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LOW DENSITY LIPROPROTEIN CHOLESTEROL GOAL LEVELS IN CARDIOVASCULAR SECONDARY PREVENTION

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ABSTRACT

The Scandinavian Simvastatin Survival Study showed that the reduction of low density lipoprotein (LDL) cholesterol levels diminished 30% all causes mortality in coronary heart disease (CHD) patients. Later trials with statins indicated a positive relationship between CHD secondary prevention and continuously lower LDL-C levels. The Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]), recommended drug treatment of CHD or CHD risk equivalents patients, with LDL-C above 130 mg/dl and optional treatment between 100 and 129 mg/dl, with a goal value < 100 mg/dl. In 2004, the same Program recommended an LDL-C goal of < 70 mg/dl when cardiovascular risk is very high. This review examines main published clinical trials (2001-2016) of statins efficacy on CV secondary prevention, specially with LDL-C levels lower than 100 mg/dl and discusses its implementation at the current medical practice.

KEYWORDS: Lipoproteins, LDL cholesterol, Coronary disease, drug therapy, Anticholesteremic Agents, Hydroxymethylglutaryl-CoA Reductase Inhibitors.

INTRODUCTION

In the secondary prevention of coronary heart disease it is important to modify major risk factors such as smoking cessation, control of hypertension and diabetes mellitus and decreased cholesterol associated with low density lipoprotein (LDL-C). Dyslipidemia is a modifiable risk factor for developing atherosclerosis and specifically ischemic heart disease risk.

The risk of developing cardiovascular disease and its relationship with plasma cholesterol levels was initially postulated and established by several epidemiological studies.[1-3] The results demonstrated that the rate of coronary heart disease was approximately constant for total cholesterol (total-C) below 200 mg / dl, doubled with values of 250 mg / dl, and quadrupled above 300mg / dl.[4] Moreover, in the clinical trial "Multiple Risk Factor Intervention Trial"[5] it was postulated that cardiovascular risk may still continue decreasing for values of total-C below 200 mg / dl, becoming 30% lower when levels reached 150 mg / dl.

From the study of the association between the different fractions of C-Total and cardiovascular risk, it was characterized the LDL-C as the best predictor factor of this risk; hence it became the main focus of treatment since then.

LIPICERES study demonstrated that at least one half of patients with coronary disease do not achieve their target lipid levels as defined in the European guidelines.[6]

EUROASPIRE IV trial showed that the large majority of coronary patients do not achieve the guidelines standards for secondary prevention related to smoking cessation, diets, physical activity or weight reduction. Conclusion of the study is that risk factor control for secondary prevention requires a preventive cardiology programme appropriately adapted to medical and cultural settings in each country and the addition of pharmacological treatment.[7]

Initial studies using lipid-lowering drugs such as fibrates and ion exchange resins, significantly reduced total-C and LDL-C levels, as well as coronary events, but without reducing mortality.[8,9] The clinical trial called "Scandinavian Simvastatin Survival Study (4S)"[10] demonstrated that simvastatin could reduced LDL-C 35% with a decrease in 30% of the total mortality rate. In the following years several studies were published showing that

different statins had efficacy for primary or secondary prevention of coronary heart disease, with increasingly lower basal plasma cholesterol values.[11-14]

Based on information available until 2001, the National Education Program Cholesterol US (NCEP)[15] recommended the use of statins for the treatment of dyslipidemia in patients with coronary disease or equivalent cardiovascular risk, when the value of LDL-C was above 130 mg /dl, trying to achieve a target LDL-C value below 100 mg / dl. According to thisguideline, LDL-C values between 100 and 129 mg / dl should be considered as optional for pharmacological treatment. Afterwards, considering new results, the same NCEP[16] recommended to reach values of 70 mg / dl LDL-C for all patients with "very high" cardiovascular risk. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines focuses on the importance of LDL-C lowering to prevent cardiovascular disease.[17] Recently Guidelines like ESC/EAS 2016 agree with this last LDL level to identify high risk persons.[18]

The objectives of this review are: 1) analyze existing evidence on the effectiveness of intensive lipid-lowering treatment with statins in secondary prevention in the presence of values of LDL-C less than 100 mg / dl and 2) assess the reasonableness of its application in routine clinical practice.

