Effectiveness of using rosuvastatin in difficult-to-control dyslipidemia patients: an audit in secondary care

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Background: A substantial proportion of patients at risk of developing or with established cardiovascular disease still fail to meet British lipid targets (low-density lipoprotein cholesterol <3 mmol/l). The redress of this failure requires improved lipid-lowering treatment strategies. **Methods:** We audited the efficacy and safety (reported liver function, glycemic index, muscle effects, headache and hypersensitivity) of rosuvastatin therapy and other lipid-lowering treatments in 216 patients, (53.7% men, mean age: 60 years) attending a lipid clinic at Sandwell General Hospital (West Midlands, UK). Patient data were obtained from notes reviewed during lipid clinic referral, lipid clinic lipid-lowering treatment before rosuvastatin and after 6 months' management with rosuvastatin. **Results:** Familial hypercholesterolemia (38.4% [95% confidence interval: 31.9–44.9%]) and combined dyslipidemia (38.4% [31.9–44.9%]) were the most common forms of hyperlipidemia. At referral, 9.1% (3.4–14.8) were achieving the low-density lipoprotein cholesterol target. Following lipid-lowering treatment at the lipid clinic (mean time: 4.1 years), 24.2% (15.8–32.7%) of patients were at target before a change to rosuvastatin and 66.7% (57.4–76.0) were at target with rosuvastatin therapy (0.5 years treatment). Overall, the mean reduction in serum cholesterol after referral with lipid-lowering treatment other than rosuvastatin was 1.6 [1.2–2.0] mmol/l ($p < 0.05$). An additional 0.7 (0.4–0.9) mmol/l reduction ($p < 0.05$) was observed with rosuvastatin. Adverse reactions to statin were no more common with rosuvastatin (2.0%) than other statins in its class (7.4%). **Conclusion:** In this setting of dyslipidemic patients, who have been difficult-to-control, rosuvastatin + lipid-lowering treatment achieved greater reduction in serum cholesterol than traditional statins, and increased the proportion of patients achieving target cholesterol within a 6-month period.

Keywords: cholesterol management, combined dyslipidemia, familial hypercholesterolemia, lipid targets

Statin-based intervention trials have established that lowering low-density lipoprotein (LDL) cholesterol (LDL-C) prevents cardiovascular disease (CVD) mortality and recent evidence provides a basis for an aggressive approach to lipid lowering [1–3]. The magnitude of LDL-C lowering is directly related to the efficacy of CVD management [4] and these findings have promoted the refinement of Adult Treatment Program (ATP) III guidelines by the National Cholesterol Education Program (NCEP) to recommend a move towards more intensive LDL-C lowering [5]. However, in practice, population surveys conclude that most of the patients with CVD do not currently achieve national LDL-C guideline targets, emphasizing the need for improved lipid-lowering treatment (LLT) strategies [6,7].

Statins are the backbone of LLT, and there is continuing deliberation over the relative efficacy and safety of one statin over another. Clinical trial data suggests, from a host of comparator statins, rosuvastatin returns the greatest improvement in lipid profiles [8]. The objective of this analysis was to investigate whether we could emulate this improved LDL-C lowering with rosuvastatin therapy among difficult-to-treat dyslipidemic patients attending a lipid clinic in inner-city Britain. In particular, we audited whether rosuvastatin could improve the number of patients achieving the current British guidelines (LDL-C < 3 mmol/l).

Methods

This audit followed patients attending the lipid clinic of Sandwell and West Birmingham National Health Service (NHS) Trust (West Midlands, UK). Information from patient notes was derived from those patients who were prescribed rosuvastatin therapy between 13 November 2002 and 8 June 2004. Our objectives were to assess the safety and efficacy of LLT before and after an exclusive change to rosuvastatin therapy, either as monotherapy or

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Table 1. Mean age, cardiovascular morbidity and dyslipidemia among patients at referral.

