Non-HDL Cholesterol and Triglycerides
Implications for Coronary Atheroma Progression and Clinical Events

Rishi Puri, Steven E. Nissen, Mingyuan Shao, Mohamed B. Elshazly, Yu Kataoka,
Samir R. Kapadia, E. Murat Tuzcu, Stephen J. Nicholls

Objectives—Non–high-density lipoprotein cholesterol (non-HDLC) levels reflect the full burden of cholesterol transported in atherogenic lipoproteins. Genetic studies suggest a causal association between elevated triglycerides (TGs)-rich lipoproteins and atherosclerosis. We evaluated associations between achieved non-HDLC and TG levels on changes in coronary atheroma volume.

Approach and Results—Data were analyzed from 9 clinical trials involving 4957 patients with coronary disease undergoing serial intravascular ultrasound to assess changes in percent atheroma volume (∆PAV) and were evaluated against on-treatment non-HDLC and TG levels. The effects of lower (<100 mg/dL) versus higher (≥100 mg/dL) achieved non-HDLC levels and lower (<200 mg/dL) versus higher (≥200 mg/dL) achieved TG levels were evaluated in populations with variable on-treatment low-density lipoprotein cholesterol (LDLC) (<70 mg/dL and C-reactive protein (<2 mg/L and in patients with or without diabetes mellitus. On-treatment non-HDLC levels linearly associated with ∆PAV. Overt PAV progression (∆PAV>0) was associated with achieved TG levels >200 mg/dL, respectively. Lower on-treatment non-HDLC and TG levels associated with significant PAV regression compared with higher non-HDLC and TG levels across all levels of LDLC and C-reactive protein and irrespective of diabetic status (P<0.001 across all comparisons). ∆PAV were more strongly influenced by changes in non-HDLC (β=0.62; P<0.001) compared with changes in LDLC (β=0.51; P<0.001). Kaplan–Meier sensitivity analyses demonstrated significantly greater major adverse cardiovascular event rates in those with higher versus lower non-HDLC and TG levels, with an earlier separation of the non-HDLC compared with the LDLC curve.

Conclusions—Achieved non-HDLC levels seem more closely associated with coronary atheroma progression than LDLC.

Key Words: atherosclerosis ■ low-density lipoprotein ■ non-HDL ■ residual risk ■ triglycerides

Statin-mediated low-density lipoprotein cholesterol (LDLC) lowering significantly reduces both primary and secondary cardiovascular events in randomized controlled trials.1 These data underscore the paradigm of statin-mediated secondary cardiovascular events in randomized controlled trials.1,2 This data underscores the paradigm of statin-mediated secondary cardiovascular events in randomized controlled trials.1 These data underscore the paradigm of statin-mediated low-density lipoprotein cholesterol (LDLC) lowering significantly reduces both primary and secondary cardiovascular events in randomized controlled trials.1

Non–high-density lipoprotein cholesterol (non-HDLC) encompasses all of the atherogenic apolipoprotein B (apoB)–containing lipoproteins (LDLC, very low-density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol, lipoprotein (a), chylomicrons, and their triglyceride (TG)-rich remnants). Population studies have outlined non-HDLC to better predict cardiovascular risk compared with LDLC alone,3,4 even among statin-treated individuals.6 Although the latest US cholesterol treatment guidelines have shifted emphasis away from targeting specific LDLC levels in patients with atherosclerotic cardiovascular disease, non-HDLC continues to receive much less attention, remaining a secondary treatment goal within current European guidelines.8 However, recently, both the International Atherosclerosis Society and National Lipid Association have flagged non-HDLC as the major form of atherogenic cholesterol and a primary therapeutic target.6,9

Recent insights from genetic studies suggest that TG-rich lipoproteins causally influence atherosclerosis and its associated complications.11–13 Furthermore, lipolysis of TG-rich lipoproteins yields TG-depleted, cholesterol-rich remnant lipoproteins that contain ≤20× more cholesterol per particle than LDLC, more avidly crossing the endothelial barrier.14 Accordingly, the

Received on: March 24, 2016; final version accepted on: August 1, 2016.

