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Determinants of Residual Risk in Secondary Prevention Patients Treated with High-Versus Low-Dose Statin Therapy: The Treating to New Targets (TNT) Study

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Abstract

Background—Cardiovascular events occur among statin-treated patients, albeit at lower rates. Risk factors for this "residual risk" have not been studied comprehensively. We aimed to identify determinants of this risk above and beyond lipid-related risk factors.

Methods and Results—9,251 coronary patients with LDL cholesterol<130 mg/dL randomized to double-blind atorvastatin 10 or 80 mg/day in the Treating to New Targets (TNT) study had complete on-treatment 1-year lipid data. Median follow-up was 4.9 years. The primary endpoint was major cardiovascular events (n=729): coronary death, non-fatal myocardial infarction, resuscitation after cardiac arrest, or fatal or non-fatal stroke. Multivariable determinants of increased risk were older age (adjusted hazard ratio 1.13 per 1-SD [8.8 years], 95% CI 1.04–1.23), increased body-mass index (BMI) (1.09, 1.02–1.17 per 4.5 kg/m^2), male gender (1.33, 1.07–1.65), hypertension (1.38, 1.17–1.63), diabetes (1.33, 1.11–1.60), baseline apolipoprotein B (1.19, 1.11–1.28 per 19 mg/dL) and blood urea nitrogen (1.10, 1.03–1.17 per 4.9 mg/dL), in addition to current smoking, prior cardiovascular disease, and calcium channel blocker use. Determinants of decreased risk were high-dose statin (0.82, 0.70–0.94), aspirin use (0.67, 0.56–0.81), and baseline apolipoprotein A-I (0.91, 0.84–0.99 per 25 mg/dL). On-treatment 1-year lipids or apolipoproteins were not additionally associated with risk in multivariable models. Known baseline variables performed moderately well in discriminating future cases from non-cases (Harrell's c-index=0.679).

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Conclusions—Determinants of residual risk in statin-treated secondary prevention patients included lipid-related and non-lipid factors such as baseline apolipoproteins, increased BMI, smoking, hypertension, and diabetes. A multi-faceted prevention approach should be underscored to address this risk.

Clinical Trial Registration Information—http://clinicaltrials.gov; Unique identifier: NCT00327691

Keywords

apolipoproteins; risk factors; risk prediction; secondary prevention

Statins are the most widely used lipid-lowering agents and the standard of care for individuals with or at high-risk for cardiovascular disease.[1, 2] It is currently estimated that 1 out of every 8 US adults are treated with lipid lowering therapy, mostly statins.[3] This number is expected to increase, since a large proportion of US adults remain untreated despite meeting guideline recommendations for therapy, including almost two-thirds of individuals at high cardiovascular risk.[3]

Current guidelines focus on low-density-lipoprotein (LDL) cholesterol lowering as the primary target of therapy, tailoring the level of optimal LDL cholesterol reduction to the individual's level of risk.[1] However, cardiovascular risk among statin-treated individuals remains high and has been termed "residual risk". Results from a meta-analysis of statin trials involving 90,056 individuals found that the rate of a major cardiovascular event (MCVE) occurring during 5 years of follow-up among statin-treated patients was 21.7% (1 in 5) for individuals with prior cardiovascular disease and 9.5% (1 in 10) for those without prior disease.[4, 5] Even after achieving low LDL cholesterol (70–100 mg/dL), residual risk was reduced but remained high in the Treating to New Targets (TNT) trial, with 8.7% of the group allocated to atorvastatin 80 mg experiencing a major event over a 5-year period.[6] Thus, there are factors other than LDL cholesterol lowering that determine risk.

The mechanisms underlying this residual risk are uncertain. Identification of these factors is important for more effective tailoring of risk reduction strategies to match the individual level of risk and for development of new treatment targets. This analysis of the TNT study aimed to identify clinical determinants of residual risk by examining the effect of various clinical and lipid-related risk factors among patients with stable coronary disease treated to low LDL cholesterol targets. A secondary aim was to evaluate differences in residual risk according to high- versus low-dose statin therapy.