Characteristic	Men (n = 116)		Women (n = 100)		Patients on statin monotherapy (n = 87)*		All patients (n = 216)	
Mean age (years)	56.4	(54.4–58.4)	64.2	(62.3–66.1)	59.8	(57.4–62.3)	60.0	(58.5–61.5)
Comorbidity								
All cardiovascular disease	43.1	(34.1–52.1)	36	(26.6–45.4)	32.2	(22.4–42.0)	39.8	(33.3–46.3)
Coronary heart disease	36.2	(27.5–44.9)	35	(25.7–44.3)	27.6	(18.2–37.0)	35.6	(35.6–29.2)
Cerebrovascular disease	4.3	(0.6–8.0)	1	(0–3.0)	1.1	(0–3.4)	2.8	(0.6–5.0)
Peripheral vascular disease	12.1	(6.2–18.0)	2	(0-4.9)	4.6	(0.2–9.0)	7.4	(3.9–10.8)
Hypertension	37.9	(29.1–46.7)	41	(31.4–50.6)	35.6	(25.6–45.7)	39.4	(32.9–45.9)
Diabetes	25.9	(17.9–33.9)	25	(16.5–33.5)	23	(14.1–31.8)	25.5	(19.7–31.3)
Dyslipidemia								
Hypercholesterolemia	22.4	(14.8–30.0)	19	(11.3–26.7)	23	(14.1–31.8)	20.8	(15.4–26.2)
Familial hypercholesterolemia	32.8	(24.3–41.3)	45	(35.2–54.8)	46	(35.5–56.4)	38.4	(31.9–44.9)
Hypertriglyceridemia	4.3	(0.6-8.0)	0		2.3	(0-5.4)	2.3	(0.3–4.3)
Combined dyslipidemia	40.5	(31.5–49.4)	36	(26.6–45.4)	27.6	(18.2–37.0)	38.4	(31.9–44.9)

Data are mean or percentage (95% confidence interval).
**Patients exclusively on statin monotherapy before a change to rosuvastatin.*

combination therapy. To facilitate this, we reviewed patient notes and biochemical results at three time points:

- At referral to the lipid clinic
- Before rosuvastatin (i.e., after management at the lipid clinic on another LLT)
- After rosuvastatin management

The following information was collected at each time point:

- Date of appointment, demographics, recorded history of CHD, stroke, peripheral vascular disease, hypertension and diabetes
- Medications including lipid-modifying therapy (statin, fibrate, cholesterol resins, fish oils, nicotinic acid derivatives and ezetimibe) and aspirin
- Biochemical results for serum cholesterol, high-density lipoprotein (HDL) cholesterol (HDL-C) and fasting triglycerides. LDL-C was calculated in those patients with serum triglycerides of 4.7 mmol/l or less
- Reported dyslipidemia, either as hypercholesterolemia, familial hypercholesterolemia, hypertriglyceridemia or combined dyslipidemia

The diagnosis of familial hypercholesterolemia was by phenotype using the Simon Broome definition where there was evidence of tendon xanthomas among patients or relatives (first or second degree) and serum cholesterol levels were 7.5 mmol/l in adults and 6.7 mmol/l in children under 16 years.

Table 2. Lipid-lowering therapy prescribed throughout the audit.

Lipid-lowering therapy	At referral (n = 216)		Before rosuvastatin (n = 216)		After rosuvastatin (n = 216)	
Statins*	25.9	(20.1–31.7)	64.8	(58.4–71.2)	100	
Statin monotherapy	22.2	(16.7–27.7)	51.4	(44.7–58.1)	62	(55.5–68.5)
Fibrates*	10.7	(6.6–14.8)	33.8	(27.5–40.1)	26.9	(21.0–32.8)
Statin + any fibrate	2.8	(0.6–5.0)	10.6	(6.5–14.7)	26.9	(21.0–32.8)
Other lipid-lowering therapies*						
Fish oils	0.5	(0–1.4)	3.7	(1.2–6.2)	4.6	(1.8–7.4)
Nicotinic acid derivatives	0		0		0.5	(0–1.4)
Cholesterol resins	0.5	(0–1.4)	0.5	(0–1.4)	0.5	(0–1.4)
Ezetimibe	0		3.2	(0.9–5.5)	6	(2.8–9.2)

Data are percentages (95% confidence interval).
**Prescribed alone or in combination.*

Table 3. Mean changes in lipid levels for patients receiving statin therapy at the lipid clinic.

