Do You Know Your HDL?

The 'good cholesterol' proves a strong predictor of coronary risk — and a potent provoker of controversy

By JANET RALOFF

First of two articles

The death of a seemingly healthy 39-year-old man in his sleep baffled the Framingham, Mass., coroner evaluating the case. Knowing the man had participated in the Framingham Heart Study, the coroner phoned the study's research office to ask whether the victim's medical history might suggest a heart attack risk. When he learned that the man's cholesterol last came to just 198 milligrams per deciliter (mg/dl) of blood — within a range generally deemed desirable — the coroner began to suspect foul play. Imagine his surprise when the autopsy revealed an arterial network clogged with massive fatty deposits.

William P. Castelli, medical director of the 40-year-old, ongoing Framingham project, says he might have prepared the coroner for this atherosclerotic revelation had he not been out of town when the call came. Castelli has seen all too many similar cases. Young as he was, the deceased "was a heart attack waiting to happen," Castelli says.

Undeniably, the man's blood levels of total cholesterol and low-density lipoprotein (LDL) cholesterol — two classic markers of coronary artery disease risk — looked good, Castelli says. But his high-density lipoprotein (HDL) cholesterol was just 29 mg/dl — far below the average of 45 to 55.

LDLs, the so-called "bad" lipoproteins, transport cholesterol to sites of fatty deposits, called plaques, in blood vessel walls. HDLs, often called the "good" lipoproteins, help clear LDL cholesterol from the bloodstream by transporting it to the liver, where it gets broken down and excreted.

Castelli suggests the man did not have enough HDLs to handle even the normal levels of cholesterol coursing through his bloodstream. In fact, his ratio of total cholesterol to HDL cholesterol — last measured at 6.8 — exceeded by more than 50 percent the "red flag" value of 4.5 that signals seriously elevated heart disease risk, according to Framingham data. To calculate this ratio, physicians divide the total cholesterol level by the HDL value.

A growing number of studies point to HDL levels — and especially the ratio of total cholesterol to HDL cholesterol — as a superior gauge for spotting people at risk of artery-clogging heart disease. However, a spirited controversy exists over whether to initiate widespread HDL screening. One faction argues that physicians must screen everyone for HDL levels if they ever hope to identify those likely to develop coronary artery disease in time to prevent impending heart attacks. Others counter that population-wide screening seems premature when scientists still do not know exactly how HDLs function or how to increase them.

The debate raged last June at a panel discussion convened in Washington, D.C., by the International Lipid Information Bureau, a drug-company-supported information center based in New York City. Castelli and several other coronary disease specialists took the National Heart, Lung, and Blood Institute (NHLBI) to task for the federal guidelines identifying people at high risk of coronary artery disease. Those guidelines largely ignore HDLs, they complained.

Basil Rifkind, who heads NHLBI's lipid metabolism and atherogenesis branch, acknowledged wide criticism of the guidelines for failing to include HDL cholesterol levels in the primary screening for early coronary disease. But he also defended the guidelines, saying "not all the evidence is in" to establish why HDL serves as such a good marker or even to suggest how patients and physicians should respond to worrisome HDL levels.

Humans, perhaps from infancy onward, spend a lifetime collecting deposits of lipids — cholesterol and fats — within their vascular networks. "About half of us eventually go on to die from the coronary heart disease this causes," Castelli says. But not everyone deposits lipids at the same rate.

To anticipate whose arteries will clog fastest, heart researchers have assembled a host of diagnostic risk factors. In October 1987, the NHLBI-administered National Cholesterol Education Program (NCEP) issued the now-controversial guidelines for gauging coronary disease risk through blood lipid assays (SN: 10/17/87, p.254). Summarized, those guidelines state:

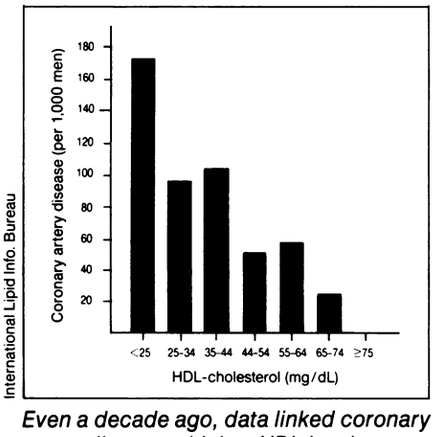
- Total cholesterol levels below 200 mg/dl are desirable and require no immediate follow-up.
- People with total cholesterol levels between 200 and 240 but no other obvious risk factors (such as smoking, hypertension, diabetes or a family history of heart disease) should receive dietary counseling now and new tests in a year. If physicians happen to know that a patient has low HDL, they should consider this a risk factor as well.
- Physicians should assay LDL cholesterol levels in the patients with additional risk factors.
- Total cholesterol levels above 240 warrant immediate lifestyle changes and possibly drug therapy.

