Redefining Coronary Heart Disease Risk Assessment: THE ROLE OF NEW CARDIOVASCULAR RISK FACTORS

Slides
&
Lecture Notes

An International Roundtable Series

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Dear Colleague:

We are happy to provide you with this set of Slides & Lecture Notes from the program, *Redefining Coronary Heart Disease Risk Assessment:* THE ROLE OF NEW CARDIOVASCULAR RISK FACTORS.

These slides form the core group of data that I presented at a series of International Roundtables held during 1993.

Updated analyses of the Prospective Cardiovascular Münster (PROCAM) Study — which follows more than 30,000 men and women for coronary heart disease (CHD) risk factors — and the Helsinki Heart Study — a 5-year primary prevention trial — have identified a group of patients at very high risk of myocardial infarction. These are patients with a triad of lipid abnormalities which is characterized by high triglycerides plus a high LDL/HDL-cholesterol ratio. One in four patients with this profile will suffer a myocardial infarction in 6 years. Yet, these are also the patients most likely to benefit from risk reduction.

PROCAM data show that these high-risk patients often have other CHD risk factors in addition to high triglycerides and low HDL. As is well known, CHD risk increases sharply with the number and severity of risk factors. Thus, therapeutic decisions should be based on assessment of the patient's entire risk-factor profile.

These key PROCAM and Helsinki slides may be used as a complete set, or you may select certain slides to intersperse in your own collection. As you know, the European Atherosclerosis Society has recently updated and simplified its risk assessment and treatment guidelines. This slide set may be supplemented with those new materials.

We hope you find these slides useful in your educational endeavors.

Sincerely,

G. Assmann

Univ.-Prof. Gerd Assmann
Director, Institute for Arteriosclerosis Research
University of Münster

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Redefining Coronary Heart Disease Risk Assessment:
THE ROLE OF NEW CARDIOVASCULAR RISK FACTORS

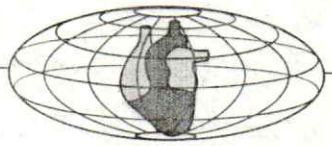
This program is supported through an educational grant from
PARKE-DAVIS
Division of Warner-Lambert Company.

SLIDE 1

Redefining Coronary Heart Disease Risk Assessment: The Role of New Cardiovascular Risk Factors

- This program examines the most recent data from
  - the Prospective Cardiovascular Münster (PROCAM) Study
  - the Helsinki Heart Study.
- PROCAM and Helsinki data
  - help the practicing physician better identify patients at high risk for coronary heart disease (CHD)
  - place particular emphasis on the syndrome of high triglycerides, low high-density lipoprotein-cholesterol (HDL-C), and elevated low-density lipoprotein-cholesterol (LDL-C) as a key factor underlying CHD risk.

Notes



SLIDE 2

PROCAM Study

The Prospective Cardiovascular Münster (PROCAM) Study: 6-Year Follow-up Data

- The PROCAM Study, launched in 1979, has examined cardiovascular disease (CVD) risk factors and subsequent cardiovascular events in more than 30,000 German men and women.
- Six-year follow-up data are available.
- Other variables being assessed by PROCAM investigators include cancer and stroke.

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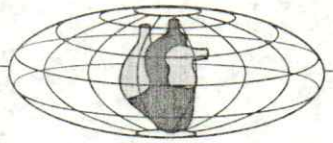

PROCAM Study

Study Design

- Ongoing prospective study initiated in 1979
- Approximately 30,000 subjects to date (1992)
- Two thirds men (mean age, 41 ± 11 years)
  One third women (mean age, 37 ± 13 years)
- Baseline examinations included lipids, lipoproteins, BP, and other CHD risk factors; exam repeated at 6-7 years
- Standardized questionnaires every 2 years (96% response rate) for mortality and CVD endpoints:
  - fatal or nonfatal MI
  - sudden cardiac death
  - stroke

Assmann G, Schulte H. Results and conclusions of the Prospective Cardiovascular Münster (PROCAM) Study. In: Assmann G, ed. *Lipid Metabolism Disorders and Coronary Heart Disease*. 2nd ed. Munich: MMV Medizin Verlag; 1993.

- ❑ Ongoing prospective study initiated in 1979.
- ❑ Approximately 30,000 subjects followed to date (1992).
- ❑ Two-thirds men (mean age 41 ± 11 years)
  One-third women (mean age 37 ± 13 years).
- ❑ Baseline examinations included fasting plasma samples of more than 30 laboratory variables, including lipids, lipoproteins, blood pressure, and CHD risk factors; repeat exam at 6 to 7 years.
- ❑ Standardized questionnaires every 2 years for CVD endpoints and mortality (96% response rate):
  - fatal or nonfatal myocardial infarction (MI)
  - sudden cardiac death
  - stroke.

