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Long-Term Use of Lipid-Lowering Drugs Slows Progression of Carotid Atherosclerosis

The Tromsø Study 1994 to 2008

Marit Herder, Kjell Arne Arntzen, Stein Harald Johnsen, Anne Elise Eggen, Ellisiv B. Mathiesen

Objective—Data on the effect of lipid-lowering drugs (LLD) on carotid atherosclerosis outside clinical trials are limited. The aim of this study was to determine the effect of LLD on change in carotid intima media thickness and total plaque area in a general population.

Approach and Results—Subjects were 1532 women and 1442 men who participated in a longitudinal population-based study with ultrasound examination of intima media thickness and total plaque area in the right carotid artery at baseline and after 13 years follow-up. Long-term use of LLD was defined as use for >5 years, any-time use of LLD was defined as use at baseline or at 6 years or at 13 years of follow-up. In multivariable models adjusted for age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, prevalent cardiovascular disease, and daily smoking, long-term use of LLD had a protective effect on progression of both intima media thickness (β=–0.0387 mm; P=0.002) and total plaque area (β=–0.400 mm^2; P=0.006). There was a weaker protective effect of any-time use of LLD on progression of intima media thickness (β=–0.024 mm; P=0.046) and total plaque area (β=–0.318 mm^2; P=0.06).

Conclusions—LLD protected against progression of carotid atherosclerosis. The protective effect was strongest in long-term users. (***Arterioscler Thromb Vasc Biol***. 2013;33:858-862.)

Key Words: atherosclerosis ■ carotid artery ■ intima media thickness ■ lipid-lowering treatment ■ plaque ■ population-based study

High cholesterol levels are known risk factors for cardiovascular morbidity, mortality, and atherosclerosis. Since the mid-1990s, statins have been the most important lipid-lowering drugs (LLD) in primary and secondary prevention of cardiovascular disease. Statins have reduced the incidence of myocardial infarction and stroke in several randomized clinical trials.[1–8] Carotid intima media thickness (IMT) and plaques assessed by ultrasound are established markers of carotid atherosclerosis, and are used as surrogates for cardiovascular disease. Randomized controlled trials and meta-analyses of randomized controlled trials have shown that statins slow the progression of intima media thickening.[9,10] A recent review indicates that statins may have beneficial effects also on plaque progression, but most of the included studies were small observational studies.[9] In a randomized controlled trial of rosuvastatin versus placebo in 492 low-risk patients, plaque progression was significantly lower in the statin group.[11] In a study on 4378 patients referred to stroke and atherosclerosis prevention clinics, the annual rate of plaque progression decreased after implementation of a more intensive medical therapy strategy, which included increase of statin to the maximum tolerated dose and addition of ezetimibe to patients already on maximum tolerated statin dose.[12]

Although randomized clinical trial is gold standard for proving the effect of a given intervention, the generalizability may be limited. There is little knowledge on whether the effect of LLD on atherosclerosis progression seen in randomized clinical trials also applies to other practice settings. The purpose of the present study was to assess the impact of LLD on progression on carotid atherosclerosis in a general population.

The Tromsø study is a single-center, longitudinal population study with repeated surveys of the inhabitants of the municipality of Tromsø, Norway. We have repeatedly, over a period of 13 years, obtained information on the use of LLD and cardiovascular risk factors, and measured IMT and total plaque area (TPA) in the right carotid artery.[13] This enables assessment of the effect of use of LLD and change in carotid atherosclerosis in unselected subjects belonging to a general population.