Castelli points out that these guidelines would never identify the roughly 15 percent of U.S. heart attack victims who, like the 39-year-old Framingham man, develop coronary disease while maintaining total cholesterol levels under 200 mg/dl. Using the total-to-HDL cholesterol ratio, physicians could flag at least 75 percent of these individuals for treatment, he argues.

Moreover, he notes, a significant number of people whose total cholesterol levels exceed 240 mg/dl will never suffer heart attacks.

NCEP recommends trying to identify likely victims by requesting follow-up LDL measurements in people with total cholesterol over 240 mg/dl. Depending on whether the patient has additional risk factors, treatment to lower blood cholesterol is usually recommended when LDL cholesterol levels move into the range of 130 to 160 mg/dl.

Yet a number of studies indicate that low HDL cholesterol levels predict coro-



Even a decade ago, data linked coronary artery disease with low HDL levels.

nary disease risk as well as do high LDL cholesterol levels — and in some cases even better.

Consider, for example, the landmark Coronary Primary Prevention Trial conducted at 12 U.S. medical centers between 1976 and 1983. This double-blind study of drug treatment, involving 3,800 middle-aged men, established the oft-quoted 2 percent drop in heart attack risk for every 1 percent drop in total serum cholesterol.

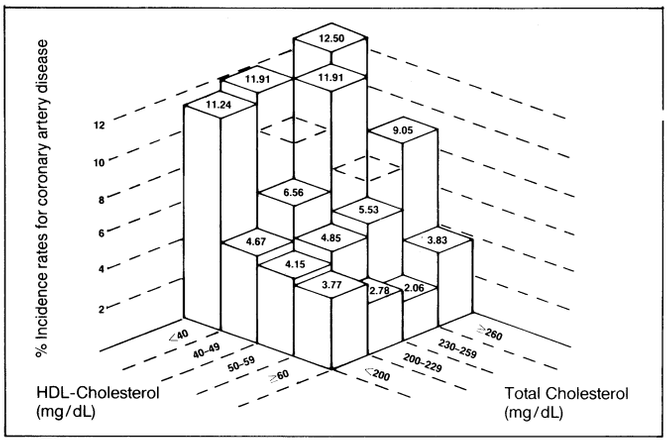
What's *not* often cited is the finding that only the men with HDL cholesterol levels of at least 35 mg/dl experienced a risk reduction, says Antonio M. Gotto Jr., an atherosclerosis researcher at the Baylor College of Medicine in Houston, one of the centers in the trial. Men whose HDL cholesterol remained under 35 mg/dl experienced "no significant decrease" in heart disease risk, he says, "even though they experienced the same degree of reduction in [total] cholesterol and LDLs as did other individuals who did benefit." Those who benefited most from total cholesterol reductions were men who maintained HDL levels above 50 mg/dl.

Women, compared with men of the same age, seldom develop significant coronary disease before menopause. A growing body of data now suggests women's lower risk springs from their relatively higher HDL levels, says Gerd Assmann, director of clinical chemistry and laboratory medicine at Westfalian-Wilhelms University in Münster, West Germany. "Estrogen, for some reason, is one of the best available rearrangers of blood fats. It raises HDL," he says.

Though women's estrogen levels normally drop after menopause, Assmann says several studies of postmenopausal women have demonstrated that estrogen supplementation can elevate their HDL cholesterol *above* premenopausal levels. Moreover, he notes, women receiving estrogen supplements show a "startlingly lower risk of dying from coronary heart disease—just one-third the risk of women not taking this hormone replacement therapy." Assmann says estrogen's protective effect appears to result largely from its role in raising HDL levels — a factor independent of the hormone's ability to lower LDL levels.