MATERIALS AND METHODS

This review has included randomized clinical trials comparing 1-statins with placebo, 2-statins vs usual care or 3-high dose vs low-dose statins in patients with coronary disease and whose initial publication is later than the recommendations NCEP-ATP III.[15] Studies that combined primary and secondary prevention were included if results for the subgroup with coronary disease were presented separately. The trials were selected if they included 1,000 or more participants, measured clinical events and had not less than 2 years of follow-up. Those studies restricted to special populations such as patients undergoing hemodialysis or kidney transplant were excluded.

The search was conducted in MEDLINE and the Cochrane controlled trials register. Two investigators independently assessed the trial eligibility according to the criteria defined for this review, resolving differences by consensus of all authors. Obtaining data from the original publications was also carried out in duplicate, resolving any differences by consensus.

In order to describe the effect of treatment on lipids, it was used the mean value of LDL-C under treatment, and, in case this was not available, the mean value of LDL-C after a year of treatment.

The results of each trial are presented first as the primary endpoint defined by the authors. To allow comparison between different studies, the variable "major coronary events" was chosen, defined as a nonfatal myocardial infarction or coronary death. From this latter variable it was calculated the number needed to treat to prevent an event.[19]

In the text the concept of standard doses of statins will be considered as the dose that produces a decrease LDL-C of 30-40%, corresponding to 10 mg / d of atorvastatin, 40 mg / d of pravastatin, 20-40 mg / d of simvastatin and 40-80 mg / d of fluvastatin.[16]

RESULTS

The literature search conducted in March 2016 showed a total of 305 citations, of which eleven studies met the inclusion criteria for this review. Three trials comparing statins with placebo combining primary and secondary coronary heart disease prevention (HPS,[20] PROSPER,[21] CORONA[22]) allowed separate analysis of the data for previous coronary patients. Another trial compared statins vs placebo after percutaneous coronary revascularization (LIPS[23]). There were two studies evaluating statins against usual care in stable coronary patients (GREACE,[24] ALLIANCE[25]). Other five compared high doses vs usual doses of statins, in stable coronary patients (TNT,[26] IDEAL[27]) and in those hospitalized for acute coronary syndrome (PROVE-IT[28] A to Z,[29] SEARCH[30]).

The results of the above trials are presented in Table 1 with the addition, as a reference, of the initial three studies that demonstrated the effectiveness of statins in secondary prevention (4S,[10] CARE[12] and LIPID[13]). Also, to facilitate comparison between different studies analyzed in Figure 1 each trial is represented by the values of LDL-C of treated patients and the corresponding rate of major coronary events observed in the experimental and control groups.

Statins vs placebo

Among the studies that compared statins with placebo the Heart Protection Study (HPS)[20] was the first to be analysed. This double-blind randomized trial aimed to evaluate the effectiveness of lipid-lowering drug therapy in patients with a wide range of values of total-

Cholesterol. The selected patients were high risk by the presence of ischemic heart disease, cerebrovascular or peripheral artery disease, diabetes mellitus, or hypertension in men over 65 years. 20,536 patients were included (men and women from 40 to 80 years old). The baseline LDL-C was 131 mg / dl. One group received simvastatin 40 mg daily and the other group, placebo. The treated patients achieved LDL-C value of 89 mg / dl while in the placebo group LDL-C was 128 mg / dl. After 5 years it was observed a statistically significant relative reduction in total mortality and the combination of coronary death and nonfatal myocardial infarction (AMI) of 13% and 27% respectively (see Table 1). Other events such as cerebrovascular accident or stroke (CVA) and need for coronary revascularization were also reduced 25 and 24% respectively. For the subgroup of patients with previous coronary heart disease there was a 24% decrease of total vascular events ($p < 0.0001$).

