Statin Therapy and Increased Coronary Heart Disease Risk in Primary Prevention of People with Enhanced Low-Grade Inflammation

Artmış Düşük Dereceli Yangı Bulunan Kişilerde Primer Koruma Amacıyla Statin Tedavisi ve Koroner Kalp Hastalığı Riskinde Artma

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ABSTRACT Objective: We investigated whether statin treatment, associated with slightly increased risk of incident diabetes, confers elevated coronary heart disease (CHD) risk, and circumstances thereof. **Material and Methods:** Totally, 2959 participants 270 of whom were medicated with statins, and free of CHD at baseline, were analyzed at 7.9-years' follow-up using Cox regression. **Results:** Participants using statin at baseline–compared with remaining participants–had significantly higher values of metabolic syndrome (MetS) components, but lower apolipoprotein B, were fewer current smokers, and had similar HDL- and LDL-cholesterol levels. Women additionally had higher plasma fibrinogen and lipoprotein[Lp](a). Adjusted Lp(a) concentrations were significantly associated with statin medication, especially in men. In Kaplan-Meier analyses for 381 incident CHD cases (stratified to gender, age category and changed status of statin usage) demonstrated steadily separating curves in statin users, compared with non-users (Log rank <0.0001). Cox regression hazard ratio for developing incident CHD was 2.42 (95% CI 1.80; 3.25) in individuals using statin, after adjustment for traditional risk factors, in men irrespective of MetS-status. **Conclusion:** Appropriately instituted statin therapy in population subsets with MetS or enhanced inflammation may increase CHD risk in a primary prevention setting. Excess risk imparting may be attributed to a modifying effect of statins on Lp(a).

Key Words: Coronary disease; autoimmunity; lipoprotein(a); primary prevention; hydroxymethylglutaryl-CoA reductase inhibitors

ÖZET Amaç: Yeni diyabet gelişmesine ılımlı bir risk yüklediği belgelenmiş statin tedavisinin koroner kalp hastalığı (KKH) riskini arttırıp arttırmadığını ve bunun koşullarını araştırmayı amaçladık. **Gereç ve Yöntemler:** Başlangıçta KKH'sı bulunmayan toplam 2959 katılımcıdan 270'inde statin tedavisi uygulanmıştı. Ortalama 7,9 yıllık takipte Cox regresyon analizi yapıldı. **Bulgular:** Geri kalan katılımcılara kıyasla başlangıçta statin kullanan bireylerde metabolik sendrom (MetS) öğelerinin anlamlı biçimde daha yüksek olmasına karşılık, apolipoprotein B daha düşük, HDL-kolesterol ve LDL-kolesterol düzeyleri benzer bulunup sigara içicilik oranı daha düşüktü. Kadınlar ayrıca daha yüksek fibrinojen ve lipoprotein[Lp](a)'ya sahipti. Ayarlanmış Lp(a) konsantrasyonları statin ilacı kullanımıyla özellikle erkeklerde ilişkili bulundu. Cinsiyet, yaş kategorisi, statin kullanımı statüsünde değişiklik yönlerinden katmanlanmış olan 381 KKH vakasının Kaplan-Meier analizi, statin almayanlara göre alanlarda giderek ayrılan eğriler sergiledi (Log rank<0,0001). Geleneksel risk faktörleri için ayarlandıktan sonra, yeni KKH gelişmesi için yapılan Cox regresyon analizinde, hazard oranı 2,42 (%95 GA 1,80;3,25) bulundu; bu, erkeklerde MetS statüsünden bağımsızdı. **Sonuç:** MetS veya artmış yangısı bulunan toplum kesimlerinde primer koruma çerçevesinde uygun statin tedavisi KKH riskini yükseltebilir. Bindirilen ek risk yükü, statinlerin Lp(a)'yı modifiye edici etkisine bağlanabilir.

Anahtar Kelimeler: Koroner hastalık; otoimmünite; lipoprotein(a); primer korunma; hidroksimetilglutaril-KoA redüktaz inhibitörleri

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Secondary and primary prevention of atherosclerotic cardiovascular disease with statin drugs has been an established method for a quarter-century.[1] Its safety and good tolerability is generally recognized.[2] Statin therapy has been found to be effective in reducing cardiovascular events also in people with diabetes.[3] However, more subjects treated with statins than in placebo groups developed diabetes in several trials including the JUPITER trial, so that two recent meta-analyses focusing on risk of incident diabetes clearly documented an -albeit slightly- increased risk of development of diabetes in participants assigned statins.[4-6] Reasons for this have remained unclear.