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PROCAM Study

Population

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The study population was drawn from employees of 52 companies and authorities in:

- ❑ Münster
- ❑ Eastern Westphalia
- ❑ Southern Münsterland
- ❑ the northern portion of the Ruhr valley.

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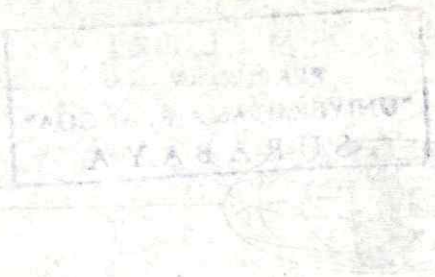
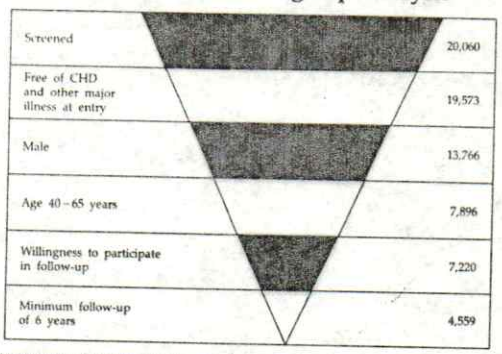


PROCAM Study

Selection Criteria for 6-Year Subgroup Analysis



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Subjects for 6-year follow-up analyses were identified in the following manner:

- Of the 20,060 men and women observed through 1985, a total of 19,573 were free of CHD and other major illness at study entry.
- Of these, two thirds (13,766) were men.
- For statistical purposes, adequate numbers of men with CHD occurred only in those aged 40 to 65 years (7,896 men).
- 4,559 (58%) of the 7,896 men aged 40 to 65 years and free of CHD were followed for 6 years.

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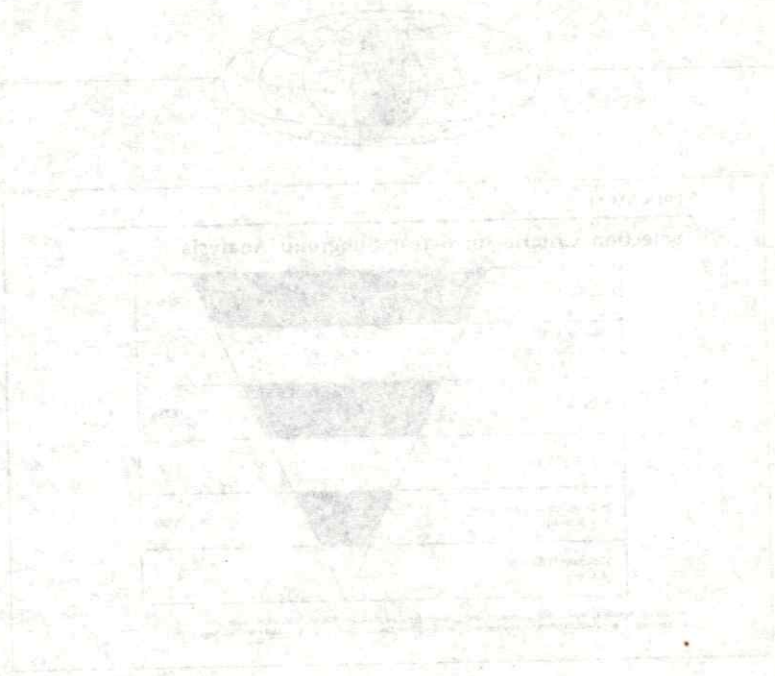

PROCAM Study Results

CHD Events

- 186 definite CHD events
  - 21 sudden cardiac deaths
  - 31 fatal MIs
  - 134 definite nonfatal MIs
- 23 nonfatal strokes
- 129 deaths other than CHD
  - 54 malignant neoplasms
  - 45 other diseases
  - 30 accidents and violence
- 4,221 subjects survived the 6 years without definite nonfatal MI or stroke, including 38 with suspect nonfatal MI

Assmann G, Schulte H. *Am J Cardiol* 1992;70:733–737.

Of the 4,559 men aged 40 to 65 years and free of CHD who were followed for 6 years:

- 186 (4%) experienced a definite CHD event.
- Of these 186 CHD events, there were:
  - 134 nonfatal MIs
  - 52 CHD deaths (31 fatal MIs and 21 sudden cardiac deaths).
- 23 (0.5%) of the 4,559 men had a nonfatal stroke.

