The Effect of Aggressive Versus Conventional Lipid-lowering Therapy on Markers of Inflammatory and Oxidative Stress

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Abstract

Purpose
Recent trial results are in favor of aggressive lipid lowering using high dose statins in patients needing secondary prevention. It is unclear whether these effects are solely due to more extensive lipid lowering or the result of the potentially anti-inflammatory properties of statins.

We aimed to determine whether aggressive compared with conventional statin therapy is more effective in reducing systemic markers of inflammation and oxidative stress.

Materials and methods
This was a multi-centre, double-blind, placebo-controlled trial. Patients with previous cardiovascular disease, who did not achieve low density lipoprotein (LDL) cholesterol levels <2.6 mmol/l on conventional statin therapy (simvastatin 40 mg) were randomized to continue with simvastatin 40 mg or to receive atorvastatin 40 mg for 8 weeks and thereafter atorvastatin 80 mg for the final 8 weeks (aggressive treatment). Lipids, C-reactive protein, soluble cellular adhesion molecules, neopterin, von Willebrand Factor, and antibodies against oxidized LDL were measured at baseline and after 16 weeks.

Results
Lipid levels decreased significantly in the aggressive treatment group (LDL-C reduction 20.8%; \( P < 0.001 \)), whereas a slight increase was observed in the conventional group (LDL-C increase 3.7%; \( P = 0.037 \)). A significant reduction in antibodies against oxidized LDL was seen in the aggressive (13.4%; \( P < 0.001 \)) and the conventional (26.8%; \( P < 0.001 \)) group, but there was no difference between groups (\( P = 0.25 \)). Furthermore, no significant differences in change in other biomarkers was observed between both groups.

Conclusions
This study does not support the hypothesis that a more profound reduction in inflammatory and oxidative stress contributes to the benefits of aggressive statin therapy.

Key words
hydroxymethylglutaryl-CoA reductase inhibitors · atorvastatin · simvastatin · arteriosclerosis · C-reactive protein · neopterin · von Willebrand Factor · oxidized low density lipoprotein · soluble cellular adhesion molecules · inflammation

Introduction

Recent trials have emphasized the need for intensive lipid lowering with hydroxymethylglutaryl-CoA reductase inhibitors (statins) in subjects with cardiovascular disease (CVD) [1, 2]. One of the potential mechanisms contributing to the beneficial effects of lipid lowering in these patients is a reduction of inflammatory and/ or oxidative stress. This effect may be due to extensive immunomodulatory properties that operate independently of lipid lowering (pleiotropic effect) [3] or solely be the result of the reduction in lipid levels [4].
It has been well established that atherosclerosis is a chronic inflammatory disorder [5], with oxidized low-density lipoprotein (LDL) cholesterol being one of the most potent inducers of inflammation [6]. Several biomarkers of inflammatory or oxidative stress have been recognized as powerful predictors of outcome in cardiovascular disease making them useful for reflecting the disease severity in clinical studies [7]. Among these biomarkers are antibodies against oxidized LDL (anti-oxLDL), C-reactive protein (CRP), neopterin (a marker of monocyte activation), von Willebrand Factor (vWF), and the soluble forms of cellular adhesion molecules such as endothelial-selectin (s-E-selectin) and intercellular adhesion molecule-1 (s-ICAM-1).

There is substantial clinical evidence that statins exhibit anti-inflammatory effects. Although this effect is thought to be unrelated to their lipid lowering properties, this is still a matter of debate [8, 9]. A currently unsolved issue in secondary prevention of vascular disease is whether the beneficial effects of additional, aggressive lipid lowering as observed in recent trials are the result of a reduction in inflammatory and oxidative stress or that of a greater lipid lowering effect per se. This study was undertaken to evaluate the effects of aggressive versus conventional lipid-lowering therapy on inflammatory biomarkers and anti-oxLDL.

