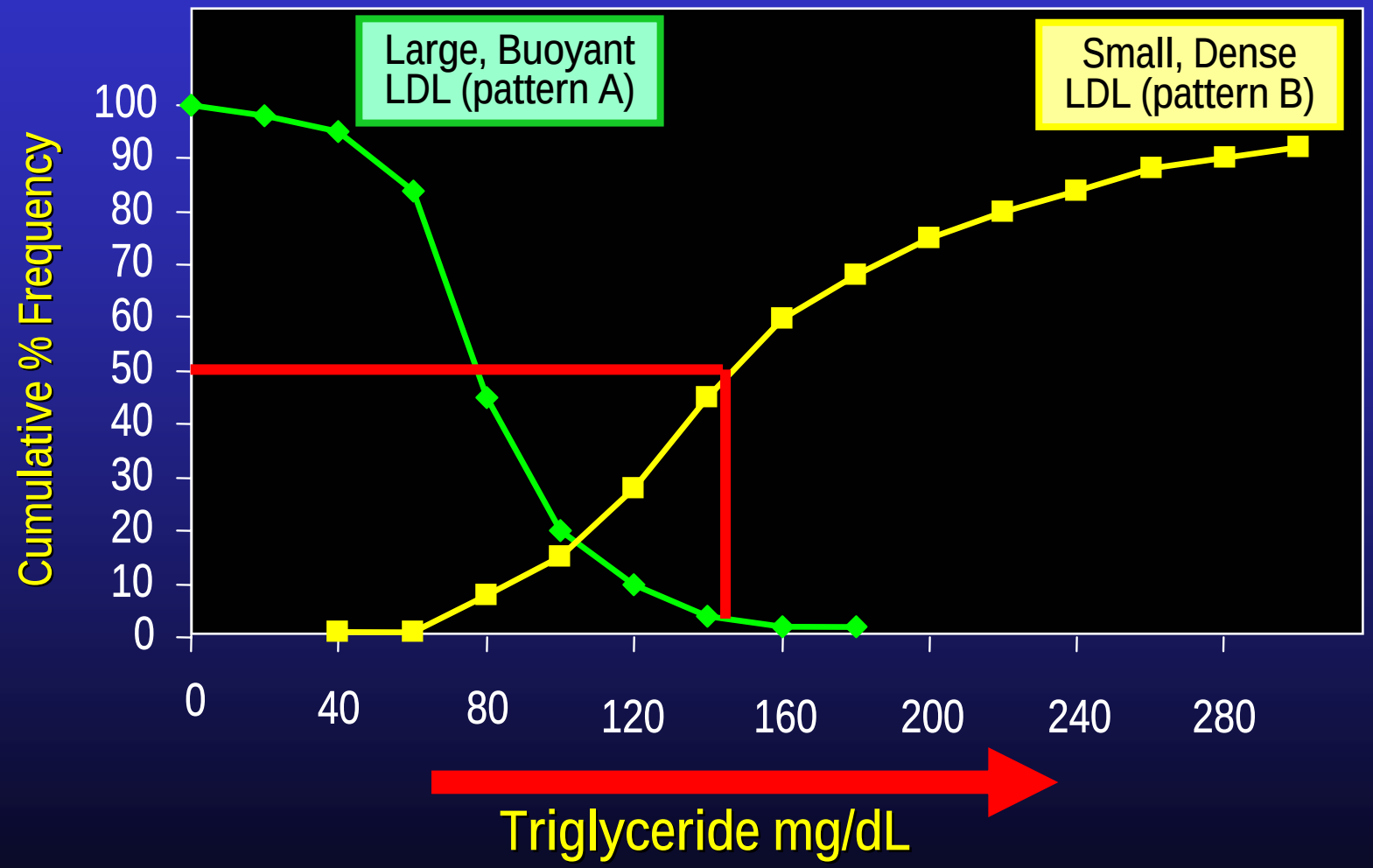
Above TG of 150 to 175 mg/dl LDL-C starts to fall

(n = 3,437)



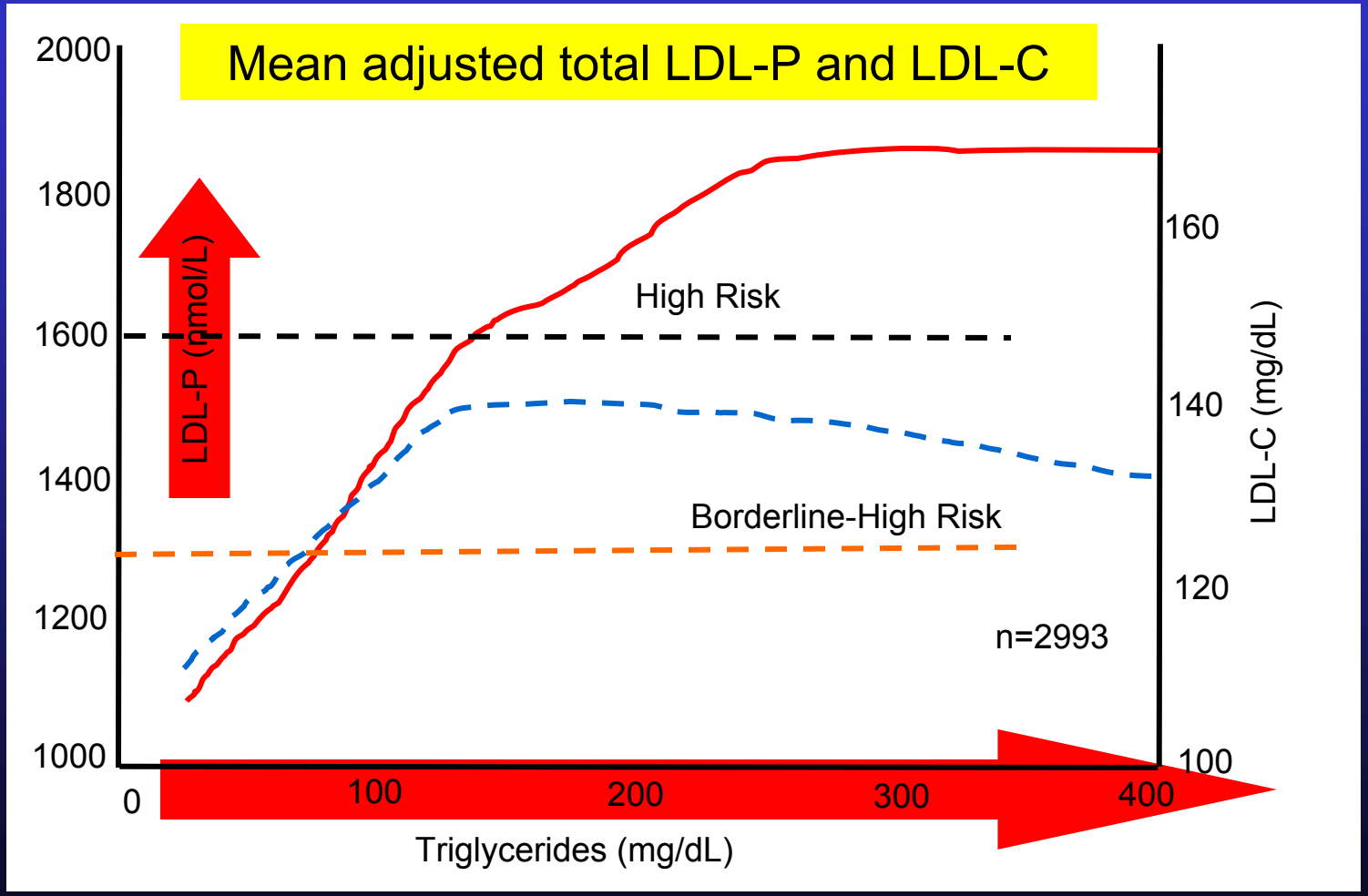
Otvos JD, Cromwell, WC. DALM Scientific Sessions, New York, NY, Sept. 2001

