

Changes in the Lipid Profile of Patients with Acute Coronary Syndromes within the First Days of Hospitalization

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SUMMARY

Background

Controversy exists regarding the temporal changes in lipid levels after an acute coronary syndrome (ACS). In our country, there is limited information about the basal characteristics of the lipid profile and the variability of its components after an ACS, and it does not include direct measuring of LDL-C or apolipoproteins.

Objectives

1) To analyze the changes in lipoprotein and apolipoprotein levels in a group of patients hospitalized with ACS, and 2) to describe the basal lipid profile and compare it with that of a healthy population.

Material and Methods

Plasma levels of total cholesterol (TC), LDL-C, HDL-C, ApoB and ApoA were measured at admission, 18 hours and 42 hours in patients hospitalized with ACS. None of the participants were taking lipid-lowering drugs or received them within 48 hours after hospitalization.

Results

A total of 31 patients were included (mean age 61 years, 87% were men, 51% with Q-wave AMI, 19% with non Q-wave AMI and 30% with unstable angina). Plasma levels of TC, non HDL-C and LDL-C presented a significant reduction during hospitalization (mean \pm standard deviation at admission, 18 hours and 42 hours, p value): TC (218 ± 53 , 206 ± 40 and 194 ± 41 ; $p=0,005$), non HDL-C (180 ± 54 , 169.8 ± 40 and 157.6 ± 39 ; $p=0,01$), LDL-C (136 ± 30 , 134 ± 33 and 127 ± 37 ; $p=0.01$). ApoB and HDL-C levels did not change in a significant fashion. Baseline ApoA levels corresponded to the 5th percentile of a healthy population and there was an early and significant reduction during hospitalization (115 ± 21 , 108 ± 18 and 106 ± 3 ; $p=0,01$).

Conclusions

In patients with ACS basal lipid profile should be evaluated at the moment of hospitalization. ApoB levels remained stable and might be used to select the therapeutic strategy. Reverse cholesterol transport was affected in more than 50% of the population.

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Key words > Apolipoproteins - Lipoproteins - Acute Coronary Syndrome

Abbreviations >

ApoA	Apolipoprotein A1	h	Hours
ApoB	Apolipoprotein B100	AMI	Acute myocardial infarction
HDL-C	High density lipoprotein-cholesterol	BMI	Body mass index
LDL-C	Low density lipoprotein-cholesterol	S	Sample
Non-HDL-C	Non-high density lipoprotein-cholesterol	ACS	Acute coronary syndrome
TC	Total cholesterol	TG	Triglycerides

BACKGROUND

There is general agreement that the evaluation of total cholesterol (TC) levels in plasma within the first 24 hours (h) from hospitalization due to acute myo-

cardial infarction (AMI) reflects its habitual value. (1-4) Therefore, the updated American guidelines that the lipid profile should be measured within that time interval in all patients hospitalized due to acute coronary syndrome (ACS). (5) However, the results

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of the studies analyzing the variations in lipid levels during the first hours after admission for ACS are controversial. (4, 6-10)

Dissimilar results have been reported in mean basal lipid values in patients hospitalized with a coronary event. (4, 7, 9, 11) The great variability in the results might be related to the time between symptoms onset to the first blood sampling, regional and ethnical factors, previous treatment with lipid-lowering drugs and the measuring techniques used.

The primary goal of our study was to analyze the changes in the plasma levels of TC, LDL-C, HDL-C, non-HDL cholesterol (non-HDL-C), triglycerides, apolipoprotein A1 (ApoA) and apolipoprotein B (Apo B) within the first 48 h after hospitalizations due to ACS in the coronary care unit.

The secondary goal was to evaluate, in an exploratory fashion, the basal lipid profile of these patients and to compare the different variables with those of a healthy population attending the same institution.

The applicability of the results of the study have the following clinical implications: 1) to determine the most appropriate time to characterize the type of basal dyslipemia in patients with ACS; 2) to allow the most adequate pharmacological treatment to be commenced earlier; and, 3) to adjust the plasma level of the lipid variable evaluated for the potential spontaneous variations due to ACS admission to the moment the variable was measured.

MATERIAL AND METHODS

Between March and August 2009 we evaluated all patients admitted to the Coronary Care Unit with a diagnosis of ACS in a non-probabilistic and consecutive fashion. We included only those patients eligible for the analysis.

