Effect of new statin treatment on carotid artery intima-media thickness: A real-life observational study over 10 years

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HIGHLIGHTS

- The real-life effect of new statin treatment on carotid intima-media thickness (IMT) was investigated over 10 years.
- A longitudinal cohort study was used.
- The statin naïve group had a higher increase in IMT over the 10 years than the group receiving statins.
- This real-life study showed new statin treatment to reduce the increase in IMT observed over 10 years.

ARTICLE INFO

ABSTRACT

Background and aims: Randomized clinical trials (RCT) have shown statin treatment to slow down the increase in carotid artery intima-media thickness (IMT) seen with ageing. However, those RCTs usually have a limited follow-up (1–3 years). Here an observational study was used to investigate the real-life effect of new statin treatment over a 10-year follow-up.

Methods: In the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, 954 individuals all aged 70 years at baseline were investigated regarding carotid artery IMT three times during 10 years (n = 771 at age 75, and n = 591 at age 80).

Results: At age 70, 503 subjects were statin-naïve and did not receive statin during the 10-year follow-up period (the never-statin group), while 197 subjects were statin-naïve but received statins during the follow-up period (the received-statin group). Low-density lipoprotein (LDL)-cholesterol increased over time in the never-statin group (+0.1 mmol/l, $p = 0.0012$), but decreased in the group receiving statin treatment (−1.1 mmol/l, $p < 0.0001$). The never-statin group increased significantly in IMT over the 10 years (+0.07 mm, $p < 0.0001$), while the numerical increase seen in the received-statin group was not significant (+0.02 mm, $p = 0.22$) A significant difference in the change in IMT over time was seen between the received-statin group and the never-statin group ($p < 0.0001$ for interaction between time and group, adjusted for a propensity score).

Conclusions: This real-life observational study showed that new statin treatment reduced the increase in IMT seen over 10 years compared to subjects not treated with statins.

1. Introduction

Statin treatment is known to reduce future cardiovascular events in subjects with and without cardiovascular disease in randomized clinical trials (RCT) [1]. In RCTs, statin treatment has also been shown to slow down the age-related progression of intima-media thickness (IMT) of the carotid artery measured by ultrasound [2–8]. This reduction in age-related progression has been documented in RCTs with the major statin groups. The length of the treatment in those RCTs has usually been in the 1-3-year range, but in some case up to 5 years [9].

Since RCTs regarding statin effects on IMT with a long follow-up period are not likely to be conducted, knowledge of the long-term effects has to be disclosed by the use of longitudinal, observational cohort studies. The present study used data from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study [10], in which IMT has been evaluated at three occasions during 10 years of follow-up. The primary hypothesis tested was that subjects who received statin therapy during this period would show a less pronounced increase in IMT compared to those who were statin naïve during the 10 years. Since we previously have shown that not only IMT, but also the echogenicity of the intima-media complex (IM-GSM) is a powerful risk factor for future cardiovascular death [11], a secondary aim was to investigate the

impact of long-term statin treatment on IM-GSM. The echogenicity is thought to reflect the content of the vascular wall in that a calcified or fibrotic wall would appear rather white (echogenic), while a lipid-rich wall would appear more black (echolucent), being more vulnerable to plaque rupture [9].

2. Materials and methods

2.1. Sample

A total of 1016 subjects, 50% women and all 70-years of age, were enrolled in the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study between the years 2001 and 2004. Multiple measures of cardiovascular function was collected at baseline and at the follow-up investigation after five (n = 826) and ten years (n = 602). A detailed description of the cohort has been published previously [9].

The study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethical committee of the University of Uppsala. Each study participant has given informed consent.

2.2. Measurements

Blood samples were collected in the morning after an overnight fast, and standard lipid measurements were performed on the fresh samples by the Clinical Chemistry Department, Uppsala University.

2.3. Carotid artery ultrasound

Bilateral ultrasound measurements (10 MHz probe, Accuson XP128, CA, USA), taken from the far wall of the last 10 mm of the carotid artery bifurcation area, were used for IMT analyses. A semi-automatic software was utilized to calculate both the IMT, from a mean of around 100 measurements, and the IM-GSM, the grey scale median value for all pixels in that area. A detailed description of the measurement technique can be found elsewhere [12]. Results are presented as the combined mean value for the left and right artery. Measurements from all three time points were performed by the same technician using the same equipment.