Relationship of Triglycerides and LDL Particle Size



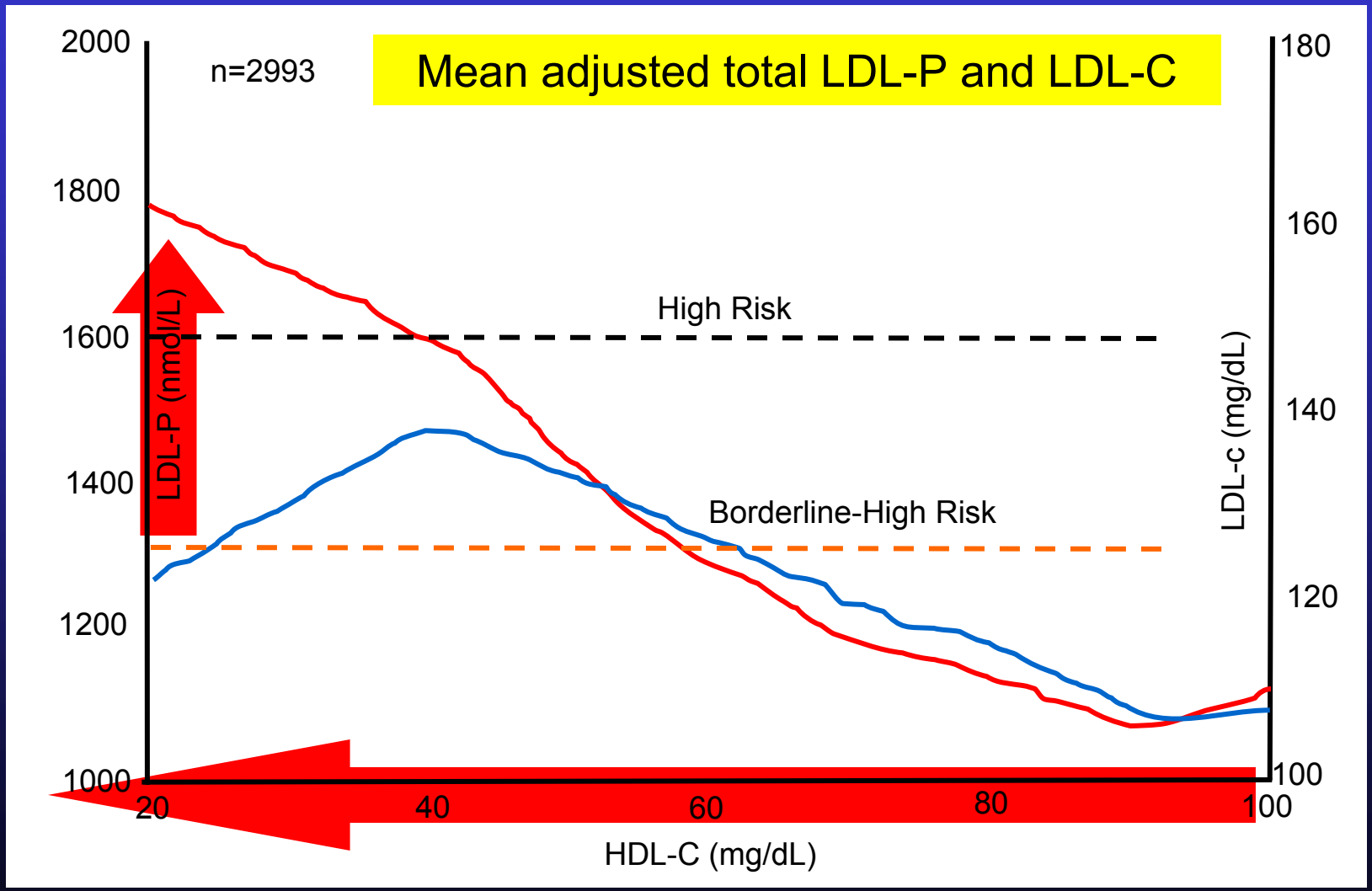
Austin M, et al. *Circulation.* 1990;82:495-506.

Framingham Offspring Study
LDL-P and Metabolic Syndrome



Kathiresan S, Otvos JD, Sullivan LM et al. *Circulation*. 2006;113:20-29.

