Peer reviewed article

Impact of enhanced compliance initiatives on the efficacy of rosuvastatin in reducing low density lipoprotein cholesterol levels in patients with primary hypercholesterolaemia

Walter F. Riesen[a], *Georg Noll*[b], *Roger Darioli*[c] *on behalf of the ORBITAL trialists*

[a] Institut für Klinische Chemie & Hämatologie und Klinische Mikrobiologie & Immunologie, Kantonsspital St. Gallen, Switzerland
[b] Klinik für Kardiologie, Universitätsspital Zürich, Switzerland
[c] Policlinique médical universitaire, Centre Hospitalier Universitaire Vaudois, Switzerland

Summary

Background: The effectiveness of lipid-lowering medication critically depends on the patients' compliance and the efficacy of the prescribed drug.

Objectives: The primary objective of this multicentre study was to compare the efficacy of rosuvastatin with or without access to compliance initiatives, in bringing patients to the Joint European Task Force's (1998) recommended low-density lipoprotein cholesterol (LDL-C) level goal (LDL-C, <3.0 mmol/L) at week 24. Secondary objectives were comparison of the number and percentage of patients achieving European goals (1998, 2003) for LDL-C and other lipid parameters.

Patients and methods: Patients with primary hypercholesterolaemia and a 10-year coronary heart disease risk of >20% received open label rosuvastatin treatment for 24 weeks with or without access to compliance enhancement tools. The initial daily dosage of 10 mg could be doubled at week 12. Compliance tools included: a) a starter pack for subjects containing a videotape, an educational leaflet, a passport/goal diary and details of the helpline and/or website; b) regular personalised letters to provide message reinforcement; c) a toll-free helpline and a website.

Results: The majority of patients (67%) achieved the 1998 European goal for LDL-C at week 24. 31% required an increase in dosage of rosuvastatin to 20 mg at week 12. Compliance enhancement tools did not increase the number of patients achieving either the 1998 or the 2003 European target for plasma lipids. Rosuvastatin was well tolerated during this study. The safety profile was comparable with other drugs of the same class. 63 patients in the 10 mg group and 58 in the 10 mg Plus group discontinued treatment. The main reasons for discontinuation were adverse events (39 patients in the 10 mg group; 35 patients in the 10 mg Plus group) and loss to follow-up (13 patients in the 10 mg group; 9 patients in the 10 mg Plus group). The two most frequently reported adverse events were myalgia (34 patients, 3% respectively) and back pain (23 patients, 2% respectively). The overall rate of temporary or permanent study discontinuation due to adverse events was 9% (n = 101) in patients receiving 10 mg rosuvastatin and 3% (n = 9) in patients titrated up to 20 mg rosuvastatin.

Conclusions: Rosuvastatin was effective in lowering LDL-C values in patients with hypercholesterolaemia to the 1998 European target at week 24. However, compliance enhancement tools did not increase the number of patients achieving any European targets for plasma lipids.

Key words: statin; rosuvastatin; hypercholesterolaemia; LDL-C, triglycerides; compliance

Introduction

Coronary heart disease (CHD) is the leading cause of death in high-income countries [1]. Major risk factors for CHD are cigarette smoking, elevated blood pressure, elevated serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), low serum high-density lipoprotein cholesterol (HDL-C), diabetes mellitus, and advancing age [2, 3]. A positive correlation was observed between plasma levels of TC or LDL-C and the risk of developing CHD [4].

Sponsor of the study: AstraZeneca AG, Grafenau 10, CH-6301 Zug Switzerland

Clinical trials of lipid modification either by diet or drugs have shown that CHD risk associated with elevated cholesterol can be substantially reduced [5].

Guidelines for the management of risk factors influencing CHD were initially based on large-scale epidemiological surveys conducted in the USA. After similar studies in other countries it became apparent that there were significant inconsistencies in the assessment of risk for CHD, and in the LDL-C or TC threshold levels indicating lipid lowering treatment [6]. In 1998 the Second Joint Task Force of European and other Societies issued recommendations on goals for LDL-C (<3.0 mmol/L) and TC levels (<5.0 mmol/L) [5]. These recommendations applied to patients with CHD (or other atherosclerotic disease) and patients with a 10-year CHD risk ≥20% either at their present age or when projected to age 60 [5].