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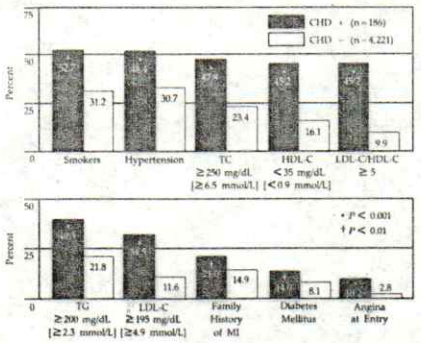
PROCAM Study – Results

Prevalence of Risk Factors in Groups With and Without CHD



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Certain PROCAM variables served to differentiate men who developed CHD from men who did not. At 6-year follow-up, men with CHD had a significantly greater prevalence of most CHD risk factors on univariate analysis than did men without CHD, including:

- ❑ High total cholesterol levels
- ❑ Low HDL-C levels
- ❑ High LDL-C/HDL-C ratio
- ❑ High triglyceride levels
- ❑ Cigarette smoking
- ❑ Hypertension.

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PROCAM Study – Results

Mean Values of CHD Risk Factors in Men Aged 40 – 65 Years With and Without CHD in 6 Years

Age-Standardized Factor	CHD + (n = 186)		SD	CHD – (n = 4,221)		SD
LDL-C / HDL-C *	4.73		1.51	3.44 **		1.20
HDL-C (mg/dL) [mmol/L]	39.5	[1.0]	10.6	45.2 **	[1.2]	11.8
LDL-C (mg/dL) [mmol/L]*	176.2	[4.6]	39.5	147.1 **	[3.8]	35.9
TC (mg/dL) [mmol/L]	251.8	[6.5]	47.3	222.9 **	[5.8]	41.0
Systolic BP (mm Hg)	139.4		21.2	132.7 **		18.9
Diastolic BP (mm Hg)	89.5		12.7	86.3 ***		11.1
BMI (kg/m^2)	26.7		2.9	26.3 †		3.0
TG (mg/dL) [mmol/L] ‡	163.0	[1.8]	67.8	134.5 **	[1.5]	58.1
Fasting blood glucose (mg/dL)	108.2	[6.0]	33.7	102.0 †	[5.7]	21.1
Uric acid (mg/dL) [mmol/L]	5.77	[343.2]	1.3	5.76	[342.6]	1.19
Age (years)		52.2	5.9	48.8		6.2

* n = 4,086 in CHD –; n = 177 in CHD +. ** $P < 0.001$. *** $P < 0.01$. † $P < 0.05$. ‡ Geometric mean.

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- Mean values for many age-standardized CHD risk factors were also significantly higher in men with CHD (except for HDL-C, which was significantly lower).
- The greatest difference between the two groups was in the LDL-C/HDL-C ratio, which was 37% higher in men with CHD.
  - triglyceride level was 21% higher
  - LDL-C level was about 20% higher
  - HDL-C level was 13% lower
  - total cholesterol level was about 12% higher.

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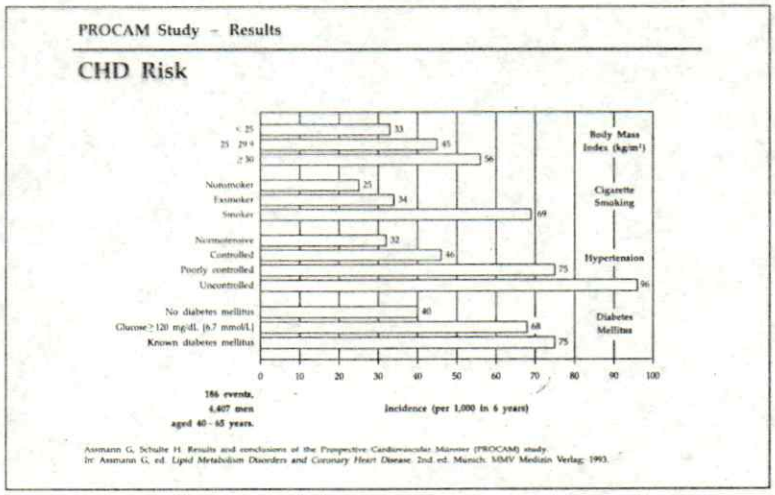

CHD risk was assessed according to the variables of body mass index (BMI), cigarette smoking, hypertension, and diabetes:

- ❑ Based on BMI, the incidence of CHD per 1,000 was highest in obese men.
- ❑ The incidence of CHD in smokers was 69 — more than double the risk in nonsmokers and ex-smokers; in smokers, there was no relationship between the number of cigarettes/day and the incidence of CHD.
- ❑ Men with poorly controlled or uncontrolled (untreated) hypertension also had more than twice the risk of normotensive men, showing that hypertension control undoubtedly affects risk of CHD.
- ❑ Men with diabetes had a CHD risk nearly double that in men with normal fasting blood glucose levels.