From the Cleveland Clinic Coordinating Center for Clinical Research (CSR) (R.P., S.E.N., M.S.), and Department of Cardiovascular Medicine (R.P., S.E.N., M.B.E., S.R.K., E.M.T.), Cleveland Clinic, OH; Department of Medicine, University of Adelaide, Australia (R.P., S.J.N.); and South Australian Health and Medical Research Institute, Adelaide, Australia (Y.K., S.J.N.).

The online-only Data Supplement is available with this article at http://atvb.ahajournals.org/lookup/suppl/doi:10.1161/ATVBAHA.116.307601/-/DC1.

Correspondence to Steven E. Nissen, Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195.

E-mail nisens@ccf.org

© 2016 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org DOI: 10.1161/ATVBAHA.116.307601
relationship between achieved non-HDLc and TG levels upon coronary atheroma progression rates has yet to be defined.

Coronary intravascular ultrasound is a sensitive imaging tool for measuring coronary atheroma volume and continues to play an important role for evaluating the antiatherosclerotic effects of novel therapies on serial measures of coronary disease progression. Post hoc analyses of serial intravascular ultrasound trials demonstrated significant associations between measures of disease progression and incident cardiovascular events. The present analysis aimed to define the relationship between achieved non-HDLc and TG levels with rates of coronary atheroma progression. The effects of higher versus lower non-HDLc and TG levels on plaque progression rates were specifically explored within patients stratified according to varying degrees of residual metabolic risk (defined according to achieved LDLc, C-reactive protein [CRP], and diabetes mellitus status).

Materials and Methods
Materials and Methods are available in the online-only Data Supplement.

Results
Clinical Characteristics of the Study Population
Table 1 describes baseline demographics, clinical characteristics, and medication use of the pooled study population (n=4957). Mean age was 57.9±9 years, 28.1% were female, 29% had diabetes mellitus, and the mean body mass index was 30.8±5.8 kg/m². Notably, 74% received prior statin therapy, and concomitant (on-trial) rates of statins, aspirin, β-blockers, and angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use were 96%, 94%, 76%, and 68%, respectively.

Plaque and Laboratory Biochemical Measurements
Table 2 describes baseline, follow-up, and changes in plaque and laboratory biochemical measurements. In the overall population, the median change in LDLc was −14.4%; non-HDLc, −13.6%; HDLc, +13.0%; TG, −7.2%; and CRP, −25.0%. These biochemical changes associated with no net change in percent atheroma volume (PAV) within the overall study population (median [95% confidence interval (CI)] change in PAV =+0.01 [−0.08, 0.11]; P=0.76).

Relationships Between Non-HDLc, TG, and Coronary Atheroma Progression
Figure 1 illustrates the relationship between the full range of average on-treatment non-HDLc and TG levels against changes in coronary PAV. Individual patient-level data are represented as LOWESS (locally weighted scatter plot smooth) plots. Although achieved non-HDLc levels and coronary atheroma progression rates seem linearly related, the rate of disease progression increases as TG levels rise >110 mg/dL and start to associate with actual disease progression (ΔPAV>0) beyond TG levels of 200 mg/dL.

Effects of Higher Versus Lower Non-HDLc and TG on Coronary Atheroma Progression
Figure 2 illustrates the effect of lower (<100 mg/dL) and higher (>200 mg/dL) on-treatment non-HDLc levels on coronary atheroma progression rates across specific populations at varying metabolic risk. These data demonstrate that lower compared with higher non-HDLc levels associated significantly with greater PAV regression, irrespective of achieved LDLc levels, CRP levels, or diabetic status (P<0.001 for all comparisons). Point estimates of changes in PAV for all patient groups are provided in Table I in the online-only Data Supplement.

Figure 3 illustrates the effect of lower (<200 mg/dL) and higher (>200 mg/dL) on-treatment TG levels on coronary atheroma progression rates across specific populations at varying metabolic risk. Similar to the results demonstrated in Figure 2, lower compared with higher TG levels associated significantly with greater PAV regression, irrespective of achieved LDLc levels, CRP levels, or diabetic status (P<0.001 for all comparisons). Point estimates of changes in PAV for all patient groups are provided in Table II in the online-only Data Supplement.