Framingham Offspring Study
LDL-P and Metabolic Syndrome



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Triglycerides and Atherogenesis

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2) Increased triglycerides result in increased concentration of LDL particles

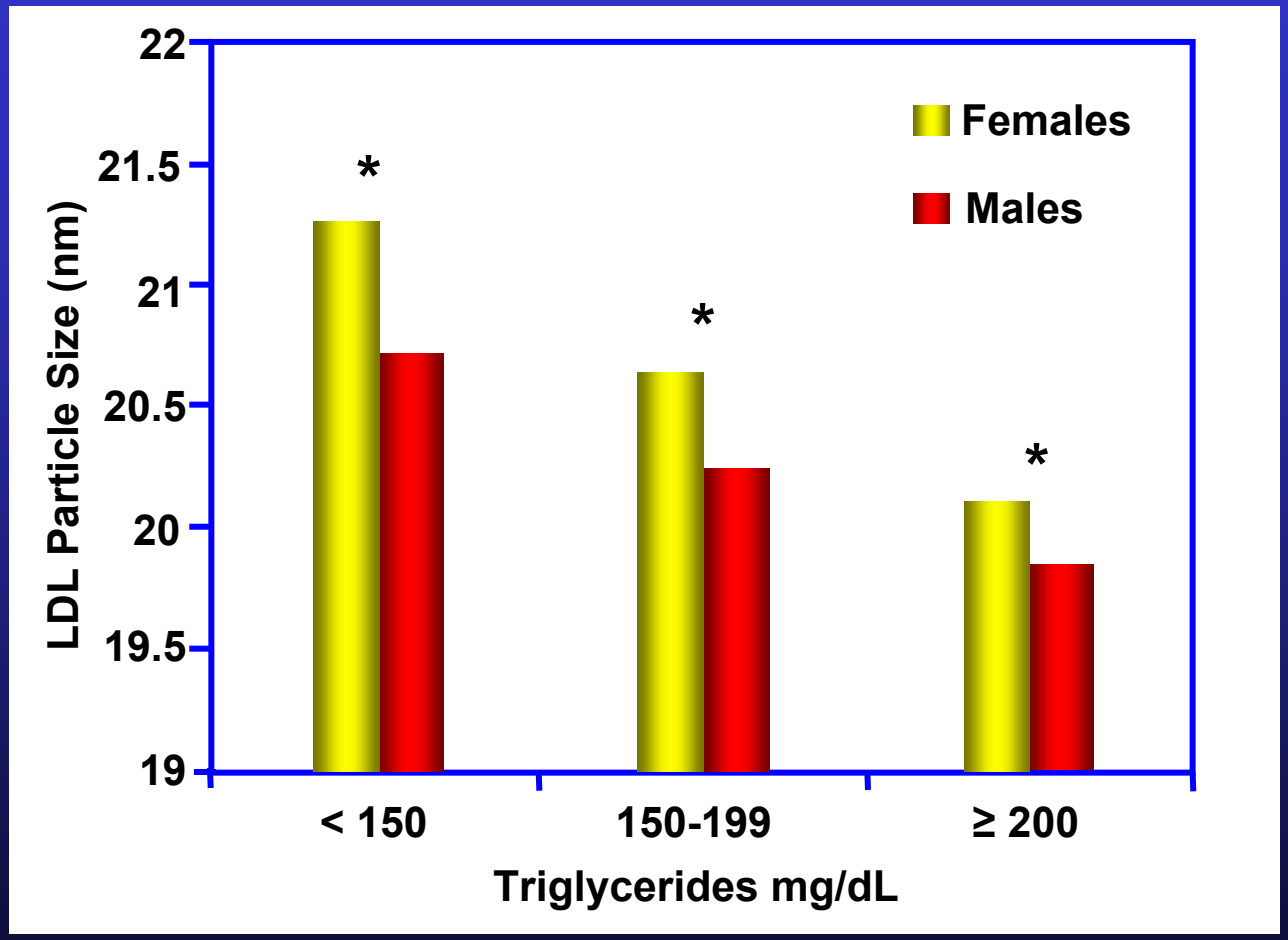
3) Increased triglycerides result in promotion of **small, dense LDL particles**

4) Increased triglycerides result in formation of small, cholesterol depleted HDL particles and decreased **HDL-C. Reverse cholesterol transport is impaired**

