Lipids, Apolipoproteins, and Their Ratios in Relation to Cardiovascular Events With Statin Treatment

John J.P. Kastelein, MD, PhD; Wim A. van der Steeg, MD; Ingar Holme, PhD; Michael Gaffney, PhD; Nilo B. Cater, MD; Philip Barter, MD, PhD; Prakash Deedwania, MD, PhD; Anders G. Olsson, MD, PhD; S. Matthijs Boekholdt, MD, PhD; David A. Demicco, PharmD; Michael Szarek, MS; John C. LaRosa, MD; Terje R. Pedersen, MD, PhD; Scott M. Grundy, MD, PhD; for the TNT and IDEAL Study Groups

Background—Low-density lipoprotein (LDL) cholesterol is the principal target of lipid-lowering therapy, but recent evidence has suggested more appropriate targets. We compared the relationships of on-treatment levels of LDL cholesterol, non–high-density lipoprotein (HDL) cholesterol, and apolipoprotein B, as well as ratios of total/HDL cholesterol, LDL/HDL cholesterol, and apolipoprotein B/A-I, with the occurrence of cardiovascular events in patients receiving statin therapy.

Methods and Results—A post hoc analysis was performed that combined data from 2 prospective, randomized clinical trials in which 10 001 (“Treating to New Targets”) and 8888 (“Incremental Decrease in End Points through Aggressive Lipid Lowering”) patients with established coronary heart disease were assigned to usual-dose or high-dose statin treatment. In models with LDL cholesterol, non-HDL cholesterol and apolipoprotein B were positively associated with cardiovascular outcome, whereas a positive relationship with LDL cholesterol was lost. In a model that contained non-HDL cholesterol and apolipoprotein B, neither was significant owing to collinearity. Total/HDL cholesterol ratio and the apolipoprotein B/A-I ratio in particular were each more closely associated with outcome than any of the individual proatherogenic lipoprotein parameters.

Conclusions—In patients receiving statin therapy, on-treatment levels of non-HDL cholesterol and apolipoprotein B were more closely associated with cardiovascular outcome than levels of LDL cholesterol. Inclusion of measurements of the antiatherogenic lipoprotein fraction further strengthened the relationships. These data support the use of non-HDL cholesterol or apolipoprotein B as novel treatment targets for statin therapy. Given the absence of interventions that have been proven to consistently reduce cardiovascular disease risk through raising plasma levels of HDL cholesterol or apolipoprotein A-I, it seems premature to consider the ratio variables as clinically useful. (Circulation. 2008;117:3002-3009.)

Key Words: apolipoproteins cardiovascular diseases cholesterol myocardial infarction prevention

Cardiovascular disease is the leading cause of death worldwide, and its contribution to disease burden is expected to increase sharply over the next 15 years.1,2 The process of atherosclerosis, which is fundamental to the occurrence of cardiovascular disease, is recognized as the consequence of the interplay of a plethora of genetic and environmental factors, but lipoproteins remain the foundation of its pathogenesis. On the basis of the robust epidemiological relationship between cardiovascular disease and levels of cholesterol present in the LDL fraction3 and solid evidence demonstrating the clinical benefits of LDL cholesterol reduction,4 guidelines for the management of cardiovascular disease risk have defined LDL cholesterol levels as the primary target of therapy.5

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Despite a wealth of clinical data firmly establishing the efficacy of this approach in terms of risk reduction, other lipoprotein measurements have been proposed as more appropriate treatment targets. These include non-HDL cholesterol (the sum of the cholesterol concentration in all proatherogenic lipoproteins [VLDL, IDL, and LDL particles]) and apolipoprotein B (the major apolipoprotein of these particles). In 2001, non-HDL cholesterol was introduced in the third report of the US National Cholesterol Education Program’s Adult Treatment Panel (ATP-III),5 but only as a secondary target in patients with triglyceride levels >200 mg/dL.
(2.3 mmol/L). Apolipoprotein B was also recognized as a secondary target of therapy for these patients, but the wider availability, greater reliability, and significantly lower costs of measurement of non-HDL cholesterol were given as reasons for its prioritization.