Increased likelihood of type-2 diabetes and of metabolic syndrome (MetS) in statin users, independently of confounders, had been noted as a side finding in a cross-sectional analysis of the Turkish Adult Risk Factor (TARF) study.[7] We had also observed in cross-sectional analysis increased association of hypertriglyceridemic dyslipidemia with statin usage that was independent of potential confounders only in women having elevated triglycerides with hyperapoB and elevated risk of incident coronary heart diseases (CHD) in an as yet unpublished prospective study, again as a side finding.[8,9]

These observations suggested that, under certain conditions, statin therapy might induce a limited increase in CHD risk that may escape recognition in studies or trials evaluating net change in this risk among participants, recruited for secondary prevention or those involved in the general population. That this is conceivable is apparent from the documented increased diabetes risk, succeeded often by elevated CHD risk. Whether additional direct links exist to the development of CHD in participants assigned to prophylactic statins, remain to be explored.

Turkish adults are recognized to have a high prevalence of abdominal obesity, MetS, and diabetes.[10-13] We aimed in the current prospective study to focus on an assessment of statin usage in relation to subsequent development of incident CHD among the TARF participants, using Cox proportional hazard analysis at an intermediate duration of follow-up. Potential circumstances that might predispose to increased risk, if any, were to be delineated as well.

POPULATION AND METHODS

POPULATION SAMPLE

The *Turkish Adult Risk Factor Study* is a prospective survey on the prevalence of cardiac disease and risk factors in adults in Turkey carried out biennially since 1990 in 59 communities of the country.[14] It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions and for rural-urban distribution.[14] Various measurements were first performed at the follow-up visit in 1997/98 or thereafter, considered study baseline, in participants 28 years of age or older. The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the Istanbul University Ethics Committee. Written informed consent was obtained from all participants. Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system, sampling of blood and recording of a resting electrocardiogram.

MEASUREMENTS OF RISK VARIABLES

Self-reported cigarette smoking was categorized into never, currentor former smokers. Blood pressure (BP) was measured in the sitting position on the right arm, and the mean of two readings at least 3 min apart was recorded. Waist circumference was measured with a tape (Roche LI95 63B 00), the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest.

Blood samples were collected, spun at 1000*g* for 10 minutes and shipped to Istanbul to be stored in deep-freeze at -75°C, until analyzed at a central laboratory. Serum concentrations of total cholesterol, fasting triglycerides, glucose, HDL-cholesterol (directly without precipitation) and creatinine were determined by using enzymatic kits from Roche Diagnostics with a Hitachi 902 autoanalyzer. LDL-cholesterol values were computed with the Friedewald formula. Concentrations of serum apoA-I and apoB, lipoprotein[Lp](a), and C-reactive

protein (CRP) were measured by Behring kits and Behring nephelometry (Behring Diagnostics, Marburg, Germany, or Westwood, MA). Plasma fibrinogen levels were assayed after an overnight fast in sodium citrate containing vacutainers by the modified Clauss method using Behring Fibrintimer II coagulometer and Multifibren U kit.

DEFINITIONS AND OUTCOMES

Individuals with the MetS were identified when 3 out of the 5 criteria of the National Cholesterol Education Program (ATP-III) were met, modified for prediabetes (fasting glucose 100-125 mg/dL and further for male abdominal obesity using as cut-point ≥95 cm, as assessed in the Turkish Adult Risk Factor study.[8,15,16]

Nonfatal CHD was identified by presence of angina pectoris, a history of myocardial infarction with or without accompanying Minnesota codes of the electrocardiography (ECG) or a history of myocardial revascularization.[17] Typical angina and, in women, age >45 years were prerequisite for a diagnosis when angina was unaccompanied by ECG alterations. ECG changes of "ischemic type" of greater than minor degree (Codes 1.1-2, 4.1-2, 5.1-2, 7.1) were considered as myocardial infarct sequelae or myocardial ischemia, respectively. CHD death comprised death from heart failure of coronary origin or fatal coronary event.

DATA ANALYSIS

Descriptive parameters were shown as mean ± standard deviation, or in percentages. Due to the skewed distribution, log-transformed (geometric) values were used for Lp(a), triglycerides and CRP. Two-sided t-tests and Pearson's chi-square tests were used to analyze the differences in means and proportions between groups. Baseline was defined as the survey of first recording of statin usage, or first recruitment among non-users at or after the 1997/98 survey. Participants (n=486; 13.2%) with no follow-up were excluded. Surveys 1997/98 to 2001/'02 constitute baseline in four-fifths of the participants. Effect of statin usage on incident CHD was tested first by estimating mean time to event with the Kaplan-Meier method, after exclusion of the cohort with prevalent CHD at baseline examination. Cox proportional hazards regression was then used to yield risk coefficients for each independent risk variable, estimating the related hazard ratio (HR, and 95% confidence intervals), expressed per 1 SD increment of continuous variables. A value of $p<0.05$ on the two-sided test was considered statistically significant. Statistical analyses were performed using SPSS-10 for Windows (SPSS Inc., Chicago, Ill).