Materials and Methods

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

Results

Mean observation time was 13.2 years. Of the 2974 participants, 190 women and 253 men had used LLD >5

Table 1. Change in Risk Factor Levels Between Baseline and Follow-Up in Never, Any-Time, and Long-Term Users of Lipid-Lowering Drugs (LLD)

	Never-Users of LLD (n=2112)			Any-Time Users of LLD (n=419)			Long-Term Users of LLD (n=443)		
	Baseline	Follow-Up	P Value	Baseline	Follow-Up	P Value	Baseline	Follow-Up	P Value
Age	58.6 (10.4)	68.6 (10.4)	…	58.44 (7.0)	71.44 (7.0)		58.5 (6.5)	71.5 (6.5)	
Male sex	967 (45.6)	…	…	222 (53.8)	…		253 (57.1)	…	
Systolic BP, mm Hg	137.07 (24.4)	145.85 (19.2)	<0.0001	144.1 (20.4)	147 (21.9)	<0.0001	147.1 (20.9)	149.8 (23.9)	0.03
Diastolic BP, mm Hg	80.07 (11.9)	78.75 (10.7)	<0.0001	83.8 (11.6)	77.1 (10.4)	<0.0001	85.6 (11.6)	77.4 (10.7)	<0.0001
BMI, Kg/cm^2	25.6 (3.4)	26.7 (4.0)	<0.0001	26.2 (3.2)	27.5 (4.0)	<0.0001	27.03 (3.55)	28.19 (4.14)	<0.0001
Triglycerides, mmol/L*	1.50(0.92)	1.45 (0.77)	0.01	1.75 (1.02)	1.49 (0.78)	<0.0001	1.61 (0.81)	2.04 (1.20)	<0.0001
HDL-cholesterol, mmol/L	1.56 (0.41)	1.59 (0.46)	<0.0001	1.49 (0.369)	1.47 (0.78)	0.7	1.42 (0.38)	1.43 (0.41)	0.6
Total cholesterol, mmol/L	6.37 (1.17)	5.97 (1.03)	<0.0001	6.97 (1.1)	4.94 (1.19)	<0.0001	7.50 (1.21)	4.94 (0.99)	<0.0001
LDL-cholesterol, mmol/L	4.13 (1.07)	3.85 (0.92)	<0.0001	4.72 (1.01)	2.97 (1.03)	<0.0001	5.17 (1.12)	2.98 (0.82)	<0.0001
Daily smoking (yes/no)	584 (28.2)	331 (16.0)	<0.0001	111 (27.5)	58 (14.4)	<0.0001	130 (29.8)	54 (12.4)	<0.0001
Diabetes mellitus (yes/no)	21(1.0)	102 (4.93)	<0.0001	11 (2.8)	54 (13.5)	<0.0001	11 (2.5)	68 (15.5)	<0.0001
CVD (yes/no)	62 (3)	155 (7.5)	<0.0001	49 (12.2)	198 (49.3)	<0.0001	118 (27.2)	271 (62.4)	<0.0001
Use of medication									
Antihypertensives (yes/no)	109 (5.2)	657 (31.1)	<0.0001	57 (13.8)	298 (72.3)	<0.0001	93 (21.2)	348 (79.3)	<0.0001
Antidiabetics (yes/no)	11 (0.5)	74 (3.5)	<0.0001	6 (1.5)	44 (10.7)	<0.0001	7 (1.6)	59 (13.3)	<0.0001
LLD (yes/no)	…	…		2 (0.69)	293 (86.9)	<0.0001	52 (11.7)	441 (99.5)	<0.0001
Measures of atherosclerosis									
IMT, mm	0.786 (0.164)	0.956 (0.2129	<0.0001	0.861 (0.173)	1.028 (0.221)	<0.0001	0.893 (0.168)	1.047 (0.227)	<0.0001
Plaque present (yes/no)	697 (32)	1104 (52)	<0.0001	216 (52.39)	284 (68.8)	<0.0001	254 (57.6)	317 (71.9)	<0.0001
TPA, mm^2*	0 (6.42)	5.138 (21.861)	<0.0001	4.25 (14.335)	15.355 (31.606)	<0.0001	6.85 (18.73)	17.52 (36.78)	<0.0001
GSM	43.96 (20.99)	67.26 (22.09)	<0.0001	44.88 (20.63)	67.37 (20.32)	<0.0001	45.58 (21.51)	65.74 (21.11)	<0.0001

BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; GSM, grey scale median; HDL, high-density lipoprotein; IMT, intima media thickness; LDL, low-density lipoprotein; LLD, lipid-lowering drugs; and TPA, total plaque area.