When re-examining 30 random subjects within 2 weeks at age 70 years, the coefficient of variation was 7.2% for IMT and 7.5% for IM-GSM.

2.4. Definition of statin groups

The individuals who were not on any statin treatment at any of the three investigations during the 10-year follow-up were denoted the "never-statin" group. The subjects who were statin naïve at age 70 (baseline), but received statin during the coming 10 years were denoted "received-statin".

2.5. Statistics

The changes in low-density lipoprotein (LDL), IMT and IM-GSM were evaluated using mixed models with random intercept. In these models, sex was used as a confounder (age same in all subjects).

Thereafter, an interaction term between time and statin group was introduced to evaluate if new statin treatment was associated with a different change in IMT or IM-GSM. All subjects were included in these primary analyses.

This step was repeated also using adjustment for a propensity score. The propensity score was calculated using logistic regression analysis with statin group as the binary outcome variable and potential important characteristics related to statin treatment and atherosclerosis, such as sex, baseline LDL, baseline IMT, high-density lipoprotein (HDL),

triglycerides, myocardial infarction, stroke, heart failure, diabetes, blood pressure, hypertensive treatment, body mass index (BMI), smoking, and waist-hip ratio, as independent variables. Data from all time-points (except LDL and IMT) were used in the calculation of the propensity score.

In secondary analyses, we reperformed the evaluation only using subjects who attended all examinations. We also performed analyses including data only from the 70 and 80-year examinations.

STATA 14 (Stata, inc, College Station, TX, USA) was used for the calculations and R 3.4.4 was used for the graphical figures.

3. Results

At age 70, 503 subjects were statin-naïve and did not receive statin during the 10-year follow-up period (the never-statin group), while 197 subjects were statin-naïve but received statin during the 10-year follow-up period (the received-statin group). In the received-statin group, 114 had received treatment within the first 5 years and the remaining individuals received treatment between year 5 and 10 of the follow-up period.

3.1. Change in lipids

LDL-cholesterol increased over time in the never-statin group (mean increase +0.1 mmol/l, $p = 0.0012$), while it decreased in the group receiving statin treatment (mean decline −1.1 mmol/l, $p < 0.0001$) (see Table 1 for details).

3.2. Change in IMT

The never-statin group increased significantly in IMT over the 10 years (+0.7 mm, $p < 0.0001$), while the numerically increase in the received-statin group was not significant (+0.02 mm, $p = 0.22$) (see Table 1 and Fig. 1). A significant difference in the change in IMT over time was seen between the received-statin group compared to the never-statin group ($p < 0.0001$ for interaction between time and group).

This pattern was seen (and being highly significant) regardless if only individuals evaluated at all three occasions were used in the analysis (n = 427, $p < 0.0001$ for interaction between time and group), or if only the 70- and 80-year data were used ($p < 0.0001$ for interaction between time and group).

The difference between the groups regarding change in IMT over time was still significant also after adjustment for a propensity score including other concomitant diseases, medications and cardiovascular risk factors ($p < 0.0001$ for interaction between time and group).

The change over time in LDL-cholesterol tended to be related to the change over time in IMT in a positive fashion in the group receiving statins, so that the individuals who experienced the greatest reduction in LDL-cholesterol showed the least increase in IMT ($p = 0.07$). This pattern was not seen in the group which never received statins ($p = 0.27$).

No relationships between the change in serum triglycerides and the change in IMT were noted in any of these groups ($p = 0.023$ and $p = 0.73$ in the never treated and received statin groups).

3.3. Change in IM-GSM

As could be seen in Table 1 and Fig. 2, IM-GSM declined significantly over time in both groups ($p < 0.0001$ in the never-statin group and $p = 0.004$ in the received-statin group). No difference in change in IM-GSM were seen between the groups ($p = 0.94$ for interaction between time and group).

Table 1
Basic characteristics in the never-treated and in the received-statins groups at the three examinations.