Comparative Influence of LDLc and Non-HDLc on Coronary Atheroma Progression/Regression
Given that LDLc and non-HDLc are intrinsically related (colinear), the relative strength of association of these...
Table 3 describes the multivariable predictors of changes in and TG plots (Figure III in the online-only Data Supplement). Corresponding LDLC (Figure II in the online-only Data Supplement) and change in PA V, compared with the corresponding relationship between non-HDLC (Figure I in the online-only Data Supplement). Visually, these curves illustrate a slightly more linear relationship between non-HDLC (Figure I in the online-only Data Supplement) and change in HDLC similarly associated with PA V regression. Increasing baseline PA V, female sex, and increasing age were similarly associated with PA V progression. Increasing baseline PA V, female sex (−0.27 [95% CI −0.46, −0.08]; P = 0.005), and increasing age (0.02 [95% CI 0.01, 0.03]; P < 0.001). Independent predictors of PA V progression included higher baseline PA V (−0.58 [95% CI −0.67, −0.49]; P < 0.001), female sex (−0.27 [95% CI −0.46, −0.08]; P = 0.005), and change in HDLC (−0.14 [95% CI −0.23, −0.05]; P = 0.002).

Table 4 describes the multivariable predictors of changes in PA V in an LDLC-adjusted model. Both baseline and change in LDLC were associated with PA V progression (0.40 [95% CI 0.26, 0.53] and 0.51 [95% CI 0.36, 0.66]; P < 0.001 for both). In this model, baseline and change in TGs also associated with PA V progression (0.49 [95% CI 0.29, 0.70] and 0.48 [95% CI 0.20, 0.76]; P < 0.001 for both). As in the non-HDL-adjusted model, the presence of diabetes mellitus, history of peripheral arterial disease, and increasing age were similarly associated with PA V progression. Increasing baseline PA V, female sex, and change in HDL similarly associated with PA V regression.

Given the nonlinear relationship between some of these lipoprotein parameters and changes in PA V (as demonstrated in Figure 1), restricted cubic spline curves were drawn to better visualize these relationships (Figures I–III in the online-only Data Supplement). Visually, these curves illustrate a slightly more linear relationship between non-HDL (Figure I in the online-only Data Supplement) and change in PA V, compared with the corresponding LDLC (Figure II in the online-only Data Supplement) and TG plots (Figure III in the online-only Data Supplement).

### Table 2. Baseline, Follow-Up, and Changes in Laboratory and Intravascular Ultrasonographic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>Change (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLC, mg/dL</td>
<td>105.5±35.4</td>
<td>83.0±27.8</td>
<td>−14.4 (−15.4, −13.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDLC, mg/dL</td>
<td>43.3±11.7</td>
<td>48.2±14.7</td>
<td>13.0 (12.2, 13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDLC/HDLC</td>
<td>2.6±1.1</td>
<td>1.9±0.8</td>
<td>−21.6 (−22.5, −20.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL, mg/dL</td>
<td>135.9±40.9</td>
<td>110.9±33.0</td>
<td>−13.6 (−14.4, −12.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, median (IQR)</td>
<td>137 (97.5, 194)</td>
<td>127 (94.5, 172)</td>
<td>−7.2 (−25.8, 16.7)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>CRP, mg/L, median (IQR)</td>
<td>2.3 (1.1, 5.2)</td>
<td>1.6 (0.7, 3.8)</td>
<td>−25.0 (−60.0, 30.8)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>IVUS§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAV, %</td>
<td>37.99±8.93</td>
<td>38.01±9.05</td>
<td>0.01 (−0.08, 0.11)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Data is presented as mean±SD unless otherwise indicated. CI indicates confidence interval; CRP, C-reactive protein; HDLC, high-density lipoprotein cholesterol; IVUS, intravascular ultrasound; LDLC, low-density lipoprotein cholesterol; and PAV, percent atheroma volume.

