Achieving lipid goals in real life: the DISCOVERY-UK study

General practitioners may not routinely uptitrate statins, even in patients not achieving target cholesterol levels. In this study, the efficacy and safety of the recommended start doses of three statins were evaluated.

Abstract

DISCOVERY-UK (the DIrect Statin COmparison of LDL-C Values: an Evaluation of Rosuvastatin therapY) was an open-label, parallel-group, multicentre study designed to compare the efficacy of recommended start doses of rosuvastatin with atorvastatin and simvastatin for reduction of low-density lipoprotein cholesterol (LDL-C) and goal attainment.

Patients with type IIa or type IIb hypercholesterolaemia and a 10-year coronary heart disease (CHD) risk > 20% or a history of CHD or other established atherosclerotic disease were randomised to receive rosuvastatin 10 mg, atorvastatin 10 mg or simvastatin 20 mg for 12 weeks.

Significantly greater LDL-C reductions were observed with rosuvastatin 10 mg compared with atorvastatin 10 mg and simvastatin 20 mg (50% versus 42% and 40%, both p<0.0001). The 1998 European goal (LDL-C < 3.0 mmol/L) was achieved by 89% of patients receiving rosuvastatin 10 mg, which was significantly more than patients receiving atorvastatin 10 mg (78%) and simvastatin 20 mg (72%) (both p<0.0001). Similar results were observed for the National Cholesterol Education Program Adult Treatment Panel III goal (LDL-C < 2.6 mmol/L) and 2003 European goals (LDL-C < 3.0 or < 2.5 mmol/L, depending on risk category).

In conclusion, rosuvastatin is more effective than atorvastatin or simvastatin for lowering LDL-C and enabling patients to achieve lipid goals at recommended start doses.

Key words: hypercholesterolaemia, statin, low-density lipoprotein cholesterol, randomised controlled trial.

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Introduction

The efficacy of statins in lowering low-density lipoprotein cholesterol (LDL-C) levels and reducing the occurrence of cardiovascular disease (CVD) is well established.[1,2] However, many patients who are eligible for statin therapy remain untreated and, among those who receive treatment, a considerable proportion fail to achieve lipid goals recommended by national and international guidelines.[3,4] Studies have shown that many patients who begin statin treatment remain at the initial dose, and dose titration is uncommon.[3,5] In the primary care setting, the availability of therapies that enable patients to achieve goals without the need for dose titration is important in optimising treatment outcomes.

> ***'Many patients who begin statin treatment remain at the initial dose'***

Rosuvastatin has been shown to be highly efficacious for lowering LDL-C levels,[6,7] and it enables more patients to achieve LDL-C goals at an initial dose of 10 mg compared with atorvastatin 10 mg and simvastatin 20 mg.[8] Rosuvastatin also has beneficial effects on other components of the lipid profile, including high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and triglycerides (TG).[7]

The DIrect Statin COmparison of LDL-C Values: an Evaluation of Rosuvastatin therapY (DISCOVERY) Programme is being conducted to assess the efficacy of recommended starting doses of rosuvastatin, atorvastatin and other statins for achieving lipid goals and improving the lipid profile. The DISCOVERY Programme is recruiting over 12,000 patients from more than 30 countries worldwide and is made up of a number of independently powered studies. Results from one of the DISCOVERY studies, conducted in the UK, are reported here.

Materials and methods

Trial design

DISCOVERY-UK (D3560/L00004) was a randomised, multicentre, open-label, three-arm, parallel-group study conducted in patients from 352 general practice centres. After dietary counselling, eligible patients were randomised 2:2:1 to receive rosuvastatin 10 mg, atorvastatin 10 mg or simvastatin 20 mg once daily for at least 12 weeks. The trial was conducted in accordance with the ethical principles in the Declaration of Helsinki, International Conference of Harmonisation Good Clinical Practice guidelines and UK regulatory requirements.

