AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: CRESTOR
ACTIVE INGREDIENT: Rosuvastatin

Study No: D3560L00052
Comparison of the Effects Noted in The ApoB/ApoA-I ratio Using Rosuvastatin and Atorvastatin in Patients with Acute Coronary Syndrome - CENTAURUS

Developmental phase: IIIb
Study Completion Date: 08 October 2007
Date of Report: 25 July 2008

OBJECTIVES:

The primary objective of this study was to compare the efficacy of rosuvastatin 20 mg versus atorvastatin 80 mg in reducing ApoB/ApoA-I ratio at 3 months in acute coronary syndrome (ACS) patients receiving the study treatment after a PCI.

The secondary objectives of the study were to assess the following in ACS patients:

1. The efficacy of rosuvastatin 20 mg versus atorvastatin 80 mg in reducing the LDL-C level at 1 month and 3 months in patients receiving the study treatment after a PCI

2. The efficacy of early started rosuvastatin 20 mg versus placebo on hs-CRP from the admission of patients (Day-6) until start of study treatment after the PCI (Day 0)

3. The efficacy of rosuvastatin 20 mg versus atorvastatin 80 mg in reducing the ApoB/ApoA-I ratio at 1 month in patients receiving the study treatment after a PCI.

The groups not formally compared were also summarised descriptively for the following endpoints:

- The changes in hs-CRP from Day-6 to 1 and 3 months,

- The change in lipid parameters at 1 and 3 months: TC, HDL-C, TG, non-HDL-C, ApoA-I, ApoB, LDL-C/HDL-C, TC/HDL-C and non-HDL-C/HDL-C,

- The number of patients who reached the established 2003 EAS LDL-C target of 2.50 mmol/L (100 mg/dL) at 3 months,

- The number of patients who reached the updated 2004 NCEP ATP III LDL-C target of 70 mg/dL (1.81 mmol/L) at 3 months,

- The changes in key inflammation markers (IL-10, IL-18 and soluble CD40-L) from Day -6 to 1 and 3 months,

- Incidence and severity of adverse events, abnormal physical examination findings, and abnormal laboratory values throughout the study,

- The incidence of Major Adverse Clinical Events (MACEs) (death from any cause, non-fatal myocardial infarction (MI), non-fatal stroke, documented unstable angina requiring hospitalisation and repeat revascularisation) throughout the study.

Other secondary objectives of the study, during the period where patients received early started rosuvastatin 20 mg versus placebo, were to describe at each assessment:

- Levels of Cardiac troponin and inflammatory markers (IL-10, IL-18 and soluble CD40-L),

- The changes in lipid parameters from Day -6 to Day 0: TC, HDL-C, TG, non-HDL-C, ApoA-I, ApoB, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C.

METHODS:

This was a 3-month, randomised, parallel-group study with two periods, comparing the efficacy and safety of rosuvastatin 20 mg versus atorvastatin 80 mg in ACS patients.

- The study involved a first double-blind, placebo-controlled period that started at hospital admission of the patient for an ACS (clinical symptoms for less than 48 hours) until hospital discharge (or for a maximum of 6 days).

- There was also a second double-blind, double-dummy, period which started at Day 0 (i.e., at hospital discharge or a maximum of 6 days after hospital admission) and lasted for 3 months.

After validation of eligibility criteria (including a first local assessment of CK, creatinine, ALT and an ECG) and the planning of a PCI within 4 days after hospital admission, the patients were randomised to one of three treatment groups:

  - early started rosuvastatin 20 mg from hospital admission until end of study (Group 1 - early rosuvastatin 20 mg),

  - placebo from hospital admission until Day 0 (i.e., until hospital discharge or for a maximum of 6 days) followed by rosuvastatin 20 mg until end of study (Group 2 - late rosuvastatin 20 mg),

– placebo from hospital admission until Day 0 (i.e., until hospital discharge or for a maximum of 6 days) followed by atorvastatin 80 mg until end of study (Group 3 - atorvastatin 80 mg).

