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Statin Therapy Alters the Relationship Between Apolipoprotein B and Low-Density Lipoprotein Cholesterol and Non–High-Density Lipoprotein Cholesterol Targets in High-Risk Patients

The MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY II) Trial

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Objectives The purpose of this analysis was to compare concentrations of low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B (apoB) before and during statin therapy.

Background Reducing LDL-C to a pre-determined goal may still leave an excess of atherogenic lipoproteins, as reflected in apoB levels.

Methods The MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY II) trial examined the effects of statin treatment in patients with high coronary heart disease (CHD) risk, LDL-C ≥130 and <250 mg/dl, and triglycerides <400 mg/dl. Therapy consisted of rosuvastatin (10 or 20 mg), atorvastatin (10 or 20 mg), or simvastatin (20 or 40 mg). The apoB and LDL-C or non–HDL-C at baseline and after 16 weeks of therapy were compared using linear regression.

Results In untreated patients, the apoB target of <90 mg/dl was roughly equivalent to an LDL-C level <100 mg/dl and a non–HDL-C level <130 mg/dl, which is consistent with existing apoB and lipoprotein guidelines. However, during statin therapy, to reach an apoB target of <90 mg/dl it was necessary to reduce non–HDL-C to <100 mg/dl or to reduce LDL-C to <70 mg/dl (in high-triglyceride patients) or <80 mg/dl (in lower-triglyceride patients). The tight correlation seen for non–HDL-C with apoB while on statin therapy ($R^2 = 0.92$) implies that non–HDL-C may be an acceptable surrogate for direct apoB measurement.

Conclusions These data are consistent with the more aggressive cholesterol goals suggested for CHD patients, because achieving such targets also reduced apoB to the recommended level. (Mercury II–Compare the Efficacy and Safety of Lipid Lowering Agents Atorvastatin and Simvastatin With Rosuvastatin in High Risk Subjects With Type IIa and IIb Hypercholesterolemia; NCT00654407) (J Am Coll Cardiol 2008;52:626–32) © 2008 by the American College of Cardiology Foundation

Virtually all cholesterol in the blood is carried in lipoprotein particles. Although the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines focus on low-density lipoprotein cholesterol (LDL-C) as the primary target of therapy unless triglyceride (TG) levels are severely elevated (1), other lipoproteins, such as intermediate-density lipoprotein, very-low-density lipoprotein remnants, and lipoprotein(a), may also be atherogenic. Patients, particularly those with high baseline TG concentrations, may still carry an excess of atherogenic particles despite lowering LDL-C to recommended goals (2–12). For these reasons, in patients with elevated TG (≥200 mg/dl), non–high-density lipoprotein cholesterol (HDL-C) concentration, which reflects the cholesterol carried by all atherogenic particles, is recommended as a secondary target

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of therapy. An alternative approach is to measure apolipoprotein B (apoB) concentration, which measures the total number of atherogenic particles in blood (2). The predictive value of apoB as the strongest single lipid-associated risk factor has been shown in large observational studies (13,14), in primary prevention trials (15), and in secondary prevention trials (16). The lowest values of apoB were associated with the lowest cardiovascular event rates. A "desirable" level of apoB of 88 mg/dl was estimated from the distribution of apoB levels in the National Health and Nutrition Examination Survey III data (17). Those data show that this approximate level (88 mg/dl) is found in younger age groups and in those with lower LDL-C values. Similarly, a target level of apoB <90 mg/dl has been proposed by Grundy (7) for high-risk patients in addition to the target of LDL-C <100 mg/dl (and non–HDL-C <130 mg/dl for hypertriglyceridemic patients), and more recently the same targets were recommended in a consensus statement from the American Diabetes Association (ADA) and the American College of Cardiology (ACC) Foundation to guide the therapy of patients with high cardiometabolic risk (18). However, the target numbers suggested in those guidelines may not accurately account for treatment-induced changes in lipid and lipoprotein parameters observed with statins, which are recommended as first-line treatment in the ATP III guidelines.

