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SUMMARY

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ACTIVE INGREDIENT: Rosuvastatin

Trial title (number): Evaluation of the efficacy of rosuvastatin in daily practice (TARGET)

Developmental phase: IV
First subject recruited: 15 February 2003
Last subject completed: 15 March 2004
Approval date: not applicable

OBJECTIVES

In an observational multi-centre study (TARGET), we assessed the effects of switching to low doses of rosuvastatin from commonly used doses of fluvastatin, pravastatin, simvastatin and atorvastatin on low-density lipoprotein cholesterol (LDL-C) goal achievement in high-risk patients. Also proportional changes in LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG) and the ratio TC/HDL-C were studied.

METHODS

Study design & patients

The TARGET study is an observational study conducted in 1,039 centres in the Netherlands. The centres consist of practices of general practitioners, specialists in internal medicine and cardiologists, representing daily practice. All patients approved to place anonymous results at the disposal of AstraZeneca. In total 7,587 patients were included in the study. Patients eligible for the study were high-risk patients with and without evident Congestive Heart Disease (CHD) who had LDL-C≥ 3.2 mmol/l and were treated at that moment with HMG-CoA-reductase inhibitor apart from rosuvastatin. Patients were aged ≥ 18 years and ≤ 70 years (men) and≤ 75 years (women), according to the advise of the Centraal Begeleidingsorgaan (CBO). The specialist or general practitioner made the decision to stop current statin and start treatment with rosuvastatin irrespective of study participation. Exclusion criteria included treatment with atorvastatin 40 or 80 mg or simvastatin 80 mg, patients familiar with muscular pain, myopathy or liver function disorders (inclusive elevation of serum transaminases) and/or contra-indications for treatment with rosuvastatin. Patients were their own historical control. Patients were seen at 2 time points. The first visit took place when the general practioner or specialist decided to stop treatment with current statin, the decision was made to start treatment with rosuvastatin and the patient had LDL-C ≥ 3.2 mmol/l. Patient characteristics, cardiac history, other medical history including diabetes, hereditary hypercholesterolemia and hypertension, smoking behaviour, current medication and if available TC, HDL-C and TG were obtained. The second visit took place when LDL-C was measured again to determine effectiveness of rosuvastatin treatment. Like in daily practice, the time between the two visits was variable. If measured, other lipids were also documented as well as serious adverse events, continuation with rosuvastatin and discontinuation as a result of (serious) adverse events.

Efficacy and safety parameters/assessments

The efficacy analysis was performed on intention-to-treat basis. Patients satisfying the inclusion criteria and where at least LDL-C at visit 1 was measured, were included. Patients older than 70 years for men and 75 years for women were also included. The primary efficacy measure was the proportion of patients reaching LDL-C goal of < 3.2 mmol/l at visit 2. Also the strict goal of LDL-C < 2.5 mmol/l was applied. Secondary efficacy measures included the proportional change from baseline of LDL-C, HDL-C, TC/HDL-C, TC and TG at visit 2. Additional analysis was carried out in order to get insight in different subgroups of medical history and previous medication. Standard safety assessments included the registration of all Serious Adverse Events (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 satisfying the inclusion criterion of LDL ≥ 3.2 mmol/l and where visit 2 was performed, were evaluated for safety.

Statistical analysis
The primary end point was the proportion of patients reaching LDL-goal of < 3.2 mmol/l at visit 2. Also the strict goal of LDL-C < 2.5 mmol/l was applied. Different subgroups, based on medical history or use of current statin, were created. Secondary end point was the proportional change from baseline of LDL-C, HDL-C, TC/HDL-C, TC and TG at visit 2. Differences from baseline to visit 2 for all lipids were tested by a paired t-test ($p<0.01$).
Additional analysis was carried out in order to get insight in different subgroups of medication.
Safety data were summarized by descriptive statistics.

RESULTS

Characteristics
A total number of 7,589 patients in 1,039 different centres were enrolled in the study by general practitioners, cardiologists and specialists in internal medicine. Patients were under treatment of a statin and the specialist or general practitioner made the decision to stop the current statin and start treatment with rosuvastatin. This decision was made irrespective of study participation. Of these 7,589 patients 324 (4.0%) did not meet the inclusion criterion of LDL-C ≥ 3.2 mmol/l and from 304 patients no information was obtained about current medication. The last group of patients was included in the analysis in order to investigate possible differences comparing to other subgroups of medication. Despite the inclusion criteria, men older than 70 years and women older than 75 years were included, because the CBO gave a directive and no binding advice considering age. The ITT analysis was carried out on all patients with a known and eligible LDL-C at start of the study (N=7,265). The main baseline characteristics are depicted in Table 1 and are mainly based on these 7,265 patients. Year of birth was missing in 32 patients, sex in 6 patients, smoking behaviour in 151 patients and the measurement of cholesterols was incomplete in 221 patients (3%). Therefore the number of patients may slightly vary between the different parameters. The daily starting dose of rosuvastatin was 10 or 20 mg. Most of the patients (80,9%) started with 10 mg a day, 18,0% started with 20 mg and for 1,1% of the patients it was unknown.