Target subject population and sample size

Men or women aged 18 years and over diagnosed with non-ST elevation acute coronary syndrome (NSTE-ACS) and onset of clinical symptoms less than 48 hours at hospital admission for whom a PCI was planned or anticipated. Patients with ST elevation myocardial infarction (STEMI) were not included. Patients were not allowed to have taken any cholesterol-lowering medications during the month prior to enrolment.

Eligible patients were randomised to Group 1 (early rosuvastatin 20 mg), Group 2 (late rosuvastatin 20 mg) or Group 3 (atorvastatin 80 mg) according to the ratio 1:2:2.

Sample size:

Primary outcome variable (superiority of rosuvastatin 20 mg over atorvastatin 80 mg in ApoB/ApoA-I ratio at 3 months): 343 evaluable patients per group were required to detect a 3% difference in percent change from Day 0 in ApoB/ApoA-I ratio between Goup 2 and Group 3 with a two-sided 5% significance level and 80% power assuming a standard deviation (SD) of 14% for the ApoB/ApoA-I ratio.

Secondary outcome variable:

- Non-inferiority between rosuvastatin 20 mg and atorvastatin 80 mg on LDL-C at 1 and 3 months: 343 evaluable patients per group afforded 80% power to demonstrate non-inferiority of Group 2 versus Group 3 in LDL-C percent reduction from Day 0, considering a non-inferiority margin of 3% a SD of 14% and a two-sided significance level of 5%. The upper limit of the two-sided 95% CI needed to be less than 3% to conclude to non-inferiority of Group 2 versus Group 3.

- Effect of early started rosuvastatin 20 mg compared with placebo on hs-CRP and the inflammation markers at Day 0: 686 patients on placebo (Groups 2 and 3 combined) and 172 patients on rosuvastatin 20 mg (Group 1) for the comparison at Day 0, afforded approximately 80% power to detect an absolute difference of 20% in hs-CRP percent change from Day -6, assuming a SD of 70% for hs-CRP percent changes (assumption based on Gaspardone et al., 2002), and adjusting by 20% for the use of non-parametric method in the analysis.

Accounting for a 20% attrition rate, a total sample size of 1 075 patients was planned for the study.

Investigational product and comparator(s): dosage, mode of administration

Rosuvastatin 1× 20 mg once daily in oral tablet form or 1× placebo matching rosuvastatin 20 mg once daily in oral tablet form.
Atorvastatin 2× 40 mg once daily in oral encapsulated tablet form or 2× placebo matching atorvastatin 40 mg once daily in oral encapsulated tablet form.

Duration of treatment

During period 1, patients were treated with either rosuvastatin 20 mg (Group 1) or placebo (Groups 2 and 3) for a maximum of 6 days.
After the first period, patients in Groups 2 and 3 were treated for 3 months with either rosuvastatin 20 mg (Group 2) or atorvastatin 80 mg (Group 3) according to the randomisation. Patients already receiving rosuvastatin 20 mg continued to receive this treatment (Group 1).
At the final visit, it was the responsibility of the investigator to ensure that each patient was offered treatment with an appropriate lipid-lowering therapy, if considered necessary.

Criteria for evaluation (main variables)

Efficacy

- Primary variable:
  Percent change from Day 0 in ApoB/ApoA-I ratio at 3 months

- Secondary variables:

1. Percent change from Day 0 in LDL-C level at 1 month and 3 months,
2. Percent change from Day -6 in hs-CRP levels at Day 0 and all assessments prior to Day 0; AUC of hs-CRP levels from Day -6 to Day 0,
3. Percent change from Day 0 in ApoB/ApoA-I ratio at 1 month,
4. Percent change from Day -6 in hs-CRP levels at 1 month and 3 months,
5. Percent changes from Day 0 in lipid parameters TC, HDL-C, TG, non-HDL-C, ApoA-I, ApoB, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C at 1 month and 3 months,
6. Percentage of patients achieving the established 2003 EAS LDL-C target of 2.50 mmol/L (100 mg/dL) at 3 months,
7. Percentage of patients achieving the updated 2004 NCEP ATP III LDL-C target of 70 mg/dL (1.81 mmol/L) at 3 months,
8. Percent changes from Day -6 in the levels of the key inflammation markers (soluble CD40-L, IL-10, IL-18) at 1 month and 3 months,
9. Percent changes from Day -6 in lipid parameters (LDL-C, TC, HDL-C, TG, non-HDL-C, ApoA-I, ApoB, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C) at Day 0,
10. Percent changes from Day -6 of cardiac troponin levels and other inflammation markers (soluble CD40-L, IL-10, IL-18) at Day 0 and all other assessments prior to Day 0,