New guidelines were issued by the Third Joint Task Force of European and other Societies in 2003 [7]. For asymptomatic patients with a 10-year risk of a fatal coronary event <5%, these guidelines contain the same goals for plasma LDL-C (<3.0 mmol/L) and TC (<5.0 mmol/L) as those recommended in 1998 [5, 7]. However, for patients with clinically established cardiovascular disease (CVD), diabetes or a 10-year risk of a fatal coronary event >5%, the new guidelines recommend lower goals for LDL-C (<2.5 mmol/L) and TC levels (<4.5 mmol/L) [7].

Statins (HMG-CoA reductase inhibitors) have been shown to be highly effective in reducing the level of LDL-C and the rate of major coronary events, and in improving overall survival in patients with CHD [8–11]. Moreover, statins are well tolerated and are cost-effective in secondary prevention of CHD [12–14]. Rosuvastatin is a highly potent statin that effectively reduces LDL-C in patients with hypercholesterolaemia [15].

Compliance is a complex behavioural process and is strongly influenced by the environment, the healthcare provider's practice, and the care delivery system [16, 17]. Several clinical trials have shown suboptimal compliance with lipid-lowering therapy with statins [18–20]. Achieving a high level of compliance presupposes that the patient has the requisite knowledge, motivation and resources to follow treatment recommendations. Several approaches may be considered to improve compliance, the most promising being combinations of interventions involving, amongst other things, patient education, self-monitoring, social support and telephone follow-up [21–24].

The primary objective of this study was to compare the efficacy of treatment with rosuvastatin, with or without access to compliance initiatives, in bringing patients to the Joint European Task Force (1998) recommended LDL-C goal (<3.0 mmol/L).

Patients and methods

Trial design

This was a cluster-randomised, multicentre, open label, parallel group study of 24 weeks' duration and conducted throughout Switzerland. A cluster randomisation procedure was used and all patients in each centre were assigned to the same treatment group.

Patients

Patients (≥18 years) attending primary care physician practices for treatment of primary hypercholesterolaemia with a 10-year CHD risk >20% (as defined by the 1998 European Guidelines [5]), CHD or other atherosclerotic disease were eligible for the study. The patients were statin naïve or on an accepted starting dose of lipid-lowering medication, which had proved ineffective in reaching the target level of LDL-C for that dose. Statin naïve patients (with an LDL-C >3.5 mmol/L fasting level) were required to complete dietary counselling before entering the study. Patients who switched from accepted starting doses of other lipid-lowering medication (with an LDL-C >3.1 mmol/L fasting level) were directly enrolled in the study. Another inclusion criterion was a fasting triglyceride (TG) level of ≤4.52 mmol/L.

Patients were excluded from the study if they were known to have heterozygous or homozygous familial hypercholesterolaemia, type III hyperlipoproteinaemia (familial dysbetalipoproteinaemia), or secondary hypercholesterolaemia. Those known to have hypersensitivity reactions or serious adverse effects (eg. myopathy) in relation to other statins were also excluded. Pregnant or breast feeding women were excluded, whilst women of child bearing potential were asked to use adequate contraception during the study. Other exclusion criteria included unstable cardiovascular disease, uncontrolled diabetes, active liver disease, renal impairment as defined by a serum creatinine level >220 µmol/L, any medical condition requiring cyclosporine therapy, and a history of alcohol and/or drug abuse.

The study was conducted in accordance with Good Clinical Practice Guidelines and local law. The study protocol was approved by the appropriate ethics committees. Written informed consent was obtained from each patient.

Study procedure

Patients received a daily oral treatment with either rosuvastatin alone (10 mg group) or with rosuvastatin and access to compliance enhancement tools (10 mg Plus group) for 24 weeks. Patients were assessed at week 4 and at week 12 to review fasting levels of TC, LDL-C, HDL-C, and triglycerides. For patients not achieving the 1998 European target for LDL-C at week 12 the daily dose of rosuvastatin was increased to 20 mg for the remainder of the study. Patients in the 10 mg Plus group received a starter pack containing a videotape and educational leaflets concerning their condition. These patients also received newsletters at regular intervals and had access to both a telephone helpline and an Internet website, all designed to reinforce the initial message in the starter pack.