*Reflects comparison between baseline and follow-up and is based on paired t test for normally distributed variables and on Wilcoxon signed rank test for non-normally distributed variables.
†Reflects % changes from baseline.
‡P Values reflect Wilcoxon signed rank test for non-normally distributed continuous variables.
§Reflects absolute changes from baseline.

individual lipoprotein measurements on plaque progression was assessed by constructing 2 separate multivariable models. Table 3 describes the multivariable predictors of changes in PA V in a non-HDL-adjusted model. Both the baseline and change in non-HDL were strongly associated with PA V progression, with β coefficients (95% CI) of 0.53 (0.41, 0.66) and +0.62 (0.47, 0.76), respectively (P < 0.001 for both). Other predictors of PA V progression were the presence of diabetes mellitus (+0.58 [95% CI 0.37, 0.79]; P < 0.001), history of peripheral arterial disease (+0.49 [95% CI 0.09, 0.89]; P = 0.016), and increasing age (+0.02 [95% CI 0.01, 0.03]; P < 0.001). Independent predictors of PA V regression included higher baseline PA V (−0.58 [95% CI −0.67, −0.49]; P < 0.001), female sex (−0.27 [95% CI −0.46, −0.08]; P = 0.005), and change in HDLC (−0.14 [95% CI −0.23, −0.05]; P = 0.002).

Table 4 describes the multivariable predictors of changes in PA V in an LDLC-adjusted model. Both baseline and change in LDLC were associated with PA V progression (0.40 [95% CI 0.26, 0.53] and 0.51 [95% CI 0.36, 0.66]; P < 0.001 for both). In this model, baseline and change in TGs also associated with PA V progression (0.49 [95% CI 0.29, 0.70] and 0.48 [95% CI 0.20, 0.76]; P < 0.001 for both). As in the non-HDL-adjusted model, the presence of diabetes mellitus, history of peripheral arterial disease, and increasing age were similarly associated with PA V progression. Increasing baseline PA V, female sex, and change in HDL similarly associated with PA V regression.

The Relationship Between Non-HDL, TG, LDLC, and Major Adverse Cardiovascular Event

Sensitivity analyses were performed comparing the impact of achieved non-HDL, TG, and LDLC levels on major adverse cardiovascular event (MACE; Figures IV and V in the online-only Data Supplement). Figure IVA in the online-only Data Supplement illustrates Kaplan–Meier curves assessing MACE across patients stratified according to on-treatment non-HDL levels < versus ≥ median. At 24 months, cumulative incidence of first MACE was significantly greater in those with achieved non-HDL levels ≥ versus < median level compared with non-HDL < median value (22.8% versus 14.6%; log-rank P < 0.001). Figure IVB in the online-only Data Supplement illustrates the comparative Kaplan–Meier curves of patients stratified according to on-treatment LDLC levels < versus ≥ median. At 24 months, cumulative incidence of first MACE was significantly greater in those with achieved LDLC ≥ versus < median value (22.0% versus 15.5%; log-rank P < 0.001). Closer inspection of Figures IVA and IVB in the online-only Data Supplement illustrates the slightly earlier and more consistent curve separation in the non–HDL-stratified population compared with the LDLC-stratified population.

Figure V in the online-only Data Supplement illustrates Kaplan–Meier curves assessing MACE across patients stratified according to on-treatment TG levels < versus ≥ median, illustrating that cumulative incidence of first MACE at 24 months was significantly greater in those with median TG levels (21.2% versus 15.9%; log-rank P < 0.001). Closer inspection of Figures VIVA and VIVB in the online-only Data Supplement illustrates the slightly earlier and more consistent curve separation in the non–HDL-stratified population compared with the LDLC-stratified population.
The present analysis is the first to demonstrate that coronary disease progression seems more tightly linked with changes in non-HDLC compared with LDLC and that on-treatment TG levels associate with coronary atheroma progression (and, thus, cardiovascular risk), especially when these levels exceed 200 mg/dL. Moreover, achieved non-HDLC and TG levels significantly modulated plaque progression–regression rates across broad categories of residual cardiovascular risk, including those with achieved LDLC levels <70 mg/dL. These findings provide mechanistic support for the possible roles of non-HDLC and TG to more definitively emerge as future therapeutic targets, especially in statin-treated patients requiring secondary prevention.