Materials and methods

Study design

The Simvastatin To Atorvastatin switch Trial (STAT) was a double-blind, parallel-group, randomized, multi-centre trial in 235 male and female patients with any clinical manifestation of atherosclerosis, and LDL-cholesterol (LDL-C) levels >2.6 mmol/l despite simvastatin 40 mg mono therapy. In addition to the principal center, the University Medical Center Groningen, ten general hospitals in The Netherlands participated in this study. The study was performed between September 1998 and July 2001, and it has therefore not been registered at a Trial Registration website.

Eligible patients were identified through screening the out-patient population of the participating centers. If eligible, patients entered a 4-week run-in period in which they received simvastatin 40 mg once daily. Baseline measurements regarding lipids, anti-oxLDL and inflammation were performed following these 4 weeks. Subsequently, patients entered a 16-week treatment phase starting on atorvastatin 40 mg or continuing with simvastatin 40 mg. After 8 weeks of treatment the dosage of atorvastatin was increased to 80 mg, whereas the dosage of simvastatin remained stable at 40 mg. Patients were kept on this dose for the remaining 8 weeks of the treatment period.

Eligibility

Eligible patients were 30–75 years of age and had been using a combination of a lipid-lowering diet and simvastatin 40 mg monotherapy once daily at bedtime for at least 8 weeks prior to the screening visit, after which LDL-C levels remained above 2.6 mmol/l. In addition, all patients had been diagnosed with a clinical manifestation of atherosclerosis, which was defined as the patient having a history of at least one of the following items: angina pectoris with an abnormal bicycle test and/or nuclear stress test, suspect for inducible myocardial ischaemia, or with a significant stenosis in the coronary arterial system on coronary angiography; myocardial infarction; percutaneous transluminal coronary angioplasty (PTCA); coronary artery bypass graft; transient ischaemic attack; carotid endarterectomy; abdominal aortic aneurysm; symptomatic peripheral arterial obstructive disease, as evidenced by a lowered ankle-brachial index (ABI<0.9), or by previous percutaneous or surgical interventions. After completion of the run-in period, only patients with persisting LDL-C levels >2.6 mmol/l were randomized.

The exclusion criteria were: all forms of secondary dyslipidemia; diabetes mellitus; dysfunction of the thyroid gland, unless adequately treated; acute cardiovascular disease, surgical procedures or inflammatory disease; all conditions affecting plasma levels of cellular adhesion molecules; active liver disease or hepatic dysfunction, as defined by aminotransferase-values over 150% of upper limit of normal; known allergic reaction to statins; clinically manifest heart failure or severe cardiac arrhythmias; uncontrolled hypertension, as defined by a systolic blood pressure >160 mmHg and/or a diastolic blood pressure >95 mmHg; severe or unstable angina pectoris; excessive alcohol consumption (over 4 units per day) or a history of drug abuse; use of systemic steroids or androgens; impaired renal function with plasma creatinine >150 µmol/l; a history of partial ileal bypass surgery; inadequate contraceptive measures, pregnancy or lactation in premenopausal women; baseline creatinine phosokinase values >150% upper limit of normal. The use of all other lipid-lowering drugs and agents known to be associated with rhabdomyolysis in combination with statins were prohibited during the course of the study. Adverse events were assessed at every visit in a nonspecific fashion documenting any new or continuing symptoms since the previous visit.

Measurements

To assess the lipid profile changes, total cholesterol (TC) and triglycerides (TG) were measured at weeks −4 (i.e. start of run-in), 0 (randomization visit), 8, and 16; high density lipoprotein cholesterol (HDL-C) and LDL-C were mea-
sured only at week 0 and 16. In fasting samples TC, TG, and HDL-C were determined by enzymatic methods on a Vitros 950 (Ortho-Clinical Diagnostics, Rochester NY, USA). HDL-C was isolated by precipitation of LDL and VLDL with phosphotungstate and magnesiumchloride. Serum LDL-C was calculated using the Friedewald formula, excluding patients with serum TG levels >5.0 mmol/l.