Rosuvastatin tablets were dispensed to all patients

during the first study visit (week 0) and at week 12. Patients were asked to return all unused rosuvastatin tablets and containers to the investigator at week 12 and week 24. The Patient's compliance was determined by the difference between the dispensed and the returned tablets in comparison with the number of days between the visits. The dropout patients were not considered for the compliance assessment. Only the data from the patients who completed the whole protocol were taken into account.

Efficacy and safety endpoints

The primary efficacy endpoint was the number and percentage of patients in both treatment groups who reached the 1998 European goal for LDL-C (<3.0 mmol/L) after 24 weeks of therapy. Secondary efficacy endpoints included the number and percentage of patients within the 1998 European goal for LDL-C at week 12, the number and percentage of patients within the 1998 European goal for TC (<5.0 mmol/l) at week 12 and week 24, and the number and percentage of patients within the 2003 European goal for LDL-C (<2.5 mmol/L) and for TC (<4.5 mmol/L) at week 12 and week 24. Other secondary efficacy endpoints were the number of patients with a dose increase to 20 mg rosuvastatin at week 12; the percentage change in LDL-C, TC, HDL-C, and TG between baseline and week 24; and the patient's compliance as measured by tablet count for both treatment groups.

Safety assessment included adverse events reporting, clinical chemistry measurements and physical examinations.

Statistical methods

Efficacy analyses were performed on data from the intention to treat (ITT) population which included patients who received ≥1 doses of drug and had ≥1 post-baseline lipid values. The last observation was carried forward (LOCF) for missing efficacy data at week 24. All analyses performed at week 12 were based upon observed data (OC). All patients who received at least one dose of rosuvastatin were included in the safety population. Comparisons were performed between treatment groups using logistic regression analysis. The number of patients achieving the EAS LDL-C target was analysed using a logistic analysis, with terms included in the model for patient type (naïve or switched), treatment group (only rosuvastatin or rosuvastatin plus compliance tool) and the interaction between treatment group and patient type. The interaction term was found to be not statistically significant (change in -2logL = 0.608, p-value = 0.4356) and was dropped from the final model. The adjusted odds ratios derived from the final model and their 95% CI (estimated from the likelihood ratio method) were shown with corresponding p-values. Statistical significance was accepted at the 5% level.

Results

Patient demographics

A total of 1128 patients were randomised to the two treatment groups, 601 patients to rosuvastatin alone (10 mg group), 527 patients to rosuvastatin with access to compliance enhancement tools (10 mg Plus group). All 1128 patients were part of the safety population. A total of 126 patients failed to provide a lipid sample at baseline or at least one lipid sample post-baseline and were excluded from the efficacy analyses. Data for 1002 patients (531 patients in the 10 mg group; 471 patients in the 10 mg Plus group) were therefore available for the efficacy analyses (ITT population). Demographic characteristics of the ITT population entering the study are shown in table 1.

Table 1

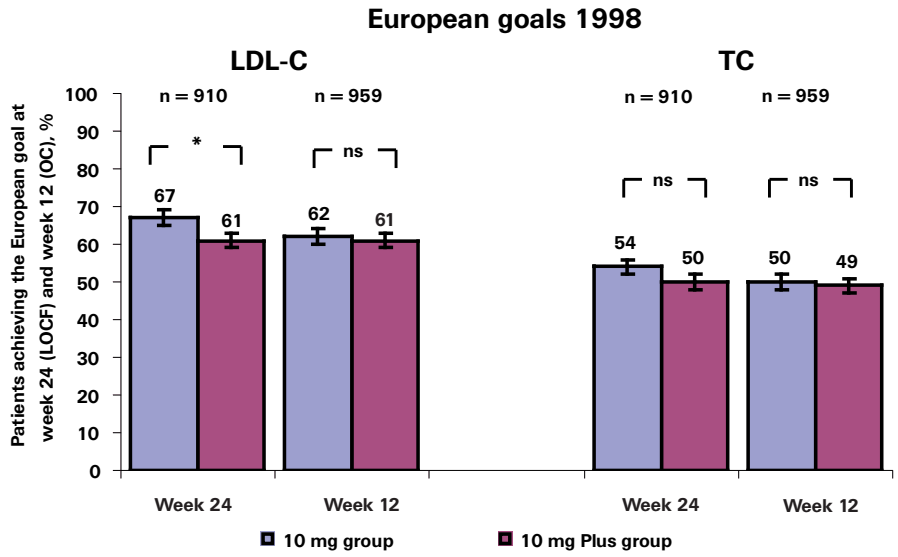
Demographic and baseline characteristics of the ITT population.

