

ORIGINAL ARTICLE

HDL Cholesterol, Very Low Levels of LDL Cholesterol, and Cardiovascular Events

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ABSTRACT

BACKGROUND

High-density lipoprotein (HDL) cholesterol levels are a strong inverse predictor of cardiovascular events. However, it is not clear whether this association is maintained at very low levels of low-density lipoprotein (LDL) cholesterol.

METHODS

A post hoc analysis of the recently completed Treating to New Targets (TNT) study assessed the predictive value of HDL cholesterol levels in 9770 patients. The primary outcome measure was the time to a first major cardiovascular event, defined as death from coronary heart disease, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. The predictive relationship between HDL cholesterol levels at the third month of treatment with statins and the time to the first major cardiovascular event was assessed in univariate and multivariate analyses and was also assessed for specific LDL cholesterol strata, including subjects with LDL cholesterol levels below 70 mg per deciliter (1.8 mmol per liter).

RESULTS

The HDL cholesterol level in patients receiving statins was predictive of major cardiovascular events across the TNT study cohort, both when HDL cholesterol was considered as a continuous variable and when subjects were stratified according to quintiles of HDL cholesterol level. When the analysis was stratified according to LDL cholesterol level in patients receiving statins, the relationship between HDL cholesterol level and major cardiovascular events was of borderline significance ($P=0.05$). Even among study subjects with LDL cholesterol levels below 70 mg per deciliter, those in the highest quintile of HDL cholesterol level were at less risk for major cardiovascular events than those in the lowest quintile ($P=0.03$).

CONCLUSIONS

In this post hoc analysis, HDL cholesterol levels were predictive of major cardiovascular events in patients treated with statins. This relationship was also observed among patients with LDL cholesterol levels below 70 mg per deciliter. (ClinicalTrials.gov number, NCT00327691.)

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POPULATION STUDIES HAVE CONSISTENTLY shown that high-density lipoprotein (HDL) cholesterol levels are a strong, independent inverse predictor of cardiovascular disease.¹⁻⁵ In the Framingham Heart Study, HDL cholesterol level was more potent as a risk factor for coronary heart disease than was the level of low-density lipoprotein (LDL) cholesterol.⁴ An analysis of data from four large studies concluded that each increase of 1 mg per deciliter (0.03 mmol per liter) in HDL cholesterol is associated with a decrease of 2 to 3% in the risk of future coronary heart disease.⁶

Intervention trials using statins to lower LDL cholesterol have consistently shown substantial reductions in major cardiovascular events in the treated groups.⁷⁻¹³ Furthermore, the magnitude of the reduction in events is a function of the extent of LDL cholesterol lowering, with each decrease of 40 mg per deciliter (1.0 mmol per liter) in LDL cholesterol corresponding to a 24% reduction in major cardiovascular events.¹³ However, in all the statin trials, there remains a substantial residual risk in the treated groups.

One explanation for this may relate to the presence of a low baseline level of HDL cholesterol, which has been shown in several trials to remain predictive of major cardiovascular events, even during treatment with statins.¹⁴ In a recent pooled analysis of four trials of statins, the moderate increase in HDL cholesterol levels seen with these drugs correlated with regression of coronary atherosclerosis.¹⁵ These findings have added support to the proposition that HDL cholesterol levels should be considered as therapeutic targets independent of the lowering of LDL cholesterol levels. However, it could also be argued that if LDL cholesterol levels are reduced to very low levels, low HDL cholesterol levels may no longer be relevant. To date, this view has remained untested.

In the Treating to New Targets (TNT) trial (ClinicalTrials.gov number, NCT00327691), 2661 subjects achieved an LDL cholesterol level below 70 mg per deciliter (1.8 mmol per liter) while receiving statin therapy.¹⁶ This target originally was proposed as an optional treatment goal in very-high-risk patients with coronary heart disease in an update to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines,¹⁷ and it has now been proposed by the American Heart Association and

the American College of Cardiology guidelines as a reasonable target for therapy in patients with coronary heart disease or other forms of atherosclerotic disease.¹⁸

This post hoc analysis of the TNT trial examined the relationship between the frequency of major cardiovascular events and HDL cholesterol levels in a population of patients with clinically evident coronary heart disease who were being treated with statins. It also investigated whether any observed relationship was maintained when LDL cholesterol was reduced below 70 mg per deciliter.