However, he adds, Framingham data indicate "the positive effects of estrogen on heart disease are not observed in smoking women." In fact, estrogen replacement therapy, for reasons unknown, can actually diminish HDL levels in smoking females, he says.

Assmann and others have shown that cigarette smoking—a significant elevator of coronary disease risk—lowers HDL. In fact, although "moderate" alcohol consumption can raise HDL levels (SN: 11/28/87, p.348), Assmann notes that many smokers also drink heavily. But his data indicate that because "the fall in HDL attributable to cigarette smoking is relatively large" — about 5 percent — it outweighs any possible beneficial HDL effect from alcohol.



Adapted by ILIB from 1986 data by Castelli *et al.*

These data, from Framingham patients aged 48 to 83, show that for people with HDL levels below 40 mg/dl, a total cholesterol level under 200 mg/dl corresponds to about the same coronary artery disease risk as having total cholesterol over 260 mg/dl — a level NCEP would classify as very risky.

Physical activity can also affect HDLs, according to several studies, including the ongoing West German PROCAM, which includes roughly 20,000 men and women aged 20 to 65. Assmann, who directs PROCAM, says that within each age group examined, "couch potatoes" have lower HDL levels than physically active individuals. Obesity presents a similar — and apparently independent — correlation. All other things being equal, PROCAM shows that "the more people weigh, the lower their HDL," observes Assmann.

But the most incriminating data linking heart disease to low HDL levels comes from the ongoing Helsinki Heart Study, begun in 1981. This placebo-controlled, double-blind drug trial in Finland is examining the lipoprotein-altering impacts of gemfibrozil (Lopid) on heart attack rates in 4,081 apparently healthy men aged 40 to 55. Gemfibrozil is a cholesterol-lowering drug marketed in the United States since 1981.

In the Aug. 5, 1988 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, Vesa Manninen of the University of Helsinki and his colleagues reported initial findings showing that gemfibrozil lowered risks of heart attack and sudden cardiac death 34 percent. All the men began the study with non-HDL serum cholesterol levels of 200 mg/dl or higher. Overall, compared with men on a placebo, those taking gemfibrozil twice daily showed a 10 percent drop in serum cholesterol, an 11 percent drop in LDL, a 35 percent drop in triglycerides and an 11 percent increase in HDL.

Analysis of the findings revealed that lipoprotein changes — far more than any drop in triglycerides—reduced the risk of heart attack. In fact, men entering the study with low HDL levels benefited more from drug treatment than those with elevated LDL levels.

Not only do the Helsinki data suggest that low HDL levels predict the degree of heart attack risk better than do elevated LDLs, Manninen says, but "we found that raising HDL alone contributed to [heart attack] risk reductions of 23 percent"—or two-thirds of the drug treatment's efficacy in reducing risks.

And last November, researchers at the Johns Hopkins University in Baltimore reported that among 288 patients with normal total cholesterol levels but with symptoms of heart problems — such as chest pain—71 percent of the men and 39 percent of the women indeed had artery-clogging coronary disease (SN: 11/26/88, p.348). Among the men, says Hopkins cardiologist Michael Miller, two out of every three with coronary disease (as diagnosed by angiography) had HDL cholesterol levels below 35 mg/dl.

These and other findings published over the past year prompt Gotto, Castelli, Assmann, Manninen and Miller to recommend that physicians begin using total-to-HDL cholesterol ratios to screen for heart attack risk. Assmann goes so far as to suggest physicians consider screening patients for this ratio during every office visit — much as they routinely monitor blood pressure. Says Manninen, "I'm already doing that."

Not everyone shares their view. W. Virgil Brown, medical director of Medlantic Research Foundation in Washington, D.C., argues that ideal HDL values have not been established. Vegetarians, he notes, often have HDLs in the 30s range, yet they run a very low heart attack risk. On the other hand, he says, though heavy drinking raises HDLs, it also can raise a person's heart attack risk. For this reason, Brown thinks the protective effect associated with high levels of HDL cholesterol may depend on how a person sustains those levels.

Castelli agrees with the point about vegetarians (a group he has studied) but says Brown's argument merely points out why HDL levels are less useful by themselves than as part of a total-to-HDL cholesterol ratio. In vegetarians, such

ratios tend to be low and therefore predictive of low coronary risk, he says.