Treatment group		Rosuvastatin alone (10 mg)	Rosuvastatin with compliance enhancement tools (10 mg Plus)	Total
ITT population	N	531	471	1002
Demographic characteristics				
Gender	Male Female	309 (58%) 222 (42%)	303 (64%) 168 (36%)	612 (54%) 390 (35%)
Age (years)	Mean (± SD)	60 (± 11.1)	60 (± 11.2)	60 (± 11.1)
Baseline characteristics				
Statin naïve patients	N (%)	274 (52%)	241 (51%)	515 (51%)
Statin switched patients	N (%)	257 (48%)	230 (49%)	487 (49%)
TC (mmol/l)	Mean (± SD)	7.0 (± 1.13)	7.0 (± 1.18)	7.0 (± 1.15)
LDL-C (mmol/l)	Mean (± SD)	4.7 (± 1.04)	4.7 (± 1.09)	4.7 (± 1.07)
TG (mmol/l)	Mean (± SD)	2.1 (± 0.93)	2.1 (± 0.86)	2.1 (± 0.90)
HDL-C (mmol/l)	Mean (± SD)	1.3 (± 0.34)	1.4 (± 0.32)	1.3 (± 0.33)
Important risk factors				
Coronary heart disease	N (%)	144 (27%)	141 (30%)	285 (28%)
Atherosclerotic disease	N (%)	195 (37%)	186 (39%)	381 (38%)
Diabetes mellitus	N (%)	85 (16%)	82 (17%)	167 (17%)
Hypertension	N (%)	344 (65%)	302 (64%)	646 (64%)
Smoking	N (%)	308 (58%)	275 (58%)	583 (58%)

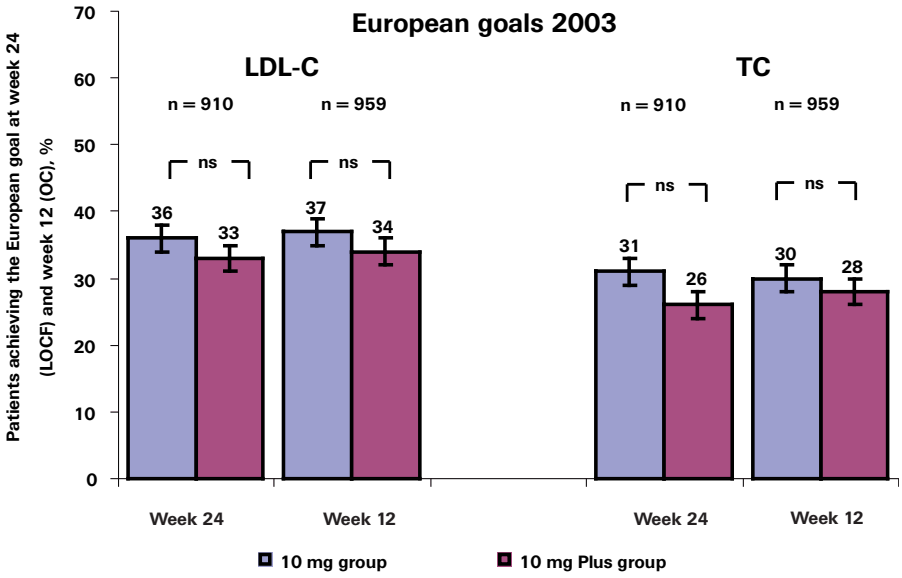
Notes: Total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high density lipoprotein cholesterol (HDL-C).

Figure 1

Percentage of subjects achieving the European goals at week 24 (LOCF) and week 12 (OC) in patients treated with rosuvastatin alone (10 mg group) or in combination with compliance enhancement tools (10 mg Plus group).



A * Odds ratio 0.74 (95% CI 0.60-0.97; p=0.032)



B

Table 2

Proportion of patients in the safety population with the most commonly reported adverse events (≥1%) according to dose of rosuvastatin at onset.