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Table 1. Baseline characteristics

Characteristics	Numbers (%)
Number of patients	7,265
Male	4,067 (56.0)
Female	3,192 (43.9)
Unknown*	6 (0.1)
Age	59.2 (10.7)
Male (years ± sd)	57.7 (10.4)
Female (years ± sd)	61.2 (10.7)
Male > 70 years	400 (5.5)
Female > 70 years	186 (2.6)
Medical History	
Hypertension	3,447 (47.4)
Diabetes Mellitus	1,642 (22.6)
Myocardial infarction	1,241 (17.1)
PTCA and/or CABG	1,111 (15.3)
Angina pectoris	1,041 (14.3)
Hereditary hypercholesterolemia	2,084 (28.7)
CHD in first degree relatives < 60 years	1,174 (16.2)
CVA	269 (3.7)
TIA	220 (3.0)
Peripheral vascular disease	560 (7.7)
Smoking behaviour	
Yes	1,825 (25.1)
No	5,289 (72.8)
Unknown*	151 (2.1)
Previous medication	
Fluvastatin 20 mg	188 (2.6)
Fluvastatin 40 mg	295 (4.1)
Fluvastatin 80 mg	196 (2.7)
Pravastatin 10 mg	145 (2.0)
Pravastatin 20 mg	518 (7.1)
Pravastatin 40 mg	1,485 (20.4)
Simvastatin 10 mg	557 (7.7)
Simvastatin 20 mg	1,581 (21.8)
Simvastatin 40 mg	827 (11.4)
Atorvastatin 10 mg	524 (7.2)
Atorvastatin 20 mg	680 (9.4)
Unknown	269 (3.6)
Cholesterols (mmol/l ± sd)	
LDL-C	4.18 (0.83)
HDL-C	1.30 (0.43)
TC	6.33 (1.05)
TG	2.16 (1.34)

** These data are not available.*

PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass surgery; CHD, coronary heart disease; CVA, cerebrovascular accident; TIA, transient ischaemic attack; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

In a considerable amount of patients one or more items of visit 2 are missing. Measurement of cholesterols at visit 2 was incomplete in 230 patients (3.2%) and the date was missing in 162 patients (2.2%). In case of 5 patients, absolutely no further information was gathered about parameters of visit 2, DAE and SAE. These patients were included for the ITT analysis provided that LDL-C at start of the study was measured. They were evaluated as not reaching LDL-C goal. For safety assessment these 5 patients were excluded and results are based on a total of 7,260 patients. Secondary end point (change in cholesterols) could not be determined in the 5 patients and was incomplete for the 230 patients mentioned earlier.

Cholesterol goal achievement

The mean time between visit 1 and 2 was 92.3 days with a standard deviation (sd) of ± 76.7. The range was very wide because this observational study represents daily practice and 1,039 centres were cooperating. The advice of the CBO was to see the patients again after 3 months. At visit 2 LDL-C goal of < 3.2 mmol/l was reached in 72.5% (99% CI: 71.1-73.8) of the ITT population. When missing values of LDL-C at visit 2 were excluded in the analysis the goal was reached in 75.4% (99% CI: 74.0-76.7). Application of the strict goal of LDL-C < 2.5 mmol/l resulted in 37.8% (99% CI: 36.3-39.3) and 39.3% (99% CI: 37.8-40.8) respectively. Above mentioned results are depicted in Table 2.

