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van Dam, M.J.

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5 A comparison of the efficacy and tolerability of titrate-to-goal regimens of simvastatin versus fluvastatin:

a randomized, double-blind study in adult patients at moderate to high risk for cardiovascular disease

M.J. van Dam, MD, H.J.A.M. Penn, MD, F.R. den Hartog, MD, J.A. Kragten, MD, M.D. Trip, MD, Rudolf J.A. Buirma, MD and John J.P. Kastelein MD for the MUST Study Group

1 Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
2 Department of Cardiology, St. Jans Gasthuis, Weert, The Netherlands
3 Department of Cardiology, Ziekenhuis Gelderse Vallei, Bennekom, The Netherlands
4 Department of Cardiology, Atrium, Heerlen, The Netherlands
5 Medical Department, Merck Sharp & Dohme B.V., Haarlem, The Netherlands

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ABSTRACT

Background
Use of cholesterol-lowering regimens has been shown to reduce the risk of coronary heart disease (CHD), both in primary and secondary prevention. However, there have been few studies of the relative benefits and risks of the various cholesterol-lowering agents in patient groups with specific factors for CHD.

Objective
The primary goal of this study was to compare the proportions of adult patients with primary hypercholesterolemia and a moderate to high risk for CHD achieving National Cholesterol Education Program low-density lipoprotein cholesterol (LDL-C) goals with titrate-to-goal regimens of simvastatin and fluvastatin.

Methods
This was a multicenter, prospective, randomized, double-blind, parallel-group study enrolling adult patient with type IIa of IIb primary hypercholesterolemia, LDL-C levels < 6.0 mmol/l, and triglyceride levels < 4.5 mmol/l, and either CHD or other atherosclerotic disease (the CHD, or high-risk, group), or multiple risk factors for CHD (the MRF, or moderate-risk, group). After a 6-week washout period, patients were randomized to 18 weeks of treatment at an initial dosage of simvastatin 10 g once daily or fluvastatin 20 mg once daily. At 6- and 12-week titration visits, the dosage in patients who had not achieved the LDL-C goal could be increased to simvastatin 20 mg once daily and then 40 mg once daily, or fluvastatin 40 mg once daily and then 40 mg twice daily. Lipid profiles were obtained at each titration visit and at the end of treatment. In addition to the comparison between treatments, secondary comparisons were made between the CHD and MRF subgroups within each treatment group. Statistical significance was assessed using analysis of variance.

Results
A total of 478 patients were enrolled, 237 in the simvastatin group and 241 in the fluvastatin group. There were no significant between-group differences in the patients' characteristics at baseline. At the end of the study 60.8% (135/222) of patients in the simvastatin group had reached target LDL-C goals, compared with 35.1% (76/216) in the fluvastatin group (p < 0.001). In the simvastatin CHD and MRF subgroups, 49% and 73%, respectively, reached the LDL-C target, compared with 19% and 50% in the corresponding fluvastatin subgroups (p< 0.001). The proportion of patients requiring titration was higher in the fluvastatin group than in the simvastatin group (87.1% and 64.1%, respectively; p=0.001). The incidence of adverse events was similar between groups.

Conclusion
In this study, more patients with primary hypercholesterolemia and CHD or multiple risk factors for CHD reached LDL-C goals with simvastatin treatment and required less titration than those who received fluvastatin treatment.
Efficacy and tolerability of titrate-to-goal regimens of simvastatin versus fluvastatin

Introduction

The risk factors for coronary heart disease (CHD) include age (> 45 years for men; > 55 years or premature menopause without estrogen replacement therapy for women); family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other first-degree male relative, or before 65 years of age in mother or other first-degree female relative); current cigarette smoking (> 10/d); hypertension (blood pressure > 140/90 mm Hg or use of anti-hypertensive medication); diabetes mellitus; and low-high-density lipoprotein cholesterol (HDL-C) levels (< 0.90 mmol/L). In addition, epidemiological studies have provided convincing evidence that elevated serum cholesterol are an important risk factor for the development of atherosclerotic disease; elevated low-density lipoprotein cholesterol (LDL-C), in particular, has been identified as a conditional risk factor for CHD.

A number of clinical studies have demonstrated that the use of cholesterol-lowering regimens reduces the risk of CHD, both in primary and secondary prevention. Based on the results of these studies, various national and international guidelines have been developed that set specific cholesterol-lowering goals for those with different degrees of risk for CHD.