Methods

Study population

The TNT design has been previously published.[6, 7] TNT was a multi-center clinical trial that randomized 10,001 men and women aged 35 to 75 years with stable coronary disease (previous myocardial infarction, previous or present angina with objective evidence of atherosclerotic coronary disease, or previous coronary revascularization procedure) in a parallel-group double-blinded treatment with atorvastatin 80 or 10 mg/day.[6, 7] At the screening visit, previously prescribed lipid-lowering drugs were discontinued for at least 6 weeks prior to an open-label 8 week run-in period with atorvastatin 10 mg daily. Patients with triglycerides >600 mg/dl (6.8 mmol/L) after discontinuation of previous lipid-lowering therapy were excluded. At the end of an open-label 8 week run-in with atorvastatin 10 mg/day, patients with mean LDL cholesterol<130 mg/dL (3.4 mmol/L) were randomized to double-blind therapy with atorvastatin 80 or 10 mg/day. In addition to the inclusion and

exclusion criteria of the TNT trial as previously published,[6] individuals were eligible for this analysis if they had complete 1-year lipid and apolipoprotein measurements and did not experience a MCVE event or death in year 1, resulting in 9,251 individuals for this analysis.

Assessment of clinical and laboratory factors

At the screening visit, an informed consent was signed, demographic characteristics were assessed, vital signs were measured, all concomitant medications were documented, and a medical history was recorded. Metabolic syndrome was defined according to the National Cholesterol Education Program's 3rd Adult Treatment Panel (ATP-III) definition.[8] A body-mass index (BMI) of 28 kg/m^2 was used instead of waist circumference which was not assessed at screening.

Baseline and 1-year measurements were performed on fasting blood samples as previously described.[2, 9] All baseline measurements were performed on 10 mg of atorvastatin at the end of an 8-week open label run-in. Concentrations of total cholesterol, HDL cholesterol, and triglycerides were quantified by standard enzymatic techniques. LDL cholesterol was calculated with the Friedewald formula when triglycerides were <400 mg/dL.[10] For triglycerides ≥400 mg/dL, LDL cholesterol was measured by ultracentrifugation. Concentrations of apolipoprotein B and A-I were measured by immunonephelometry (Behring Nephelometer BNII, Marburg, Germany).[2, 9] Other laboratory measurements included white blood cells, uric acid, creatinine, blood urea nitrogen and lactate dehydrogenase.

Assessment of outcomes

Participants were followed for a median of 4.9 years. The primary endpoint was a composite endpoint of MCVE defined as coronary death, nonfatal myocardial infarction, resuscitated cardiac arrest, and fatal or nonfatal stroke. For this analysis, we also examined the expanded secondary endpoint of MCVE plus death, documented angina or arterial revascularization. An independent endpoints committee adjudicated all potential endpoints in a blinded fashion.

Statistical analyses

Summary statistics were calculated according to the occurrence of the primary or secondary endpoint. Candidate variables that could be related to residual risk were selected *a priori* based on the prior literature and known risk factors. Statistical tests for outcomes were performed according to intention-to-treat on all subjects who survived to year 1 without the endpoint occurring and who also had complete year 1 lipid and apolipoprotein data. Year 1 was chosen because on-treatment lipids and apolipoproteins were part of the major predictor variables in the analysis and this was the first time-point at which a complete panel of lipids and apolipoproteins was measured. The association of each of the candidate variables in relation to the risk of primary (or secondary) endpoint was assessed by univariable Cox proportional hazard models that calculated the hazard ratios (HRs), 95% confidence intervals (CIs), and the χ^2 statistics.

Then, also on an *a priori* basis, we grouped together a set of variables that are the traditional risk factors of age, gender, smoking, diabetes, and hypertension (family history was not obtained in TNT). We included this set of variables, together with randomized treatment assignment in a single model, referring to this model as the "basic model." Next, variables that were statistically significant at a p-value of <0.10 from the univariable analysis were then entered into the multivariable model. Using an unbiased statistical method of forward stepwise regression, variables that met a critical p-value of <0.05 were selected into the multivariable model.

We then conducted two sensitivity analyses. First, we performed the multivariable model after excluding baseline medication use other the randomization treatment assignment. Second, we expanded the basic model to include the on-treatment 1-year lipids and apolipoproteins in order to identify predictors that remained statistically significant independent of the achieved levels of on-treatment lipids and apolipoproteins.

Treatment-by-variable interactions were assessed using likelihood ratio χ^2 statistic and Wald's p-values to compare models with and without the interaction term. Interactions between the levels of on-treatment lipids and apolipoproteins with the multivariable predictors were also assessed.