METHODS

The TNT trial was a randomized, double-blind, parallel-group, multicenter clinical trial, the design of which has been described in detail previously.^{16,19} The trial was sponsored by Pfizer and developed by the steering committee (see the Appendix) in collaboration with the sponsor. The trial data were retained by the sponsor.

The steering committee proposed and designed the analysis of HDL cholesterol data. The analysis was performed by one of the authors, who was employed by the sponsor. All the data and analyses were made available to the steering committee without restriction. All steering-committee members participated in the writing and critical appraisal of the manuscript. The steering committee assumes overall responsibility for the integrity of the data, the accuracy of the data analyses, and the completeness of the material reported.

PATIENT POPULATION

Subjects eligible for inclusion were men and women aged 35 through 75 years with clinically evident coronary heart disease, defined as a previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic coronary heart disease, or a previous coronary revascularization procedure. The major exclusion criteria were statin hypersensitivity, current liver disease, nephrosis, pregnancy, uncontrolled risk factors for coronary heart disease, a coronary heart disease event or revascularization procedure within the preceding month, congestive heart failure, unexplained creatine kinase levels greater than six times the upper limit of normal, any non-skin cancer, malignant melanoma, other survival-limiting disease, and immunosuppressive treatment.

STUDY PROTOCOL

Any previously prescribed lipid-regulating drugs were discontinued at screening, and all subjects underwent a washout period of 1 to 8 weeks (8 weeks for those who had previously received lipid-regulating drugs and 1 week for those who had not). To ensure that all subjects at baseline achieved LDL cholesterol levels consistent with then-current guidelines for the treatment of stable coronary heart disease, patients with LDL cholesterol levels between 130 and 250 mg per deciliter (3.4 and 6.5 mmol per liter) and triglyceride levels of 600 mg per deciliter (6.8 mmol per liter) or less entered an 8-week open-label period with 10 mg of atorvastatin per day. At the end of the run-in phase (baseline), subjects with a mean LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) (determined 4 weeks and 2 weeks before randomization) were randomly assigned to double-blind therapy with 10 mg or 80 mg of atorvastatin per day, as previously described.¹⁶ The primary efficacy outcome measure was the time to first occurrence of a major cardiovascular event, defined as death from coronary heart disease; nonfatal non-procedure-related myocardial infarction; resuscitation after cardiac arrest; or fatal or nonfatal stroke.

STATISTICAL ANALYSIS

For this study, the 9770 subjects in the TNT trial for whom HDL cholesterol data were available were stratified into quintiles based on their HDL cholesterol levels determined at month 3 of the double-blind treatment phase. The baseline clinical characteristics of these five patient groups were compared.

Cox regression models were fitted to determine the expected 5-year risk of a first major cardiovascular event from nonparametric survivor function estimates determined by quintile of HDL cholesterol level at month 3 of the trial, unadjusted and after adjustment for important covariates. The covariates considered in the analyses were sex, age, smoking status, body-mass index, systolic blood pressure, fasting glucose level, LDL cholesterol level, triglyceride level, ratio of apolipoprotein B to apolipoprotein A-I, LDL cholesterol and triglyceride levels at month 3 of the trial, and the presence or absence of a history of diabetes, myocardial infarction, cardiovascular disease, and hypertension.

A stratified regression analysis was performed to determine the interaction between HDL and LDL cholesterol levels in patients receiving statins, using specific LDL cholesterol cutoff points (<70, 70 to 100, and >100 mg per deciliter [<1.8 , 1.8 to 2.6 , and >2.6 mmol per liter]). This analysis was adjusted for treatment, sex, age as a continuous variable, smoking status, body-mass index, systolic blood pressure, fasting glucose level, the triglyceride level at month 3, and the presence or absence of a history of diabetes, myocardial infarction, cardiovascular disease, and hypertension. A separate analysis of patients receiving statins in the lowest LDL stratum (<70 mg per deciliter) was performed according to quintile of HDL cholesterol level during statin therapy, likewise adjusted for the variables listed above.