All values are means (SD) or numbers (%), unless indicated.

*Median (interquartile range).

Long-term use of LLD was defined as use for >5 years; any-time use of LLD was defined as use of LLD in any 1 of the 3 surveys, excluding long-term users.

years (Table 1). At baseline, in 1994 to 1995, the proportion of current LLD users among the study participants was low 1.6% (n=51). In the 6th survey (2007–2008), the percentage of current users had risen to 27% (n=799). At baseline, 89% of those who reported brand names (n=46) used statins, the rest used cholestyramine. At follow-up, all who reported brand names (n=713) used statins, whereas only 4 persons used ezetimib. Use of LLD was associated with male sex, higher age, systolic blood pressure, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and higher baseline prevalence of cardiovascular disease and antihypertensives than never-use of LLD. LLD users had significantly thicker intima media layer, higher plaque prevalence, and a larger TPA.

Change in risk factor levels over time is shown in Table 1. In general, there was a favorable change in lipid levels from baseline to follow-up, most pronounced in long-term LLD group. Mean change (SD) in LDL-cholesterol was –2.22 (1.05) mmol/L in long-term users, –1.77 (1.11) mmol/L in any-time users, and –0.31 (0.79) mmol/L in never-users (P<0.0001). The proportion of daily smokers fell substantially in the whole cohort, whereas body mass index and diabetes mellitus prevalence increased.

The multivariable-adjusted mean change (95% confidence interval [CI]) in IMT was 0.174 mm (95% CI, 0.167–0.182) in long-term users, 0.162 mm (95% CI, 0.145–0.179) in any-time users, and 0.139 mm (95% CI, 0.122–0.156) in never-users (P for trend, 0.002; Figure, A). The corresponding numbers for mean multivariable-adjusted change in TPA (square-root-transformed) was 1.450 (95% CI, 1.342–1.558) in long-term users, 1.391 (95% CI, 1.151–1.630) in any-time users, and 1.098 (95% CI, 0.854–1.342) in never-users (P for trend, 0.009; Figure, B).

In multivariable-adjusted regression analysis, long-term use of LLD was an independent predictor for both ΔIMT (β=–0.0387 mm; P=0.0002) and ΔTPA (β=–0.400 mm^2; P=0.006), showing a protective effect against progression of atherosclerosis (Table 2). Any-time use of LLD also showed a protective, but weaker effect on ΔIMT (β=–0.024 mm; P=0.046) and ΔTPA (β=–0.318 mm^2; P=0.06; Table 2), indicating a dose–response relationship. The estimates were not substantially changed when we excluded participants who reported cardiovascular disease at baseline or at follow-up (n=649), neither for long-term use of LLD (β=–0.0616 mm; P<0.0001 for ΔIMT; and β=–0.376 mm^2; P=0.02 for ΔTPA) or any-time use of LLD (β=–0.0308 mm; P=0.002 for ΔIMT; and
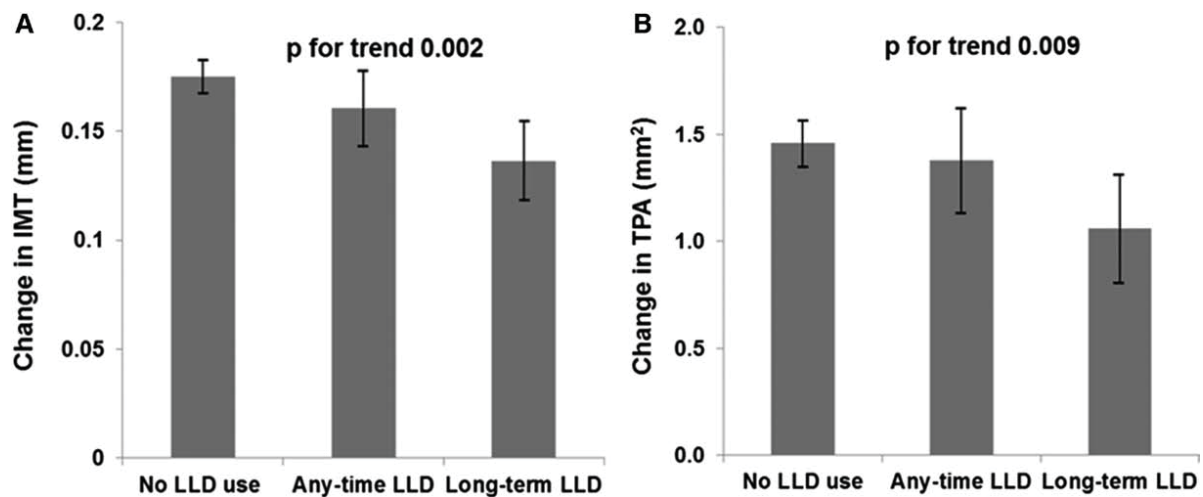
Figure. Change in IMT (**A**) and TPA (**B**) in never use, any-time use, and long-term use of lipid-lowering drugs (LLD). IMT indicates intima media thickness; and TPA, total plaque area.