	At referral (A)		Before rosuvastatin (B)		After rosuvastatin (C)		Reduction in mean lipid levels*			
							A versus B		B versus C	
All patients‡ (n = 87)										
Serum cholesterol (mmol/l)	7.4	(7.1–7.8)	6	(5.7–6.2)¶	5.3	(5.0–5.5)¶	1.6	(1.2–2.0)	0.7	(0.4–0.9)
Triglycerides§ (mmol/l)	2.9	(2.0–4.5)	2.3	(1.6–3.4)¶	2.1	(1.5–2.7)¶	0.4	(0–0.9)	0.4	(0.2–0.7)
HDL cholesterol (mmol/l)	1.2	(1.2–1.3)	1.3	(1.3–1.4)	1.3	(1.3–1.4)	-0.1	(-0.2–0)	0	
Males‡ (n = 40)										
Serum cholesterol (mmol/l)	7.1	(6.5–7.6)	5.7	(5.3–6.2)¶	5	(4.7–5.4)¶	1.3	(0.8–1.9)	0.7	(0.3–1.1)
Triglycerides§ (mmol/l)	2.9	(2.3–4.9)	2.3	(1.6–3.6)#	2.4	(1.5–3.1)	0.7	(0.3–1.1)	0.4	(0–1.0)
HDL cholesterol (mmol/l)	1.1	(1.0–1.2)	1.2	(1.1–1.3)#	1.2	(1.1–1.3)	-0.1	(-0.2–0)	0	
Females ‡ (n = 47)										
Serum cholesterol (mmol/l)	7.7	(7.3–8.2)	6.1	(5.8–6.5)¶	5.5	(5.1–5.8)¶	1.7	(1.2–2.3)	0.7	(0.3–1.0)
Triglycerides§ (mmol/l)	2.8	(1.6–4.3)	2.2	(1.6–3.2)#	1.9	(1.4–2.6)#	0.1	(0–1.0)	0.5	(0.1–0.9)
HDL cholesterol (mmol/l)	1.4	(1.2–1.5)	1.5	(1.4–1.5)	1.4	(1.4–1.5)	0		0	
Patients with familial hypercholesterolemia (n = 45)										
Serum cholesterol (mmol/l)	7.1	(6.6–7.6)	6	(5.6–6.5)¶	5	(4.7–5.4)¶	1.1	(0.5–1.6)	1	(0.6–1.4)
Triglycerides§ (mmol/l)	2.5	(1.5–3.1)	2.2	(1.7–2.6)#	1.6	(1.2–2.3)#	0.3	(-0.2–0.7)	0.4	(-0.1–0.9)
HDL cholesterol (mmol/l)	1.3	(1.1–1.5)	1.4	(1.3–1.6)	1.5	(1.3–1.6)	0.2	(0–0.3)	0	
Patients with hypercholesterolemia (n = 21)										
Serum cholesterol (mmol/l)	7.7	(7.2–8.2)	5.9	(5.5–6.3)¶	5.4	(5.0–5.7)¶	1.8	(1.2–2.3)	0.5	(0.2–0.9)
Triglycerides§ (mmol/l)	2.6	(1.8–3.3)	2	(1.5–3.1)#	2	(1.5–2.8)#	0.3	(-1.4–0.9)	0.3	(-0.3–0.8)
HDL cholesterol (mmol/l)	1.3	(1.1–1.4)	1.3	(1.2–1.4)	1.3	(1.2–1.4)	0		0	
Patients on statin/fibrate combination (n = 13)										
Serum cholesterol (mmol/l)	6.3	(5.6–7.0)	5.9	(5.5–6.3)	5.1	(4.5–5.7)¶	0.4	(-0.3–1.1)	0.8	(0.3–1.3)
Triglycerides§ (mmol/l)	5	(4.0–6.0)	3.2	(2.6–3.8)#	2.4	(1.6–3.2)	0	(-0.4–4.1)	0.4	(-0.2–1.0)
HDL cholesterol (mmol/l)	1	(0.8–1.2)	1.2	(1.0–1.3)#	1.2	(1.1–1.3)	0.2	(0–0.4)	0	

Data are mean (95% confidence interval).

**Reduction in levels for serum cholesterol, triglycerides and HDL cholesterol.*

‡Patients on maximum tolerated statin therapy at B, those patients who experienced a change from mono to combination therapy at C were excluded from the analysis.

§Median levels for triglycerides (25th, 75th percentiles).

¶p < 0.001 and #p < 0.05 (significance of changes using paired t-test or Wilcoxon§: A vs. B or B vs. C).