High-risk patients frequently have higher baseline levels of apoB than predicted by the level of LDL-C because of increased concentration of small dense LDL particles. Furthermore, statin therapy reduces LDL-C by a greater percentage than it does apoB (19). Therefore, we examined the relationship between apoB, LDL-C, and non–HDL-C levels and, most importantly for clinicians, what levels of LDL-C and non–HDL-C on statin therapy are equivalent to the suggested apoB target level of 90 mg/dl, using data from the MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY II) trial, which enrolled almost 2,000 high-risk patients with hyperlipidemia (20).

Methods

Full details of the methods of the MERCURY II trial are reported elsewhere (20). In this multicenter, international, open-label trial, 1,993 high-risk patients requiring lipid-lowering therapy underwent a 6-week dietary lead-in phase and were randomized to receive rosuvastatin 20 mg, atorvastatin 10 or 20 mg, or simvastatin 20 or 40 mg for 8 weeks, after which they either remained on initial treatment or were switched to mg-equivalent or lower doses of rosuvastatin for an additional 8 weeks. Patients had a documented history of coronary heart disease (CHD) or other established atherosclerotic disease, diabetes, or ATP III 10-year risk of CHD >20% (1) and had fasting LDL-C ≥130 and <250 mg/dl and TG <400 mg/dl. Baseline lipid levels were the average of 2 measurements before the start of randomized treatment; lipids were measured again after 8 and 16 weeks of therapy. All laboratory samples were analyzed at a central laboratory (Medical Research Laboratories, Highland Heights, Kentucky). The level of LDL-C was calculated by the Friedewald equation except for those visits at which TG was >400 mg/dl, when the level of LDL-C was measured by beta-quantification. Efficacy measures included the proportions of patients meeting the ATP III LDL-C goal of <100 mg/dl for high-risk patients and changes from baseline in lipids at 8 and 16 weeks. Supplemental analyses included proportions of hypertriglyceridemic patients, defined as those with TG levels ≥200 mg/dl at baseline, who met both the LDL-C target and the non–HDL-C target (<130 mg/dl) (1) and the proposed apoB target of <90 mg/dl (7) and proportions of patients meeting the optional very-high-risk LDL-C target of <70 mg/dl (21). Very-high-risk patients were those with established cardiovascular disease and ≥1 of the following: multiple major risk factors, severe and poorly controlled risk factors, or multiple risk factors of the metabolic syndrome.

Abbreviations and Acronyms

ACC = American College of Cardiology
ADA = American Diabetes Association
AHA = American Heart Association
apoB = apolipoprotein B
CHD = coronary heart disease
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
TG = triglyceride

The present analysis assessed the relationship between apoB and LDL-C or non–HDL-C levels at baseline and after 16 weeks of treatment with the study statins. Goal attainment analysis was applied to all patients with 16-week data. Linear regression analyses were performed for LDL-C versus apoB levels and non–HDL-C versus apoB levels of pooled data for all patients with available data for those variables, for those with baseline TG ≥200 mg/dl (high TG), and for those with baseline TG <200 mg/dl (lower TG, i.e., normal or borderline-high). For the regression analyses, only patients with paired baseline and 16-week values for LDL-C and apoB or non–HDL-C and apoB were included.

Table 1 Demographic Characteristics of Randomized Population

Characteristic, n (%) Unless Noted	Randomized Population (n = 1,993)
Male gender	1,112 (55.8%)
Age, yrs, mean (SD)	61.9 (10.4)
Weight, kg, mean (SD)	87.4 (19.8)
Body mass index, kg/m^2, mean (SD)	30.64 (6.1)
History of atherosclerosis	1,235 (62.0%)
Diabetes	900 (45.2%)
TG ≥200 mg/dl	725 (36.4%)

All patients were "high CHD event risk" because of 1 of 3 qualifications: overt CHD, CHD risk-equivalent disease (e.g., diabetes, atherosclerosis), or calculated 10-year CHD risk >20%. Adapted from Ballantyne et al. (20).
CHD = coronary heart disease; TG = triglycerides.

