

Presenter Disclosure Information

Management of Dyslipidemia in the Chinese Population

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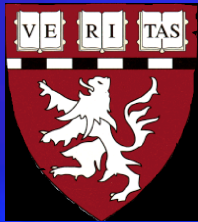
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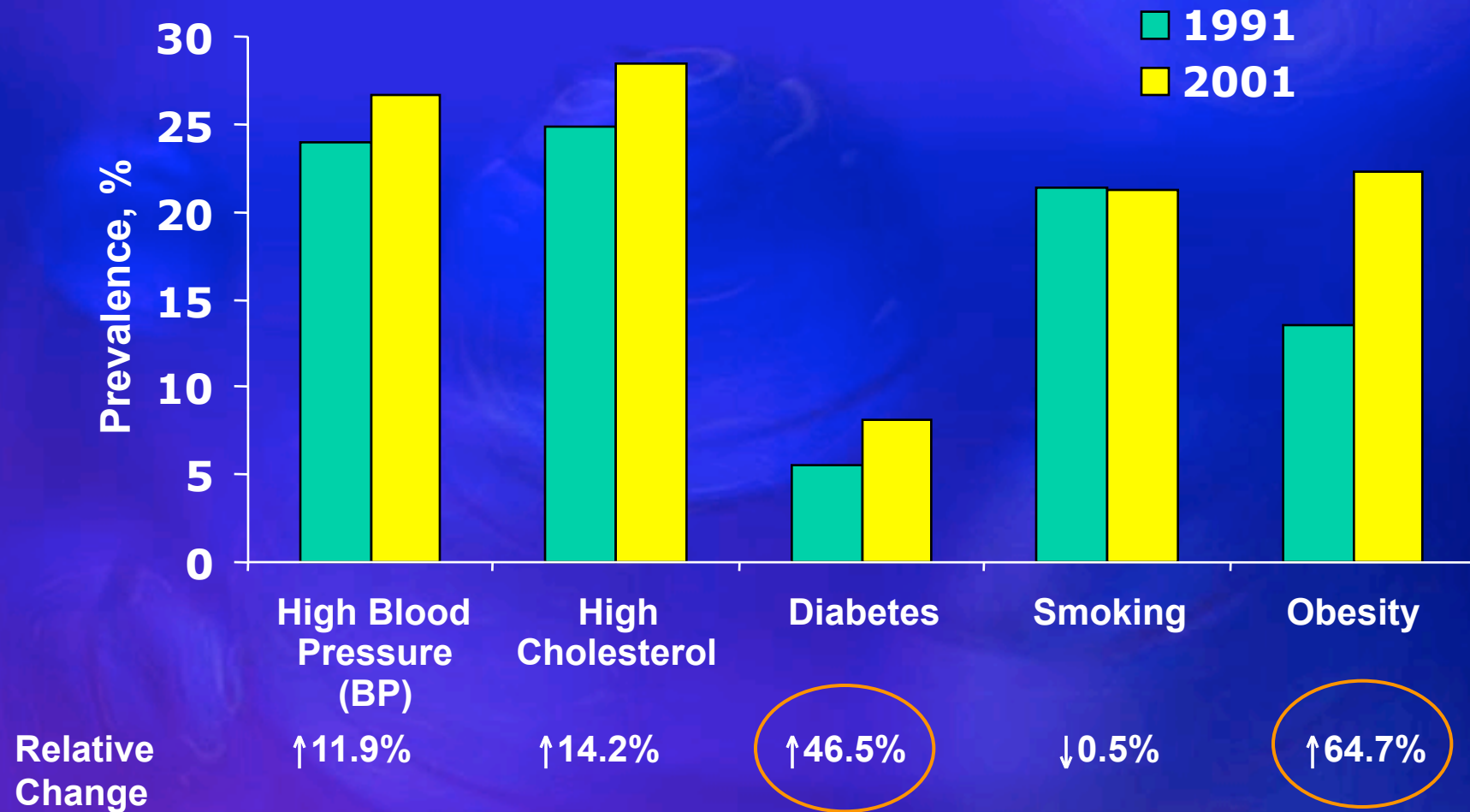
14th International Conference
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Management of Dyslipidemia in the Chinese Population

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Brigham & Women's Hospital

Prevalence of Most CHD Risk Factors and CHD Risk Equivalents Is Increasing

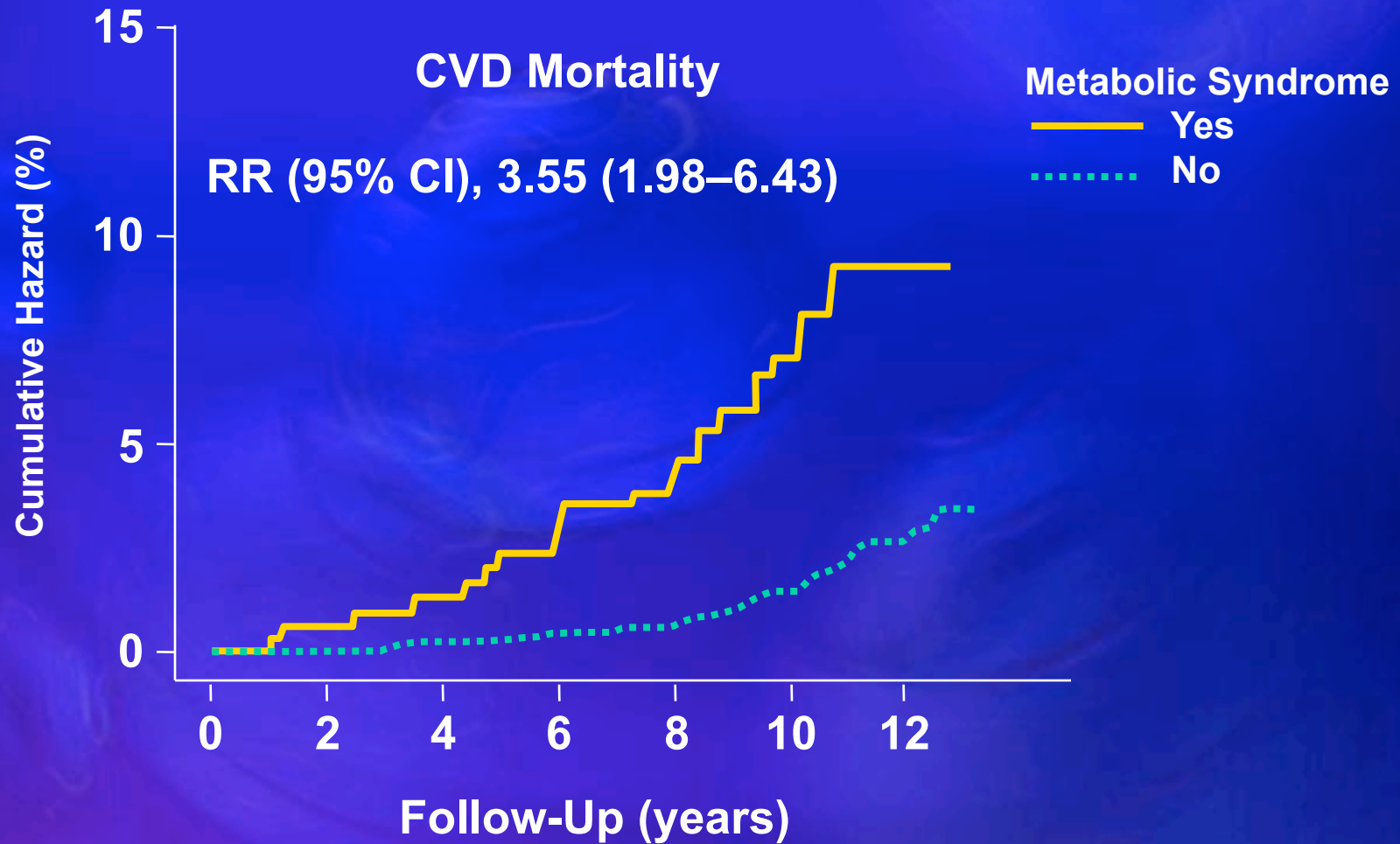


Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2004;53:4-7.

The Metabolic Syndrome

- Incidence is rapidly increasing world-wide, related to increasing obesity
- Characterized by a constellation of underlying causes and metabolic risk factors
- Risk for developing CHD exceeds that predicted by LDL-C only or Framingham Risk Score

CVD Mortality Increased with the Metabolic Syndrome



The Metabolic Syndrome: NCEP ATP III Criteria

Risk Factor

Defining Level

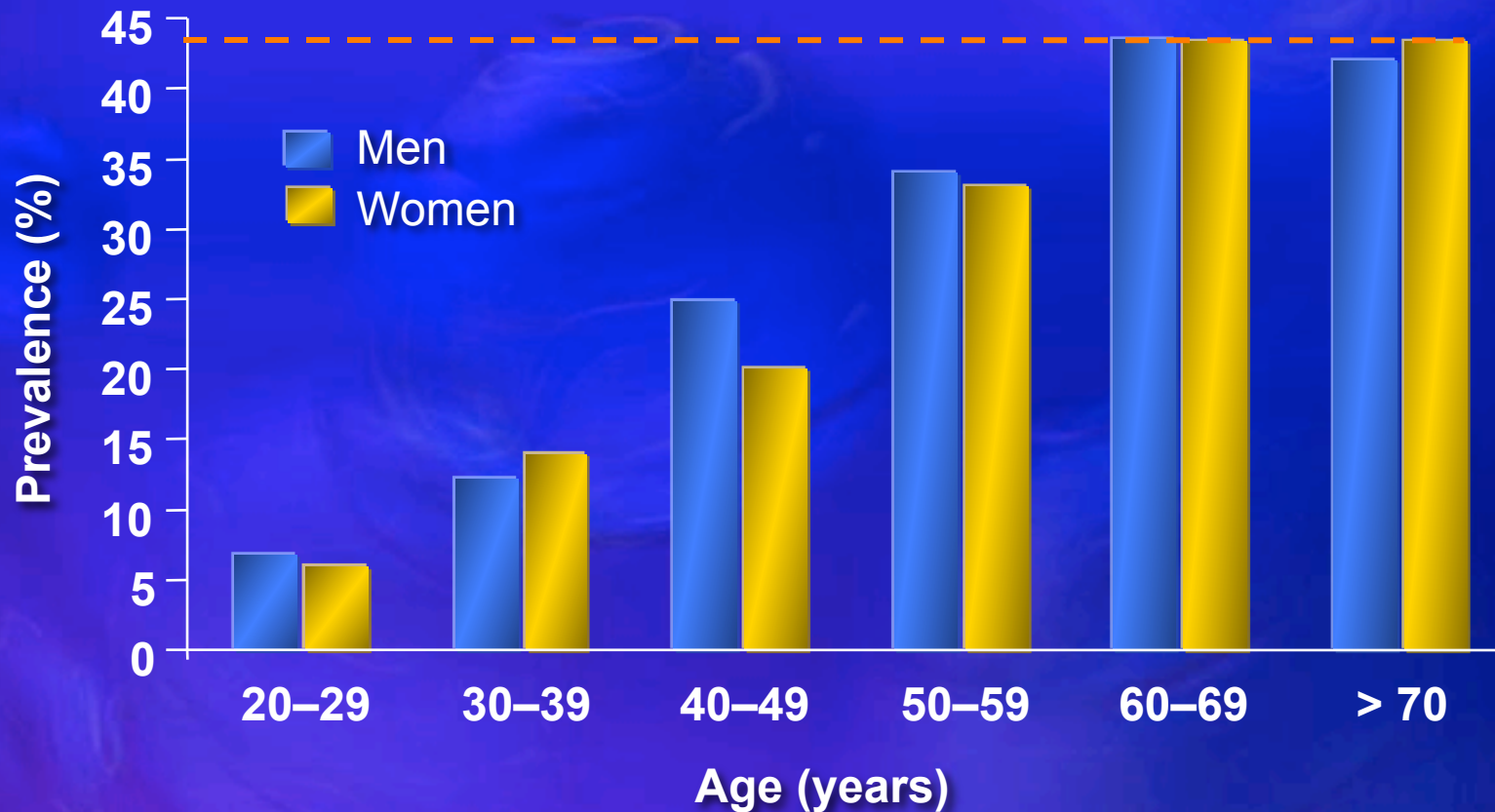
- Abdominal obesity
 - Men Waist > 102 cm → 90 cm
 - Women Waist > 88 cm → 80 cm
- TG ≥ 1.7 mmol/L
- HDL-C
 - Men < 1.04 mmol/L
 - Women < 1.30 mmol/L
- Blood pressure $\geq 130/\geq 85$ mm Hg
- Fasting glucose ≥ 5.6 mmol/L