Inflammation markers and anti-oxLDL were assessed during the randomization visit and after 16 weeks of study treatment. CRP was measured using a routine high sensitivity nephelometric method (Dade-Behring, Germany). IgG anti-oxLDL antibodies were measured using an in house sandwich-ELISA, of which details have been described earlier [10]. In vitro oxLDL was generated by modification of low density cholesterol with malondialdehyde as well as copper. Anti-oxLDL values are presented as levels of auto-antibodies against oxLDL relative to auto-antibodies against native LDL. Levels of s-E-selectin and s-ICAM-1 were analyzed by sandwich ELISA (British Biotechnology Products) as described earlier [11]. Plasma level of von Willebrand factor (vWF) was determined as the amount of antigen using a sandwich-ELISA with OPD/horse-radish peroxidase and subsequent UV detection (Boehringer, Germany). Neopterin levels were quantified by a commercially available radioimmunoassay (IMMU test Neopterin, Germany). All assays had an inter- and intra-assay coefficient of variation of <10%.

**Ethics**

The study design was approved by the local medical ethical committees and written informed consent was obtained from each participant.

**Statistics**

The study was powered at the difference in change in LDL-C levels after 16 weeks of treatment from baseline between both treatment groups, which was assessed using analysis of covariance (ANCOVA), correcting for baseline levels of LDL-C. To show at least a 5% difference in plasma LDL-C levels between the atorvastatin treated- and simvastatin treated group, and based on an inter-subject coefficient of variation of 11%, a type 1 error of 0.05 and a power of 90%, a minimum of 106 patients was needed for each group. To correct for premature discontinuation a total of 240 patients had to be included. In case of skewed distribution, logarithmic transformation was performed. In addition, potential differences at baseline were corrected for by adding the variable as covariate to the ANCOVA analysis. The same analysis methods were used for the other variables, i.e. the difference in change in other lipids and the biomarkers between both treatment groups.

Normal distribution of variables was tested with the Kolmogorov-Smirnov test. Group mean differences between

| Table 1  | Baseline characteristics |
|----------|--------------------------|
|          | Simvastatin               | Atorvastatin               | P value |
| Age (years) | 58 (10)                  | 58 (9)                    | 0.65    |
| Weight (kg)   | 82 (14)                  | 86 (14)                  | 0.11    |
| Height (cm)    | 174 (9)                  | 174 (9)                  | 0.94    |
| Body mass index (kg/m²) | 27.2 (3.6)              | 28.4 (4.1)              | 0.04    |
| Systolic blood pressure (mmHg) | 140 (130–150)  | 140 (130–150)  | 0.76    |
| Diastolic blood pressure (mmHg) | 80 (80–85)          | 80 (80–90)            | 0.29    |
| Heart rate (BPM) | 68 (10)                 | 69 (10)                 | 0.50    |
| Total cholesterol (mmol/l) | 5.62 (0.94)           | 5.72 (0.95)           | 0.48    |
| Triglycerides (mmol/l) | 1.61 (1.22–2.28)      | 1.64 (1.2–2.4)         | 0.64    |
| HDL cholesterol (mmol/l) | 1.16 (0.33)           | 1.16 (0.30)           | 1.00    |
| LDL cholesterol (mmol/l) | 3.59 (0.79)           | 3.70 (0.83)           | 0.40    |
| Male gender    | 71 (77%)                 | 75 (82%)                | 0.38    |
| Smoking        | Current                  | 22 (24%)                | 30 (33%) | 0.20* |
|               | Past                     | 50 (54%)                | 49 (54%) |        |
|               | Never                    | 20 (22%)                | 12 (13%) |        |
| History of hypertension | 65 (71%)              | 63 (69%)                | 0.83    |
| History of myocardial infarction | 55 (60%)              | 53 (58%)                | 0.83    |
| History of angina pectoris | 63 (69%)              | 66 (73%)                | 0.55    |
| History of claudication | 11 (12%)              | 9 (10%)                 | 0.65    |
| History of cardiovascular intervention | 55 (60%)            | 49 (54%)                | 0.36    |
| History of other cardiovascular disease | 21 (23%)           | 16 (18%)                | 0.36    |

Values are mean (SD), median (P25–P75), or numbers (percentages) P value indicates students t-test for difference between groups; *, P value for trend
the intervention and non-intervention groups were performed with unpaired t-tests. Paired t-tests were used to test the treatment and non-treatment effects within the intervention and non-intervention group, respectively. In case of categorical variables the chi-square test or Fisher’s exact test was used. Descriptive statistics are presented as mean values ± SD, as median (inter quartile range) for skewed variables, or as percentages. A two-sided \( P \) value<0.05 was considered statistically significant. All statistical analyses were carried out with the Statistical Package for Social Science (SPSS, version 12.0.2, 24 March 2005).

