HDL: The Highly Desirable and Hotly Debated Cholesterol

The 36th Annual Advances in Internal Medicine Program
UCSF

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UCSF
Distribution of HDL-C in Men With CAD

Framingham Heart Study

Risk of CAD in men aged 50 to 70 yr according to HDL-C and LDL-C levels over 4 yr of follow-up

Adapted from Castelli WP et al. JAMA 1986;256:2835
Limone sul Garda
Apolipoprotein A1 Milano

- Valerio Dagnoli from Limone sul Garda had very low HDL-C, high triglycerides, no atherosclerosis, and familial longevity
- 40 of the 1,000 inhabitants of Limone, all descendants of Giovanni Pomaroli and Rosa Giovaneli (1780), share a genetic mutation of apo A1, a cysteine to arginine substitution at position 173
- apo A1 Milano has a higher capacity to extract cholesterol from peripheral tissues compared to wild type apo A1, as shown in both human carriers and transgenic mice
- in animal models, apo A1 Milano exerts favorable effects on thrombosis, restenosis and atherosclerosis

Chiesa and Sirtori, Curr Opin Lipidol 2003;14:159
HDL-C: Reverse Cholesterol Transport
HDL-C

Vascular Tone
↑ NO
↑ PGI₂
? ET-1

Inflammation
↓ CAMs
↓ PAF

Hemostatis
↑ NO
↑ PGI₂
↓ PAF
↓ vWF
↓ TF
↑ TFPI
± tPA

Endothelial Integrity
↑ EC migration
↑ EC proliferation
↓ EC apoptosis

Endothelial Protection

Calabresi et al, ATVB 2003;23:1724
Multiple Effects of HDL on Vascular Endothelium

functional endothelial cells are dark blue and dysfunctional cells are light blue.
CAM = cellular adhesion molecule  PAF = platelet activating factor; vWF = von Willebrand factor

Calabresi et al, ATVB 2003;23:1724
Clinical Efficacy of Therapies That Affect HDL-Cholesterol Levels

The Expectation:
In observational studies, a 1mg/dl ↑ in HDL-C is associated with a 2% ↓ in CAD risk in men and a 3% ↓ in women

<table>
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<tr>
<td>Raise HDL</td>
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<td>fenofibrate</td>
<td>estrogen torcetrapib</td>
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<tr>
<td></td>
<td></td>
<td>niacin</td>
<td></td>
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<tr>
<td>Lower HDL</td>
<td>low fat diet</td>
<td>probucol</td>
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<td>succinobucol</td>
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Fixing the lab report does not necessarily fix the patient.
ILLUMINATE: Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events

15 000 patients
- Men and women
- Aged 45-75 years
- 250 sites in 7 countries
- CHD or risk equivalent, any HDL-C level, statin eligible

Primary End Point
- Composite of fatal CHD, nonfatal MI, and stroke

Torcetrapib 60 mg + titrated atorvastatin dose

Titrated atorvastatin dose

4.5-year follow-up (~984 events)

Trial terminated by DSMB 12/1/06 due to increased mortality in torcetrapib arm (82 vs 51, p=0.007)
Torcetrapib Favorably Affected Blood Lipids

Torcetrapib/ Atorvastatin Group (Post Run-In)

Study Month

Baseline 1 3 6 12

Lipids (mg/dL)

-9% (-27,+13)*

+72.1% (34.7) ††

-24.9% (28.5) †

*median % change (IQR) for TG at month 12; p<0.001 vs atorvastatin
† mean % change (SD) for LDL-C, HDL-C at month 12; p<0.001 vs atorvastatin

Barter PJ et al, N Engl J Med
2007;357:2109
Primary Endpoint:
Time to First MCVE*:
Kaplan-Meier Plot

Hazard Ratio 1.25
P=0.001

Days from Randomization

Event Free (%)
0 90 180 270 360 450 540 630 720 810

Atorvastatin (A) events = 373
Torcetrapib/Atorvastatin (T/A) events = 464

*Major cardiovascular event: CHD death, non-fatal MI, stroke or hospitalization for unstable angina
Your Next Patient...