Finally, we evaluated the multivariable model discrimination using Harrell's c-index, which estimates the probability that, of two randomly chosen patients, the patient with the higher prognostic score will be more likely to be a case compared with the patient with the lower prognostic score. [11] Values of c-index near 0.5 indicate that the prognostic score is no better than a coin-flip, while values near 1.0 indicate that the model variables virtually always determine which patient has a better prognosis.

Results

During a median follow-up of 4.9 years, a total of 729 (7.8%) MCVE primary and 1870 secondary endpoints occurred after year 1. Table 1 shows the baseline characteristics for MCVE incident cases and non-cases, which were similar to the overall TNT study population.[6] The prevalence of cardiovascular risk factors and prior cardiovascular disease was typical of a population with coronary disease, with a worse cardiovascular risk profile among cases compared with non-cases. Similar results were found when cases were categorized according to the expanded secondary endpoint (results not shown).

Univariable determinants of risk

The primary endpoint of MCVE that occurred after year 1 was reduced with atorvastatin 80 mg versus 10 mg by 18% (P=0.007; Table 2), similar to the overall TNT relative risk reduction of 22%.[6] Associations for each of the clinical risk factors, baseline and 1-year laboratory parameters in relation to the primary endpoint of MCVE were obtained from separate Cox regression models (Table 2). Most of the clinical risk factors, and all the baseline and 1-year lipids and apolipoproteins, in addition to baseline white blood cell count, glucose, uric acid, blood urea nitrogen, and lactate dehydrogenase were each statistically significantly associated with MCVE. Similar associations were also noted in relation to the expanded secondary endpoint that included all-cause death, angina, and revascularization (data not shown).

Multivariable determinants of risk

Using forward stepwise regression, statistically significant variables were added to the basic model (randomization treatment, age, gender, smoking, diabetes, and hypertension). Multivariable determinants of increased risk (Table 3) were older age, increased BMI, male gender, hypertension, diabetes, baseline apolipoprotein B and blood urea nitrogen, current smoking, prior cardiovascular disease, and calcium channel blocker use. Determinants of decreased risk were high-dose statin, aspirin use, and baseline apolipoprotein A-I. On-treatment 1-year levels of lipids and apolipoproteins were not selected into the multivariable model because they were not associated with risk after taking into account baseline apolipoproteins and clinical risk factors. When we repeated the multivariable analysis in Table 3 for the secondary expanded endpoint, nearly identical results were obtained, except that both baseline apolipoprotein B and 1-year apolipoprotein B and A-I were also statistically significant (data not shown).

Sensitivity analyses

We performed 2 additional sensitivity analyses. First, we repeated the multivariable analysis in Table 3 after excluding baseline concurrent medication use, obtaining very similar results (Supplementary Table).

Then, in order to determine if the multivariable determinants remained associated with risk independent of the achieved levels of on-treatment 1-year lipids and apolipoproteins, we performed a second sensitivity analysis by expanding the basic model to include the 1-year lipids and apolipoproteins. None of the 1-year lipids or apolipoproteins were associated with risk of the primary or secondary endpoint.

Tests for interactions

We tested for whether the randomization treatment of atorvastatin 80 mg versus 10 mg modified the association of the multivariable determinants of risk. Generally similar predictors of risk were seen among subjects allocated atorvastatin 10 mg vs 80 mg (Table 4). There were no statistically significant interactions at a P value of <0.01.

Since individuals who achieve lower lipid targets on therapy still experience events, we determined whether the multivariable determinants differed among patients based on their achieved levels of 1-year lipids and apolipoproteins. There were no statistically significant interactions at a P value of <0.01.

Prognostic model discrimination

Finally, we assessed the overall model discrimination for the multivariable model using Harrell's c-index,[11] a generalization of the area under the receiver operator characteristic curve. The multivariable model (Table 3) provided acceptable discrimination of cases from non-cases, with a c-index of 0.679. A similar multivariable model that excluded baseline medication use (Supplementary Table) resulted in a slightly lower c-index of 0.673.