The relationships between the quintile of the ratio of LDL cholesterol to HDL cholesterol at month 3, the quintile of the ratio of total cholesterol to HDL cholesterol at month 3, and the incidence of major cardiovascular events were also summarized overall and according to treatment group. Finally, the relationship between continuous HDL cholesterol levels (both at baseline and at 3 months) and time to a first major cardiovascular event was determined in univariate and multivariate Cox regression models, including all covariates listed above as well as treatment assignment.

RESULTS

BASELINE CHARACTERISTICS

The baseline characteristics and lipid levels of the subjects in each of the quintiles of HDL cholesterol level during statin treatment (month 3) are shown in Table 1. Subjects with higher HDL cholesterol levels were older, more likely to be female, and leaner than those with lower HDL cholesterol levels. Current smokers were less common in the higher quintiles of HDL cholesterol levels, and subjects with higher HDL cholesterol levels were more likely to have never smoked. The proportion of past smokers was similar in all quintiles.

As expected, subjects with higher HDL cholesterol levels during statin treatment (month 3) had higher concentrations of apolipoprotein A-I (a structural component of HDL) and lower plasma triglyceride levels. The concentration of apolipoprotein B (a structural component of the non-

Table 1. Baseline Characteristics of the Patients According to Quintile of HDL Cholesterol Level at Month 3.*

Characteristic	Quintile 1, <38 mg/dl (N=1710)	Quintile 2, 38 to <43 mg/dl (N=1981)	Quintile 3, 43 to <48 mg/dl (N=1959)	Quintile 4, 48 to <55 mg/dl (N=1998)	Quintile 5, ≥55 mg/dl (N=2122)
No. receiving 10 mg of atorvastatin	834	937	989	1043	1093
No. receiving 80 mg of atorvastatin	876	1044	970	955	1029
Male sex — %	91.5	89.4	83.7	78.0	65.0
White race — %†	94.0	93.7	94.1	94.2	94.4
Age — yr	58.9±9.1	59.9±8.8	61.2±8.7	61.6±8.6	62.9±8.4
Age ≥65 yr — %	29.4	33.3	38.4	40.7	46.7
Body-mass index‡	29.9±4.7	29.1±4.9	28.6±4.4	28.0±4.1	27.2±4.3
Never smoked — no. (%)	317 (18.5)	419 (21.2)	486 (24.8)	505 (25.3)	561 (26.4)
Former smoker — no. (%)	1041 (60.9)	1251 (63.1)	1239 (63.2)	1291 (64.6)	1353 (63.8)
Current smoker — no. (%)	352 (20.6)	311 (15.7)	234 (11.9)	202 (10.1)	208 (9.8)
Lipids — mg/dl§					
LDL cholesterol	96.7±17.7	97.3±17.4	97.6±17.2	98.4±17.6	97.2±17.8
HDL cholesterol	35.7±4.5	41.1±4.6	45.2±4.8	50.4±5.8	61.5±10.1
Total cholesterol	169.2±24.1	171.3±24.0	172.1±22.6	176.4±22.8	183.1±23.0
Total triglycerides	185.6±81.7	166.1±76.5	146.7±63.9	138.7±59.5	122.0±54.1
Apolipoprotein A-I	123.1±14.9	134.1±14.8	142.4±15.4	152.9±17.7	173.1±24.1
Apolipoprotein B	116.2±19.5	113.3±19.3	110.6±18.5	109.8±18.7	106.4±18.7
Cardiovascular history — no. (%)					
Myocardial infarction	1077 (63.0)	1202 (60.7)	1141 (58.2)	1128 (56.5)	1150 (54.2)
Coronary-artery bypass grafting	855 (50.0)	972 (49.1)	921 (47.0)	887 (44.4)	916 (43.2)
Coronary angioplasty	921 (53.9)	1071 (54.1)	1068 (54.5)	1083 (54.2)	1145 (54.0)
Cerebrovascular accident	100 (5.8)	114 (5.8)	94 (4.8)	101 (5.1)	95 (4.5)
Angina	1402 (82.0)	1618 (81.7)	1621 (82.7)	1607 (80.4)	1715 (80.8)
Peripheral vascular disease	248 (14.5)	238 (12.0)	229 (11.7)	208 (10.4)	222 (10.5)
Hypertension	973 (56.9)	1060 (53.5)	1069 (54.6)	1060 (53.1)	1127 (53.1)
Arrhythmia	347 (20.3)	327 (16.5)	379 (19.3)	355 (17.8)	380 (17.9)
Congestive heart failure	177 (10.4)	169 (8.5)	145 (7.4)	127 (6.4)	134 (6.3)
Diabetes	363 (21.2)	338 (17.1)	286 (14.6)	256 (12.8)	224 (10.6)

* Plus-minus values are means ±SD.