Although the benefits of LDLC lowering are well established, many patients continue to experience cardiovascular events, despite achieving low LDLC levels. The global obesity, diabetes mellitus, and metabolic syndrome epidemic is increasing the prevalence of atherogenic TG-rich remnant lipoproteins, which are more effectively accounted for by measuring the non-HDLC, but not the LDLC fraction. The present analysis outlines a consistent antiatherosclerotic effect of lower achieved non-HDLC levels, even within populations whose residual risk is already considered to be low (patients with LDLC <70 mg/dL and CRP <2 mg/L). Although we uncovered a relatively stronger correlation between coronary plaque progression–regression and non-HDLC levels compared with LDLC levels, Kaplan-Meier sensitivity analyses (see online-only Data Supplement) also revealed higher non-HDLC levels to associate with an earlier, slightly more dominant effect on MACE compared with corresponding LDLC stratification. Our observations are, therefore, consistent with the known capacity of non-HDLC to better predict MACE compared with LDLC in epidemiological studies, supporting the potential role of non-HDLC as possible primary therapeutic targets in future prospective clinical trials.

Although the exact role of TGs in mediating atherosclerosis continues to be debated, genetic studies strongly suggest that elevated TG-rich lipoprotein concentrations are a causal risk factor for atherosclerotic disease. Elevated TG concentrations reliably indicate raised levels of remnant cholesterol (the cholesterol content of TG-rich lipoproteins). However, clinical trials testing the efficacy of TG-lowering strategies have largely been negative. This may be in part because of baseline TG levels in these trials being potentially too low to demonstrate an anti-atherosclerotic effect, with the median baseline TG levels in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) and ORIGIN (Outcome Reduction With an Initial Glargine Intervention) trials being 162 and 142 mg/dL, respectively. The current analysis suggests that the rate coronary disease progression (and, thus, atherosclerotic risk) seems well established when TG levels exceed 200 mg/dL. Collectively, these data support the notion that patients with TG levels >200 mg/dL are more likely to derive clinical benefit from a TG-lowering intervention. This hypothesis is currently being tested in 2 large-scale clinical trials (NCT02104817 and NCT01492361).

The comparative multivariable analyses in Tables 3 and 4 demonstrate the significant dual effect of both higher LDLC and TG levels independently associating with disease progression. However, the non-HDLC-adjusted analysis outlined a more dominant effect of non-HDLC levels on plaque progression. Cholesterol-rich remnants found within the non-HDLC fraction more avidly cross the endothelial barrier. These processes promote foam cell accumulation, lipid-core expansion, and plaque progression. Histological analysis of severely stenotic carotid plaques demonstrated a direct association between macrophage content and TG-rich lipoprotein remnants synonymous with the non-HDLC fraction.
To complement histological findings, human plaque imaging studies have been pivotal in elucidating mechanisms promoting atheroma progression, stabilization, and regression. However, the present analysis represents the first description of the direct impact of on-treatment non-HDLC and TG levels on serial changes in coronary plaque volume.
Our findings also have possible implications for clinical practice. There is a notable discordance between non-HDL cholesterol and LDL cholesterol levels in the US population. A sizeable proportion of individuals with LDL cholesterol levels <70 mg/dL harbor non-HDL cholesterol levels ≥100 mg/dL, effectively reclassifying their cardiovascular risk. Previous guidelines set non-HDL cholesterol goals 30 mg/dL higher than respective LDL cholesterol goals and relegated non-HDL cholesterol as a secondary treatment target only in patients...
The latest US cholesterol treatment guidelines no longer advocate LDL targets, our data provides mechanistic support for adopting non-HDLC treatment goals, particularly in high-risk patients receiving statins. This strategy has been postulated to prevent 300,000 more MACE in the US over a 10-year period compared with an LDL-only treatment strategy. Thus, further consideration could be given for setting non-HDLC goals in high-risk patients or in those with established atherosclerotic disease. In the absence of current LDL targets, our data provides mechanistic support for adopting non-HDLC treatment goals, particularly in high-risk patients receiving statins. This strategy has been postulated to prevent 300,000 more MACE in the US over a 10-year period compared with an LDL-only treatment strategy. Thus, further consideration could be given for setting non-HDLC goals in high-risk patients.