ApoB ↑

ApoA ↓

Relationship of Small LDL to Triglycerides

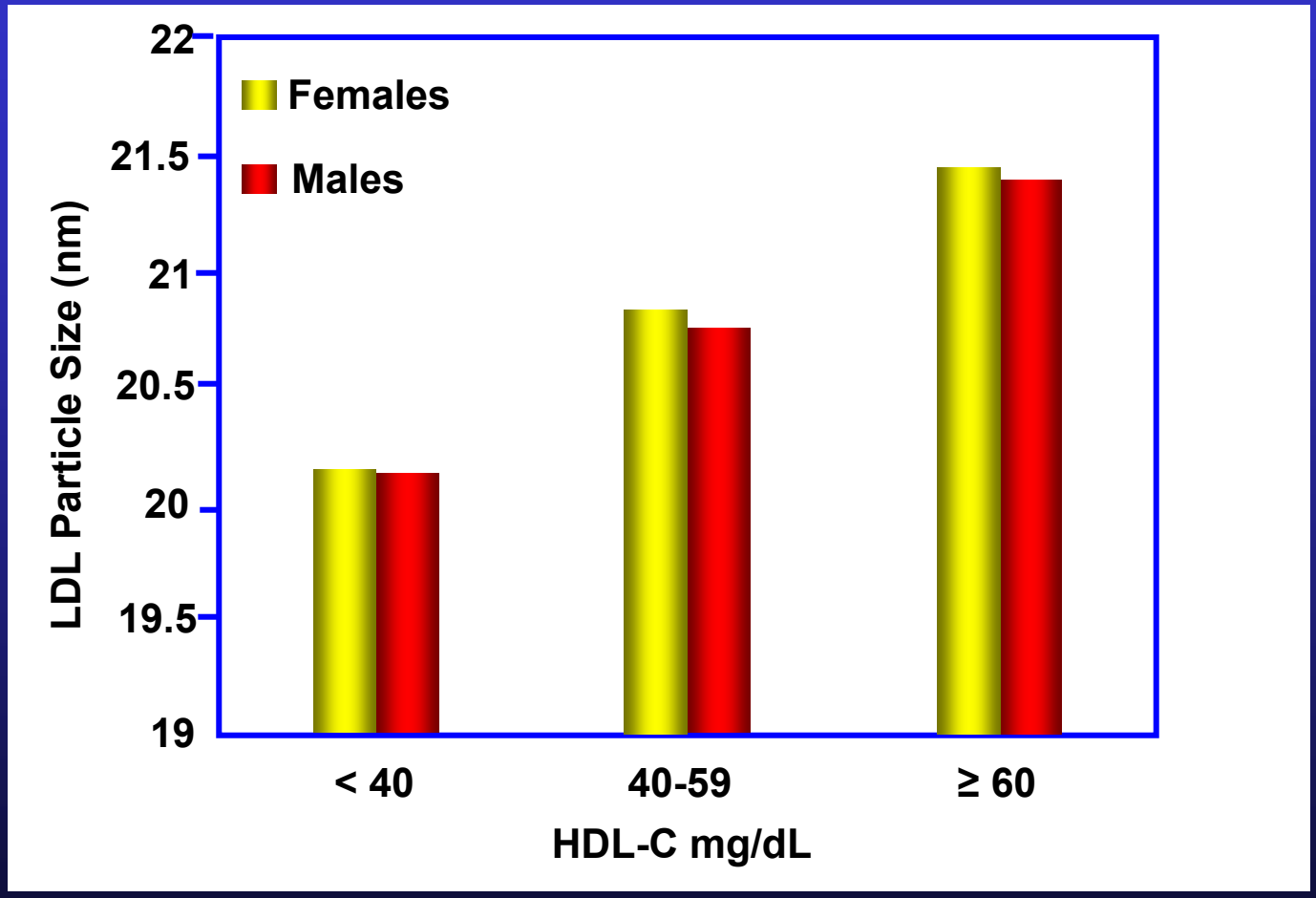


Mean LDL particle size was significantly smaller (*p <0.05) in men compared with women for any given TG category

NMR Spectroscopy

Hanak, V. et al. Am J Cardiol 2004;94:219–222

Relationship of Small LDL to HDL-C

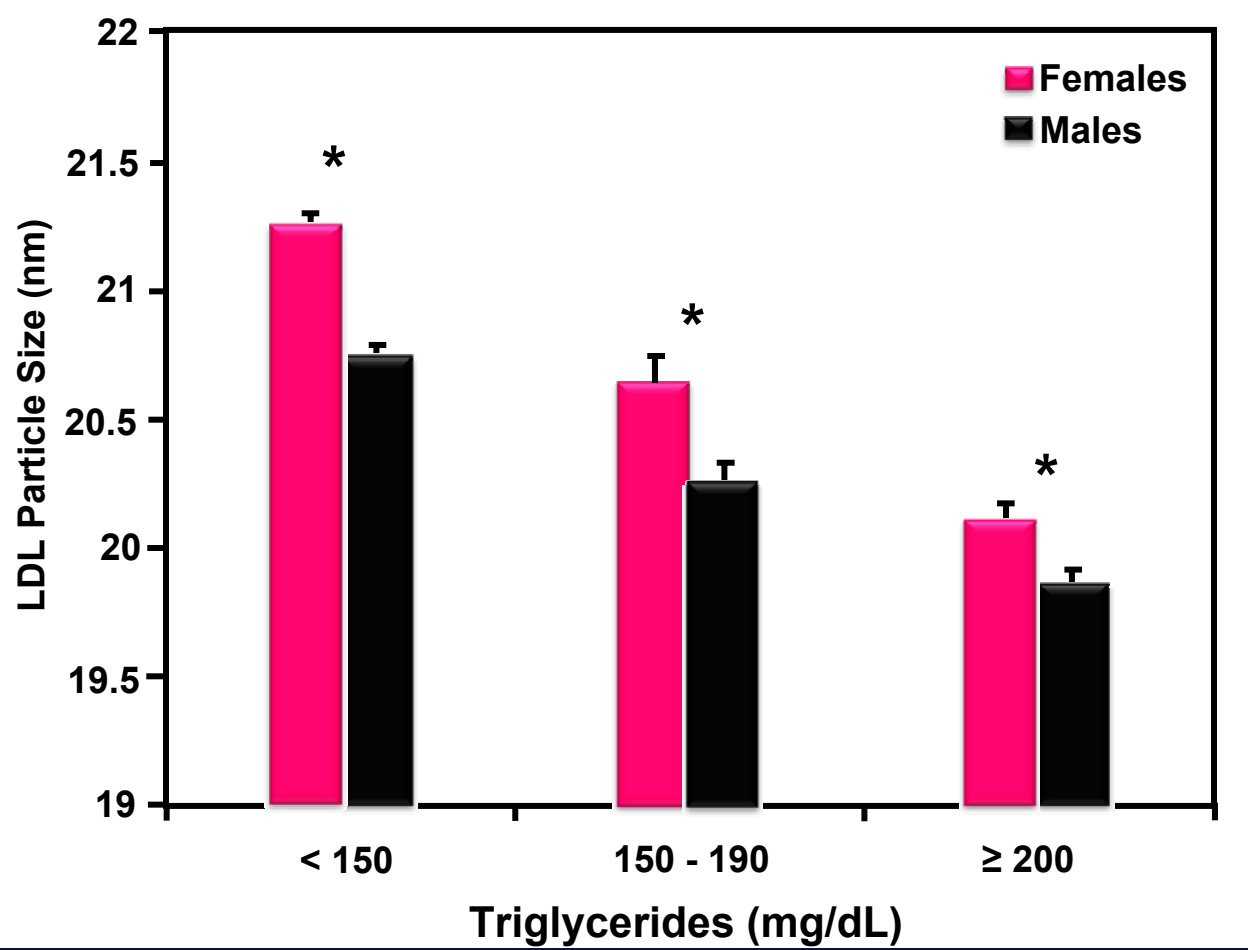


Mean LDL particle size was smaller (p = NS) in men compared with women for any given HDL-C category