The major reason, however, for the restricted use of non-HDL cholesterol or apolipoprotein B as a treatment target is the paucity of results from large studies that robustly show that these variables are indeed more accurate in risk assessment than LDL cholesterol in patients receiving statin therapy. Such studies are limited to a post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, which did not evaluate all lipoprotein variables available. Therefore, we sought to directly compare the strength of the relationships with cardiovascular event occurrence for LDL cholesterol, non-HDL cholesterol, and apolipoprotein B in patients receiving statin therapy. Similarly, we evaluated ratios of proatherogenic to antiatherogenic lipoprotein measurements, including total to HDL cholesterol (total/HDL cholesterol), LDL to HDL cholesterol (LDL/HDL cholesterol), and apolipoprotein B to apolipoprotein A-I (apolipoprotein B/A-I). These composite variables have been put forth as better treatment targets than the single proatherogenic measurements, but direct comparisons in large studies of patients receiving statin treatment are lacking. To accomplish these objectives, we used data from the combined database of the Treatment to New Targets (TNT) and Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) trials.

Methods

Study Population

The TNT and IDEAL studies have been published previously. In summary, both TNT and IDEAL are prospective, randomized, multicenter trials comparing the efficacy of high-dose statin treatment with usual-dose statin treatment for the secondary prevention of cardiovascular events. In TNT, 10,001 patients with stable coronary heart disease and LDL cholesterol levels <130 mg/dL (3.4 mmol/L) were randomly assigned to receive either 10 or 80 mg of atorvastatin per day and followed up for a median of 4.9 years. Mean LDL cholesterol levels during treatment were 101 mg/dL (2.6 mmol/L) and 77 mg/dL (2.0 mmol/L) for the 10- and 80-mg groups, respectively. In IDEAL, 8,888 patients with a history of myocardial infarction were enrolled, randomized to receive 20 to 40 mg of simvastatin or 80 mg of atorvastatin, and followed up for a median of 4.8 years. Mean on-treatment levels of LDL cholesterol were 104 mg/dL (2.7 mmol/L) in the simvastatin group and 81 mg/dL (2.1 mmol/L) in the atorvastatin group. The similarity of inclusion criteria and treatment regimens of these trials enabled us to pool the 2 data sets.

Laboratory Measurements

Lipid and apolipoprotein measurements were performed on fasting blood samples. Levels of total cholesterol, HDL cholesterol, and triglycerides were quantified by standard methodologies. LDL cholesterol was calculated with the Friedewald formula. When triglyceride levels were 400 mg/dL (4.5 mmol/L) or higher, LDL cholesterol was measured directly by ultracentrifugation. Non-HDL cholesterol was calculated as the difference between total cholesterol and HDL cholesterol. Plasma concentrations of apolipoproteins B and A-I were determined by immunonephelometry (Behring Nephelometer BNII, Marburg, Germany) with calibration traceable to the International Federation of Clinical Chemistry primary standards.

For the present analysis, we used the 1-year on-treatment lipid and apolipoprotein measurements in TNT, which was the first time that both these variables were measured. Patients without lipid and apolipoprotein values at this time point or those with a major cardiovascular event (MCVE; defined below) before 9 months (defined as a reasonable window to associate events before the 1-year measurement) were excluded from the present analysis (n=682; 134 MCVEs). In IDEAL, these measurements were performed at 3 and 6 months and at 1 year. Patients without lipid and apolipoprotein values at 1 of these time points or those with MCVE before 2 months (defined as a reasonable window to associate events before the 3-month measurement) were also excluded from the present analysis (n=189; 105 MCVEs).

Outcome Definition

The occurrence of MCVE was selected as an outcome measure for the present analysis. MCVE was defined as coronary death, nonfatal myocardial infarction, resuscitation after cardiac arrest, and fatal or nonfatal stroke. This outcome measure equals the primary end point in TNT and corresponds with the composite secondary end point in IDEAL.