RESULTS

At baseline, 5.6% of men and 12.2% of women ($p<0.001$) were medicated with statins (270 of 2959 persons) in primary coronary prevention. Mean follow-up was 7.9±3.73 years (total follow-up 23,380 person-years). Incident CHD developed in 14.3 (men) and 16.4 (women) per 1000 person-years.

Clinical characteristics at baseline examination are available in Table 1, stratified by gender and statin usage. Participants treated with statins were overall 4.3±0.9 years older, had significantly higher waist girth, BP, total cholesterol, fasting glucose and triglycerides, had significantly higher apoA-I (1.438 vs 1.336 g/L, $p<0.001$), lower physical activity grades, and were fewer current smokers. HDL- and LDL-cholesterol levels were similar. In contrast, as information added to Table 1, nonHDL-cholesterol values ≥160 mg/dl were displayed in 48.4% of statin users vs 30.3% in non-users ($p<0.001$). Women treated with statins additionally had significantly higher plasma fibrinogen, Lp(a) and CRP levels. Interestingly, apoB levels were lower among male and female statin users combined (1.085 vs 1.17 g/L, $p=0.04$). Mean Framingham risk score (using total cholesterol) among non-users was 4.50 points vs. 8.74 in statin users, and 3.7 points difference was derived merely from age difference, leaving 0.5 point difference for the remaining factors.

Change in adiposity measures over the follow-up period was examined in paired samples stratified to statin usage. Increase in body mass index (BMI) ($p<0.001$ in each) was observed in 2297 non-using individuals from 27.5 to 28.7

TABLE 1: Baseline characteristics of the study sample, by gender and statin usage (n=2959).

		Men			Women		
	n	Non-statin user Mean SD	Statin user Mean SD	p-value	Non-statin user Mean SD	Statin user Mean SD	p-value
Sex, n, %	2959	1341	79 5.6%		1348	191 12.4%	<0.001
Age, yrs	2959	49.1±12.2	52.1±10.7	0.034	48.2±12	53.3±9.3	<0.001
Waist circumfer, cm	2937	93.6±10.9	99.3±9.8	<0.001	90±12.7	95.8±12.2	<0.001
Systolic BP, mmHg	2959	126.3±21.6	129.6±19.2	0.19	131.5±25	139±24	<0.001
Diastolic BP, mmHg	2959	80.5±12.4	82.5±11.6	0.16	82.3±13.6	84.5±13	0.029
Total cholest, mg/dl	2939	181.2±36.3	198.1±46.1	0.002	187±37	205±45	<0.001
LDL cholest, mg/dl	2002	112.4±30.6	112.9±39	0.93	116.7±31	120±40.7	0.36
HDL cholest, mg/dl	2856	37.3±11.5	36.6±10.2	0.57	45.2±12.5	46.6±12.2	0.16
F.triglyceride¶ mg/dl	2106	132±1.71	189.6±1.75	<0.001	113.2±1.65	149.5±1.75	<0.001
NonHDL-chol, mg/dl	2845	143.8±36.8	160.3±43	0.001	141.7±37.2	158.5±45.2	<0.001
Fast glucose, mg/dl	2462	98.6±27	116±49.6	0.006	99.6±28	110±47.7	0.006
ApolipoproteinA-I, g/L	849	1.245±0.29	1.352±0.27	0.088	1.425±0.32	1.465±0.21	0.18
Apolipoprotein B, g/L	974	1.17±0.36	1.08±0.38	0.24	1.173±0.43	1.087±0.31	0.10
Lipoprotein(a)¶ mg/dl	169	10.7±3.4	9.77±3.4	0.80	9.03±3.23	13.2±2.84	0.13
Lp(a)¶ final exam.	1950	9.31±2.84	11.5±3.50	0.21	11.2±2.90	14.4±2.79	0.01
Creatinine, mg/dl	2027	.99±0.20	1.06±0.25	0.014	.83±0.45	.82±0.19	0.92
Fibrinogen, g/dl	2302	3.12±1.06	3.12±0.75	1.00	3.35±1.02	3.56±0.97	0.017
C-react.prot.,¶ mg/L	1809	2.54±1.51	2.56±1.46	0.88	2.54±1.50	2.75±1.41	0.014
Phys. activity grade	2944	2.45±1.04	2.22±0.90	0.055	2.21±0.71	2.03±0.62	<0.001
Current; past smokers, %	2951	51.5; 21.8	34.2; 35.4	0.004	19.5; 3.6	14.7; 5.2	0.19
Diabetes baseline, n,%	2959	69; 5.1	25; 31.6	<0.001	75; 5.6	42; 22	<0.001
Incident CHD, n, %‡	2959	146; 10.9	24; 30.4	<0.001	168; 12.5	43; 22.5	<0.001

¶ log-transformed values, SD range is obtained by dividing or multiplying with the given SD.