Nonetheless, contends NHLBI's Rifkind, "we've still got insufficient evidence" to warrant a national HDL screening campaign. "There's no doubt that HDL is an independent and powerful risk factor for heart disease. And whatever else we learn about HDL, that will never disappear." But several gaps exist in scientists' understanding of HDL, he says, and lipid researchers must fill those gaps — using animal and human studies — before they can say low HDL levels play a direct role in promoting coronary disease.

Indeed, Rifkind notes, while a whole spectrum of evidence indicted high LDLs in coronary disease as early as the late 1960s, "it was only in 1985 that we got the green light for a national program to [reduce] LDLs. Many of us think the same [cautious development of a firm scientific database] should be required of HDLs" before physicians begin routine screening and risk-reduction treatments.

Moreover, he asks, "if we find that HDL is low, what do we do?" Physicians have plenty of data to justify drug treatment for patients with elevated LDLs or total cholesterol, he says, but they lack sufficient data to justify similar efforts to raise low HDLs. And though lifestyle changes — reducing obesity, quitting smoking, increasing exercise — can raise HDLs, "they don't do it consistently," Rifkind says. Because "HDL is not nearly as malleable to change as is LDL," adds Medlantic's Brown, many patients who make dramatic lifestyle changes grow frustrated when these don't yield the HDL increases they've been led to expect.

Miller of Hopkins says that observation explains why drug therapy may be appropriate in these patients. However, he notes, while the Helsinki study showed drugs could elevate HDLs in people whose total cholesterol levels were quite high, "we have no evidence yet that drugs will prove similarly effective in raising low HDLs in persons with normal total cholesterol levels."

Miller is about to begin a pilot study investigating just that — in people whose only lipid abnormality is low HDL cholesterol. If drug therapy works, he will seek NHLBI support for a multicenter study — much like the Coronary Primary Prevention Trial — to investigate whether raising HDLs in people with low levels reduces their heart disease risk.

One of the biggest objections to routine HDL screening today, Rifkind says, stems from the concern that it might complicate the physician's already complex task of evaluating lipid profiles. In fact, he says, the task force charged with drawing up the NCEP recommendations "felt that while we might gain something scientifically [by recommending HDL analysis], we also worried we might lose a great deal with respect to physician compliance." So, he says, the guideline writers chose to "uncomplicate the message."

Castelli contends doctors are already confused — because NCEP's current guidelines make things unduly complicated. "If physicians can't carry all the numbers [needed to evaluate a patient's lipid profile] around in their head, they aren't going to use them," he says.

NCEP's guidelines ask physicians to evaluate total cholesterol (determining whether it falls under 200, between 200 and 239, or over 300 mg/dl) and perhaps LDL cholesterol (is it under 130 with no risk factors, between 130 and 160 with risk factors, or over 160 mg/dl?), HDL when it's known (is it under 35?) and triglycerides (are they over 240? — or, among the conservative contingent, over 150?).

Castelli asks how anyone can consider this battery of figures less complicated than remembering merely that a patient's total-to-HDL cholesterol ratio should be under 4.5, and the lower the better. If the physician has a head for numbers, Castelli says, he or she can always tack on a second screening criterion: total cholesterol concentrations under 150. "These people are not going to get a heart attack" regardless of their HDL, LDL or triglyceride values, he says.

Finally, Castelli argues, every patient has the responsibility of knowing his or her lipid levels. "One of the greatest myths in America today is that your doctor knows what your [lipid] values are and is keeping a scorecard for you," he says. "Your doctor doesn't know your numbers." In fact, he says, patients can't safely count on their doctors to even know how to evaluate lipid risk factors.

He thinks patients should demand that their doctors perform the necessary tests to determine total-to-HDL cholesterol ratios. "And if more individuals do that, they are eventually going to help others, because they're going to educate their doctors," he says. "We found out that this is what happened when the blood pressure campaign got started [in 1972]." Patient requests for blood pressure measurements eventually hammered home to many physicians the importance of hypertension as a treatable risk factor in stroke, he says.

Before NCEP began, adds Gotto, "surveys indicated that the general public was more convinced cholesterol was important than were physicians." So NCEP directed its first campaign toward educating doctors about the value of measuring their patients' cholesterol and basing treatment on those findings. Now, according to Castelli, Miller, Gotto and others, it's time to gear up for the next campaign — one that aims to educate patients and doctors alike on the importance of HDL screening. □

Next: Insulin and Heart Disease