† Race was determined by the investigator.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ To convert values for LDL, HDL, and total cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

HDL lipoproteins) declined slightly with increasing HDL cholesterol levels ($P<0.001$). The prevalence of diabetes in the lowest quintile of HDL cholesterol levels was double that in the highest quintile. There were no significant differences in any of these baseline characteristics between the two atorvastatin treatment groups within each HDL cholesterol group.

CARDIOVASCULAR EVENTS ACCORDING TO QUINTILE OF HDL CHOLESTEROL LEVEL

The expected 5-year risk of major cardiovascular events was determined for each quintile of HDL cholesterol level in patients receiving statins across the entire TNT trial cohort. In the univariate model, the event rate was reduced by 40% in the highest quintile relative to the lowest. When the anal-

ysis included adjustments for covariates (Fig. 1A), the quintile of HDL cholesterol level remained a significant predictor of major cardiovascular events, with a reduction in major cardiovascular events from 9.5% in the lowest quintile to 7.1% in the highest quintile, a 25% reduction in risk (hazard ratio, 0.75; 95% confidence interval [CI], 0.60 to 0.95). The risk of major cardiovascular events differed significantly across HDL cholesterol quintiles ($P=0.04$).

The relationship between HDL cholesterol levels in patients receiving statins and the frequency of major cardiovascular events seen in the overall cohort was also apparent in each of the two atorvastatin treatment groups. The incidence of major cardiovascular events was substantially lower in the group receiving 80 mg of atorvastatin per day than in the group receiving 10 mg per day in all quintiles. However, in each treatment group, the frequency of major cardiovascular events increased with decreasing levels of HDL cholesterol (Fig. 1B). After adjustment for covariates, among subjects assigned to 10 mg of atorvastatin, those in the highest quintile were significantly less likely to have a major cardiovascular event than those in the lowest quintile (hazard ratio, 0.71; 95% CI, 0.52 to 0.96). In subjects assigned to 80 mg of atorvastatin, the difference in cardiovascular risk between the highest and the lowest quintile did not reach significance (hazard ratio, 0.81; 95% CI, 0.58 to 1.14).

EFFECT OF LDL CHOLESTEROL LEVEL

We performed a stratified regression analysis to determine the interaction between HDL and LDL cholesterol levels in patients receiving statins. In a multivariate model (Fig. 2A), the quintile of HDL cholesterol level was of borderline significance as a predictor of major cardiovascular events ($P=0.05$), with no evidence of interaction with the quintile of LDL cholesterol level ($P=0.67$). The hazard ratios and 95% confidence intervals for quintiles 2 through 5 of HDL cholesterol level (with quintile 1 as a reference) were 1.00 (95% CI, 0.82 to 1.21), 0.80 (95% CI, 0.65 to 0.99), 0.92 (95% CI, 0.74 to 1.13) and 0.75 (95% CI, 0.60 to 0.95).

A separate analysis was conducted to evaluate the influence of HDL cholesterol on outcome among subjects in the lowest LDL cholesterol stratum (<70 mg per deciliter). In this group, according to multivariate analysis (Fig. 2B), the risk of a major cardiovascular event differed significantly