Patients

Patients (aged ≥ 18 years) with type IIa and IIb hypercholesterolaemia were eligible for inclusion if, in the opinion of the investigator, they would benefit from the introduction of lipid-lowering therapy. Patients also had to meet the following criteria: no previous statin treatment; LDL-C ≥ 3.5 mmol/L; fasting

TG ≤ 4.52 mmol/L; a 10-year coronary heart disease (CHD) risk > 20%;[9] or a history of CHD or other established atherosclerotic disease. Exclusion criteria included active liver disease or hepatic dysfunction, known uncontrolled diabetes, uncontrolled hypertension and unexplained serum creatine kinase (CK) 3 x the upper limit of normal (ULN).

Assessments

Visits were designed to mimic general practice procedures as closely as possible. Patients were enrolled and assessed for eligibility at visit 1, and were randomised 3–14 days later at visit 2. Patients returned after 12 weeks for blood sampling (visit 3a), and the final safety and tolerability assessment was performed one week later (visit 3). Blood samples for measurement of fasting lipids and clinical chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, CK, creatinine and glucose) were collected at visits 1 and 3a and sent to a central laboratory (Quest Diagnostics Ltd, Heston, Middlesex, UK) for analysis.

> ***'Significantly greater LDL-C reductions were observed with rosuvastatin 10 mg compared with atorvastatin 10 mg and simvastatin 20 mg'***

Statistical analyses

The primary end point was the proportion of patients achieving the 1998 European LDL-C goal of < 3.0 mmol/L after 12 weeks of treatment. Secondary end points included: the percentage of patients achieving National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C goals (< 2.6 mmol/L);[10] the percentage of patients achieving 1998 European TC goals (< 5.0 mmol/L);[9] and the percentage change from baseline in TC, LDL-C, HDL-C and TG at 12 weeks. The 2003 European guidelines on CVD prevention became available during the study and *post hoc* analyses were performed to assess the proportion of patients achieving these goals (LDL-C < 3.0 or < 2.5 mmol/L, TC < 5.0 or < 4.5 mmol/L, depending on risk category).[11] *Post hoc* analyses of the percentage of patients achieving the combined National Service Framework (NSF) LDL-C goal (< 3.0 mmol/L and ≥ 30% reduction) and combined TC goal (< 5.0 mmol/L and ≥ 25% reduction)[12,13] were also conducted.

All efficacy results shown are from the intention-to-treat population, which consisted of patients with a baseline reading, at least one post-baseline reading and who had received at least one dose of study drug. Logistic regression was used to compare the percentage of patients achieving goal. The regression model included treatment as a factor. The percentage change in lipid levels was compared across groups by analysis of covariance. The statistical model included treatment as the main effect and mean baseline lipid level as a covariate.

Sample size was determined for the primary end point, such that a difference in goal attainment of 5% (rosuvastatin versus atorvastatin) and 10% (rosuvastatin versus simvastatin) could be detected. It was calculated that 1,718 patients would be required to achieve 90% power at a two-sided significance level of 5%. Randomisation of approximately 1,910 patients was planned to allow for a 10% withdrawal rate.

The incidence and severity of adverse events and abnormal laboratory results were assessed. The safety set included all randomised patients who received at least one dose of study medication, and data were summarised descriptively.

Table 1. Patient characteristics at enrolment

	Rosuvastatin 10 mg (n=712)	Atorvastatin 10 mg (n=709)	Simvastatin 20 mg (n=349)
Age, years, mean (SD)	66.3 (8.8)	66.6 (8.6)	66.8 (8.3)
Range	32–89	35–89	36–86
Male (%)	62.1	63.6	61.6
Body mass index, kg/m², mean (SD)	28.3 (4.9)[a]	28.1 (4.6)[b]	27.9 (4.3)[c]
Diabetes (%)	17.8	15.8	16.0
Cardiovascular disease (%)	40.7	37.9	45.0
SCORE evaluation (%)			
Symptomatic	65.0	59.7	63.0
Asymptomatic, total risk ≥ 5%	35.0	40.3	37.0
Baseline lipid levels, mmol/L, mean (SD)			
TC	6.7 (0.9)	6.7 (0.8)	6.7 (0.9)
LDL-C	4.5 (0.7)[d]	4.5 (0.7)	4.5 (0.7)
HDL-C	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)
TG	2.1 (0.8)	2.0 (0.8)	2.0 (0.8)