Age: 44 years  
Weight: 206 lbs  
Height: 5’ 4”  
BMI: 35.4  
BP: 142/88 mmHg  
Fasting blood sugar 116 mg/dl  
Total C: 240 mg/dl  
**HDL-C: 36 mg/dl**  
Triglycerides: 420 mg/dl  
LDL-C: 134 mg/dl  
hs-CRP: 2.6 mg/dl  
Non-smoker
What Is the 10-Year Risk of Cardiac Death or MI in This Patient According to Framingham?

- 2%
- 4%
- 6%
- 10%
- 14%
- 18%
What Is the 10-Year Risk of Cardiac Death or MI in This Patient According to Framingham?

- 2% is the correct answer. However, the Framingham calculator does not count hs-CRP, triglycerides or BMI, and does not include other coronary events or any cerebrovascular events in the endpoint.
- 4%
- 6%
- 10%
- 14%
- 18%
Lifetime Risk of CV Disease in the Framingham Cohort

- 3,564 men and 4,362 women age 50 free of CVD
- 1,757 CVD events and 1,641 died free of CVD during follow-up
- CV event = CV death, MI, coronary insufficiency, angina, atherothrombotic stroke, or claudication
- Lifetime risk at age 50 for CVD was 51.7% in men and 39.2% in women
- Lifetime risk with 2 or more risk factors was 68.9% in men and 50.2% in women
- Lifetime risk with optimal risk factors (<5% of subjects) was 5.2% in men and 8.2% in women

Lloyd-Jones DM et al, Circulation 2006;113:791
Cumulative Incidence of CVD Adjusted for the Competing Risk of Death According to Risk Factor Burden at Age 50

Lloyd-Jones DM et al, *Circulation* 2006;113:791
Effects of Diet and Exercise in Men and Postmenopausal Women with Low HDL-C

• 180 postmenopausal women aged 45-64 with HDL-C <60 mg/dl and 197 men aged 30-64 with HDL-C <45 mg/dl
• randomized to NCEP step 2 diet, exercise (equivalent to 10 miles of jogging/walking per week), both, or neither
• interventions continued for 1 year
• mean baseline HDL-C was 47 mg/dl in women and 36 mg/dl in men; baseline LDL-C averaged 158 mg/dl

Effects of Diet and Exercise in Women with Low HDL-C

Prevention of Type 2 Diabetes by Lifestyle Changes Among Subjects with Impaired Glucose Tolerance

• 522 patients with impaired glucose tolerance (mean age 55, mean BMI 31) randomly assigned to weight reduction and exercise or to control group

• mean weight loss of 4.2 Kg in intervention group versus 0.8 Kg in control group at one year (p<0.001)

• diabetes defined by 1985 WHO criteria

• cumulative incidence of diabetes at 4 years was 11% in the intervention group and 25% in the control group, a 58% reduction (p<0.001)

• the reduction in the incidence of diabetes was directly associated with changes in lifestyle

Effect of Smoking Cessation on HDL-Cholesterol Levels

- meta-analysis of 27 studies from 1966-2000
- smoking cessation increased HDL-C by 1.8 mg/dl (95% CI 1.4-2.2)
- increase greater in women and subjects with higher baseline HDL-C
- no change in total or LDL-cholesterol, or triglycerides

Potential Drug Therapy

- fibrate
- niacin
- statin
- metformin
- glitazone
- rimonabant
- antihypertensive
- aspirin
Helsinki Heart Study

- 4,081 men with no evidence of coronary disease
- randomized to gemfibrozil 600 mg BID or placebo and followed for 5 years
- mean HDL-C increased from 47 to 52 mg/dl (1.2 to 1.3 mmol/L) and triglycerides decreased from 175 to 103 mg/dl (2.0 to 1.2 mmol/L); LDL-C decreased from 189 to 173 mg/dl (4.9 to 4.5 mmol/L)
- primary endpoint, cardiac death + nonfatal MI, reduced by 34%, from 84 to 56 ($p=0.02$)

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

- 2,531 men with coronary disease, an HDL-C ≤40 mg/dl and an LDL-C ≤140 mg/dl
- randomized to gemfibrozil 1,200 mg/day or placebo
- median follow-up = 5.1 years
- primary endpoint = coronary death + nonfatal MI
- HDL-C 6% higher and triglycerides 31% lower at 1 year in gemfibrozil group; no difference in LDL-C
- event rate 21.7% in placebo and 17.3% in gemfibrozil group, a 22% relative risk reduction ($p=0.006$)

