Disparate Effects of Atorvastatin Compared With Simvastatin on C-Reactive Protein Concentrations in Patients With Type 2 Diabetes

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OBJECTIVE — Reduction in LDL and high sensitivity (hs) C-reactive protein (CRP) are independent indicators of successful cardiovascular risk reduction with statins. This study compared the effect of equivalent LDL-lowering doses of simvastatin and atorvastatin on hsCRP in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A crossover study of 26 patients with type 2 diabetes taking either 40 mg simvastatin or 10 mg atorvastatin was undertaken. After 3 months on one statin, lipids and hsCRP were measured on 10 occasions over a 5-week period. The same procedure was then followed taking the other statin.

RESULTS — LDL was comparable on either treatment: atorvastatin 2.2 ± 0.2 vs. 2.1 ± 0.3 mmol/l (mean ± SD; P = 0.19). CRP of individuals taking atorvastatin was significantly lower than when they were taking simvastatin (median 1.08 vs. 1.47 mg/l, P = 0.0002) and was less variable (median SD of logCRP 0.0036 vs. 0.178, P = 0.0001).

CONCLUSIONS — Compared with simvastatin, atorvastatin reduced hsCRP and its variability in type 2 diabetic patients. This enhanced anti-inflammatory effect may prove beneficial if lower CRP is associated with improved cardiovascular risk.

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The ability of high sensitivity (hs) C-reactive protein (CRP) to predict cardiovascular risk has been confirmed in diverse population cohorts including type 2 diabetic patients (1). Patients who have lower hsCRP levels after statin therapy have better clinical outcomes regardless of the resultant level of LDL (2,3). Reduction in LDL and hsCRP are independent indicators of the success of statins in reducing cardiovascular risk (4). To assess any difference between the effect of long and short half-life statins on hsCRP and its variability, we conducted a crossover study with equivalent lipid-lowering doses of simvastatin and atorvastatin.

RESEARCH DESIGN AND METHODS — All subjects gave their informed consent, which had been approved by the Research Ethics Committee. A total of 30 consecutive Caucasian patients with type 2 diabetes and A1C between 6 and 9% were recruited. There were 19 patients taking 10 mg atorvastatin and 11 patients on 40 mg simvastatin before bed. The biological variation of hsCRP was assessed by measuring fasting blood samples at 4-day intervals on 10 consecutive occasions. Thereafter, the patients on simvastatin were changed to the equivalent dose of atorvastatin and vice versa (5). After 3 months, the biological variation was again assessed by measuring fasting blood samples at 4-day intervals on 10 consecutive occasions. Duplicate samples were randomized and then analyzed using a single batch (6,7). Serum CRP was measured by the high-sensitivity method on a Beckman DXC analyzer. The intra-assay CV was 4% using the study samples.

Statistical analysis
The distribution of hsCRP concentrations within and between individuals is non-Gaussian, so the Wilcoxon signed-rank test was used to compare the median hsCRP values of individual patients taking simvastatin compared with atorvastatin. To compare the hsCRP variability while on the statins, each hsCRP measurement was log-transformed. Biological variability of CRP on each drug was analyzed by calculating the analytical and within-subject variability (8). The distribution of these standard deviation (SD) values within the study population was non-Gaussian, so the Wilcoxon signed-rank test was used to compare the individual SDs of patients when they were taking each statin.

RESULTS — The baseline demographics, duration of diabetes, and glycemic control were comparable in both groups (9), as was the baseline hsCRP in patients who were taking atorvastatin or simvastatin initially (median [interquartile range] 1.18 [0.78–3.88] vs. 1.37 [0.70–5.21] mg/l, P = 0.52). LDL was comparable on either treatment (atorvastatin 2.2 ± 0.2 vs. 2.1 ± 0.3 mmol/l [mean ± SD], P = 0.19); however, the degree of lowering with each statin was not assessed, since the patients were already established on a statin at study entry. One patient from each group dropped out after completing one arm because of poor compliance, one patient withdrew because of developing myalgia without any rise in creatinine kinase when changed to simvastatin, and another withdrew because of developing lethargy on starting simvastatin.

The median hsCRP when taking atorvastatin was significantly lower than...
One of the features of hsCRP measurement that complicates interpretation is its wide intra-individual variability (11,12). Our data have shown that patients taking atorvastatin not only had lower hsCRP concentrations, but had markedly less biological variability than when taking equivalent doses of simvastatin. A single value on atorvastatin treatment is therefore more likely to reflect the true hsCRP concentration of the patient. However, the potential clinical benefits of this reduced variability are less clear than that of purely lowering average hsCRP values.

Looking for existing evidence that atorvastatin leads to fewer cardiovascular events than simvastatin at the same degree of LDL lowering is hampered by the fact that most clinical trials involving the two agents have deliberately aimed to show a difference in LDL. Nonetheless, in these comparative studies, event rates have been more favorable with atorvastatin in both randomized controlled studies (13) and observational studies (14).

There was a significant deterioration of median hsCRP and its variability when patients on atorvastatin were changed over to simvastatin. On the other hand, median hsCRP and its variability improved when patients on simvastatin were changed over to atorvastatin. The difference in variability of hsCRP and direct LDL could be due to the difference in stability of lipids while taking a relatively short half-life statin such as simvastatin (2–3 h) compared with that of a longer half-life statin such as atorvastatin (24 h) (15). These changes may need to be taken into account when considering switching patients between the two statins on any grounds.

In conclusion, an equivalent lipid-lowering dose of atorvastatin improves hsCRP as well as reduces the variability compared with simvastatin in type 2 diabetic patients.

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