Metabolic Syndrome Affects Women to the Same Degree as Men

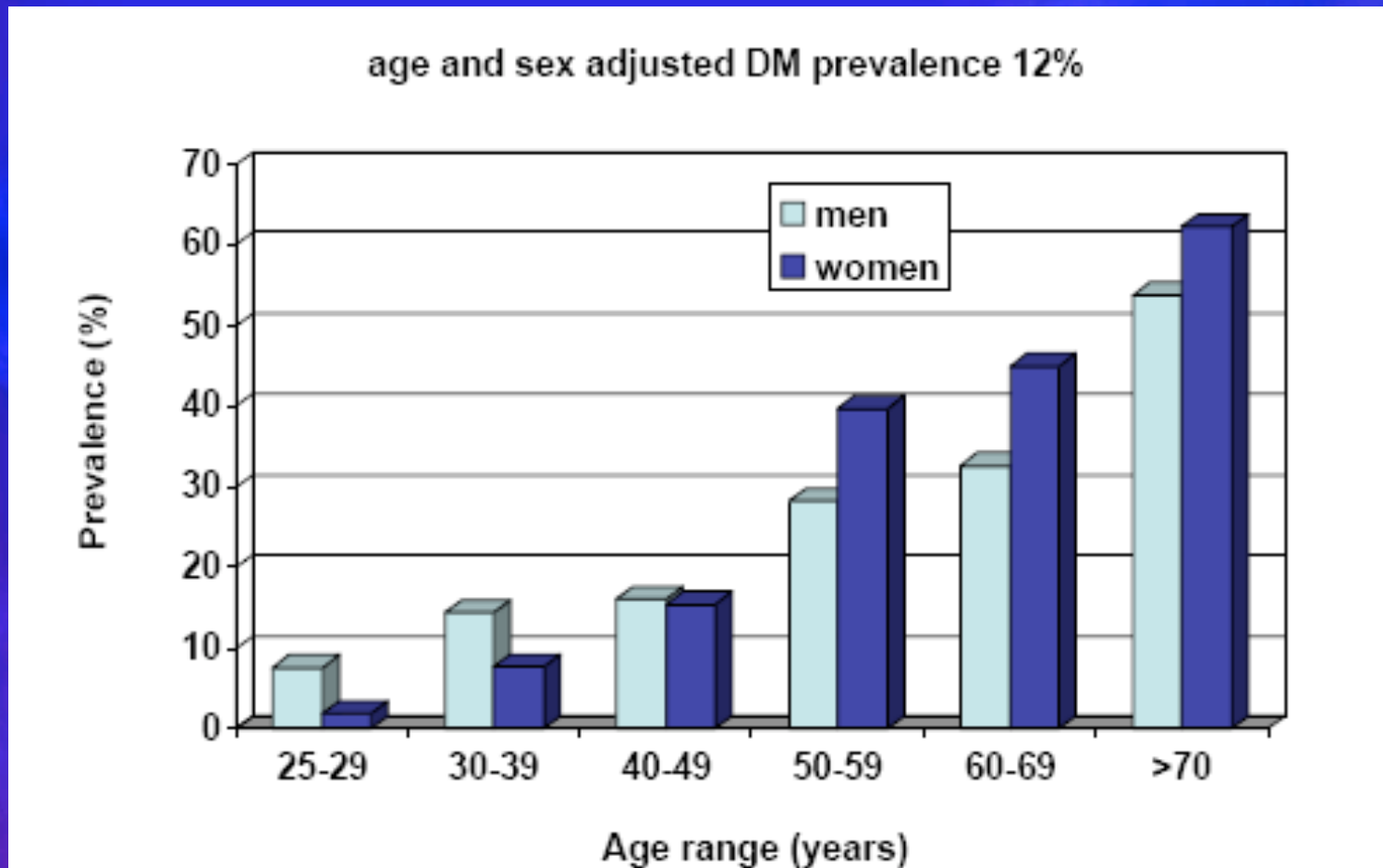
Age-adjusted Prevalence (%) among US Adults Aged ≥ 20 years

	NHANES 1994	NHANES 1999-2000	Relative Change (%)
Women	27.0	32.9	21.8
20-39 y	10.8	19.1	76.7 ←
40-59 y	30.5	33.8	10.9
>60 y	50.3	56.0	11.3
Men	31.4	31.8	1.4
20-39 y	15.7	16.5	4.9
40-59 y	36.3	40.3	10.9
≥ 60 y	50.5	46.4	-8.2
All	29.2	32.3	10.9

Prevalence of the Metabolic Syndrome Among US Adults



Metabolic Syndrome in HK Chinese



Does This Chinese Man Have Metabolic Syndrome?

- 48 year old Chinese man presents for annual physical
- self-employed entrepreneur
- not seen in office for over 3 years - on no meds
- smoker x 15 years
- drinks alcohol when socializing with clients
- Ht 180 cm, wt 90 kg
- WC 100 cm (>90 cm Asians)
- BP 138/85 (>130/85)
- TC 5.3, TG 2.8, HDL 0.9, LDL 3.2 (TG>1.7; HDL<1.04)
- FPG 6.1 (≥5.6)

Chinese Man with Metabolic Syndrome

What is this patient's 10-year CHD risk?

- 1) 5%
- 2) 10%
- 3) 15%
- 4) >20%

CHD, coronary heart disease.

What is the 10-Year Framingham Risk for Cardiovascular Events?

- 48 year old Chinese man presents for annual physical
- self-employed entrepreneur
- not seen in office for over 3 years - on no meds
- smoker x 15 years
- drinks alcohol when socializing with clients
- Ht 180 cm, wt 90 kg
- WC 100 cm
- BP 138/85
- TC 5.3, TG 2.8, HDL 0.9, LDL 3.2
- FPG 6.1

Assessing Framingham 10-Year Risk

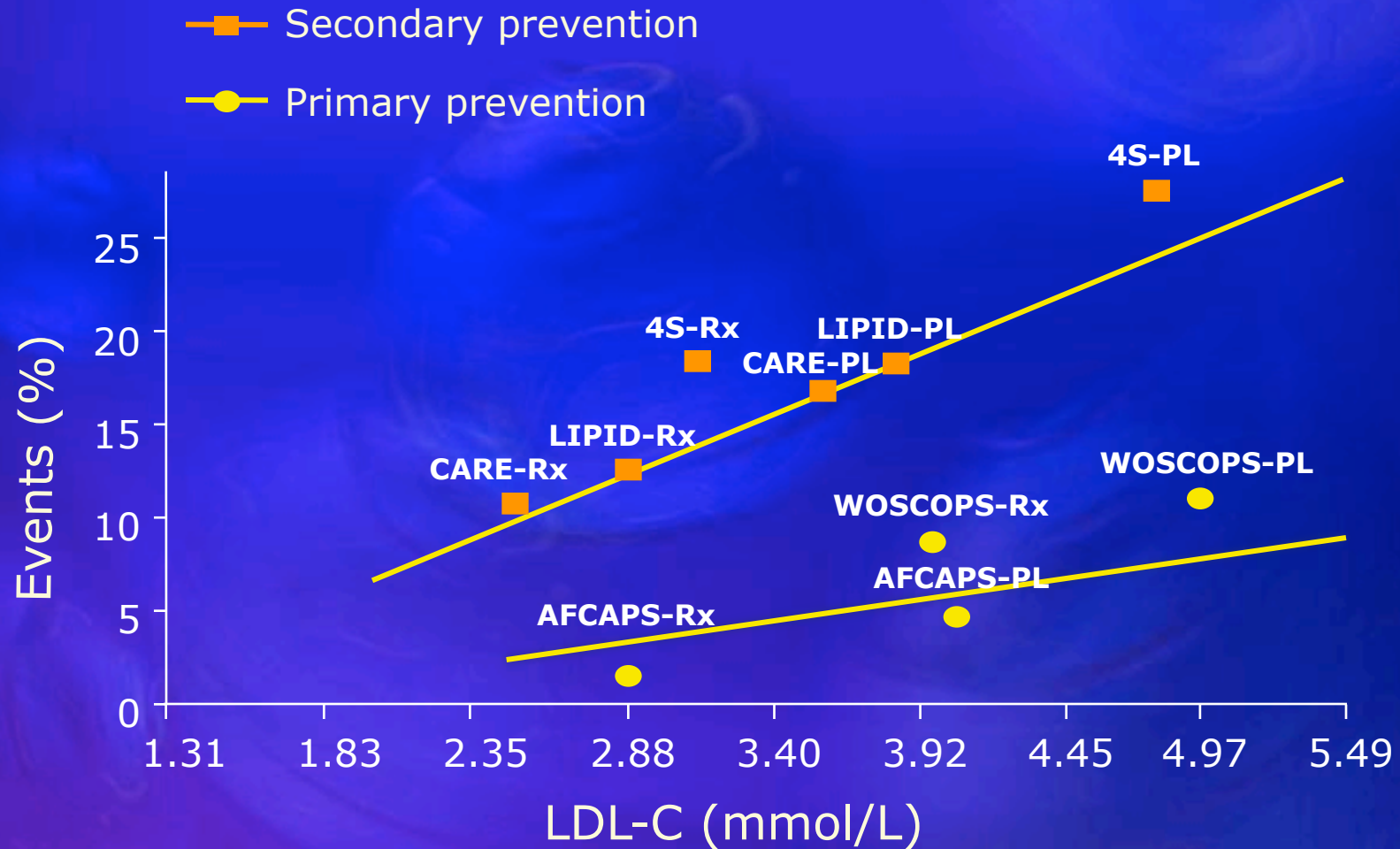
Patients By Age		Total Cholesterol (mmol/L), Male Age 40-49 y		Smoker, Male Age 40-49 y		TOTAL	
Age, y	Points	TC	Points		Points	Point Total	10-Year Risk, %
20-34	-9	<4.16	0	Nonsmoker	0	<0	<1
35-39	-4	4.16-5.18	3	Smoker	5	1	1
40-44	0	5.19-6.14	5			2	1
45-49	3	6.24-7.25	6			3	1
50-54	6	≥7.28	8			4	1
55-59	8					5	2
60-64	10					6	2
65-69	11					7	3
70-74	12					8	4
75-79	13					9	5
						10	6
						11	8
						12	10
						13	12
						14	16
						15	20
						16	25
						≥17	≥30

