

ACTUALIZACIÓN

Rosuvastatin: Role in Cardiovascular High-risk Patient

Papel de la Rosuvastatina en el paciente con alto riesgo cardiovascular

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|Summary|

Statins are the lipid-lowering drug family of first choice in situations of hypercholesterolemia or mixed dyslipidemia with predominant increase in cholesterol. The evidence shows conclusively that each one of the commercially available statins have proven benefits on outcomes of cardiovascular morbidity and mortality. However, rosuvastatin has certain pharmacokinetic efficacy and cost-effectiveness characteristics that make it an attractive molecule to be the statin of choice in patients at high cardiovascular risk.

Key Words: Hydroxymethylglutaryl-CoA Reductase Inhibitors, cardiovascular diseases, dyslipidemias, Cost-Effectiveness Evaluation (MesH).

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Resumen

Las estatinas son la familia farmacológica hipolipemiente de primera opción en situaciones de hipercolesterolemia o dislipidemia mixta con predominio de aumento en el coles-

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terol. La evidencia demuestra contundentemente que cada una de las estatinas disponibles en el mercado ha mostrado beneficios en desenlaces de morbi-mortalidad cardiovascular. Sin embargo, la rosuvastatina presenta ciertas características farmacocinéticas de eficacia y de costo-efectividad que la hacen una molécula atractiva para ser la estatina de elección en pacientes de alto riesgo cardiovascular.

Palabras clave: Inhibidores de Hidroximetilglutaril-CoA Reductasas, enfermedades cardiovasculares, dislipidemias, evaluación de Costo-Efectividad (DeCS).

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Introduction

Statins competitively inhibit hydroxy methylglutaryl coenzyme A (HMG CoA) reductase, the enzyme involved in cholesterol endogen production that regulates its formation velocity (2), thereby increasing the availability of cholesterol low density lipoproteins (LDL-C) in the cell membrane and allowing for its levels to decrease (Figure 1).

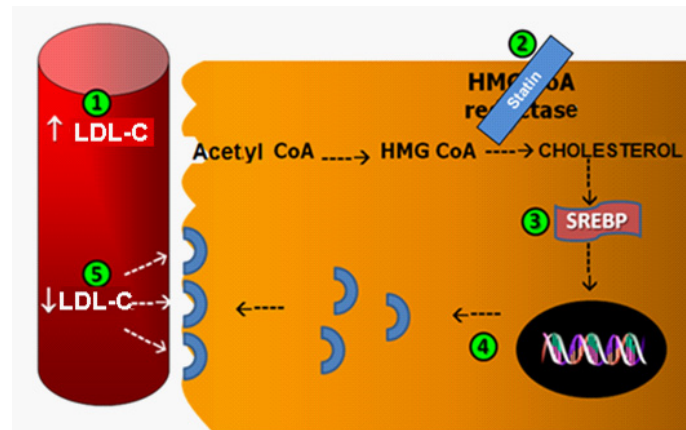


Figure 1. 5-Step statin action mechanisms: When LDL-C levels are high (1), a statin is given in order to inhibit the HMG-CoA reductase in the hepatocyte (2). This leads to intracellular cholesterol reduction thereby eliciting the activation of a transcription factor named SREBP (Sterol and Retinol Binding Protein) and its translocation to the nucleus (3). This way, LDL-C receptors expression is promoted (4) and its removal from circulation is increased.

	Risk of coronary events	LDL Goal (mg/dL)	Indications for statins use according to LDL (mg/dL)
VERY HIGH	> 20%	< 70	Immediately
HIGH	> 20%	< 100	≥ 130 100 – 129 when TLC fail for 3 months < 100 currently statin-controlled
MEDIUM	10-20%	< 130	≥ 160 130 – 159 when TLC fail for 3 months < 130 currently statin-controlled
LATENT	< 10%	< 160	≥ 190 when TLC fail for 3 months

Figure 2. LDL-C goal levels and recommendations for use of statins for each of four (coronary) cardiovascular risk levels. TLC: Therapeutic Lifestyle Changes.