MedDRA preferred term	Rosuvastatin 10 mg (N = 1128)		Rosuvastatin 20 mg (N = 334)	
	n	(%)	n	(%)
Myalgia	32	(3)	2	(1)
Back pain	21	(2)	2	(1)
Bronchitis	16	(1)	6	(2)
Headache	21	(2)	0	(0)
Nausea	15	(1)	4	(1)
Blood creatinine kinase increased	15	(1)	3	(1)
Arthralgia	16	(1)	1	(0)
Depression	14	(1)	2	(1)
Influenza	15	(1)	0	(0)
Constipation	14	(1)	0	(0)
Vertigo	12	(1)	2	(1)
Abdominal pain upper	12	(1)	1	(0)

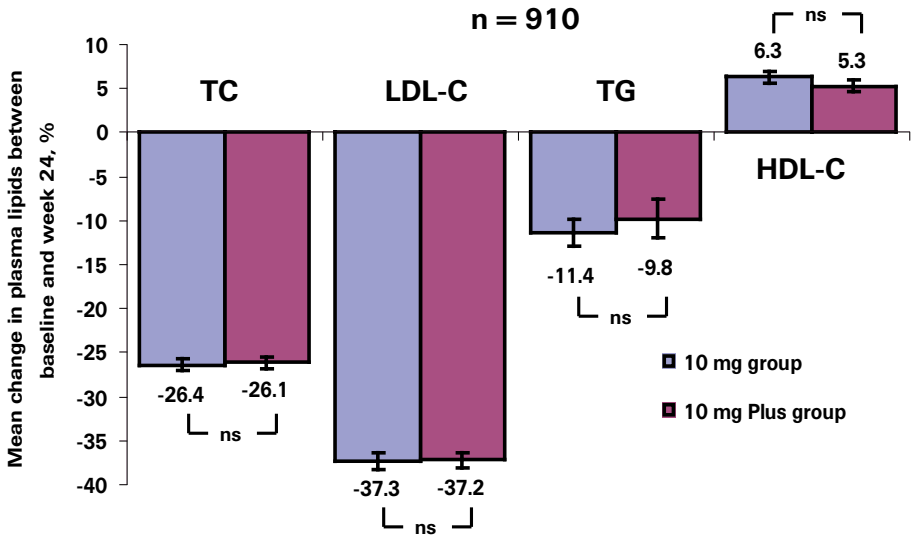


Figure 2

Mean percentage change in plasma lipids between baseline and week 24 in patients treated with rosuvastatin alone (10 mg group) or in combination with compliance enhancement tools (10 mg Plus group).

121 patients (63 patients in the 10 mg group; 58 patients in the 10 mg Plus group) discontinued treatment during the study. The main reasons for discontinuation were adverse events (39 patients in the 10 mg group; 35 patients in the 10 mg Plus group) and loss to follow-up (13 patients in the 10 mg group; 9 patients in the 10 mg Plus group).

Patients in both treatment groups received rosuvastatin for similar periods of time. The mean duration of treatment was 177 days for patients in the 10 mg group and 174 days for those in the 10 mg Plus group. At week 12, 309 patients (31%) in the ITT population (162 patients in the 10 mg group; 147 patients in the 10 mg Plus group), were titrated up to 20 mg rosuvastatin.

Primary efficacy analysis

In the 10 mg group, 67% of patients (358) achieved the 1998 European LDL-C goal (<3.0 mmol/L) at week 24 (LOCF) compared to 61% of patients (286) in the 10 mg Plus group, as shown in Figure 1. A patient assigned to the 10 mg Plus treatment group has 0.74 (95% CI 0.60-0.97; p = 0.032) lower odds of achieving the target than a patient assigned to the 10 mg (alone) group.

Secondary efficacy analyses

In the 10 mg group, 62% (316 patients) achieved the 1998 European LDL-C goal at week 12 (OC), compared to 61% (272 patients) in the 10 mg Plus group (figure 1) (difference not statistically significant (ns)). Patients in both treatment groups were found to have the same likelihood of achieving either the 1998 European LDL-C goal or the 2003 European LDL-C goal (<2.5 mmol/L) at week 12 and week 24. Similar findings were obtained for the 1998 European TC goal (<5.0 mmol/L) at week 12 and week 24, and for the 2003 European TC goal (<4.5 mmol/L) at week 12 and week 24.