	70 years		75 years		80 years	
Never treated	N	Mean (SD)/proportion	N	Mean (SD)/proportion	N	Mean (SD)/proportion
LDL-cholesterol (mmol/l)	501	3.40 (0.77)	455	3.59 (0.84)	358	3.45 (0.81)
HDL-cholesterol (mmol/l)	503	1.57 (0.45)	455	1.53 (0.47)	359	1.41 (0.41)
Serum triglycerides (mmol/l)	503	1.17 (0.53)	455	1.32 (0.65)	358	1.19 (0.56)
IMT (mm)	482	0.88 (0.15)	431	0.95 (0.15)	354	0.95 (0.16)
IM-GSM	497	65 (19)	435	61 (14)	348	60 (15)
Myocardial infarction (%)	502	3	455	2	359	4
Stroke (%)	504	2	455	4	359	6
Heart failure (%)	505	3	455	4	359	7
Diabetes (%)	503	3	455	5	359	7
Systolic blood pressure (mmHg)	504	146 (22)	455	147 (19)	359	146 (19)
Diastolic blood pressure (mmHg)	504	77.9 (9.7)	454	75.3 (8.9)	359	73.5 (9.1)
Antihypertensive Treatment (%)	502	22	455	37	359	48
Smoker (%)	505	8	451	5	355	3
BMI (kg/m^2)	506	26.6 (4.2)	455	26.5 (4.2)	357	26.6 (4.3)
Diabetes mellitus (%)	506	6	454	8	357	12
WHR	504	0.90 (0.08)	449	0.94 (0.08)	352	0.94 (0.08)
Received statins	N	Mean (SD)/proportion	N	Mean (SD)/proportion	N	Mean (SD)/proportion
LDL-cholesterol (mmol/l)	197	3.87 (0.81)	171	3.09 (1.06)	142	2.72 (0.84)
HDL-cholesterol (mmol/l)	197	1.46 (0.41)	171	1.44 (0.45)	142	1.35 (0.37)
Serum triglycerides (mmol/l)	197	1.40 (0.58)	171	1.44 (0.63)	142	1.22 (0.53)
IMT (mm)	180	0.91 (0.16)	155	0.96 (0.17)	137	0.93 (0.14)
IM-GSM	194	64 (18)	156	61 (16)	136	60 (14)
Myocardial infarction (%)	197	4	171	14	142	20
Stroke (%)	196	3	171	12	142	21
Heart failure (%)	195	3	171	5	142	10
Diabetes (%)	196	10	171	18	142	18
Systolic blood pressure (mmHg)	195	154 (22)	171	148 (19)	143	147 (18)
Diastolic blood pressure (mmHg)	195	80.5 (10.8)	171	75.6 (9.5)	142	74.7 (8.4)
Antihypertensive Treatment (%)	197	36	171	69	142	83
Smoker (%)	197	11	171	7	143	3
BMI (kg/m^2)	197	27.3 (4.1)	171	27.1 (4.7)	142	26.7 (4.5)
Diabetes mellitus (%)	197	14	175	23	140	21
WHR	195	0.90 (0.07)	169	0.95 (0.07)	139	0.96 (0.07)

