Relation Between Baseline and On-Treatment Lipid Parameters and First Acute Major Coronary Events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

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Background—The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) is the first primary-prevention study in a cohort with average total cholesterol (TC) and LDL cholesterol (LDL-C) and below-average HDL cholesterol (HDL-C). Treatment with lovastatin (20 to 40 mg/d) resulted in a 25% reduction in LDL-C and a 6% increase in HDL-C, as well as a 37% reduction in risk for first acute major coronary event (AMCE), defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. This article describes the relation between baseline and on-treatment lipid and apolipoprotein (apo) parameters and subsequent risk for AMCEs.

Methods and Results—With all available data from the entire 6605-patient cohort, a prespecified Cox backward stepwise regression model identified outcome predictors, and logistic regression models examined the relation between lipid variables and AMCE risk. Baseline LDL-C, HDL-C, and apoB were significant predictors of AMCE; only on-treatment apoB and the ratio of apoB to apoAI were predictive of subsequent risk; on-treatment LDL-C was not. When event rates were examined across tertiles of baseline lipids, a consistent benefit of treatment with lovastatin was observed.

Conclusions—Persons with average TC and LDL-C levels and below-average HDL-C may obtain significant clinical benefit from primary-prevention lipid modification. On-treatment apoB, especially when combined with apoAI to form the apoB/AI ratio, may be a more accurate predictor than LDL-C of risk for first AMCE. (Circulation. 2000;101:477-484.)

Key Words: lipids ● coronary disease ● prevention ● risk factors ● apolipoproteins

The benefit of modification of serum cholesterol has been confirmed in both primary- and secondary-prevention trials of individuals with hypercholesterolemia.1,2 In secondary prevention, studies have indicated that this benefit can be extended to coronary heart disease (CHD) patients who have mild to moderate elevations in serum total cholesterol (TC) and LDL cholesterol (LDL-C).3,4

In primary prevention, data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) extended the benefit to those with average TC and LDL-C concentrations who also have below-average HDL cholesterol (HDL-C).5 Although the AFCAPS/TexCAPS cohort was at lower CHD risk than cohorts in previous CHD primary-prevention trials, their level of risk was similar to that of a comparable US reference population from the third National Health and Nutrition Examination Survey (NHANES III), defined as men 45 to 73 years old and women 55 to 73 years old without prior history of CHD. In brief, after a mean follow-up of 5.2 years, lovastatin therapy reduced the risk for the first acute major coronary event (AMCE), defined as the composite end point of fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death, by 37% (P<0.001).5

In light of these findings, we were interested in examining the relation between baseline and on-treatment lipid param-
Ratio of TC to HDL-C was 3.23 and 3.33 mmol/L (125 to 129 mg/dL) were included when the LDL-C between 1.16 mmol/L (45 mg/dL) for men or ≤1.21 mmol/L (47 mg/dL) for women, and triglycerides ≤4.52 mmol/L (400 mg/dL). In addition, those with LDL-C between 1.16 mmol/L (45 mg/dL) for men or ≤1.21 mmol/L (47 mg/dL) for women, and triglycerides ≤4.52 mmol/L (400 mg/dL). In addition, those with LDL-C between 1.16 mmol/L (45 mg/dL) for men or ≤1.21 mmol/L (47 mg/dL) for women, and triglycerides ≤4.52 mmol/L (400 mg/dL). In addition, those with LDL-C between 1.16 mmol/L (45 mg/dL) for men or ≤1.21 mmol/L (47 mg/dL) for women, and triglycerides ≤4.52 mmol/L (400 mg/dL). In addition, those with LDL-C between 1.16 mmol/L (45 mg/dL) for men or ≤1.21 mmol/L (47 mg/dL) for women, and triglycerides ≤4.52 mmol/L (400 mg/dL).

A specified Cox backward stepwise regression model was performed to identify variables that were related to the risk for a first AMCE and served as a starting point for other analyses.