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

Treating the Dyslipidemia Associated With Metabolic Syndrome

- Dyslipidemia:
 - Elevated TG ≥ 1.7 mmol/L and low HDL-C < 1.04 mmol/L
- ATP-III specific advice:
 1. Treat the LDL-C first
 2. For patients with TG ≥ 200 mg/dL, treat the non-HDL-C
 - NonHDL-C = total cholesterol – HDL-C
(atherogenic lipoproteins: LDL + VLDL)
 - NonHDL-C goal = LDL-C goal + 0.78 mmol/L
- Primary target for treatment of dyslipidemia associated with the Metabolic Syndrome is LDL-C

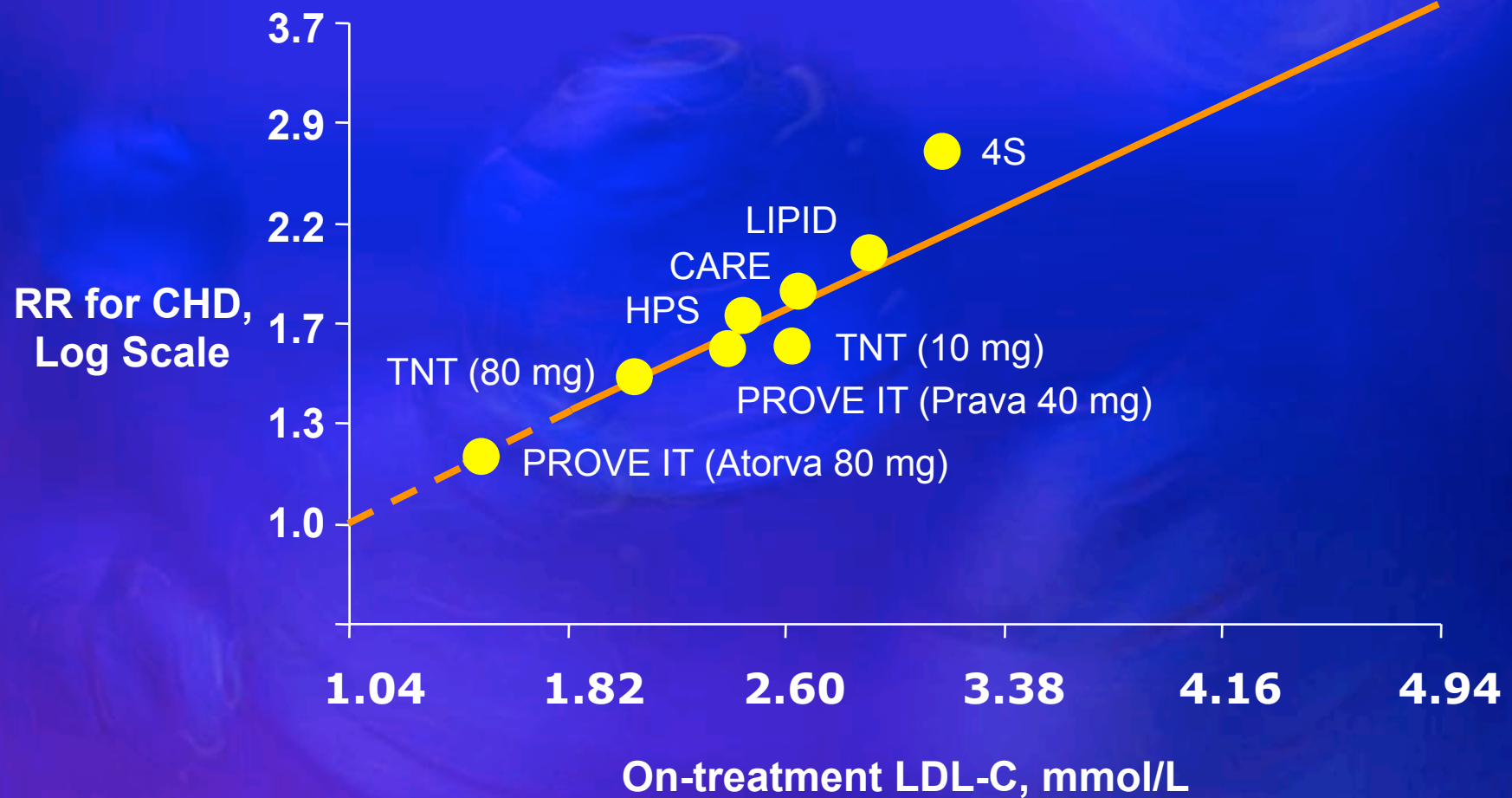
LDL-C Lowering With Statins



PL, placebo groups; Rx, treatment groups.

Adapted with permission from Illingworth DR. *Med Clin North Am.* 2000;84:23-42.

Recent Evidence from Statin Trials Suggests Lower LDL-C Levels Are Better



Grundy SM, et al, for the Coordinating Committee of the NCEP. *Circulation*. 2004;110:227-239.

Implications for High-Risk Patients: LDL-C Goals and Cutpoints for Therapy

		LDL-C Goal, mmol/L	LDL-C to Initiate Therapy,* mmol/L
High Risk and Very High Risk	CHD or CHD Risk Equivalents; 10-Year Risk >20%	<2.6 (optional goal <1.8 [†] or 2.0)	≥2.6 (<2.6: consider drug options [‡])
Moderately High Risk	2+ Risk Factors; 10-Year Risk 10-20%	<3.4 (optional goal <2.6)	≥3.4 (2.6-3.4: consider drug options [‡])

* All high-risk and moderately high-risk patients with lifestyle-related risk factors are candidates for TLC. Patients without lifestyle-related risk factors should begin TLC if their LDL-C is above goal.

†Particularly for patients at very high risk.

‡Initiating drug therapy in high-risk patients with LDL-C <2.6 mmol/L and moderately high-risk patients with LDL-C 2.6 to 3.4 mmol/L are options that have clinical support.

Grundy SM, et al, for the Coordinating Committee of the NCEP. *Circulation*. 2004;110:227-239.

Targeting High Risk Patients (Canadian and European Guidelines)

- High risk is defined as patients with diagnosis of atherosclerotic vascular disease or a calculated $\geq 20\%$ ten-year risk of CHD death or non fatal MI (? $\geq 10\%$ ten-year risk with FHx of CHD)
- Most people with type 1 or type 2 diabetes should be considered at high risk for vascular disease (*Class 1; Level A*)
- However, some people with diabetes may not be, such as younger patients with shorter duration of disease and without complications of diabetes and without other risk factors (*Class 2b; Level C*)
 - Primary target: LDL-C < 2.0 mmol/L (*Class 1; Level A*)

Therapeutic Options for Achieving a >50% LDL Reduction in High Risk Patients

Drug	Dose, mg/d	LDL Reduction, %
Atorvastatin	40-80	>50
Rosuvastatin	10-20 [†]	>50
Ezetimibe/simvastatin	10/20-10/40 [§]	>50

*Available at doses of up to 80 mg/d; doubling of dose will produce an additional 6% decrease in LDL-C.

† Available at doses up to 40 mg/d; a 6% increase in LDL-C reduction is observed when dose is doubled.

§ Available at doses up to 10/80 mg/d; a 5% increase in LDL-C reduction is observed when dose is doubled.

Grundy SM, et al, for the Coordinating Committee of the NCEP. *Circulation*. 2004;110:227-239.

Cholesterol Goal Attainment in the Real World: The REALITY Asia Study

- To evaluate lipid-lowering therapy prescribing patterns and cholesterol goal achievement in patients with and without CHD and other risk factors in the “real world” setting in 6 major Asian countries