With the introduction of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors, a new therapeutic class became available for the treatment of hypercholesterolemia. Current members of this class are simvastatin, pravastatin, lovastatin, fluvastatin, atorvastatin and cerivastatin. The efficacy and safety of these agents have been extensively studied in clinical trials. However, the relative benefits and risks of the various cholesterol-lowering agents in patients groups with the specific risk factors for CHD remain to be clarified.

A recent meta-analysis including 56 monotherapy trials and 20 trials of combination therapy trials underscored the importance of taking a stratified approach for different patient groups. The present article reports the results of a multicenter, randomized, double-blind comparison of the efficacy and tolerability of titrate-to-goal regimens of simvastatin and fluvastatin in patients with primary hypercholesterolemia at differing degrees of risk for CHD.

Patients and methods

At the time of the study, the use of a titrate-to-goal regimen of statins in the treatment of hypercholesterolemia was new to clinical practice in The Netherlands, and fluvastatin was new on the market. The primary goal of the study was to compare the efficacy and tolerability of titrate-to-goal regimens of simvastatin and fluvastatin, as indicated by the proportion of patients achieving LDL-C goals set by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: < 2.6 mmol/l for the subgroup with CHD or other atherosclerotic disease (the CHD, or high-risk, group) and < 3.5 mmol/l for the subgroup with multiple (≥ 2) risk factors for CHD (the MRF, or moderate-risk, group). Secondary goals were to compare the mean percentage reductions in LDL-C and total cholesterol (TC) with the 2 regimens, the proportion of patients requiring titration, and the tolerability of the 2 treatments.

The institutional review boards of all participating centers approved the study protocol. Participants gave written informed consent before receiving any study treatment.
**Study population**
Eligible patients were men and women between the ages of 20 and 70 years with type IIa or IIb primary hypercholesterolemia, LDL-C levels ≤ 6.0 mmol/l (CHD group, 3.5-6.0 mmol/l; MRF group, 4.0-6.0 mmol/l) while following a lipid-lowering diet, and triglyceride levels < 4.5 mmol/l. At each participating site, there were to be ≥ 12 patients each in the CHD and MRF groups.

The exclusion criteria were as follows: hypersensitivity to simvastatin, fluvastatin or any component of either drug; pregnancy or lactation; inadequate contraception in premenopausal women; active liver disease, hepatic dysfunction, or unexplained persistent elevations of serum aminotransferase levels > 1.5 times upper limit of normal (ULN); serum creatine phosphokinase elevations > 1.5 times ULN not clearly explained by trauma or exercise; homozygous familial hypercholesterolemia and all forms of secondary hypercholesterolemia; inadequately controlled diabetes mellitus (fasting serum glucose > 10.0 mmol/l); recent history of alcohol or drug abuse; history of myocardial infarction, coronary bypass surgery, or angioplasty within the past 3 months; unstable angina or clinically significant ventricular arrhythmia; current therapy with any drug known to interact with the study medications or to affect lipid levels; any condition or therapy that in opinion of the investigator, might pose a risk to the patient or confound the results of the study. Any previous lipid-lowering therapy must have been discontinued for ≥ 6 weeks before study entry.

**Study design**
This was a multicenter, prospective, randomized, double-blind, parallel-group study conducted by 25 investigators at 20 centers in The Netherlands. After a 6-week washout period, which included a 2-week placebo period, patients were randomized to 18-weeks of double-dummy treatment at doses within the approved ranges for both study drugs. Initial doses were simvastatin 10 mg once daily or fluvastatin 20 mg once daily. At 6- and 12-week titration visits, the dosages in patients who had not achieved the LDL-C goal could be increased to simvastatin 20 mg once daily and then 40 mg once daily, or to fluvastatin 40 mg once daily and then 40 mg twice daily.

**Study measurements**
At week -6, -2, 0, 6, 12, 18, blood samples were drawn after ≥ 12-hour fast for determination of blood chemistry and lipid profile Total cholesterol, HDL-C and triglyceride levels were measured using standard techniques. Commercially available enzymatic methods were used to determine TC and triglyceride levels\(^{11-13}\); HDL-C levels were measured after precipitation of apolipoprotein B-containing lipoproteins using an enzymatic calorimetric procedure\(^{14}\); and LDL-C was calculated according to the Friedewald formula.\(^ {15,16}\) Blood pressure was measured in the supine position using a sphygmomanometer and stethoscope.

Coordination of laboratory assessments through a virtual central laboratory (VCL) allowed titration to goal in a double-blind fashion. Whereas laboratory assessments were performed at the local hospital laboratories at the investigative sites, the VCL performed central data management. Use of a common calibrator and a common reference range harmonized lipid results for the study population. This process has been described elsewhere.\(^ {17,18}\)
**Efficacy and tolerability assessment**

The primary study end point was the percentage of patients reaching target LDL-C levels. Secondary end points included percentage reductions in LDL-C and TC levels in all patients and in the CHD and MRF subgroups, as well as the proportion of patients requiring titration.