Methods
The trial design has been described in detail elsewhere.8 Figure 1 provides a summary of the study design. AFCAPS/TexCAPS was a randomized, double-blind, placebo-controlled primary-prevention trial with 6605 men and women and was conducted at 2 sites: Wilford Hall Medical Center at Lackland Air Force Base in San Antonio, Tex, and the University of North Texas Health Science Center in Fort Worth, Tex. All participants provided written informed consent, and the study protocol was approved by both institutional review boards.

Participant Recruitment and Follow-Up
Men (aged 45 to 73 years) and postmenopausal women (aged 55 to 73 years) who met the lipid entry criteria and had no prior history of or signs or symptoms of definite myocardial infarction, angina, claudication, cerebrovascular accident, or transient ischemic attack were eligible for participation. Lipid inclusion criteria were TC 4.65 mmol/L (180 to 254 mg/dL), LDL-C 3.36 to 4.91 mmol/L (130 to 190 mg/dL), HDL-C ≥1.16 mmol/L (45 mg/dL) for men or ≤1.21 mmol/L (47 mg/dL) for women, and triglycerides ≤4.52 mmol/L (400 mg/dL). In addition, those with LDL-C between 3.23 and 3.33 mmol/L (125 to 129 mg/dL) were included when the ratio of TC to HDL-C was >6.0.

Measurement of Lipid and Lipoprotein Components
Venous blood was collected after subjects had fasted for 12 to 14 hours, and it was allowed to coagulate for 1 to 2 hours at room temperature. For analysis of changes in lipids, frozen sera (−70°C) obtained immediately before the start of active treatment and at the year 1 visit (posttreatment) were assayed at a specialized lipid laboratory at Johns Hopkins University, Baltimore, Md. The laboratory was standardized for lipid and lipoprotein measurements through the Centers for Disease Control and Prevention–National Heart, Lung, and Blood Institute Lipid Standardization Program.9 All LDL-C values were calculated on the basis of the Friedewald estimation.10

End Point
AFCAPS/TexCAPS was designed and powered to investigate whether chronic lipid modification with lovastatin would decrease the rate of first AMCEs compared with placebo. The procedures for end-point adjudication were described in detail previously.8 Only the first end point for an individual patient was included in the analysis. In addition, participants who experienced an event in the first year of the study were excluded from the analyses of the relation of on-treatment lipids with AMCEs. Posttreatment samples from these participants were not analyzed, because we wished to avoid the statistical dilemma of using the year 1, or postevent, lipid measurements to predict the prior AMCE.

Statistical Analyses
Relation of Baseline Characteristics to Risk for an Event
A number of baseline demographic characteristics, as well as baseline lipid and apo parameters, were evaluated individually in a Cox regression model with treatment groups combined to examine their relation with the primary end point. The demographic and baseline characteristics tested were sex, age (in 5-year groups), race, diabetes mellitus, hypertension, obesity, smoking, drinking, amount of drinking, dietary compliance, exercise, marital status, education level, military versus civilian status, study site, prior therapy with calcium channel blockers, parental history of premature CHD, sibling history of premature CHD, and family (either parental or sibling) history of premature CHD. The baseline lipid and apo parameters tested were TC, LDL-C, HDL-C, triglycerides, LDL-C/ HDL-C, TC/HDL-C, apoAI, apoAII, apoB, and apoB/AI. The variables that showed a trend (P<0.20) were then evaluated in a Cox regression model with a backward stepwise strategy used to eliminate nonsignificant (P>0.05) parameters. As a final step, each significant factor was evaluated for its interaction with treatment one at a time in a model with all the significant main effects. This method is a modification of that described by Tukey.11 This analysis was planned before study unblinding.