‡ Newly developing CHD after exclusion of prevalent CHD cases.

BP: Blood pressure; CHD: Coroner heart disease; Lp: Lipoprotein.

kg/m^2 and in 203 statin users from 30.9 to 31.6 kg/m^2. Similarly, waist circumference widened ($p<0.001$ in each) in 2355 non-using individuals from 91.1 to 94.3 cm and in 203 statin users from 95.5 to 98.3 cm. Moreover, serum apoB value, available in 660 non-using paired samples, declined in the follow-up from 1.164 ±0.4 to 1.048 ±0.33 g/L whereas it remained similar ($p=0.65$) in 76 statin users (1.076±0.38 vs. 1.061±0.29 g/L).

Kaplan-Meier analysis was performed for statin usage by stratifying the study sample to gender, across age 50 years and status of statin usage (Table 2). Mean time to incident CHD was 12.1±0.05 years among 2689 non-users, 9.81±0.32 years in 314 statin users. Log rank was <0.0001 in each analysis displaying curves that separated early and steadily throughout the entire follow-up, including that for changed statin usage (Table 2, Figure 1). While incident CHD developed in 10.9% and 12.5% of men and women, respectively, not subject to lipid-lowering therapy, this risk was 30.4% and 22.5%, respectively, among statin users ($p<0.0001$ in each). The difference corresponded to an absolute risk of 24.7 and 12.7 per 1000 person-years in men and women, respectively; in other words, of every 40 men and every 79 women using statins, 1 each developed CHD in 1 year in excess of non-users. Of statin users developing CHD, only 23.6% had diabetes at baseline.

Table 3 shows Cox regression analysis for incident CHD, adjusted for sex, age, statin therapy and other established risk factors. HR for statin usage was 2.42 (95% CI 1.80; 3.25).We stratified the sample to presence of MetS and obtained con-

TABLE 2: Results of Kaplan-Meier tests for statin usage at baseline in stratified participants.

	Mean duration to CHD, years		CHD/Partic.†	CHD/Particip.†	Incidence, %	Log Rank p-value
	Non-user	User	Non-user	User	Non-us/User	
Men & women	12.1±0.05	9.81±0.32	314/2689	67/270	11.7/24.8	<0.0001
Men	12.1±0.07	9.39±0.59	146/1341	24/79	10.9/30.4	<0.0001
Women	12.0±0.08	9.89±0.89	168/1348	43/191	12.5/22.5	<0.0001
Age <50 yrs	12.6±0.04	10.9±0.50	101/1599	14/71	6.3/19.7	<0.0001
Age ≥50 yrs	11.2±0.11	9.22±0.41	213/1090	53/199	19.5/26.6	<0.0001
	Men	Women	Men	Women	M/W	
Non-user	12.2±0.08	12.1±0.07	133/1310	154/1306	10.2/11.8	<0.0001
Discontinuer	9.55±0.70	9.17±0.33	15/48	26/120	21.3/21.7	<0.0001
Late starter*	10.4±0.65	10.4±0.61	13/31	14/42	41.9/33.3	<0.0001
Persistent	9.3±1.02	9.4±0.71	9/31	17/71	29/23.9	<0.0001

* Participants (n=73) who initiated statin therapy later on at follow-up and were included among non-users at baseline.

† No. incident cases/No. at risk.

M/VW: Men/Women.

ferring of similar magnitude in CHD risk by usage of statins in men, regardless of MetS. In contrast, among women treated with statins, only females with MetS displayed significantly raised HRs whereas statin treatment in females without MetS conferred no significant independent risk; instead, their risk imparted by diabetes and nonHDL-cholesterol levels were high, contrasted to males.

Table 4 shows logistic regression analysis in a subset in whom serum Lp(a) measurements were available at baseline and final examinations for association with baseline statin usage, adjusted for sex, age and presence of diabetes.Assessed in few individuals at baseline, Lp(a) concentrations (OR 1.12 [1.004; 1.25]) and diabetes at final examination were significantly associated with statin medication in combined sexes. The association with Lp(a) was significant in men at an OR 1.19, did not reach significance in women, at an OR 1.08.