HMG-CoA reductase inhibitors are the first-choice drugs (against other lipid-lowering drugs such as the bile acids sequestering agents or ezetimibe) in hypercholesterolemia and mixed dyslipidemia patients with predominance of increased cholesterol. The decision for use, according to the addenda of NCEP-ATP III (National Cholesterol Educational Program–Adult Treatment Panel III) clinical guidelines recommendations is dependent on the cardiovascular risk (Figure 2), specified in four levels (2,3).

Very high risk

It occurs when there exists a previous cardiovascular episode (myocardial infarction), stable or unstable angina, coronary artery procedure such as angioplasty or bypass, of otherwise clinically significantly myocardial ischemia evidence) involving more than one risk factor (e.g. diabetes, hypertension, persistent smoking).

High risk

It occurs under prior coronary disease conditions or its equivalent (peripheral artery disease, aneurism of abdominal aorta, carotid disease (including transient ischemic attack or apoplexy of carotid origin or >50% obstruction of any carotid artery) or primary atherogenic dyslipidemia), as well as in those people which multiple risk factors involve >20% risk of 10 years coronary disease.

Intermediate risk

Occurs in people with metabolic syndrome or which multiple risk factors involve 10 to 20% coronary disease 10 year risk.

Latent risk

Exists in those people which risk factor involve <10% 10-year coronary disease risk.

Table 1. Male cardiovascular risk stratification. For instance, a smoker patient (5 points) aged 47 (3 points), 220 mg/dL total cholesterol level (5 points) and 43 mg/dL HDL cholesterol with untreated systolic blood pressure 135 mmHg levels (1 point), will have 15 scoring, which means that its (coronary) cardiovascular risk is high because it percent is 20%.

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

	age 20-39	age 40-49	age 50-59	age 60-69	age 70-79
< 160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
> 280	11	8	5	3	1

	age 20-39	age 40-49	age 50-59	age 60-69	age 70-79
No Smoker	0	0	0	0	0
Smoker	8	5	3	1	1

	Male
HDL	
> 60	-1
50-59	0
40-49	1
< 40	2

	Treatment	
Systolic Pressure	No	Yes
< 120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
> 160	2	3

Total Score	% Risk
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
>= 17	>= 30

Table 2. Women cardiovascular risk stratification. For instance, any non smoker woman (0 points) aged 65 (12 points), with 240 mg/dL (3 points) total cholesterol levels (3 points) and 55 mg/dL (0 points) HDL cholesterol, with 140 mmHg (5 points) systolic blood pressure, will have 20 score, which means her cardiovascular risk to be intermediate inasmuch as her score is 11%.

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
< 160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
> 280	13	10	7	4	2

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
No Smoker	0	0	0	0	0
Smoker	9	7	4	2	1

	Female
HDL	
> 60	-1
50-59	0
40-49	1
< 40	2

	Treatment	
Systolic Pressure	No	Yes
< 120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
> 160	4	6

Total Score	% Risk
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
>= 25	<= 30

The risk factors, taking into account for cardiovascular risk stratification based on the tables derived from Framingham, study (Tables 1 & 2) are the following: sex (the tables and scores are different for male and female), age (the older age the higher risk score), total cholesterol (which in turn is dependent of the age), HDL cholesterol (which becomes protective, i.e., decreases score when its levels raise to 60 mg/dL), smoking habit (taken in a dichotomy manner: smoking or no-smoking), and systolic blood pressure (the score of which will vary whether or not patient is under pharmacological treatment).

This classification, however, implies some limitations as it only establishes the risk of coronary events (myocardial infarction due to coronary disease) and fails to take into account other significant cardiovascular event, such as cerebrovascular disease. Additionally criticism against the paradigm “to treat until the target” the LDL-C, requesting that the next clinical guides of the ATP IV recommend the treatment with statins in accordance with individual cardiovascular risk independent

from LDL cholesterol levels (4).