There were favourable changes in lipid levels from baseline to week 24 (figure 2). Mean percentage decrease from baseline to week 24 in LDL-C, TC and TG levels were similar for both treatment groups (ns). LDL-C, TC and TG decreased in the 10mg group by 37.3%, 26.4% and 11.4% respectively and in the 10mg Plus group by 37.2%, 26.1% and 9.8% respectively. In general, higher reductions in LDL-C, TC and TG levels were reported for statin-naïve patients in comparison with those who switched from other lipid-lowering medication A statin-switched patient has 0.38 (95%; CI 0.29–0.51; p = 0.0001) lower odds of achieving the EAS LDL-C target than a statin-naïve patient. In the 10 mg group, 75.5% of statin-naïve vs. 58.8% of switched patients achieved the primary endpoint, compared to 66.4% statin-naïve vs. 54.8% of switched patients in the 10 mg Plus group.

Patient compliance with treatment was reported as high, with mean values of 97% (10 mg group) and 100% (10 mg Plus group) between week 12 and week 24.

Safety and tolerability

Table 2 shows the common adverse events occurring in more than 1% of patients. The two most frequently reported adverse events were myalgia (34 patients, 3% respectively) and back pain (23 patients, 2% respectively). The overall rate of temporary or permanent study discontinuation due to adverse events was 9% (n = 101) in patients receiving 10 mg rosuvastatin and 3% (n = 9) in patients titrated up to 20 mg rosuvastatin.

74 patients reported serious adverse events (SAEs). The two most common SAEs were myocardial infarction (4 patients) and angina pectoris (3 patients). One patient died from a sudden cardiac event while receiving 20 mg rosuvastatin. According to the investigator the death of this patient was not treatment-related. 6 patients experienced SAEs for which a causal relation with rosuvastatin therapy was suspected. These SAEs were hepatitis (1 patient), creatinine elevation (2 patients), dyspnoea (1 patient), muscle pain

(1 patient), and blood pressure elevation (1 patient).

Changes in clinical laboratory parameters were generally minor. Three patients experienced clinically important creatinine (>upper limit of normal and >100% over baseline) elevations. Three patients had clinically important ASAT and ALAT elevations (>3x the upper limit of normal). There were no patients with a clinically important increase of creatine kinase (>10x upper limit of normal).

There were no clinically significant changes in body weight, blood pressure and heart rate of patients during the study.

Discussion

Statins (HMG-CoA reductase inhibitors) are effective therapeutic agents for reducing plasma lipid levels and lowering cardiovascular morbidity and mortality in patients with CHD. Evidence from multiple clinical trials suggests that rosuvastatin offers the highest lipid-lowering efficacy at the lowest dose for the treatment of patients with hyperlipidaemia [25–27]. It is suggested that this lipid-lowering efficacy is based on the higher affinity of rosuvastatin to HMG-CoA reductase compared with other statins including atorvastatin, simvastatin and pravastatin [28].

In this study up to 67% of the patients treated with rosuvastatin reached the 1998 European goal for LDL-C (<3.0 mmol/L) at week 24. This was achieved although the initial dosage of 10mg rosuvastatin had to be increased to 20 mg in only 31% of patients. These findings differed from similar studies where as many as 74–88% of the patients achieved the 1998 European goal for LDL-C during treatment with a 10 mg daily dose of rosuvastatin [27, 30–32]. However, baseline levels of TC and LDL-C were higher in this study than in other similar studies and 49% of the patients were already pre-treated with another statin. This could explain why fewer patients achieved the 1998 European goal and is supported by data showing that reductions in levels of LDL-C in patients in this study were similar to reductions reported in other studies.

Rosuvastatin effectively reduced the mean plasma levels of LDL-C in patients who were either statin naïve or had switched from other lipid-lowering medication by 49.2% and 31.2% respectively. The mean reduction in LDL-C was comparable with findings from other studies showing reductions of 42–52% with 5 mg or 10 mg daily doses of rosuvastatin [26, 33].

The reduction in TC and TG levels and increase in HDL-C levels achieved with rosuvastatin in this study was comparable to those reported in other studies [26, 27, 34].