Analysis of Event Rates Across Baseline Tertiles of Lipid Parameters
Primary end-point event rates (number of first AMCEs per 100 person-years at risk) were calculated by tertiles of baseline lipid parameters. In the calculation of case rates, the number of person-years contributed by each participant was the number of years measured from the date of randomization to the earliest of (1) the first occurrence of an AMCE or (2) the date of censoring. The date of censoring was the last date that complete end-point information was available for the participant. All analyses were performed according to the intention-to-treat principle. Summaries by tertiles were prespecified in the study protocol.

Logistic Regression Analyses of Baseline and On-Treatment Lipids and Apos and Events
Logistic regression models were examined to evaluate the relation of AMCEs to lipids and apoproteins measured at baseline and year 1 and the percent change from baseline at year 1. These models included treatment group, the lipid or apo parameter, and the interaction between treatment and the lipid/apo parameter, and it also included as covariates the demographic factors that were found to be associated with outcome in the Cox backward stepwise regression model described above. For percent change from baseline, models with and without the baseline value of the parameter as an additional covariate were examined. Probability values reported were from the main effects model (model without interaction) unless the interaction was significant (P<0.100). Logistic regression plots were from models with treatment groups evaluated separately.
Results

Relation of Baseline Characteristics to Risk for an Event

When the preplanned analysis of baseline demographic characteristics was first run, apoAI and apoB had not been assayed, and therefore the only lipid parameters considered were TC, LDL-C, HDL-C, triglycerides, TC/HDL-C, and LDL-C/HDL-C. The final model from this initial analysis included treatment group ($P < 0.001$), sex ($P < 0.001$), age ($P < 0.001$), hypertension ($P < 0.001$), premature family history of CHD ($P = 0.002$), smoking ($P < 0.001$), baseline LDL-C ($P = 0.029$), and baseline HDL-C ($P = 0.010$). For a 0.5 mmol/L ($=19$ mg/dL) increment in baseline LDL-C between individuals, there was a 16% (95% CI 2% to 32%) incremental risk for an AMCE; for a 0.125 mmol/L ($=5$ mg/dL) decrement in HDL-C between individuals, there was a 14% (95% CI 3% to 27%) incremental risk.

This analysis was repeated with the apo data when they became available. Baseline and 1-year, on-treatment concentrations of the lipid and apo parameters are reported in Table 1. With the inclusion of these baseline data, the final model again included treatment group ($P < 0.001$), sex ($P < 0.001$), age ($P < 0.001$), hypertension ($P < 0.001$), premature family history of CHD ($P = 0.002$), and smoking ($P < 0.001$). It also included marital status ($P = 0.0499$) (previously, marital status narrowly missed inclusion, with $P = 0.052$) and apoB/AI ratio ($P < 0.001$), which replaced LDL-C ($P = 0.513$) and HDL-C ($P = 0.517$), which were no longer significant in the second model. For a 0.25 increment in baseline apoB/apoAI ratio between individuals, there was a 36% (95% CI 16% to 59%) incremental risk for an AMCE.

Analysis of Event Rates Across Baseline Tertiles of Lipid Parameters

In AFCAPS/TexCAPS, risk reduction for the first AMCE was evident in all tertiles of baseline LDL-C (Figure 2). The placebo event rate appeared greatest for both the highest tertile of LDL-C and the lowest tertile of HDL-C (Figure 2). For both LDL-C and HDL-C tertiles, the magnitude of improvement with lovastatin within the tertiles suggests a trend; however, when these baseline lipids were tested as continuous variables in the previously described Cox models, the magnitude of benefit was independent of baseline LDL-C or HDL-C. Event rates as broken down by the LDL-C/HDL-C ratio likewise suggest benefit in each tertile of this parameter (Figure 2), with lovastatin-treated participants experiencing fewer events than placebo participants and with