Rosuvastatin vs other statins

Statins show similar chemical structures as they all show an analogy similar the radical beta-hydroxyl-beta methyl glutaryl (HMG). Rosuvastatin, however, has a methyl-sulfonamide group which allows more interaction with some amino acid residues of the MHG CoA reductase, and this way to have a high affinity for the active site of the enzyme (5). Additionally, rosuvastatin hepatic selectivity shall be taken into account as it is a relatively hydrophilic (the same as pravastatin), compared to other statins, and therefore its uptake by other type of different cells would be limited (6). In fact, classic head-to-head randomized controlled clinical trials (RCT) such as STELLAR (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin), have shown rosuvastatin to be the inhibitor of HMGCoA reductase significantly achieving greater LDL-C decreases (Table 3)(7).

Table 3. Comparison Statins of pharmacological properties (5,6) and efficacy (ref. STELLAR study (7), excepting for fluvastatin and lovastatin ref. CURVES study (8). LDL-C: LDL cholesterol; HDL-C: HDL-C; TG: Triglycerides

Characteristics Statin	Min Dose	% LDL-C Reduction	% HDL-C Increase	% TG Reduction	Cytochrome P450 Metabolism	Half-life (hrs)
Fluvastatin	20 mg	17%	1%	5%	2C9	1-3
Pravastatin	10 mg	20%	3%	8%	---	1-3
Simvastatin	10 mg	28%	5%	12%	3 A4	2-5
Lovastatin	20 mg	29%	7%	12%	3 A4	2-5
Atorvastatin	10 mg	37%	6%	20%	3 A4	14
Rosuvastatin	10 mg	46%	8%	20%	2C9/2C19	20

Table 4. Mean \pm standard deviation changes of lipidic parameters with different dose of statins and percentage of patients reaching the goal of LDL-C <70 mg/dL or <100mg/dL when their LDL-C base is \geq 160 mg/dL (*) or between 130 and 159 mg/dL (**). σ = represents less than 10 patients. ND= No Available (Ref. 9)

Statin	Rosuvastatin				Atorvastatin				Simvastatin			
Dose	5 mg	10 mg	20 mg	40 mg	10 mg	20 mg	40 mg	80 mg	10 mg	20 mg	40 mg	80 mg
LDL-C	-38.8 \pm 0.9	-44.1 \pm 0.6	-49.5 \pm 0.5	-54.7 \pm 0.4	-35.5 \pm 0.6	-41.4 \pm 0.5	-46.2 \pm 0.5	-50.2 \pm 0.4	-27.4 \pm 1.4	-33.0 \pm 0.6	-38.9 \pm 0.9	-45.0 \pm 1.0
Non HDL-C	-35.4 \pm 0.8	-40.2 \pm 0.5	-45.1 \pm 0.4	-49.9 \pm 0.3	-32.8 \pm 0.5	-38.2 \pm 0.5	-42.6 \pm 0.5	-46.6 \pm 0.4	-24.8 \pm 1.2	-30.1 \pm 0.5	-35.0 \pm 0.8	-40.5 \pm 0.9
TG	-15.2 \pm 1.4	-18.7 \pm 0.5	-20.1 \pm 0.7	-21.9 \pm 1.0	-16.4 \pm 0.5	-18.9 \pm 0.6	-20.7 \pm 1.2	-25.0 \pm 1.1	-9.3 \pm 2.5	-12.7 \pm 0.7	-13.3 \pm 1.4	-14.5 \pm 1.8
% patients with LDL-C < 70 mg/dL *	3.2%	11.4%	20.5%	31.7%	2.0%	4.1%	9.8%	18.1%	0%	1.6%	1.5%	4.0%
% patients with LDL-C < 70 mg/dL **	0% σ	33.0%	57.2%	67.6%	8.8%	26.2%	45.2%	52.4%	0% σ	7.0%	19.9%	ND
% patients with LDL-C < 100 mg/dL *	38.0%	56.8%	64.5%	74.1%	28.7%	45.0%	56.6%	71.4%	8.8%	24%	34.2%	38.5%
% patients with LDL-C < 100mg/dL **	66.7% σ	75.9%	90.1%	95.4%	62.1%	83.8%	91.1%	86.4%	50.0% σ	57.3%	76.7%	ND

This last assertion was confirmed by a meta analysis (VOYAGER) of data from more than 32000 individual patients derived from 37 studies (9), which determined the ratio between the increment of dosing from three statins frequently used in the clinical practice (rosuvastatin vs. atorvastatin vs. simvastatin) and their capacity to increase atherogenic parameter reduction, as well as the achievement of treatment goals established (see below). It was demonstrated that by duplicating statin dose, a 4% and 7% additional reduction of LDL-C was obtained. In the same way, it was documented that both statin dose and LDL-C level base are predictors to reach treatment goals in high-risk patients (Table 4).