Safety

1. Incidence and severity of AEs and abnormal laboratory values,

2. Incidence of MACEs during the study.

Statistical methods

- Percent change from Day 0 in ApoB/ApoA-I ratio at 3 months was compared between Group 2 and Group 3 using Wilcoxon test with the Hodges-Lehman

median estimate of the between-group difference and its non parametric 95% CI. The hypothesis of superiority of rosuvastatin over atorvastatin was tested by the upper limit of the 95% CI of the between-treatment difference being less than zero.

- Percent change from Day 0 in LDL-C levels was compared between Group 2 and Group 3 in the same way as for the main efficacy variable. Two-sided 95% CIs are presented for the between-treatment difference in LDL-C changes from Day 0 to demonstrate the non-inferiority. The upper limit of the two-sided 95% CI of the difference needed to be less than 3% to conclude to non-inferiority of rosuvastatin versus atorvastatin.

- Percent changes from Day 0 in other lipids at 1 month and 3 months are summarised descriptively, except for the statistical comparison of the efficacy on ApoB/ApoA-I ratio of late rosuvastatin 20 mg versus atorvastatin 80 mg at 1 month which was carried out in the same way as for the primary efficacy endpoint.

- Percent change from Day -6 in hs-CRP at Day 0 was compared between early rosuvastatin 20 mg (Group 1) and placebo (Groups 2 and 3 combined) using the non-parametric Wilcoxon Rank Sum test. Data were also described by the median and 10^{th}, 25^{th}, 75^{th} and 90^{th} percentiles.

- The other time points before Day 0 and at 1 month and 3 months, as well as the other inflammation markers and cardiac troponin values were summarised descriptively in the same way. The data related to hs-CRP from Day -6 to Day 0 were also explored using plots and AUCs (assuming that at least three measurements were available between Day -6 and Day 0).

- The percentages of patients achieving the 2003 EAS LDL-C target and the updated 2004 NCEP ATP III LDL-C target are presented with the corresponding exact 95% CIs for the three groups.

- Safety data and MACEs are summarised descriptively by treatment groups.

Subject population

Table S1 summarises key information on disposition and baseline characteristics of study subjects.

Table S1 Subject population and disposition

		Early R20		Late R20		A80	
Population							
N randomised and treated (N planned)		221	(230)	437	(460)	450	(460)
Demographic characteristics (safety population)							
Sex (n and % of subjects)	Male	150	(67.9%)	321	(73.5%)	344	(76.4%)
	Female	71	(32.1%)	116	(26.5%)	106	(23.6%)
Age (years)	Mean (SD)	61.8	(11.5)	59.5	(11.4)	59.5	(12.0)
	Range	19 to 89		29 to 87		30 to 88	
Baseline characteristics (ITT1 population)							
Mean (SD) ApoB/ApoA-I ratio		0.85	(0.24)	0.91	(0.27)	0.90	(0.27)
Mean (SD) LDL-C level (mg/dL)		127.63	(36.89)	134.12	(37.19)	131.47	(37.57)
Mean (SD) LDL-C level (mmol/L)		3.30	(0.95)	3.47	(0.96)	3.40	(0.97)
Median hs-CRP level (mg/dL)		4		4.7		4.4	
Disposition							
N (%) of subjects who	completed	184		359		369	
	discontinued	37		78		81	
N analysed for safetya		221		437		450	
N analysed for efficacy - 1st period (ITT1)		217		429		440	
N analysed for efficacy - 2nd period (ITT2)		189		369		384	
N analysed for efficacy - 2nd period (PP)		126		226		252	