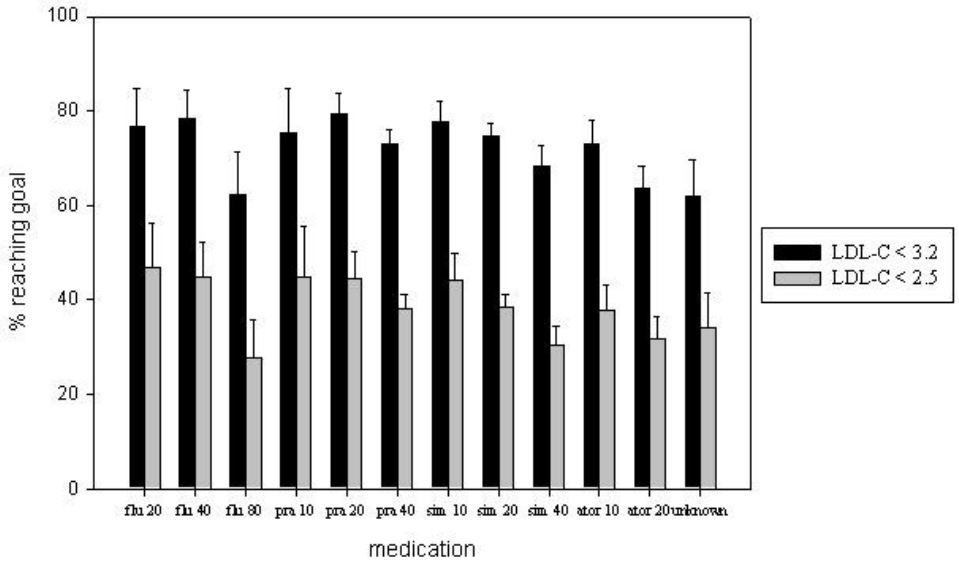
Table 2. Proportion of patients (%) reaching different LDL-C goals.

Goal	*ITT-population*	*ITT (excluding missings)*
LDL-C < 3.2 mmol/l	*72.5 (71.1-73.8)*	*75.4 (74.0-76.7)*
LDL-C < 2.5 mmol/l	*37.8 (36.3-39.3)*	*39.3 (37.8-40.8)*

( ) 99% Confidence Interval

Figure 1 shows the proportion of patients achieving the goal of LDL-C < 3.2 mmol/l and the goal of LDL-C < 2.5 mmol/l for different subgroups of medication.

Figure 1. Proportion of patients achieving the goal of LDL-C < 3.2 or < 2.5 mmol/l (99% CI).



The groups of statins with high doses (80 mg fluvastatin, 40 mg simvastatin and 20 mg atorvastatin) and the unknown group seem to have lower proportions. Table 3 shows the proportion of patients reaching LDL-C < 3.2

mmol/l for different risk factors like smoking, diabetes mellitus and CHD alone or CHD in combination with hypertension.

Table 3. Proportion of patients reaching LDL-C < 3.2 for different subgroups.

Risk factor	*Proportion (99% CI)*
Smoking (N=90)	*73.3 (61.0 - 85.7)*
Not smoking (N=252)	*69.1 (61.5 - 76.6)*
DM (N=390)	*79.7 (74.5 - 85.0)*
No DM (N=369)	*69.4 (63.2 - 75.6)*
CHD or CHD + hypertension (N=435)	*70.9 (65.3 - 76.4)*

The subgroups in this table are relatively small, because the different risk factors were studied separate. This means that smoking was studied in a group of patients with no combination of other risk factors like Diabetes Mellitus (DM), Myocardial Infarction (MI), Angina Pectoris (AP), Cerebrovascular Accident (CVA), Transient Ischaemic Attack (TIA) or hereditary hypercholesterolaemia. When the risk factors diabetes mellitus and hereditary hypercholesterolemia are analysed irrespective the presence of other risk factors, the groups are much larger. In this case, patients with diabetes mellitus achieved LDL-C goal in 77.8% (99% CI: 75.1-80.4) of the patients. This was almost comparable to the results seen in table 3. For hereditary hypercholesterolemia LDL-C goal was reached in 63.7% (99% CI: 61.0-66.4) of the patients. To see the impact of rosuvastatin on secondary prevention, all patients with an event but without DM and hypercholesterolemia were analysed. Patients with secondary prevention were defined as having one or more of the following items in medical history: CVA, MI, PTCA/CABG, peripheral vascular disease and/or TIA. Totally 1,847 patients (25.0%) had an event in the past and 77.6% (99% CI: 75.1-80.1) reached LDL-C goal < 3.2 mmol/l.

Lipid changes

At visit 2 rosuvastatin reduced LDL-C by 33.5% (99% CI: 32.9-34.0), TC by 22.0% (99% CI: 21.1-22.9), TG by 6.9% 99% CI: 5.2-8.5) and the ratio TC/HDL-C by 22.4% (99% CI: 21.2-23.5). HDL-C increased by 6.9% (99% CI: 4.6-9.3). All changes were significant with a p-value < 0.0001. Table 4 summarizes the cholesterol values from baseline to visit 2 for all subgroups of medication.

