STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Crestor
ACTIVE INGREDIENT: Rosuvastatin

Study No: 25V07
Assessment of the efficacy of rosuvastatin in patient groups with a dissimilar risk profile in an observational study (HEROS).

Developmental phase: IV
Study Completion Date: 04-06-2005
Date of Report: 01-30-2007

OBJECTIVES:

In an observational multi-centre study (HEROS), the effects of starting treatment with rosuvastatin were assessed, on low-density lipoprotein cholesterol (LDL-C) goal achievement, in patients with a dissimilar high-risk profile who had not been treated with cholesterol lowering drugs at least in the past three months. Also set-up costs of rosuvastatin treatment and proportional changes in LDL-C and high-density lipoprotein cholesterol (HDL-C) were studied.

METHODS:

Study design & patients
The HEROS study is an observational study conducted in 659 centres in the Netherlands, representing daily practice. This implies that no rules of conduct are imposed on the physician and the patient and that no actions are demanded from the patient beyond standard practice. All patients approved to place anonymous results at the disposal of AstraZeneca. The centres consisted of practices of general practitioners. In total 5,372 patients were included in the study. Patients eligible for the study were patients who had not been treated with cholesterol lowering drugs at least in the past three months, with an LDL-C $\geq$ 3.2 mmol/l. Patients were aged $\geq$ 18 years and $\leq$ 70 years (men) and $\leq$ 75 years (women), according to the advise of the Centraal Begeleidingsorgaan (CBO) and could be included in one of the following risk groups: secondary prevention, DM or primary prevention. The following patients were included in the group of secondary prevention: patients with (1) myocardial infarction (MI) and/or angina pectoris (AP), (2) cerebrovascular atherosclerotic disease (CVA) and/or transient ischeamic attack (TIA), or (3) peripheral arteriosclerosis (PA).

Patients being treated for secondary prevention always belonged to this group irrespective other diseases. Patients being treated for DM belonged to the group of DM, except for the patients where also secondary prevention was involved. The following patients were included in the group of primary prevention: patients not complying the criteria for secondary prevention and DM, but having one of the following risk factors: (1) drug treatment for hypertension, (2) smoking, (3) coronary cardiopathy occurring in first degree relatives before they reach the age of sixty. Exclusion criteria included patients with symptoms of myalgia, myopathy or liver function insufficiency (including raised serum transaminases) which bear a causal relation to the treatment with statins, patients with familiar dyslipideamia and/or patients with contra-indications for treatment with rosuvastatin. Patients were their own historical control. The general practitioner made the decision to start treatment with rosuvastatin irrespective of study participation. The patients were treated in accordance with the physicians own standards. At baseline, date of the visit, patient characteristics, risk profile, starting dose of rosuvastatin (daily 10 or 20 mg) and the lipid profile were obtained and rosuvastatin treatment was started. Optional follow-up visits were performed each time a lipid determination was made, the rosuvastatin dosage was adapted (from 10 mg to 20 mg or from 20 mg to 40 mg), and/or the patient visited the physician with regard to the rosuvastatin therapy (in which the criteria for the final visit had not been met yet). The study was maximised until 6 months after the initial visit. Only in case a patient was not set up correctly within 6 months, an additional last visit was possible as part of the HEROS study. The final visit always had to be completed and was filled out in case one of the following situations occurred: (1) the patient was set up correctly according to the physician and continued treatment with rosuvastatin in the current dosage; (2) the patient stopped prematurely with rosuvastatin, or switched to another cholesterol lowering therapy, or started treatment with additional cholesterol lowering drugs; (3) the patient was treated for 6 months or longer with rosuvastatin, but was not yet set up correctly at that time in the opinion of the physician. End point of the study, with respect to the costs, was different for the 3 options mentioned above. In the first situation, the end point was the visit during which the physician decided that the patient was set up correctly. In the second option, the end point was the moment that the set up of monotherapy with rosuvastatin was discontinued. In the third option, the end point was the last visit, even if the physician's opinion was that the patient was not set up correctly at that time.
The observational character of the study implies that the number of visits to set up the rosuvastatin treatment will vary.