LDL, low-density lipoprotein; HDL, high-density lipoprotein; IMT, intima-media thickness; IM-GSM, echogenicity of the Intima-media complex; BMI, body mass index; WHR, waist/hip ratio.
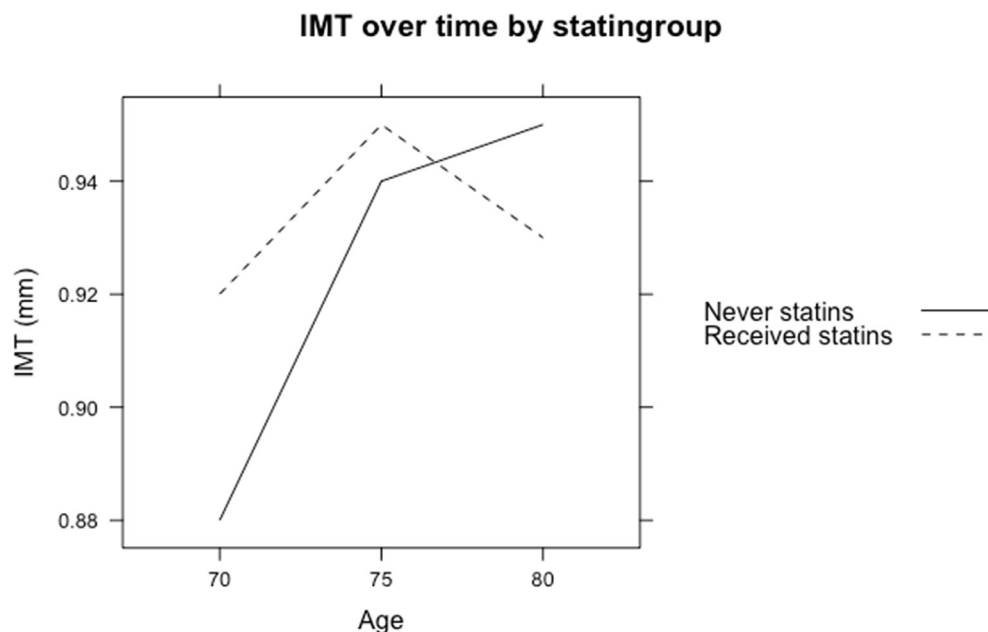
Fig. 1. Intima-media thickness.
Mean values of intima-media thickness (IMT) at three examinations during 10 years divided in two groups, never-statin or received-statin after age 70. In this figure, only data from the subjects attending all three examinations are shown. $p < 0.0001$ for interaction between group and age.
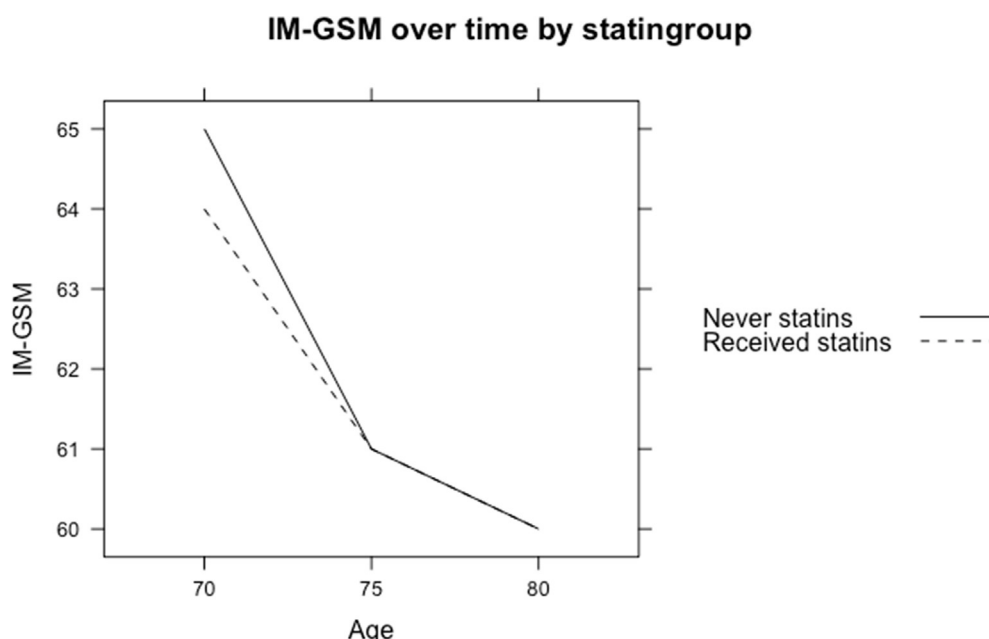
IM-GSM over time by statingroup

Fig. 2. Echogenicity of the intima-media complex.

Mean values of the echogenicity of the intima-media complex (IM-GSM) at three examinations during 10 years divided in two groups, never-statin or received-statin after age 70. In this figure, only data from the subjects attending all three examinations are shown. No significant interaction between group and age was seen.

4. Discussion

The present study, using real-life data for an observational longitudinal study, showed that new statin treatment was associated with a less pronounced increase in IMT over 10 years, as compared to individuals who were statin-naïve. New statin treatment did not influence the echogenicity of the intima-media complex.