Rosuvastatin ensures HMG CoA reductase sustained inhibition as it has more extended half-life (20 hrs) among statins (Table 3) (6). This characteristic makes it to outstand as a valuable therapeutic option in the intolerance context of statins as described in several case report (10) and retrospective studies (11,12) where up to 72.5% of patients with intolerance resolve their symptoms by delivering rosuvastatin once every other day such dosing (5.6mg mean) reducing LDL cholesterol by 34.5%. In fact, two controlled clinical studies assessed rosuvastatin 10 or 20 mg once every other day versus rosuvastatin 10mg/daily (13,14) during six weeks, resulting in LDL-C reduction up to 48.5% for daily dose and up to 40.9% for 20 mg once every other day ($p=0.012$).

Rosuvastatin also is advantageous because of its minimum metabolism through P450 cytochrome (CTP), especially through CYP2C9 and CYP2C19 isoenzyme CYP3A4, as most of the statins (simvastatin, lovastatin and atorvastatin), which is involved in a broad variety of drug interactions (6). Such drugs usually present in patients under therapy with verapamil, diltiazem, and macrolides, such as erythromycin or clarithromycin, among others (15).

Statins are usually well tolerated. Most common adverse effects include myalgia, constipation, asthenia, abdominal pain, and nausea (16). Several meta-analysis have found all statins to have a similar safety profile (17,18), the most fre-

quent adverse effects occurring with higher doses of statins (19). Someone could believe, however, that rosuvastatin could have difference related to adverse as against other statins. Notwithstanding, a meta-analysis of four pharmacoepidemiological studies conducted on several international databases that evaluated rosuvastatin safety profile versus other statins, evidenced that there was no higher incidence of rare adverse events such as hospitalizations due to myopathies (0.5 episodes per 10000 years-patient; IC95%: -0.6 a 1.6), rhabdomyolysis (0.7 episodes per 10000 years-patient; IC95%: -0.3 a 1.6), acute renal failure (-0.2 episodes per 10000 years-person; IC95%: -2.9 a 2.5) or acute hepatic damage (-0.8 cases per 10000 years-person; IC95%: -1.8 a 0.2) with the use of rosuvastatin (20). What certainly was found is that the therapy with most of statins can impair glycemic control, or slightly increase diabetes mellitus risk by 9% average (OR=1.09; IC95%: 1.02 a 1.17)(18, 21). Due to occurrence, FDA (US Food and Drug Agency) has added up a warning in the labeling from all statins advising that they may increase glycemia and hemoglobin A1c levels, recognizing, however, statins cardiovascular benefits overweight such mildly increases. (22).

Those benefits are important cardiovascular (CV) morbidity and mortality reductions (CV) evidenced by all and any of the statins in several different scenarios (Table 5).

In fact, a meta-analysis involving some number of studies included in Table 4, determined that a LDL-C reduction by 39 mg/dl was associated to 21% reduction of the incidence at 5-year of major coronary events, revascularization, and cerebrovascular accident, as well as 12% mortality reduction by all causes, regardless of baseline lipidic values (35) and such benefits are extended to populations with or without coronary disease established (36). Other effects additional to LDL-C reduction by statins include enhancement of endothelial dysfunction, diminution of vascular inflammation, stabilization or regression of atherosclerotic plate and platelet aggregation inhibition (37).

Table 5. Studies supporting the use of statins by demonstrating the prevention of cardiovascular morbidity-mortality. TC: Total cholesterol. hsCRP: High sensitive C reactive protein.