<table>
<thead>
<tr>
<th>TABLE 1. Baseline and On-Treatment Lipid Concentrations*</th>
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</thead>
<tbody>
<tr>
<td>Lipid Parameter and Treatment Group</td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>TC, mmol/L</td>
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<tr>
<td>Lovastatin</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>LDL-C, mmol/L</td>
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<tr>
<td>Lovastatin</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>HDL-C, mmol/L</td>
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<td>Placebo</td>
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<tr>
<td>LDL-C/HDL-C</td>
</tr>
<tr>
<td>Lovastatin</td>
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<tr>
<td>Placebo</td>
</tr>
<tr>
<td>TG,‡ mmol/L</td>
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<tr>
<td>Lovastatin</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>Apo AI, g/L</td>
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<td>Lovastatin</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>Apo B, g/L</td>
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<tr>
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<td>Apo B/AI</td>
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<tr>
<td>Lovastatin</td>
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<tr>
<td>Placebo</td>
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</tbody>
</table>

TG indicates triglycerides.

*Based on data from Johns Hopkins laboratory.

‡All between-group differences are significant ($P < 0.001$).

Median TG values given.

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placebo participants in the higher tertiles at greater risk for an event.

Similar analyses of baseline apoB and apoAI concentrations support the above observations (Figure 3). Event rates were highest in participants in the highest tertile of apoB (the major apo of LDL and VLDL) and the lowest tertile of apoAI (a major apo of HDL). Furthermore, participants in the highest tertile for the apoB/AI ratio appeared to be at the greatest risk for an event (Figure 3).

**Logistic Regression Analyses of Baseline and On-Treatment Lipids and Apos and Events**

The probability value of various logistic regression models performed with baseline and 1-year, on-treatment lipid parameters are shown in Table 2. These models included as covariates those demographic and CHD risk factors found to be associated with outcome in the Cox backward stepwise regression model reported above, namely, treatment group, age, sex, smoking, hypertension, family history of premature CHD, and marital status. Interestingly, LDL-C and TC did not achieve significance as predictors of risk either at baseline or at year 1. Instead, baseline concentrations of HDL-C, apoAI, and apoB and the ratios of LDL-C/HDL-C, TC/HDL-C, and apoB/AI were significantly associated with the primary outcome. The value at year 1 was significantly associated with primary outcome only for apoAI, apoB, and the ratio of apoB/AI. For percent change from baseline, only apoAI had a significant relation with the primary outcome in the models with or without baseline apoAI. Percent change in apoB/AI was also significant when baseline apoB/AI was included in the model.

In Figure 4, logistic regression plots, adjusted for covariates, demonstrate a flattening of the risk curve for developing a primary end point in the lovastatin-treated group compared with the placebo group with respect to baseline HDL-C level (Figure 4a) and apoAI levels (Figure 4b). This difference
implies that lipid modification with lovastatin abolishes the excess risk for CHD associated with having a low HDL-C level at baseline. At year 1, there were inverse relations between the change in concentrations of apoAI (data not shown) and HDL-C (data not shown) and the subsequent risk for developing a primary end point among those treated with lovastatin, although only on-treatment apoAI achieved statistical significance as a predictor of outcome.

Figure 5 illustrates the effect of lowering LDL-C and apoB on subsequent risk. At baseline, there was a similar relation between LDL-C (data not shown) and apoB (data not shown) levels and the risk for developing a primary end point. However, at year 1, little relation \( (P = 0.162) \) between on-treatment LDL-C (Figure 5a) and risk for an AMCE was observed. On-treatment apoB (Figure 5b), on the other hand, proved to be a strong predictor of outcome \( (P < 0.001) \). The overlap of the regression lines for this parameter suggests a continuous relation between on-treatment apoB concentration and CHD risk, independent of treatment group. A similarly positive relation was observed with the on-treatment ratio of apoB/AI (Figure 6b).