HDL: High-density lipoprotein.

Statistical analysis

All data were entered into a Microsoft Access database and validated by crosschecking for duplicate, incomplete and unexpected values. Data were then transported for analysis using SPSS (SPSS Inc., IL, USA). Descriptive analysis of the data were summarized by percentages with 95% confidence intervals (CIs) for men and women. Differences between the proportions of each variable were further compared using the Chi-square test. Means and 95% CI were generated for parametric continuous data, where a paired t-test was used to determine the significance of changes. For data on triglycerides, which were non-normally distributed, medians along with the 25th and 75th percentiles were calculated and the Wilcoxon paired t-test was used for hypothesis testing.

Results

Data from a total of 116 men and 100 women were available for analysis. Generally, patients were of European Caucasian descent (94.8%), and most male and female patients were at high cardiovascular risk. This risk was manifest as frequent histories of coronary heart disease (40% of

Table 4. Percentage of patients at LDL cholesterol target (<3 mmol/l).

	Patients at target at referral		Patients at target before rosuvastatin		Patients at target after rosuvastatin	
All patients (n = 99)*	9.1	(3.4–14.8)	24.2	(15.8–32.7)	66.7	(57.4–76.0)
Patients with cardiovascular disease (n = 38)*	7.9	(0–16.5)	26.3	(12.3–40.3)	78.9	(66.0–91.9)
Patients on monotherapy with statin (n = 64)‡	9.1	(0–21.1)	28.1	(17.1–39.1)	62.5	(50.6–74.4)

Data are mean percentage (95% confidence interval).
**Patients for whom a LDL value could be calculated throughout the audit (triglycerides <4.7 mmol/l), and excludes those introduced to mono or combination therapy at visit three.*
‡For those exclusively on statins after referral, patient numbers are calculated on 22 patients.
LDL: Low-density lipoprotein.

patients), hypertension (40%) and diabetes (25%). Women in the analysis were older than men, but cardiovascular morbidities and forms of dyslipidemia were equally common (Table 1). Familial hypercholesterolemia and combined dyslipidemia were the most frequent forms of hyperlipidemia among patients.

Statin therapy was the most common form of LLT used among patients, and on analysis, the percentage use of statin increased from 26% at referral to 100% (all rosuvastatin) by the end of the audit (Table 2). The most common prescriptions of statin at referral were 10 mg atorvastatin (95% CI: 17.9 [7.9–27.9]), 40 mg pravastatin (16.1 [6.5–25.7]) and 20 mg simvastatin (14.3 [5.1–23.5]). Before patients were changed to rosuvastatin, the most common statin used in the lipid clinic was 40 mg simvastatin (15.7 [9.7–21.7]), 40 mg atorvastatin (15.7 [9.7–21.7]) and 80 mg atorvastatin (13.6 [7.9–19.3]). The mean time for LLT in the lipid clinic between referral and a change to rosuvastatin was 4.1 years (3.5–4.6). The mean follow-up time after the change to rosuvastatin was 0.5 years [0.4–0.6]. Statin with fibrate was the most common combination therapy, and was used for all forms of dyslipidemia. Whether as monotherapy or in combination, the fibrate used was almost exclusively fenofibrate. The percentage of men and women (M/W) receiving fibrates were: at referral, 13.8/7.0%; LLT before the change to rosuvastatin, 42.2/24.0% and 33.6/19.0% after the change to rosuvastatin. Individuals who were not on combination therapy who were subsequently introduced to fibrate and other LLT with rosuvastatin were excluded for subsequent analysis of lipid levels.

Of those patients who were exclusively on statin therapy at the lipid clinic before being changed to rosuvastatin, there were marked serial reductions in serum cholesterol (Table 3). In addition, there were moderate reductions in serum triglycerides, but HDL-C remained unchanged. Mean serum cholesterol levels were lowest in patients on rosuvastatin, including women and patients with familial hypercholesterolemia ($p < 0.05$). Generally, statin therapy with rosuvastatin offered an additional reduction in serum cholesterol, relative to other statins and this was observed in all dyslipidemias (except hypertriglyceridemia) and those on combination therapy (Table 3). Among 36 patients on 40 mg of either atorvastatin, simvastatin or pravastatin before a change to rosuvastatin at doses of less than 40 mg (i.e., 39% on 10 mg and 61% on 20 mg rosuvastatin), there was a 1.65 mmol/l (95% CI: 1.15–2.14) reduction in serum cholesterol with statins other than rosuvastatin with respect to referral levels, and an additional 0.70 mmol/l (0.33–1.07) reduction with rosuvastatin. Similarly, these same patients experienced a 0.81 mmol/l (0.30–1.30) reduction in triglycerides with 40 mg doses of statins other than rosuvastatin, and a further 0.35 (0–0.68) reduction with rosuvastatin. Neither type of statin therapy changed levels of HDL-C.