[a]n = 708; [b]n = 707; [c]n = 348; [d]n = 711

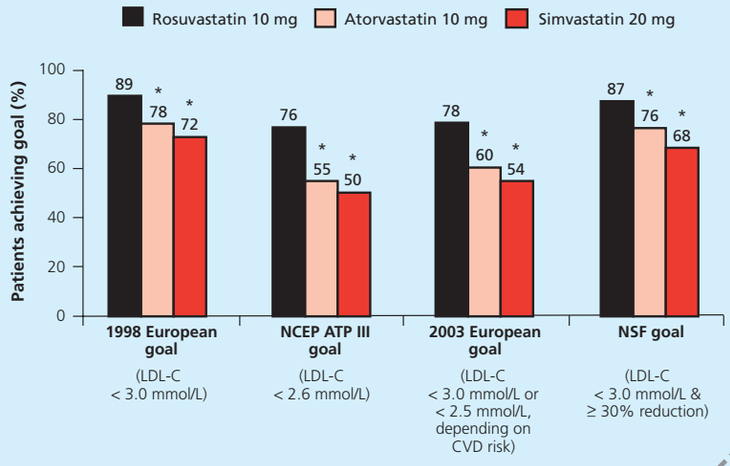
Key: SD = standard deviation; SCORE = Systematic Coronary Risk Evaluation; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides

Results

Patient characteristics

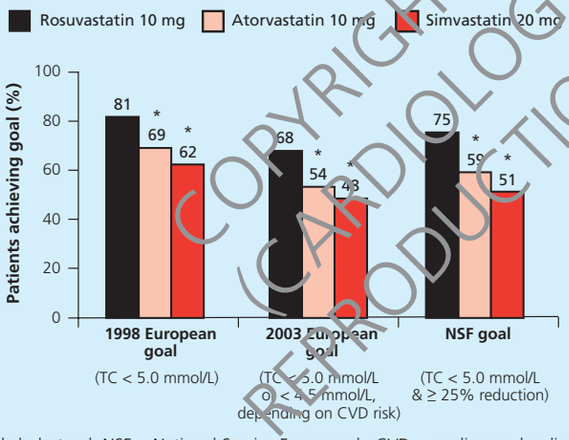
From a total of 2,506 patients enrolled, 1,874 were randomised and 1,760 patients (93.9%) completed the study. Overall discontinuation rates (discontinuation for any reason) were low (rosuvastatin 10 mg, 54 [7.1%]; atorvastatin 10 mg, 39 [5.2%]; simvastatin 20 mg, 21 [5.7%]). The groups were similar at baseline in terms of demographic, clinical and lipid variables (table 1). More than 35% of patients had a history of

Figure 1. Patients achieving LDL-C goals after 12 weeks in the DISCOVERY-UK study



Key: LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Programme Adult Treatment Panel III; NSF = National Services Framework; CVD = cardiovascular disease
*p<0.0001 versus rosuvastatin

Figure 2. Patients achieving TC goals after 12 weeks in the DISCOVERY-UK study



Key: TC = total cholesterol; NSF = National Service Framework; CVD = cardiovascular disease
*p<0.0001 versus rosuvastatin

CVD and the majority of patients (approximately 60%) were eligible to meet the 2003 European goals of TC < 4.5 mmol/L and LDL-C < 2.5 mmol/L.