Discussion

In the TNT trial of secondary prevention patients with low LDL cholesterol and triglycerides less than 600 mg/dL, residual risk was multi-factorial and related to baseline lipid-related and non-lipid risk factors, including baseline apolipoproteins, increased BMI, smoking, hypertension, and diabetes. Generally similar determinants of risk were identified among subjects allocated to high-versus low-dose statin therapy. Known baseline clinical and lipid-related variables performed moderately well in discriminating cases from non-cases. Thus, a multi-faceted secondary prevention approach emphasizing modifiable traditional risk factors should be underscored in order to reduce residual risk.

It is commonly believed that residual risk on statin treatment is related to the achieved levels of high-density-lipoprotein (HDL) cholesterol or triglycerides, in addition to achieved LDL cholesterol.[12] At first glance, the findings of this TNT analysis may seem discordant with the results of a prior TNT analysis that found an inverse association of HDL cholesterol with MCVE. But in the prior analysis, there was no association between HDL cholesterol and MCVE (p-value=0.45) after adjustment for baseline apolipoproteins.[13] The current study also found univariable associations for HDL cholesterol and triglycerides with risk that became non-statistically significant in multivariable models that additionally adjusted for baseline apolipoproteins and other risk factors. In contrast, among primary prevention patients with low LDL cholesterol but elevated C-reactive protein in the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, neither on-treatment HDL cholesterol nor triglycerides were associated with residual risk,

even without adjusting for apolipoproteins.[14, 15] The JUPITER study population differed from TNT in being a primary prevention non-diabetic population recruited on the basis of chronic inflammation, and these differences in the study populations may contribute to differences in prognostic markers. However, several other trials also did not find statistically significant associations for on-treatment HDL cholesterol or triglycerides with residual risk among the active or more intensely treated arms.[16–18]

There is limited prior data evaluating the magnitude of residual risk that is explained by clinical risk factors. However, 2 prior studies from hypercholesterolemic primary prevention populations identified similar risk factors for residual risk as were found in the current TNT study of secondary prevention. In a previous study from the West of Scotland Coronary Prevention Study (WOSCOPS), which only included middle-aged hypercholesterolemic men without prior myocardial infarction, important predictors of risk included older age, smoking, blood pressure, diabetes, and baseline total/HDL cholesterol ratio, and a 5-year risk score for residual risk was modeled.[19, 20] In a subsequent analysis from hypercholesterolemic asymptomatic men and women from the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study, the risk factors for incident coronary events were male sex, older age, diabetes, hypertension, smoking, low baseline HDL cholesterol, and increased BMI (women only).[21]

Furthermore, the current findings do not support the routine re-measurement of on-treatment 1-year lipids or apolipoproteins once a baseline measurement has been obtained on statin therapy, because 1-year levels were not related to residual risk above and beyond the initial (on-treatment) values and clinical risk factors. A prior TNT analysis found positive association for on-treatment apolipoproteins and non-HDL cholesterol with residual risk in minimally-adjusted models (age- and sex-adjusted). [2] The current study extends the prior findings by demonstrating that once additional clinical risk factors and baseline levels of apolipoproteins are included in more comprehensive multivariable models, there is no independent association for 1-year on-treatment levels of apolipoproteins with residual risk. Notably, in both MEGA and WOSCOPS, on-treatment lipid values were not associated with risk in multivariable models.[20, 21]

Risk factors for CVD often cluster such that individuals with dyslipidemia may also have a number of cardiovascular risk factors.[22,23] Even after achieving low LDL cholesterol levels, as in TNT, a greater duration and/or burden of atherosclerotic disease are often present among coronary patients that increase their residual risk. For example, the increased risk associated with calcium channel blocker use is at least in part related to “confounding by indication”, since patients taking calcium channel blockers at baseline probably had a higher burden (severity and/or frequency) of angina. For the rest of the multivariable determinants of risk, we believe that our results show the expected (and not paradoxical) relationships of established risk factors with clinical outcomes in the secondary prevention setting because of 1) better assessment of potential confounders in the TNT trial and 2) less differential surveillance bias. Detailed risk factor data and information about potential confounders were well-assessed in the TNT clinical trial, and hence the results are less prone to the confounder bias that may be seen in other prospective studies that did not account sufficiently for potential confounders and which likely resulted in the “paradox phenomenon”.[24] We also believe that there was less differential surveillance bias in the TNT study, since it was a randomized double-blinded clinical trial, as compared with unblinded prospective studies that may be more prone to this type of bias.