Efficacy, costs and safety parameters/assessments

Efficacy

The efficacy analysis was performed on intention-to-treat basis (ITT). Patients satisfying inclusion criteria were included. Primary efficacy measure was the proportion of patients reaching LDL-C goal of < 3.2 mmol/l at the last post-enrolment visit. Since recent adjustments in formulation of targets were formulated by the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice, additional analysis were performed [2]. These included the proportion of patients reaching LDL-C goal of < 3.0 mmol/l for the primary prevention subgroup and LDL-C < 2.5 mmol/l for the secondary prevention subgroup and the DM subgroup. In case LDL-C at the last post-enrolment visit was unknown, patients were evaluated as not reaching LDL-C targets.
Secondary efficacy measures included the proportional change from baseline of LDL-C and HDL-C at the last post-enrolment visit for the ITT-group, secondary prevention subgroup, DM subgroup and primary prevention subgroup.

Costs

In order to get a picture of the costs necessary to set up treatment with rosuvastatin for a patient in a particular risk group, five different scenarios were defined. The seven studied risk groups were: MI and/or AP, CVA and/or TIA, PA, DM, drug treatment for hypertension, CHD occurring in first degree relatives before they reach the age of sixty, and smoking. In all patients the healthcare consumption with regard to the start of a treatment with rosuvastatin was mapped. The costs were calculated from the healthcare consumption of each subgroup times a price per unit divided by the number of responders within the subgroup. The result represented the costs needed to successfully start a treatment with rosuvastatin for one responding patient. Only the healthcare consumption in respect to hypercholesterolaemia was taken into consideration. These included: (1) the number of visits to the general practitioner (could also be a telephonic visit, except for the enrolment visit); (2) the number of visits to a physician, specialist or dietician for the treatment with rosuvastatin; (3) the number of lipid measurements; (4) the used rosuvastatin medication. Prices per unit used for calculation of costs were based on Dutch prices in 2006.

On the basis of the three end points described in section 'study design & patients', five different scenarios were defined to determine care consumption:

(1) Within 6 months or at the first visit after 6 months, the physician regarded the patient as being successfully set up and the patient had achieved a LCL-C < 3.2 mmol/l at this or an earlier visit. The health care consumption was calculated from enrolment visit until the visit the patient became a responder (LDL-C < 3.2 mmol/l);
(2) Within 6 months or at the first visit after 6 months, the physician regarded the patient as being successfully set up, but the patient had never achieved a LCL-C < 3.2 mmol/l at this or an earlier visit. If the physician regarded the patient a responder within 6 months of treatment, the health care consumption was extrapolated to 6 months treatment. If the physician regarded the patient a responder after 6 months or more, the health care consumption was calculated for this whole period.
(3) At the first visit after 6 months, the physician regards the patient as not being successfully set up and ended the treatment with rosuvastatin. The health care consumption was calculated from enrolment until the first visit after 6 months, irrespective if the patient was a responder during the treatment with rosuvastatin.
(4) At the first visit after 6 months, the physician regarded the patient as not being successfully set up and continued the treatment with rosuvastatin. If the patient was a responder at or before this visit, the health care consumption was calculated from enrolment until the patient became a responder.
(5) Within 6 months or before the first visit after 6 months, the physician prematurely ended treatment with rosuvastatin or started an additional treatment. The health care consumption was extrapolated to 6 months treatment irrespective of the patient was a responder during the treatment with rosuvastatin.

Safety

Standard safety assessments included the registration of all SAE's and adverse events resulting in discontinuation (DAE) of rosuvastatin. All SAE's were to be documented and reported within 1 day to AstraZeneca. A SAE was defined as an AE leading to death, life-threatening situation, in-patient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity, a congenital abnormality/birth defect, or an important medical event. All patients of the ITT population were evaluated for safety.

Statistical analysis

All data were analysed according to the Intention To Treat (ITT) principle. The ITT analysis set was defined as all patients having LDL-C ≥ 3.2 mmol/l, measured at a time point that the patient was not treated with cholesterol lowering medication, and the patient could be included in one of the following risk groups: secondary prevention, DM or primary prevention. All variables were analysed within each subgroup. Last Observation Carried Forward (LOCF) was used for primary and secondary variables, if measurements were available at any post-enrolment visit. The measurements of the initial visit were not carried forward. If there was no LDL-C level measured after initial visit, the patient was regarded as having a LDL-C above the target.

Primary end point was the proportion of patients, with corresponding 95% confidence intervals, reaching LDL-C < 3.2 mmol/l at the last post-enrolment visit per risk group.

