ORIGINAL ARTICLE

Response to Statins in Cardiovascular Prevention: Hypo-Responders´ Evaluation

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ABSTRACT

Introduction
Numerous clinical trials have shown that statins reduce cardiovascular events, both in primary and secondary prevention. There is, however, considerable individual variation in the expected response for each dose and type of statin; therefore, detection of hypo responder patients would allow considering additional hypolipidemic treatment.

Objectives
The aims of this study were to evaluate the response to statins in cardiovascular prevention patients and to analyze the characteristics of hypo-responder subjects.

Methods
Consecutive outpatients receiving statins were included. The treating physician defined the type and dose of statin used. The lipid profile was assessed at baseline and post-treatment (6-24 weeks). The distribution of LDL-C reduction for each type and dose of statin was analyzed and "low response" was defined according to two strategies: if the percent reduction was below the median or below the 25th percentile. Univariate and multivariate analyses were performed.

Results
A total of 446 patients (52% female, 25% diabetic, 80% primary prevention, age 58 ± 11 years) were included in the study. Mean LDL-C reduction was 27%, 38% and 43% for simvastatin 10 mg, 20 mg and 40 mg, respectively, 36% and 43% for atorvastatin 10 mg and 20 mg, respectively, and 44% and 49% for rosuvastatin 10 mg and 20 mg, respectively. Hyporesponsiveness defined by both strategies (median and 25th percentile) showed that male gender (OR 2.54 and 2.31), diabetes (OR 2.0 and 3.85), age (every 5 years, OR 0.87 and 0.83) and baseline LDL-C (every 10 mg/dL, OR 0.78 and 0.77) were independently associated with greater chance of being hypo-responder.

Conclusions
LDL-C reduction by different statins was similar to previous reports. Men, diabetics, younger subjects or with lower baseline LDL-C were more likely to show poor response to statins.

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Key words > Statins, LDL cholesterol, Hypo-responders

Abbreviations >

CACEI	Angiotensin converting enzyme inhibitors	**LDL-C**	Low-density lipoprotein cholesterol
ARB	Angiotension II receptor blockers	**HbA1c**	Glycated hemoglobin
HDL-C	High-density lipoprotein cholesterol		

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INTRODUCTION

In the last 20 years, numerous clinical trials have demonstrated that statins reduce cardiovascular events in both primary (1) and secondary prevention. (2, 3) The benefit generated by the decrease in low-density lipoprotein cholesterol (LDL-C) levels is greater when the patient's absolute risk is higher and is more related to the degree of LDL-C lowering than to the initial absolute value. Statin therapy reduces nearly one-fifth the incidence of major coronary events, coronary revascularization and stroke for each 1 mmol/L (≈ 39 mg/dL) drop in LDL-C level. (4)

The average LDL-C reduction in response to statins varies according to the type of drug and dose used. (5-7) However, assuming that adherence to treatment and lifestyle changes are adequate, there is considerable individual variation in the expected response for each dose and type of statin which is affected by inheritance (genetic polymorphisms) (8, 9) and environmental questions (diet, drug interaction, level of immune response, and intestinal flora characteristics). (10-14)

We do not know whether in our country LDL-C reduction with different statins and doses is consistent with reports from other regions of the world. On the other hand, the detection of statin hypo- responders, preferably with clinical variables easily accessed from the office, could allow considering additional lipid-lowering therapy. For example, although there is no conclusive evidence, it is known that statin hypo-responders are intestinal hyper-absorbers of cholesterol, which may benefit from the addition of ezetimibe or other drugs acting at this level. (15 -17)

Taking into account the above considerations, the purpose of this study was 1) to evaluate the response to statins in a population of patients in cardiovascular prevention and to compare it with previously published historical averages, and 2) to assess the characteristics of hypo- responders to different statins (and different doses) frequently used in our country.