Laboratory studies in this work were not made in fasting status and the direct measurement of LDL-C was taken as reference. In the other analyzed studies, determinations were made in fasting state and LDL-C was calculated using the Friedewald formula [LDL-C = C-Total - (C-HDL + Triglycerides [TG] / 5)]. With this formula, intermediate density lipoproteins are computed as LDL-C, increasing by about 15% its value. Therefore, the LDL-C values referred to in this paper are not directly comparable with those of other studies. For example, a baseline LDL-C 131 mg / dl in the HPS corresponds to a value 15% higher (approximately 150 mg / dl) in the other studies.[16] Subgroup analysis of HPS study showed benefits for all values of baseline LDL-C levels even lower than 100 mg / dl, corresponding to a calculated LDL-C of 115 mg / dl following the previous reasoning.

The PROSPER[21] study is a randomized double-blind essay against placebo. It aimed to assess the benefits of drug therapy with pravastatin in elderly patients. It recruited 5804 patients of 70 to 82 years old with previous cardiovascular events or multiple risk factors such as diabetes, smoking and hypertension. The baseline LDL-C was 147 mg / dl. Patients were randomized to pravastatin 40 mg / d or placebo. The chosen primary events were death from coronary heart disease, nonfatal myocardial infarction and stroke. The study duration was 3.2 years. The values of LDL-C achieved in the experimental group were 97 mg / dl and 147 mg / dl in the control group. A significant reduction in primary events of 15% was found, at the expense of a 19% reduction in coronary death or nonfatal AMI. No differences in the development of stroke were demonstrated. If we perform subgroup analysis we can see that there is a tendency to concentrate the benefits in patients with previous cardiovascular disease

(secondary prevention) events where the reduction reaches 22%, compared to only 6% in primary prevention. No significant benefit was demonstrated with values of baseline HDL-C greater than 43 mg / dL, confirming the prognostic significance of low levels of HDL-C increased risk for cardiovascular events in the elderly.

The LIPS[23] study was a double-blind randomized study against placebo, aimed to investigate whether therapy with fluvastatin (40 mg twice daily) can prolong the survival time free of important cardiac events in patients with coronary disease treated with angioplasty. 1677 patients from 18 to 80 years old were recruited before hospital discharge after surgery. Mean follow-up was 3.9 years. The chosen primary events were cardiac death, nonfatal AMI, or the need for a revascularization procedure for symptomatic recurrence. The average level of baseline LDL-C was 131 mg / dl and was reduced by 27% after six weeks of treatment with fluvastatin, while in the control group rose 11% in the same period. There was a statistically significant reduction of 22% in the development of new events. For the secondary outcome of nonfatal coronary death or AMI, the decline in risk was 31%, without reaching statistical significance.

The CORONA study[22] included 5011 patients at least 60 years old with class II, III, or IV ischemic, systolic heart failure which were randomly assigned to receive Rosuvastatin or placebo. The primary outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The results of the study showed that there were no significant differences between the two groups in the coronary outcome or death from cardiovascular causes 11,6% vs 12,3% (p 0.12).

Statins vs usual care

GREACE[24] is a trial in which 1600 patients with established coronary heart disease were randomized to treatment with atorvastatin or "usual care." The dose of atorvastatin was titrated from 10 to 80 mg / d increasing it every 6 weeks to reach the target LDL-C less than 100 mg / dl. Patients "usual care" were followed by their family doctors who could indicate any treatment (including atorvastatin) to individual judgment.

The average follow-up was 3 years. Total and coronary mortality, nonfatal AMI, unstable angina, congestive heart failure, revascularization and stroke were the seven primary variables chosen.

The mean dose of atorvastatin required to reach the target LDL-C was 24 mg / d. In 4% of patients that goal was achieved with 10 mg / d, in 82% with 20 mg / d, 11% of the patients required 40 mg / d and only 3% needed the maximum dose of 80 mg / d.