**Discussion**

Analyses based on lipid parameters in the AFCAPS/TexCAPS cohort have yielded a number of interesting insights into lipid-based risk in this population. Most individuals with characteristics similar to the AFCAPS/TexCAPS cohort would not be recommended for lipid-modifying drug treatment and would be considered to be “at goal” with an LDL-C level \( < 4.14 \text{ mmol/L} \) (160 mg/dL). Treatment with lovastatin (20 to 40 mg/d) resulted in mean on-treatment LDL-C values of 2.96 mmol/L \( (114.6 \text{ mg/dL}) \) and HDL-C 1.02 mmol/L \( (39.3 \text{ mg/dL}) \) at year 1, as a result of a mean reduction in LDL-C of 25% and a mean increase in HDL-C of 6%. As previously reported, lovastatin-mediated changes in these lipids were associated with a 37% decrease in

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Value at Baseline</th>
<th>Value at Year 1</th>
<th>% Change From Baseline at Year 1</th>
<th>% Change From Baseline at Year 1</th>
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<td>LDL-C</td>
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<td>NS</td>
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<tr>
<td>ApoB/AI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>0.019</td>
</tr>
</tbody>
</table>

*Treatment group is included as a covariate in the models. All \( P \) values except for baseline apoA1 are from the main effects models, because interactions between treatment group and lipid parameter were not significant.

†Treatment group is modeled separately for lovastatin group only.

‡Baseline lipid value is included as a covariate in the model, and treatment group is modeled separately for lovastatin group only.

§Interaction between treatment group and apoA1 was significant \( (P = 0.043) \).

Figure 4. Logistic regression models adjusted for age, sex, marital status, hypertension, smoking, and family history of relation between AMCEs and (a) baseline HDL-C or (b) baseline apoAI, with 95% CI. Dashed line represents placebo; solid line, lovastatin.
AMCEs (defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death). These results, taken in aggregate with other large-scale clinical trials of HMG-CoA reductase inhibitors, demonstrate the benefit of reducing LDL-C and increasing HDL-C across a broad range of baseline cholesterol values. Somewhat more controversial is the relation between the degree of LDL-C reduction and achievable clinical benefit.

There is no evidence from AFCAPS/TexCAPS to support a threshold of benefit below which LDL-C reduction is not of clinical benefit. The magnitude of risk reduction was comparable across tertiles of baseline LDL-C, HDL-C, apo B and AI, and the ratio of apoB to apoAI. The absence of a threshold of benefit in a cohort consisting of relatively healthy men and women, middle-aged and older, at lower risk for CHD has important implications for primary prevention of coronary disease and supports the evidence from epidemiological studies.

Although the Cox regression model did show a significant relation between risk and baseline LDL-C, it was predictive only if baseline HDL-C was also included in the model (data not shown). The lack of a statistically significant association with the logistic regression models between baseline TC or LDL-C, as individual analyses, and CHD risk in this cohort may be explained in several ways. First, these participants would not have been considered at high risk for a coronary event based solely on the TC or LDL-C concentration. In fact, under current US guidelines, a fasting lipid profile would not have been recommended for 2137 (32%) of the AFCAPS/TexCAPS cohort with TC, 6.21 mmol/L (240 mg/dL). The Framingham risk score based on the AFCAPS/TexCAPS annual placebo event rate of ≈1% would define this population as “average” risk. It may be that within these ranges, TC and LDL-C are less specific for risk prediction. Second, in the logistic regression models, the baseline ratios of TC/HDL-C and LDL-C/HDL-C were significant predictors of outcome, which suggests that for a cohort with average LDL-C levels, LDL-C is not predictive unless considered in conjunction with HDL-C. In other words, HDL-C measurement is an essential component of risk assessment in these individuals.

Although on-treatment LDL-C failed to predict risk in the AFCAPS/TexCAPS cohort, on-treatment apoB proved to be a significant predictor of coronary risk. ApoB was in fact the single most significant and consistent lipid measurement to predict risk both at baseline and on treatment. In the logistic

Figure 5. Logistic regression models adjusted for age, sex, marital status, hypertension, smoking, and family history of relation between AMCE and (a) year 1 on-treatment LDL-C and (b) year 1 on-treatment apoB, with 95% CI. Dashed line represents placebo; solid line, lovastatin.