The multivariable model that included these clinical risk factors, concurrent medication use, and prior cardiovascular history resulted in acceptable discrimination of future cases and non-cases. Studies are needed to identify additional factors that may contribute to residual

risk, and to test the comparative effectiveness of treatment strategies that simultaneously target multiple risk factors.

The present study has potential limitations and several strengths. TNT excluded patients with LDL cholesterol >130 mg/dL on atorvastatin 10 mg or untreated triglycerides >600 mg/dL. This prospective analysis, while conducted within a clinical trial, was observational and may be subject to bias, since individuals who become cases may differ from non-cases in unmeasured ways. While we examined clinical and traditional risk factor data, novel risk factor data was not available on the entire TNT population for analysis. However, a prior case-control study found little association for a selected group of non-lipid biomarkers with residual risk.[25] Finally, it is unclear if our results would be applicable to other individuals from primary or secondary prevention who were excluded from the trial.

Strengths of the study are the large number of individuals with baseline and 1-year lipids and apolipoproteins, as well as the detailed information on clinical risk factors. To our knowledge this is the first analysis of the role of clinical risk factors in a secondary prevention study, in particular one in which baseline LDL cholesterol was low and the achieved LDL cholesterol was even lower with half the study population allocated to potent statin therapy. Finally, because the TNT study design tested a low- and high-dose statin in a randomized fashion, we were able to take advantage of this clinical trial design using the intention-to-treat analysis to test for treatment-by-variable interactions.

Conclusions

In summary, the key finding from this study is that residual risk among statin-allocated coronary patients was multi-factorial and related to baseline lipid-related and non-lipid risk factors, including baseline apolipoproteins, increased BMI, smoking, hypertension, and diabetes. Known baseline clinical and lipid-related variables performed moderately well in discriminating future cases from non-cases. Thus, a multi-faceted secondary prevention approach targeting modifiable risk factors should be underscored as the cornerstone of optimal cardiovascular risk assessment and prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of cases and non-cases of major cardiovascular events (MCVE) during 4.9 year follow up (N = 9,251)*

	Major cardiovascular events	
	Cases (n=729)	**Non-cases (n=8522)**
Treatment: Atorvastatin 80 mg, %	45.1	50.4
Age, years	62.2 (8.9)	60.9 (8.8)
Height, cm	173 (9)	172 (9)
Weight, kg	87.2 (16.9)	84.5 (15.3)
BMI, kg/m^2	29.3 (5.0)	28.5 (4.5)
Blood pressure, mmHg		
Systolic	132.9 (17.7)	130.4 (16.6)
Diastolic	78.3 (9.9)	77.9 (9.4)
Men, %	83.4	80.9
White, %	93.3	94.4
Cardiovascular history, %		
Smoking		
Current	18.1	12.5
Previous	61.3	63.7
Never	20.6	23.8
Diabetes	23.2	14.0
Hypertension	66.3	52.7
Myocardial infarction	67.9	57.2
Angina	85.5	81.1
Cerebrovascular disease	11.1	4.5
Peripheral vascular disease	20.4	10.9
Congestive heart failure	15.5	6.9
Arrhythmia	23.7	17.8
Coronary revascularization		
Angioplasty	52.3	54.2
Bypass	55.3	45.8
Metabolic syndrome, %	64.3	54.8
Chronic kidney disease, %	38.9	31.5
Baseline lipids and apolipoproteins, mg/dL: Mean (SD)		
Total cholesterol	176.9 (24.6)	174.3 (23.6)
LDL cholesterol	100.2 (17.5)	97.1 (17.4)
HDL cholesterol	45.4 (10.1)	47.6 (11.0)
Triglycerides	158.0 (77.4)	148.9 (69.0)
Median [25th, 75th percentiles]	138.5 [103.5,194.3]	133.5 [101.0,181.0]
Apolipoprotein A-I	142.9 (23.1)	146.5 (24.9)
Apolipoprotein B	115.1 (20.2)	110.5 (19.0)