METHODS

Study design: prospective, observational, naturalistic study.
Population: between January and June 2013, patients > 21 years with statin indication according to the 2012 Consensus for Cardiovascular Prevention of the Argentine Society of Cardiology, (18) and with lipid profile assessed before and after treatment were included in the study. Patients were referred by outpatient Cardiology services from five healthcare centers of the City of Buenos Aires and the Greater Buenos Aires. Patients with the following characteristics: 1) chronic inflammatory diseases; 2) hospitalization for medical or surgical reasons within 3 months prior to study entry; 3) history of thyroid disease (with or without treatment); 4) severe chronic renal failure (creatinine clearance < 30); 5) documented contraindication for statins or 6) receiving ezetimibe or other hypolipidemic agents were excluded from the study.
Treatments: type and dose of statin, as well as other concomitant medical treatments, were left to the discretion of the treating physician. The formal medical recommendation was to take statins at night. Information was recorded in an anonymous database in compliance with the personal data protection act. The following statins and doses were analyzed: simvastatin 10, 20 and 40 mg/day; atorvastatin 10 and 20 mg/day; rosuvastatin 10 and 20 mg/day. There were no records of patients receiving pravastatin or fluvastatin, and rosuvastatin 40 mg/day and atorvastatin 40 mg/day were not analyzed because they were observed in only two patients.
Lipid profile determinations: pre-treatment lipid tests (i.e. those routinely performed to the patient leading to statin indication) were considered as basal values and any test performed within 6 to 24 weeks after treatment initiation was taken as final value. Included patients (whose adherence was controlled through a questionnaire) underwent a second intra-treatment test, having taken the last statin dose on the night previous to blood withdrawal.
Definition of hypo-responder patient: the distribution of LDL-C reduction was analyzed for each statin and dose. As there is no universally accepted definition of "hypo-responder", "low response" was defined by two strategies: 1) if percent LDL-C reduction was below the median for each statin and dose and 2) if the percent reduction was below the 25th percentile for each dose and drug type.

Statistical analysis

Differences between basal and post-treatment lipid values were expressed as percent reduction. Univariate analysis was used to compare variables between the hypo-responder population (defined by both strategies) and the one not classified as hypo-responder. A multiple regression logistic model was performed to identify independent characteristics associated with low response to statins, including all variables with $p > 0.05$ in the univariate analysis.

Continuous data between groups were analyzed using the t test for normal distribution or the Wilcoxon Mann Whitney test for non-normal distribution, and categorical data were analyzed using the chi-square test. Continuous variables were expressed as mean ± standard deviation and categorical variables as percentages. A p value < 0.05 was considered as statistically significant.

The study was performed in agreement with medical investigation recommendations suggested by the Declaration of Helsinki, Good Clinical Practice guidelines and applicable ethical regulations.

RESULTS

A total of 446 patients (234 women and 212 men) with mean age of 58 ± 11 years were included in the study. Among this group, 80% of patients were in primary prevention and the prevalence of diabetes was 25%. Population characteristics are shown in Table 1. Total cholesterol and average LDL-C reduction was 25% and 27% for simvastatin 10 mg; 28% and 38% for simvastatin 20 mg; 33% and 43% for simvastatin 40 mg; 28% and 36% for atorvastatin 10 mg; 34% and 43% for atorvastatin 20 mg; 34% and 44% for rosuvastatin 10 mg; and 42% and 49% for rosuvastatin 20 mg. Table 2 shows the comparison between previously published data and LDL-C levels found in the present study.

Average triglyceride level reduction was 6%, 12% and 18% for simvastatin 10, 20 and 40 mg; 14% and 24% for atorvastatin 10 and 20 mg; and 16% and 26% for rosuvastatin 10 and 20 mg, respectively. Average high-density lipoprotein cholesterol (HDL-C) increase

Table 1. Baseline population characteristics.

n = 446	
Age, years	58 ± 11
Systolic pressure, mmHg	129 ± 14
Diastolic pressure, mmHg	80 ± 10
Total cholesterol, mg/dL	262 ± 49
LDL-C, mg/dL	182 ± 45
HDL-C, mg/dL	51 ± 20
Triglycerides, mg/dL	151 ± 92
Non-HDL cholesterol, mg/dL	211 ± 49
Glycemia, mg/L	101 ± 19
Creatinine, mg/dL	0.91 ± 0.20
HbA1c, %*	6.95 ± 1.12
Diabetes duration, years*	8.4 ± 6.9
Time to second test, weeks	12 ± 5
Body mass index, kg/m2	28.32 ± 4.74
Men, n (%)	201 (45)
Smoking, n (%)	89 (20)
Hypertension, n (%)	214 (48)
Diabetes, n (%)	112 (25)
Treatment	
Beta-blockers, n (%)	134 (30)
Calcium blockers, n (%)	54 (12)
Diuretics, n (%)	58 (13)
ACEI/ARB, n (%)	174 (39)
Aspirin, n (%)	161 (36)
Hypoglycemic agents, n (%)	103 (23)
Insulin, n (%)	36 (8)
Family history of coronary heart disease**, n (%)	89 (20)
Primary prevention, n (%)	357 (80)