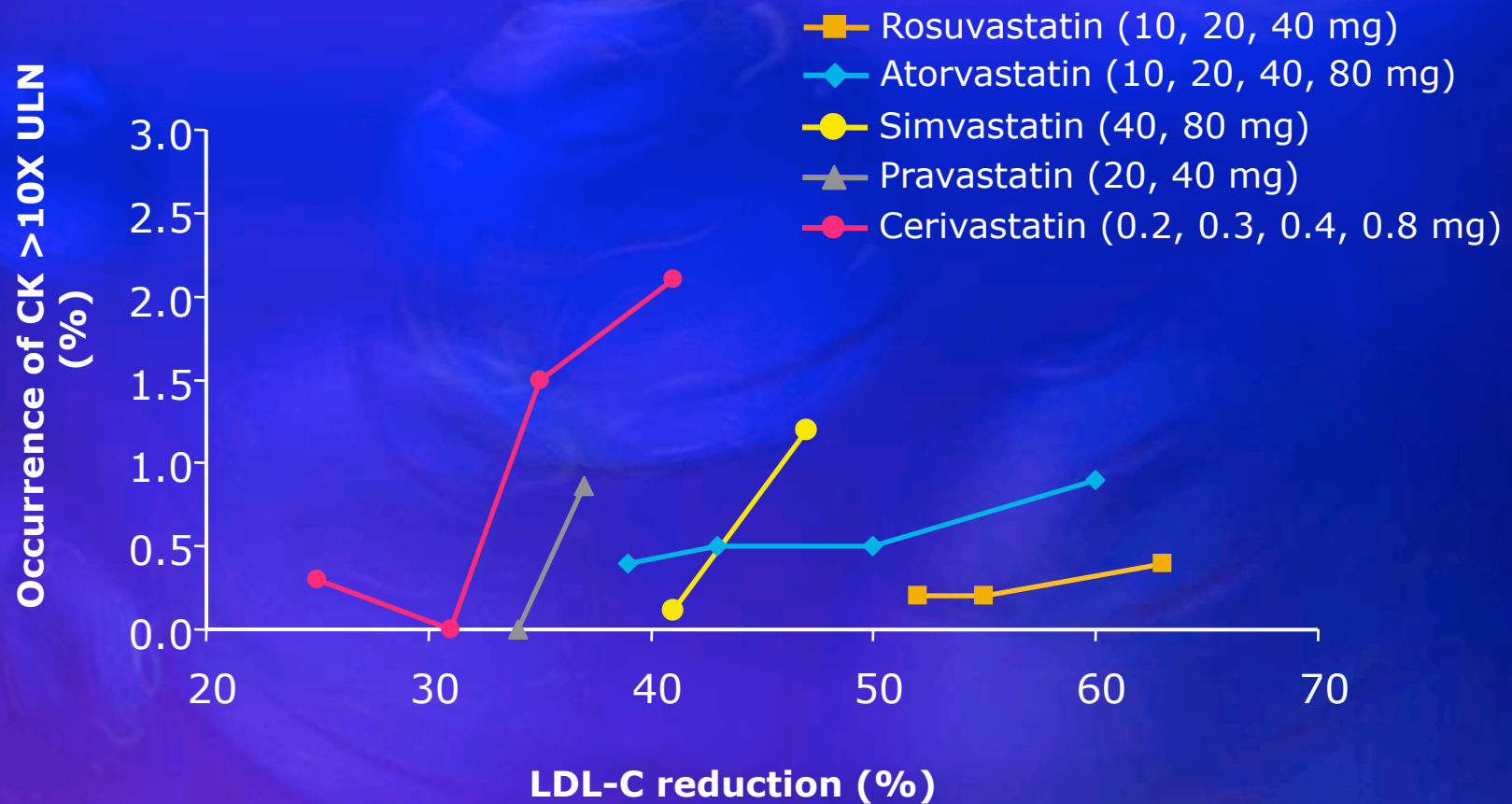


Cholesterol Goal Attainment in the Real World: The REALITY Study

- Most patients received statins as index therapy
 - Only **16%** of regimens were adjusted to increase potency
 - Only **4 out of 10** patients achieve their target cholesterol goals
-

Side-effects of Statins are Dose-related

CK >10X ULN: Frequency by LDL-C Reduction



Health Canada Prescribing Recommendations for Statin Therapy

“The dosage of all statins should be individualized according to baseline LDL-C, TC/HDL-C Ratio and/or TG levels to achieve the recommended target lipid values at the **lowest possible dose.**”

Increased Sensitivity of Asians to Statins

Safety and Efficacy of Statins in Asians

James K. Liao, MD^{a,b,*,†}

Asian patients frequently have heightened responses to therapeutic drugs. As a consequence, the recommended drug doses are often lower in Asian countries than in Western countries. This practice extends to the use of cardiovascular drugs, including statins for the treatment of dyslipidemia. Pharmacokinetic investigations have noted higher plasma levels of statins in Asians compared with Caucasians, although postmarketing data for all statins have not identified any particular safety issues, even when statins are given at equivalent doses. The potential mechanisms of heightened response to statins in Asians are related to genetically based differences in the metabolism of statins at the level of hepatic enzymes and drug transporters. Studies indicate that lower statin doses achieve lipid improvements in Asian patients comparable with those observed with higher doses in Caucasians. In conclusion, prescribing lower starting doses of statins in Asians appears warranted while research on this subject continues. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:410–414)

Characteristics of Dyslipidemia in Metabolic Syndrome and Asians

- Elevated serum triglycerides
- Reduced HDL cholesterol
- Usually normal LDL cholesterol level

Is a Normal LDL Concentration Atherogenic in Metabolic Syndrome and Type 2 Diabetes?

Despite “normal” LDL-C concentrations, there is

- A preponderance of small, dense LDL
- Modification of LDL
 - Oxidation
 - Glycation

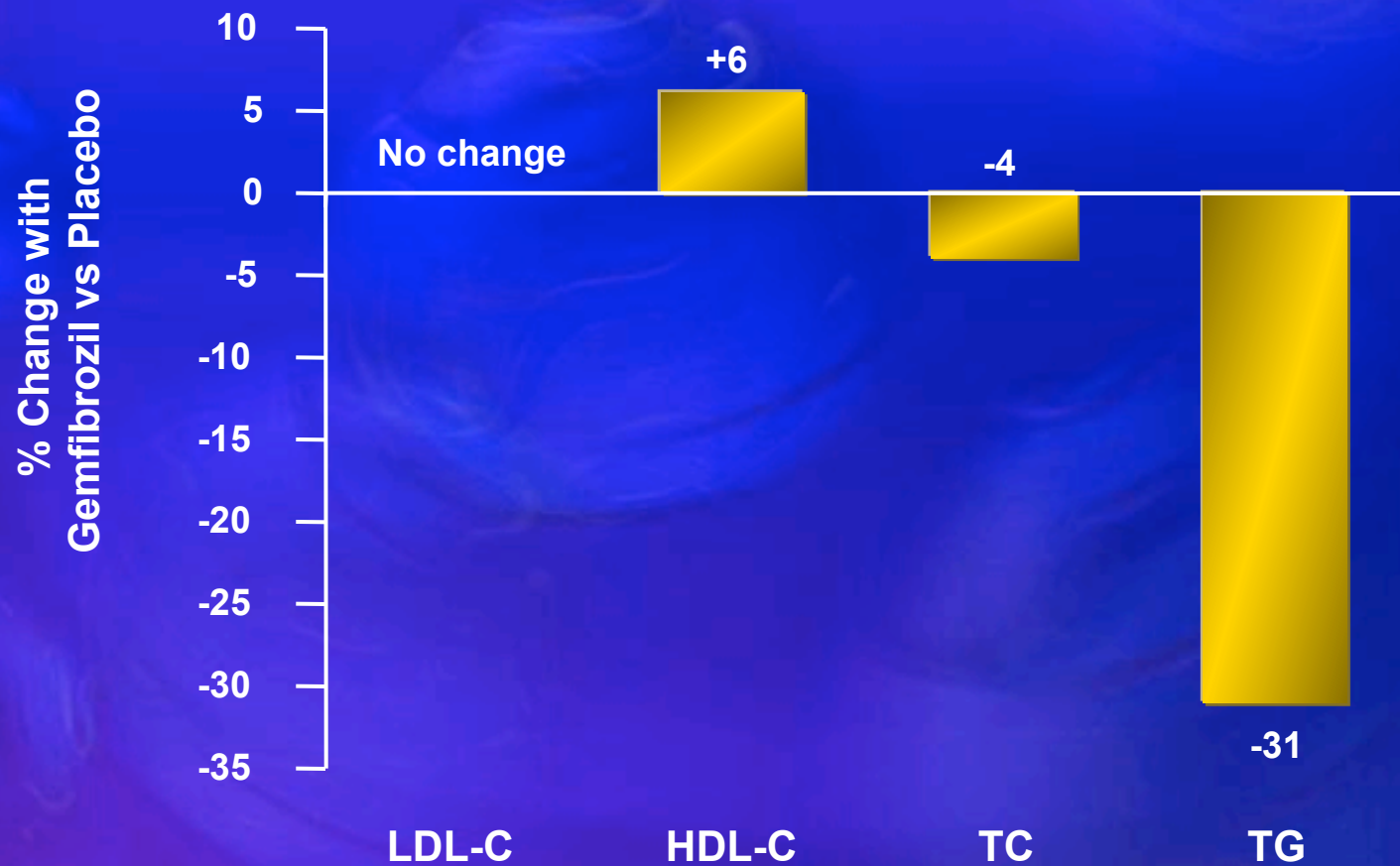
HDL and Triglycerides

Risk factors or innocent bystanders?

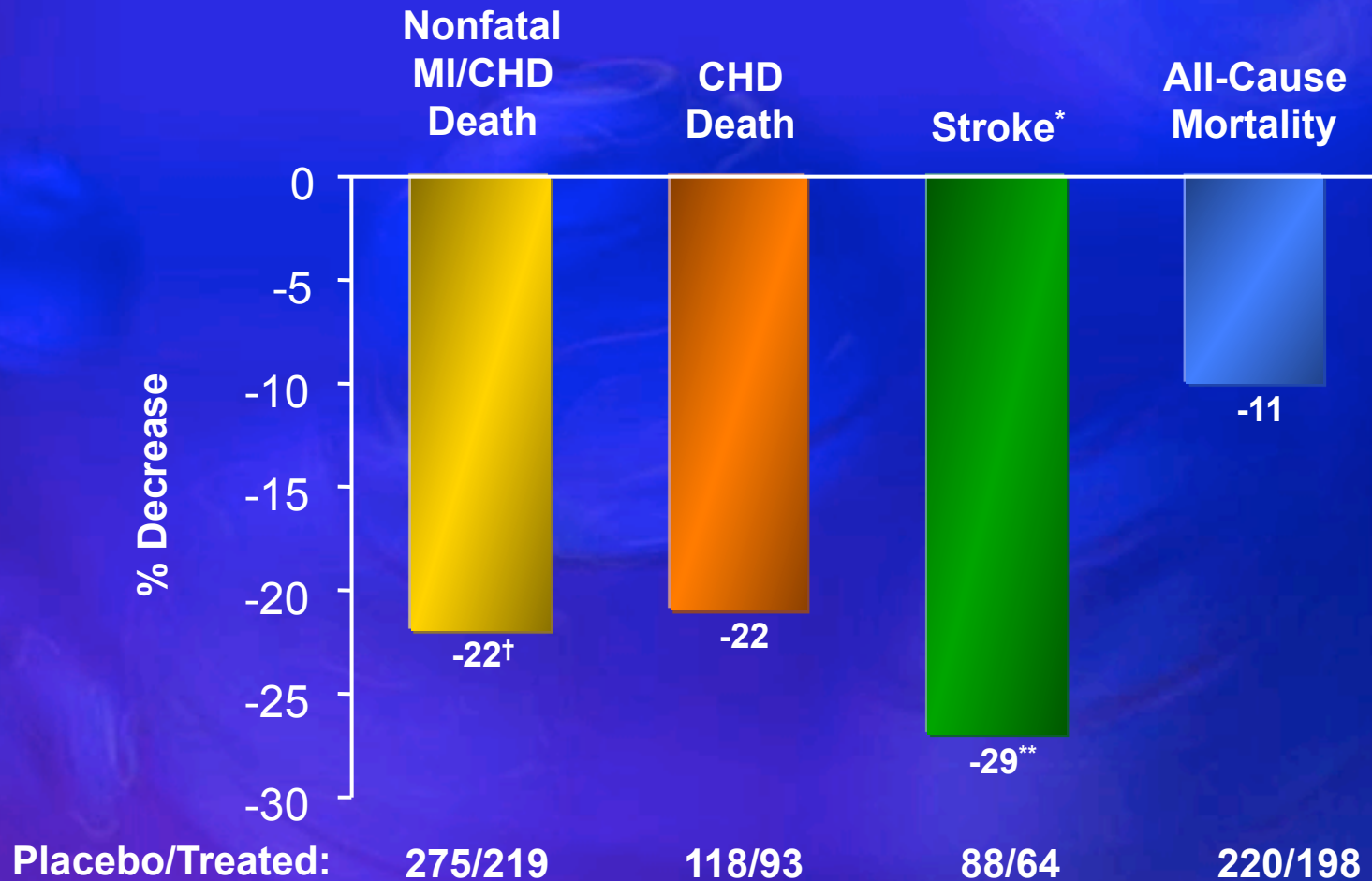
Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)