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Results

Full results of the MERCURY II trial are reported elsewhere (20); demographic characteristics are summarized in Table 1. At 16 weeks, patients switching from atorvastatin 10 and 20 mg to rosuvastatin 10 and 20 mg, respectively, or from simvastatin 20 and 40 mg to rosuvastatin 10 and 20 mg, respectively, had significantly greater reductions in LDL-C than those remaining on initial treatment. At the end of the trial, 1,802 patients had both apoB and lipid data: 1,082 of this total were being treated with rosuvastatin, 357 with atorvastatin, and 363 with simvastatin.

At 16 weeks, overall least-squares mean reductions in LDL-C ranged from 32.1% to 53.7%, least-squares mean reductions in non–HDL-C ranged from 28.7% to 48.6%, and least-squares mean reductions in apoB ranged from 25.0% to 42.6% (20). To produce robust correlation analyses, data from all treatment arms were pooled, providing a large dataset with a wide range of lipid and apoB levels.

The overall distributions of LDL-C and apoB were plotted in Figure 1 for all patients who had paired data at both baseline and end of treatment (n = 1,783). Similarly, the distributions of non–HDL-C and apoB were plotted in Figure 2 for all patients who had paired data at both baseline and end of treatment (n = 1,784). For the analyses shown in Tables 2 and 3, these data were also stratified into patients with high TG (baseline TG ≥200 mg/dl; n = 656) and patients with lower TG (baseline TG <200 mg/dl; n = 1,127 for LDL-C; n = 1,128 for non–HDL-C).

ApoB and LDL-C. The concentrations of LDL-C and apoB were well fitted by a linear regression model both at baseline and during statin therapy (Table 2, Fig. 1). Overall, at baseline, an apoB of 90 mg/dl corresponded to an LDL-C of 112.8 mg/dl (Table 2, Fig. 1A). Thus, in untreated patients at baseline, LDL-C values appeared to correspond to apoB values that were consistent with targets suggested by Grundy in 2002 (7) and in the ADA/ACC consensus statement (18). For this analysis, patients were divided by baseline TG values into high TG (≥200 mg/dl) and lower TG (<200 mg/dl) groups. The linear regression models of each group were close in slope but offset in intercept. Before treatment, an apoB of 90 mg/dl corresponded to an LDL-C of 93.3 mg/dl in the high-TG subgroup and to 110.5 mg/dl in the lower-TG subgroup (Table 2).

However, statin therapy altered the relationship between apoB and LDL-C, causing the linear regression lines to shift. Similar results were seen for each treatment arm, for weaker as well as for stronger statins. The overall pooled regression is shown in Table 2. For patients with high baseline TG levels, an apoB of 90 mg/dl on statin therapy corresponded to an LDL-C of 71.0 mg/dl (22.3 mg/dl lower than at baseline). This corresponds to the LDL-C target of <70 mg/dl recommended as "optional" for very-high-risk patients in the ATP III update (21) and as "reasonable" for all patients with CHD or other atherosclerotic vascular disease in the ACC/American Heart Association (AHA) guidelines for secondary prevention (22). For patients with lower baseline TG levels, an apoB of 90 mg/dl on statin therapy corresponded to an LDL-C of 82.5 mg/dl (28.0 mg/dl lower than at baseline). No differences were found when analyzing the relationship between LDL-C and apoB in subgroups based on gender or diabetic status. In statin-treated patients, the scatter of the apoB versus LDL-C data points was reduced (Fig. 1B), leading to higher correlation coefficients, and the slopes of the linear regression lines became steeper (Table 2).