β=–0.260 mm²; *P*=0.2 for ΔTPA). Long-term or any-time use of LLD was not independently associated with change in GSM.

Discussion

The main finding of our study was that long-term use of LLD, as well as any-time use of LLD, protected against progression of IMT and TPA during the 13 years observation time. The protective effect of long-term use of LLD on atherosclerosis progression was stronger than for any-time use of LLD, indicating a dose–response relationship. This coincided with a favorable change in lipid levels, most pronounced in long-term LLD users.

The study results imply that the effect of LLD on progression of carotid atherosclerosis seen in randomized clinical trials[3,10,14] and patient series[12,15] also applies to subjects belonging

to the general population. A meta-analysis of 11 randomized controlled trials showed regression of IMT in 7 trials and slowing of progression in 4 trials, indicating a benefit of statin in early stages of the atherosclerotic process.[16] Another review showed that the strength of the statin effect on IMT was closely associated with reduction in LDL-cholesterol.[17] This is in accordance with our findings, where the reduction of LDL was greatest in the long-term users.

Progression of carotid IMT and TPA are correlated, but probably represent different atherosclerotic entities. Few clinical studies have studied the effect of statins on progression of carotid plaque burden, and most of these have been with small sample size.[9] One larger study used a plaque score method based on plaque presence and severity, and showed a significant difference in plaque score change between statin use and placebo,[18] and similar results have also been found

Table 2.   Multivariable-Adjusted Regression Analysis* of the Effect of Use of Lipid-Lowering Drugs (LLD) and Cardiovascular Risk Factors on Progression of Atherosclerosis

	ΔIMT, mm		ΔTPA,† mm²	
	β (SE)	*P* Value	β (SE)	*P* Value
Age, y	0.0005 (0.0004)	0.2	0.0278 (0.005)	<0.0001
Male sex	0.019 (0.007)	0.006	0.347 (0.098)	0.0004
Systolic blood pressure, mm Hg	0.0002 (0.0002)	0.4	0.008 (0.002)	0.001
HDL-cholesterol, mmol/L	−0.009 (0.009)	0.3	0.0723 (0.123)	0.6
Total cholesterol, mmol/L	0.011 (0.003)	0.0005	0.149 (0.0042)	0.0005
Cardiovascular disease (yes/no)	0.017 (0.013)	0.2	0.211 (0.181)	0.243
Daily smoking (yes/no)	0.024 (0.007)	0.001	0.568 (0.104)	<0.0001
Use of LLD				
Any-time use of LLD	−0.024 (0.012)	0.046	−0.318 (0.172)	0.06
Long-term use of LLD (yes/no)	−0.0387 (0.01)	0.0002	−0.400 (0.146)	0.006

HDL indicates high-density lipoprotein; IMT, intima media thickness; ΔIMT and ΔTPA, change in IMT and TPA from baseline to follow-up; and TPA, total plaque area.

Values are regression coefficients (SE) expressed in mm change in IMT and mm² change in TPA for a 1-unit/SD change in continuous variables and for presence vs absence of categorical variables.