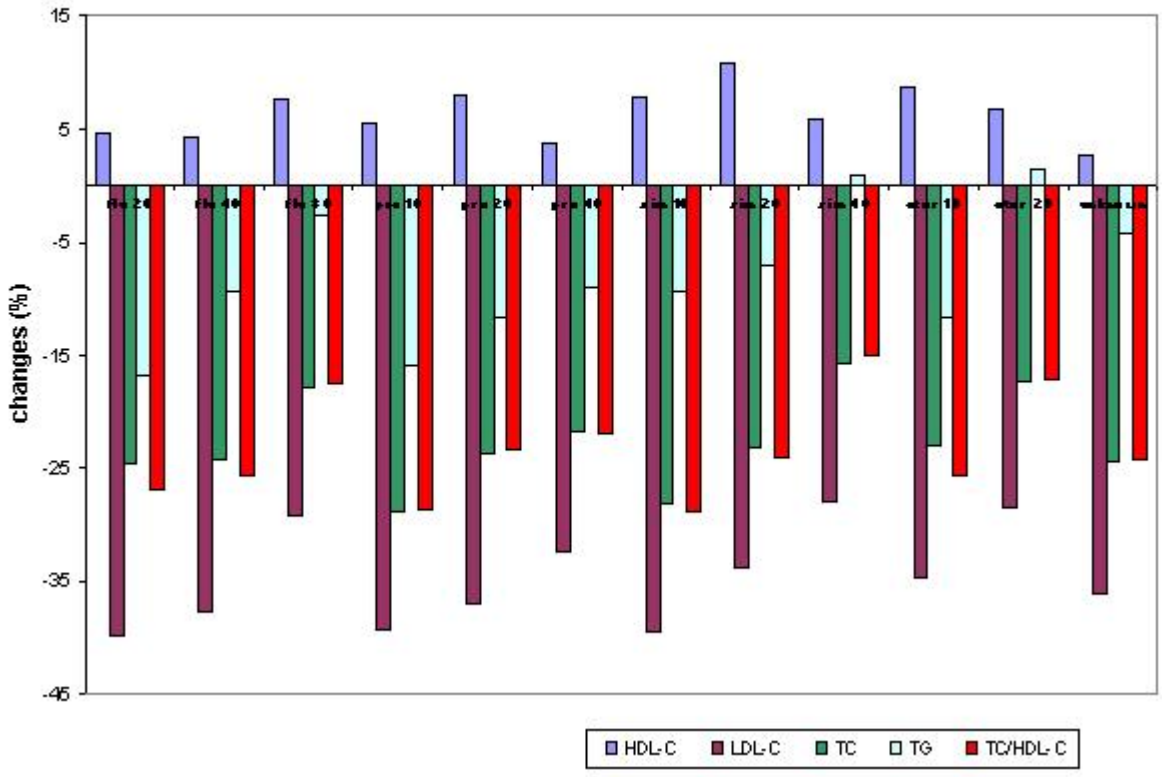
Table 4. Lipid changes from baseline to visit 2 for different medication groups.