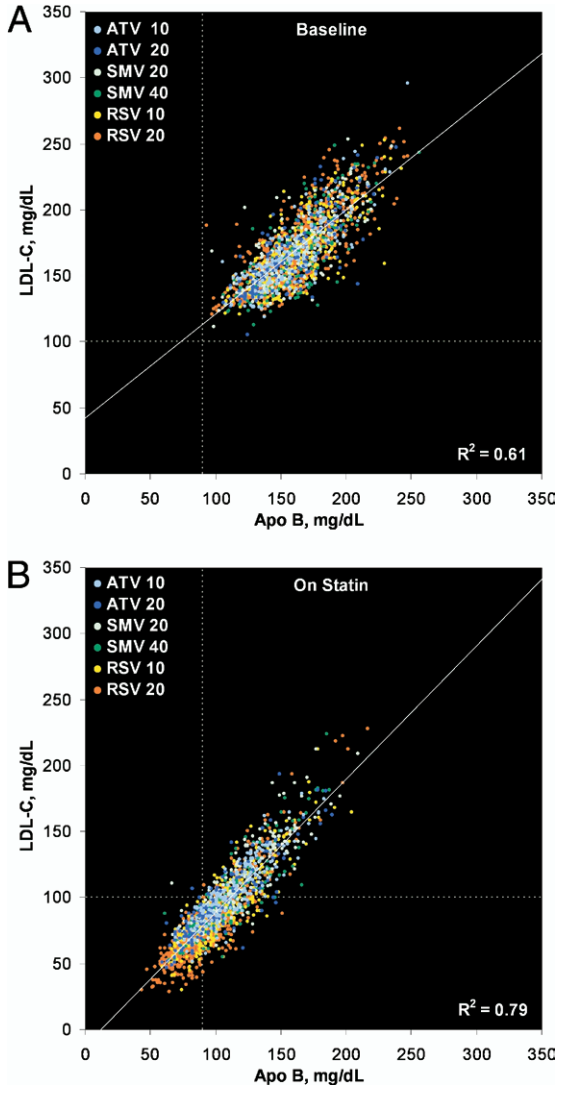

Figure 1 Patterns of ApoB Versus LDL-C Among All Patients Before and After Statin Therapy

(A) All patients untreated (baseline). **(B)** All patients on statin therapy. **Horizontal lines** show the upper threshold of the LDL-C goal of <100 mg/dl, and **vertical lines** show the upper threshold of the proposed secondary apoB goal of <90 mg/dl. **Colors of data points** denote treatment during the final 8 weeks of the trial of each patient. ApoB = apolipoprotein B; ATV = atorvastatin; LDL-C = low-density lipoprotein cholesterol; RSV = rosuvastatin; SMV = simvastatin.

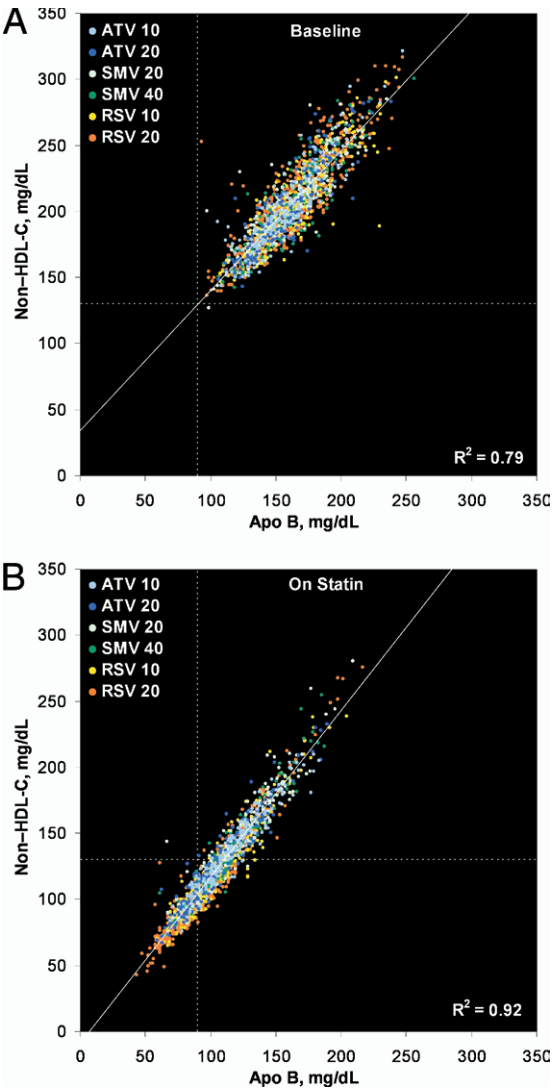

Figure 2 Patterns of ApoB Versus Non–HDL-C Among All Patients Before and After Statin Therapy

(A) All patients untreated (baseline). **(B)** All patients on statin therapy. **Horizontal lines** show the upper threshold of the non–HDL-C goal of <130 mg/dl, and **vertical lines** show the upper threshold of the proposed secondary apoB goal of <90 mg/dl. **Colors of data points** denote treatment during the final 8 weeks of the trial of each patient. HDL-C = high-density lipoprotein cholesterol; other abbreviations as in Figure 1.