Total-C decreased by 36%, LDL-C by 46% and TG by 31%, HDL-C increased by 7%. 95% of patients in the atorvastatin group had LDL-C <100 mg / dl. In the group of "usual care" only 14% received lipid-lowering drugs throughout the duration of the study and only 3% reached the target LDL-C <100 mg / dl. Total mortality was reduced 43% in the atorvastatin group, and the variable of a new coronary event or death was reduced in 54%, both of these values were statistical significant.

The ALLIANCE[25] study was an open randomized trial aimed at evaluating an aggressive lipid-lowering therapy compared with usual treatment in patients with stable ischemic heart disease. 2442 patients over 18 years old with a history of myocardial infarction, unstable angina or coronary revascularization were enrolled in the protocol. Baseline LDL-C was 147 mg / dl. Atorvastatin was used with an initial dose of 10 mg / d, doubled every 4 weeks to obtain a LDL-C lower than 80 mg / dl or reach the maximum dose of 80 mg / in the group of patients with intensive treatment. The usual care group was kept in a lipid-lowering treatment program at the discretion of their physicians. The chosen primary events were cardiac death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization or unstable angina. Intensive treatment patients achieved a reduction of LDL-C of 34% and reached a final value of 95 mg / dl. The usual care group achieved a 23% reduction, reaching a mean LDL-C value of 111 mg / dl. Reducing primary events obtained with intensive treatment was 17% and coronary death and nonfatal MI 43%, both statistically significant results. However, there were no significant differences in total mortality variable.

High doses of statins vs low-dose statins

PROVE IT study[28] aimed to compare a strategy of intensive drug treatment with a less intensive one in patients with acute coronary syndrome. 4162 patients were selected within 10 days of hospitalization for the initial event. They were randomized on a 1: 1 ratio to receive atorvastatin 80 mg / day vs. pravastatin 40 mg / day. The primary selected events were death from any cause, nonfatal MI, unstable angina, coronary revascularization or stroke. Mean baseline LDL-C was 106 mg / dl, it was reduced to 95 mg / dl in the pravastatin group and 62 mg / dl in the atorvastatin group. After 24 months the reduction of new events in the atorvastatin group was 16% (statistically significant value); the secondary endpoint of

nonfatal MI and coronary death had a reduction of 16% without statistical significance; overall mortality did not vary. The benefit was greater among patients with baseline LDL-C of at least 125 mg / dl, a pre-specified subgroup with reduced events of 34%, compared to a 7% reduction in patients with LDL-C basal less than 125 mg / dl (p 0.02).[28]

Another study aimed to compare two strategies of lipid lowering drug therapy in patients with acute coronary syndrome was the A to Z.[29] The study included patients from 21 to 80 years old, with a baseline C- total colesterol less than 250 mg / dl. 4497 patients were randomized to simvastatin 40 mg / day for a month and then 80 mg / day (experimental group) or placebo for 4 months followed by simvastatin 20 mg / day (control group). The study duration was 2.1 years. In the experimental group baseline LDL-C was reduced from 111 mg / dl to 67 mg / dl with the dose of 40 mg / day and another 6% with the 80 mg / day dose, reaching 62 mg / dl. In the control group LDL-C increased from 111 to 124 mg / dl the first 4 months and then dropped to 77 mg / dl. The primary events were cardiovascular death, MI, readmission or stroke in coronary unit. The results showed a tendency to reduce new cardiovascular events by 11%, which was not statistically significant. No differences in cardiovascular mortality or nonfatal myocardial infarction were demonstrated. The explanations proposed by the authors for this result included: 1) fewer than estimated primary events; 2) a high rate of drug discontinuation (33%); 3) an average difference in LDL-C of both groups of only 14 mg / dl between 4 and 24 months of follow up; 4) enlistment early after acute ischemic event, which could have moved to this secondary prevention trial part of the initial episode morbidity and mortality; and 5) lack of anti-inflammatory effects in the experimental group due to the lower dose of simvastatin used in the first month of treatment.