	flu 20	*flu 40*	*flu 80*	*pra 10*	*pra 20*	*pra 40*	*sim 10*	*sim 20*	*sim 40*	*ator 10*	*ator 20*	*unknown*
LDL-C baseline	*4.29 (0.78)*	*4.27 (0.85)*	*4.22 (0.85)*	*4.34 (0.84)*	*4.19 (0.79)*	*4.07 (0.79)*	*4.37 (0.89)*	*4.16 (0.80)*	*4.05 (0.80)*	*4.25 (0.86)*	*4.16 (0.83)*	*4.60 (1.01)*
LDL-C visit 2	*2.54 * (0.70)*	*2.63 * (0.71)*	*2.95 * (0.85)*	*2.59 * (0.77)*	*2.60 * (0.74)*	*2.72 * (0.79)*	*2.59 * (0.77)*	*2.70 * (0.77)*	*2.88 * (0.82)*	*2.72 * (0.81)*	*2.93 * (0.95)*	*2.89 * (1.08)*
HDL-C baseline	*1.35 (0.38)*	*1.27 (0.36)*	*1.25 (0.35)*	*1.41 (0.69)*	*1.29 (0.45)*	*1.29 (0.38)*	*1.33 (0.44)*	*1.32 (0.44)*	*1.31 (0.40)*	*1.30 (0.41)*	*1.26 (0.47)*	*1.35 (0.59)*
HDL-C visit 2	*1.40 ** (0.39)*	*1.31*** (0.36)*	*1.32 ** (0.42)*	*1.42 ns (0.52)*	*1.34*** (0.41)*	*1.31** (0.39)*	*1.36*** (0.39)*	*1.36 * (0.41)*	*1.34*** (0.45)*	*1.37 * (0.42)*	*1.29 ns (0.43)*	*1.36 ns (0.62)*
TC baseline	*6.42 (1.06)*	*6.33 (1.12)*	*6.32 (1.10)*	*6.53 (0.94)*	*6.40 (1.03)*	*6.20 (0.99)*	*6.54 (1.09)*	*6.30 (1.01)*	*6.20 (1.06)*	*6.41 (1.08)*	*6.27 (1.03)*	*6.66 (1.19)*
TC visit 2	*4.59 * (0.83)*	*4.63 * (0.79)*	*5.01 * (1.05)*	*4.59 * (0.90)*	*4.72 * (0.92)*	*4.74 * (0.95)*	*4.59 * (0.88)*	*4.75 * (0.92)*	*5.03 * (1.03)*	*4.81 * (0.95)*	*5.03 * (1.05)*	*4.91 * (1.22)*
TG baseline	*2.04 (1.44)*	*2.13 (1.51)*	*2.08 (1.19)*	*2.08 (1.10)*	*2.26 (1.30)*	*2.16 (1.36)*	*2.13 (1.44)*	*2.14 (1.27)*	*2.11 (1.22)*	*2.11 (1.15)*	*2.28 (1.51)*	*2.33 (1.72)*
TG visit 2	*1.53 * (0.92)*	*1.70 * (1.73)*	*1.87 ** (1.14)*	*1.62 * (0.86)*	*1.79 * (0.89)*	*1.77 * (0.95)*	*1.68 * (0.89)*	*1.78 * (0.99)*	*1.92 * (1.09)*	*1.74 * (1.04)*	*2.08 * (1.63)*	*1.91 * (1.13)*
TC/HDL-C baseline	*5.10 (1.59)*	*5.34 (1.85)*	*5.38 (1.67)*	*5.10 (1.44)*	*5.50 (3.11)*	*5.16 (1.58)*	*5.42 (3.08)*	*5.25 (3.26)*	*5.11 (1.69)*	*5.36 (1.90)*	*5.50 (3.02)*	*5.50 (1.96)*
TC/HDL-C visit 2	*3.49 * (1.01)*	*3.77 * (1.24)*	*4.25 * (2.92)*	*3.48 * (1.06)*	*3.85 * (1.15)*	*3.85 * (1.15)*	*3.59 * (1.08)*	*3.74 * (1.21)*	*4.07 * (1.93)*	*3.77 * (1.24)*	*4.22 * (1.45)*	*3.99 * (1.63)*

LDL-C, HDL-C, TC and TG are depicted in mmol/l (sd).
*ns: not significant, *p < 0.001, **p < 0.01, *** p < 0.05.*
Flu 10 = fluvastatin 10 mg per day, pra = pravastatin, sim = simvastatin, ator = atorvastatin.

For all groups the reduction in LDL-C, TC-C, TG-C and TC/HDL-C were highly significant. The increase of HDL-C was highly significant in the group simvastatin 20 and atorvastatin 10 mg per day. No significance was reached in pravastatin 10, atorvastatin 20 and the unknown group. Proportional changes are depicted in Figure 2. The changes in the higher medication groups like fluvastatin 80, pravastatin 40, simvastatin 40 and atorvastatin 20 seem to be smaller compared to the other groups.

Figure 2. Changes in lipids (%) in different medication groups.



Safety

In total 7,260 patients were included for safety assessment. In 5 out of 7,265 patients no information was gathered at visit 2. SAE's were reported in 12 patients (0.17%). Two patients died due to CVA and cardiogenic shock. Rosuvastatin was stopped during the study in 3.8% of the patients (N=275). The main reason to stop medication was because of an AE or SAE (72%). 78 Patients (28%) stopped medication for other reasons. In 3.0% of all patients (N=195) 267 DAE's were reported. The most reported DAE's are depicted in Table 5.

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Table 5. Most frequent adverse events leading to discontinuation of medication

Adverse event (DAE)	*Frequency*
Myalgia / muscle discomfort	*59*
Headache	*30*
Nausea	*31*
Abdominal discomfort / pain / cramps	*16*
Dizzy / dizziness	*16*
Stomach discomfort / ache	*11*

Reference:
Not published yet.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Crestor™ (rosuvastatin), Healthcare Professionals should view their specific country information.