**Results**

For this study, 331 potential patients were screened, of which 235 patients were randomized: 119 were allocated to receive simvastatin and 116 to receive atorvastatin. Of these patients, 16 dropped out prematurely, of which 2 died (both in simvastatin group), and 219 completed the study. Furthermore, 44 patients were excluded after completion because of protocol violation or missing/irretrievable/ unusable blood samples. Drop-out rates and excluded patients were evenly distributed over both treatment groups (Chi-Square, 0.58; \( P=0.75 \)).

Patients who did not complete the study did not differ significantly from patients who completed the study in terms of demographic and lipid parameters, except for HDL-C, which was significantly lower in these patients. During the entire study period, 155 adverse events occurred (simvastatin: 52 mild; 17 moderate; 6 severe; atorvastatin: 52 mild; 24 moderate; 4 severe). There was no difference between treatment groups (Chi-Square, 1.44; \( P=0.49 \)).

Baseline characteristics are outlined in Table 1. The two groups of patients were well matched with regard to baseline characteristics, with the exception of body mass index, which was significantly higher in patients allocated to atorvastatin.

**Effect on lipids**

The course of TC and TG levels during the study is presented in Fig. 1, demonstrating that in the simvastatin treated group TC increased slightly but significantly, whereas TC decreased significantly in the atorvastatin treated group. Additionally, TG levels decreased significantly in the atorvastatin group only. Table 2 demonstrates that also LDL-C was significantly reduced in the atorvastatin group and increased in the simvastatin group.

After correction for baseline, the change in LDL-C from baseline was significantly greater in atorvastatin treated patients compared with simvastatin treated patients. Similar effects were seen on TC and TG, whereas there was not a significantly different effect on HDL-C.

**Effect on biomarkers**

Table 2 demonstrates the treatment effect on biomarkers measured in this study. Aggressive lipid-lowering did not have a significant effect on CRP, s-ICAM-1, s-E-selectin, neopterin, and vWF when comparing 16 week levels with baseline levels. In both treatment groups anti-oxLDL decreased significantly. However after correction for baseline, atorvastatin was not superior to simvastatin. Because the groups differed on baseline body mass index, an additional correction for body mass index was performed when analyzing the treatment effect on all biomarkers. This did not influence the results.

Patients with peripheral artery disease had higher levels of CRP at baseline, but did not differ significantly on other biomarkers. This group, however, was too small to assess difference in treatment effect (i.e. \( N=19 \)). Smokers (\( N=50 \)) also presented with higher median baseline levels of CRP (4.1 (3.0–7.8) vs. 2.6 (1.6–7.1); \( P=0.001 \)), but with no differences in the other biomarkers. No significant differences in treatment effect between both statins were observed (ANCOVA; \( P=0.098 \)).
Markers (CRP, s-ICAM-1, s-E-selectin, neopterin, and vWF).

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Discussion

The results from this study confirm that intensifying lipid
lowering therapy from simvastatin 40 mg to atorvastatin 80 mg
is beneficial with regard to lowering TC, TG, and LDL-C after
16 weeks of therapy. However, the change in therapeutic regimen did not result in lower levels of oxidative stress (anti-
LDL) and inflammatory and endothelial dysfunction biomarkers (CRP, s-ICAM-1, s-E-selectin, neopterin, and vWF).