TNT study[26] aimed to compare a strategy of intensive drug treatment and other less intensive in patients with stable ischemic heart disease. To this end they selected a group of patients with stable angina and LDL-C values less than 130 mg / dl. This double-blind study included 10,001 patients and lasted 4.9 years. It compared atorvastatin 10 mg / d (control group) and atorvastatin 80 mg/d (experimental group). The mean value of LDL-C under treatment was 101 mg / dl in the control group and 77 mg / dl in the experimental group. The primary combined endpoint of fatal and non-fatal heart attack, stroke, cardiac arrest and death from ischemic heart disease showed an statistically significant reduction of 22%. Cardiovascular mortality was reduced by 20% and non-cardiovascular up to 25%, both without statistical significance. Overall mortality did not vary.

The IDEAL[27] was a randomized, open-label study, which included a group of 8888 patients of 40 to 80 years old. The study compared 80 mg / d of atorvastatin (experimental group) with 20 mg / d of simvastatin, which increased to 40 mg / d if the total-C was above 190 mg / dl at 24 week (control group). The primary combined endpoint was coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation. The study duration was 4.8 years. The group treated with simvastatin reached LDL-C of 104 mg / dl and atorvastatin group LDL-C of 81 mg / dl. The primary event showed a non statistically significant reduction of 11%. No variation in mortality from coronary origin was detected. A risk reduction of 17% of AMI and 13% of stroke events was obtained.

The SEARCH study[30] included 12,064 myocardial infarction survivors who were randomized to simvastatin 80 mg versus 20 mg daily groups. After 6.7 years of median follow-up, major vascular events occurred in 24·5% of participants allocated 80 mg simvastatin versus 25·7% of those allocated 20 mg, corresponding to a non-statistically significant 6% proportional reduction.

In J-Stars trial,[42] patients were treated with pravastatin 10 mg vs placebo. Initial LDL-C of the patients treated, was reduced in average in 21 mg/dl. However, the primary endpoint (stroke) did not demonstrate differences between both group and differs from the CV risk considered in the other Clinical Trials included in this work.

Although Leibowitz et al.,[44] published an observational cohort study (not an experimental trial); because it is a huge population work that included several thousands patients in order to demonstrate LDL level obtained with statin treatment; we decided to mentioned in this paper. The conclusion of this work is that patients taking statins that reached LDL-C levels of 70 to 100 mg/dL had lower risk of CV adverse outcomes compared with those with LDL-C levels between 100 and 130 mg/dL. However, patients that reached LDL-C of 70 mg/dL have not additional benefit.[44]

Table 1: Results of Clinical Trial using Statins in Secondary Prevention.

	Study	Pacients			Duration (years)	Treatments (mg/d)	Cholesterol LDL (mg/dl)			Primary Endpoint		Coronary death o Non fatal coronary event	
		Sex Age	Clinical condition	N			Basal	Experimental Group	Control Group	Components	RR (IC 95%) p	RR (IC 95%) p	NNT
Statin vs placebo	SSSS[10] (1994)	MF 35-70	AMI or angina	4444	5,4	EG: Simvastatin 10 a 40 CG: Placebo	190	125	192	Overall Mortality	0,70 (0,58-0,85) p=0,0003	0,66 (0,59-0,75) p=0,00001	11 (9-15)
	CARE[12] (1996)	MF 21-75	AMI	4159	5	EG: Pravastatin 40 CG: Placebo	139	97	135	Dead related to Cardiac Disease + non fatal infarct	0,76 (0,64-0,91) p=0,003	0,76 (0,64-0,91) p=0,003	33 (20-95)
	LIPID[13] (1998)	MF 31-75	AMI or UA	9014	6,1	EG: Pravastatin 40 CG: Placebo	150	108	150	Dead related to Cardiac Disease	0,76 (0,65-0,88) p<0,001	0,76 (0,68-0,85) p<0,001	28 (20-48)
	HPS[20] (2002)	MF 40-80	CE or St or DBT o (M>65 + HTA)	20536 †	5	EG: Simvastatin 40 CG: Placebo	131	89	128	Overall Mortality	0,87 (0,81-0,94) p=0,0003	0,73 (0,67-0,79) p<0,0001	33 (26-45)