Statistical Analyses

The strengths of the associations of lipid and apolipoprotein variables with the occurrence of MCVE were analyzed by the Cox proportional hazard model, which yielded Wald CIs and probability values. The regression model included the effects of study, age, and sex for the combined estimates for TNT and IDEAL. Study-specific estimates and the test of consistency of these estimates between TNT and IDEAL were obtained by the addition of the study-by-measurement interaction effect to the Cox model. Standardized lipid and apolipoprotein measurements were used in the analyses, and consequently, the regression coefficient from the Cox model is the log of the hazard ratio per standard unit change of the variable.

To investigate the rank order of the lipoprotein variables in terms of strength of association with MCVE, their corresponding regression coefficients were determined individually. To directly compare the association of these variables with MCVE occurrence, pairs of measurements were subsequently included in the Cox model. The resulting coefficients give the strength of the association, taking into account the paired measurement. First, we investigated which of the single proatherogenic measurements (LDL cholesterol, non-HDL cholesterol, and apolipoprotein B) was the strongest MCVE risk marker. Then, we investigated whether ratios that included proatherogenic and antiatherogenic lipoprotein measurements (total/HDL cholesterol, LDL/HDL cholesterol, and apolipoprotein B/A-I) were more closely associated with MCVE occurrence than the strongest single proatherogenic marker. Finally, we evaluated which of the ratios per se was the strongest marker of MCVE occurrence. As a result of their biological relationships, these lipid and apolipoprotein variables show close statistical correlations, the strongest of which were among the single parameters (LDL versus non-HDL cholesterol 0.90; LDL cholesterol versus apolipoprotein B 0.86; and non-HDL cholesterol versus apolipoprotein B 0.94). However, the corresponding variance inflation factors, which ranged from 2.1 to 8.6, were below the suggested threshold (<10), and the tests performed here are likelihood ratio χ² tests. Moreover, supplementary residual analysis was performed, which yielded virtually identical conclusions compared with the direct pairwise comparisons (data not shown).

To address clinical relevance, we investigated whether the study variables remained associated with MCVE risk in patients who achieved the primary LDL cholesterol treatment target defined in ATP-III. To accomplish this, the strengths of association of these variables with MCVE occurrence were determined in patients with LDL cholesterol <100 mg/dL (2.6 mmol/L; n=12 287). This subgroup analysis was then repeated for all other variables evaluated. For fair statistical comparison, we selected the corresponding cutoff levels that yielded approximately equal numbers of patients in the subgroups, ie, 130 mg/dL (3.4 mmol/L; n=12 646) for non-HDL cholesterol, 110 mg/dL (n=11 978) for apolipoprotein B, 4.0
HDL cholesterol, LDL/HDL cholesterol, and apolipoprotein B, total/HDL cholesterol, and non-HDL cholesterol, apolipoprotein B, and the ratios of LDL/HDL cholesterol, non-HDL cholesterol, apolipoprotein B, total/HDL cholesterol, and apolipoprotein B/A-I were each associated with the occurrence of MCVE at a P<0.001 level of significance (Table 2). Among the proatherogenic variables, non-HDL cholesterol and apolipoprotein B had the strongest relationships (hazard ratio 1.19, 95% CI 1.14 to 1.25 and hazard ratio 1.19, 95% CI 1.14 to 1.24, respectively), which indicates a 19% increase in MCVE occurrence per standard unit increase of non-HDL cholesterol (32.7 mg/dL) or apolipoprotein B (27.2 mg/dL). When considered against the background of these 2 variables, the association between LDL cholesterol and MCVE occurrence was less pronounced (hazard ratio 1.15, 95% CI 1.10 to 1.20), which indicates a 15% increase in MCVE occurrence per standard unit increase of LDL cholesterol (101.2 mg/dL) or apolipoprotein B/A-I ratio (hazard ratio 1.24, 95% CI 1.20 to 1.29).