Adverse events were assessed by the investigator at each visit and classified as mild (the patient was aware of the event but could easily tolerate it), moderate (sufficient to interfere with daily activities) or severe (incapacitating, leading to inability to carry out daily activities). Tolerability was assessed based on the number of patients discontinuing treatment because of clinical adverse experiences and on changes in laboratory values (alanine aminotransferase, aspartate aminotransferase, creatine phosphokinase).

**Statistical analyses**

The study was designed to have 80% statistical power to detect a difference in mean percentage change from baseline LDL-C in each subgroup. Allowing for a dropout rate of 15%, 115 patients were required in each subgroup of each arm, for a total of 230 patients in each treatment arm. This sample size would give > 95% power to detect a difference in the overall percentage of patients reaching LDL-C goals.

The baseline comparability of the 2 treatment groups with respect to demographic and clinical characteristics and baseline lipid levels was assessed using the Fisher exact test for dichotomous variables, the Wilcoxon rank sum test for ordered categorical variables, and the 2-sample t-test for the continuous variables. Baseline values were derived from the mean of the values obtained at week -2 and day 0 for lipids and vital signs and the last measurement obtained during the baseline period for laboratory safety variables.

Efficacy analyses were performed using all-the-patients-treated approach. All patients with lipid-level data both from baseline and during treatment were included in the study analyses. If data were missing for a particular visit, values were carried forward from the previous visit. Between-group comparisons of response were made using Cochran-Mantel-Haenszel test, with stratification for risk factor status and center. Between-group comparisons of the percentage reductions in lipid levels were performed using an analysis-of-variance model, which included treatment, investigator, and risk factor status as main effects. Consistency of treatment response between centers and between risk factor subgroups was assessed by separate examinations of the interaction of treatment by risk factor status for all weeks.

Normality of residuals and homogeneity of variances were tested using the Shapiro-Wilks test and the Levene's test, respectively. The Fisher's exact test was used to compare treatment groups with respect to the incidence of clinical and laboratory adverse experiences. Statistical significance was assessed at the 5% level of probability.

**Results**

A total of 478 patients were randomized to the 2 treatment groups; 237 in the simvastatin group (CHD 119; MRF 118) and 241 in the fluvastatin group (CHD 121; MRF 120). The characteristics of the treatment groups did not differ significantly at baseline (Table I). No significant interaction of treatment-by-risk factor status interaction was found, nor was there any significant of sex or age with any of the outcome variables.
Table 1  Patient characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin</th>
<th>Fluvastatin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 237</td>
<td>n = 241</td>
<td>n= 478</td>
</tr>
<tr>
<td>Age (years ± SD)</td>
<td>56.5 (8.7)</td>
<td>56.0 (8.8)</td>
<td>56.4 (8.7)</td>
</tr>
<tr>
<td>Sex (percentage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>162 (68.4 %)</td>
<td>170 (70.5 %)</td>
<td>332 (69.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>75 (31.6 %)</td>
<td>71 (29.5 %)</td>
<td>146 (30.5 %)</td>
</tr>
<tr>
<td>CHD status (percentage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>119 (50.2 %)</td>
<td>121 (50.2%)</td>
<td>240 (50.2 %)</td>
</tr>
<tr>
<td>MRF</td>
<td>118 (49.8 %)</td>
<td>120 (49.8 %)</td>
<td>238 (49.8%)</td>
</tr>
<tr>
<td>TC (mmol/l ±SD)</td>
<td>6.76 (0.74)</td>
<td>6.77 (0.76)</td>
<td>6.77 (0.75)</td>
</tr>
<tr>
<td>LDL-C (mmol/l ±SD)</td>
<td>4.74 (0.61)</td>
<td>4.70 (0.57)</td>
<td>4.72 (0.59)</td>
</tr>
<tr>
<td>HDL-C (mmol/l ±SD)</td>
<td>1.14 (0.28)</td>
<td>1.18 (0.34)</td>
<td>1.16 (0.31)</td>
</tr>
<tr>
<td>TG (mmol/l ±SD)</td>
<td>1.94 (0.86)</td>
<td>1.98 (0.92)</td>
<td>1.96 (0.89)</td>
</tr>
<tr>
<td>Total cholesterol/ HDL-C ratio</td>
<td>6.23</td>
<td>6.14</td>
<td>6.19</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, SD = standard deviation, CHD = coronary heart disease, MRF = multiple risk factors for coronary heart disease, TC = total cholesterol, LDL = low density lipoprotein, HDL = high density lipoprotein, TG = triglycerides, differences were not significant.