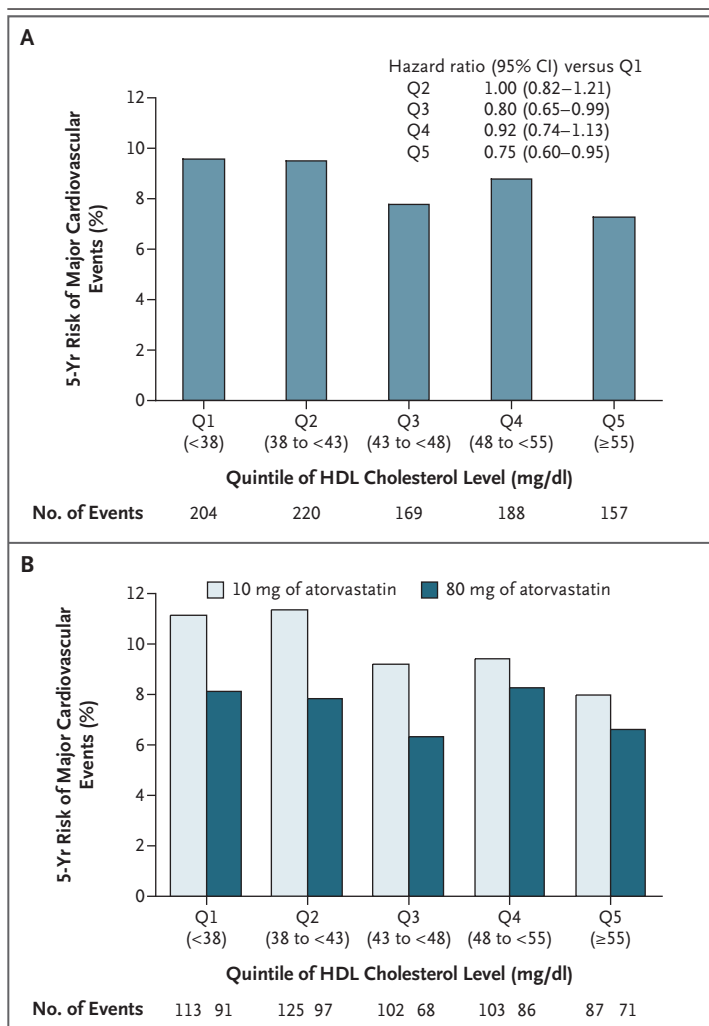
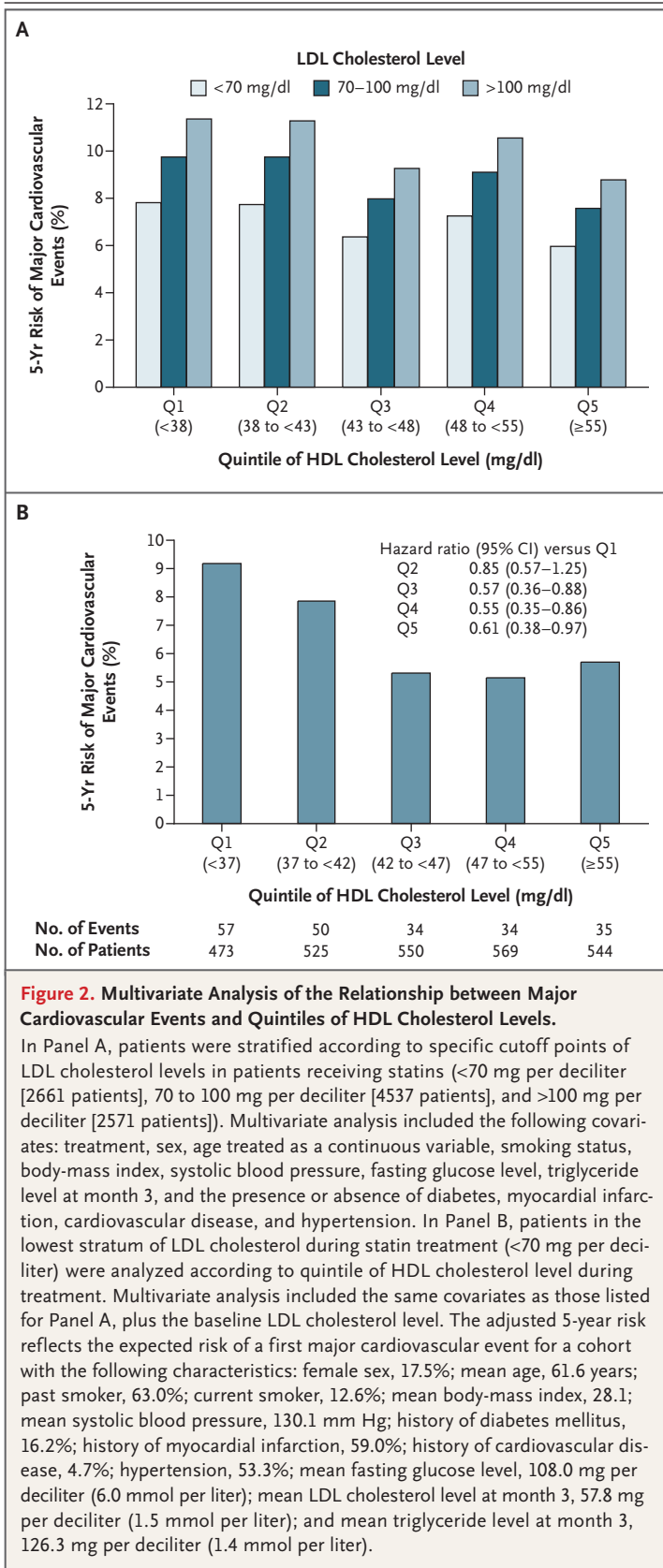