NMR Spectroscopy

Hanak, V. et al. Am J Cardiol 2004;94:219–222

Relationship of LDL Particle Size to Triglyceride Categories

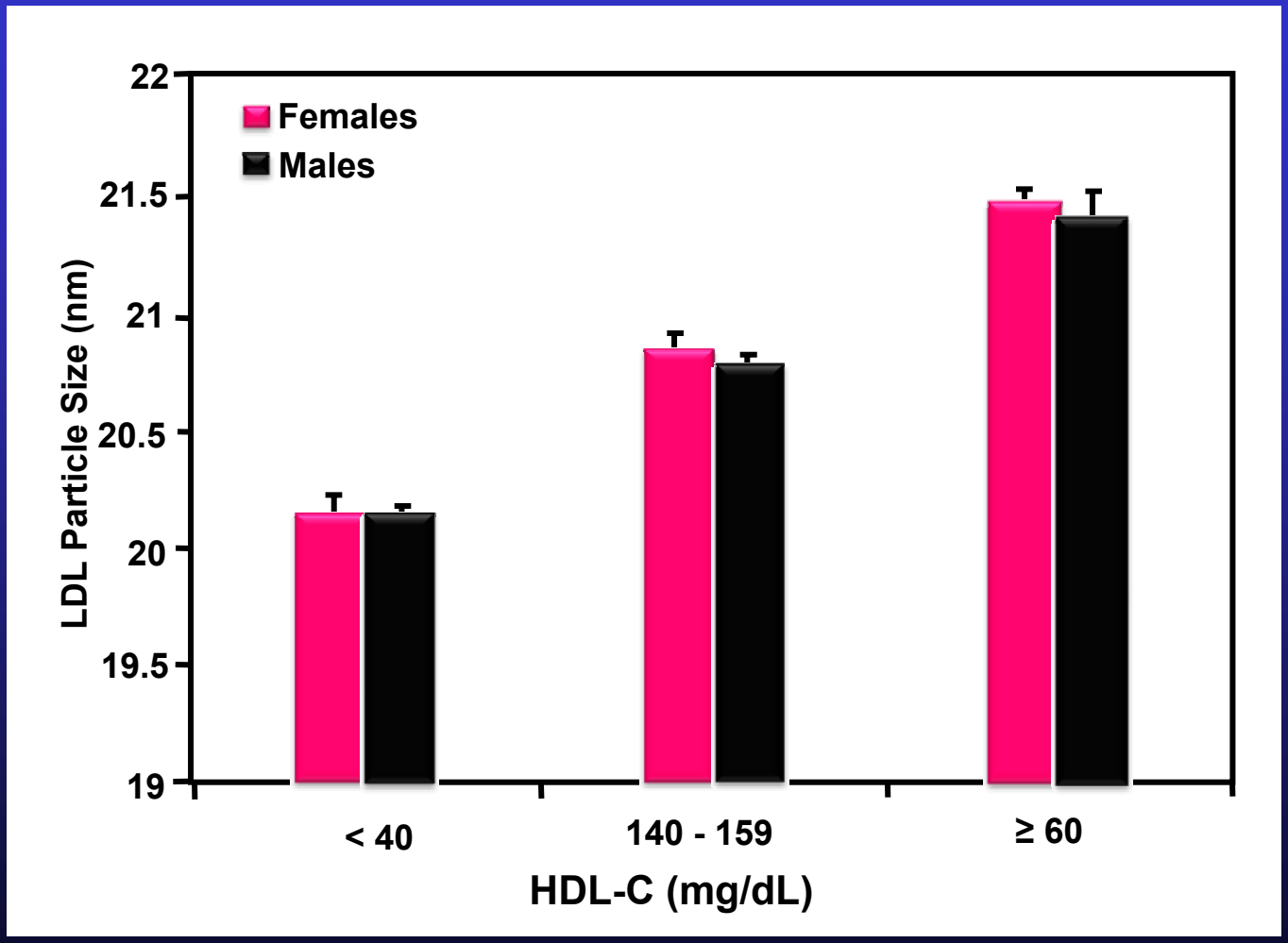


Mean LDL Particle Size in Men and Women plotted by TG Categories (based on NCEP ATP-III

Mean LDL Particle Size was significantly smaller (*p <0.05) in men compared for women for any given TG category

Hanak, V. et al. Am J Cardiol 2004;94:219–222

Relationship of LDL Particle Size to HDL-C Categories

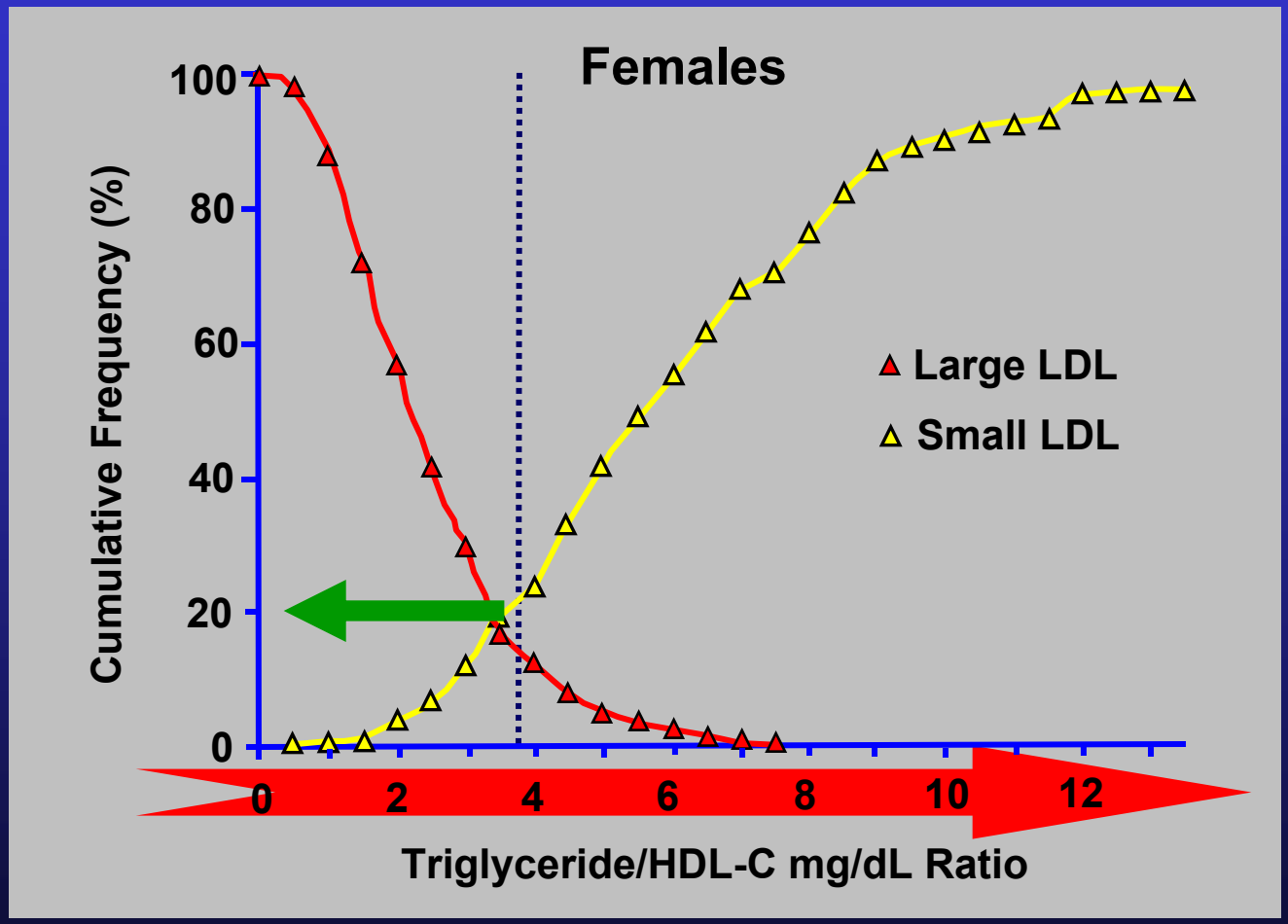


Mean LDL Particle Size in Men and Women plotted by HDL-C Categories (based on NCEP ATP-III