	Major cardiovascular events	
	Cases (n=729)	**Non-cases (n=8522)**
Year 1 lipids and apolipoproteins, mg/dL: Mean (SD)		
Total cholesterol	166.8 (34.6)	162.2 (32.3)
LDL cholesterol	91.8 (27.1)	87.7 (25.5)
HDL cholesterol	44.6 (10.5)	46.3 (11.1)
Triglycerides	153.3 (82.2)	142.2 (81.8)
Median [25th, 75th percentiles]	132.0 [95.0, 192.0]	123.0 [90.0, 171.0]
Apolipoprotein A-I	140.7 (24.7)	144.4 (24.8)
Apolipoprotein B	106.5 (25.6)	101.7 (23.9)
Concomitant medication, %		
ACE inhibitor	36.4	26.4
Angiotensin II receptor blockers	6.6	5.0
Beta blockers	55.6	53.8
Calcium channel blockers	34.3	26.0
Aspirin	80.5	87.3
Coumadin or other antiplatlets	4.5	2.9
Prior use of statins	60.6	62.7
Other laboratory parameters: Mean (SD)		
White blood cells (10^3/mm^3)	6.57 (1.64)	6.27 (1.62)
Glucose (mg/dL)	113.4 (36.7)	106.9 (29.4)
Uric acid (mmol/L)	6.43 (1.50)	6.17 (1.38)
Blood urea nitrogen (mg/dL)	17.77 (5.74)	16.79 (4.77)
Lactate dehydrogenase (mg/dL)	83.5 (17.5)	81.6 (17.3)

*The analysis includes only subjects who survived to the year 1 visit without a MCVE and with complete year 1 lipids data since year 1 lipids data were included in the analysis model as predictor variables in all of the subsequent analyses. SD= standard deviation.

Table 2

Univariable determinants of post year 1 major cardiovascular events (MCVE)

		Major cardiovascular events		
Risk factors	**SD or %**	**Hazard Ratio (95% CI)** *	**χ2 Statistics***	**P-value***
Treatment: Atorvastatin 80 mg	50.0%	0.82 (0.71, 0.95)	7.22	0.007
Age	8.8 years	1.15 (1.07, 1.23)	13.92	<0.001
Height	9 cm	1.04 (0.97, 1.12)	1.20	0.27
Weight	15.4 kg	1.18 (1.10, 1.26)	21.89	<0.001
BMI	4.5 kg/m^2	1.17 (1.10, 1.25)	23.02	<0.001
Blood pressure				
Systolic	16.7 mmHg	1.15 (1.07, 1.24)	15.31	<0.001
Diastolic	9.5 mm Hg	1.03 (0.96, 1.11)	0.67	0.41
Men	81.1%	1.18 (0.97, 1.43)	2.64	0.10
White	94.3%	0.82 (0.62, 1.10)	1.75	0.19
Cardiovascular history				
Smoking				
Current	12.9%	1.65 (1.31, 2.08)	17.53	<0.001
Previous	63.5%	1.11 (0.93, 1.34)	1.31	0.25
Never	23.6%	1.00	------	------
Diabetes	14.7%	1.82 (1.54, 2.17)	46.85	<0.001
Hypertension	53.8%	1.74 (1.49, 2.02)	49.52	<0.001
Myocardial infarction	58.0%	1.57 (1.34, 1.83)	32.14	<0.001
Angina	81.6%	1.34 (1.09, 1.65)	7.71	0.006
Cerebrovascular disease	5.0%	2.53 (2.01, 3.18)	61.80	<0.001
Peripheral vascular disease	11.7%	2.03 (1.70, 2.44)	59.76	<0.001
Congestive heart failure	7.5%	2.40 (1.96, 2.93)	73.23	<0.001
Arrhythmia	18.2%	1.43 (1.21, 1.70)	16.94	<0.001
Coronary revascularization:				
Angioplasty	54.1%	0.92 (0.80, 1.07)	1.25	0.26
Bypass	46.6%	1.46 (1.26, 1.69)	25.93	<0.001
Metabolic syndrome	55.6%	1.47 (1.26, 1.71)	24.81	<0.001
Chronic kidney disease	32.1%	1.37 (1.18, 1.59)	17.22	<0.001
Baseline lipids and apolipoproteins:				
Total cholesterol	23.7 mg/dL	1.10 (1.03, 1.18)	7.17	0.007
LDL cholesterol	17.5 mg/dL	1.17 (1.09, 1.26)	18.37	<0.001
HDL cholesterol	47.4 mg/dL	0.81 (0.75, 0.88)	25.85	<0.001
Triglycerides	69.7 mg/dL	1.12 (1.05, 1.20)	12.16	<0.001
Apolipoprotein A-I	24.8 mg/dL	0.86 (0.79, 0.92)	16.04	<0.001
Apolipoprotein B	19.1 mg/dL	1.24 (1.16, 1.33)	36.22	<0.001
Year 1 lipids and apolipoproteins:				