A total of 471 patients (98.5 %) had diagnosis secondary to hypercholesterolemia at screening, most commonly of a cardiovascular nature, with similar proportions of patients in the 2 treatment groups having such diagnoses. Sixty patients had previously taken lipid-lowering therapy, 31 (13.1 %) in the simvastatin group and 29 (12.0 %) in the fluvastatin group. A total of 426 patients took concomitant medications (none of them lipid-lowering drugs), while receiving study therapy, 207 (87.3 %) in the simvastatin group and 219 (90.9 %) in the fluvastatin group.

Of the 478 patients entering the study, 438 (91.6 %) completed all 18 weeks of treatment, 222 (93.7 %) in the simvastatin group and 216 (89.6 %) in the fluvastatin group. Thirty-three patients (14 [5.9 %] in the simvastatin group and 19 [7.5 %] in the fluvastatin group) discontinued treatment because of a clinical adverse experience. One patient in the simvastatin group and 6 in the fluvastatin group discontinued treatment for other reasons. There were no significant differences between the treatment groups with respect to discontinuations.

At the end of the study, 60.8 (135/222) of the patients in the simvastatin group (CHD 49 %, MRF 73%) had achieved target LDL-C levels, compared with 35.1 % (76/216) of patients in the fluvastatin group (CHD 19 %, MRF 50 %). The odds ratio of attaining the LDL-C goal was 1.77 for simvastatin versus fluvastatin (95 % C.I. 1.47 to 2.13). At each time point, there was a significant difference between the proportion of patients reaching treatment goals with simvastatin and fluvastatin (p < 0.001). The same effect was observed in the 2 risk factor subgroups, although the difference was more pronounced in the CHD group. The odds ratio was 2.56 for simvastatin versus fluvastatin in the CHD group (95% C.I. 1.76-3.75), compared with 1.44 (95% C.I. 1.17-1.77) in the MRF group. Figure 1 shows the percentages of patients achieving treatment goals each week, by treatment group and risk factor subgroup.

Separate analyses of the percentage change from baseline in TC, LDL-C, HDL-C, triglyceride levels and TC/HDL-C ratio were performed at weeks 6, 12 and 18. The mean percentage changes from baseline in the lipid profile are summarized in Table II.
Table 2  Efficacy at week 18

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin</th>
<th>Fluvastatin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>-26.6 %</td>
<td>-20.1 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHD</td>
<td>-30.2 %</td>
<td>-24.2 %</td>
<td></td>
</tr>
<tr>
<td>MRF</td>
<td>-23.1 %</td>
<td>-19.5 %</td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>-35.9 %</td>
<td>-27.8 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHD</td>
<td>-41.1 %</td>
<td>-31.8 %</td>
<td></td>
</tr>
<tr>
<td>MRF</td>
<td>-35.2 %</td>
<td>-26.9 %</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>+9.7 %</td>
<td>+6.5 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-17.8 %</td>
<td>-10.7 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol/ HDL-cholesterol</td>
<td>-31.9 %</td>
<td>-23.7 %</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease, MRF = multiple risk factors for coronary heart disease, LDL = low density lipoprotein, HDL = high density lipoprotein.

Figure 1  Proportion of patients achieving target low-density lipoprotein cholesterol (LDL-C) levels at the 3 study visits, by treatment group and risk factor subgroup. CHD = coronary heart disease; MRF = multiple risk factors for CHD. All differences were significant (p<0.001).

The overall TC reduction at the end of the study was 26.6 % in the simvastatin group and 20.1 % the fluvastatin group (p < 0.001). By risk factor subgroup, the CHD and MRF subgroups had respective TC reductions of 30.2 % and 25.1 % with simvastatin, compared to 24.2 % and 19.5 % with fluvastatin (p <0.001). At the end of study, LDL-C levels had decreased significantly more in the simvastatin group than in the fluvastatin group (35.9 % vs 27.8 %, respectively; p < 0.001) (Figure 2). Differences between simvastatin and fluvastatin were also significant at week 6 (31.5% vs 19.7 %; p < 0.001) and week 12 (33.6% vs 23.3%; p < 0.001. There were significantly greater increases in HDL-C levels with simvastatin than with fluvastatin at week 12 (7.8 % vs 5.0 %; p = 0.025) and week 18 (9.7 % vs 6.5 %; p = 0.035) (Figure 3). Triglyceride levels decreased significantly more in the simvas-
Wee k k

Figure 2

Mean (± SE) percentage reduction from baseline in low-density lipoprotein cholesterol levels, all-patients-treated approach. At the end of study (week 18), mean percent reduction from baseline in LDL-Cholesterol was 36% in the simvastatin group and 28% in the fluvastatin group. At all weeks, there was a significant (p<0.001) difference between simvastatin and fluvastatin with respect to mean percent change from baseline in LDL-Cholesterol.