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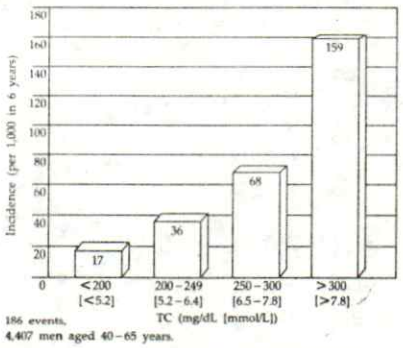
PROCAM Study – Results

CHD Risk According to Total Cholesterol Values



186 events,
4,407 men aged 40–65 years.

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- ❑ PROCAM data confirm the relationship of hypercholesterolemia to CHD.
- ❑ With each successive increase in total cholesterol levels based on the European Atherosclerosis Society (EAS) classifications (200 to 249 mg/dL [*5.2 to 6.4 mmol/L*]; 250 to 300 mg/dL [*6.5 to 7.8 mmol/L*]; >300 mg/dL [*>7.8 mmol/L*]), the incidence of CHD approximately doubled.
- ❑ In men with total cholesterol levels >300 mg/dL (*>7.8 mmol/L*), the incidence of CHD was more than nine times higher than it was with cholesterol levels <200 mg/dL (*<5.2 mmol/L*), 159 vs 17 events, respectively.

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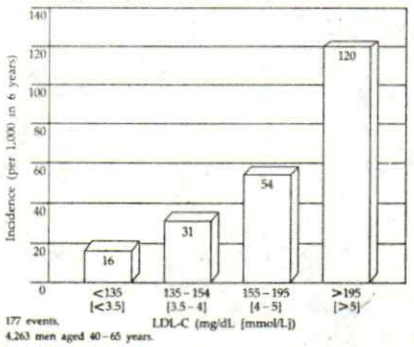
PROCAM Study – Results

CHD Risk According to LDL-Cholesterol



177 events.
4,263 men aged 40 – 65 years.

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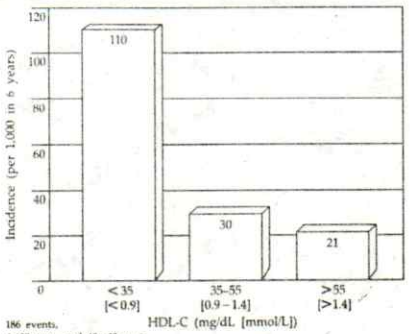
- Incidence-rate data from PROCAM also showed the linear increase in CHD risk with increased LDL-C levels.
- CHD risk increased almost twofold for each LDL-C quartile.
- In men with LDL-C >195 mg/dL (*>5 mmol/L*), the CHD risk was more than seven times the risk for men with low LDL-C values (<135 mg/dL; *<3.5 mmol/L*), 120 vs 16 events, respectively.

Notes

PROCAM Study – Results

CHD Risk According to HDL-Cholesterol



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Low HDL-C levels were associated with increased CHD risk in PROCAM men. At 6-year follow-up, men with HDL-C levels <35 mg/dL (*<0.9 mmol/L*) had an increased CHD risk that was:

- Almost four times greater than for men with HDL-C levels of 35 to 55 mg/dL (*0.9 to 1.4 mmol/L*)
- More than five times greater than for men with HDL-C levels >55 mg/dL (*>1.4 mmol/L*).

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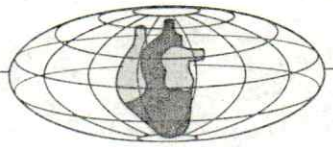
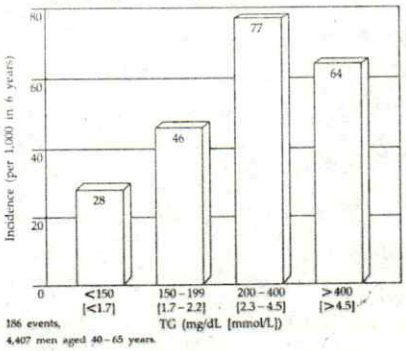


PROCAM Study – Results

CHD Risk According to Triglycerides



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- PROCAM data show the importance of the triglyceride level.
- The incidence of CHD increased significantly at triglyceride levels above 150 mg/dL (*1.7 mmol/L*).
- Univariate analysis revealed a significant association between triglyceride levels and atherosclerotic CHD.
- Triglyceride levels did *not* correlate with atherosclerotic CHD in a multivariate analysis that included data for total or HDL-cholesterol.
- Studies by Austin and Krauss show that triglyceride levels >140 mg/dL (*>1.6 mmol/L*) are associated with a predominance of small, dense LDL particles (LDL phenotype B), which are more atherogenic than larger, more buoyant LDL (phenotype A).