Efficacy

Rosuvastatin 10 mg reduced LDL-C levels by 50%; this was significantly greater than atorvastatin 10 mg (42%, p<0.0001) and simvastatin 20 mg (40%, p<0.0001) after 12 weeks. Consistent with these greater LDL-C reductions, 1998 European LDL-C goals were achieved by significantly more patients receiving rosuvastatin 10 mg (89%) compared with those receiving atorvastatin 10 mg (78%, p<0.0001) and simvastatin 20 mg (72%, p<0.0001) (figure 1). The proportion of patients achieving NCEP ATP III LDL-C goals was also highest in the rosuvastatin 10 mg group (76%) compared with the atorvastatin 10 mg group (55%, p<0.0001) and simvastatin 20 mg group (50%, p<0.0001) (figure 1).

TC reductions were also significantly greater in patients receiving rosuvastatin 10 mg (34%) compared with patients receiving atorvastatin 10 mg (30%, p<0.0001) and simvastatin 20 mg (28%, p<0.0001). In addition, 1998 European TC goals were achieved by 81% of those receiving rosuvastatin 10 mg, compared with 69% receiving atorvastatin 10 mg and 62% receiving simvastatin 20 mg (both p<0.0001) (figure 2).

In *post hoc* analyses, significantly more patients receiving rosuvastatin 10 mg achieved the more stringent 2003 European LDL-C and TC goals and combined NSF goals compared with patients receiving atorvastatin 10 mg or simvastatin 20 mg (all p<0.0001) (figure 1, figure 2).

All treatments increased HDL-C and decreased TG at 12 weeks, but there were no significant differences between treatment groups.

'All treatments were well tolerated in this study'

Safety and tolerability

All treatments were well tolerated. Fewer than 5% of patients discontinued treatment as a result of an adverse event (rosuvastatin 10 mg, 4.8%; atorvastatin 10 mg, 3.7%; simvastatin 20 mg, 4.1%). The percentage of patients who reported adverse events was also similar among groups (rosuvastatin 10 mg, 47.7%; atorvastatin 10 mg, 46.5%; simvastatin 20 mg, 46.4%). Two patients died from causes considered to be unrelated to treatment (one received atorvastatin [and died from acute myocardial infarction] and one received simvastatin [and died from lobar pneumonia and ischaemic heart disease]).

The most frequent treatment-emergent adverse event was lower respirato-

Table 2. Most frequent (> 1.5% overall) treatment-emergent adverse events (safety population)

	Number (%) of patients with adverse event		
	Rosuvastatin 10 mg (n=754)	Atorvastatin 10 mg (n=752)	Simvastatin 20 mg (n=364)
Lower respiratory tract infection NOS	23 (3.1)	24 (3.2)	17 (4.7)
Headache	20 (2.7)	12 (1.6)	13 (3.6)
Constipation	23 (3.1)	13 (1.7)	5 (1.4)
Upper respiratory tract infection NOS	11 (1.5)	18 (2.4)	11 (3.0)
Arthralgia	20 (2.7)	11 (1.5)	8 (2.2)
Cough	16 (2.1)	12 (1.6)	10 (2.7)
Pain in limb	21 (2.8)	10 (1.3)	5 (1.4)
Myalgia	12 (1.6)	13 (1.7)	8 (2.2)
Diarrhoea NOS	14 (1.9)	13 (1.7)	5 (1.4)
Nausea	13 (1.7)	9 (1.2)	7 (1.9)

Key: NOS = not otherwise specified

Key messages

- There remains a considerable treatment gap in the lipid management of patients with cardiovascular disease
- Many patients who begin statin treatment remain at the initial dose
- The choice of statin has a significant impact on the proportion of patients achieving lipid goals in the primary care setting
- Lipid-lowering drugs that enable most patients to attain goals without the need for titration to higher doses will help to reduce the treatment gap

ry tract infection, followed by headache and constipation (table 2). No clinically significant CK elevations (> 10 x ULN) occurred. Changes from baseline of all serum chemistry parameters were small and similar across treatment groups. An increase in creatinine > 30% from baseline was experienced by a total of 36 patients, eight of whom had values outside the normal range (rosuvastatin 10 mg, two; atorvastatin 10 mg, four; simvastatin 20 mg, two). AST and ALT levels > 3 x ULN were detected in one patient but were considered to be unrelated to treatment (rosuvastatin 10 mg).

