Low-Density Lipoprotein, Non–High-Density Lipoprotein, and Apolipoprotein B as Targets of Lipid-Lowering Therapy

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Although low-density lipoprotein (LDL) is widely recognized as the major atherogenic lipoprotein and the primary target of lipid-lowering therapy,¹ other lipoprotein species nonetheless appear to be involved in atherogenesis. These include very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and high-density lipoproteins (HDL). Both VLDL and IDL are triglyceride-rich lipoproteins (TGRLP). Thus, in the aftermath of unequivocal evidence that LDL lowering reduces risk for major coronary events and stroke,² the field of lipid study is turning more of its attention to the other lipoproteins that appear to be involved in atherosclerosis. The recent Adult Treatment Panel III (ATP III) report¹ of the National Cholesterol Education Program has summarized our current understanding of the relationship between other lipoprotein species and risk for coronary heart disease (CHD).

ATP III¹ placed more emphasis on TGRLP and HDL as secondary targets of lipid-modifying therapy than did previous ATP reports.³ There is an emerging consensus that among TGRLP, cholesterol-rich remnant lipoproteins carry atherogenic potential. This view led ATP III to designate LDL+IDL+VLDL cholesterol (called non-HDL cholesterol) as “atherogenic cholesterol” and to identify it as a secondary target of therapy, after LDL cholesterol. In the ATP III report, however, non-HDL cholesterol as a secondary target is limited to persons who have elevated serum triglyceride levels (>200 mg/dL). In the majority of people who have lower triglyceride levels, LDL cholesterol contains the bulk of “atherogenic cholesterol” and thus is a sufficient target alone.

The designation of elevated non-HDL cholesterol as a treatment target depended strongly on increasing data showing that high levels of cholesterol-rich TGRLP raise risk for CHD. Several reviews summarize the evidence for atherogenicity of triglyceride-rich remnants.⁴–⁶ On the other hand, only a limited number of studies⁷,⁸ have examined the strength of association between non-HDL cholesterol and risk for CHD. The current report of Bittner et al⁹ contributes to a growing body of information on the predictive power for major coronary events of non-HDL cholesterol. In the discussion to follow, the current status of non-HDL cholesterol as predictor of major coronary events and as a target of lipid-lowering therapy will be examined.

Predictive Power of Lipoproteins

Epidemiological studies reveal a strong independent relation between serum cholesterol levels and risk for CHD.¹⁰ Since LDL is the major cholesterol-carrying lipoprotein of serum, it too is widely accepted as an independent risk factor.¹ Prospective surveys¹¹ further document that reduced serum levels of HDL cholesterol independently predict CHD incidence. The case for high serum triglycerides as a marker for TGRLP has been less robust.¹¹ Since HDL cholesterol and triglycerides are inversely correlated, when HDL is entered into multivariate predictive models, triglycerides are generally found to be weak predictors of CHD.¹² Nonetheless, recent meta-analyses of a large number of epidemiological studies reveal that elevated triglyceride levels carry independent predictive power.¹³,¹⁴ For many years, the case was made that independent association between lipoprotein fractions and CHD incidence implies causation. In other words, the independent association of both high LDL levels and low HDL levels with CHD incidence encouraged the view that both are directly atherogenic. Since higher triglycerides have reduced association with CHD events when HDL is in the predictive model, some epidemiologists have assumed that high levels of TGRLP are less atherogenic than a low HDL level.¹ It must be noted, however, that triglycerides are more variable than are HDL levels, and this variability could weaken a true causative link between TGRLP and CHD. In fact, because of the high inverse correlation between triglyceride and HDL, it is possible that elevated TGRLP concentrations are in fact more atherogenic than are low HDL concentrations. Evidence supporting the atherogenicity of remnant TGRLP agrees with this view.⁴–⁶

Atherogenicity of Different Lipoprotein Species

It has been exceedingly difficult to determine which species of lipoproteins are truly atherogenic and how they vary in relative atherogenicity. Epidemiological data do not provide univocal answers. For example, within the LDL fraction, several subspecies exist, including large, middle-sized, and small LDL. One or another of these subspecies have been claimed to be the most atherogenic form of LDL; but so far, the question of differential atherogenicity among the LDL subspecies remains unresolved. TGRLP likewise consist of

See p 2537

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2526
multiple subspecies. Most investigators believe that smaller, cholesterol-enriched, remnant TGRLP are the most athero-
genic; such nonetheless has been difficult to prove with certainty.