An intensive lipid lowering regimen with high dose statins for secondary prevention has been proven to reduce mortality and morbidity [1, 2, 12] and may significantly attenuate atherosclerotic plaque progression [13–15]. Although the additional LDL-C lowering effect of high dose statins is beyond doubt an important mechanism in reducing the atherosclerotic burden, some attribute a beneficial effect to so-called pleiotropic activity of high dose statins [4]. It has also been demonstrated that high dose statins are more potent in lowering CRP compared with moderate dose statins, but these results were obtained against a statin naïve background [16]. Furthermore, CRP reduction was associated with a lower progression rate of the atherosclerotic process as measured by intima media thickness [16]. These data were confirmed in later studies [15, 17, 18]. In one of these trials, reduction is CRP was independently associated with less progression of atherosclerotic plaques, measured with intravascular ultrasound [15].

Trials investigating the additional effect of aggressive statin therapy on other biomarkers show inconsistent results. Some studies support a beneficial effect on fibrinogen, a well validated acute phase protein [17], but this was not confirmed by other studies [19, 20]. Also a beneficial effect on markers of haemostasis, including vWF and endothelial activation has not been consistently shown [17, 20]. A small study of 17 patients reported that the enhanced LDL-C lowering effect of atorvastatin 10 mg compared with pravastatin 20 mg also resulted in a significantly greater reduction in malondialdehyde modified LDL [21]. However, in a sub-study from the ASAP trial, no effect was seen of both regimens on anti-oxLDL or in vitro susceptibility of LDL to oxidation [22].

Explanation of findings and study limitations

In current clinical practice most patients with established CVD are already on standard dose statins for secondary prevention. To our knowledge, no study has investigated the additional effect of switching from standard to high dose statin on inflammatory and oxidative stress biomarkers in a randomized controlled trial. For example, the three largest trials demonstrating beneficial effects of aggressive statin therapy on CRP were preceded by a placebo run-in phase [15, 16] or included predominantly statin naïve patients [23]. Interestingly, in the PROVE-IT TIMI-22 trial,
the aggressive regimen was only beneficial in the statin naïve patients, whereas in those with prior statin therapy (e.g. 25%), there was a neutral effect of both regimens and only those patients with LDL-C levels >125 mg per deciliter had an apparent benefit from aggressive statin therapy [1].

Another important issue is that, although experimental studies suggest that inflammatory mediators other than CRP may also be influenced by statin therapy [4], clinical studies are not consistent. A large meta-analysis recently reported that apart from the apparent beneficial effect on CRP, current evidence does not support such an effect of any statin compared with placebo on other biomarkers, including oxLDL [24].

In subjects allocated to atorvastatin, there was a dose escalation from 40 mg to 80 mg at week 8. Therefore, they only received 80 mg for the final 8 weeks. It has been shown that this time span is long enough to show a significant effect on CRP [23], but the effect on other biomarkers after such a short treatment period is questionable [25], although studies have reported beneficial effects on oxLDL [26]. However, the half life of IgG antibodies directed against oxLDL has been shown to be around 15 days [27], and therefore 8 weeks should have been long enough to observe a difference between two interventions, if present. Furthermore, whereas the mean LDL-C level achieved in the aggressive statin group was 2.95 mmol/l, current guidelines recommend that LDL-C reduction below 1.8 mmol/l is reasonable [28]. Therefore, a future study is warranted to investigate whether a greater reduction in LDL-C than achieved in the current study will have a greater effect on pleiotropic factors. Finally, it should be noted that, although we did not observe a significant effect of aggressive statin therapy on biomarkers studied in this study, this does not preclude that this regimen could have beneficial effect on the production of other inflammatory mediators such as cytokines, chemokines, matrix metalloproteinases, nitric oxide or the activation of nuclear factor kappa B.

Conclusions

The results from the current study do not support the hypothesis that switching from conventional statin therapy to aggressive statin therapy improves circulating levels of specific oxidative stress and inflammatory biomarkers measured in this study. As suggested in previous publications, our data do not support that the beneficial effect of statin treatment on hard end points as reported in patients with ACS or in other patients at high risk for major vascular events can be attributed to a modulatory effect on the inflammatory response [8, 29, 30]. Although a study of longer duration or one studying other biomarkers is warranted, our study does not provide evidence to intensify statin treatment, merely for its anti-inflammatory effect in secondary prevention patients that already have achieved their LDL-C treatment goal.

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