Discussion

The results of DISCOVERY-UK demonstrate that the choice of statin has a significant impact on the proportion of patients achieving lipid goals in the primary care setting. DISCOVERY-UK was designed to mimic general practice procedures as closely as possible and provides an accurate reflection of how more efficacious agents may reduce CVD risk without the need for dose titration in a 'real life' setting. Rosuvastatin 10 mg was more effective in enabling patients to achieve goals than the other statins studied. These data are consistent with findings from previously reported trials in patients with hypercholesterolaemia, which have shown that rosuvastatin 10 mg reduces LDL-C to a greater extent than atorvastatin 10 mg and simvastatin 20 mg, and enables more patients to achieve LDL-C goals.[7,8]

Many patients fail to achieve lipid goals: contributing factors include the use of low doses and limited drug effectiveness.[3] The Performance For Life study surveyed prescribing data from more than 14,000 patients with CHD who were treated with fluvastatin, pravastatin, simvastatin or atorvastatin.[3,14] More than half of patients on statins did not reach NSF goals at the initial dose, and of the patients not at goal, only one third received additional management in the form of increasing doses or switching to a more efficacious statin.[3,14] On the basis of findings from the Heart Protection Study,[1] there has been an increasing trend among clinicians to adopt a starting dose for simvastatin of 40 mg, removing the need for dose titration and ensuring greater efficacy at initial statin dose.[15] However, data indicate that rosuvastatin 10 mg remains the most effective initial statin dose for reducing cholesterol below European goals, even assuming acceptability of a 40 mg initial dose of simvastatin.[7]

Achievement of lipid goals may be improved by implementation of the new General Medical Services (GMS) contract, which places substantial emphasis on attainment of CHD risk factor targets in primary care.[16] Using the GMS contract, general practices receive additional remuneration if 60% of their patients with CHD have TC $\leq$ 5 mmol/L. The availability of a statin that enables nine out of 10 patients to achieve lipid goals at the starting dose without the need for dose titration may be highly valuable in enabling general practitioners to optimise lipid management and reach GMS targets.

In addition to efficacy, clinicians are likely to consider drug safety when selecting an appropriate therapy. Extensive safety data from the phase II/III programme indicate that rosuvastatin has a similar safety profile to other statins.[17] Consistent with these data, all treatments were well tolerated in this study, with a similar incidence of adverse events. Another important consideration is cost. Several studies have shown the most efficacious statins to be the most cost-effective in treating patients to recommended cholesterol goals.[18,19] A recent assessment of statins for the

National Institute for Clinical Excellence included cost-effectiveness modelling.[20] The assessment did not distinguish between the different statins but it did demonstrate that statin therapy in secondary prevention is cost-effective when compared with other standard treatments that are available on the NHS. For primary prevention, the cost-effectiveness is dependent on the level of CHD risk and age.

Recent evidence indicating that intensive LDL-C lowering improves cardiovascular outcomes is expected to drive recommended lipid goals downwards.[21,22] This trend was evident in the latest European guidelines[11] and recommendations related to the use of statins in patients with hypertension have been updated with new British targets to lower TC by 25% or LDL-C by 30% or to reach TC < 4.0 mmol/L or LDL-C < 2.0 mmol/L, whichever is the greater.[23] Furthermore, a recent NCEP ATP III recommendation suggests a LDL-C goal of < 1.8 mmol/L as a therapeutic option for very high-risk patients, such as those with established CVD and multiple risk factors including diabetes.[24] As lipid goals are lowered, there is increasing need for effective statins that enable most patients to achieve these more stringent goals. Lipid-lowering drugs that enable most patients to attain goals without the need to titrate to higher doses have the potential to optimise lipid levels in primary clinical practice.

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Conflict of interest

AM: none declared. AF has attended advisory boards for Astra-Zeneca, Pfizer, BMS, Sanofi-Aventis and received honoraria for speaking and attending symposia from all these companies.

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