ApoB and non–HDL-C. The concentrations of non–HDL-C and apoB for all patients as a group were well fitted by a linear regression model both at baseline and during statin therapy (Table 3, Fig. 2). When patients were separated into high baseline TG and lower baseline TG subgroups, the linear regression lines were similar, although the baseline data points for the high-TG patients were clustered at higher values of apoB and non–HDL-C compared with the lower-TG patients. At baseline, an apoB of 90 mg/dl corresponded to a non–HDL-C of 129.8 mg/dl (Table 3, Fig. 2A). Thus, in untreated patients at baseline, non–HDL-C values appeared to correspond to apoB values consistent with the non–HDL-C target level of <130 mg/dl suggested by Grundy in 2002 (7). The linear regression lines of the apoB and non–HDL-C values in untreated patients with high TG and lower TG had similar slopes (Table 3).

Table 2 Linear Regression of ApoB Versus LDL-C at Baseline (Untreated) and on Statin Therapy

	Slope	Intercept	R^2	LDL-C (ApoB = 90), mg/dl
Baseline				
Lower TG	0.89	+30.0	0.67	110.5
High TG	0.92	+10.4	0.66	93.3
All patients	0.79	+42.1	0.61	112.8
On statin				
Lower TG	1.11	−17.6	0.85	82.5
High TG	1.03	−21.2	0.83	71.0
All patients	1.01	−12.3	0.79	79.0

ApoB = apolipoprotein B; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

However, as seen with the LDL-C relationship, statin therapy altered the relationship between apoB and non–HDL-C, shifting the linear regression lines (Table 3, Fig. 2B). Although mean non–HDL-C reductions among statin treatment arms varied widely (ranging from −29% to −49%), the separate apoB versus non–HDL-C regression lines among these treatment groups were similar. Therefore, we were able to use a single regression line to describe the pooled data. For patients with high baseline TG levels, an apoB of 90 mg/dl on statin therapy corresponded to a non–HDL-C of 104.1 mg/dl (31.7 mg/dl lower than at baseline). For patients with lower baseline TG levels, an apoB of 90 mg/dl on statin therapy corresponded to a non–HDL-C of 104.6 mg/dl (26.1 mg/dl lower than at baseline). These values are close to the target non–HDL-C value recommended as "optional" for very-high-risk patients in the ATP III update (21) and as "reasonable" for all patients with CHD or other atherosclerotic vascular disease in the ACC/AHA guidelines for secondary prevention (22). No differences were found when analyzing the relationship between non–HDL-C and apoB in subgroups based on gender or diabetic status. Statin treatment reduced the

Table 3 Linear Regression of ApoB Versus Non–HDL-C at Baseline (Untreated) and on Statin Therapy

	Slope	Intercept	R^2	Non–HDL-C (ApoB = 90), mg/dl
Baseline				
Lower TG	1.02	+38.8	0.76	130.7
High TG	1.02	+44.1	0.71	135.8
All patients	1.06	+34.4	0.79	129.8
On statin				
Lower TG	1.27	−10.0	0.92	104.6
High TG	1.25	−8.3	0.92	104.1
All patients	1.26	−8.9	0.92	104.4

HDL-C = high-density lipoprotein cholesterol; other abbreviations as in Table 2.