Secondary end points were:

(1) The proportion of patients reaching its subgroup specific target, as defined by the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice [2]: LDL-C < 3.0 mmol/l for the primary prevention subgroups and LDL-C < 2.5 mmol/l for the secondary prevention subgroups and the DM subgroup;
(2) Percentage of LDL-C decrease at the last post-enrolment visit compared to baseline, per risk group;
(3) Percentage of HDL-C decrease at the last post-enrolment visit compared to baseline, per risk group;
(4) The healthcare costs related to treatment with rosuvastatin. The set up costs were calculated per responder of each subgroup. To that end, the healthcare consumption of each subgroup times a price per unit was divided by the number of responders, resulting in the costs to successfully treat one patient with rosuvastatin.

RESULTS:

Characteristics

General practitioners from 659 different centres enrolled a total number of 5,372 patients from various risk groups in the study . Patients had not been treated with cholesterol lowering medication in at least the past three months. The general practitioner made the decision to start treatment with rosuvastatin. This decision was made irrespective of study participation. In order to imitate the practical situation as closely as possible, no demands were made on the physician with regard to dosage of target cholesterol value. The study did not impose rules of conduct on the patient, nor did it ask any actions beyond standard practice.

A total of 196 of all 5,372 patients (3.6%) did not meet the inclusion criterion of LDL-C ≥ 3.2 mmol/l. From the remaining 5,176 patients, 87 (1.6% of all included patients) could not be attributed to one of the following risk groups: MI and/or AP, CVA and/or TIA, PA, DM, drug treatment for hypertension, CHD occurring in first degree relatives before they reach the age of sixty, and smoking. Three patients had their second visits before the introduction of rosuvastatin .in the Netherlands. These patients were also excluded. This leaded to an ITT population of 5,086 patients. Despite the inclusion criteria, men older than 70 years and women older than 75 years were included, because the CBO gave a directive and not a binding advice considering age.

The baseline characteristics are depicted in Table 1. The number of patients in the medical history section are individual numbers, not taking the definition of the three high-risk groups into account: primary prevention, DM and secondary prevention (as described in Material & Methods). As patients may have a combination of all different risk factors, the total number of patients exceeds 5,086.

The characteristics in Table 1 are based on the ITT-population of 5,086 patients. However, the measurement of HDL-C was missing in 72 patients (1.4%), measurement of TC in 24 patients (0.5%) and TG in 123 patients (2.4%). As a result, the number of patients may slightly vary between the different parameters. Daily starting dose of rosuvastatin was 10 or 20 mg. Most of the patients (93.4%) started with 10 mg a day, 6.2% started with 20 mg and for 21 patients (0.4%), the starting dose was unknown.

Table 1. Baseline characteristics

Characteristics	Numbers (%)
Number of patients (ITT)	5,086
Male	2,510 (49.4)
Female	2,569 (50.5)
Unknown*	7 (0.1)
Age (years ± sd)	58.8 (10.4)
Male (years ± sd)	56.5 (10.3)
Female (years ± sd)	60.9 (10.0)
Medical History	
MI / AP	578 (11.4)
CVA/TIA	336 (6.6)
Peripheral arteriosclerosis	460 (9.0)
Diabetes Mellitus	1,703 (33.5)
Drug treatment for hypertension	2,184 (42.9)
CHD in first degree relatives < 60	1,662 (32.7)
Smoke	1,662 (32.7)
Risk groups**	
Secondary prevention	1,253 (24.6)
DM	1,418 (27.9)
Primary prevention	2,415 (47.5)
Cholesterol (mmol/l ± sd)	
LDL-C (N = 5,086)	4.74 (0.95)
HDL-C (N = 5,014)	1.32 (0.48)
TC (N = 5,062)	6.90 (1.27)
TG (N= 4,963)	2.31 (1.42)

** These data are not available.*
*** Risk groups as defined in Material & Methods.*
MI, myocardial infarction; AP, angina pectoris; CVA, cerebrovascular accident; TIA, transient ischemic attack; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Cholesterol goal achievement
At the last post-enrolment visit of each patient, LDL-C goal of < 3.2 mmol/l, as defined by the CBO-norm, was reached in 78.3% (95% CI: 77.1–79.4) of the ITT population. In case LDL-C was unknown, patients were evaluated as not reaching LDL-C targets. Table 2 shows the percentage of patients that achieve LDL-C goal of < 3.2 mmol/l, for each of the previously described 7 risk groups. It also presents the results for the three main high-risk groups: primary prevention, DM and secondary prevention.