Scenario	Study (reference)	Used statin / Comparator / Duration	Relative risk significant reduction of:
With recent Acute Myocardial Infarction			
3086 patients with coronary event 24 to 96 before	MIRACL (23)	Atorvastatin 80 mg vs. placebo for 16-weeks	26% ischemia recurrence
4162 patients with coronary event 10 days before	PROVE-IT (24)	Atorvastatin 80 mg vs. pravastatin 40 mg for 24months	16% cardiovascular events
CV high-risk patients			
4444 patients with prior coronary disease and hypercholesterolemia (CT:212 a 309 mg/dL)	4S (25)	Simvastatin 40 mg vs. placebo for 5.4 year	30% total death Death due to coronary disease 42% Coronary events 34%

Continues

4154 patients with prior coronary disease and "normal" cholesterol levels: LDL-C (115-174 mg/dL)	CARE (26)	Pravastatin 40 mg vs. placebo for 5 years	24% coronary events 31% Cerebrovascular accidents Angioplasty 23%
9014 patients with prior coronary disease and cholesterol "slightly raised" levels (CT: 150-270 mg/dL)	LIPID (27)	Pravastatin 40 mg vs. placebo for 6.1 years	Total death 22% Death due to coronary disease 25%
20536 patients coronary of equivalent disease (Arterial peripheral or diabetes) "normal" cholesterol levels (>135 mg/dL)	HPS (28)	Simvastatin 40 mg vs. placebo for 5 years	Total Mortality 12.9% Fatal or non fatal infarction 26% Cerebrovascular accident 24%
10305 patients with not prior heart disease but with some risk factors and cholesterol "normal" risk factors (CT < 250 mg/dL)	ASCOT-LLA (29)	Atorvastatin vs. placebo for 3.3 years	Fatal or non fatal infarction 36% All events CV 21% Cerebrovascular events 27%
5804 Elderly (>70 year)with CV high risk	PROSPER (30)	Pravastatin 40 mg vs. placebo for 3.5 years	Coronary events 15% Fatal or non-fatal infarction 19% Death for coronary disease 24%
2838 patients with diabetes mellitus 2 in primary prevention with normal LDL-C (<160 mg/dL)	CARDS (31)	Atorvastatin 10 mg vs. placebo for 3.9 years	Cardiovascular events 32% Coronary events 36% Cerebrovascular events 48%
Patients of Primary prevention			
6595 patients of primary prevention with hypercholesterolemia (LDL-C: 174 a 232 mg/dL)	WOSCOPS (32)	Pravastatin 40 mg vs. placebo for 4.9 years	Fatal or non fatal infarction 31% Death due to coronary disease 29%
5608 patients of primary prevention with "average of cholesterol" levels (LDL-C: 130 to 170g/dL)	AFCAPS/TexCAPS (33)	Lovastatin 40 mg vs. placebo for 5.2 years	Coronary events 33% Fatal or non-fatal infarction 40%
17802 patients of primary prevention with LDL-C <130 mg/dL and hsCRP ≥2.0 mg/L levels	JUPITER (34)	Rosuvastatin 20 mg vs. placebo for 1.9 years	Cardiovascular events 44% Myocardial infarction 54% Cerebrovascular accident 48%

Rosuvastatin: studies in high cardiovascular risk patients

In the scenario where atorvastatin (MIRACL and PROVE IT studies (23,24) was successful, it was determined that rosuvastatin carries more people to the goal: SPACE ROCKET (Secondary Prevention of Acute Coronary Events – Reduction of Cholesterol to Key European Targets) study evaluated the lipid-lowering effects of rosuvastatin 10 mg/day vs. simvastatin 40 mg/day for three months in the emergence context due to an acute myocardial infarction in the previous two weeks (38). A higher number of subjects randomized to rosuvastatin (45%) reached the goal of LDL-C <70mg/dL compared to those subjects with simvastatin therapy (37.8%; $p=0.007$), with a hepatic, renal and muscular similar profile.