DISCUSSION

In this large population-based, 8-year prospective study, we investigated the independent effect of statin usage in primary prevention against CHD risk in a sample that had a relatively high prevalence of abdominal obesity. Statin was medicated at baseline examination in 270 adults (9.1%) in individuals who had significantly higher values of MetS components (excepting HDL-cholesterol), lower apoB, were fewer current smokers; and women additionally had significantly higher plasma fibrinogen, Lp(a) and CRP levels. Noteworthy, apoA-I levels were higher among statin users, while LDL-cholesterol levels were similar to non-users.

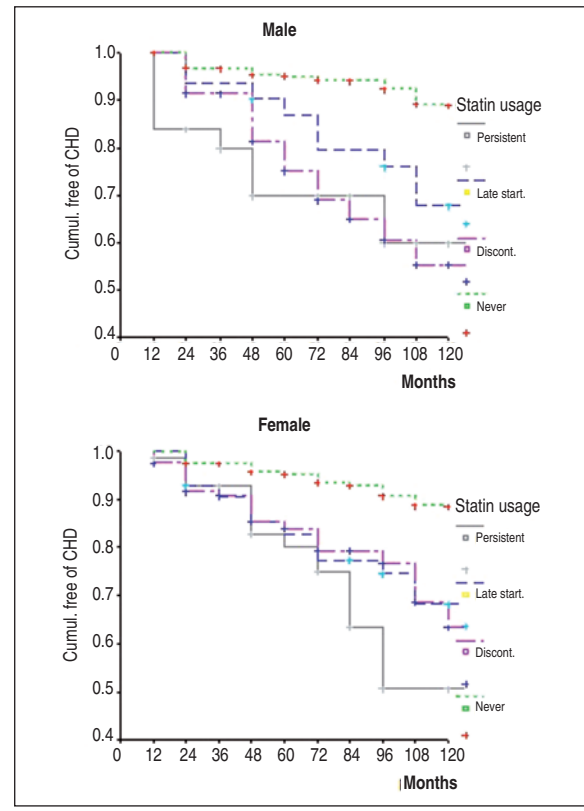

FIGURE 1: Kaplan-Meier curves in men and women remaining free of CHD over a 10-year period, stratified to groups of no medication (n=2689), discontinuation (n=168), late starting (n=73) and persistent usage (n=102) of statins (Log rank <0.0001 in each).

(See color figure at http://www.turkiyeklinikleri.com/journal/cardiovascular-sciences/1306-7656/)

TABLE 3: Cox regression models for incident CHD in men and women, stratified by presence of MetS*

	Total		Men		Women	
	HR	95% CI	HR	95% CI	HR	95% CI
Total sample	359/2810†*		163/1353†		196/1457†	
Sex, female	1.25	0.96; 1.62				
Age, 11 years	1.54	1.38; 1.71	1.59	1.35; 1.86	1.51	1.31; 1.75
Statin usage	2.42	1.80; 3.25	3.20	1.94; 5.27	2.22	1.54; 3.21
Current vs never smoking	1.27	0.97; 1.67	1.60	1.08; 2.38	1.01	0.66; 1.55
Presence of diabetes, y/n	2.15	1.60; 2.90	1.46	0.90; 2.38	3.03	2.06; 4.46
Waist circumference, 12 cm	1.27	1.13; 1.43	1.27	1.05; 1.53	1.28	1.10; 1.48
Systolic BP, 24 mmHg	1.27	1.15; 1.43	1.33	1.13; 1.61	1.21	1.05; 1.40
NonHDL-chol., 35 mg/dl	1.23	1.11; 1.32	1.23	1.04; 1.42	1.23	1.07; 1.37
HDL-cholesterol, 12 mg/dl	0.82	0.73; 0.93	0.85	0.71; 1.05	0.78	0.68; 0.92
Without MetS	99/1428†*		56/745†		43/683†	
Sex, female	1.29	0.78; 2.13				
Age, 11 years	1.67	1.40; 2.00	1.82	1.41; 2.33	1.52	1.15; 2.02
Statin usage	1.82	0.89; 3.73	2.97	1.09; 8.09	1.34	0.46; 3.90
Current vs never smoking	1.42	0.86; 2.37	1.69	0.86; 3.31	1.28	0.56; 2.93
Presence of diabetes, y/n	2.99	1.40; 6.40	2.22	0.88; 5.57	4.42	1.04; 18.8
Waist circumference, 12 cm	1.46	1.15; 1.84	1.53	1.08; 2.18	1.43	1.04; 1.97
Systolic BP, 24 mmHg	1.21	0.95; 1.50	1.24	0.89; 1.73	1.18	0.82; 1.69
NonHDL-chol., 35 mg/dl	1.23	1.04; 1.52	1.15	0.87; 1.47	1.37	1.04; 1.80
HDL-cholesterol, 12 mg/dl	0.92	0.75;1.13	0.94	0.70; 1.25	0.89	0.65; 1.18
With MetS	260/1381†*		107/607†		153/774†	
Sex, female	1.17	0.85; 1.61				
Age, 11 years	1.48	1.30; 1.69	1.51	1.22; 1.86	1.51	1.28; 1.78
Statin usage	2.59	1.87; 3.60	3.40	1.91; 6.05	2.41	1.62; 3.60
Current vs never smoking	1.23	0.89; 1.70	1.57	0.96; 2.58	0.96	0.58; 1.59
Presence of diabetes, y/n	1.96	1.41; 2.71	1.25	0.71; 2.22	2.82	1.87; 4.26
Waist circumference, 12 cm	1.15	1.001; 1.33	1.09	0.85; 1.38	1.20	1.00; 1.41
Systolic BP, 24 mmHg	1.24	1.10; 1.43	1.33	1.07; 1.65	1.21	1.02; 1.43
NonHDL-chol., 35 mg/dl	1.19	1.07; 1.32	1.23	1.04; 1.52	1.15	1.00; 1.32
HDL-cholesterol, 12 mg/dl	0.83	0.71; 0.98	0.87	0.65; 1.15	0.78	0.65; 0.95