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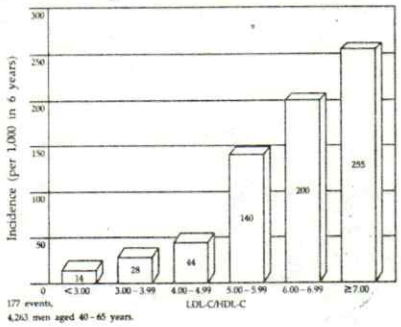
PROCAM Study – Results

CHD Risk According to LDL-C/HDL-C Ratio



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- Individuals at low and high risk for CHD can be identified by measuring LDL-C and HDL-C.
- A man with an LDL-C/HDL-C ratio <3 has a very low risk for CHD (14 per 1,000 in 6 years).
- A man with a ratio ≥7 has a very high risk for CHD (255 per 1,000 in 6 years) — approximately 1 in 4 persons.
- There is a greater than threefold increased risk for CHD when the LDL-C/HDL-C ratio reaches 5.00 to 5.99. For this reason, an LDL-C/HDL-C ratio > 5.00 was used as the cutoff point for data analysis.

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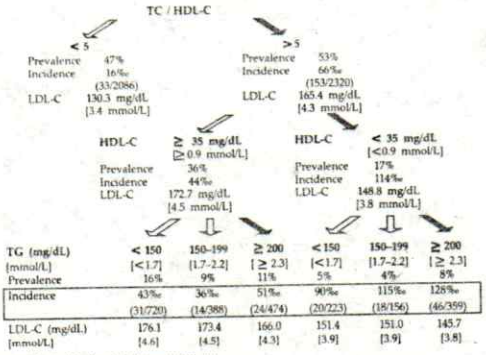
PROCAM Study – Results

Dyslipidemia and Risk of CHD



Assmann G, Schulte H. *Eur J Epidemiol.* 1992;8(suppl 1):99–103.

- A total cholesterol/HDL-cholesterol (TC/HDL-C) ratio >5 conferred a CHD risk that was more than four times higher than a ratio <5, 66 vs 16 per 1,000 in 6 years.
- When the high ratio was due to a low HDL-C level, CHD risk increased almost threefold compared with a high ratio and high HDL-C levels — 114 vs 44/1,000.
- Hypertriglyceridemia (triglycerides ≥200 mg/dL; *≥2.3 mmol/L*) was an additive CHD risk factor in high ratio and low HDL-C level patients.
- The PROCAM Study reveals a dyslipidemic patient population at high risk for CHD. These are patients with a TC/HDL-C ratio >5, an HDL-C <35 mg/dL (*<0.9 mmol/L*), and triglycerides ≥ 200 mg/dL (*≥2.3 mmol/L*). Patients in this high-risk group had an almost threefold increase in the incidence of CHD compared to patients with a higher HDL-C (≥35 mg/dL; *≥ 0.9 mmol/L*) and triglycerides <150 mg/dL (*<1.7 mmol/L*), 128 vs 43 events per 1,000 in 6 years.
- Patients in this high-risk group had eight times the CHD risk of normolipidemic subjects.
- It is interesting to note that mean LDL-C levels were relatively similar across the subgroups.

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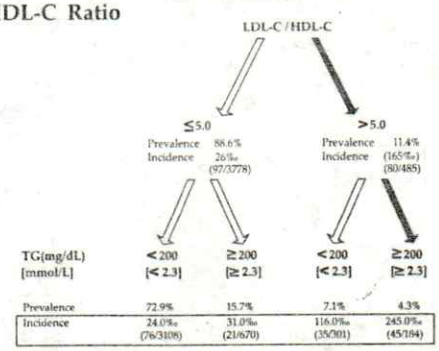
PROCAM Study – Results

CHD Incidence According to Triglycerides and LDL-C/HDL-C Ratio



Assmann G, Schulte H. Am J Cardiol. 1992;70:733–737.

- The incidence of CHD was also analyzed according to the LDL-C/HDL-C ratio and the triglyceride level.
- When the LDL-C/HDL-C ratio is low (≤5), triglyceride levels do not appreciably affect risk (24 and 31 per 1,000 in 6 years for normal and high triglyceride levels, respectively).
- Men with an LDL-C/HDL-C ratio >5.0 had more than six times as many CHD events as did men with a ratio ≤ 5.0 (165 vs 26 per 1,000 in 6 years).
- In men with a high LDL-C/HDL-C ratio and elevated triglycerides (≥200 mg/dL; ≥*2.3 mmol/L*), the incidence of CHD events per 1,000 in 6 years rose from 165 to 245 events, indicating that 1 in 4 men (245/1,000) would have an MI in 6 years.