* Only in the diabetic population (25%).
** First degree relatives, men <55 years or women <65 years. HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol. HbA1c :Glycated hemoglobin
ACEI: Angiotensin converting enzyme inhibitors.
ARB: Angiotension II receptor blockers

was not above 3% with any statin or dose used.

The analysis of hypo-responder characteristics taking as reference median LDL-C reduction, revealed that they were younger (57 ± 12 vs. 60 ± 10 years, $p < 0.001$), had greater body mass index (29.03 ± 5.05 vs. 27.64 ± 4.33, $p < 0.005$), lower total cholesterol level (247 ± 49 vs. 277 ± 45, $p < 0.001$), lower LDL-C level (167 ± 44 vs. 197 ± 41, $p < 0.001$) and greater prevalence of male gender (58% vs. 32%, $p < 0.001$), smoking (24% vs. 16%, $p = 0.01$), diabetes (37% vs. 13%, $p < 0.001$), family history of coronary heart disease (26% vs. 15%, $p < 0.05$) and subjects in secondary prevention (27% vs. 12%, $p < 0.001$) compared to subjects with normal response to stations. When the analysis was performed defining hypo-responders with the second strategy (according to the 25th percentile), similar results were obtained, in addition to greater hypertension prevalence in hypo responders (65% vs. 42%, $p < 0.05$). Univariate analysis results comparing hypo-responders with subjects exhibiting a normal response by the two strategies (according to the median and the 25th percentile) are shown in Tables 3 and 4.

Diabetic hypo-responders had an average of more years diabetes compared with normoresponder diabetics, both in the median (9.5 vs.5.2 years, $p < 0.005$) as in the 25th percentile (9.4 vs. 6.8 years, $p = 0.05$) analyses. Glycemic control assessed by HbA1c showed no significant differences (see Table 3). However, hypo-responder diabetics were more frequently insulinized compared with normoresponder diabetics (according to the median strategy: 38% vs. 7%, $p < 0.05$ and according to the 25th percentile strategy: 82% vs. 18%, $p< 0.005$).

In the multivariate analysis, male gender (according to the median strategy: OR 2.54, 95% CI 1.45-4.43 and according to the 25th percentile strategy: OR 2.31, 95% CI 1.16-4.62) and presence of diabetes (according to the median strategy: OR 2.00, 95% CI 1.06-3.79 and according to the 25th percentile strategy: OR 3.85, 95% CI 1.88-7.87) were independently associated with greater probability of being a hypo-responder. Moreover, in the same analysis and independently of the strategy used to define "low response", as age or basal LDL-C level were higher, the possibility of presenting a poor response to statins was lower (Table 5).

DISCUSSION

Statins are the most effective and most widely used drugs for the treatment of dyslipidemia, reducing cardiovascular risk in relation to the lowest LDL-C achieved. This lipoprotein is the primary lipid target recommended by leading clinical practice guidelines. (18-20)

However, in the "real world", these objectives are not easily achieved. A 2008 study assessing LDL-C targets in a United States population showed that the LDL-C target of < 100 or < 70 mg/dL in subjects with a history of coronary artery disease was achieved in 64.8% and 21.4% of cases, respectively. (21) Similarly, in a Spanish population of diabetics, only 36% of patients attained the LDL-C target of < 100 mg/dL. (22) Failure to achieve the objectives is due to many causes, including non-adherence or poor response to drugs. (23, 24) Hyporesponsiveness to statins may be explained by several reasons, some genetically determined and others due to environmental issues. Several inherited polymorphisms that predominantly relate to statin pharmacokinetics and endocytosis of lipoprotein particles by the LDL receptor are common in the general population and influence individual patient response to statin therapy. For example, Chasman et al. analyzed subgroups of patients with different genetic origin and found a variability of up to 22 mg/dL in LDL-C reduction with rosuvastatin. (25) However, there are no genetic tests available in our daily practice, and if we had them they would be very expensive. Our study assessed easy to evaluate clinical variables,

Table 2. LDL-C reduction compared with historical values.