Compared with their status at referral, a greater percentage of patients achieved target LDL-C (<3 mmol/l) after management with statins (24.2%), this proportion increased significantly when statin therapy was changed to rosuvastatin (66.7%). Hence, after the change to rosuvastatin, most patients were achieving target LDL-C. Among those with CVD, almost 80% were at LDL-C target. Even among those patients on statin monotherapy where there was a modest increase in patients achieving target with rosuvastatin, more than 60% of patients were at target (Table 4).

Table 5. Adverse effects of lipid-lowering therapy.

Adverse reactions	Before rosuvastatin (n = 216)	On rosuvastatin (n = 216)
None reported	200	209
Muscle effects	4	2
Headache	3	3
Gastrointestinal effects	6	1
Hypersensitivity	3	1

Overall there were 16 reports (7.4%) of adverse effects associated with LLT before the change to rosuvastatin, four relating to muscle effects, three to headache, six to gastrointestinal and three to hypersensitivity. With rosuvastatin, there was a similar distribution of adverse effects, but there were seven in total (3.2%) (**Table 5**).

Discussion

The results from this audit clearly support the results of clinical trials, which conclude that rosuvastatin therapy is an effective therapeutic strategy for achieving LDL-C targets in high CVD-risk patients in comparison with therapy from other comparator statins [8–11]. Importantly, rosuvastatin therapy appeared to be as safe as other statins in its class in this population of difficult-to-treat patients. Less tangible in this audit approach are any immediate financial benefits associated with rosuvastatin therapy in comparison with previous therapy. Cost–efficacy analysis of statin use in the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial, estimated a benefit associated with rosuvastatin compared with atorvastatin, pravastatin and simvastatin in relation to cholesterol lowering and patients achieving LDL targets [12].

Of note, rosuvastatin therapy was shown to offer additional lowering of serum cholesterol in a range of difficult-to-treat patients, in particular, among patients with familial hypercholesterolemia. Similarly, rosuvastatin therapy was reported to be well tolerated and effective in achieving NCEP targets in patients with heterozygous familial hypercholesterolemia [13]. Rosuvastatin appeared to be tolerated equally well in monotherapy and in combination with fibrate (fenofibrate). While the number of patients on combination therapy was too few to assess the efficacy of triglyceride lowering, Durrington and colleagues have reported that rosuvastatin therapy was as safe and efficacious in lowering triglycerides as fenofibrate in a randomized placebo-controlled trial amongst Type 2 diabetics with combined dyslipidemia [14]. There were no adverse changes in the lipid profile associated with rosuvastatin therapy and the HDL-C remained unchanged.

Conclusion

Rosuvastatin therapy provides a safe and effective option for achieving target LDL-C guidelines in difficult-to-treat patients. While this audit approach is limited in its design with respect to data collection, it allows insight into the management of dyslipidemia of high CVD-risk patients in the UK outside of the clinical trial setting.

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Highlights

- Recent evidence provides a basis for an aggressive approach to lipid management (in particular lowering low-density lipoprotein cholesterol) in primary and secondary cardiovascular disease prevention.
- 'Statins' form the backbone of lipid lowering therapy and clinical trial data suggests that rosuvastatin returns the greatest improvement in lipid profiles.
- The objective of this study was to investigate whether improved lipid lowering therapy with rosuvastatin could be emulated in difficult-to-treat, high risk patients in practice.
- The results of this audit support the view that rosuvastatin is a more effective strategy for achieving current low-density lipoprotein cholesterol guidelines in 'difficult to treat' patients than other comparator statins.
- The implication is that rosuvastatin provides an effective, safe and potentially cheaper approach to lipid lowering management.

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