a Number of subjects who took at least 1 dose of study treatment. ApoB, ApoA-I=Apolipoproteins B and A-I; hs-CRP=high-sensitivity C-reactive protein; ITT=Intention-to-treat; LDL-C=Low-density lipoprotein cholesterol; N=Number; PP=Per-protocol; SD=Standard deviation, R20=rosuvastatin 20 mg; A80=atorvastatin 80 mg

A total of 101 centres recruited 1121 patients of whom 1108 were randomised and entered the first study period (rosuvastatin: 221; placebo: 887). Of these, 67 patients discontinued the study during the first period, mainly because of voluntary discontinuation (22 patients). 1041 patients entered the second period of treatment (early rosuvastatin: 212; late rosuvastatin: 406; atorvastatin: 423), of whom 129 prematurely withdrew from the study during the second treatment period, mainly because of voluntary discontinuation (44 patients), or adverse events (41 patients). Thus, 912 patients completed the study.

The safety population was comprised of 1108 patients of whom 627 received at least one dose of rosuvastatin, 423 at least one dose of atorvastatin, and 58 only placebo (i.e., discontinued before the second period of treatment). The ITT1 population (ITT of the first study period) was comprised of 1086 patients, of whom 217 were treated with rosuvastatin and 869 received placebo. The ITT2 population (ITT of the second study period) was comprised of 942 patients, of whom 558 were treated with rosuvastatin and 384 were treated with atorvastatin.

A total of 338 patients presented at least one major protocol deviation during the second period of treatment and were excluded from the per-protocol (PP) population.

The overall population mainly included male patients (73.6% of patients). Mean age of patients was 59.96 years. In the ITT1 population, mean ApoB/ApoA-I ratio before inclusion was 0.9, mean LDL-C level was 131.7 mg/dL (3.4 mmol/L), and mean hs-CRP level was 11.7 mg/dL. Concomitant cardiovascular disorders were present in most patients, mainly hypertension (52.6% of patients), dyslipidaemia including hypercholesterolaemia (35.2%), unstable angina pectoris (28.9%), and/or diabetes mellitus mainly from type II (19.2%).

RESULTS:

Efficacy Results

Table S2 summarises key efficacy results.

Table S2 Analysis of the percent change from Day 0 at 1 and 3 months in lipid parameters (LOCF, ITT2 population / observed, PP population) and from admission at Day 0 in hs-CRP (observed, ITT1 population) comparing rosuvastatin 20 mg and atorvastatin 80 mg

	Late R20	A80	Late R20 vs A80
Primary			
ApoB/ApoA-I (ITT2 – 3 months)			
N for % change	361	378	
Mean ± SD	-41.19 ± 20.05	-41.73 ± 17.07	
Median	-44.44	-44.44	0.00[a] (p=0.87)
CI of difference vs A80			-2.49 to 1.70

	Late R20	A80	Late R20 vs A80
Secondary			
LDL-C (ITT2 – 1 month)			
N for % change	359	371	
Mean ± SD	-45.87 ± 23.11	-46.07 ± 19.85	
Median	-50.00	-50.00	-0.27[a] (p=0.81)
CI of difference vs A80			-2.67 to 2.08
LDL-C (ITT2 – 3 months)			
N for % change	367	383	
Mean ± SD	-40.55 ± 27.67	-42.83 ± 22.87	
Median	-47.17	-47.77	0.96[a] (p=0.47)
CI of difference vs A80			-1.63 to 3.48
LDL-C (PP – 1 month)			
N for % change	218	241	
Mean ± SD	-48.89 ± 17.80	-47.97 ± 17.28	
Median	-50.00	-51.07	-0.65[a] (p=0.62)
CI of difference vs A80			-3.46 to 2.00
LDL-C (PP – 3 months)			
N for % change	214	232	
Mean ± SD	-46.40 ± 18.94	-45.99± 18.59	
Median	-49.29	-48.49	-0.52[a] (p=0.73)
CI of difference vs A80			-3.49 to 2.48
ApoB/ApoA-I (ITT2 – 1 month)			
N for % change	353	368	
Mean ± SD	-43.11 ± 16.45	-40.46 ± 16.30	
Median	-44.44	-42.86	-2.55[a] (p=0.02)
CI of difference vs A80			-4.54 to -0.01
	Early R20	**Placebo**	**Early R20 vs placebo**
Secondary			
hs-CRP (ITT1 – Day 0)			
N for % change	207	831	
Mean ± SD	413.30 ± 1192.78	448.20 ± 1357.88	
Median	59.46	78.72	-7.46[a] (p=0.53)
CI of difference vs placebo			-31.53 to 16.00