Three blood samples (S) were taken to measure the lipid profile: S1 (non-fasting sample) when the patient was admitted in the ER, and two fasting samples, S2 and S3, taken in the morning of the days 1 and 2 after hospitalization, respectively.

Basal lipid values were compared with those corresponding to a sample of healthy subjects. In this healthy population we explored which percentiles of LDL-C, HDL-C, ApoB and ApoA corresponded to patients with ACS.

Patients who had been receiving lipid-lowering drugs previous to admission were excluded.

Therapy with statins was not initiated before obtaining the third blood sample.

Measurement of variables

Plasma levels of TC were measured by enzymatic methods; TG levels were determined by enzymatic/GPO Trinder method and HDL-C was measured using the homogenous method (Synchron LX Clinical Systems[®] by Beckman Coulter). We performed a direct measurement of LDL-C instead of using the Friedewald formula as we considered it was a better option in nonfasting blood samples or in the presence of hypertriglyceridemia. (12) We used a homogeneous assay (Synchron LX Clinical Systems[®] de Beckman Coulter). Plasma levels of ApoA and Apo B were measured by immunonephelometry (Beckman-Coulter MMAGE[®]O). We also calculated non-HDL-C (TC - LDL-C), Castelli index (TC/HDL-C) and ApoB/ApoA ratio. Intra-and inter-assay coeffi-

cients of variation corresponding to the methods used were as follows: TC (2% and 1%), TG (2.5% and 1%), HDL-C (2% and 1%), ApoA-1 (4.5% and 4%), ApoB (5.5% and 4%), and LDL-C (2% and 3%). Lipid and apolipoprotein values were expressed in mg/dl.

Statistical Analysis

Data were expressed as mean \pm standard deviation (SD) and categorical variables as percentage.

Continuous data between two groups were analyzed using t test or Wilcoxon Mann-Whitney test for normal and abnormal distributions, respectively. The differences among lipid values data obtained in the three samples were analyzed using repeated-measures ANOVA. Scheffé's method for multiple comparisons was used to evaluate pairwise differences among the samples. A two-tailed p value < 0.05 was considered statistically significant.

Ethical considerations

The study was conducted following the recommendations regarding medical research of the Declaration of Helsinki, the Guidelines for Good Clinical Practice and the rules of the local Committee on Ethics.

RESULTS

A total of 31 patients were included. The diagnoses at admission were Q-wave AMI (51%), non Q-wave AMI (19%) and unstable angina (30%). Mean age was 61 ± 14 years. Most patients were men (87%); 69% had hypertension, 35% were current smokers and 15% had type 2 diabetes mellitus. Only 6% of patients had a history of cardiovascular events. Body mass index (BMI) was 27.97 ± 3.8 ; waist circumference was 86.5 ± 6 cm in women and 105 ± 11 cm in men.

The mean time from symptoms onset to the moment of the first blood sampling (S1) at admission was 7.7 ± 6 h. S2 and S3 were obtained at a mean time of 17.6 h and 41.7 h after admission, respectively. The following lipid values were recorded at admission: TC 218 ± 53 , LDL-C 136 ± 30 , HDL-C 38 ± 11 , TG 181 ± 109 , ApoB 107 ± 26 and Apo-A1 115 ± 21 . Catelli index was 6.16 ± 2.7 and ApoB/ApoA ratio was 0.93 ± 0.25 . Fifty percent of women and 52% of men had HDL-C < 50 and < 40 mg/dl, respectively.

Plasma levels of TC showed a progressive reduction between admission, S2 and S3 (218 ± 53 vs. 206 ± 40 mg/dl vs. 194 ± 41 mg/dl, respectively; $p = 0.005$), representing a reduction of 5.5% and 11% at 18 h and 42 h, respectively. A similar pattern was observed with non-HDL-C (180 ± 54 vs. 170 ± 40 vs. 158 ± 39 ; $p = 0.01$); representing a reduction of 5.7% and 12.4% at 18 h and 42 h, respectively. The reduction in LDL-C levels was minimal 18 h after admission but significant at 42 h (136 ± 30 vs. 134 ± 33 vs. 127 ± 37 mg/dl; $p = 0.01$). This represents a reduction of 1.5% in S2 and 6.6% in S3 (Table 1, Figure 1).