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Trial

- 9,795 patients with type II diabetes randomized to micronized fenofibrate 200 mg/day or to placebo and followed for 5 years
- total cholesterol 3.0-6.5 mmol/L with either a TC/HDL-C ratio $\geq 4$ or triglycerides 1.0-5.0 mmol/L
- primary outcome (coronary death or nonfatal MI) occurred in 5.2% of fenofibrate and 5.9% of placebo patients (HR 0.89, 95% CI 0.75-1.05, $p=0.16$)
- 24% reduction in nonfatal MI (HR 0.76, 95% CI 0.62-0.94) but a 22% increase in coronary death (HR 1.19, 95% CI 0.90-1.57)
- total coronary events reduced with treatment in the 7,664 patients without previous CAD, 8.9% vs 10.8%, $p<0.001$
- benefit seen in patients with low HDL-C, 13.0% vs 15.1%, $p=0.02$

FIELD: Primary Outcome

- **CHD events (non-fatal MI plus CHD death)**

  - **Cumulative risk (%)**
  - Placebo
  - Fenofibrate

  - HR 0.89 (95% CI 0.75–1.05), p=0.16

- **Numbers at risk**
  - Placebo: 4900, 4835, 4741, 4646, 4547, 2541, 837
  - Fenofibrate: 4895, 4837, 4745, 4664, 4555, 2553, 850
Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Trial

- 9,795 patients with type II diabetes randomized to micronized fenofibrate 200 mg/day or to placebo and followed for 5 years
- total cholesterol 3.0-6.5 mmol/L with either a TC/HDL-C ratio ≥4 or triglycerides 1.0-5.0 mmol/L
- primary outcome (coronary death or nonfatal MI) occurred in 5.2% of fenofibrate and 5.9% of placebo patients (HR 0.89, 95% CI 0.75-1.05, \( p=0.16 \))
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Potential Drug Therapy

- fibrate
- niacin
- statin
- metformin
- glitazone
- rimonabant
- antihypertensive
- aspirin
Niacin in the Coronary Drug Project

• 8,341 men aged 30-64 with previous MI randomized to low or high dose estrogen, dextrothyroxine, clofibrate, niacin 3 gm/day or placebo between 1966-69
• the 2 estrogen arms and the dextrothyroxine arm were discontinued early due to excess adverse events, and clofibrate showed no benefit
• niacin (n=1,119) and placebo (n=2,789) patients followed for 6.2 years
• primary endpoint, total mortality, was 24.8% in niacin group and 25.9% in placebo group (p=ns)
• however, MI was significantly reduced in the niacin group (10.4% versus 14.7%)

Coronary Drug Project Research Group, JAMA 1975;231:360
Niacin After the Coronary Drug Project

- 5 years after publication of the results, the investigators followed up the patients to assess long term adverse effects of treatment on mortality.
- with a mean follow-up of 15 years, nearly 9 years after the end of the trial, all-cause mortality in the other drug groups were all similar to placebo.
- but in the niacin group, mortality was reduced by 11% (52.0% versus 58.2%, p=0.0004).
- the investigators estimated that only 10 of the 69 fewer deaths in the niacin group could be attributed to the lower infarction rate during the trial.

Canner PL et al, J Am Coll Cardiol 1986;8:1245
Niacin in Trials With Surrogate Endpoints

**HATS**
- the combination of simvastatin + niacin lowered LDL-C by 42%, increased HDL-C by 26%, and halted progression of coronary disease by angiography compared to placebo over 3 years in a study of 160 patients
  

**ARBITER 2**
- adding 1,000 mg of extended-release niacin to statin-treated patients with CAD halted progression of carotid intima-media thickness over 12 months, while progression occurred in placebo-treated statin patients despite LDL-C of 86 mg/dL
  
ARBITER 2: Carotid IMT Results

Taylor AJ et al, Circulation 2004;110:3512
AIM HIGH: Atherosclerotic Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes

3300 patients
- Men and women
- Aged ≥45 years
- Established vascular disease and atherogenic dyslipidemia (low HDL-C and high triglycerides)

Primary End Point
- Composite of CHD death, nonfatal MI, ischemic stroke, or hospitalization for high-risk ACS with objective evidence of ischemia

Key Secondary End Points
- Composite of CHD death, nonfatal MI, or ischemic stroke