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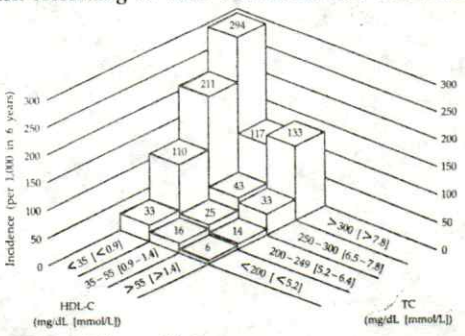
PROCAM Study – Results

CHD Risk According to Total Cholesterol and HDL-Cholesterol



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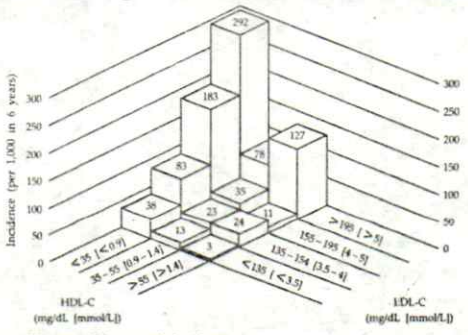
- Within each subgroup of HDL-C, CHD risk increases steeply as total cholesterol levels increase, showing that HDL-C and total cholesterol are independent risk factors for CHD.
- Low HDL-C levels (<35 mg/dL; *<0.9 mmol/L*) led to a four- to fivefold increased CHD risk if total cholesterol levels ranged from 200 to 300 mg/dL (*5.2 to 7.8 mmol/L*).

Notes

PROCAM Study – Results

CHD Risk According to LDL-Cholesterol and HDL-Cholesterol



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- Men with a favorable lipid profile (LDL-C <135 mg/dL; *<3.5 mmol/L* and HDL-C >55 mg/dL; *>1.4 mmol/L*) had a negligible CHD risk (3 events per 1,000 in 6 years).

- Men with low HDL-C levels (<35 mg/dL; *<0.9 mmol/L*) had a much higher CHD risk within each LDL-C level than did men with higher HDL-C values.

- The incidence of CHD rose dramatically, to 292 per 1,000 — approximately 1 in 3 men — for an LDL-C >195 mg/dL (*>5 mmol/L*) and HDL-C <35 mg/dL (*<0.9 mmol/L*).

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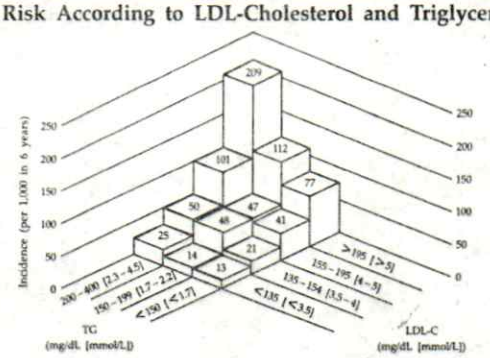
PROCAM Study – Results

CHD Risk According to LDL-Cholesterol and Triglycerides



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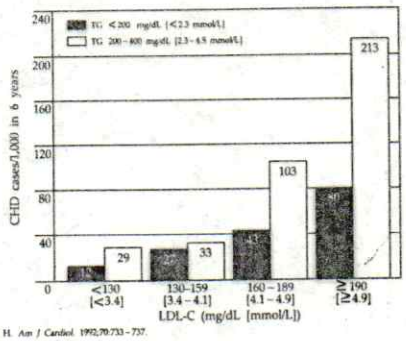
- ❑ At each level of LDL-C, elevated triglyceride levels (≥200 mg/dL; ≥ *2.3 mmol/L*) were associated with higher CHD risk.
- ❑ In men with LDL-C levels ≥ 155 mg/dL (≥*4 mmol/L*), the addition of hypertriglyceridemia (≥200 mg/dL; ≥*2.3 mmol/L*) more than doubled the risk of CHD.

Notes

PROCAM Study – Results

CHD Incidence According to Triglycerides and LDL-Cholesterol



Assmann G, Schulte H. *Am J Cardiol.* 1992;70:733–737.

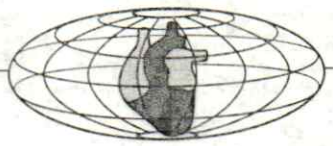
- When LDL-C levels were analyzed according to the risk categories of the National Cholesterol Education Program (USA), hypertriglyceridemia was associated with a higher incidence of CHD events in each LDL-C category.

- At "high-risk" LDL-C levels (≥160 mg/dL; *≥4.1 mmol/L*), hypertriglyceridemia was associated with more than double the CHD risk of normotriglyceridemia (<200 mg/dL; *<2.3 mmol/L*).

Notes

- A number of hemostatic variables have been included in the PROCAM Study, including plasminogen activator inhibitor activity, factor VII, and fibrinogen.
- Six-year data analyzed by tertiles of fibrinogen and LDL-C showed that in men in the lowest tertile of fibrinogen (<2.36 g/L), the LDL-C level had little impact on the incidence of CHD.
- However, in men in the highest tertile of fibrinogen (>2.77 g/L), the incidence of CHD events was approximately three times greater than in those in the middle tertile.
- CHD risk in a man in the highest tertiles of fibrinogen and LDL-C was five times greater than that in a man in the lowest tertiles, 103 vs 19 events, respectively.