The highest rate of patients reaching LDL-C goal of < 3.2 mmol/l was found in the DM group (84.3%), followed by the secondary prevention group (78.9%) and finally the primary prevention group (74.4%). Differences within a specific high-risk group were insignificant for the secondary prevention group (range: 78.2%-80.7%), and somewhat more pronounced for the primary prevention group (range: 71.9%-78.1%). The more recent and widely accepted LDL-C targets, as defined by the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice [2], were also applied. The results are also presented in Table 2 and show largely the same trends as seen in LDL-C goal of < 3.2 mmol/l. In the ITT population LDL-C goal of < 3.0 mmol/l was reached in 72.2% (95% CI: 71.0–73.5) and LDL-C goal of < 2.5 mmol/l in 50.4% (95% CI: 49.0–51.8) of the population.

Table 2. Percentages of patients reaching different LDL-C targets for different risk groups.

Risk group		LDL-C goal (mmol/l)		
		< 3.2	**< 3.0**	**< 2.5**
ITT-population	5,086	78.3 (77.1 – 79.4)	72.2 (71.0 – 73.5)	50.4 (49.0 – 51.8)
Secondary prevention*	1,253	78.9 (76.6 – 81.1)		53.1 (50.3 – 55.8)
MI / AP	578	78.2 (74.8 – 81.6)		50.2 (46.1 – 54.3)
CVA / TIA	336	80.7 (76.4 – 84.9)		58.9 (53.6 – 64.2)
Peripheral arteriosclerosis	460	79.6 (75.9 – 83.3)		54.6 (50.0 – 59.1)
Diabetes Mellitus	1,418	84.3 (82.4 – 86.2)		62.9 (60.4 – 65.4)
Primary prevention*	2,415	74.4 (72.7 – 76.2)	67.0 (65.2 – 68.9)	
Drug treatment for hypertension	1,100	78.1 (75.6 – 80.5)	70.6 (67.9 – 73.3)	
CHD in first degree relatives	1,305	72.5 (70.1 – 74.9)	65.8 (63.2 – 68.3)	
Smoke	972	71.9 (69.1 – 74.7)	63.0 (59.9 – 66.0)	

* The total numbers of patients in the subgroups of primary and secondary prevention exceeds respectively 1,253 and 2,415, because a combination of different risk factors in a specific high-risk group may occur.

Lipid changes

The percentage of LDL-C and HDL-C decrease between the last post-enrolment visit and the baseline could be determined for respectively 4,719 (92.8%) and 4,652 (91.5%) patients. The observed decrease in LDL-C was 47.0% (95% CI: 46.5-47.5), while the increase in HDL-C was 6.0% (95% CI: 5.2-6.8) by rosuvastatin treatment in the ITT-population. These overall results as well as those for the subgroups are given in Table 3. All changes were significant with a p-value < 0.0001. The reductions in LDL-C vary slightly between the groups. The smallest change was seen for the MI and/or AP group: 43.6% (95% CI: 41.6-45.6), the largest for the diabetic group: 48.6% (95% CI: 47.7-49.5). The increases in HDL-C vary from 4.6% (95% CI: 3.2-6.1) for the medical treatment for hypertension group, up to 7.3% (95% CI: 4.6-9.9) for the CVA/TIA group. Table 3 also summarizes baseline LDL-C and HDL-C values in the ITT group and the different risk-groups. Baseline LDL-C levels were relatively low in the diabetic group (4.38 mmol/l, SD: 0.81), and in the secondary prevention groups (4.53 mmol/l, SD: 0.91), but high in the primary prevention group (5.05 mmol/l, SD: 0.94). Baseline HDL-C levels were also low in the diabetic group (1.24 mmol/l, SD: 0.42) but higher in the secondary (1.31 mmol/l, SD: 0.49) and primary prevention groups (1.36 mmol/l, SD: 0.49).