	PROSPER[21] (2002)	MF 70-82	CE o St or DBT or HTA or TBQ	5804‡	3,2	EG: Pravastatin 40 CG: Placebo	147	97	147	Dead related to Cardiac Disease + non fatal infarct + Stroke	0,85 (0,74-0,97) p=0,014	0,81 (0,69-0,94) p=0,006	47 (27-199)
	LIPS[23] (2002)	MF 18-80	Post-percutaneous revacularizatio n	1677	3,9	EG: Fluvastatin 80 CG: Placebo	131	96	143	Dead related to Cardiac Disease + non fatal infarct + Revascul arization			
	CORONA[22] (2007)	MF > 60	Previous AMI or HF	5011	2,7	EG: Rosuvastatin 10 CG: Placebo	137	76	138	Dead related to Cardiac Disease + non fatal infarct + Revascul arization	0,78 (0,64-0,95) p=0,01	0,69 (0,46-1,02) p=0,07	□
	J-STARS (2017)	MF >45-80	Previous AMI	1578	4,9	EG: Pravastatin 10 CG: Placebo		-21		Stroke transient + ischemic attack (TIA)	0.97 (0.73–1.29) p=0,08		□

Statin vs usual care	GREACE [24] (2002)	MF < 75	Previous AMI or stenosis > 70% of at least 1 vessel	1600	3	EG: Atorvastatin 10 a 80 (up to LDL-C < 100 mg/dl) CG: usual care	180	97	169	Overall Mortality	0,57 (0,39-0,78) p=0,0021	0,46§ (0,32-0,66) p>0,0001	17 (11-30)
	ALLIANCE[25] (2004)	MF >18	AMI or UAI	2442	4,2	EG: Atorvastatin 10 a 80 (up to LDL-C-< 80 mg/dl) CG: usual care	147	95	111	Dead related to Cardiac Disease + non fatal infarct + Stroke+ + Revascularizatión	0,83 (0,71-0,97) p=0,02	0,57 (0,44-0,75) p=0.0001	21 (14-41)
Statin (two diffe rent doses) dosis usual	PROVE-IT[28] (2004)	MF >18	AMI or UA in the previous 10 days	4162	2	EG: Atorvastatin 80 CG: Pravastatin 40	106	62	95	Dead related to Cardiac Disease + non fatal infarct + Stroke+ Overall Mortality	0,84 (0,74-0,95) p=0,005	0,84♦ (0,68-1,03) NS	□

	A to Z[29] (2004)	MF 21-80	AMI or UA in the previous 5 days	4497	2,1	EG: Simvastatin 40 x 1 mes, luego Simvastatin 80 CG: Placebo x 4 meses, luego Simvastatin 20	111	63*	77*	Dead related to Cardiac Disease + Stroke	0,89 (0,76-1,04) p=0,14	0,96 # (0,77-1,21) p=0,74	
	TNT[26] (2005)	MF 35-75	Stable cardiac event	10001	4,9	EG: Atorvastatin 80 CG: Atorvastatin 10	98	77	101	Dead related to Cardiac Disease + non fatal infarct + Stroke+ Cardiac arrest	0,78 (0,69-0,89) p<0,001	0,80♣ (0,69-0,92) p=0,002	60 (37-159)
	IDEAL[27] (2005)	MF ≤80	Previous AMI	8888	4,8	EG: Atorvastatin 80 CG: Simvastatin 20-40	121	81	104	Dead related to Cardiac Disease + non fatal infarct + Cardiac arrest	0,89 (0,78-1,01) p=0,07	0,89♣♣ (0,78-1,01) p=0,07	

	SEARCH [30] (2010)	MF >18-80	Previous AMI	12064	4,5	EG: Simvastatin 80 CG: Simvastatin 20	98	78	97	Dead related to Cardiac Disease + non fatal infarct + Cardiac arrest	0,94 (0,88-1,01) p=0,01	0,96 (0,89-1,04) p=0,04	□

M = males; F = females ; EG = experimental group; CG = control group; AMI = accute micardial infarct; IA = unstable angina; CD = coronary disease; HF= Heart Failure; St = Stroke; PA = peripheral arteriopathy; DBT = diabetes mellitus HTA = arterial hypertension; TBQ = tabaquism ; CE = Cardiac Event

† From 20.536 pacients, 13.386 had previous coronary disease.