Notes



Helsinki Heart Study Analysis

Helsinki Heart Study Analysis: Using Serum Triglycerides and LDL- and HDL-Cholesterol Levels to Predict Coronary Risk and Response to Gemfibrozil

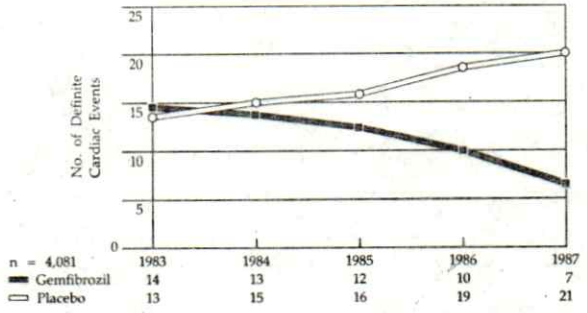
Manninen V. et al. Circulation. 1992;85:37.

- The Helsinki Heart Study was a 5-year, double-blind, placebo-controlled, primary prevention trial in more than 4,000 middle-aged dyslipidemic men:
  - 2,046 men were randomized to gemfibrozil
  - 2,035 men were randomized to placebo.
- CHD endpoints included fatal and nonfatal MI and cardiac death.
- The 1992 analysis of the Helsinki Heart Study reported the effects of baseline triglyceride and lipoprotein cholesterol levels on
  - CHD risk
  - risk reduction associated with gemfibrozil.

Notes

Helsinki Heart Study Analysis

Definite Cardiac Events by Year



n = 4,081	1983	1984	1985	1986	1987
Gemfibrozil	14	13	12	10	7
Placebo	13	15	16	19	21

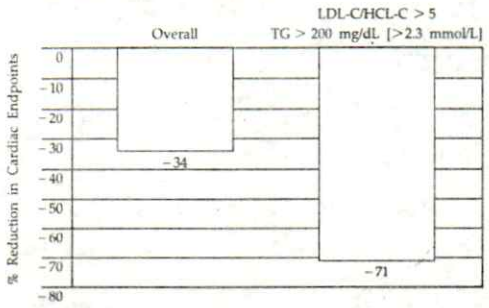
Frick MH, et al. *N Engl J Med.* 1987;317:1237.

- Five-year follow-up of the Helsinki Heart Study showed that the number of definite cardiac events was significantly reduced with gemfibrozil treatment compared with placebo (56 vs 84 events for gemfibrozil vs placebo, respectively; $P < 0.05$).
- At year 5 of the study (1987), there was a 66% difference in the number of cardiac events — 7 vs 21 events in the gemfibrozil and placebo groups, respectively.

Notes _____

Helsinki Heart Study Analysis

Reduction in Incidence of Cardiac Events After Treatment with Gemfibrozil



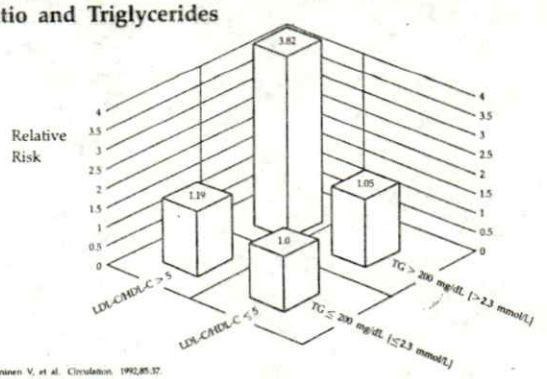
Manninen V, et al. Circulation. 1992;85:37. Manninen V, et al. JAMA. 1988;260:64.

- The overall reduction in CHD risk after gemfibrozil therapy was 34% in the Helsinki Heart Study.
- In the subgroup of 154 men with an LDL-C/HDL-C ratio >5.0 and triglyceride levels >200 mg/dL (*>2.3 mmol/L*), treatment with gemfibrozil resulted in a 71% reduction in risk for cardiac events — from a relative risk of 3.82 to 1.08.

Notes

Helsinki Heart Study Analysis

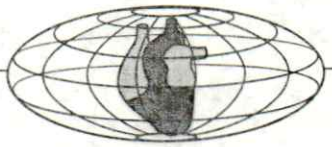
Relative Risk of Cardiac Events Based on LDL-C/HDL-C Ratio and Triglycerides