		Major cardiovascular events		
Risk factors	**SD or %**	**Hazard Ratio (95% CI)** *	**χ2 Statistics***	**P-value***
Total cholesterol	32.5 mg/dL	1.13 (1.06, 1.22)	12.56	< 0.001
LDL cholesterol	25.7 mg/dL	1.16 (1.08, 1.24)	16.93	<0.001
HDL cholesterol	11.1 mg/dL	0.85 (0.79, 0.92)	16.62	<0.001
Triglycerides	81.9 mg/dL	1.10 (1.05, 1.16)	13.12	<0.001
Apolipoprotein A-I	24.1 mg/dL	0.86 (0.80, 0.93)	15.55	<0.001
Apolipoprotein B	24.1 mg/dL	1.20 (1.12, 1.28)	26.43	<0.001
Concomitant medication				
ACE inhibitor	27.2%	1.57 (1.35, 1.83)	34.45	<0.001
Angiotensin II receptor blockers	5.2%	1.31 (0.98, 1.76)	3.27	0.07
Beta blockers	53.9%	1.07 (0.93. 1.24)	0.91	0.34
Calcium channel blockers	26.7%	1.46 (1.25, 1.70)	23.52	<0.001
Aspirin	86.8%	0.62 (0.51, 0.74)	26.88	<0.001
Coumadin or other antiplatlets	3.0%	1.55 (1.09, 2.19)	5.96	0.01
Prior use of statins	62.6%	0.93 (0.80, 1.08)	0.87	0.35
Other laboratory parameters:				
White blood cells (natural log)	0.25 $10^3/mm^3$	1.20 (1.12, 1.29)	24.55	<0.001
Glucose	30.1 mg/dL	1.18 (1.11, 1.24)	32.32	<0.001
Uric acid	1.39 mmol/L	1.18 (1.10, 1.27)	22.38	<0.001
Blood urea nitrogen	4.86 mg/dL	1.17 (1.11, 1.24)	29.30	<0.001
Lactate dehydrogenase	17.3 mg/dL	1.10 (1.03, 1.16)	9.02	0.003

*Hazard ratios, 95% confidence intervals (CIs), and p-values are based on unviariable Cox proportional hazard analysis including the corresponding variable in the model. Hazard ratios and the corresponding 95% CIs are calculated based on 1 standard deviation (SD) increase for the continuous variables.

Table 3

Multivariable determinants of post year 1 major cardiovascular events (MCVE)

	Major cardiovascular events		
Risk factors	**Hazard Ratio (95% CI) ***	**χ^2 Statistics ***	**P- value ***
Basic model			
Treatment (Atorvastatin 80 mg)	0.82 (0.70, 0.94)	7.43	0.006
Age (years): per 1SD	1.13 (1.04, 1.23)	8.04	0.005
Men	1.33 (1.07, 1.65)	6.69	0.01
Smoking			
Current	1.65 (1.28, 2.12)	15.35	<0.001
Previous	1.00 (0.82, 1.20)	0.01	0.96
Never	1.00	------	------
Hypertension	1.38 (1.17, 1.63)	14.51	<0.001
Diabetes	1.33 (1.11, 1.60)	9.48	0.002
Variables selected by forward stepwise elimination			
Body mass index(kg/m^2): per 1SD	1.09 (1.02, 1.17)	6.34	0.01
Myocardial infarction	1.60 (1.36, 1.87)	32.79	<0.001
Angina	1.36 (1.10, 1.68)	8.16	0.004
Cerebrovascular disease	1.73 (1.36, 2.19)	19.80	<0.001
Peripheral vascular disease	1.32 (1.09, 1.61)	7.84	0.005
Congestive heart failure	1.54 (1.24, 1.90)	15.59	<0.001
Coronary revascularization: Bypass	1.26 (1.08, 1.47)	8.44	0.004
Baseline apolipoprotein A-I (mg/dL): per 1SD	0.91 (0.84, 0.99)	5.23	0.02
Baseline apolipoprotein B (mg/dL): per 1SD	1.19 (1.11, 1.28)	21.87	<0.001
Use of calcium channel blockers	1.31 (1.12, 1.54)	10.99	<0.001
Use of aspirin	0.67 (0.56, 0.81)	17.31	<0.001
Baseline blood urea nitrogen (mg/dL): per 1SD	1.10 (1.03, 1.17)	8.92	0.003