Direct Pairwise Comparisons of the Relationships With MCVE
To compare the strengths of the association of the study variables with MCVE risk, variables were introduced in a pairwise fashion into the Cox proportional hazards model. First, the single proatherogenic measurements were compared

### Table 2. Individual Relationships Between On-Treatment Levels of LDL Cholesterol, Non-HDL Cholesterol, Apolipoprotein B, or Their Ratios and MCVEs in TNT and IDEAL

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>1.15</td>
<td>1.10–1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL cholesterol†</td>
<td>1.19</td>
<td>1.14–1.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>1.19</td>
<td>1.14–1.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>1.21</td>
<td>1.17–1.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL/HDL cholesterol</td>
<td>1.20</td>
<td>1.16–1.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoprotein B/A-I</td>
<td>1.24</td>
<td>1.20–1.29</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Calculated by a Cox proportional hazard model with adjustment for the effects of study, age, and sex.†Calculated as total cholesterol minus HDL cholesterol.
with each other (Table 3). When LDL cholesterol and non-HDL cholesterol were included simultaneously, the positive relationship between LDL cholesterol and MCVE was lost, whereas non-HDL cholesterol retained its positive association with the occurrence of MCVE (hazard ratio 1.31, 95% CI 1.19 to 1.44). In this model, the hazard ratio of LDL cholesterol decreased significantly to below 1.00 (hazard ratio 0.90, 95% CI 0.82 to 0.99), which indicates that for a given non-HDL cholesterol level, an increase in LDL cholesterol was associated with a decrease in MCVE risk. This may be due to increased LDL particle size or a reduction in plasma levels of VLDL cholesterol. When LDL cholesterol and apolipoprotein B were entered into the same regression model, LDL cholesterol was no longer associated with MCVE risk, whereas apolipoprotein B remained a significant positive MCVE risk determinant (hazard ratio 1.24, 95% CI 1.13 to 1.36). When non-HDL cholesterol and apolipoprotein B were entered jointly, neither was significant owing to collinearity (hazard ratio 1.14, 95% CI 1.00 to 1.30 and hazard ratio 1.05, 95% CI 0.92 to 1.20, respectively). Subsequently, the ratio variables were compared with the single proatherogenic measures directly (Table 3). Given the inferiority of the relationship for LDL cholesterol as derived from the previous comparisons, LDL cholesterol and LDL/HDL cholesterol were excluded as study variables. In this analysis, both total/HDL cholesterol and apolipoprotein B/A-I remained associated with MCVE occurrence, whereas non-HDL cholesterol and apolipoprotein B lost their statistically significant relationship. Finally, the strengths of the associations for the ratio variables were compared directly with one other (Table 3). On inclusion of both total/HDL cholesterol and apolipoprotein B/A-I into a single Cox model, the relationship between the lipid ratio and MCVE was lost, as represented by the corresponding hazard ratio of 1.00 (95% CI 0.92 to 1.10). In contrast, apolipoprotein B/A-I remained a statistically significant predictor of outcome (hazard ratio 1.24, 95% CI 1.13 to 1.36) in this analysis.