- Double-blind study
- Gemfibrozil (600 mg BID) versus placebo
- 2531 men with CHD
- LDL-C \leq 3.64 mmol/L, HDL-C \leq 1 mmol/L, TG \geq 2.5 mmol/L
- Mean age: 64 y (76.5% > 60 y)
- Study duration: 7 y
- Median follow-up: 5.1 y
- Primary end point: nonfatal MI or coronary death

VA-HIT: Effects on Lipid Levels at 1 Year



VA-HIT: Effects of Fibrate on CVD Events in CHD Patients with Isolated Low HDL-C

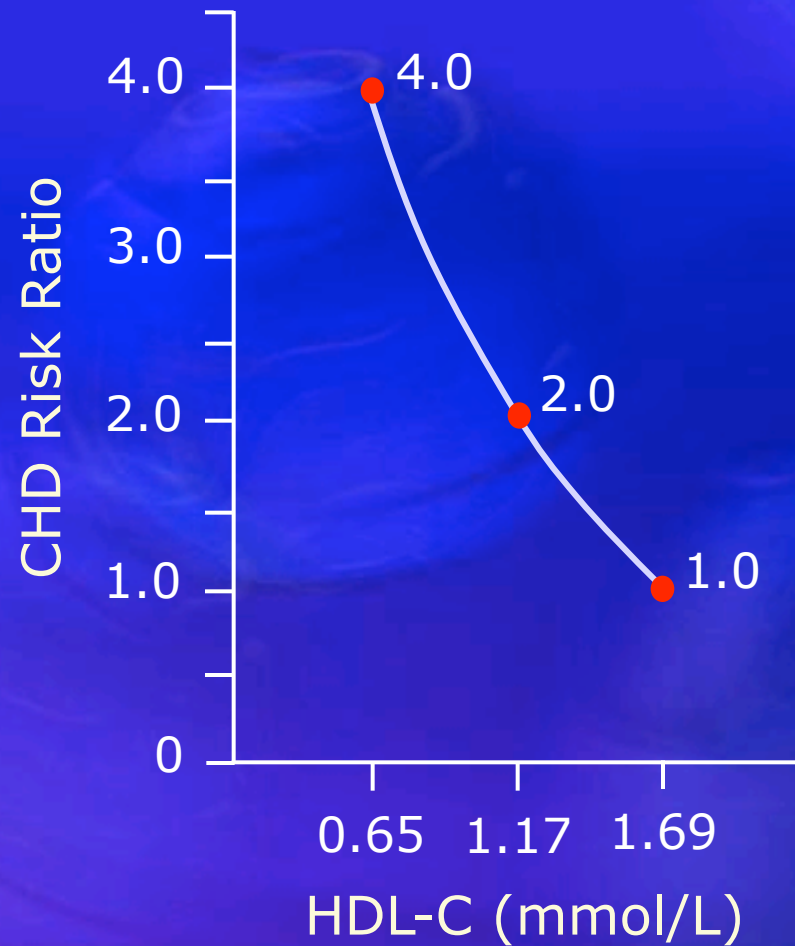


*Investigator-designated

[†] $P = 0.006$; ^{**} $P = 0.04$.

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

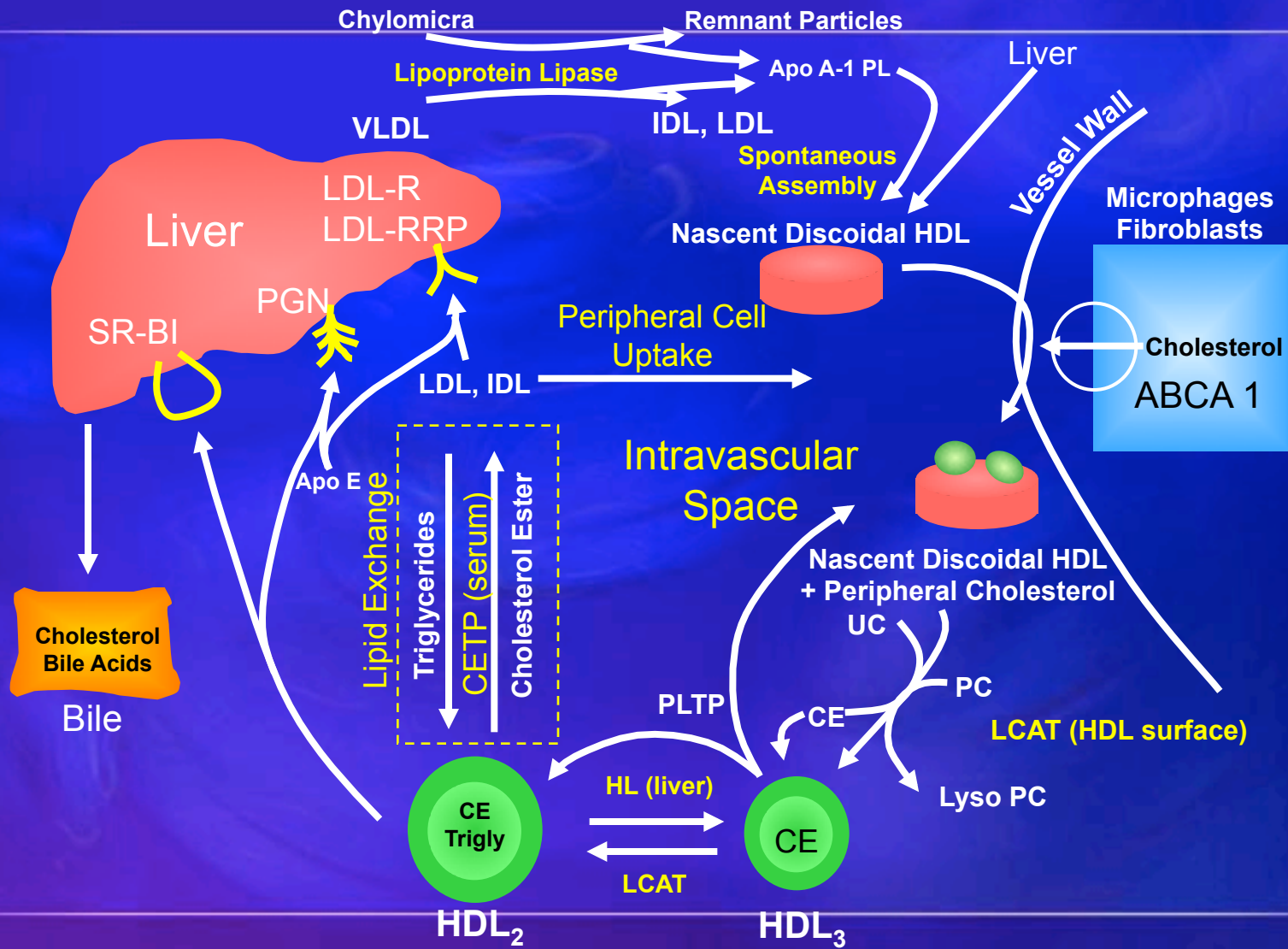
CHD Risk According to HDL-C Levels Framingham Study



HDL as CAD Risk Factor

NCEP ATP III recognizes that any serum HDL level <1.04 (men) and <1.29 (women) constitutes an independent risk factor for CAD and therapeutic effort should be made to raise HDL above this threshold

Reverse Cholesterol Transport



Prevalence of Low HDL-C in Hong Kong Chinese Population with Metabolic Syndrome

Prevalence of individual components of the metabolic syndrome based on National Cholesterol Education Adult Treatment Panel III (NCEP ATP III) guidelines in 2843 Hong Kong Chinese

Metabolic syndrome components	Male (<i>n</i> = 1388) (%)	Female (<i>n</i> = 1455) (%)	Total (<i>n</i> = 2843) (%)
Hyperglycaemia	24.0	26.1	25.1
High blood pressure	32.3	26.5	29.3
Hypertriglyceridaemia	24.0	14.7	19.3
Low HDL-cholesterol	40.7	47.6	44.2
Central obesity NCEP	3.5	10.5	7.1
Central obesity WHO	22.0	29.4	25.8

High blood pressure: systolic/diastolic blood pressures were $\geq 130/85$ mmHg or were receiving blood pressure lowering drugs; hyperglycaemia: fasting plasma glucose was ≥ 6.1 mmol/L or were receiving glucose lowering drugs; hypertriglyceridaemia: fasting plasma triglycerides ≥ 1.69 mmol/L; low HDL-cholesterol: fasting HDL-cholesterol < 1.04 or 1.29 mmol in males and females, respectively; Central obesity: NCEP (WHO) waist circumference > 88 or 102 cm (≥ 80 or ≥ 90 cm) in females and males, respectively [2,12].

CV Risk Factors: Findings From UKPDS

Risk Factor	P Value*
LDL-C	<0.0001
HDL-C	0.0001
HbA _{1c}	0.0022
Systolic BP	0.0065
Smoking	0.056

*Based on multivariate modeling.
Turner et al. *BMJ*. 1998;316:823.