It should be stressed that the LUNAR (Limiting Undertreatment of Lipids in Acute Coronary Syndrome with Rosuvastatin) (39) study which compared head-to-head atorvastatin 80mg/day (atorva 80) peak dose as against rosuvastatin 20 mg/day (rosu 20) and 40 mg/day (rosu 40) in hospitalized patients due to acute coronary syndrome within 48 h of the beginning of ischemic symptoms. In the Figure 3 below, the efficacy of LDL lowering and HDL increase is shown. Adverse effects related to treatment were similar for the three groups 9.4% for rosu20, 14.8% for rosu 40 and 15.6% for atorva 80 and included myalgias, fatigue, and headache, inter alia. Treatment discontinuation due to

adverse effect was 3.7% for rosu 20, 6.1% for rosu 40 and 9.3% for atorva 80. Cardiovascular events were infrequent in the three groups (3.4% for rosu20, 1.9% for rosu40 and 2.2% for atorva 80), this way showing higher LDL-C reductions with rosu 40 versus atorva 80, with a similar safety profile.

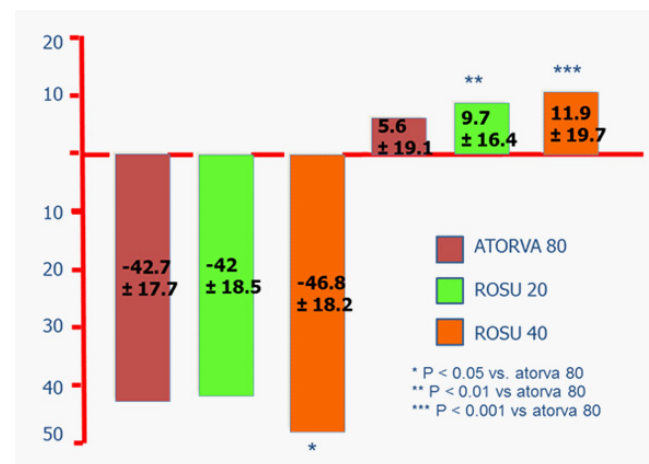


Figure 3. Percentage of mean (\pm standard deviation) change in LDL-C and HDL-c for the three LUNAR study treatment groups. Atorva 80: atorvastatin 80mg/day, Rosu 20: rosuvastatin 20mg/day, Rosu 40: rosuvastatin 40mg/day (39).

Several RCTs such as PULSAR (Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin) (40), MERCURY II (Measuring Effective

Reduction in Cholesterol Using Rosuvastatin therapy II) (41) and POLARIS (Prospective Optimization of Lipids by Atorvastatin or Rosuvastatin Investigated in high risk Subjects with hypercholesterolemia) (42) indicated the superiority of rosuvastatin over other statins to reach the goals of lipidic parameters in patients with cardiovascular risk. We emphasized on the studies of the series DISCOVERY (Direct Statin Comparison of LDL-C Values: an Evaluation of Rosuvastatin therapy), a set of nine independent studies the general purpose of which was to compare the efficacy of rosuvastatin 10 mg/day versus other statins (according to the appropriate initial dose of the one of them) to reach the goals recommended in high cardiovascular risk patients (cardiovascular risk at 10 years >20%, prior myocardial acute infarction or an equivalent atherosclerotic disease) (43-51). In Table 6, a summary of the findings of those studies is found. All of the studies had a safety profile similar among the statins involved. The study DISCOVERY PENTA (50) evaluated specifically South America populations (Brazil, Mexico, Colombia and Venezuela) and Portugal: 1124 patients with hypercholesterolemia (50% out of which were cardiovascular high-risk patients) were authorized to receive rosuvastatin 10mg/day vs. atorvastatin 10mg/day. LDL-C goals, according to NCEP-ATP III were obtained by 71.2% in rosuvastatin group and 61.4% in the other group ($p<0.001$).