Cases of prevalent CHD excluded.

Units following the independent variables denote 1 standard deviation.

Eighty males and 188 females were statin users; 93 males and 112 females had diabetes at baseline.

Former smoking, included in each model, was not significant in any. Significant values are highlighted in boldface.

†Number of cases/number at risk

*Sum covariates were missing in 5% of the sample.

TABLE 4: Logistic regression for the association of statin usage in participants with serum lipoprotein(a), measured at baseline and final examinations.

	Total		Men		Women	
	HR	95% CI	HR	95% CI	HR	95% CI
At baseline	71/129†*		20/48†		51/81†	
Sex, female	2.46	1.12; 5.41				
Age, 11 years	2.02	1.28; 3.15	1.88	0.94; 3.80	2.13	1.24; 4.19
Lipoprotein(a)¶ mg/dl 3-fold	1.20	0.95; 1.52	1.01	0.70; 1.46	1.41	0.99; 2.01
Presence of diabetes	2.01	0.72: 5.58	1.92	0.40: 9.20	2.20	0.53: 9.07
Final examination	174/1950†*		64/908†		110/1042†	
Sex, female	0.73	0.52; 1.03				
Age, 11 years	1.38	1.18; 1.62	1.33	1.04; 1.67	1.44	1.17; 1.78
Lipoprotein(a)¶ mg/dl 3-fold	1.12	1.004; 1.25	1.19	1.003; 1.40	1.08	0.93; 1.25
Presence of diabetes	3.57	2.51: 5.09	2.46	1.42: 4.26	4.78	2.99: 7.62

¶log-transformed values. †Number of users/total participants involved

350 individuals had diabetes at final examination.

Kaplan-Meier analyses (taking also into account change in statin status over time) demonstrated in statin users highly significantly separating curves for incident CHD, compared with non-users. Cox regression analysis for incident CHD disclosed an HR of 2.42 (95% CI 1.80; 3.25) for statin usage, after adjustment for conventional risk factors, and irrespective of MetS-status in males. This risk imparting may be attributed to an Lp(a)-modifying effect of statins, with or without mediation of autoimmune activation, which presumably contributed significantly to the CHD risk.

Validity of conclusions on net effect in statin users on the whole, cannot necessarily be applied to subgroups of populations in whom a null-effect or an adverse effect may be concealed. Our findings suggest that people with abdominal obesity and hypertriglyceridemia are at risk of statins mediating a modification in Lp(a) concentrations.

INDICATION OF STATINS AND RISK PROFILE OF RELATED PARTICIPANTS

Half of participants on statin drugs had nonHDL-cholesterol concentrations exceeding 160 mg/dl, the threshold recommended by ATP-III guidelines for primary prevention with statins.[15] HDL-cholesterol exhibited evidence of impaired atheroprotection, particularly in individuals without MetS. Kaplan-Meier analyses yielded a 10-year CHD risk of over 20% in strata of the sample with lipid-lowering therapy. Hence, statin administration appears to be appropriately indicated.

HDL-dysfunction in individuals without MetS seemed to be clearly linked to enhanced inflammation largely mediating a wide waist, while in those with MetS, the CHD risk conferredby waist circumference became attenuated to a great extent concomitantly with a less common HDL dysfunctionality (due to low HDL-C selected by a definition serving as referent). Findings suggest that a pro-inflammatory state (along with HDL dysfunction) develops among middle-aged Turkish men before they acquire the MetS components that currently define MetS. Enhanced inflammation and HDL dysfunction may originate from excess oxidized phospholipids situated on Lp(a) in men; in women having elevated Lp(a) levels, the statin effect may get prominence only after autoimmune activation leads to MetS.