**Subgroup Analyses**

To demonstrate clinical relevance of these findings, we determined which of the study variables were still significantly related to MCVE occurrence in the subgroup of patients who had achieved the ATP-III LDL cholesterol treatment target (≤100 mg/dL or ≤2.6 mmol/L; n = 12 252) or corresponding values for non-HDL cholesterol (≤130 mg/dL or ≤3.4 mmol/L; n = 12 646), apolipoprotein B (≤110 mg/dL; n = 11 978), or the ratio variables (total/HDL cholesterol ≤4.0, n = 12 480 and apolipoprotein B/A-I ≤0.8, n = 12 700; Table 4). In patients with on-treatment LDL cholesterol levels ≤100 mg/dL (2.6 mmol/L), there was no longer a significant relationship between LDL cholesterol and risk of MCVE (hazard ratio 1.08, 95% CI 0.97 to 1.20). In contrast, both non-HDL cholesterol and apolipoprotein B were still significantly associated with MCVE occurrence (hazard ratio 1.15, 95% CI 1.05 to 1.25 for both). Also, the ratio variables remained related to MCVE occurrence in this subgroup in a statistically significant way (hazard ratio 1.22, 95% CI 1.14 to 1.30 for total/HDL cholesterol and hazard ratio 1.31, 95% CI 1.21 to 1.41 for apolipoprotein B/A-I). Similar results were obtained in subgroups characterized by low levels of non-HDL cholesterol (≤130 mg/dL or ≤3.4 mmol/L) or apolipoprotein B (≤110 mg/dL). When patients were selected according to the predefined cutoff values for total/HDL cholesterol or apolipoprotein B/A-I, the relationships for most of the single proatherogenic variables lost statistical significance. Only non-HDL cholesterol showed a significant association with MCVE in the apolipoprotein B/A-I subgroup, but this relationship was rather modest (hazard ratio 1.09, 95% CI 1.00 to 1.18). In contrast, the ratio variables remained related to outcome to a statistically significant degree, both in patients with total cholesterol/HDL ≤4.0 (hazard ratio 1.26, 95% CI 1.11 to 1.42 for total/HDL cholesterol and hazard ratio 1.25, 95% CI 1.14 to 1.38 for apolipoprotein B/A-I) and in those with low values of apolipoprotein B/A-I (hazard ratio 1.22, 95% CI 1.11 to 1.35 for total/HDL cholesterol and hazard ratio 1.23, 95% CI 1.11 to 1.37 for apolipoprotein B/A-I).

**Discussion**

In the present analysis of TNT and IDEAL, we directly compared the association between values of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B and ratios of proatherogenic to antiatherogenic lipoprotein measurements
with the occurrence of future cardiovascular disease in patients receiving statin treatment. We sought to identify which among these variables was most strongly associated with risk of MCVE. With the pooled data set of these studies, it became obvious that on-treatment levels of non-HDL cholesterol and apolipoprotein B were more strongly related to cardiovascular outcome than levels of LDL cholesterol. Evaluation of the ratios revealed a greater statistical association with cardiovascular disease than single measurements of non-HDL cholesterol or apolipoprotein B, with apolipoprotein B/A-I showing the strongest relationship.

Table 4. Individual Relationships Between On-Treatment Levels of LDL Cholesterol, Non-HDL Cholesterol, Apolipoprotein B, or Their Ratios and MCVEs in Selected Subgroups of TNT and IDEAL

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio*</th>
<th>95% Cl</th>
<th>P</th>
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<tbody>
<tr>
<td>LDL cholesterol ≤100 mg/dL (n = 12 252)</td>
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<tr>
<td>LDL cholesterol</td>
<td>1.08</td>
<td>0.97–1.20</td>
<td>0.16</td>
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<tr>
<td>Non-HDL cholesterol†</td>
<td>1.15</td>
<td>1.05–1.25</td>
<td>0.002</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>1.15</td>
<td>1.05–1.25</td>
<td>0.002</td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>1.22</td>
<td>1.14–1.30</td>
<td>0.001</td>
</tr>
<tr>
<td>Apolipoprotein B/A-I</td>
<td>1.31</td>
<td>1.21–1.41</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-HDL cholesterol ≤130 mg/dL (n = 12 646)</td>
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<tr>
<td>LDL cholesterol</td>
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<td>Non-HDL cholesterol†</td>
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<td>1.01–1.24</td>
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<tr>
<td>Apolipoprotein B</td>
<td>1.11</td>
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<td>Total/HDL cholesterol</td>
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<td>1.17–1.38</td>
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<tr>
<td>Apolipoprotein B/A-I</td>
<td>1.30</td>
<td>1.20–1.41</td>
<td>0.001</td>
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<tr>
<td>Apolipoprotein B ≤110 mg/dL (n = 11 978)</td>
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<tr>
<td>Apolipoprotein B/A-I</td>
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<td>Total/HDL cholesterol ≤4.0 (n = 12 480)</td>
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<td>LDL cholesterol</td>
<td>1.04</td>
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<tr>
<td>Apolipoprotein B/A-I</td>
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<td>1.11–1.37</td>
<td>0.001</td>
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*Calculated by a Cox proportional hazard model with adjustment for the effects of study, age, and sex.
†Calculated as total cholesterol minus HDL cholesterol.