The DISCOVERY BELUX study is worth of especial mention. This study was conducted in Belgium and Luxembourg and its objective was to evaluate how many CV high risk patients reached LDL cholesterol goal (in this event <115 mg/dL, according to the protocol of study and the goals of European Atherosclerosis Society (EAS) by that time) after randomization to rosuvastatin 10 mg/day or atorvastatin 10 mg/day. In the first group 85% of patients reached the goal versus 67% of the second group after 12 weeks of treatment. Interestingly, those patients failing to reach the goal with rosuvastatin 10 mg/day and with atorvastatin 10 mg, were switched to a rosuvastatin dose 20 mg/day and 10 mg/day, respectively, during 12 additional weeks. This resulted that additionally at the end of such period, 57% of the first group and 65% of the second group reached LDL-C goal. This study was the only made in the DISCOVERY series that conducted an economic evaluation from the payer's perspective and found that rosuvastatin 10 mg/day is more cost-effective than atorvastatin 10 mg/day in this scenario (47). The study ECLIPSE (Evaluation to Compare Lipid-lowering effects of rosuvastatin and atorvastatin In forced titrated patients: a Prospective Study of Efficacy and tolerability), on its side, assessed the efficacy of the double rosuvastatin dose 10 mg and atorvastatin 10 mg every 6 weeks, until reaching the peak dose of both two medicaments (40 and 80 mg, respectively) to reach the LDL-C goals (<100 mg/dL) in 1036 patients of cardiovascular with hypercholesterolemia high risk. At the

end of 24 weeks of treatment, 83.6% of patients randomized to rosuvastatin and 74.6% patients with atorvastatin reached LDL-C goal ($p<0.001$). In fact, since the first 6 weeks with the initial and peak dosing of rosuvastatin 10 mg/day and atorvastatin 10 mg/dL, the differences between the several percentages of patients who reached the goal with such treatments was remarkable (52.8% vs. 27.6%, respectively; $p<0.001$). Similarly, upon the completion of 24 weeks of follow-up, in the subgroup of patient in high cardiovascular risk, rosuvastatin carried more patients to the goal <70 mg/dL (38.0%) than atorvastatin (20.2%; $p<0.001$). Once again, the differences between percent of CV very high risk patients in goal were significant since the first 6 weeks with the minimal dose of rosuvastatin (7.5%) versus atorvastatin (1.8%; $p<0.001$) (52).

In general, the group of studies known as DISCOVERY show that, after 12 weeks follow-up of cardiovascular high risk patients, rosuvastatin 10 mg/day may imply that significantly far much more cardiovascular high-risk patients (between 50 to 75%) obtain LDL-C goal <100 mg/dL, as compared to atorvastatin 10 mg/day (25 to 55%) or simvastatin 20 mg/day (18.5% to 50%). In the same way, according to the results from VOYAGER (9) meta-analysis, it shall be taken into account that the reaching the LDL baseline cholesterol and the dose of statin used (Table 4).

Rosuvastatin: economic evaluation in cardiovascular high-risk patient

Several economic evaluations based on STELLAR study with one year horizon time and under payer's perspective of Canada and the United States (considering the percentage of change of lipidic parameters and the people reaching LDL-C goal), have evidenced that branding rosuvastatin in 10mg/day dosing is more cost-effective than branding atorvastatin (10 and 20 mg/day) and simvastatin (20 and 40 mg/day) and pravastatin generics (20 and 40 mg/day) (53-55).

In the same way, other economic evaluations made in Europe and North America have used clustered efficacy data from several rosuvastatin controlled clinical assays compared head-to-head to other statins, concluding once again that rosuvastatin 10 mg/day is more cost-effective than other therapeutic options, such as atorvastatin 10mg/day, from the primary caregivers' perspective in the United Kingdom (56).