This analysis has limitations. These findings are applicable to patients with established coronary artery disease with an indication for coronary angiography and cannot be extrapolated to patients without clinically evident atherosclerotic disease. Despite the known association between changes in intravascular ultrasound–derived coronary atheroma volume and MACE,17–19 none of the reported serial intravascular ultrasound trials in the current analysis were powered to detect differences in MACE. However, our serial plaque imaging data are extremely consistent with more contemporary epidemiological, genetic, and mechanistic observations that collectively outline the dominant role of non-HDLC and TG in mediating atherosclerotic risk. Although our multivariable models were appropriately adjusted for clinical trial, time-dependent variations of these trials (18–24 months), and a range of baseline and on-treatment covariates, we cannot exclude unmeasured confounding variables that could have biased our results. Even though information on baseline and concomitant medications and general cardiovascular risk factors were prospectively collected across all clinical trials, various dietary and lifestyle interventions that could have influenced non-HDLC and TG levels were not collected as per routine study protocol. It is difficult to perform sound statistical analyses of the comparative strength of association between non-HDLC, LDL, and TG levels with changes in PAV, given that many of these measures are closely correlated and arise from within the same database. The restricted cubic spline curves do, however, illustrate a slightly more linear relationship between non-HDLC and changes in PAV when compared with the corresponding curves of LDL and TG, supported by data in Figures 2–3 and the MACE data. We used simple quantifications of cholesterol levels (as opposed to direct measurements) as an attempt to offer a more clinical pragmatic approach to lipoprotein assessment. However, calculated LDL levels as opposed to measured LDL levels may have undermined the true biological differences observed between the presented TG data. Nuclear magnetic resonance analysis might have provided added insight, although in a large study, nuclear magnetic resonance was shown to be equivalent to that of standard lipid/protein analyses.34 The presence of prior statin therapy might have further influenced disease progression rates and, thus, the relationships with non-HDLC and TG.

In conclusion, the present analysis is the first to describe the relationship between achieved non-HDLC and TG levels with coronary atheroma progression–regression rates in a large cohort of patients with established coronary disease. Plaque progression overall was more closely tied with changes in non-HDLC than with changes in LDL and appeared to associate with TG levels only beyond 200 mg/dL. Importantly, lower on-treatment non-HDLC and TG levels systematically associated with plaque regression in individuals across broad categories of athero-sclerotic risk. Other factors considered in the multivariable analysis included race (white/nonwhite), baseline BMI, history of MI, history of PCI, hypertension, smoking, baseline ACE inhibitor use, concomitant ACE use, baseline HDLC. Clinical trial was also controlled for as a random effect. Δ indicates change; ACE, angiotensin-converting enzyme; BMI, body mass index; CI, confidence interval; HDLC, high-density lipoprotein cholesterol; IVUS, intravascular ultrasound; MI, myocardial infarction; non-HDLC, non–high-density lipoprotein cholesterol; PAV, percent atheroma volume; and PCI, percutaneous coronary intervention.

### Table 3. Multivariable Linear Regression Model for Change in PAV (Non–HDLC Adjusted)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Estimated β Coefficient (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PAV</td>
<td>−0.58 (−0.67, −0.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline non-HDLC</td>
<td>0.53 (0.41, 0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ non-HDLC</td>
<td>0.62 (0.47, 0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ HDLC</td>
<td>−0.14 (−0.23, −0.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.58 (0.37, 0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.02 (0.01, 0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>−0.27 (−0.46, −0.08)</td>
<td>0.005</td>
</tr>
<tr>
<td>History of peripheral arterial disease</td>
<td>0.49 (0.09, 0.89)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Model controls for differences in duration of the IVUS clinical trials. Baseline PAV, baseline and Δ non-HDLC, and Δ HDLC are reported per standard deviation. Other factors considered in the multivariable analysis included race (white/nonwhite), baseline BMI, history of MI, history of PCI, hypertension, smoking, baseline ACE inhibitor use, concomitant ACE use, baseline HDLC. Clinical trial was also controlled for as a random effect. Δ indicates change; ACE, angiotensin-converting enzyme; BMI, body mass index; CI, confidence interval; HDLC, high-density lipoprotein cholesterol; IVUS, intravascular ultrasound; MI, myocardial infarction; non-HDLC, non–high-density lipoprotein cholesterol; PAV, percent atheroma volume; and PCI, percutaneous coronary intervention.