a estimate of median difference. ApoB, ApoA-I=Apolipoproteins B and A-I; CI=Confidence interval, hs-CRP=high-sensitivity C-reactive protein; ITT=Intention-to-treat; LDL-C=Low-density lipoprotein cholesterol; N=Number; PP=Per-protocol; SD=Standard deviation, vs=versus, R20=rosuvastatin 20 mg; A80=atorvastatin 80 mg

- Primary endpoint: ApoB/ApoA-I ratio at Month 3

At Month 3, in the ITT2 population, the reduction in ApoB/ApoA-I ratio was similar in both late R20 and A80 groups with an estimated median difference in reduction of 0.00% (95% CI = [-2.49, +1.70]). In conclusion, the study failed to demonstrate superiority of R20 over A80, as assessed by the reduction in ApoB/ApoA-I ratio at Month 3, since the upper limit of the 95% CI (1.70%) of the between-group difference was not less than 0. Moreover, the 95% CI of the between-group difference was narrow enough to exclude a difference of at least 3% in favour of any of the two groups as it was hypothesized in the study protocol.

- Secondary endpoints

LDL-C level, ITT population
At month 1, LDL-C levels had decreased in both the late R20 and A80 groups. The reduction in LDL-C levels was similar in both groups with an estimated median difference in reduction of -0.27% (95% CI = [-2.67, +2.08]) in favour of the late R20 group. The non-inferiority of late R20 compared to A80 was demonstrated since the upper limit of the 95% CI of the between-group difference (2.08%) was below the non-inferiority margin of 3%.

At month 3, the reduction in LDL-C levels was slightly less in the late R20 group than in the A80 group with an estimated median difference in reduction of +0.96% (95% CI = [-1.63, +3.48]) in favour of the A80 group. The non-inferiority of late R20 could not be demonstrated since the upper limit of the 95% CI of the between-group difference (3.48%) was above the non-inferiority margin of 3%.

In the ITT2 population, non-inferiority of R20 versus A80, as assessed by the reduction in LDL-C level, was thus demonstrated at Month 1 but not at Month 3.

LDL-C level, PP population
At Month 1, LDL-C levels had decreased in both the late R20 and A80 groups. The reduction in LDL-C levels was similar in both groups with an estimated median difference in reduction of -0.65% (95% CI = [-3.46, +2.00]) in favour of the late R20 group. The non-inferiority of late R20 compared to A80 was demonstrated since the upper limit of the 95% CI of the between-group difference (2.00%) was below the non-inferiority margin of 3%.

At Month 3, the reduction in LDL-C levels was similar in both the late R20 and A80 groups with an estimated median difference in reduction of -0.52% (95% CI = [-3.49, +2.48]) in favour of the late R20 group. The non-inferiority of late R20 compared to A80 was demonstrated since the upper limit of the 95% CI of the between-group difference (2.48%) was below the non-inferiority margin of 3%.