*Hazard ratios, 95% confidence intervals (CIs), and p-values are based on multivariable Cox proportional hazard analysis forcing age, gender, smoking, hypertension, and diabetes in the model; and the remaining significant ($p< 0.10$) variables identified from the univariable analyses were entered into the model by forward stepwise selection process with a critical value of 0.05. Hazard ratios and the corresponding 95% CIs are calculated based on 1 standard deviation (SD) increase for the continuous variables.

Table 4

Multivariable determinants of post year 1 major cardiovascular event by randomization treatment groups (atorvastatin 80 mg versus 10 mg)

	Major cardiovascular events				
	Atorvastatin 10 mg (N = 4628)		Atorvastatin 80 mg (N = 4623)		
Risk factors	**Hazard Ratio (95% CI)***	**P-value***	**Hazard Ratio (95% CI)***	**P-value***	**P for interaction†**
Basic model					
Age (years): per 1SD	1.09 (0.98, 1.23)	0.13	1.17 (1.03, 1.33)	0.01	0.68
Men	1.21 (0.91, 1.62)	0.19	1.52 (1.09, 2.11)	0.01	0.47
Smoking					
Current	1.57 (1.19, 2.08)	0.002	1.70 (1.26, 2.31)	<0.001	0.74
Previous	0.95 (0.74, 1.23)	0.70	1.01 (0.81, 1.43)	0.61	0.49
Never	1.00	------	1.00	------	
Hypertension	1.30 (1.04, 1.62)	0.02	1.47 (1.15, 1.89)	0.002	0.44
Diabetes	1.35 (1.05, 1.74)	0.02	1.29 (0.99, 1.69)	0.06	0.84
Variables selected by forward stepwise selection					
Body mass index (kg/m^2): per 1SD	1.06 (0.97, 1.16)	0.22	1.15 (1.03, 1.28)	0.01	0.38
Myocardial infarction	1.43 (1.16, 1.76)	<0.001	1.83 (1.43, 2.35)	<0.001	0.17
Angina	1.39 (1.04, 1.85)	0.02	1.32 (0.97, 1.81)	0.08	0.70
Cerebrovascular disease	1.78 (1.29, 2.45)	<0.001	1.68 (1.17, 2.41)	0.005	0.79
Peripheral vascular disease	1.21 (0.92, 1.59)	0.17	1.48 (1.12, 1.97)	0.007	0.30
Congestive heart failure	1.29 (0.95, 1.75)	0.10	1.83 (1.36, 2.48)	<0.001	0.09
Coronary revascularization: Bypass	1.35 (1.10, 1.67)	0.005	1.15 (0.91, 1.44)	0.25	0.31
Baseline apolipoprotein A-I (mg/dL):per 1SD	0.88 (0.79, 0.99)	0.03	0.94 (0.83, 1.06)	0.33	0.67
Baseline apolipoprotein B (mg/dL) :per 1SD	1.25 (1.14, 1.38)	<0.001	1.12 (1.00, 1.25)	0.05	0.05
Use of calcium channel blockers	1.52 (1.23, 1.89)	<0.001	1.08 (0.85, 1.38)	0.53	0.04
Use of aspirin	0.73 (0.56, 0.95)	0.02	0.61 (0.46, 0.79)	<0.001	0.25
Baseline blood urea nitrogen (mg/dL): per 1SD	1.11 (1.02, 1.22)	0.02	1.08 (0.93, 1.18)	0.07	0.63

*Hazard ratio, 95% confidence intervals (CIs), and p-values are based on multivariable Cox proportional hazard analysis including all specified variables in the model. Hazard ratios and the corresponding 95% CIs are calculated based on 1 standard deviation (SD) increase for the continuous variables.

†The p-values for the interaction terms between treatment and the corresponding variables are based on the Wald's test of the corresponding interaction terms in the multivariable model listed above.