Dose per day, (n)	LDL-C decrease (range), % Clinical trials (5)	Average LDL-C decrease, % Stellar Study (6)	Average LDL-C decrease, % Meta-analysis (7)	Average LDL-C decrease, % (present study)	Median and 25th percentile LDL-C reduction, % (present study)
Atorvastatin					
10 mg, (102)	28.9 – 40.2	37	37	36	37-27
20 mg, (87)	38.4 – 46.1	43	43	43	46-29
Rosuvastatin					
10 mg, (133)	37.1 – 50.6	46	43	44	46-34
20 mg, (52)	45.0 – 52.4	52	48	49	52-38
Simvastatin					
10 mg, (33)	26.0 – 33.1	28	27	27	26-18
20 mg, (29)	19.0 – 40.0	35	32	38	39-27
40 mg, (10)	34.3 – 43.0	39	37	43	43-34

Table 3. Differences between responder and hypo-responder subjects. Univariate analysis of continuous variables.

Variables, mean ± SD	Analysis according to the median			Analysis according to the 25th percentile		
	Low response	Normal response	p	Low response	Normal response	p
Age, years	57 ± 12	60 ± 10	<0.005	56 ± 13	59 ± 11	<0.01
Systolic pressure, mmHg	130 ± 15	128 ± 14	0.19	131 ± 16	129 ± 14	0.18
Diastolic pressure, mmHg	80 ± 10	79 ± 9	0.23	80 ± 11	79 ± 9	0.22
Baseline total cholesterol, mg/dL	247 ± 49	277 ± 45	<0.001	227 ± 44	274 ± 45	<0.001
Baseline LDL-C, mg/dL	167 ± 44	197 ± 41	<0.001	148 ± 37	194 ± 41	<0.001
Baseline HDL-C, mg/dL	49 ± 20	53 ± 19	0.02	45 ± 18	53 ± 20	<0.001
Baseline triglycerides, mg/dL	160 ± 95	143 ± 88	0.05	170 ± 101	144 ± 87	<0.05
Time between tests, weeks	13 ± 6	11 ± 3	<0.05	14 ± 6	11 ± 4	<0.05
BMI, kg/m2	29.03 ± 5.05	27.64 ± 4.33	<0.005	30.01 ± 5.37	27.73 ± 4.36	<0.001
Glycemia, mg/L	105 ± 21	98 ± 16	<0.001	109 ± 22	99 ± 17	<0.001
HbA1c, %*	7.0 ± 1.2	6.7 ± 0.9	0.16	7.0 ± 1.1	6.9 ± 1.2	0.84
Creatinine, mg/dL	0.95 ± 0.23	0.87 ± 0.18	<0.001	1.0 ± 0.25	0.88 ± 0.18	<0.001
Diabetes time, years*	9.5 ± 7.3	5.2 ± 4.1	<0.05	9.4 ± 7.4	6.8 ± 5.8	0.05

* Only in the diabetic population (25%).
SD: standard deviation; HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol. BMI: Body mass index. HbA1c : Glycated hemoglobin

with the purpose of determining the characteristics of subjects with lower response to statins.

Average LDL-C decrease for all doses and statins used in the present study were in the range previously published by clinical trials and similar to those reported by the STELLAR trial, which was specifically designed to evaluate the response to various statin doses. (5, 6)

In our study, although many variables in unadjusted analysis showed significant differences between subjects with or without hyporesponsiveness to statins, only age, gender, diabetes and baseline LDL-C levels were independently associated after multivariate analysis.

Recent evidence suggests that patients with type-2 diabetes have defects in the formation and assembly of chylomicrons and a significant increase in mRNA expression of the Niemann -Pick C1-like 1 duodenal receptor, indicative of alterations in cholesterol absorption. (26, 27) Some studies showed that patients

Table 4. Differences between responder and hypo-responder subjects. Univariate analysis of categorical variables.