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Table 4 Percentages of Patients After 16 Weeks of Statin Therapy at an LDL-C or Non–HDL-C Target Who Also Reached ApoB <90 mg/dl

Target	Group	Patients Reaching Target	Patients Reaching Target With ApoB <90 mg/dl
LDL-C <100 mg/dl	Lower TG	67% (765/1,137)	58% (441/765)
	High TG	64% (423/664)	30% (129/423)
	All patients	66% (1,188/1,801)	48% (570/1,188)
LDL-C <70 mg/dl	Lower TG	21% (242/1,137)	95% (230/242)
	High TG	22% (145/664)	71% (103/145)
	All patients	21% (387/1,801)	86% (333/387)
Non–HDL-C <130 mg/dl	Lower TG	73% (829/1,138)	54% (444/829)
	High TG	53% (350/664)	37% (129/350)
	All patients	65% (1,179/1,802)	49% (573/1,179)
Non–HDL-C <100 mg/dl	Lower TG	35% (403/1,138)	92% (372/403)
	High TG	17% (111/664)	91% (101/111)
	All patients	29% (514/1,802)	92% (473/514)

Abbreviations as in Tables 2 and 3.

scatter of apoB versus non–HDL-C data points (Fig. 2B), leading to an even higher R^2 value of 0.92. On statin treatment, the slopes of the linear regression lines became steeper (Table 3).

Success in meeting dual cholesterol and apoB targets. Tables 4 and 5 show the likelihood of success in reaching a cholesterol or an apoB target when the other target is first met. Looking at each target separately, Table 4 shows that about two-thirds of statin-treated patients in the MERCURY II trial met high-risk lipid targets (non–HDL-C <130 mg/dl or LDL-C <100 mg/dl). Lipid-lowering success ranged from 28% for patients treated with simvastatin 20 mg to 80% for patients treated with rosuvastatin 20 mg. However, of those meeting either the LDL-C target or the non–HDL-C target, overall only one-half succeeded in also reaching apoB <90 mg/dl. Applying the optional lipid targets for very-high-risk patients vastly decreased the overall proportion of success to 21% for LDL-C <70 mg/dl and 29% for non–HDL-C <100 mg/dl. However, of those who met those optional lipid targets, 86% and 92%, respectively, also met the target of apoB <90 mg/dl.

A converse question can also be asked: Of those who reach the apoB target of <90 mg/dl, what proportion reaches the lipid targets? Table 5 shows that overall, 32% of statin-treated patients reached apoB <90 mg/dl, ranging from 10% of patients treated with simvastatin 20 mg to 47% of patients treated with rosuvastatin 20 mg. In addition, the high-TG group showed only a 19% overall success at reaching the apoB goal. However, virtually all of the patients who reached the apoB target also met the individual high-risk lipid targets of LDL-C <100 mg/dl (99%) and non–HDL-C <130 mg/dl (99.8%). Examination of the optional lipid targets for very-high-risk patients indicated that of those who met the apoB target (apoB <90 mg/dl), 58% achieved LDL-C <70 mg/dl and 82% achieved non–HDL-C <100 mg/dl (Table 5).

Discussion

These analyses from the MERCURY II trial show linear correlations between LDL-C and apoB and between non–HDL-C and apoB both before and during statin cholesterol-lowering therapy in high-risk patients. Earlier studies noted linear correlations of LDL-C and non–HDL-C with apoB in untreated patients and found that the correlations were affected by TG levels (12,19). In ACCESS (Atorvastatin Comparative Cholesterol Efficacy and Safety Study), statin treatment was shown to affect the strength of those correlations and to reduce LDL-C by a greater percentage than it did apoB (19).

The data from high-risk patients in the MERCURY II trial indicate that to drive the atherogenic particle concentration down to the suggested apoB target value of 90 mg/dl, it is necessary for statin therapy to achieve a

Table 5 Percentages of Patients After 16 Weeks of Statin Therapy at ApoB <90 mg/dl Who Also Reached LDL-C or Non–HDL-C Targets

Group	ApoB <90 mg/dl	Patients With ApoB <90 mg/dl Who Have . . . LDL-C <100 mg/dl	LDL-C <70 mg/dl	Non–HDL-C <130 mg/dl	Non–HDL-C <100 mg/dl
Lower TG	39% (445/1,138*)	99% (441/445)	52% (230/445)	99.8% (444/445)	84% (372/445)
High TG	19% (129/664)	100% (129/129)	80% (103/129)	100% (129/129)	78% (101/129)
All patients	32% (574/1,802†)	99% (570/574)	58% (333/574)	99.8% (573/574)	82% (473/574)

*n = 1,137 for LDL-C; †n = 1,801 for LDL-C.
Abbreviations as in Tables 2 and 3.