Mean LDL Particle Size was similar in men (p=NS)

Hanak, V. et al. Am J Cardiol 2004;94:219–222

Relationship of Small LDL to Triglyceride/HDL-C Ratio

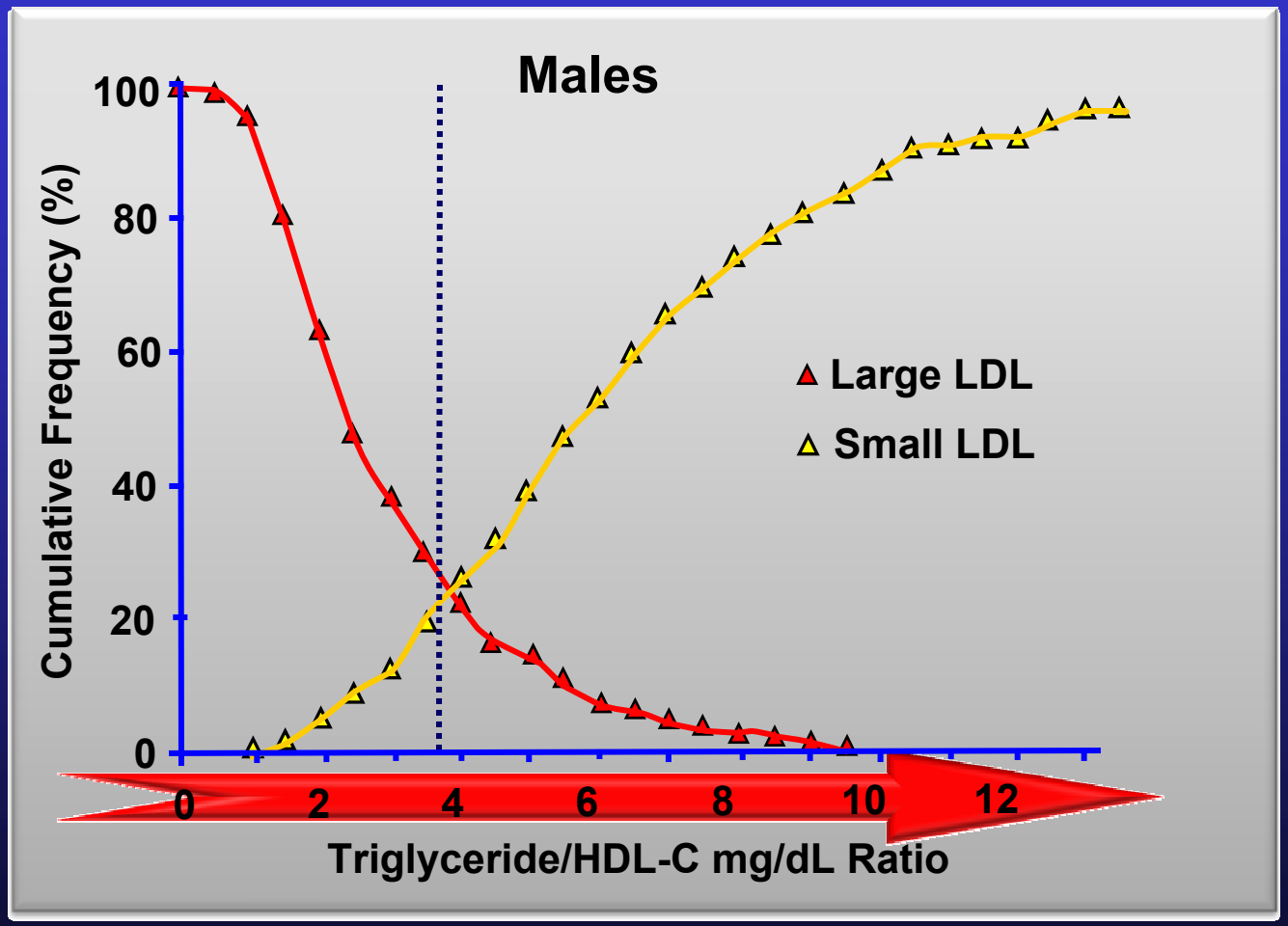


At a ratio ≥ 3.8, 80% of patients will have small LDL phenotype

NMR Spectroscopy

Hanak, V. et al. Am J Cardiol 2004;94:219–222

Relationship of Small LDL to Triglyceride/HDL-C Ratio

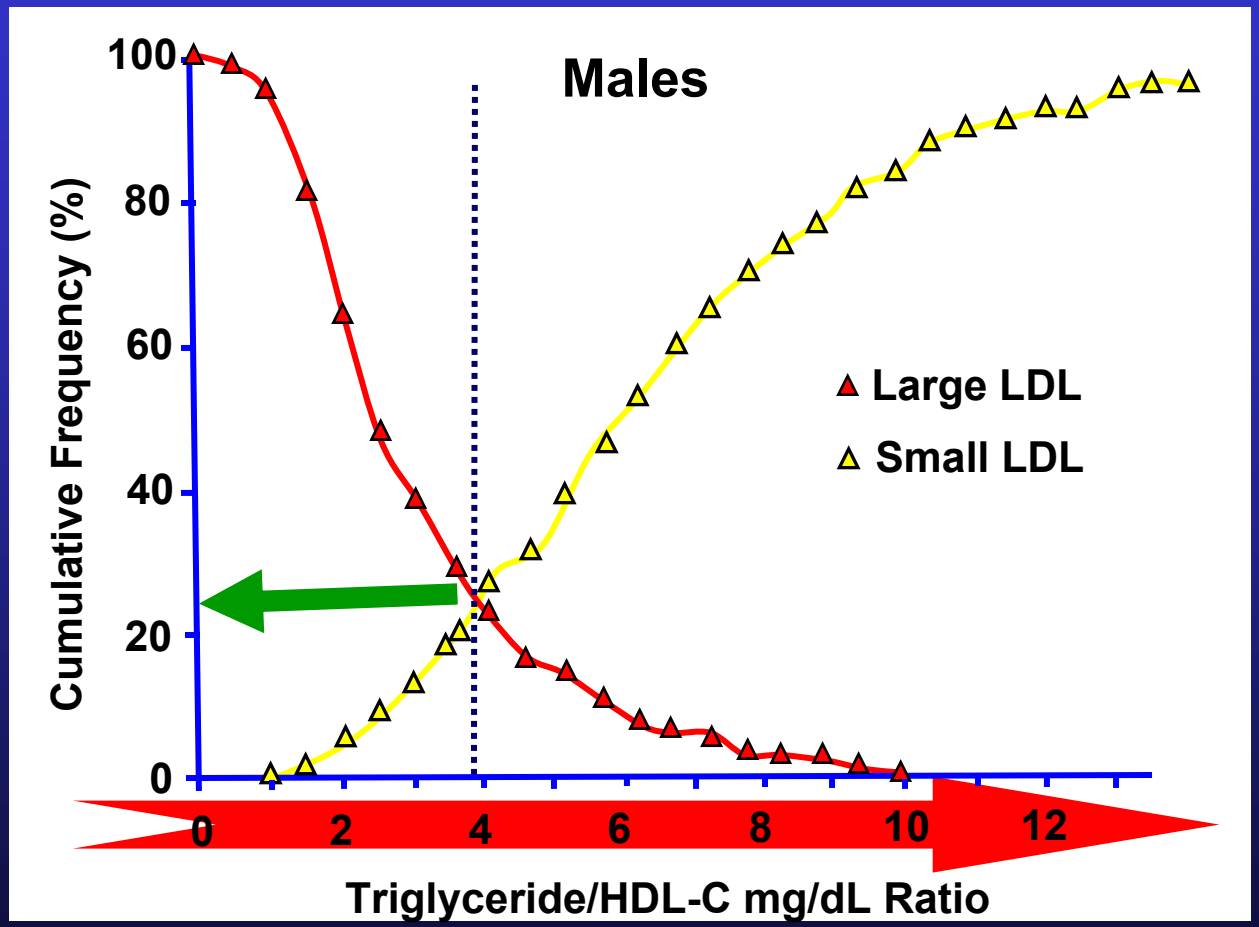


In men, 76% of the LDL phenotype A was less than and 77% of phenotype B was greater than the cutoff of 3.8.