Figure 1. Multivariate Analysis of the Relationship between HDL Cholesterol Levels at Month 3 and the Risk of Major Cardiovascular Events.

Panel A shows the results for all patients. Quintile 1 is the reference group. The adjusted 5-year risk reflects the expected risk of a first major cardiovascular event for a cohort with the following characteristics: female sex, 19.0%; mean age, 61.0 years; past smoker, 63.2%; current smoker, 13.4%; mean body-mass index, 28.5; mean systolic blood pressure, 130.7 mm Hg; history of diabetes mellitus, 15.0%; history of myocardial infarction, 58.3%; history of cardiovascular disease, 5.2%; hypertension (systolic blood pressure, >140.0 mm Hg or patient receiving antihypertensive therapy), 54.1%; mean fasting glucose level, 107.7 mg per deciliter (6.0 mmol per liter); mean LDL cholesterol level at month 3, 85.8 mg per deciliter (2.2 mmol per liter); and mean triglyceride level at month 3, 140.1 mg per deciliter (1.6 mmol per liter). Panel B shows the results for the 10-mg and 80-mg atorvastatin groups. The lipid levels at month 3 in the 10-mg atorvastatin group were 98.9 mg of LDL cholesterol per deciliter (2.6 mmol per liter) and 151.8 mg of triglycerides per deciliter (1.7 mmol per liter). The lipid levels at month 3 in the 80-mg atorvastatin group were 72.6 mg of LDL cholesterol per deciliter (1.9 mmol per liter) and 128.2 mg of triglycerides per deciliter (1.4 mmol per liter). To convert values for HDL cholesterol to millimoles per liter, multiply by 0.02586.



among quintiles of HDL cholesterol levels ($P=0.03$). Subjects in the highest HDL cholesterol quintile had a lower risk of major cardiovascular events than subjects in the lowest quintile (hazard ratio, 0.61; 95% CI, 0.38 to 0.97).

RATIOS OF LDL CHOLESTEROL AND TOTAL CHOLESTEROL TO HDL CHOLESTEROL

The ratio of LDL cholesterol to HDL cholesterol at month 3 of the trial was also highly predictive of major cardiovascular events. There were major differences at the extremes: the event rate of 5.8% in subjects with the lowest ratio was less than half that in subjects with the highest ratio (13.5%). The ratio of LDL cholesterol to HDL cholesterol among patients receiving statins (month 3) remained highly predictive ($P=0.006$) of major cardiovascular events, even after adjustment (Fig. 3A). Subjects in the quintile with the highest ratio of LDL cholesterol to HDL cholesterol had a significantly greater risk of major cardiovascular events than did subjects in the lowest quintile (hazard ratio, 1.82; 95% CI, 1.32 to 2.51).

The ratio of total cholesterol to HDL cholesterol at month 3 was also predictive of major cardiovascular events (Fig. 3B). After adjustment, subjects in the quintile with the highest ratio were at significantly greater risk of major cardiovascular events than were those in the quintile with the lowest ratio, with a hazard ratio after adjustment for potential confounders of 1.72 (95% CI, 1.26 to 2.35).

CONTINUOUS HDL CHOLESTEROL LEVELS

The risk of a major cardiovascular event was also determined for each increment of 1 mg per deciliter (0.03 mmol per liter) in HDL cholesterol level at baseline and during statin treatment (Table 2). In a model adjusted for covariates, an increase of 1 mg per deciliter in the HDL cholesterol level at month 3 could be expected to reduce the risk of major cardiovascular events by 1.1% ($P=0.003$) (Table 2).