The present study would serve as an important complement to RCTs for two reasons. First, most RCTs in this field have only a follow-up of 1–3 years, and since the development of atherosclerosis takes place during several decades it is important to obtain knowledge of the long-term effects of statins. Second, as the gold standard for the evaluation of drug treatment effects, RCTs often have the disadvantage that they do not reflect the situation in real life, since usually less sick individuals are enrolled in RCTs compared to the general patient population. Another important aspect of real life is that many individuals in reality are taking lower dosages of a drug than given in the RCT. Thus, real-life studies serve as an important complement to RCTs. The major drawback is that no randomization is performed, and individuals receiving medication are therefore likely to be different in a number of important characteristics compared to those who do not. In the present study, such differences were adjusted for by using a propensity score, but with that technique it is not possible to adjust for non-measured characteristics that in the RCT setting would be distributed equally between the groups by the randomization procedure.

In the present study, the reduction in LDL-cholesterol is of the same magnitude as seen in RCTs with statins, confirming that the history of new statin treatment is valid. Also, the increase in IMT over time in the never-statin group is in accordance with other observational studies [2–8].

This longitudinal study was carried out in an elderly population. Not everyone came back on the two repeated examinations. Since it is likely that those who dropped out of the study were sicker than the rest of the population, we carried out a secondary analysis only including the individuals who attended all three examinations. As could be seen in Fig. 1, the magnitude of change over time was almost identical as when the total population was used (see Table 1), and a formal statistical test showed that the effect of new statin treatment on change in IMT was highly significant also in the subpopulation attending all three examinations.

It was further noted that the major increase in IMT in the never-statin group was seen during the first 5 years of the follow-up. To assure that this non-linear increase in IMT with ageing did not influence the statistical calculations, we performed a secondary analysis only including the 70- and 80-year data, but also this additional analysis showed a highly significant effect of new statin treatment on the change in IMT.

The reduction in LDL-cholesterol in the group receiving statins tended to be related to the change in IMT over time, while this pattern was not seen in the group not receiving statins. This result must however be taken with caution since the p-value was not significant ($p = 0.07$) in the statin treated group. The statin treated group is rather small and therefore has a rather poor power to investigate the relationship between change over time in LDL-cholesterol *vs* the change over time in IMT.

The primary analysis was conducted in the total sample, since that approach gives the best power and mixed models do handle drop-outs. In that analysis, IMT was stable between age 75 and 80 years in those never treated with statins (Table 1). This is probably due to the fact that almost 100 individuals died during these 5 years and it is likely that those individuals had higher IMT than the rest of the sample, and therefore an increase in IMT during those 5 years could be masked. When we, as a secondary analysis, investigated only those who attended all three examinations (Fig. 1), a slight increase in IMT between 75 and 80 years was indeed noted.

We also noted a slight reduction in LDL-cholesterol (and serum triglycerides) between age 75 and 80 years in the primary analysis conducted in the total sample. It is known that lipid levels decline after age 70 [13], possibly due to a poor nutrition at old age. This reduction in lipids seen also in the never treated group might also be involved in the slowed down increase in IMT seen between age 75 and 80 years.

Another issue is that we do not have data on the exact start of the statin medication, just information if the individuals were on treatment at the three examinations. It is however likely that the effects seen on IMT are due to chronic exposure, since the main effect on LDL-cholesterol was seen already after 5 years in this group and the effect after 10 years on LDL-cholesterol was very similar compared to that seen in RCTs. In addition, if a subject had an elevated LDL-cholesterol level at any of the examinations, they were informed about this and told to see their general practitioner for dietary advice and drug treatment. It is therefore likely that most of the subjects in the received-statin group received medication shortly after entering the study at age 70, or

shortly after the 75-year examination.

Another limitation is that we do not have data on type of statin and dosages. During this period in Sweden, simvastatin (20–40 mg) was the statin used in the vast majority of individuals.

This study was carried out in elderly, Swedish individuals, and therefore the results have to be confirmed in other age and ethnic groups.

In conclusion, this real-life observational study showed that new statin treatment reduced the increase in IMT seen over 10 years compared to subjects not treated with statins.

Financial support

CRediT authorship contribution statement

Lars Lind: Conceptualization, Formal analysis, Funding acquisition, Writing - original draft.

Declaration of competing interest

The author declared he does not have anything to disclose regarding conflict of interest with respect to this manuscript.

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