Both LDL and TGRLP contain apolipoprotein B-100 (apo B) as their major apolipoprotein. A growing view holds that most, if not all of apo B-containing lipoproteins are athero-
genic. Although different subspecies of apo B-containing lipoproteins may vary in their atherogenic potential, a simplifying concept is that most of these subspecies carry similar atherogenicity. If so, then measurement of serum total apo B signifies the atherogenic potential of the whole lipoprotein fraction. Total apo B levels are clearly a strong predictor of CHD risk.15

Total apo B levels correlate relatively strongly with non-
HDL cholesterol levels.16,17 The correlation is particularly strong in the absence of elevated serum triglycerides, but weakens somewhat as triglyceride levels rise.16,17 Still, non-
HDL cholesterol includes all of the cholesterol in apo B-containing lipoproteins. Because there is one apo B mole-
cule per lipoprotein particle, total apo B concentrations are a measure of total particle number in LDL+TGRLP, whereas non-HDL cholesterol provides the cholesterol content of these same lipoproteins. Whether total apo B or non-HDL cholesterol is a better predictor of CHD risk has not been determined through robust prospective studies. In routine clinical practice, non-HDL cholesterol is more readily avail-
able, more reliable, and less expensive than total apo B. On the other hand, methodology for measurement of total apo B is improving and is becoming more widely available. Physi-
cians therefore have an option whether to use non-HDL cholesterol or total apo B levels.

Relative Risk Versus Absolute Risk: Significance of Different Lipoprotein Fractions

Absolute risk for CHD is the likelihood of developing a coronary event over a given period of time. Relative risk is the ratio of absolute risks associated with high and low levels of any given risk factor. Most prospective studies provide estimates of relative risk imparted by risk factors. In the past, much emphasis was placed on estimates of relative risk for CHD accompanying different lipoprotein fractions. Lipidolo-
gists have championed one fraction or another (LDL cholesterol, HDL cholesterol, total cholesterol/HDL cholesterol ratios, small LDL particles, remnant lipoproteins, or total apo B) as the best predictor of CHD. The study9 in the current issue of Circulation supports non-HDL cholesterol as the best predictor of future CHD events. Nonetheless, any prediction based on lipoprotein fractions alone gives relative risk, not absolute risk. A single risk factor cannot estimate absolute risk for future cardiovascular events. Such predictions require combining all CHD risk factors into integrated risk-prediction algorithms. For example, ATP III guidelines1 adopted Framingham risk equations for estimating absolute risk. Because intensity of lipid management increasingly depends on absolu-
tate risk estimates, knowing the relative risk imparted by different risk factors gives insufficient information for any single risk factor to be a good guide to therapy. The failure to distinguish between relative risk for single risk factors and absolute risk imparted by all risk factors commonly leads to inappropriate clinical decisions as to type and intensity of therapy. To date, most putative lipid risk factors have never been incorporated into risk equations to determine their incremental predictive power beyond simple lipid measurements.

CHD Risk Factors: Predictor Versus Target of Therapy

A common assumption is that strong risk predictors constitute appropriate targets for risk-reduction therapies. This assumption, however, may not be entirely valid, as revealed by controlled clinical trials. Several examples are worth citing. Hyperglycemia in patients with diabetes is an independent risk factor for CHD; to date, however, therapeutic reduction of glucose levels has not been shown unequivocally to reduce risk for CHD. Hypertension is another powerful independent risk factor. Therapeutic lowering of blood pressure does in fact reduce risk for CHD,18 but only about one-half as much as might be projected from epidemiological studies. A low HDL-cholesterol level is another strong independent risk factor, but it remains to be shown that specifically raising of HDL cholesterol will significantly reduce risk for coronary events. The reverse picture has emerged for total cholesterol and LDL cholesterol. For instance, in older persons, epidemi-
ological studies fail to show that the relative risk accompanying higher cholesterol levels is much greater than that for lower levels.19 In contrast, clinical trials demonstrate that cholesterol-lowering therapy in older persons markedly reduces risk for future CHD events.20 Thus, it cannot be assumed a priori that therapeutic modification of a risk factor will reverse risk for coronary events, as might be predicted from prospective studies. Several factors undoubtedly con-
found the relationship between epidemiological prediction and clinical trial results. In the case of non-HDL cholesterol, therefore, it cannot necessarily be assumed that it is a better target of lipid-lowering therapy than LDL cholesterol, espe-
cially without clinical trial evidence. ATP III1 nevertheless concluded on the basis of several types of data that an elevated non-HDL cholesterol in patients with hypertriglyc-
eridemia will continue to impart increased risk even after the goal of LDL cholesterol has been achieved. If this conclusion is correct, therapy beyond LDL lowering should be beneficial in patients with elevated triglycerides.

Non-HDL Cholesterol (or Total Apo B): Replacement for LDL Cholesterol?