The reduction in TG levels was not significant (181 ± 109 vs. 158 ± 86 mg/dl vs. 145 ± 52 mg/dl; $p = 0.07$) (Table 1).

ApoB levels remained stable in the three determinations (107 ± 26 vs. 106 ± 25 vs. 104 ± 25 mg/dl; p

Variable lipídica (mg/dl)	Sample 1 Mean ± SD	Sample 2 Mean ± SD (% de reducción)	Sample 3 Mean ± SD (% de reducción)	p value
Total cholesterol	218 ± 53	206 ± 40 (5.5)	194 ± 41*(11)	0.005
Non-HDL-cholesterol	180 ± 54	170 ± 40 (5.7)	158 ± 39*(12.4)	0.01
LDL-cholesterol	136 ± 30	134 ± 33 (1,5)	127 ± 37*(6.6)	0.01
Triglycerides	181 ± 109	158 ± 86	145 ± 52	0.07
Colesterol-HDL	38 ± 11	36 ± 9 (5)	36 ± 11 (5)	0.48
Apolipoprotein B	107 ± 26	106 ± 25 (0.9)	104 ± 25 (2.8)	0.56
Apolipoprotein A1	115 ± 21	108 ± 18 (6)	106 ± 3 (7.8)	0.01*

Table 1. Mean lipid values at admission, and 18 and 42 h after hospitalizationhoras de la internación

* Significant difference between samples 1 and 3 using Scheffé's method. SD: Santdard deviation

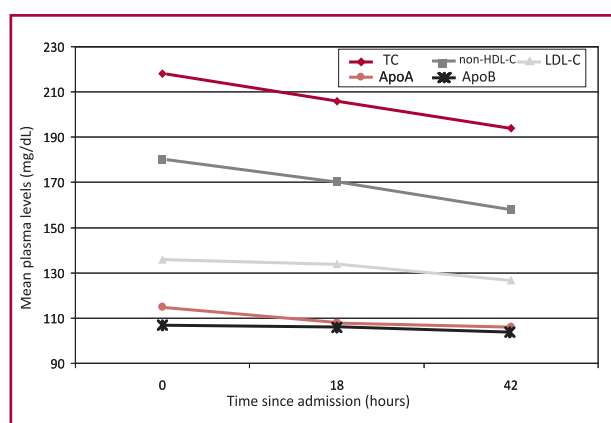


Fig. 1. Mean lipid values at admission (S1), 18 h (S2) and 42 h after hospitalization (S3). The reduction in TC and non-HDL-C was rapid and significant. The reduction in LDL-C was pronounced after 18 hs. ApoB and ApoA levels are similar 18 h after admission, demonstrating an increase in the atherogenic risk during hospitalization.

= 0.56). The difference between S1 and S3 was of only 3% (Table 1, Figure 1).

HDL-C presented a slight and not significant reduction between S1 and S2, and its value was in S3 (38 ± 11 vs. 36 ± 9 vs. 36 ± 11 mg/dl; p = 0.48) (Table 1).

Plasma levels of ApoA presented an early and significant reduction (115 ± 21 vs. 108 ± 18 vs. 106 ± 30 mg/dl; p = 0.01). Therefore, comparing the percentages of the values at admission with those obtained at 42 h, the decrease in ApoA levels was greater than that of HDL-C levels (8% vs. 5%) (Table 1, Figure 1).

We did not find significant differences in ApoB/ApoA ratio (0.93 ± 0.25 vs. 0.98 ± 0.28 vs. 0.98 ± 0.29) or Castelli index (6.16 ± 2.7 vs. 6.06 ± 1.9 vs. 5.76 ± 1.9).

Basal lipid profiles of the 31 patients with ACS were compared with a population of healthy blood donors attending our hospital's blood bank (age: 41.9 ± 14 years, male gender: 64%, body mass index: 26.2 ± 4, current smoking: 31%). Patients with ACS had greater mean levels of TC (218 ± 53 vs. 198 ± 40

mg/dl; p < 0.01), LDL-C (136 ± 30 vs. 128 ± 38 mg/dl; p < 0.0001) and ApoB (107 ± 26 vs. 95 ± 29 mg/dl; p = 0.01) and lower levels of HDL-C (38 ± 11 vs. 48.3 ± 13 mg/dl; p < 0.001) and ApoA (115 ± 21 vs. 156 ± 32; p < 0.0001). In addition, Castelli index (6.16 ± 2.7 vs. 4.32 ± 1.3; p < 0.0001) and ApoB/ApoA ratio (0.93 ± 0.25 vs. 0.62 ± 0.21; p < 0.0001) were also greater

In patients with ACS, mean levels of LDL-C, ApoB, HDL-C and ApoA1 corresponded to percentiles 60, 70, 20 y 5 of the healthy population. (Figure 2 A and B).