DIABETOGENIC (AND POSSIBLE ATHEROGENIC) EFFECT OF STATINS IN CERTAIN POPULATION SUBSETS

Our hypothesis offers an explanation as to why statins clearly have the potentiality to induce diabetes.[5,6,18] The large JUPITER and PROSPER trials of all 13 trials evaluated were the ones disclosing the highest (1.3-fold) odds for diabetes risk in individuals on statin treatment: older age, higher BMI and C-reactive protein (CRP), impaired HDL dysfunction, a high proportion of elevated triglycerides and impaired fasting glucose were characteristics, compared to other trials.[6] A study on 42,000 beneficiaries of Taiwan National Health Insurance evaluated outcomes at 7.2 years among statin users in the general population.[18] Though statin users had overall fewer major cardiovascular events (HR 0.91), HR of diabetes development was increased (1.15 [95%CI 1.08 to 1.22]). Subjects with statin-mediated diabetes had a significantly increased risk of cardiovascular events (HR 1.38) compared with nondiabetic controls. In analyzing the ~154,000 postmenopausal women of the Women's Health Initiative, 7% of whom was taking statin drugs at baseline, statin use was found to increase diabetes risk at a HR 1.48 (95% CI 1.38; 1.59), after adjusting for multiple potential confounders and regardless of types of statin medication and presence of cardiovascular disease.[19]

Compared with lower dose statin therapy, atorvastatin 80 mg/day increased new-onset diabetes by 24% when 2 or more (MetS) risk factors for diabetes existed at baseline in the TNT and IDEAL trials, suggesting the special role of proneness to MetS in the potential diabetogenic effect of statins.[20]

A paradoxical progression of atherosclerosis (carotid intima-media thickness) with greater LDL-cholesterol reduction during ezetemibe therapy was observed in 159 patients with coronary artery disease treated with a statin and randomized to ezetimibe within ARBITER 6-HALTS trial.[21] Given the patient group characterized by susceptibility to impaired glucose tolerance (predominance of mid-

dle-aged and elderly non-smoking male adults, high prevalence of abdominal obesity, impaired fasting glucose and diabetes), the progression in carotid intima-media thickness increasing linearly with greater LDL-cholesterol reduction suggests that ezetimibe and/or statins induced a mechanism similar to that observed in patients with rheumatoid arthritis preceding its clinical onset.[22] In a recent report of the Swedish Obese Subjects study on bariatric surgery and long-term cardiovascular effects, lipid-lowering medication among the adjusted variables emerged a significant independent factor conferring a 2-fold HR for total cardiovascular end-points in men.[23]

The argument against our main finding that subjects receiving statins had a higher risk to begin with is not justified since the higher risk was related only to a moderate age difference and not to other risk factors comprised in the Framingham risk score. Over twice a risk in statin users than in nonusers persisted after adjustment for age and other conventional factors. The characteristics of statin users to tend to impaired glucose tolerance and hypertriglyceridemic waist phenotype are crucial.

OBSERVATIONS SUGGESTIVE OF UNDERLYING EXCESS Lp(a) AND ITS OXIDIZED PHOSPHOLIPIDS

Participants treated at baseline with statins had lower apoB than those not treated, despite having similar LDL-C levels; this can be ascribed to Lp(a) being comprised in an immune complex whereby Lp(a) protein mass was not assayable while Lp(a) cholesterol was contained in the measured non-HDL-cholesterol. Since apoA-I concentrations were significantly higher in statin-treated individuals, it may be presumed that apoA-I was aggregated to Lp(a) to form an immune complex.

Lp(a) protein mass is generally quantified using immunoassay methods. Signals produced by different antibodies to apo(a) (due to varying number of kringle 4 repeats) have been suggested to account for a degree of variability of Lp(a) measurements.[24] Data in Fig. 5 of the study by Baudhuin and associates provide evidence in numerous samples of a) lower than anticipated Lp(a) mass as well as of b) a wide range of intermediate and elevated Lp(a) mass with undetectable Lp(a) cholesterol by ultracentrifuge (highly correlated with whole serum Lp(a) cholesterol).[24] Discrepancy in both sets of samples is consistent with Lp(a) protein being involved in an autoimmune process. Complexes of ß2-glycoprotein I-Lp(a) have been, indeed, found associated with stable CHD, and immunoassay results have been pointed out to be potentially interfered, due to failure by capture antibodies to recognize oxidized epitopes.[25]

GENDER AND PRESENCE OF MetS MODULATE THE NET STATIN EFFECT

Cox analyses showed that the whole of excess CHD risk documented in Kaplan-Meier analyses cannot be accounted for by an inherent excess risk of individuals subjected to statin therapy. We found a robust association of a 2-3-fold CHD risk among statin users with MetS independent of conventional risk factors, especially nonHDL-cholesterol. However, in individuals without MetS, findings were consistent with different mediation: whereas statin usage in women seemed to mediate increases in Lp(a) and triglycerides, statins appeared to induce an otoimmune activation in men whereby Lp(a) and triglyceride levels declined, and the significant risk imparted by the presumed immune complex formation rested nearly solely on statin usage, as judged by a loss of nonHDL-cholesterol's association with CHD risk.