‡ From 5.804 pacients, 2.565 had previous coronary disease.

& Values of LDL-C at 1 year of follow up, extracted from Fig 4 of the original paper.

□ The value of the NNT- number of patients needed to treat- was not calculated since the reduction of the risk it was not significant

§ Calculated from original data

♦ Values extracted from Fig 4 of the original paper. P value was not informed.

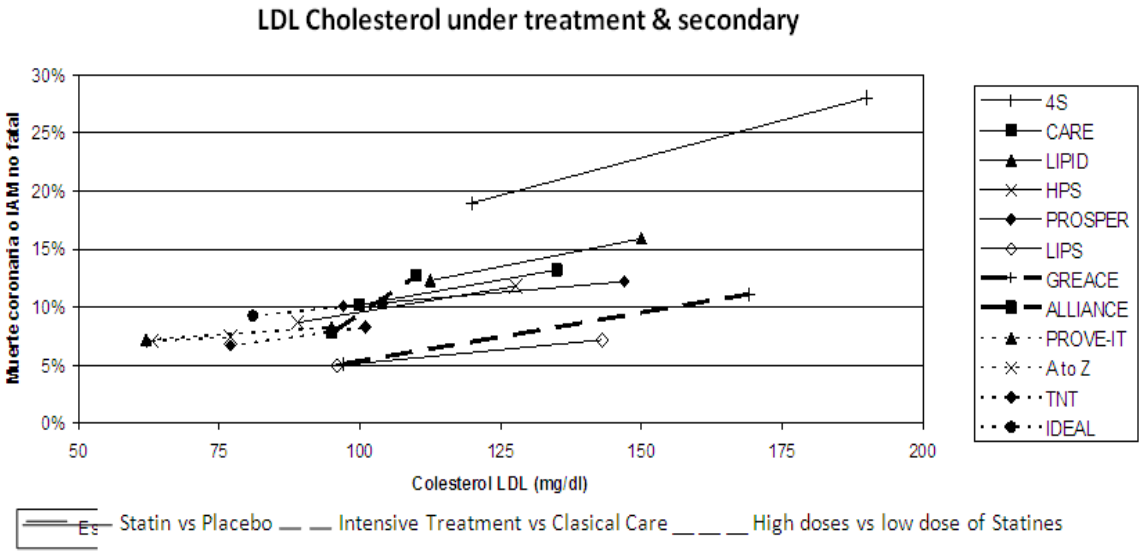
* Values of LDL-C at 8 months of follow up.

AMI fatal + AMI no fatal events.

♣ Includes resurrected heart attack which represents 6,7% of all events.

♣♣ Includes resurrected heart attack

Figure 1.



DISCUSSION

In this paper we summarized the results of major clinical trials with statins in patients with coronary disease, including the papers just considered and adding as reference the three initial studies: 4S, CARE and LIPID, as seen in table 1 and Figure 1.

Studies comparing statins with placebo obtained a difference in LDL-C between the experimental and control groups of 38 to 63 mg / dl; the primary outcome showed a significant reduction in all of them. Major coronary events also decreased significantly, with the exception of the LIPS study. The NNT increases as the baseline LDL-C lowers, from a value of 11 in the 4S (baseline LDL-C 190 mg / dl) to a range of 25 to 33 for others (LDL-C baseline: 131 -150).