CV Risk Factors: Findings From INTER-HEART Study

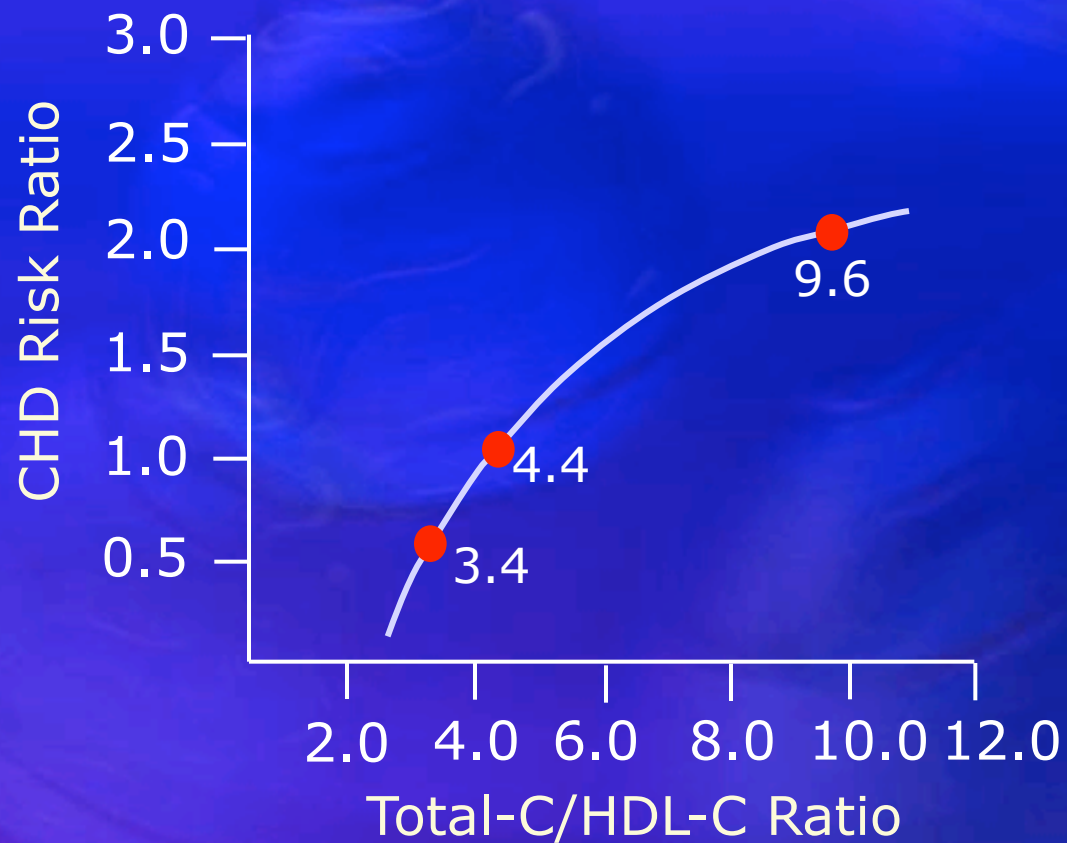
Risk Factor	Odds Ratio*
ApoB/ApoA-1 (LDL:HDL ratio)	3.25
Smoking	2.87
Psychosocial Factors	2.67
Diabetes	2.37
Hypertension	1.91
Abdominal Obesity	1.12

*Population attributable risk

S. Yusuf et al. *Lancet* 2004;364:937-52.

Most Important Predictor of Cardiovascular Event

Framingham Study (Men)



Risk Categories and Target Levels

Risk Level

Treat to:

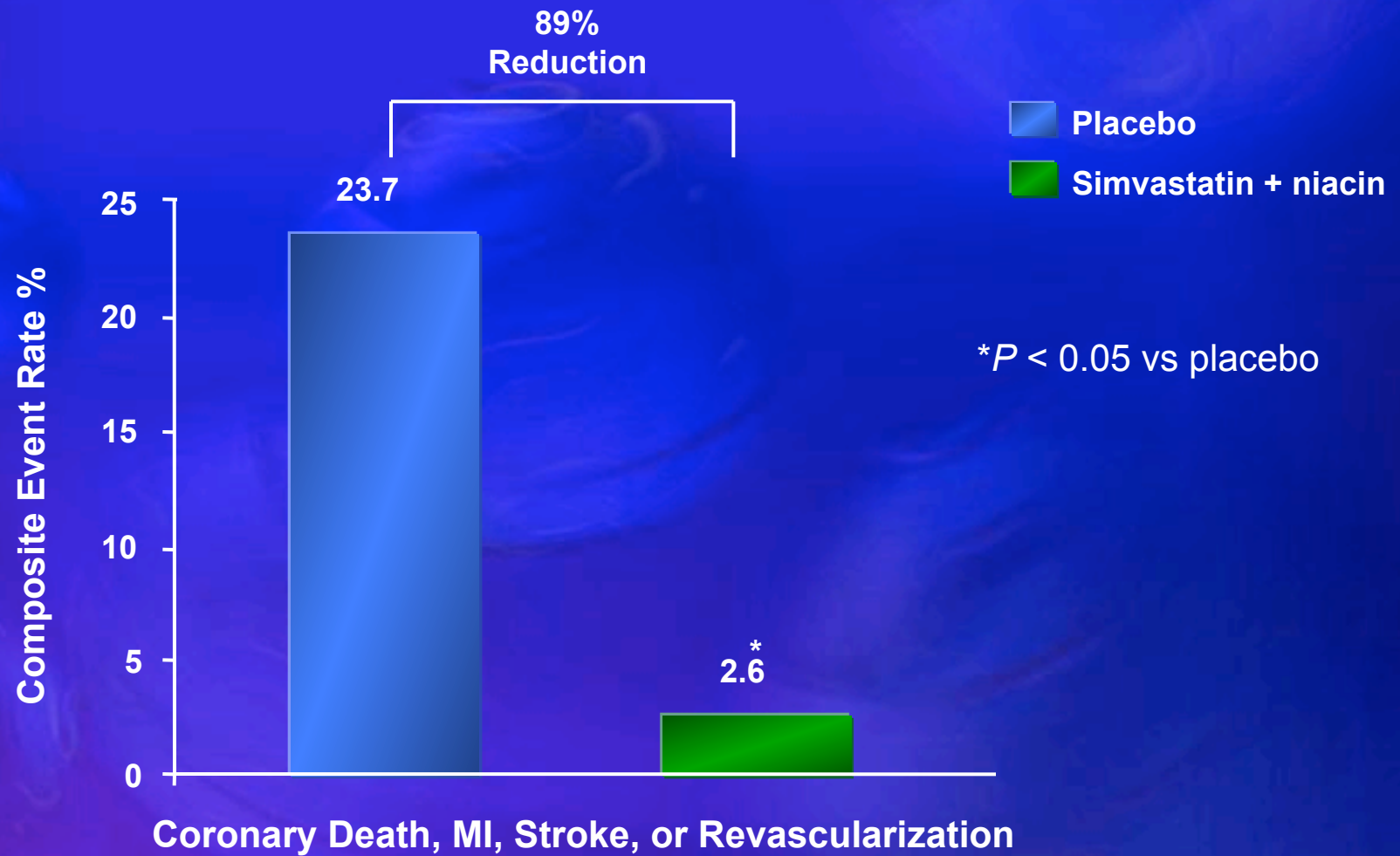
		LDL-C		TC/HDL-C Ratio
High	$\geq 20\%$	< 2.0	&	< 4.0

Treat If:

		LDL-C		TC/HDL-C Ratio
Moderate	10-19%	≥ 3.5	or	≥ 5.0
Low	$< 10\%$	≥ 5.0	or	≥ 6.0

May initiate treatment at lower or higher levels if family history or other investigations indicate elevated or reduced risk. Optimal apo B < 1.2 g/L low risk, < 1.05 g/L intermediate risk, < 0.85 g/L in high risk patients.

HATS: Clinical End Points



Conditions/Activities Related to Low HDL-C Levels (<1.04 mmol/L)

- **Lifestyle**
 - Cigarette smoking
 - Physical inactivity
- **Diet/body weight**
 - Obesity (in particular, abdominal obesity)
 - Low-fat, high-carbohydrate diets
 - Diets high in processed and refined grains
 - Uncontrolled Type 2 diabetes, insulin resistance
- **Medication**
 - Some beta blockers
 - Thiazide diuretics
 - Anabolic steroids
 - Progestational agents
- **Medical abnormality/disease**
 - Elevated TG
 - Liver or kidney failure
 - Hyperthyroidism
 - Hepatic lipase abnormalities

Weight and HDL-C

- Inverse correlation between body weight and HDL-C is consistently observed in both men and women
- For every 3.2 kg of weight loss, HDL-C levels increase **1.2 mmol/L**

Smoking Cessation and HDL-C

- In study by Moffatt, smokers had HDL-C levels 15%–20% lower than nonsmokers ($P < 0.05$)¹
 - PROCAM showed less of an effect of smoking on HDL-C (7% lower than nonsmokers)²
- HDL-C levels returned to normal within 30–60 days after smoking cessation¹
- In 8 women who smoked > 1 pack per day for 5 years, HDL-C levels increased from 1.3 to 1.7 mmol/L after quitting for 60 days¹

¹Moffatt RJ. *Atherosclerosis*. 1988;74:85-89.

²Cullen P et al. *Eur Heart J*. 1998;19:1632-1641.

Chronic Exercise and HDL-C

- Regular exercise increases HDL-C level
- Kokkinos et al reported a clear dose-response relationship between aerobic exercise (running) and HDL-C levels in healthy men

HDL-C (mmol/L)					
Non Runner	9 km/wk	15 km/wk	21 km/wk	29 km/wk	53 km/wk
(n = 685)	(n = 335)	(n = 512)	(n = 376)	(n = 602)	(n = 96)
1.2	1.3*	1.4*†	1.4*†	1.5*‡	1.6*‡

* $P < 0.001$ vs nonrunners; † $P < 0.01$ vs nonrunners and 8.5 km/wk;
‡ $P < 0.01$ vs all other groups.

Kokkinos PF et al. *Arch Intern Med.* 1995;155:415-420.