The reductions in LDL-C, TC and TG levels were generally higher for statin naïve patients than for those switched from other lipid-lowering medication. Moreover, statin naïve patents treated with rosuvastatin showed a greater increase in HDL-C levels compared to those switched from other lipid-lowering medication. These changes in the level of plasma lipids were in agreement with observations other studies [34].

The effectiveness of lipid-lowering therapy crucially depends on the patient's compliance [35], which was determined by counting tablets during the study. Excellent compliance with treatment was indicated by mean values of 97% (10 mg group) and 100% (10 mg Plus group) between week 12 and week 24. It is unusual that compliance proportions of 100% are achieved in clinical trials. This may be due to missing values resulting from unreturned medication. It was assumed that all the unreturned tablets had been taken.

Compliance enhancement initiatives employed during the present study were not found to increase the number of patients achieving 1998 or 2003 European goals for plasma lipids. However, this may be explained by the fact that patients in both groups were already very compliant with their treatment regimens. Moreover, patients participating in a clinical trial are more likely to be compliant with their treatment than in real life – regardless of which treatment group they are in.

Rosuvastatin was generally well tolerated. The adverse events and safety profile for rosuvastatin were similar to that of other statins [36]. Myalgia was the most commonly reported adverse event, affecting 3% of patients.

This study shows that rosuvastatin was effective in reducing LDL-C in the majority of patients with hypercholesterolaemia to the 1998 European goals for LDL-C at week 24. Compliance was high and the use of compliance enhancement tools did not increase the number and percentage of patients achieving European goals for plasma lipids. Rosuvastatin has a safety profile similar to that of other statins and was well tolerated by patients.

The authors acknowledge the support of AstraZeneca AG (Zug, Switzerland) for this trial. They express gratitude to archimed medical communication ag (Zofingen, Switzerland) for providing medical writing support and to the investigators and patients who participated in the study.

Correspondence:
Prof. Dr. Dr. h.c. Walter F. Riesen
Vorsteher
Institute für Klinische Chemie & Hämatologie und Klinische Mikrobiologie & Immunologie
Kantonsspital
CH-9007 St. Gallen
E-Mail: walter.riesen@ikch.ch

References

1 World Health Organization. The top ten causes of death. Fact sheet no. 310, February 2007, www.who.int/mediacentre/factsheets/.

2 Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937–52.

3 Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation. 1999;100:1481–92.

4 Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA. 1986;256:2823–8.

5 Wood D, DeBacker G, Faergeman O, Graham I, Mancia G, Pyörälä K. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. Eur Heart J. 1998;19:1434–503.

6 Durrington PN, Prais H, Bhatnagar D, France M, Crowley V, Khan J, et al. Indications for cholesterol-lowering medication: comparison of risk-assessment methods. Lancet. 1999;353:278–81.

7 De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003;24:1601–10.

8 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–9.

9 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333:1301–7.

10 Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335:1001–9.

11 Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279:1615–22.

12 Jonsson B, Johannesson M, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost-effectiveness of cholesterol lowering. Results from the Scandinavian Simvastatin Survival Study (4S). Eur Heart J. 1996;17:1001–7.

13 Szucs TD, Guggenberger G, Berger K, Marz W, Schafer JR. Pharmacoeconomic evaluation of pravastatin in the secondary prevention of coronary heart disease in patients with average cholesterol levels. An analysis for Germany based on the CARE study. Herz. 1998;23:319–29.

14 Maclaine GD, Patel H. A cost-effectiveness model of alternative statins to achieve target LDL-cholesterol levels. Int J Clin Pract. 2001;55:243–9.

15 Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, Cain VA, Blasetto JW; STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol. 2003;92(2):152–60.

16 Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. Circulation. 1997;95:1085–90.

17 Riesen WF, Darioli R, Noll G. Lipid-lowering therapy: strategies for improving compliance. Curr Med Res Opin. 2004;20:165–73.

18 Kulkarni SP, Alexander KP, Lytle B, Heiss G, Peterson ED. Long-term adherence with cardiovascular drug regimens. Am Heart J. 2006;151:185–91.