A few investigators propose that non-HDL cholesterol21,22 or its correlate, total apo B,15 should replace LDL cholesterol in clinical cholesterol guidelines. Several arguments favor this proposal. First, both non-HDL cholesterol and apo B are markers for all of the potentially atherogenic lipoproteins, ie, LDL, IDL, and atherogenic VLDL. Among these, both LDL and IDL are widely accepted as being atherogenic, and evidence is growing that most of the apo B-containing lipoproteins in VLDL contribute to atherosclerosis. Second, prospective epidemiological data provide some evidence for a greater predictive power of non-HDL cholesterol over LDL.
cholesterol. Third, several smaller studies indicate that elevated total apo B predicts a relative risk for CHD more than LDL cholesterol does. Finally, use of non-HDL cholesterol (or apo B) adds an element of simplicity to guidelines by combining all atherogenic lipoproteins into a single fraction.

On the other hand, ATP III chose not to replace LDL cholesterol with non-HDL cholesterol (or apo B) as the primary target of therapy. Several reasons were cited. First, LDL is clearly the predominant atherogenic lipoprotein for most people, and hence represents the most robust target of therapy. Second, earlier ATP reports, making use of both epidemiological data and clinical trial results, designated LDL cholesterol as the primary target. This designation has been widely accepted by the medical community, such that LDL is recognized by most physicians as the first target of treatment. Modifying the primary target without stronger evidence would introduce considerable confusion into the medical community. Moreover, statins generally are considered to have a major effect on LDL; hence, the powerful results of clinical trials with statin therapy have kept the focus on LDL cholesterol as the preferred primary target.

Despite these arguments for maintaining of LDL cholesterol as the primary target, ATP III recognized that increasing information points to an atherogenic role for most TGRLP, notably, IDL and VLDL remnants. Consequently, non-HDL cholesterol was introduced as a secondary target of treatment because it provides the cholesterol content of all the atherogenic lipoproteins. Total apo B was acknowledged as an alternative to non-HDL cholesterol, but non-HDL cholesterol was highlighted because of wide availability and reliability of estimation. Whether non-HDL cholesterol or total apo B may someday replace LDL cholesterol altogether as the primary target must depend on the acquisition of enough new data to justify a major conceptual shift in cholesterol management.

**Therapeutic Goals for Atherogenic Lipoproteins**

An important feature of ATP III is that it places first emphasis on goals of therapy for LDL cholesterol and non-HDL cholesterol rather than on treatment initiation levels. This emphasis, however, is not absolute; baseline levels are taken into account when choosing type of therapy. Nonetheless, the focus on goals of therapy has simplified guidelines and cholesterol management. As indicated before, a specific goal for non-HDL cholesterol levels was introduced only in those patients with baseline triglyceride levels from 200 to 500 mg/dL. The goal for non-HDL cholesterol is a level 30 mg/dL higher than that for LDL cholesterol. This rule for a secondary goal is best applied when serum triglycerides are in the range of 200 to 500 mg/dL. In those relatively rare patients in whom triglycerides exceed 500 mg/dL, it is frequently impossible to achieve stated goals for non-HDL cholesterol; moreover, attention should be given to reducing triglyceride levels to <500 mg/dL to prevent development of acute pancreatitis. Regardless, even in patients with elevated triglycerides, LDL cholesterol remains the primary target, and the LDL-cholesterol goal should be achieved before considering other lipid risk factors. It must be kept in mind that statins lower non-HDL cholesterol by the same percentage as LDL cholesterol because they reduce cholesterol in remnant TGRLP similarly to LDL cholesterol. Thus, in some patients with hypertriglyceridemia, the non-HDL cholesterol goal will be met when the LDL-cholesterol goal is achieved. Even so, in many others, additional therapy is required to attain the non-HDL cholesterol goal. Often a higher dose of statins or another lipid-lowering drug (eg, fibrate or nicotinic acid) will be necessary.

The Table summarizes ATP III’s therapeutic goals for LDL cholesterol and non-HDL cholesterol. Also shown are corresponding goals for total apo B, which are derived from the known relationship between total apo B and non-HDL cholesterol. Total apo B represents an alternative secondary target of therapy. Although some investigators would give priority to total apo B rather than non-HDL cholesterol as a target of treatment, it remains to be proven that total apo B is superior in clinical practice. Regardless, there is growing interest in the possibility that additional risk reduction may be obtained by incremental lipid-lowering therapy after ATP III’s goals for LDL cholesterol have been met. If so, the next
logical therapeutic target is non-HDL cholesterol (or total apo B). These do not exhaust the list of potential lipid targets (eg, HDL cholesterol, small LDL particles, and lipoprotein [a]), however, but they nonetheless appear to be a logical extension of the priority given to LDL cholesterol.

References


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