Alcohol and HDL-C

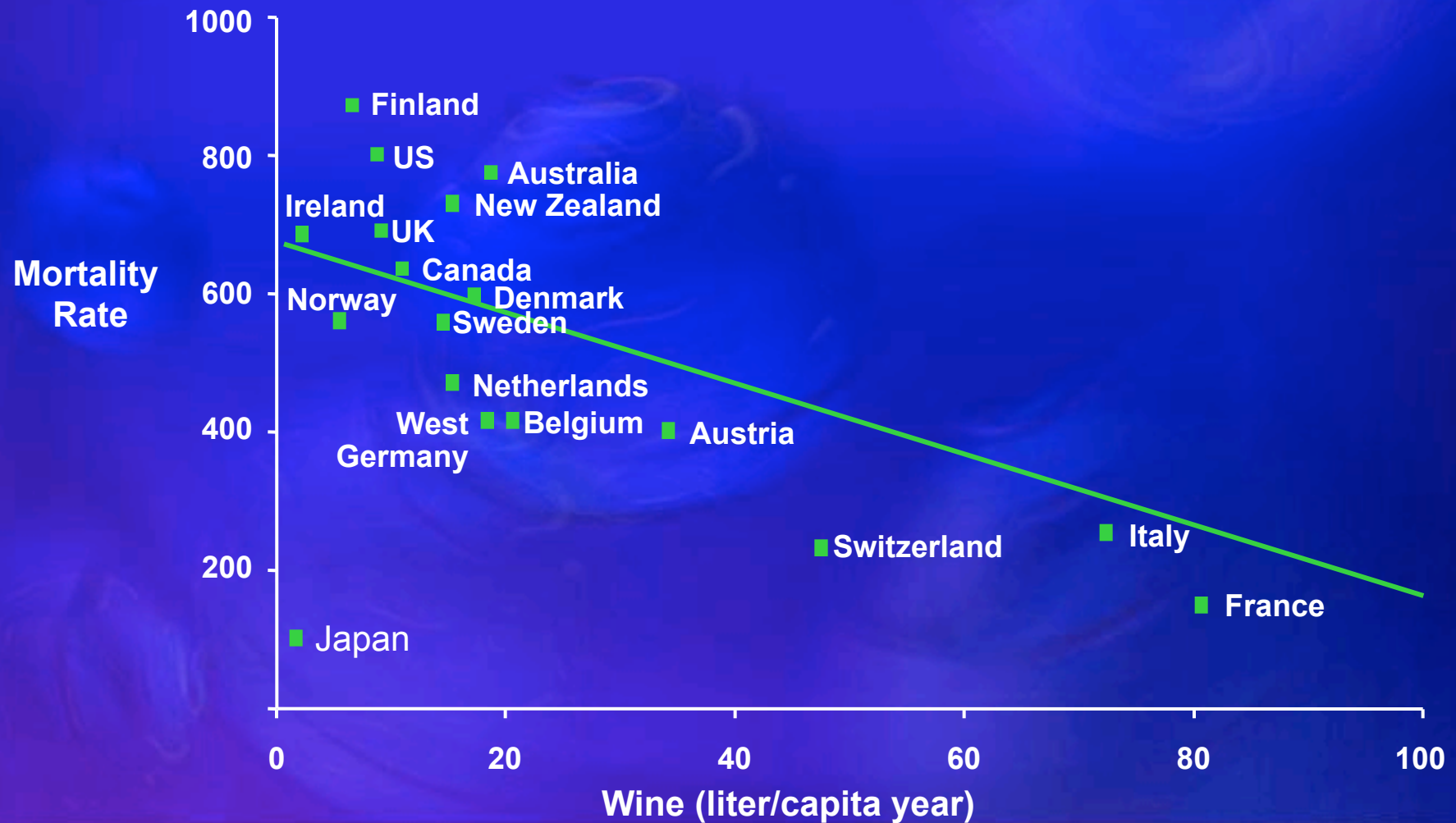
- Alcohol increases HDL-C level in a dose-dependent manner
- Half bottle of wine per day (39 g alcohol) for 6 weeks significantly increased mean HDL-C level by **0.2 mmol/L** in 12 healthy subjects¹
 - Wine intake did not significantly affect TC, TG, or LDL-C¹
- 1 beer per day (13.5 g alcohol) for 6 weeks significantly increased mean HDL-C level by **0.05 mmol/L** in 20 healthy subjects²
 - Beer intake did not significantly affect LDL-C, VLDL-C, TG, or ApoB

VLDL-C, very low density lipoprotein cholesterol.

¹Thornton J et al. *Lancet*. 1983;2:819-822.

²McConnell MV et al. *Am J Cardiol*. 1997;80:1226-1228.

Wine Consumption and CHD



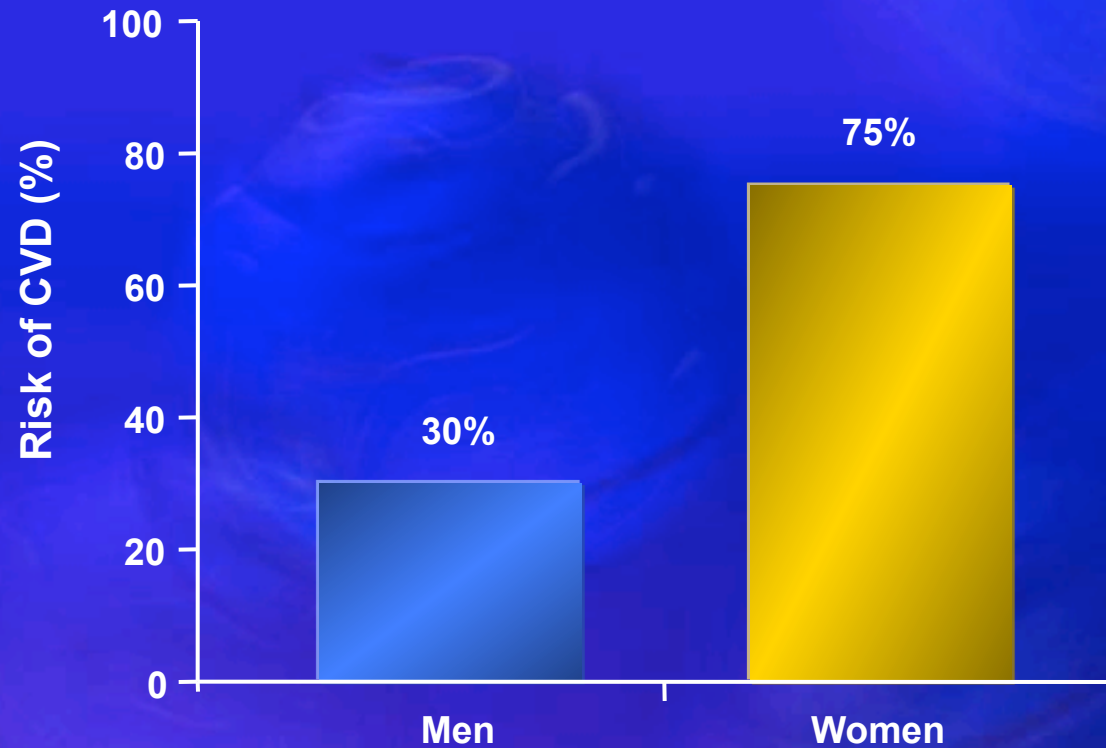
Effects of Drugs on HDL-C Levels

Nicotinic acid	↑	15%–35%
Fibrates	↑	10%–15%
Estrogens	↑	10%–15%
Statins	↑	5%–10%
Alcohol	↑	10%

TG and CAD

- Elevated serum TG levels are a strong risk factor of CHD independent of other major risk factors
 - Non-HDL-C is a secondary target of therapy in patients with high TG
 - The metabolic syndrome confers a risk for developing CHD that exceeds the risk predicted by LDL-C alone or Framingham Risk Score and should be incorporated in risk assessment and management
-

High TG and CHD Risk



Relative risks and 95% CI calculated and standardized with respect to a 1 mmol/L increase in TG

TG Definitions

Normal	<1.7 mmol/L
Borderline high	1.7 - 2.2 mmol/L
High	2.2 - 5.6 mmol/L
Very high	≥ 5.6 mmol/L

The Metabolic Syndrome and Therapeutic Lifestyle Change (TLC)

- Greatest benefit from successful implementation of TLC will occur in patients with the metabolic syndrome
- Prioritize limited resources for implementing TLC in these patients

Essential Components of TLC

Component

Recommendation

LDL-C-raising nutrients

- Saturated fats
- Dietary cholesterol

Less than 7% of total calories
Less than 200 mg/day

Therapeutic options for LDL-C lowering

- Plant stanols/sterols
- Increased viscous (soluble) fiber

2 g/day
10–25 g/day

Total calories

Adjust caloric intake to maintain desirable body weight/prevent weight gain

Physical activity
exercise

Include enough moderate to expend at least 200 Kcal/day

Macronutrient Recommendations for the TLC Diet

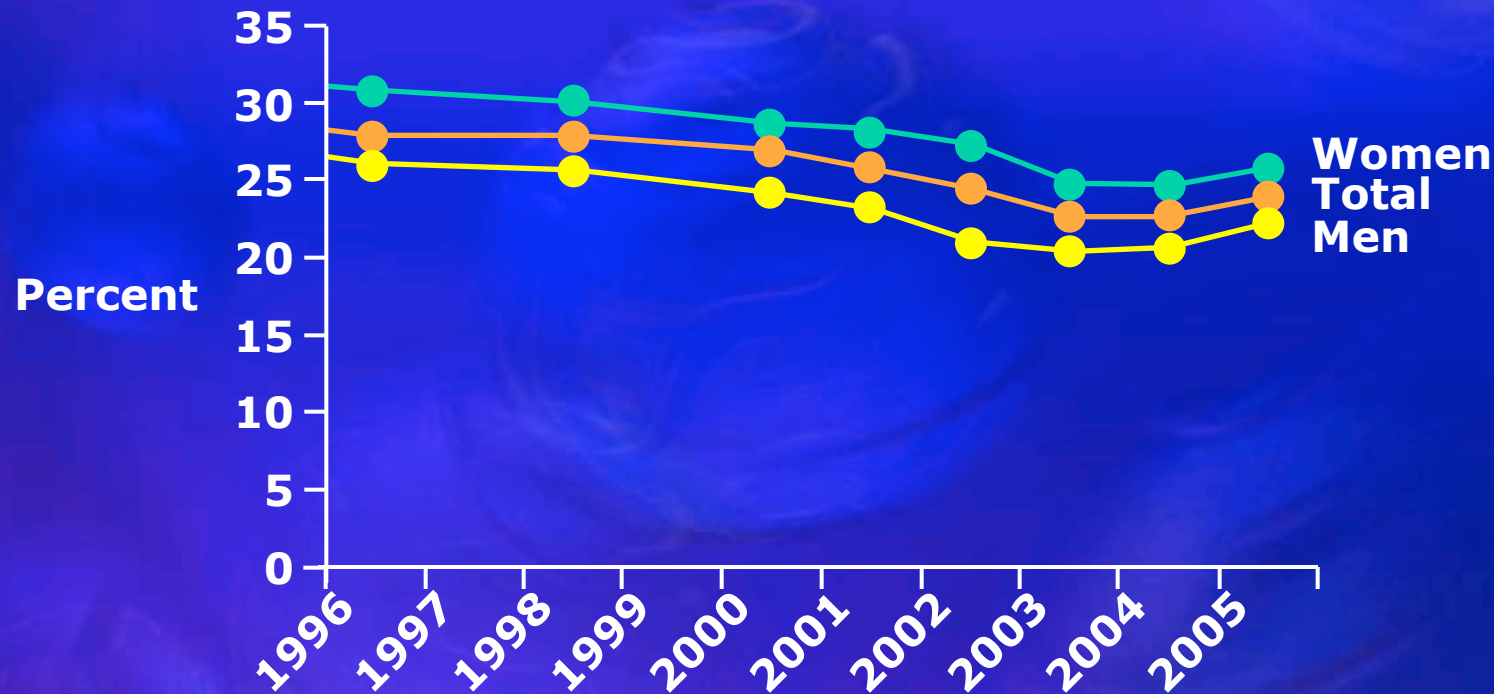
Component	Recommendation
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25%–35% of total calories*
Carbohydrate [†]	50%–60% of total calories*
Dietary fiber	20–30 g/day
Protein	Approximately 15% of total calories

*NCEP ATP III allows an increase of total fat to 35% of total calories and a reduction in carbohydrate to 50% for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat.