NMR Spectroscopy

Hanak, V. et al. Am J Cardiol 2004;94:219–222

Relationship of Small LDL to Triglyceride/HDL-C Ratio

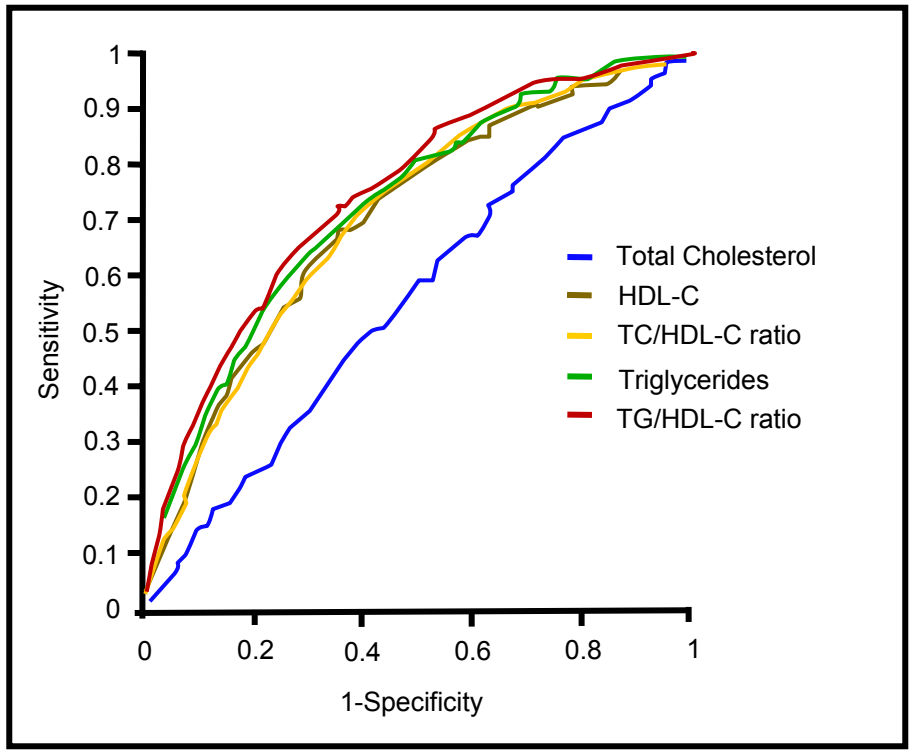


At a ratio ≥ 3.8, 77% of patients will have small LDL phenotype

NMR Spectroscopy

Hanak, V. et al. Am J Cardiol 2004;94:219–222

Framingham Offspring Study TG/HDL-C vs. TC/HDL-C in Predicting Insulin Resistance



These prospective analyses suggested that lipid variables (including TG/HDL cholesterol ratio) were imperfect surrogates of IR.

The findings are threefold.