Long-term use of LLD was defined as use for >5 yr; any-time use of LLD was defined as use of LLD in any 1 of the 3 surveys, excluding long-term users.

*Each variable is adjusted for all the other variables presented in the table.

†Square-root-transformed values.

for coronary plaque.[11] Statins were the dominating LLD in our study, whereas only 4 participants used a combination of statins and ezetimib, which has been found to be associated with regression of TPA,[15] but with increase in IMT.[19] A recent review of 9 randomized and 8 observational studies with number of participants ranging from 8 to 149 showed that statin treatment tended to halt plaque progression and increase plaque echogenicity.[9] We observed no effect of statins on plaque echogenicity (GSM) in our study.

Our study has some important weaknesses. The use of LLD in the population increased considerably over the 13-year study period. It can be questioned whether our estimates of use of LLD over time truly reflect the participants' use of LLD in the observation period. We calculated duration of use based on information from both questionnaires and lists of current medication at 3 points in time. Although previous studies have shown that repeated self-reported use of drug that are used regularly reflect chronic exposure,[20,21] subjects may have failed to report use of LLD because they were not aware of the nature of the drug they were taking, and they could have forgotten to fill-in all brand names in the medication lists. The study results may have been influenced by selection bias caused by nonattendance at follow-up because of death, disease, or disability.[13] Progression of atherosclerosis may have been more pronounced and use of LLD more frequent in nonattendees. However, immortal time bias is avoided,[22] as the outcome variable is progression of atherosclerosis over a 13-year period, and can be measured in both users and nonusers of LLD. Progression of IMT is prone to measurement error, and is suggested as the reason for lack of association between progression of IMT and cardiovascular end points in a recent meta-analysis.[23] Use of 3-dimensional ultrasound to measure plaque volume could have increased the ability to demonstrate change in plaque burden.[24] The use of different ultrasonography equipment in the 4th and the 6th survey, and nonstandardized uptake angles is likely to have increased the measurement error.[25] Any such misclassification would affect the exposed and unexposed groups equally. Furthermore, misclassification both of the exposure to LLD and of progression of atherosclerosis would lead to underestimation of the true effect of use of LLD.

It has been debated whether statins have a role as a primary prevention tool for cardiovascular disease, or whether the effect is limited to secondary prevention in patients who manifest disease.[26–29] In our study, use of LLD independently predicted slower progression of carotid atherosclerosis also in participants without prevalent cardiovascular disease. However, the observational study design does not allow inferences about whether the beneficial effect of LLD on atherosclerosis outweighs any possible negative effects of LLD in primary prevention.

The strengths of the study are the large study cohort, the population-based design, and a follow-up of >13 years, enabling us to assess whether the effect of LLD on atherosclerosis also applies to subjects treated outside the more rigorous terms of a randomized controlled trial.

In conclusion, our study shows that LLD slowed the progression of carotid atherosclerosis in the setting of a population-based observational study. The protective effect was strongest for long-term users.

Disclosures

None.

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Significance

Our population-based longitudinal study has shown that lipid-lowering drugs (LLD) have a protective effect on the progression on carotid atherosclerosis in a general population, including healthy subjects with no clinical disease. There was a stronger protective effect in long-time users (>5 years) than in any-time users (use of LLD at any point of time in the observational period) and never-users, indicating a dose–response relationship. Change toward a more favorable LDL-cholesterol level was most pronounced in long-time users. The estimates did not change significantly when subjects with cardiovascular disease were excluded. Our study could indicate that LLD may be useful in primary prevention of atherosclerosis progression.

Materials and methods

Subjects

Eligible for the present study were all who participated in the carotid ultrasound examination in the 4th (1994-1995; baseline) and the 6th (2007-2008; follow-up) survey of the Tromsø study. The follow-up time was 13 years. In the 4th survey, all inhabitants aged 55–74 years and random 5-10% samples of subjects in the age groups 20–54 years and 75–84 years were invited to a carotid ultrasound examination, and 6727 (76% of the eligible population) attended. During follow-up, 1515 persons died and 468 persons moved out of the municipality. Of the remaining 4744 subjects who were invited to participate in the 6th survey, 2975 subjects attended the follow-up carotid ultrasound examination. One participant was excluded due to lack of valid written consent, leaving 2974 subjects to be included in the present study.