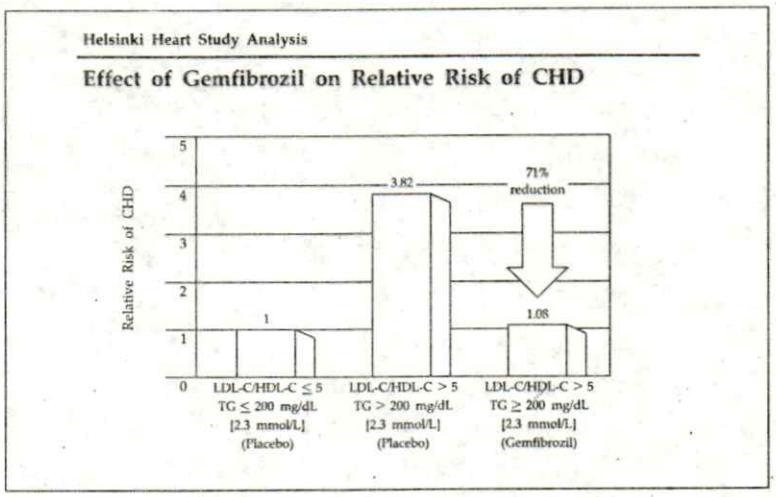


Manninen V, et al. Circulation. 1992;85:37.

- In placebo-treated subjects, an LDL-C/HDL-C ratio ≤5.0 and triglyceride levels ≤200 mg/dL (≤*2.3 mmol/L*) conferred a relative risk of 1.0 during 5 years of follow-up (the reference group).
- In placebo-treated men with an LDL-C/HDL-C ratio >5.0 and triglyceride levels >200 mg/dL (>*2.3 mmol/L*), the relative risk rose to 3.82 — almost four times the risk of men with lower values.

Notes





- A key finding from the Helsinki Heart Study was that the incidence of cardiac events in men with a high LDL-C/HDL-C ratio and high triglycerides was significantly decreased when treated with gemfibrozil. These high-risk triad subjects experienced the greatest benefit from gemfibrozil treatment.

- If the cardiac risk of placebo-treated men with a low LDL-C/HDL-C ratio (≤5) and a low triglyceride level (≤200 mg/dL; ≤*2.3 mmol/L*) is set to 1.0, the relative risk of men with a high LDL-C/HDL-C ratio and elevated triglyceride levels is 3.82.

- Gemfibrozil treatment in these high-risk men (with a high LDL-C/HDL-C ratio and elevated triglyceride levels) reduced the relative risk from 3.82 to 1.08 — a 71% reduction compared with placebo.

- At the new level of 1.08, CHD risk in these gemfibrozil-treated men was virtually identical to that in men with lipid levels associated with the lowest CHD risk. Thus, one could argue that men in this particular high-risk subgroup benefited the most from gemfibrozil treatment.

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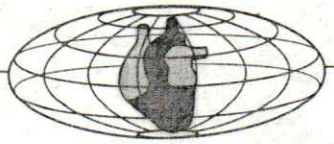

PROCAM Study and Helsinki Heart Study

Redefining CHD Risk Assessment

- Data from PROCAM and the Helsinki Heart Study show the strong interrelationship between CHD risk and the lipid triad (elevated LDL-C, low HDL-C, high TG).
- In PROCAM, a TC/HDL-C ratio >5 with an HDL-C <35 mg/dL and TG >200 mg/dL confers the highest CHD risk.
- Similarly, in the Helsinki Heart Study, an LDL-C/HDL-C ratio >5 and TG >200 mg/dL confers the highest CHD risk.
- In the Helsinki Heart Study, treatment with gemfibrozil in high-risk triad subjects "normalized" CHD relative risk (from 3.82 to 1.08).
- PROCAM and Helsinki Heart Study data show that a "high-risk strategy" can be used to identify and treat triad subjects who are at high risk of developing CHD.
- Coagulation factors may have a role in CHD risk.

❑ Data from the PROCAM Study and the Helsinki Heart Study identify the strong interrelationship between CHD risk and the lipid triad (elevated LDL-C, low HDL-C, high triglycerides).

❑ In PROCAM, a TC/HDL-C ratio >5, especially in subjects with HDL-C <35 mg/dL (*<0.9 mmol/L*) and triglycerides ≥ 200 mg/dL (*≥ 2.3 mmol/L*) confers the highest CHD risk.

❑ Similarly, in the Helsinki Heart Study, subjects with an LDL-C/HDL-C ratio >5 and triglycerides >200 mg/dL had the highest incidence of CHD events.

❑ In the Helsinki Heart Study, treatment with gemfibrozil in subjects with this high-risk lipid profile reduced CHD by 71%, "normalizing" the relative risk of CHD (from 3.82 to 1.08).

❑ Based on expanding clinical evidence, we are now able to employ a "high-risk strategy" in identifying and treating triad patients who are at the highest risk of developing CHD:
- high triglycerides (>200 mg/dL; *>2.3 mmol/L*)
- low HDL-C (<35 mg/dL; *<0.9 mmol/L*)
- elevated LDL-C/HDL-C ratio (>5).

❑ Coagulation factors may also have a role in CHD risk.

Notes


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