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Table 3. **Absolute LDL-C and HDL-C baseline levels, and percentage of LDL-C and HDL-C changes at final visit compared to baseline for different risk groups.**

Risk group	LDL-C		HDL-C	
	Baseline (sd)[1]	**% change (95% CI)**	**Baseline (sd)[1]**	**% change (95% CI)**
ITT-population	4.74 (0.95)	-47.0% (-47.5 - -46.5)*	1.32 (0.48)	6.0% (5.2 – 6.8)*
Secondary prevention	4.53 (0.91)	-45.7% (-46.9 - -44.6)*	1.31 (0.49)	6.5% (5.0 – 7.9)*
MI / AP	4.44 (0.98)	-43.6% (-45.6 - -41.6)*	1.28 (0.43)	6.8% (4.6 – 9.1)*
CVA / TIA	4.50 (0.81)	-47.0% (-48.8 - -45.1)*	1.33 (0.50)	7.3% (4.6 – 9.9)*
Peripheral arteriosclerosis	4.61 (0.87)	-47.4% (-49.1 - -45.7)*	1.35 (0.58)	5.8% (3.6 – 8.1)*
Diabetes Mellitus	4.38 (0.81)	-48.6% (-49.5 - -47.7)*	1.24 (0.42)	5.8% (4.1 – 7.6)*
Primary prevention	5.05 (0.94)	-46.8% (-47.5 - -46.1)*	1.36 (0.49)	5.9% (4.9 – 7.0)*
Drug treatment for hypertension	4.90 (0.88)	-47.1% (-48.1 - -46.1)*	1.38 (0.49)	4.6% (3.2 – 6.1)*
CHD in first degree relatives	5.13 (0.97)	-46.3% (-47.2 - -45.3)*	1.35 (0.47)	6.5% (5.0 – 7.9)*
Smoke	5.06 (0.98)	-45.8% (-46.8 - -44.7)*	1.32 (0.53)	6.8% (4.9 – 8.6)*

[1] LDL-C and HDL-C are depicted in mmol/l (sd).
***** $p < 0.0001$

Costs

Table 4 presents the costs to set up a therapy with rosuvastatin for the seven different risk groups. Total costs are calculated from the healthcare consumption of a particular subgroup, multiplied by a price per unit, divided by the number of responders (patients having a LDL-C<3.2 mmol/l). Prices per unit used to calculate the costs are given in Table 5, and are based on Dutch prices in 2006.

Table 4. Costs per responder related to treatment with rosuvastatin per risk group.

Risk group	Responders		Costs
	N	%	Per responder
MI/AP	470	81.3%	292.99
CVA/TIA	275	81.8%	266.06
PA	372	80.9%	280.24
DM	1,244	87.7%	252.67
Hypertension	892	81.1%	285.27
CHZ	989	75.8%	318.93
Smoke	738	75.9%	326.73

Table 4 also shows the percentage of responders. It must be recognized that a responder is defined as a patient who achieved LDL-C < 3.2 mmol/l at the last, or any earlier visit. Accordingly, the percentage of responders is somewhat higher than those mentioned in Table 3, where only the last post-enrolment visit of a patient was considered. The costs per responder vary slightly per subgroup, ranging from € 252.67 for the diabetic group up to € 326.73 for the smoking group.

Table 5. Unit prices (2006) used to calculate the set up costs for rosuvastatin therapy.

Type of healthcare consumption	Unit price (€)
Consultation general practitioner	20.85
Telephonic consultation general practitioner	10.42
Consultation specialist	57.79
Dietician per hour	48.08
Lipid measurement	14.90
Rosuvastatin per 3 months 10 mg	77.28
Rosuvastatin per 3 months 20 mg	124.02
Rosuvastatin per 3 months 40 mg	153.66
Repeat prescription	10.42
Delivery costs medication per 3 months	6.10

Safety

All patients of the ITT population (N=5,086) were included for safety assessment. SAE's were reported with 16 patients (0.3%). Three patients died; one due to a metastasis of kidney carcinoma in the lung, one due to pancreas carcinoma and one died a sudden death. The other reported SAE's were angina pectoris related (N=5), acute coronary syndrome (N=2), thrombosis, aorta stenosis, circulatory collapse, adenocarcinoma of colon, ovarian cancer and TIA.
In 5.3% of the patients (N=271), rosuvastatin treatment was stopped during the study. The main reason to stop medication was because of a DAE (2.7% of all patients). In this group 220 DAE's were reported. The most frequently reported DAE's are shown in Table 6.

Table 6. **Most frequent adverse events leading to discontinuation of medication**

Adverse event (DAE)	***Frequency***
Myalgia	*46*
Headache	*13*
Nausea	*12*
Dizzy	*10*
Stomach Discomfort	*7*
Tiredness	*7*