In the multivariate analysis, the relationship between baseline HDL cholesterol level and the risk of major cardiovascular events was almost identical to that observed between HDL cholesterol level and the risk of major cardiovascular events during statin treatment. However, inclusion of the baseline ratio of apolipoprotein B to apolipoprotein A-I in the analysis model reduced the predictive relationship to nonsignificance ($P=0.46$).

Interaction tests indicated that relationships between HDL cholesterol levels at baseline or during statin treatment and the risk of major cardiovascular events did not depend on sex ($P=0.11$ for baseline levels, $P=0.34$ for levels during statin treatment), age ($P=0.75$ for baseline levels, $P=0.31$ for levels during statin treatment), smoking status ($P=0.55$ for baseline levels, $P=0.64$ for levels during statin treatment), body-mass index ($P=0.13$ for baseline levels, $P=0.09$ for levels during statin treatment), or any of the other covariates considered in the analysis (all $P>0.10$ for levels at baseline and during statin treatment).

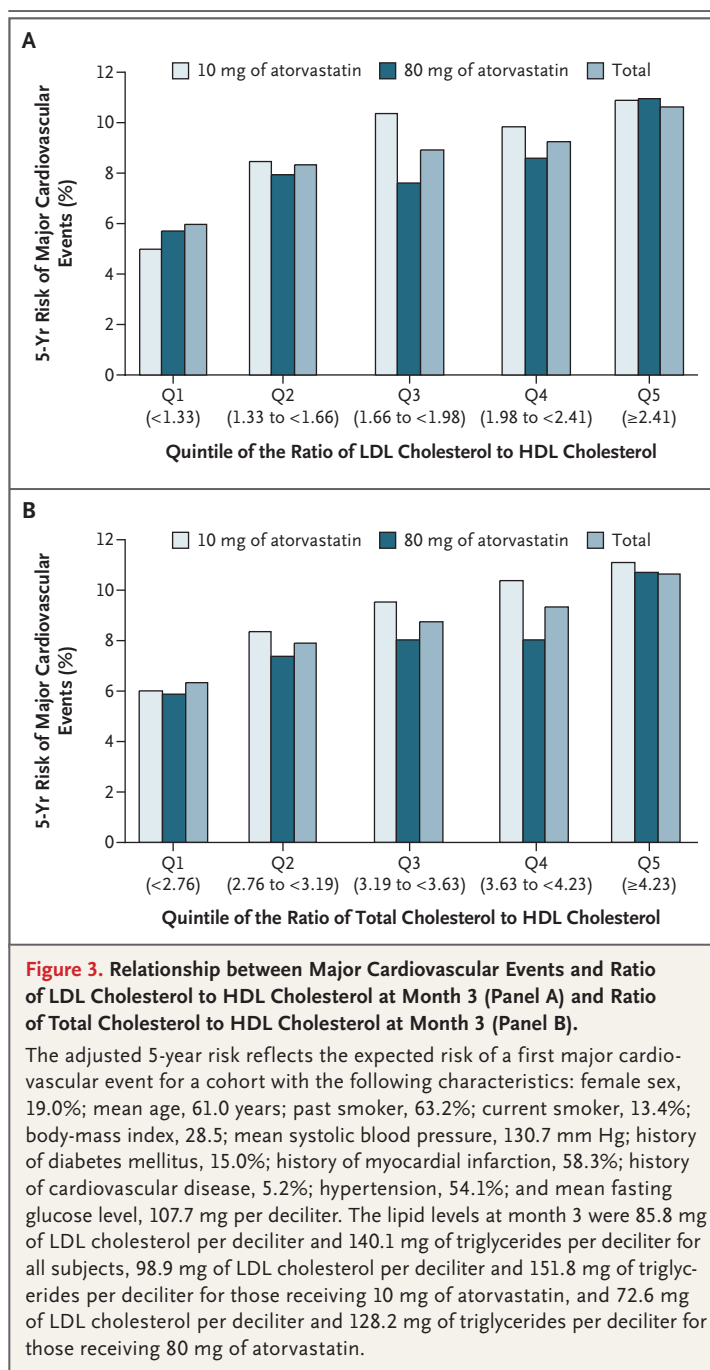
DISCUSSION

It has long been known that a low level of HDL cholesterol is a powerful predictor of increased cardiovascular risk,¹⁻⁶ but it has not been clear whether a low HDL cholesterol level would remain a significant risk factor in people whose LDL cholesterol was reduced to very low levels. Indeed, it has been argued hypothetically that if the LDL cholesterol level were reduced sufficiently, the level of HDL cholesterol might become irrelevant.