The Tromsø Study is approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Data Protection Authority.

Lipid-lowering drugs

To assess the use of LLD over time, we provided data on use of medication from the 4th, 5th and 6th surveys. Information was based on questionnaire data and self-reported written lists of all current medication, checked by a trained technician. In the 4th survey (baseline), participants below the age of 70 were asked 'Have you used cholesterol lowering drugs during the last 14 days?' (yes/no). In the 5th survey in 2001-2002, all participants were asked about current or previous use of LLD ('Do you use cholesterol lowering drugs?', answer categories: currently/previously/never). In the 6th survey, all participants were asked about current or previous use of LLD ('Do you use, or have you used cholesterol lowering drugs?', answer categories: currently/previously/never) and the age when they first started with LLD

('If you use or have used cholesterol lowering drugs, how old were you the first time?'). In addition, the participants were asked to write a list of the brand names of all current medication they had used the previous week (4th survey) or the preceding four weeks (5th and 6th survey) and/or bring the medication with them to the study center. The questionnaire was checked by a trained technician at the study site, and participants had to confirm if no medication use was reported. Based on data from all three surveys, we calculated the duration of use of LLD. Any-time use of LLD was defined as use of LLD in any one of the three surveys, excluding those with a known duration of more than five years. Long-term use of LLD was defined as use either more than 5 years (current age minus age at start), or reported use in at least two of the three surveys (each conducted more than 5 years apart).

Cardiovascular risk factors at baseline

Non-fasting lipid levels were measured at baseline and follow-up. In the 4th survey, lipid levels were measured twice with an interval of 4–12 weeks and the averages of these values were used in the analyses. Analyses of non-fasting serum total cholesterol, HDL-cholesterol and triglycerides were done by enzymatic colorimetric methods. As serum low density lipoprotein (LDL) concentration was not measured in the 4th survey, we calculated LDL levels according to Friedewald's formula: LDL-cholesterol = Total cholesterol – HDL-cholesterol – (0.45 x triglycerides) in subjects with triglyceride levels below 4.52 mmol/L. LDL was analyzed by homogeneous enzymatic colorimetric method in the 6th survey. All analyses were performed at the Department of Laboratory Medicine, University Hospital of North Norway. Height and weight were measured in participants wearing light clothing and no footwear. Blood pressure was recorded three times at one-minute intervals after two minutes of seated resting with the use of an automatic device (Dinamap Vital Signs Monitor 1846, Criticon) and by specially trained technicians. The mean of the last two recordings was used for analyses.

Information on angina pectoris, myocardial infarction, stroke, daily smoking, diabetes, use of antihypertensives and antidiabetics was obtained from questionnaires at baseline and follow-up. Cardiovascular disease was defined as prevalent angina pectoris and/or previous myocardial infarction and/or stroke.

Carotid ultrasound measurements

High-resolution B-mode ultrasonography at baseline was performed with Acuson Xp10 128, ART-upgraded duplex scanners equipped with 7.5 MHz linear array transducers, while GE Vivid 7 duplex scanners with linear 12 MHz transducers were used at follow-up.[1] The ultrasonographers were blinded to laboratory and clinical data. Subjects were examined in the supine position with the head slightly tilted to the left side. The sonographers were instructed to view the arteries from all possible angles, in order to find the optimal view for visualization of plaque and IMT in each subject. No fixed angle of insonation was used. ECG-triggered uptakes of the 10 mm distal segment of the far (CCA-FW-IMT) and near wall (CCA-NW-IMT) of the common carotid artery and of the proximal 10 mm segment of the far wall of the carotid bifurcation (BULB-FW-IMT) were obtained. Plaques were included in the IMT measurements if present in the predefined location of interest. Mean IMT from the 3 pre-selected images was calculated for each location. The average of the mean IMT from the three locations was used in the analyses. A plaque was defined as a localized protrusion into the vessel lumen of more than 50% thickening compared to the adjacent IMT. Six locations were scanned for the presence of plaques, the far and near walls of the right common carotid artery (CCA), bifurcation (bulb) and internal carotid artery (ICA). The outline of each plaque was marked manually on still images, with calculation of plaque area. In subjects with more than one plaque, TPA was calculated as the sum of all plaque areas. Plaque echogenicity was assessed as the standardized median of the gray scale distribution of each plaque (GSM).[2] In subjects with more than one plaque, the GSM of the total plaque area was estimated as a