Simvastatin ≥40 mg + ER niacin 2 g

Simvastatin ≥40 mg

4-year follow-up

Estimated completion: 2010

ER, extended release
HPS2—THRIVE: Heart Protection Study 2
Treatment of HDL to Reduce the Incidence of Vascular Events

20,000 patients
- Men and women
- Aged 50-80 years
- History of MI, stroke, or PAD
- ~7000 patients with diabetes
- Coordinating centers in UK, China, and Scandinavia

Statin therapy to optimal LDL-C level

ER niacin+MK-0524A combination tablet

Placebo

Primary End Point
- MI, stroke, revascularization procedures

4-year follow-up

Estimated completion: 2012
Potential Drug Therapy

- fibrate
- niacin
- **statin**
- metformin
- glitazone
- rimonabant
- antihypertensive
- aspirin
Potentially Beneficial Effects of Statins in the Metabolic Syndrome

- lowering LDL-C and shifting LDL particle size upward
- lowering high triglyceride levels
- minor increase in HDL-C levels
- improvement in endothelial dysfunction
- reduction in levels of inflammatory markers such as hs-CRP
- normalization of platelet hyperaggregability

Furthermore, statins have been shown to reduce events in patients with diabetes (CARDS, HPS), hypertension (ASCOT), and low HDL-C (AFCAPS/TexCAPS)
AFCAPS/TexCAPS: Primary Endpoint: First Acute Major Coronary Event*

- Includes unstable angina, fatal and nonfatal MI and sudden cardiac death

Downs JR et al, *JAMA* 1998;279;1615

![Graph showing cumulative incidence over years of follow-up.

- Placebo curve
- Lovastatin curve

37% Risk Reduction
($p < 0.001$)

- Years of follow-up
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - >5

Cumulative incidence
AFCAPS/TexCAPS: Primary End Point

Events by HDL-C Tertile at Entry and by Treatment

- Placebo
- Lovastatin

Downs JR et al, JAMA 1998;279:1615
Potential Drug Therapy

- fibrate
- niacin
- statin
- **metformin**
- glitazone
- rimonabant
- antihypertensive
- aspirin
Metformin and Lifestyle Changes for Prevention of the Metabolic Syndrome: the Diabetes Prevention Program

- 3,234 participants with impaired glucose tolerance randomized to placebo, intensive lifestyle changes or metformin 850 mg BID
- 53% of participants had MS at baseline
- at 3 years the rates of disappearance of MS were 18% in the placebo group, 23% in the metformin group and 38% in the lifestyle group (p<0.001)
- among those without MS at baseline, appearance rates by 3 years were 53% in the placebo group, 47% in the metformin group and 38% in the lifestyle group
- both interventions favorably affected low HDL-C, increased waist circumference and high fasting glucose levels
- lifestyle, but not metformin, also reduced high BP and triglycerides

Orchard TJ et al, Ann Int Med 2005;142:611
Potential Drug Therapy

- fibrate
- niacin
- statin
- metformin
- glitazone
- rimonabant
- antihypertensive
- aspirin
Prevention of Diabetes by Rosiglitazone Among Subjects with Impaired Fasting Glucose or Glucose Tolerance
The DREAM Trial

- 5269 adults with impaired fasting glucose, impaired glucose tolerance, or both, and no evidence of cardiovascular disease were randomized to placebo or rosiglitazone 8 mg/day and followed for 3 years
- primary endpoint was composite of death or diabetes
- primary endpoint occurred in 306 rosiglitazone and 686 placebo pts (11.6% vs 26.0%, HR 0.40, 95% CI 0.36-0.46, p<0.0001)
- 1330 rosiglitazone and 798 placebo pts became normoglycemic (50.5% vs 30.3%, HR 1.71, 95% CI 1.57-1.87, p<0.0001)
- heart failure developed in 14 rosiglitazone and 2 placebo patients (p=0.01)

Gerstein HC et al, Lancet 2006;368:1096
Does Rosiglitazone Increase Cardiac Risk?

A drug commonly used to control diabetes increases the risk of heart attacks and possibly death, researchers reported yesterday in the latest episode to raise safety concerns about a widely prescribed drug.

The drug, Avandia, which about 1 million Americans take to keep their blood sugar at safe levels, boosts the risk of a heart attack by 43 percent and may increase the risk of dying from a heart attack or stroke by 64 percent, the analysis found.