In the PP population, non-inferiority of R20 versus A80 on LDL-C level was thus demonstrated at both Month 1 and Month 3.

hs-CRP level

During the first period of treatment, hs-CRP levels increased progressively until Day 0 regardless of the treatment group. The increase was comparable between the early R20 and placebo groups at each timepoint (within 4 h before PCI, and 24-48 h after PCI). At Day 0, the increase in hs-CRP was slightly less in the early R20 than in the placebo group in the ITT1 population, as well as in the subpopulation of patients who underwent a PCI (mean ± SD: 293.05 ± 562.84% versus 378.13 ± 831.30%, median: 79.40% versus 100.00%). The estimated median difference in change was -7.46% (95% CI = [-31.53, +16.0]) in the ITT1 population and -10.23% (95% CI = [-44.81, +22.32]) in the subpopulation of patients who underwent a PCI, both in favour of a smaller increase in the early R20 group. In both populations the study failed to demonstrate any significant difference between early R20 and placebo. It must be noted that the observed standard deviations were much larger than assumed in the protocol (a standard deviation of 70% was expected).

During the second period of treatment, in the ITT1 population, the hs-CRP levels progressively declined to return to baseline values at Month 3 in all treatment groups. Again, the three treatment groups appeared to remain comparable throughout the study.

ApoB/ApoA-I ratio level at Day 0 and Month 1

At Day 0, in the ITT1 population, ApoB/ApoA-I ratio was reduced by -12.29 ± 18.71% from Day-6 in the early R20 group, while it had increased by 9.82 ± 20.83% from Day-6 in the placebo group.

At month 1, ApoB/ApoA-I ratio had decreased from Day 0 in both the late R20 and A80 groups. The reduction in ApoB/ApoA-I ratio was significantly greater in the late R20 group (p=0.02) with between-group difference of -2.55% (95% CI = [-4.54, -0.01]).

Other lipid parameters

During the first period of treatment, all lipid parameters decreased in the early R20 group except TG levels which increased slightly. The decrease was slightly greater in the early R20 group than in the placebo group for LDL-C, ApoB, TC, non-HDL-C levels, and for the LDL-C/HDL-C, non-HDL-C/HDL-C and TC/HDL-C ratios.

For all other lipid parameters the observed changes during the second study period were consistent with the known statin effects: at Month 1, ApoB, TC, TG and non-HDL-C levels, and LDL-C/HDL-C, non-HDL-C/HDL-C and TC/HDL-C ratios had decreased by 17 to 51%, while ApoA-I and HDL-C levels had increased by 5 to 15%. No notable difference between the two treatments was observed. The responses achieved at Month 1 were sustained until Month 3 with no worsening or improvement of the previous assessments for both groups of treatment, indicating that a plateau of optimal response was already reached after 1 month of treatment.

The early benefit versus placebo observed after the first period of treatment was not sustained throughout the study after placebo was changed for R20 or A80. All three groups of treatment were comparable at Month 3 for the above lipid parameters. The

responses to early R20 observed after 6 days of treatment were also not fully representative of the final responses to treatment, since the outcomes of three parameters (ApoA-I, HDL-C and TG levels) were reversed between Day 0 and Month 1.

LDL-C targets

In the ITT2 population, the percentages of subjects reaching the 2003 EAS and 2004 NCEP ATP III LDL-C targets at Month 3 were higher in the early R20 group (90.0% and 59.3%, respectively) than in the two other treatment groups (late R20: 82.7% and 56.6%, respectively; A80: 84.6% and 57.6%, respectively).

Cardiac troponin and other inflammatory markers

During the first period of treatment, the changes in the levels of cardiac troponin and soluble CD40-L appeared to be comparable between early R20 and placebo groups.

During the second period of treatment, soluble CD40-L levels remained elevated in all groups of treatment. The increase observed in the early R20 group appeared to be comparable to that in the A80 group, while it was greater in the late R20 group.

Data about IL-10 and IL-18 remained within normal ranges throughout the study whatever the treatment group.

Safety Results

In the overall exposed population, mean treatment duration was 82.32 ± 31.24 days.

A summary of adverse events in each category occurring during the whole study period (first and second periods) is presented in Table S3.