cholesterol level considerably lower than expected according to existing recommendations (7,18). These findings are relevant because the data used to develop existing goals for apoB were from untreated subjects. Therefore, the data presented in this analysis of patients on statin therapy have implications for guidelines that recommend treatment goals for apoB, non–HDL-C, and LDL-C, because statins are recommended as first-line therapy in high-risk patients. This analysis suggests that to reach an apoB level of 90 mg/dl, one would need to set a target LDL-C of <70 to 80 mg/dl, rather than <100 mg/dl, and a target non–HDL-C of <100 mg/dl, rather than <130 mg/dl. These lipid values are close to the lipid targets recommended as "optional" for very-high-risk patients in the ATP III update (21) and as "reasonable" for all patients with CHD or other atherosclerotic vascular disease in the ACC/AHA guidelines for secondary prevention (22). Furthermore, the target of non–HDL-C <100 mg/dl works equally well for patients who have high baseline TG and those with lower baseline TG. Therefore, to simplify therapeutic goals, it may be appropriate to consider a non–HDL-C target of <100 mg/dl for all high-risk patients.

The atherogenic lipoprotein paradigm suggests that the total number of atherogenic particles is a more important determinant of cardiovascular risk than conventional lipid measures such as LDL-C levels (2). One molecule of apoB is present in each atherogenic particle of LDL, very-low-density lipoprotein, intermediate-density lipoprotein, large buoyant LDL, small dense LDL, and lipoprotein(a). Therefore, measures of apoB provide an estimate of the total number of potentially atherogenic particles (10). An apoB level <90 mg/dl has been suggested as an optional therapeutic target in patients with very high risk (21), and others have suggested that a more aggressive target level of <80 mg/dl may be considered (10). The recent ADA/ACC consensus statement suggested LDL-C <70 mg/dl, non–HDL-C <100 mg/dl, and apoB <80 mg/dl for patients with highest risk (18).

Statins directly inhibit the rate-limiting step for cholesterol synthesis in the liver and thus stimulate expression of hepatic LDL receptors (23). Statins lower LDL-C, very-low-density lipoprotein cholesterol, and TG, but the reduction in LDL-C is greater than the reductions in TG and apoB (20). Therefore, on therapy, the level of apoB may not be reduced as much as expected by the reduction of LDL-C levels. Thus, after treatment, many individuals with LDL-C <100 mg/dl continue to have apoB >90 mg/dl. For example, in the trial analyzed here, of overall patients who had elevated TG before treatment, only 64% achieved LDL-C <100 mg/dl and only 30% of individuals with LDL-C <100 mg/dl also achieved an apoB <90 mg/dl (Table 4).

One management option for the high-risk patient is to measure apoB during statin therapy to make sure that the total number of atherogenic particles is reduced. Another more practical approach, which would not entail any additional cost, is to measure non–HDL-C, which has a good correlation with apoB at baseline and particularly on statin therapy ($R^2 = 0.92$). Unfortunately, the clinician must still calculate non–HDL-C (non–HDL-C = total cholesterol − HDL-C), because it is not routinely reported by major clinical laboratories, and therefore, non–HDL-C is not routinely used in daily clinical practice. Requiring laboratories to calculate and report non–HDL-C as part of a standard lipid profile, just as LDL-C is already calculated and reported, would conveniently provide important information on this treatment target.

Conclusions

In summary, in untreated high-risk patients, we found that an apoB level of 90 mg/dl was approximately equivalent to an LDL-C level of 100 mg/dl and a non–HDL-C level of 130 mg/dl, which is consistent with the numbers suggested by Grundy (7) and the ADA/ACC consensus statement (18). However, to achieve apoB <90 mg/dl on statin therapy, it was necessary for patients to achieve LDL-C <70 (with high baseline TG) or <80 mg/dl (with lower baseline TG) or non–HDL-C <100 mg/dl. These findings provide additional support for the ACC/AHA guidelines for secondary prevention, which suggest that LDL-C <70 mg/dl and non–HDL-C <100 mg/dl are reasonable targets in all patients with CHD or other atherosclerotic vascular disease, because achieving these targets also reduced apoB to the recommended level.

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