Comparison With Other Studies

With respect to LDL cholesterol, non-HDL cholesterol, or apolipoprotein B in relation to cardiovascular event occurrence, the current literature consists primarily of a series of epidemiological studies that evaluated these relationships in the general population. In most of these studies, both non-HDL cholesterol and apolipoprotein B were found to be more accurate risk predictors than LDL cholesterol, and in a recent study that directly compared non-HDL cholesterol with apolipoprotein B, the latter was found to be superior.

Similar analyses of data on subjects receiving lipid-lowering therapy are scarce and only available from 2 post hoc analyses: 1 from the AFCAPS/TexCAPS and another from the LIPID7 trial. In AFCAPS/TexCAPS, 6605 subjects without prevalent cardiovascular disease and with below-average HDL cholesterol levels were assigned to lovastatin or placebo. Participants receiving lovastatin (n = 2933) achieved a mean LDL cholesterol level of 114 mg/dL (2.9 mmol/L). In this group, apolipoprotein B proved to be significantly associated with the risk of developing a first major coronary event. In contrast, LDL cholesterol showed no significant relationship. The LIPID trial was a secondary prevention study investigating the clinical benefit of pravastatin versus placebo. Among participants assigned to pravastatin (n = 4512), on-treatment levels of LDL cholesterol were only weakly associated with the occurrence of the primary end point, whereas the association for apolipoprotein B was more pronounced. Non-HDL cholesterol was not evaluated in either study. The results of the present analysis of TNT and IDEAL provide important additional information on this issue, because the data set is much larger, direct comparisons can be performed, and non-HDL cholesterol was also included in the analysis. These data demonstrate superiority of non-HDL cholesterol and apolipoprotein B compared with LDL cholesterol in predicting residual risk for individuals undergoing statin therapy.

With regard to composite variables that include both proatherogenic and antiatherogenic lipoprotein measurements, data for direct comparisons are limited to studies based on the general population. In the post hoc analyses of the AFCAPS/TexCAPS and LIPID studies, some of the ratios were included as study variables, but direct comparisons were not performed. In the present study, we showed that ratios that included the antiatherogenic lipoprotein fraction exhibited a stronger association with future cardiovascular disease than the single proatherogenic measurements. Among the ratios evaluated, apolipoprotein B/A-I showed the strongest relationship.

Pathophysiological Considerations

The pathophysiological background for the observed differences in the relationship with MCVE for the lipoprotein measurements evaluated is likely related to differences in the biology of lipids and apolipoproteins. Whereas LDL cholesterol is a measure of the amount of cholesterol present in LDL particles, non-HDL cholesterol represents the cholesterol content of all atherogenic lipoproteins, including triglyceride-rich lipoproteins (VLDL, IDL) and LDL. Under normolipidemic conditions, the majority of atherogenic cholesterol is present in the LDL particle, which results in a very tight
correlation between LDL cholesterol and non-HDL cholesterol.29 The concordance between LDL cholesterol and non-HDL cholesterol diminishes when triglyceride-rich lipoproteins accumulate in the circulation,28,29 a condition characterized by increased plasma levels of triglycerides. These considerations have led to a restriction in the use of non-HDL cholesterol, ie, limited to patients with mild to moderate hypertriglyceridemia (≥200 mg/dL or ≥2.6 mmol/L).5 The present analysis of TNT and IDEAL, however, demonstrates greater accuracy for non-HDL cholesterol over and above that of LDL cholesterol in patients with mostly normal triglyceride levels. These results suggest a pathophysiological role for VLDL and IDL particles under normotriglyceridemic conditions.