"This is very concerning," said Steven E. Nissen of the Cleveland Clinic, who conducted the analysis with colleague Kathy Wolski.


meta-analysis of 42 randomized, controlled studies of rosiglitazone lasting >24 weeks
odds ratio for MI was 1.43 (95%CI 1.03-1.98, p=0.03)
odds ratio for CV death was 1.64 (0.98-2.74, p=0.06)
Pioglitazone and Risk of Cardiovascular Events in Patients With Type II Diabetes

- meta-analysis of 19 trials enrolling 16,390 patients
- treatment duration ranged from 4 months to 3.5 years
- death, MI, or stroke occurred in 375 of 8,554 pioglitazone patients (4.4%) and in 450 of 7,836 controls (5.7%); hazard ratio 0.82, 95% CI 0.72-0.94, \( p = 0.005 \)
- separation of time-to-event curves became apparent after about 1 year of therapy
- serious heart failure was reported in 200 (2.3%) of the pioglitazone-treated patients and 139 (1.8%) of the controls; hazard ratio 1.41, 95% CI, 1.14-1.76; \( p = 0.002 \)
- both favorable and unfavorable effects were homogeneous across trials of different durations, for different comparators, and for patients with or without established vascular disease

Lincoff AM et al, *JAMA* 2007;298:1216
Age: 44 years
Weight: 206 lbs
Height: 5’ 4”
BMI: 35.4
BP: 142/88 mmHg
Fasting blood sugar 116 mg/dl
Total C: 240 mg/dl
HDL-C: 36 mg/dl
Triglycerides: 420 mg/dl
LDL-C: 134 mg/dl
hs-CRP: 2.6 mg/dl
Metabolic Syndrome: Definition

- abdominal obesity – increased waist circumference
- atherogenic dyslipidemia – low HDL-C, high triglycerides, increased remnant lipoproteins, small LDL and HDL particles
- elevated blood pressure
- insulin resistance → glucose intolerance → type II diabetes
- proinflammatory state – increased CRP
- prothrombotic state – increased fibrinogen and PAI-1

Clinical Management of the Metabolic Syndrome

“The underlying risk factors that promote development of the metabolic syndrome are overweight and obesity, physical inactivity, and an atherogenic diet. All current guidelines on the management of the individual components of the metabolic syndrome emphasize that lifestyle modification (weight loss and physical activity) is first-line therapy.”

Obesity Trends* Among U.S. Adults

BRFSS, 1990

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults

BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)

In 15 years we have gone from no states with >14% obesity to only 4 small states with <20% obesity rates!

Source: Behavioral Risk Factor Surveillance System, CDC.
WHY ARE WE SO fat?
Portion Sizes Are Enormous
Lack of Physical Activity
Does Urban Sprawl Contribute to Obesity?

A typical white male living in an isolated residential only neighborhood weighs about 10 pounds more than one living in a walkable, mixed-use community.

Lawrence Frank, 2004

Densely built urban areas such as Vancouver’s downtown may encourage pedestrian traffic and promote physical activity.

Harder B, Science News Online, 2007;171:43

Metropolitan Atlanta, often called a poster child for urban sprawl, has undergone rapid geographical expansion.
High-powered ambulance chaser, Milford Godfrey, Manhattan, New York, snacks on a full-size rotisserie chicken while conducting business on his cell phone. He keeps a Rotisserie basting oven in his Lincoln Navigator and a George Foreman Grill in his brief case to squeeze in feedings between malpractice trials.
Age: 44 years
Weight: 206 lbs
Height: 5’ 4”
BMI: 35.4
BP: 142/88 mmHg
Fasting blood sugar 116 mg/dl
Total C: 240 mg/dl
HDL-C: 36 mg/dl
Triglycerides: 420 mg/dl
LDL-C: 134 mg/dl
hs-CRP: 2.6 mg/dl
Conclusions

- low HDL-C is a common, important risk factor
- however, treatments that increase HDL-C may not improve outcomes; in fact, some of them may cause harm
- fibrates and niacin have favorable effects on HDL-C and may provide clinical benefit (gemfibrozil yes, fenofibrate no, niacin maybe)
- low HDL-C is often one component of the metabolic syndrome, an expanding epidemic portending disastrous consequences in terms of diabetes and vascular disease
- the causes, excess caloric intake and lack of exercise, are cultural and environmental
- the optimal treatment, diet and exercise, is usually ineffective