In this post hoc analysis from the TNT trial, HDL cholesterol level was a significant predictor of major cardiovascular events across the entire study cohort, even after all other baseline risk factors, including baseline LDL cholesterol level, had been taken into account. This effect was more pronounced in the analyses using HDL cholesterol level as a continuous variable than in those using quintiles of HDL cholesterol levels at month 3 of the trial, a result suggesting that outlier HDL cholesterol levels may have had an important role in the relationship we observed.

The effect of LDL cholesterol levels during statin treatment on the predictive value of HDL cholesterol was examined. After adjustment for covariates, the predictive value of HDL cholesterol levels was of borderline significance, a result consistent with a suggestion that in patients with coronary heart disease, higher HDL cholesterol levels may offset the increased risk associated with higher LDL cholesterol levels.

In a further analysis, we examined the relationship between the quintile of HDL cholesterol level during statin treatment with risk in those patients in the lowest stratum of LDL cholesterol level (<70 mg per liter). This analysis demonstrated that even among patients in this very low LDL cholesterol stratum, the risk of major cardiovas-



cular events was reduced in those with higher rather than lower HDL cholesterol levels.

Given that HDL and LDL cholesterol levels during statin treatment were both independently predictive of major cardiovascular events across the whole range of HDL and LDL cholesterol levels in this analysis, it was not surprising to find that the ratio of LDL to HDL cholesterol was also

Table 2. Relationship between HDL Cholesterol Levels and the Risk of Major Cardiovascular Events.

Variable	No. of Subjects	No. of Events	Relative Risk (95% CI)*	P Value
Baseline HDL cholesterol†				
Model 1	9956	974	1.1 (0.4 to 1.8)	0.002
Model 1 and baseline ratio of apolipoprotein B to apolipoprotein A-I	9917	971	0.4 (–0.7 to 1.5)	0.46
Model 2‡	9732	938	1.1 (0.4 to 1.7)	0.003

* The relative risk is for changes in HDL cholesterol levels in increments of 1 mg per deciliter.

† Model 1 is adjusted for treatment, sex, age, smoking status, body-mass index, systolic blood pressure, baseline LDL cholesterol level, baseline triglyceride level, glucose level measured after an overnight fast, and the presence or absence of a history of diabetes, myocardial infarction, cardiovascular disease, and hypertension.

‡ Model 2 is for HDL cholesterol levels at month 3 of the trial and is adjusted for treatment, sex, age, smoking status, body-mass index, systolic blood pressure, fasting glucose level, LDL cholesterol level at month 3, triglyceride level at month 3, and the presence or absence of a history of diabetes, myocardial infarction, cardiovascular disease, and hypertension.

highly predictive of the risk of major cardiovascular events. A similar result was observed for the ratio of total cholesterol to HDL cholesterol. These results are consistent with previous studies.²⁰⁻²³

There are several limitations of this study that should be considered when evaluating our findings. The groups of patients defined by quintile of HDL cholesterol level were not similar with respect to other cardiovascular risk factors (Table 1), and there may have been other differences that were not evaluated but that could have influenced the results of the analysis. We did not measure waist circumference or insulin levels in our study population, and thus we cannot determine to what degree the observed effect of HDL cholesterol level may be due to the coincidence of a low HDL cholesterol level with the metabolic syndrome. This relationship is suggested in our data by the fact that most of our study subjects who had low HDL cholesterol levels were also obese and had elevated plasma triglyceride levels.

In summary, this analysis from the TNT trial evaluated the effect of HDL cholesterol levels in patients with clinically evident coronary heart disease who were receiving statin therapy to reduce LDL cholesterol levels. Across the entire study cohort in multivariate analysis, HDL cholesterol levels were a significant inverse predictor of subsequent major cardiovascular events. When

the effect of the LDL cholesterol level achieved in patients receiving therapy was taken into account, the role of HDL cholesterol was less marked, though still of borderline significance. The relationship remained significant even in patients whose LDL cholesterol level was less than 70 mg per deciliter.

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