Figure 6. Logistic regression models adjusted for age, sex, marital status, hypertension, smoking, and family history of relation between AMCE and (a) ratio of baseline ApoB/AI and (b) ratio of year 1 on-treatment apoB/AI, with 95% CI. Dashed line represents placebo; solid line, lovastatin.
models, it was only slightly improved by the incorporation of a second measurement, apoAI, to form the apoB/AI ratio. The apoB/AI ratio was the best discriminator of baseline risk. When analyzed by tertiles for the placebo group, the ratio identified not only the highest-risk group, with roughly 1.6 events per 100 patient-years at risk, but also the lowest-risk group, with 0.8 events per 100 patient-years (Figure 3). To explore this finding further, we assessed the relative importance of lipids when analyzed on a paired basis in predicting event risk (data not shown), in an analysis similar to one performed in 4S. In this model, on-treatment LDL-C was not a significant primary predictor of risk, whereas on-treatment apoB and the ratio of on-treatment apoB to on-treatment apoAI were. When evaluated together with a second lipid parameter, only the percent change in apoAI added significant additional predictive information for these 2 measures. This suggests that the mechanism of the benefit associated with lovastatin-mediated changes in LDL-C and HDL-C may be, in part, a function of the changes in apoB and apoAI.

Another interesting observation was that of an apparent difference in risk between active treatment and placebo within the overlapping range of on-treatment LDL-C (Figure 6a). This appeared to be similar to findings from WOSCOPS. However, this apparent gap was markedly reduced when apoB was substituted for LDL-C and was totally eliminated when on-treatment apoB/AI ratio was assessed (Figure 5b and Figure 6b, respectively). It is well documented by many observational studies, including most recently the Quebec Cardiovascular Study, that apoB is a more powerful independent predictor of CHD than LDL-C. Although apoB is associated with known atherogenic lipoprotein species, such as IDL remnants and small, dense LDL (a distinct, highly atherogenic subpopulation), LDL has a variable cholesterol content. This variability in the composition of LDL has been hypothesized to explain the clinically observed variation in risk that appears to be independent of LDL-C. Our results suggest that it may be more valid to use apoB rather than LDL-C to assess the on-treatment effect of reducing the atherogenic burden, especially when LDL-C is not markedly elevated. In the present analysis, the use of the apoB/AI ratio, which takes into consideration most, if not all, of the beneficial changes in lipoprotein metabolism produced by statins, provides a remarkable continuum of risk, with no apparent threshold to benefit (Figure 6b). Furthermore, in the last few years, the measurement of apolipoprotein B and AI has become more widely available, lower in cost, and, because of international efforts, more standardized. These results suggest that reconsideration should be given to apo B and AI in risk assessment and that treatment goals based on apoB and/or the apoB/AI ratio be further explored in certain populations.

AFCAPS/TexCAPS has important implications for the optimal identification of persons at low to moderate CHD risk who may achieve significant clinical benefit with lipid modification. The study’s results confirm the importance of a treatment strategy that allows for individualization of dose to target an LDL-C goal of ≤3.36 mmol/L (130 mg/dL). Titrating enabled less-responsive persons to achieve clinically meaningful LDL-C reduction while exposing those who did not require titration to the lowest clinically effective dose and resulted in an overall relative benefit that was similar to what has been observed in studies of cohorts at much greater absolute risk. These findings suggest that it may be possible to refine primary-prevention guidelines by improving identification of at-risk individuals and populations who may benefit from lipid-modifying intervention. Specifically, consideration should be given to HDL-C and apo B and AI in risk assessment, and recommendations may be made for appropriate goals and the treatment that would most likely achieve clinical benefit.

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