Apolipoprotein B is the major apolipoprotein of VLDL, IDL, and LDL particles. In line with non-HDL cholesterol, plasma levels of apolipoprotein B represent all atherogenic lipoproteins in the circulation; however, because every atherogenic particle contains a single apolipoprotein B molecule, apolipoprotein B levels also provide an accurate reflection of the number of atherogenic particles.30,31 We, in fact, showed that apolipoprotein B and non-HDL cholesterol exhibit similar associations with the risk of future MCVEs. One explanation for this observation might lie in the fact that apolipoprotein B and non-HDL cholesterol may only be differentially associated with cardiovascular risk under conditions in which the average particle number increases, such as diabetes mellitus and the metabolic syndrome. However, a significant proportion of subjects enrolled in the TNT and IDEAL studies had diabetes or metabolic syndrome,5,9,32 which therefore does not yield a likely cause for this observation. Conversely, statin therapy that achieves low LDL cholesterol levels might diminish the discordance between non-HDL cholesterol and apolipoprotein B, thereby reducing the difference between the 2 variables in terms of risk prediction.

The present data demonstrated that on-treatment variables that included both a proatherogenic and an antiatherogenic lipoprotein measurement were more closely related to outcome than non-HDL cholesterol or apolipoprotein B in isolation. This observation might reflect the fact that the extent of atherosclerosis is tightly regulated by the balance between proatherogenic and antiatherogenic lipoproteins. Among all composite variables evaluated in the present study, apolipoprotein B/A-I showed the strongest relationship with outcome. This resulted not only from the presence of the strongest proatherogenic risk determinant (ie, apolipoprotein B) in this variable but also from superiority of apolipoprotein A-I over HDL cholesterol in terms of association with MCVEs (data not shown). This parallels several observations that apolipoprotein A-I is more important than the HDL particle cholesterol content for pathways that reduce HDL antiatherogenic, including ATP binding cassette A-1-mediated cellular cholesterol efflux,33 lecithin-cholesteryl acyltransferase-mediated maturation of HDL particles,34 and several antioxidative processes.35

**Study Limitations**

The present post hoc analysis has several limitations. First, in both TNT and IDEAL, patients were only eligible for study participation if they had clinically evident coronary artery disease. Also, all patients received statin therapy. Moreover, a large proportion of the study population was male and of relatively old age. These study characteristics should be taken into consideration before these results are extrapolated to other populations. In particular, the findings of the present post hoc analysis only apply to the secondary prevention setting. Second, the end point evaluated in the present analysis comprises several types of atherosclerotic disease. Given the need for maximum statistical power to detect small differences between associations for the lipoprotein measurements evaluated, categorization of the combined end point was not included in the primary objectives of the present study. Reanalysis of the data with myocardial infarction as the end point, however, rendered identical conclusions (data not shown). Third, the selection of patients with a narrow range of LDL cholesterol limits, by definition, the association of this variable with MCVE. However, the observation that this variable also loses its relationship in other statistical models (ie, after selection on the basis of either LDL cholesterol, non-HDL cholesterol, or apolipoprotein B) demonstrates that this phenomenon is not likely to result in invalid conclusions.