[†]Carbohydrate should derive predominantly from foods rich in complex carbohydrates, including grains, especially whole grains, fruits, and vegetables.

Prevalence of US men and women reporting no leisure-time physical activity

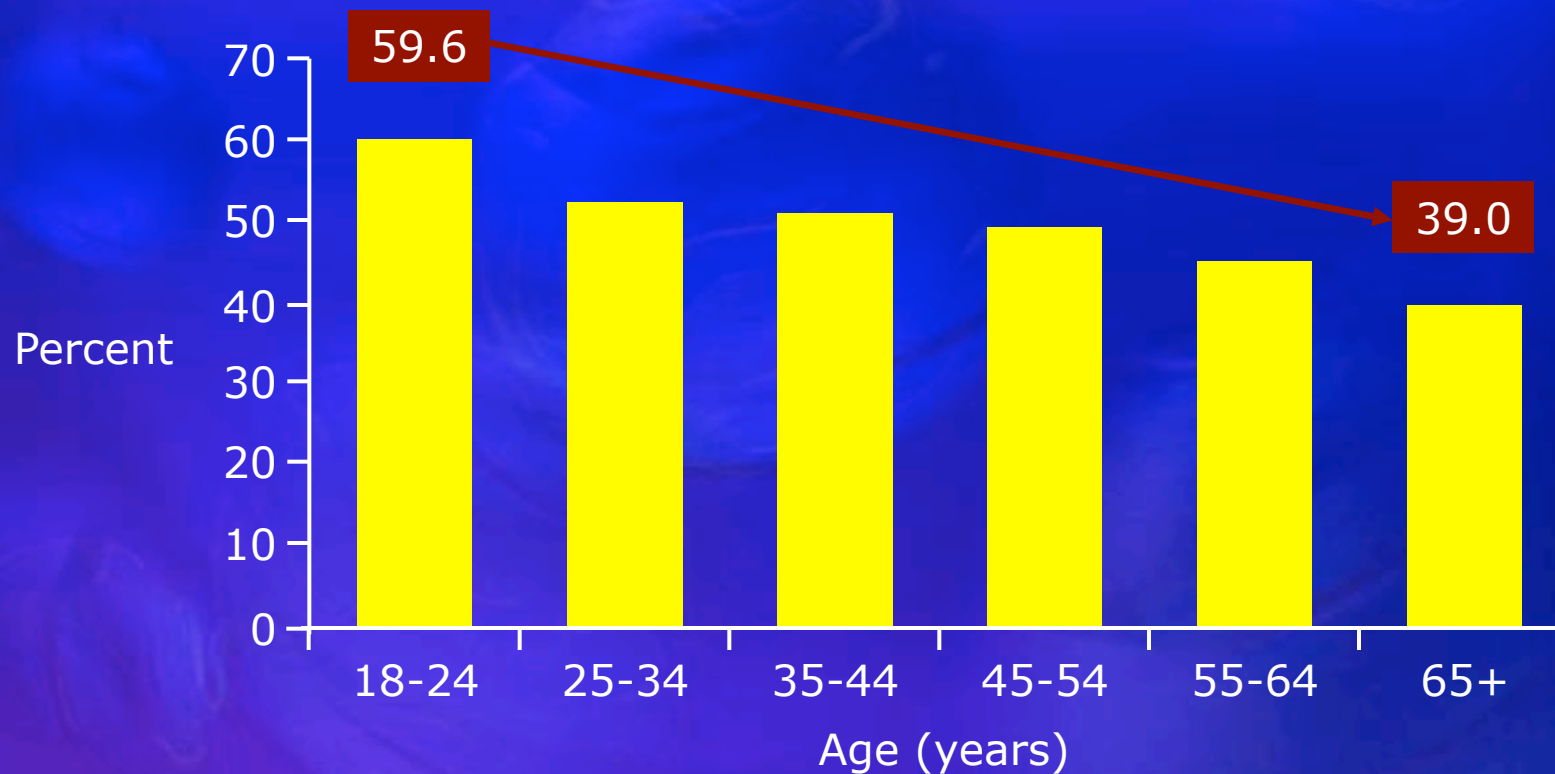
CDC Behavioral Risk Factor Surveillance System (1996-2005)



In 2005, 23.7% of adults reported no leisure-time physical activity

Proportion of adults meeting physical activity recommendations declines with age

CDC Behavioral Risk Factor Surveillance System (2005)



Haskell WL et al. *Circulation*. 2007;116.

ACSM/AHA 2007: Physical activity recommendations for healthy adults (aged 18-65 years)

- Perform moderate-intensity aerobic physical activity ≥ 30 min, 5 days a week or vigorous-intensity aerobic physical activity ≥ 20 min, 3 days a week I (A)*
- Combine moderate- and vigorous-intensity activities to meet this recommendation (eg, walk briskly 30 min twice a week and jog 20 min on 2 other days) IIa (B)*
- Accumulate shorter bouts of moderate-intensity activities (≥ 10 min each) to meet 30-min minimum I (B)*

*Class of recommendation and level of evidence

ACSM = American College of Sports Medicine

AHA = American Heart Association

Examples of moderate- and vigorous-intensity aerobic activity

Moderate-intensity

- Brisk walk (3-4 mph)
- Noticeably accelerates heart rate

Vigorous-intensity

- Very brisk walk (4.5 mph) or jogging
- Causes rapid breathing and a substantial increase in heart rate

Incorporating the Metabolic Syndrome in Risk Assessment and Management

- Presence of the metabolic syndrome may be indication for more aggressive lipid lowering:

LDL-C < 2.6 mmol/L (<2.0 mmol/L)

TG < 1.7 mmol/L and HDL-C > 1.04 mmol/L

- Options: statins as first choice
- Add drugs that lower TG and raise HDL-C:
nicotinic acid or fibrates plus statin
 - Target non-HDL-C as goal of treatment
(< 3.4 mmol/L, especially if TG > 2.5 mmol/L)

Drug Treatment of the Metabolic Syndrome

- Decrease small, dense LDL-C particles
 - Statins
 - Nicotinic acid (niacin)
 - Fibrates
 - (Statins may be more effective in reducing total number of LDL-C particles)
- Decrease TG
 - Fibrates
 - Omega-3 fatty acid
 - Nicotinic acid (niacin)
 - Statins
- Increase HDL-C
 - Nicotinic acid (niacin)
 - Fibrates, especially if hypertriglyceridemia is present

Principles of Combination Lipid Drug Therapy

- Additive effects for reducing LDL-C
 - Statin + bile-acid sequestrant
 - Statin + ezetimibe
- Additional benefit for reducing non-HDL-C in mixed dyslipidemia
 - Statin + fibrate
 - Statin + nicotinic acid
 - Statin + fish oil

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

Jones PH. *Am Heart J*. 2004;148:S9-S13.

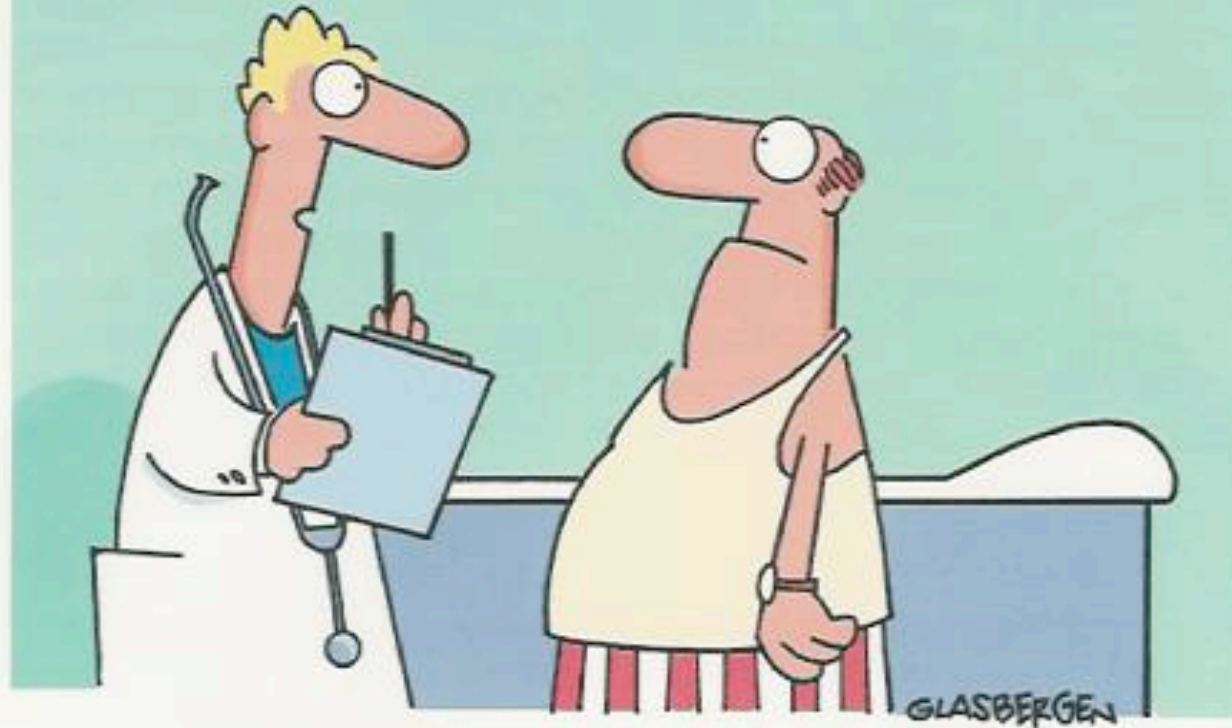
Drug Treatment of the Metabolic Syndrome

- Correct insulin resistance
 - Weight reduction
 - Increased physical activity
 - Drugs that decrease insulin resistance have not been proven to reduce CHD risk
- Control diabetes mellitus

Management of Dyslipidemia in Metabolic Syndrome and the Chinese Population

- Elevated serum TG levels and low HDL-C are strong risk factors of CHD independent of other major risk factors
- Non-HDL-C is a secondary target of therapy in patients with high TG
- The metabolic syndrome confers a risk for developing CHD that exceeds the risk predicted by LDL-C alone or Framingham Risk Score and should be incorporated in risk assessment and management
- Lifestyle modification contributes significantly to the management of low serum HDL levels and high TG levels

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“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”