FURTHER EVIDENCE FOR STATIN ADMINISTRATION MODIFYING Lp(a), AND EXPLANATION

Statins either do not affect Lp(a) levels or cause an increase, often dose dependent.[26-28] When one evaluates changes in Lp(a) in response to statins as a mean percentage change from baseline in the same patients, an increase in Lp(a) is consistently seen among patients.[27-30] It may be postulated that the statin-mediated increase in Lp(a) levels and the associated CHD risk are confined to subjects with enhanced low-grade inflammation. Gonbert et al. stated that statins might possibly induce modulation of apo(a) proteolysis when administered for a prolonged period and urged the assessment of the role of statins in the fragmentation of the apo(a)

moiety.[26] The permeability-glycoprotein transport system might conceivably be interacted by antibodies against apo(a) glycoprotein of Lp(a), via inhibition by statins, which may be contributing to elevated cardiovascular risk.[31]

Poor LDL-cholesterol lowering by statins was observed among apoE ε4 allele carriers, but the link of statins to hypertriglyceridemic dyslipidemias is independent of apoE genotype according to our reported and unpublished observations.[7,32,33]

In a metabolic study on simvastatin-treated patients and matched controls, treated patients were found glucose intolerant and muscle coenzyme Q_{10} content was decreased, accompanied by decreased maximal mitochondrial oxidative phosphorylation capacity.[34]

We provided herein evidence in both genders for statin usage significantly modifying the levels of Lp(a), independently of traditional risk factors. Two potential pathways are available for "raised" Lp(a) regarding risk of diabetes and CHD: excess levels reflecting a pro-inflammatory state confer a direct risk. The second, perhaps, more often pathway is mediated by immune complex formation (in men though not in women) comprising Lp(a) as antigen (and apoA-I or adiponectin as an antibody) whereby Lp(a) is assayed lower than actually existing, due to partial lack of assay ability of the aggregated Lp(a) protein. The immune complex may induce diabetes or CHD, again via concurrent pro-inflammatory state. The immune complex induced by Lp(a) may involve other proteins serving as antigen (such as thyrotropin or creatinine in our experience). The ultimate net effect of analogous processes in the population at large is an inverse relationship between Lp(a) and presence of diabetes (shown in a meta-analysis[35]) and a slightly positive relationship between Lp(a) and presence of CHD.[35,36]

Implications: A notion that enhanced low-grade inflammation induced by excess oxidized Lp(a) may contribute substantially to the risk of CHD implicates the need of surmounting the difficulties in identifying such individuals in whom Lp(a) concentrations are low or at an intermediate level (<30 mg/dl found in ¾ of Turkish adults). Assaying immunometrically Lp(a) and measuring electrophoretically serum Lp(a) cholesterol, or measuring oxidized Lp(a) using an ELISA system with special monoclonal antibody may possibly provide a clue in discrepant instances to the operation of autoimmune activation for the clinician.[37]

Strengths and limitations: The large population-based sample size of both sexes, the prospective design, adequate length of follow-up and number of CHD cases, are all clear strengths of the current study. Sensitivity analysis performed for altered statin usage over time is a further strength. Evaluation of the study aim only in a primary prevention setting using Cox proportional hazard models, together with adjustment for conventional cardiovascular risk factors (including non-HDL-cholesterol), allowed the eliciting of robust hazard ratios for the independent association with risk of incident CHD of statin therapy, the overall cardiovascular event-reducing effect of which is established. Since the studied population is one prone to MetS, findings may not be applicable to younger population segments or populations with a low prevalence of MetS. Confirmation of results, beyond the stated ARBITER 6-HALTS trial, is warranted in future studies.

Conclusions: In a middle-aged population-based sample having a relatively high MetS prevalence and being free of CHD, statin was found to be medicated at baseline in a group of individuals at high cardiovascular risk characterized by MetS components but similar HDL- and LDL-cholesterol levels, compared to non-users. A 2- to 3-fold incident CHD risk was observed in statin users compared with non-users, independent of conventional cardiovascular risk factors and in men irrespective of MetS-status. This risk imparting is considered to be mediated by modified Lp(a) levels with or without subsequent autoimmune activation.

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