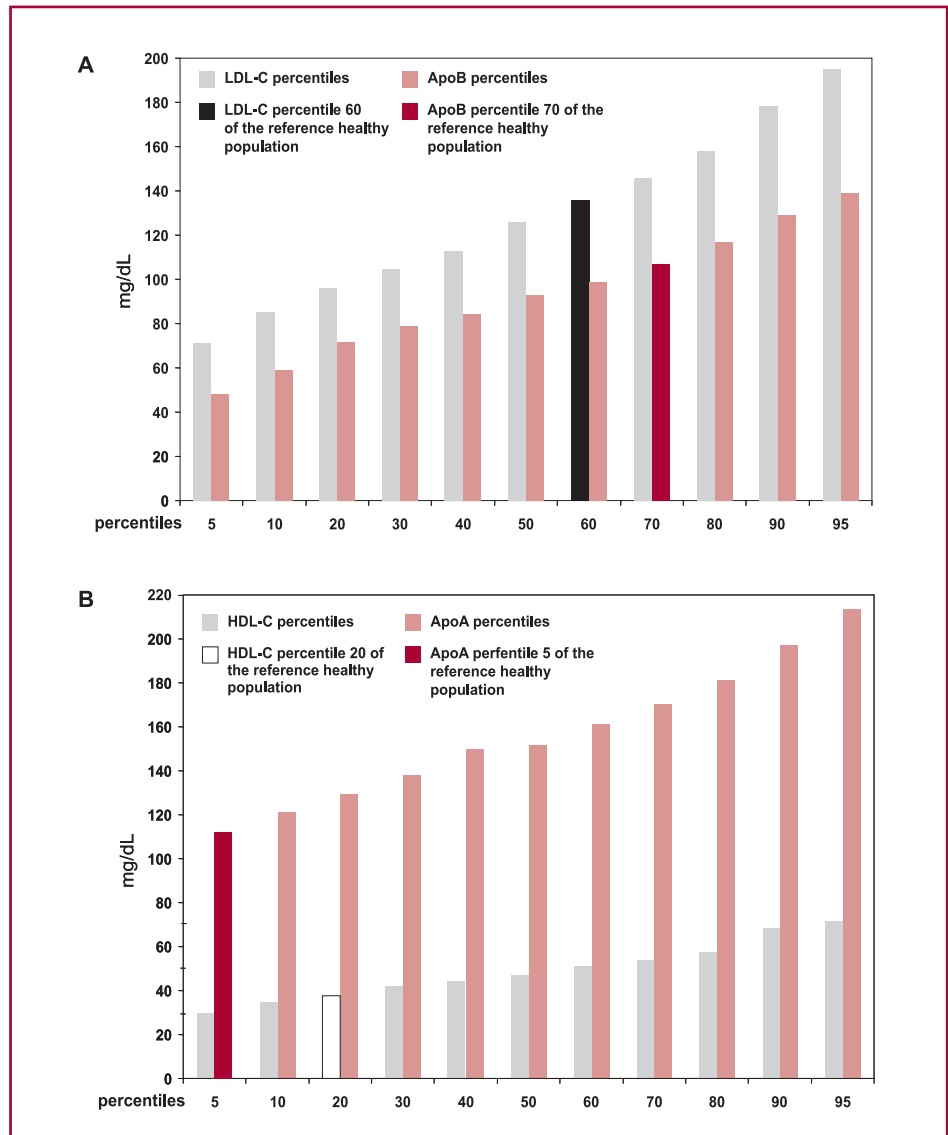
DISCUSSION

Early therapy with statins in the setting of an ACS produces short-term clinical benefits by reducing the incidence of coronary events and total mortality. (13, 14) Patients with ACS are at very high risk of cardiovascular events and require very low targets levels of LDL-C and ApoB. (15, 16) Several meta-analyses and sub-analyses have demonstrated the clinical benefits of lowering LDL-C under 70 mg/dl and TG under 150 mg/dl. (17, 18) However, multivariate analyses have shown that the statistical significance of TG levels is lost after adjusting for ApoB levels. (19, 20) The relationship between cholesterol reverse transport and ApoA plasma levels has prognostic and therapeutic interest in patients with ACS. (21, 22)