### Table 4. Multivariable Linear Regression Model for Change in PAV (LDL-Adjusted)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Estimated β Coefficient (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PAV</td>
<td>−0.58 (−0.67, −0.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline LDL</td>
<td>0.40 (0.26, 0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ LDL</td>
<td>0.51 (0.36, 0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline triglycerides</td>
<td>0.49 (0.29, 0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ triglycerides</td>
<td>0.48 (0.20, 0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ HDLC</td>
<td>−0.14 (−0.23, −0.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.57 (0.36, 0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.02 (0.01, 0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>−0.27 (−0.46, −0.08)</td>
<td>0.006</td>
</tr>
<tr>
<td>History of peripheral arterial disease</td>
<td>0.49 (0.09, 0.89)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Model controls for differences in duration of the IVUS clinical trials. Baseline PAV, baseline and Δ LDL, and Δ HDLC are per standard deviation. Baseline and Δ triglycerides are log-transformed. Other factors considered in the multivariable analysis included race (white/nonwhite), baseline BMI, history of MI, history of PCI, hypertension, smoking, baseline ACE inhibitor use, concomitant ACE use, baseline HDLC. Clinical trial was also controlled for as a random effect. Δ indicates change; ACE, angiotensin-converting enzyme; BMI, body mass index; HDLC, high-density lipoprotein cholesterol; IVUS, intravascular ultrasound; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; PAV, percent atheroma volume; and PCI, percutaneous coronary intervention.
residual cardiovascular risk. These observations, in parallel with contemporary epidemiological and genetic data, provide a more compelling argument for non-HDLc to emerge as a primary therapeutic target for cardiovascular risk prevention, as well as providing mechanistic support for the antiatherosclerotic effects of TG-lowering strategies in patients with elevated TG levels.

Acknowledgments

We acknowledge the technical expertise of the Atherosclerosis Imaging Core Laboratory, Cleveland Clinic Coordinating Center for Clinical Research (CSR).

Disclosures

Dr Nicholls has received research support from InfraRedx, AstraZeneca, Resverlogix, Eli Lilly, Novartis, Pfizer, AstraZeneca, Resverlogix, and Boehringer Ingelheim. Dr Nicholls has received research support to perform clinical trials through Omthera, Amgen, CSL Behring, and Boehringer Ingelheim. Dr Nicholls SI. Exploring coronary atherosclerosis with intravascular imaging. Int J Cardiol. 2013;168:670–679. doi:10.1016/j.ijcard.2012.08.1026.


Despite effective low-density lipoprotein cholesterol lowering, a considerable portion of statin-treated individuals continue to experience subsequent cardiovascular events, indicative of their residual cardiovascular risk. Non–high-density lipoprotein cholesterol levels reflect the full burden of cholesterol transported in atherogenic lipoproteins, and genetic studies suggest a causal association between elevated triglyceride-rich lipoproteins and atherosclerosis.

The present analysis is the first to demonstrate that coronary disease progression seems more tightly linked with changes in non–high-density lipoprotein cholesterol compared with low-density lipoprotein cholesterol and that on-treatment triglyceride levels associate with coronary atheroma progression (and, thus, cardiovascular risk), especially when these levels exceed 200 mg/dL.

Achieved non–high-density lipoprotein cholesterol and triglyceride levels significantly modulated plaque progression–regression rates across broad categories of residual cardiovascular risk, including those with achieved low-density lipoprotein cholesterol levels <70 mg/dL.

These findings provide mechanistic support for the possible roles of non–high-density lipoprotein cholesterol and triglycerides to more definitively emerge as future therapeutic targets, especially in statin-treated patients.

Highlights