Variables, mean ± SD	Analysis according to the median			Analysis according to the 25th percentile		
	Low response	Normal response	p	Low response	Normal response	p
Male gender	58	32	<0.001	67	37	<0.001
Smoking	24	16	0.01	28	17	<0.05
Hypertension	52	44	0.09	65	42	<0.05
Diabetes	37	13	<0.001	57	13	<0.001
Secondary prevention	27	12	<0.001	36	14	<0.001
Treatment						
Beta-blockers	39	20	<0.001	53	22	<0.001
Calcium blockers	15	8	0.01	23	8	<0.001
Diuretics	16	11	0.15	24	11	0.08
ACEI	38	20	<0.001	56	20	<0.001
ARB	24	11	<0.05	32	13	<0.01
Aspirin	49	23	<0.001	66	26	<0.001
Hypoglycemic agents	32	14	<0.001	51	13	<0.001
Insulin	15	1	<0.001	25	2	<0.001
Family history *	26	15	<0.05	33	16	<0.001

* First degree relatives, men < 55 years or women < 65 years
ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers.

Table 5. Differences between responder and hypo-responder subjects. Multivariate analysis.

Variables	Analysis according to the median			Analysis according to the 25th percentile		
	OR*	95% CI	p	OR*	95% CI	p
Age**	0.87	0.78-0.97	0.015	0.83	0.72-0.96	0.01
Male gender	2.54	1.45-4.43	0.001	2.31	1.16-4.62	0.018
Basal LDL-C***	0.78	0.66-0.92	0.004	0.77	0.63-0.95	0.016
Diabetes	2.00	1.06-3.79	0.03	3.85	1.88-7.87	<0.001

*Model adjusted by age, gender, hypertension, smoking, diabetes, body mass index, basaline lipid values, secondary prevention, serum creatinine, time between two blood samples and treatment.
** For every 5 years increase in age.
*** For every 10 mg/dL increase in LDL-C.
OR: Odds Ratio; 95% CI: 95% confidence interval. LDL-C: Low-density lipoprotein cholesterol.

with coronary heart disease and diabetes or metabolic syndrome have higher intestinal cholesterol absorption and, in contrast, lower cholesterol hepatic synthesis. (28, 29) For example, a study in a diabetic population indicated that a change of dietary cholesterol absorption by 1% changed cholesterol synthesis by 27 mg/day in the opposite direction. (30) In our study, according to the strategy used to define hyporesponsiveness, diabetics were between two and almost four times more likely to be hypo-responders to statins compared to non-diabetics, even after adjusting for the other variables.

Previous data have shown that in general, the response to statins is similar between men and women, although male gender shows a better response to a combination therapy with ezetimibe. (31) Similarly, another study showed that the addition of ezetimibe to diabetic patients receiving statins reduced cholesterol level more significantly in men than in women. (32) Being more responsive to ezetimibe may suggest they are hyper-absorbers with a decreased hepatic synthesis and therefore less responsive to statins. In agreement with this reasoning, our study showed that men, regardless of the other risk factors explored, had more chance of presenting hyporesponsiveness to statins compared to women. However, we did not explore whether the type of diet or physical activity was different between genders, a condition that could have changed the results.

In our work we saw that young subjects were more

likely to be hypo-responders. A previous study reported increased LDL-C reduction with lovastatin in subjects < 45 years compared with patients < 65 years. (33) However, this difference was very small and preferably in women. In the same line, although evaluating targets and not reduction percentages, Cone et al. found that age was an independent predictor to reach LDL-C targets in a secondary prevention population. (34) The presence of inherited dyslipidemia, not diagnosed in the younger population, could partly explain these findings. In this sense, several reports indicate that there is significant variability in the response to statins in patients with familial hypercholesterolemia. (35, 36)

The study showed that baseline LDL-C level was also associated with increased hypo-responsive probability. This finding has already been reported (32), associating subjects with higher baseline LDL-C absolute value to a greater reduction in relative terms. Patients with homozygous familial hypercholesterolemia, although with extremely high LDL-C, would be an exception to the above as they usually have a poor response to statins.

Finally, the In-Cross study comparing the response to rosuvastatin vs. dual therapy (ezetimibe + simvastatin) in patients with inadequate response to other statins showed that men, subjects < 65 years and diabetics had better response to dual therapy, suggesting they might be hyper-absorber populations and indirectly less responsive to statins due to lower hepatic synthesis of cholesterol. (37) In conjunction with this work, we found an independent association among these three subgroups (men, young subjects and diabetics) and the possibility of hyporesponsiveness to statins.