The use of statins during hospitalization increases the adherence to treatment at the mid- and long-terms, a therapeutic decision that has strong influence when the basal values of the lipid profile are known. (23-26)

Patients hospitalized due to ACS usually do not have a history of cardiovascular events; for this reason, they may have information regarding their habitual lipid profile. Knowing the lipid profile of patients admitted with an ACS might allow an early classification of an eventual dyslipemia and select the type and intensity of lipid-lowering therapy. The analysis of the eventual variations of these parameters within the first days of hospitalization will determine the most adequate time window to perform the first measurement of the lipid profile.

Fig. 2. A. Comparison between the increasing percentiles of LDL-C with those of ApoB in a sample of healthy subjects. The mean level of LDL-C in patients with ACS corresponds to the percentile 60 of the healthy population (black column), while the mean level of ApoB corresponds to the percentile 70 (red column). This difference suggests that patients with ACS have smaller atherogenic particles. **B.** Comparison between the increasing percentiles of LDL-C with those of ApoA in the same population. The mean level of LDL-C in patients with ACS corresponds to the percentile 20 of the healthy population (light grey column), while the mean level of ApoA corresponds to the percentile 5 (light pink column). These findings suggest a marked abnormality in reverse cholesterol transport.



The clinical usefulness of measuring the lipid profile within 24 hours after hospitalization due to ACS as recommended by the guidelines is controversial, as lipoproteins and apolipoproteins vary during the first hours. Our results are coincidental with the initial reports on this issue and, more recently, with the results of the studies conducted in Israel and in Italy (the LATIN trial) that showed early changes in the levels of TC and LDL-C. (4, 7) For example, the latter demonstrated a 7% and 10% reduction in TC and LDL-C levels, respectively, in patients with AMI, from the moment of hospitalization to the following morning (median 10 h), and a 5% and 6% reduction in those admitted due to unstable angina. However, the LUNAR trial reported that the differences observed in the lipid parameters in the first days of hospitalization did not seem to be clinically meaningful, suggesting that the determination of the lipid profile might be delayed until

day 4. (9, 10) In the LUNAR trial, the first determination was performed 26 h after symptoms onset.

In our study the first blood sample was obtained very early and apolipoproteins B and A1 very also determined together with the lipid profile. The level of LDL-C was determined by direct measuring. The greatest reduction in TC levels occurred between admission and 18 h, and the greatest variation in LDL-C between 18 and 42 h. In this setting, the results of the LUNAR trial are consistent with ours, considering that our second determination was performed earlier than the first measurement of the LUNAR trial. The study analyzed the effect of the time interval between the onset of symptoms and the first blood sample on LDL-C levels. The results of this study were similar to ours in the 69 patients in whom the first blood sample was taken between 0 and 12 h, with a 4.4% reduction in LDL-C.

We found very little differences in the level of ApoB during the first days of hospitalization. The significant reduction in TC, LDL-C and non-HDL-C levels with minimal changes in ApoB suggests that the number of atherogenic particles remain stable but with reduction in particle size. These results might be due to changes in cholesterol metabolism and liver regulation induced by the acute phase response. (27)

ApoA levels showed an early decrease that was greater than that of HDL-C. The reduction in ApoA levels during ACS are supported by basic research studies. A displacement of ApoA from HDL-C secondary to complex inflammatory mechanisms occurs. This phenomenon might produce changes in the structure and function of HDL-C during ACS. (28, 29)