**Clinical Implications**

Ever since the first set of guidelines for cardiovascular disease risk management was published, statin treatment has been the core of every therapy, with LDL cholesterol as the primary target variable.5,36,37 Here, we demonstrate superiority of non-HDL cholesterol or apolipoprotein B compared with LDL cholesterol as a cardiovascular risk predictor during statin treatment. Patients who were treated adequately according to current guidelines (ie, LDL cholesterol ≤100 mg/dL or ≤2.6 mmol/L) still had residual MCVE risk that could be recognized by the evaluation of levels of non-HDL cholesterol or apolipoprotein B. These data suggest that future guidelines should favor the use of non-HDL cholesterol or apolipoprotein B instead of LDL cholesterol as the primary treatment target, especially because targets are currently adjusted downward to very low LDL cholesterol levels. The present results do not favor non-HDL cholesterol or apolipoprotein B over one another; however, although measurements for both variables are reliable and standardized5,36,37 and do not require fasting blood sampling, non-HDL cholesterol has the advantage of being easily calculated with the total cholesterol and HDL cholesterol measurements that are already part of current guidelines and routine clinical practice. In addition, the present data suggest that ratios of proatherogenic to antiatherogenic measurements, in particular the apolipoprotein B/A-I ratio, are better risk determinants than single proatherogenic measurements. However, in view of the absence of trials revealing robust risk reduction by targeting HDL cholesterol or apolipoprotein A-I, the additive value of such composite variables as treatment targets remains a matter of debate. Implementation of the ratios as treatment targets awaits final confirmation that a direct increase of the antiatherogenic lipoprotein is consistently associated with risk reduction comparable to that obtained by decreasing the proatherogenic fraction.
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Disclosures
Dr Kastelein has received research funding from, served as a consultant for, and received honoraria for lectures from AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer, Schering Plough, and Sanjogyo. Dr Holme has received honoraria from Pfizer as steering committee member. Drs Gaffney, Cater, Demicco, and Szarek are Pfizer employees. Dr Barter received consultancy fees from AstraZeneca and Pfizer, honoraria from Abbott, AstraZeneca, Fournier, Merck, Pfizer, and Sanofi-Aventis, and research grants from Pfizer. Dr Deedwania has served as a consultant for and has received honoraria for lectures from AstraZeneca and Pfizer. Dr Olsson has consultancy agreements with AstraZeneca, MSD, and Pfizer. Dr LaRosa has received consulting fees from Pfizer, Merck, Bristol-Myers Squibb, and AstraZeneca and lecture fees from Pfizer. Dr Pedersen has received consultation fees and speaker’s honoraria from Pfizer, Merck, Merck AG, and AstraZeneca and research grants and steering committee fees from Pfizer and Merck. Dr Grundy has been an investigator on research grants awarded to the University of Texas Southwestern Medical Center, Dallas from Merck, Abbott, and Kos Pharmaceuticals in the past 5 years; over the same period, he has received consulting fees from Pfizer, Merck, Abbott, and Kos Pharmaceuticals. Drs Gaffney, Cater, Demicco, and Szarek are Pfizer employees. Drs Gaffney, Cater, Demicco, and Szarek are Pfizer employees. Drs Gaffney, Cater, Demicco, and Szarek are Pfizer employees.

References
CLINICAL PERSPECTIVE

In guidelines for cardiovascular disease risk management, low-density lipoprotein (LDL) cholesterol is the principal target of lipid-lowering therapy; however, recent evidence has suggested more appropriate targets, including non–high-density lipoprotein (HDL) cholesterol, apolipoprotein B, and ratios of proatherogenic to antiatherogenic lipoprotein parameters (total/HDL cholesterol, LDL/HDL cholesterol, and apolipoprotein B/A-I). To assess whether these parameters are indeed more appropriate treatment targets, we compared the relationships of levels of these parameters with the occurrence of cardiovascular events using data from 2 prospective, randomized clinical trials, the Treating to New Targets (TNT; n = 10,001) and Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL; n = 8888) trials. In these studies, patients with established coronary heart disease were assigned to usual-dose or high-dose statin treatment and followed up for a median of 4.9 and 4.8 years, respectively. The present post hoc analysis demonstrated non-HDL cholesterol and apolipoprotein B to be more closely related to cardiovascular outcome than LDL cholesterol. A comparison of non-HDL cholesterol versus apolipoprotein B revealed no significant difference. Moreover, it became clear that total/HDL cholesterol and apolipoprotein B/A-I were more closely associated with outcome than any of the individual lipoprotein parameters. Among all study variables, the apolipoprotein B/A-I ratio was the best determinant of residual risk.

This outcome, as well as the fact that non-HDL cholesterol and apolipoprotein B can be measured reliably under nonfasting conditions, supports the use of these parameters as a target of lipid-lowering therapy. Implementation of the ratios as treatment targets awaits final confirmation that any increase in the antiatherogenic lipoprotein is associated with risk reduction.
Lipids, Apolipoproteins, and Their Ratios in Relation to Cardiovascular Events With Statin Treatment


for the TNT and IDEAL Study Groups

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