Table S3 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]					
	Early R20 (n=221)		Late R20[b] (n=437)		A80[b] (n=450)	
Any adverse events	152	(68.8%)	290	(66.4%)	299	(66.4%)
Serious adverse events	41	(18.6%)	66	(15.1%)	78	(17.3%)
Deaths or serious adverse events leading to death	3	(1.4%)	4	(0.9%)	9	(2.0%)
Serious adverse events not leading to death	38	(17.2%)	63	(14.4%)	70	(15.6%)
Discontinuations of study treatment due to adverse events[c]	12	(5.4%)	23	(5.3%)	29	(6.4%)
Study drug-related adverse events	21	(9.5%)	33	(7.6%)	32	(7.1%)
Confirmed major adverse clinical events	19	(8.6%)	23	(5.3%)	38	(8.4%)
	Total number of adverse events					

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]		
	Early R20 (n=221)	Late R20[b] (n=437)	A80[b] (n=450)
Adverse events	535	897	926
Serious adverse events	63	88	102
Discontinuations of study treatment due to adverse events[c]	15	25	33
Study drug-related adverse events	29	50	45
Confirmed major adverse clinical events	22	30	45

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.
[b] Subjects received placebo during the first study period.
[c] Reason for discontinuation according to CRF termination page.

Overall, the number of patients presenting an AE in each category was similar between all treatment groups, except for SAEs and MACEs, which occurred slightly less frequently in the late R20 group.

Of the 1108 patients of the safety population, 16 patients (1.4%) died during the study period. Twelve of them were defined as "cardiovascular death". All causes of death were deemed unrelated to study drug by the investigator.

A total of 171 patients (15.4%) experienced at least one non-fatal SAE. Only 5/1108 patients (0.4%) presented a SAE considered by the investigator as related to study drug (2 patients in the early R20 group, 2 in the late R20 group, and 1 in the A80 group).

The high number of SAEs that were reported during the study may be inherent to the studied population, which is an aging population with several risk factors related to the disease.

A total of 64 patients (5.8%) discontinued the study due to an AE. Discontinuations were considered as related to study drug by the investigator for 31/1108 patients (2.8%). For 18 of these 31 patients, the study drug-related AE resolved after study treatment discontinuation.

No specific AE emerged with either Rosuvastatin, regardless of the time of treatment start, or with Atorvastatin treatment.

The most common adverse events, summarised by preferred term, are shown in Table S4. Only treatment emergent adverse events (i.e., with onset date equal or greater than the date of first intake of study treatment in the first study period, and up to 30 days after the last dose of study treatment) are presented.

Table S4 Number (%) of subjects with the most commonly reporteda treatment emergent adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (preferred term)	Number (%) of subjects who had an adverse event							
	Early R20 (n=221)		Late R20[b] (n=437)		A80[b] (n=450)		Total (n=1108)	
Headache	22	(10.0%)	44	(10.1%)	53	(11.8%)	119	(10.7%)
Chest pain	23	(10.4%)	34	(7.8%)	39	(8.7%)	96	(8.7%)
Nausea	10	(4.5%)	22	(5.0%)	23	(5.1%)	55	(5.0%)
Anxiety	6	(2.7%)	17	(3.9%)	18	(4.0%)	41	(3.7%)
Constipation	10	(4.5%)	16	(3.7%)	12	(2.7%)	38	(3.4%)
Catheter site haematoma	11	(5.0%)	15	(3.4%)	11	(2.4%)	37	(3.3%)
Hypokalaemia	9	(4.1%)	14	(3.2%)	10	(2.2%)	33	(3.0%)
Insomnia	9	(4.1%)	10	(2.3%)	11	(2.4%)	30	(2.7%)
Hypotension	10	(4.5%)	9	(2.1%)	7	(1.6%)	26	(2.3%)
Vomiting	9	(4.1%)	5	(1.1%)	11	(2.4%)	25	(2.3%)

a Events with a total frequency of ≥4% across all treatment groups are included in this table.

b Subjects received placebo during the first study period.