19 Huser MA, Evans TS, Berger V. Medication adherence trends with statins. Adv Ther. 2005;22:163–71.

20 Schwed A, Fallab CL, Burnier M, Waeber B, Kappenberger L, Burnand B, et al. Electronic monitoring of compliance to lipid-lowering therapy in clinical practice. J Clin Pharmacol. 1999;39:402–9.

21 Morisky DE, Levine DM, Green LW, Shapiro S, Russell RP, Smith CR. Five-year blood pressure control and mortality following health education for hypertensive patients. Am J Public Health. 1983;73:153–62.

22 Edmonds D, Foerster E, Groth H, Greminger P, Siegenthaler W, Vetter W. Does self-measurement of blood pressure improve patient compliance in hypertension? J Hypertens Suppl. 1985;3:S31–4.

23 Daltroy LH, Godin G. The influence of spousal approval and patient perception of spousal approval on cardiac participation in exercise programs. J Cardiopulm Rehabil. 1989;9:363–67.

24 Taylor CB, Houston-Miller N, Killen JD, DeBusk RF. Smoking cessation after acute myocardial infarction: effects of a nurse-managed intervention. Ann Intern Med. 1990;113:118–23.

25 Lopez LM. Rosuvastatin: a high-potency HMG-CoA reductase inhibitor. J Am Pharm Assoc. (Wash DC) 2005;45:503–13.

26 Teramoto T, Watkins C. Review of efficacy of rosuvastatin 5 mg. Int J Clin Pract. 2005;59:92–101.

27 Strandberg TE, Feely J, Sigurdsson EL. Twelve-week, multicenter, randomized, open-label comparison of the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: a DISCOVERY study. Clin Ther. 2004;26:1821–33.

28 Culhane NS, Lettieri SL, Skae JR. Rosuvastatin for the treatment of hypercholesterolemia. Pharmacotherapy. 2005;25:990–1000.

29 Lloret R, Ycas J, Stein M, Haffner S. Comparison of rosuvastatin versus atorvastatin in Hispanic-Americans with hypercholesterolemia (from the STARSHIP trial). Am J Cardiol. 2006;98:768–73.

30 McKenney JM, Jones PH, Adamczyk MA, Cain VA, Bryzinski BS, Blasetto JW. Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: results from the STELLAR trial. Curr Med Res Opin 2003;19:689–98.

31 Shepherd J, Hunninghake DB, Barter P, McKenney JM, Hutchinson HG. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. Am J Cardiol. 2003;91:11C–17C; discussion 17C–19C.

32 Schuster H, Barter PJ, Stender S, Cheung RC, Bonnet J, Morrell JM, et al. Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. Am Heart J. 2004;147:705–13.

33 Blasetto JW, Stein EA, Brown WV, Chitra R, Raza A. Efficacy of rosuvastatin compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. Am J Cardiol. 2003;91:3C–10C; discussion 10C.

34 Fonseca FA, Ruiz A, Cardona-Munoz EG, Silva JM, Fuenmayor N, Marotti M. The DISCOVERY PENTA study: a DIrect Statin Comparison of LDL-C Value – an Evaluation of Rosuvastatin therapy compared with atorvastatin. Curr Med Res Opin. 2005;21:1307–15.

35 Schectman G, Hiatt J. Drug therapy for hypercholesterolemia in patients with cardiovascular disease: factors limiting achievement of lipid goals. Am J Med. 1996;100:197–204.

36 Shepherd J, Hunninghake DB, Stein EA, Kastelein JJ, Harris S, Pears J, et al. Safety of rosuvastatin. Am J Cardiol. 2004;94:882–8.

Established in 1871

Formerly: Schweizerische Medizinische Wochenschrift

SMW Swiss Medical Weekly

The European Journal of Medical Sciences

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising. The 2006 impact factor is 1.346.
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of professional statisticians for every article with statistical analyses

- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts:	submission@smw.ch
Letters to the editor:	letters@smw.ch
Editorial Board:	red@smw.ch
Internet:	http://www.smw.ch

EMH FMH Schwabe
Editores Medicorum Helveticorum

Official journal of the Swiss Society of Infectious Diseases, the Swiss Society of Internal Medicine and the Swiss Respiratory Society

Supported by the FMH (Swiss Medical Association) and by Schwabe AG, the long-established scientific publishing house founded in 1488