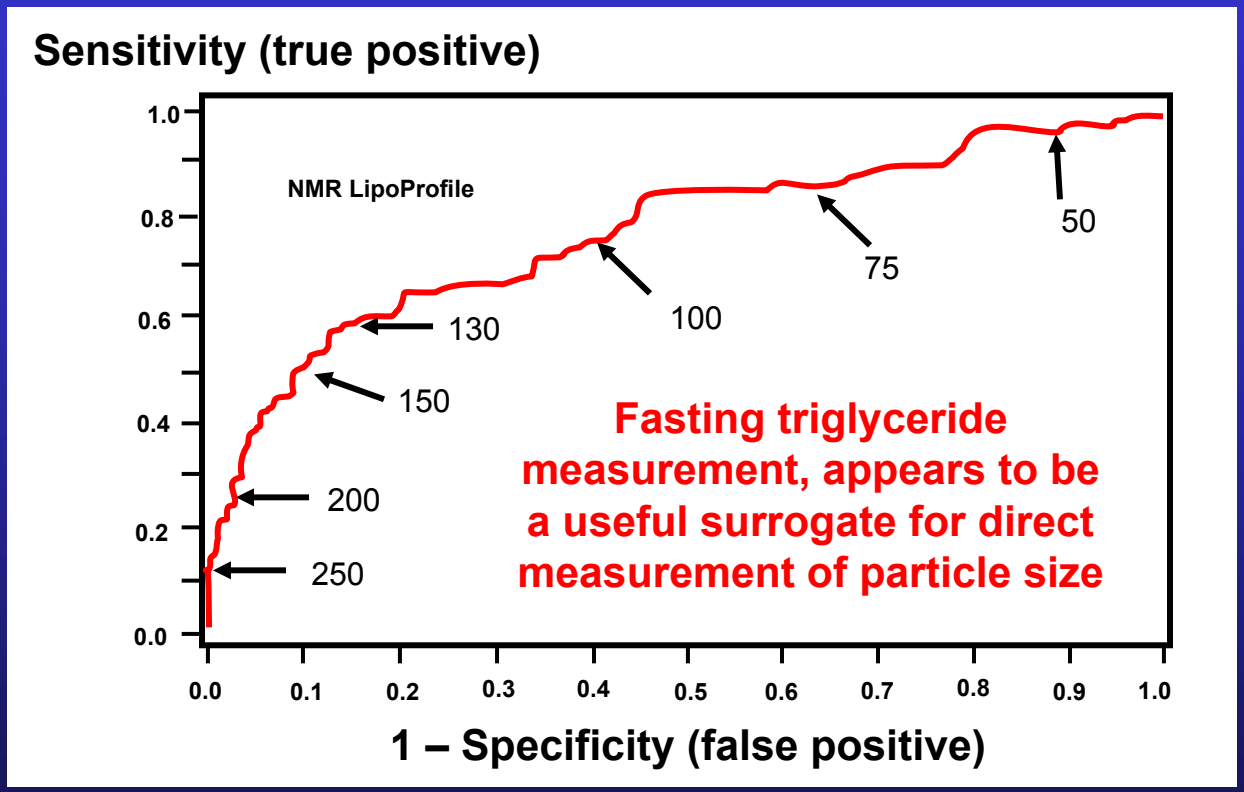
►First, cross-sectional analyses suggested that of the several candidate lipid markers evaluated, TG/HDL cholesterol ratio was the best correlate of IR.

►Second, longitudinal analyses showed that even after adjustment for lipid variables (including TG/HDL cholesterol ratio), IR was significantly and strongly associated with CHD risk.

►Third, total/HDL cholesterol ratio was almost as powerful a predictor of insulin resistant CHD risk as TG/HDL cholesterol ratio.

Kannel WB et al. Am J Cardiol 2008;101:497–501

Relationship of Small LDL to Triglyceride in African Americans



A triglyceride level of 130 to 150 mg/dl identified subjects who had pattern B with good sensitivity and excellent specificity.

In subjects whose triglyceride level was ≥150 mg/dl, 67% had pattern B, whereas only 17% of subjects whose triglyceride level was < 150 mg/dl had pattern B. Therefore, the positive predictive value of triglyceride levels > 150 mg/dl for predicting pattern B is 67% and the negative predictive value is 83%.

Benton J. et al. Am J Cardiol 2005;95:1320–1323

Triglyceride Effects on Lipoproteins

1) Elevated TG are often associated with atherogenic chylomicron and VLDL remnants

2) Increased hepatic TG result in excess concentration of LDL particles

3) Increased hepatic TG concentrations result in overproduction of TG rich VLDL particles which contribute to formation of **small, dense LDL particles**

4) Elevated hepatic TG concentrations result reduction of HDL particles : **HDL-C drops**

National Cholesterol Education Program

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Goals of Therapy

- **Normalize LDL-C**
  - 130 mg/dl in moderate risk patients (10-20% 10 year risk)
  - <100 mg/dl in high risk patients (>20% 10 year risk)

- **Hypertriglyceridemia**

NCEP ATP III Chapter VI pp25-26

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Risk of Triglycerides: Lipoprotein Remnants

Renewed interest in the importance of elevated triglycerides has been stimulated by the publication of meta-analyses that found that raised triglycerides are in fact an ***independent risk factor*** for CHD.

This independence suggests that some triglyceride-rich lipoproteins (TGRLP) are atherogenic.

The most likely candidates for atherogenic TGRLP are remnant lipoproteins. These lipoproteins include small very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL). They are cholesterol enriched particles and have many of the properties of LDL.

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

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Elevated Triglycerides

Evidence statement

Some species of triglyceride-rich lipoproteins, notably, cholesterol-enriched remnant lipoproteins, promote atherosclerosis and predispose to CHD.

Recommendation: In persons with high serum triglycerides, elevated remnant lipoproteins should be reduced in addition to lowering of LDL cholesterol.

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program Adult Treatment Panel III NCEP-ATP III Risk of Triglycerides

When **triglyceride levels are ≥200 mg/dL**, the presence of increased quantities of atherogenic remnant lipoproteins can heighten CHD risk **substantially** beyond that predicted by LDL cholesterol alone.

For these reasons, **ATP III modified the triglyceride classification** to give more attention to moderate elevations.

NCEP ATP III Chapter II Circulation December 2002 pp3169

National Cholesterol Education Program
Adult Treatment Panel III NCEP-ATP III
Treatment of Triglycerides

- If triglycerides are very high **(≥500 mg/dL),** attention turns first to prevention of acute pancreatitis, which is more likely to occur when triglycerides are >1000 mg/dL.

- Triglyceride-lowering drugs (fibrate or nicotinic acid) **become first line therapy**; although statins can be used to lower LDL cholesterol to reach the LDL goal, in these patients

NCEP ATPIII. Chapter IV ***Circulation December 2002 pp 3247***

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Adult Treatment Panel III NCEP-ATP III

Treatment of Triglycerides

What is the NCEP ATP III **goal for TG therapy,** if baseline TG is 200-500 mg/dL?

1) Normalize LDL-C

2) Normalize the non HDL-C value

} ↓ **ApoB**

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421