At the end of the study, a greater proportion of patients required titration in the fluvastatin group than in the simvastatin group (87.1% vs 64.1%; p = 0.001). This finding held true in both the CHD and MRF subgroups (CHD, 96.7% fluvastatin vs 83.2% simvastatin; MRF 77.5% vs 44.9%).

A total of 197 patients had ≥1 clinical adverse experience during treatment, 91 (38.4%) in the simvastatin group and 106 (44.0%) in the fluvastatin group. The investigator judged 77 of these events (32 [13.5%] in the simvastatin group, 45 [18.7%] in the fluvastatin group) to be possibly or definitively related to treatment. Fifteen patients had serious adverse experiences during treatment period, 8 (3.4%) in the simvastatin group, 7 (2.9%) in the fluvastatin group. Thirty-three patients (14 [5.9%] in the simvastatin group, 19 [7.9%] in the fluvastatin group) were withdrawn from treatment because of a clinical adverse experiences. None of these differences were statistically significant.

DISCUSSION

In this study, simvastatin was more effective than fluvastatin in a titrate-to-goal regimen. However, because of the inclusion and exclusion criteria, these results cannot be extrapolated to the general population. In patients with multiple risk factors for CHD, a significantly greater proportion of patients achieved LDC-C goals with simvastatin than did
Figure 3  Mean (± S.E) percentage increase from baseline in high-density lipoprotein cholesterol levels, all-patients-treated approach. At the end of study (week 18), mean percent increase from baseline in HDL-cholesterol was 10% in the simvastatin group and 7% in the fluvastatin group. At week 12 and 18, there was a significant difference (respectively p = 0.025 and p = 0.035) between simvastatin and fluvastatin.

Figure 4  Mean (± S.E) percentage reduction from baseline in triglyceride levels, all-patients-treated approach. At the end of study (week 18), mean percent reduction from baseline in triglyceride levels was 18% in the simvastatin group and 11% in the fluvastatin group. At week 12 and 18, there was a significant difference (respectively p = 0.008 and p = 0.011) between simvastatin and fluvastatin.
fluvastatin; in patients with CHD or other atherosclerotic disease, this proportion was even greater. Over 18 weeks of treatment, the proportion of patients requiring titration was lower with simvastatin than with fluvastatin. Compared with fluvastatin, simvastatin was significantly more effective in reducing TC, LDL-C and triglyceride levels, and the TC/HDL-C ratio. Both regimens were well tolerated, with no significant differences in the incidence of clinically relevant adverse experiences between treatments.

**Conclusions**

Lowering LDL-C levels to or below recommended levels has been shown to prevent coronary events. As all class, the HMG-CoA reductase inhibitors have potent LDL-C lowering effects and are well tolerated. We compared doses within the approved range for simvastatin with those for fluvastatin, at the time a new entry on the Dutch market. The 2 drugs were effective in lowering LDL-C levels with similar tolerability profiles. However, at the end of the study at the end of the study, 60.8% of patients in the simvastatin group had reached target LDL-C levels (CHD 49%, MRF 73%), compared to 35.1% of patients in the fluvastatin group (CHD 19%, MRF 50%). Thus, simvastatin was the more effective statin, producing greater LDL-C reductions at lower milligram-equivalent doses than fluvastatin. These results may be helpful in selection of the most effective and efficient regimens for patients at differing degrees of risk for CHD.

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*Following are the locations of the primary lipid clinics and investigators who participated in the MUST Study:*

Amsterdam: Trip MD and Voogt, WG de
Bennekom: Hartog, FR den
Blaricum: Smit, J
Boxmeer: Peters, JRM
Dokkum: Vries, LJ de
Dordrecht: Kofflard, MJM and Stoel, I
Eindhoven: Bonnier, JJRM
Harderwijk: Dijkgraaf, R
Heerlen: Lustermans, FAT and Kragten, JA
Hengelo: Bucx, JJJ and Wester, A
Hoorn: Basart, DCG
Rotterdam: Baggen, MGA and Scheffer, MG
Tilburg: Vet, AJTM
Velp: Kempen, LHJ van
Venlo: Troquay, RPT
Voorburg: Walinga, H
Weert: Penn, HJAM
Zevenaar: Vring, J van de
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