It has been determined that for patients with increasingly higher coronary risk, the therapy with statins is more cost-effective (57,58). And the question raised in this connection is whether rosuvastatin is more cost-effective than other statins, specifically in cardiovascular high-risk risk patients. The answer is yes, and it was confirmed by DISCOVERY BELUX study (47), as did as well POLARIS study (42). Additionally,

other study used a Markov model to Project the number of CV events and the cost associated to a high-risk population in several pharmacological treatment context, established that using rosuvastatin instead of other statins may reduce cardiovascular events in this type of population and saving cost for several US dollars of United States health systems (59). These results have been confirmed in other RCTs including subjects from other geographic locations, among which PULSAR study (38, 60). For example, in a study using Monte Carlo probabilistic simulation model and based on JUPITER study for long-term cost-effectiveness of rosuvastatin Brand (CRESTOR®) at 20 mg/day versus simvastatin or atorvastatin generics 40 mg/day for CV morbidity-mortality prevention in CV high-risk Sweden population (from Sweden health system payer's perspective and a permanent time-horizon), found that the higher cost-effectiveness and cost-utility of rosuvastatin was basically by the number of CV prevented (60).

Rosuvastatin cost-effectiveness could be determined in the context of Latin America countries, where the cost of medicinal products varies from country to country, using RCT as a basis such as STELLAR or JUPITER studies, as made by other economic evaluations or otherwise, using RCT made in South American population, such as DISCOVERY PENTA study.

In conclusion, it is possible to assert that rosuvastatin is more advantageous than other statins with regard to its pharmacokinetics, LDL-C reduction and percentage of patients reaching a goal, with a similar safety profile. Similarly, rosuvastatin has conclusively demonstrated in the several different economic evaluations to be the most cost-effective compared to other pharmacological options. By taking into account these assertions together with the quality of evidence found in the studies aforementioned; rosuvastatin could be considered as the first-choice for cardiovascular high-risk patients.

Table 6. Studies included in DISCOVERY series (Direct Statin Comparison of LDL-C Values: and Evaluation of Rosuvastatin therapy)

	DISCOVERY THE NETHER- LANDS/DUTCH	DISCOVERY TRIPLE COUNTRY	DISCOVERY ASIA	DISCOVERY ALFA	DISCOVERY BELUX	DISCOVERY BETA	DISCOVERY PENTA	DISCOVERY UK
Author / yr	Bots y Kastelein 2005 (43)	Strandberg et al 2004 (44)	Zhu et al 2007 (45)	Binbrek et al 2006 (46)	Herregods et al 2006 (47)	Laks et al 2008 (48)	Fonseca et al 2005 (50)	Middleton y Fuat 2006 (51)
Population	1215 CV High risks patients	911 CV High risks patients	1482 CV High risks patients	1506 CV High risks patients	938 CV High risks patients	504 CV High risks patients	1124 (50% CV High risks)	1874 CV High risks patients
Place / Length	Netherlands 12 weeks	Iceland, Ireland and Finland 12 weeks	Asia 12 weeks	East Europe, Central America, Chile and Middle East 12 weeks	Belgium and Luxembourg 12 weeks	Estonia 12 weeks	South America and Portugal 12 weeks	England 12 weeks
Drug given	1. Rosu 10 mg 2. Atorva 10 mg 3. Simva 20 mg 4. Prava 40 mg	1. Rosu 10 mg 2. Atorva 10 mg	1. Rosu 10 mg 2. Atorva 10 mg	1. Rosu 10 mg 2. Atorva 10 mg	1. Rosu 10 mg 2. Atorva 10 mg	1. Rosu 10 mg 2. Simva 20 mg	1. Rosu 10 mg 2. Atorva 10 mg	1. Rosu 10 mg 2. Atorva 10 mg 3. Simva 20 mg
Outcomes (% patients with LDL-C <100 mg/dL)	1. 50.2% 2. 24.9% 3. 26.3% 4. 18.5% P<0.001 vs. rosu	1. ≈ 4% 2. ≈ 52% P<0.001 vs. rosu	1. 65.8% 2. 49.5% P<0.0001 vs. rosu*	1. 57.5% 2. 39.2% P<0.001 vs. rosu	1. 71.8% 2. 46.5% P<0.05 vs. rosu*	1. 44.5% 2. 22.2% P<0.001 vs. rosu *	1. 71.2% 2. 61.4% P<0.0001 vs. rosu	1. 76% 2. 55% 3. 50% P<0.0001 vs. rosu

* LDL-C goal < 115 ó 100 mg/dL with established CV disease or DM.

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