The analysis of the basal lipid profile of patients admitted with ACS is also controversial. The results of the lipid levels from a large cohort of patients hospitalized with a coronary event obtained in the first 24 h have been recently published. Mean TC and LDL-C levels were markedly low: 174 and 105 mg/dl, respectively, lower than those of our healthy population. (11) In our study, patients with ACS had had higher levels of TC and LDL-C (218 and 136 mg/dl), corresponding to the percentile 60 of the healthy population. The aforementioned differences might be related to the sample size, differences in the laboratory techniques, lipid lowering treatment (21.1% of patients in the mentioned study) and/or differences in the moment of blood sampling. In our study, blood samples were obtained when the patient was admitted in the ER, and patients under therapy with lipid lowering drugs were excluded from the study. Probably, our results are more representative of the real world, and are similar to those of the Argentine FRICAS trial, which reported that 50% of patients hospitalized with AMI had TC levels > 218 mg/dl. (30)

In our study, mean levels of HDL-C and ApoA of patients with ACS corresponded to extremely low percentiles of the healthy population. There is agreement in the literature that about 50% of men and women with an ACS had HDL-C levels < 40 and < 50 mg/dl, respectively. (31).

Study Limitations

It is not possible to extrapolate the results of the basal lipid profile obtained when the patient was admitted to other populations with ACS due to the small sample size. We are currently developing other studies to increase the knowledge on this topic; the results will be informed at the proper time.

CONCLUSIONS

In this sample of patients with ACS, the levels of TC and non-HDL-C decreased during the first 18 h after admission, while the reduction of LDL-C levels (measured directly) was observed later. ApoB levels,

which represent the number of atherogenic particles, remained stable. The low concentrations of LDL-C and ApoA at admission and the downward trend of ApoA during hospitalization suggest a progressive compromise in the reverse cholesterol transport and/or HDL-C function.

Clinical implications

The moment of admission of patients with ACS is the most appropriate for the evaluation of the lipid profile and, hence, for choosing the most adequate treatment. Measuring ApoB levels would be an alternative option and would increase the time window until the second day of hospitalization. In this way, the intensity of lipid lowering therapy might be estimated. Probably, increased ApoA levels or the improvement in HDL-C function might turn out to be new therapeutic goals in a near future.

RESUMEN

Variación del perfil lipídico durante los primeros días de la internación en pacientes con síndrome coronario agudo

Introducción

Existen controversias sobre las variaciones temporales en los niveles lipídicos luego de un síndrome coronario agudo (SCA). En nuestro país, la información sobre las características del perfil lipídico basal y la variabilidad de sus componentes luego de un SCA es limitada y no incluye la medición directa de C-LDL ni de apolipoproteínas.

Objetivos

1) Analizar las variaciones en los niveles de lipoproteínas y apolipoproteínas en un grupo de pacientes internados por SCA y 2) describir el perfil lipídico basal y compararlo con el de una población saludable.

Material y métodos

Se midieron los niveles plasmáticos de colesterol total (CT), triglicéridos, C-LDL, C-HDL, ApoB y ApoA al ingreso, a las 18 h y a las 42 h en pacientes internados por SCA. Ningún paciente recibía fármacos hipolipemiantes ni fue tratado con ellos durante las primeras 48 h de la internación.

Resultados

Se incluyeron 31 pacientes (edad media 61 años, 87% hombres, IAM con onda Q 51%, IAM no Q 19% y angina inestable 30%). Las concentraciones de CT, C-noHDL y C-LDL se redujeron significativamente durante la internación (media \pm desviación estándar de la admisión, 18 h y 42 h, valor de p): CT (218 ± 53 , 206 ± 40 y 194 ± 41 ; $p = 0,005$), C-noHDL (180 ± 54 , $169,8 \pm 40$ y $157,6 \pm 39$; $p = 0,01$), C-LDL (136 ± 30 , 134 ± 33 y 127 ± 37 ; $p = 0,01$). Los niveles de ApoB y de C-HDL no variaron en forma significativa. El nivel basal de ApoA correspondió al percentil 5 de una

población saludable y se observó un descenso precoz y significativo durante la internación (115 ± 21 , 108 ± 18 y 106 ± 3 ; $p = 0,01$).

Conclusiones

La admisión es el momento más adecuado para evaluar el perfil lipídico basal del paciente con SCA. Los niveles de ApoB se mantuvieron estables y podrían utilizarse como alternativa para seleccionar la estrategia terapéutica. El transporte reverso del colesterol estaba afectado en más del 50% de la población.

Palabras clave > Apolipoproteínas - Lipoproteínas - Síndrome coronario agudo

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