Hyporesponsiveness is not just a genetic or pharmacological condition; it has a strong clinical impact. Several studies show that hypo-responding patients have more events and worse prognosis. (38, 39) In this sense; a study that evaluated a subgroup of coronary patients of the 4S trial showed that patients with high cholesterol absorption (high cholestanol /cholesterol ratio) and low cholesterol synthesis benefited less from statins, with greater recurrence of coronary events. (40)

Limitations

Firstly, the definition used independently of cholesterol decrease, classifies 50% and 25% of patients respectively as "hypo-responders." This definition could instead be based not on the outcome of each statin but on the expected effect. Although all patients were recommended lifestyle modifications, type of food or exercise level were not assessed in our work. Secondly, not all statins or doses were tested, although the ones mostly used in our country were included. Finally, our population showed markedly elevated baseline LDL-C levels (associated with greater response). Extrapolation of our results to other less dyslipidemic populations should be investigated.

Clinical implications

It is clear that in the context of cardiovascular prevention, whether to administrate or not a statin is not enough. Constant evaluation of the response considering the scope and therapeutic targets should be performed. Our study provides efficacy data in the context of real life patients. It is likely that in men, younger subjects, those with not so high LDL-C levels and essentially diabetics, if hyporesponsiveness is detected, the use of additional therapeutic measures should be considered.

CONCLUSIONS

In this population of patients in cardiovascular prevention, the average reduction in LDL-C provided by the different doses of statins was similar to previously published data. Younger subjects, men, diabetics and patients with lower baseline LDL-C levels were associated with increased likelihood of statin hyporesponsiveness.

RESUMEN

Respuesta a las estatinas en prevención cardiovascular: Evaluación de los hipo-respondedores.

Introducción

En numerosos ensayos clínicos se demostró que las estatinas reducen los eventos cardiovasculares, tanto en prevención primaria como secundaria. Sin embargo, existe una variación individual considerable en la respuesta esperada para cada dosis y tipo de estatina, por lo que detectar al paciente hiporrespondedor a las estatinas permitiría considerar un tratamiento hipolipemiante adicional.

Objetivos

Evaluar la respuesta a las estatinas en pacientes en prevención cardiovascular y analizar las características de los sujetos hiporrespondedores.

Material y métodos

Se incluyeron en forma consecutiva pacientes ambulatorios con indicación de estatinas. El médico tratante definía la estatina y la dosis utilizada. Se analizaron los valores basales y postratamiento (6-24 semanas) del perfil lipídico. Se analizó la distribución de la reducción del C-LDL para cada tipo y dosis de estatina y se definió "baja respuesta" según dos estrategias: si el porcentaje de reducción se encontraba por debajo de la mediana o por debajo del percentil 25. Se realizaron análisis univariados y multivariados.

Resultados

Se incluyeron 446 pacientes (52% mujeres, 25% diabéticos, 80% prevención primaria, edad 58 ± 11 años). La reducción del C-LDL promedio fue del 27%, 38% y 43% para simvastatina 10 mg, 20 mg y 40 mg, respectivamente, del 36% y 43% para atorvastatina 10 mg y 20 mg, respectivamente, y del 44% y 49% para rosuvastatina 10 mg y 20 mg, respectivamente. Definiendo hiporrespuesta por ambas estrategias (mediana y percentil 25), el sexo masculino (OR 2,54 y 2,31), la diabetes (OR 2,0 y 3,85), la edad (cada 5 años, OR 0,87 y

0,83) y el nivel basal de C-LDL (cada 10 mg/dl, OR 0,78 y 0,77) se asociaron independientemente con una chance mayor de ser hiporrespondedor.

Conclusiones

La reducción del C-LDL por las diferentes estatinas fue similar a lo previamente publicado. Los hombres, los diabéticos, los sujetos más jóvenes o con niveles basales más bajos de C-LDL tuvieron mayor probabilidad de mostrar baja respuesta a las estatinas.

Palabras clave > Estatinas - Colesterol LDL - Hiporrespondedores

Conflicts of interest
None declared.

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