weighted mean of the GSM value of each single plaque. There was acceptable inter- and intra-observer and inter-equipment reproducibility of IMT and plaque measurements.[1-4]

Statistical analysis

Differences between groups were analyzed using *t*-test or Wilcoxon rank sum tests (continuous variables) and χ (dichotomous variables). Within-group changes between baseline and follow-up were tested by paired (repeated) *t*-test for continuous variables and McNemar's test for categorical variables. Values are presented as means (SD), median (interquartile range) or numbers (%). TPA was square-root-transformed to approximate normal distribution. Change in IMT (ΔIMT) and squared TPA (ΔTPA) was calculated subtracting the values obtained in the 4th survey from the values from the 6th survey. We used ANCOVA (proc glm procedure in SAS) to calculate the adjusted mean change in IMT and TPA in categories of LLD use, adjusted for age, sex and cardiovascular risk factors. Linear regression models were used to calculate p for trend across categories (never-, anytime-, and long-term use of LLD). Linear regression models were fitted with ΔIMT and ΔTPA as dependent variables, and age, sex, systolic blood pressure, total cholesterol and HDL-cholesterol, cardiovascular disease, daily smoking and use of LLD as independent variables. Categories of LLD-use were entered as dummy-variables, with never-use of LLD as the reference. Two-sided p-values < 0.05 were considered statistically significant. Stata SE 12 (StataCorp LP, College Station, TX, USA) and the SAS software, version 9.2, were used for all analyses.

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Errata Art 3

Submitted to Atherosclerosis, Thrombosis and Vascular Biology, Aug 14, 2013

To the Editors of Atherosclerosis, Thrombosis and Vascular Biology,

Correction regarding our article "Long term use of Lipid-Lowering Drugs Slows Progression of Carotid Atherosclerosis. The Tromsø Study 1994 to 2008", ATVB 2013;33:858-862;doi:10.1161/ATVBAHA.112.300767.

Dear Editor,

We are sorry to inform you that we have discovered an error in the article mentioned above, and are hereby presenting a correction.

The incorrect paragraph is on page 859, in the "Results" section, second column, the first paragraph**:**

The multivariable-adjusted mean change (95% confidence interval [CI]) in IMT was 0.174 (95% CI: 0.167-0.182) in long-term users, 0.162 (95% CI: 0.145-0.179) in any-time users and 0.139 mm (95% CI: 0.122-0.156) in never-users (p for trend 0.002, Figure 1). The corresponding numbers for mean multivariable-adjusted change in TPA (square-root-transformed) was 1.450 (95% CI: 1.342-1.558) in long-term users, 1.391 (95% CI: 1.151-1.630) in any-time users and 1.098 (95% CI: 0.854-1.342) in never-users (p for trend 0.009).

This paragraph should be substituted with the following paragraph:

The multivariable-adjusted mean change (95% confidence interval [CI]) in IMT was 0.174 (95% CI: 0.167-0.182) in never-users, 0.162 (95% CI: 0.145-0.179) in any-time users and 0.139 mm (95% CI: 0.122-0.156) in long-users (p for trend 0.002, Figure 1). The corresponding numbers for mean multivariable-adjusted change in TPA (square-root-transformed) was 1.450 (95% CI: 1.342-1.558) in never-users, 1.391 (95% CI: 1.151-1.630) in any-time users and 1.098 (95% CI: 0.854-1.342) in long-time users (p for trend 0.009).

The corrections do not affect the conclusions made in the study.

Best regards

Marit Herder

 corresponding author