Studies comparing intensive care vs usual care - GREACE and Alliance - are distinguished by the magnitude of the observed benefit, being the only ones to achieve a reduction in major coronary events above 40% (see Table 1), outweighing the effect observed in statin trials against placebo. As they are open-label studies, it can be assumed that differences in the care received by patients in the "intensive group" and those of "usual care" would not be limited to the use of lipid-lowering drugs, but that other measures contribute to this result. Figure 1 lets see how in the ALLIANCE trial a difference of only 16 mg / dl in LDL-C in treatment is associated with a 43% reduction of major coronary events, which is reflected in a steep slope that contrasts with the rest of the evidence presented. For this reason we believe that, although the results of these two studies confirms the value of statins in coronary patients,

they do not contribute to the precise definition of benefits at different levels of LDL-C at baseline and subsequent discussion of the goals to be achieved.

The four studies comparing high dose vs usual-dose statins are the focus of the discussion, since the proposal to lower the target LDL-C below 70 mg / dl is based in them. In these studies baseline LDL-C is in the range of 98-121 mg / dl and LDL-C difference obtained with treatment is also lower, between 14 and 33 mg / dl. In contrast with the findings in studies versus placebo, here a statistically significant difference for the primary endpoint was observed in only 2 of the 5 trials (PROVE-IT and TNT) and, for major coronary events, only in TNT, requiring the treatment of 60 patients for 4.9 years to prevent one event.

Figure 1 corroborates the same data: the large decrease in LDL-C and the event rate in the placebo study contrasts with the reduction of the benefit as the LDL-C of control group is lowered. It is important to note that five studies (LIPS, PROVE-IT, A to Z, IDEAL, SEARCH) fail to obtain significant differences for the variable coronary death or nonfatal MI, resulting in the gentle slope of the respective lines.

Subgroup analyzes according to baseline LDL-C

When applying the results of research into clinical practice we want to know how to respond to treatment subjects whose characteristics are similar to those of our current patient. In all studies evaluated baseline cholesterol have a wide dispersion around the average value reported, so it is relevant to find out how subjects with different levels of LDL-C baseline behave.

The HPS study showed that 40 mg / day of simvastatin are more effective than placebo even in patients whose baseline LDL-C, measured directly, was less than 100 mg / dl, value corresponding to about 115 mg / dl with the calculation method used in the other studies.

Of the studies comparing maximum vs usual statin dose and showing significant benefit in the primary endpoint, only the PROVE-IT reports results according to the baseline LDL-C: the relative reduction in events was 34% with baseline C LDL- greater than 125 mg / dl but only 7% if the baseline LDL-C was less than 125 mg / dl. Moreover, in a subsequent letter to the editor the authors provide the results for the subgroup with baseline LDL-C less than 100 mg / dl, in whom the relative decline of the main variable is only 3%.[31] That is, the benefits of using high doses of statins instead of low doses are negligible when baseline LDL-C is less than 100 mg / dl.

As for the TNT study, the original publication does not describe the event rate based on the value of baseline LDL-C. That information was requested in the letters to the editor commenting on the trial,[32] but the authors have not responded to such concerns.

With the available information we can conclude:
When comparing high and low doses of statins, the benefit decreases with baseline LDL-C less than 125 mg / dL and is almost null below 70 or 100 mg / dll.[44]

Side effects of high doses of statins

The systematic use of maximum doses of statins raises the problem of dose-dependent adverse effects. While these studies are not designed to detect benefits in total mortality, sometimes the decline in deaths from cardiovascular disease has been offset by an increase in non-cardiovascular deaths, as noted in the study TNT.[26] Although these results can due to chance, they raise concern in light of the significant increase in cancer deaths in the PROSPER study.[21]

As for liver toxicity, in TNT study[26] the rate of elevated liver enzymes was 6 times higher with 80 mg / d of atorvastatin than with 10 mg / d of the same drug (1.2% vs 0.2%); in the PROVE-IT[28] was 3 times more frequent with 80 mg / d of atorvastatin than with 40 mg / d of pravastatin (3.3% vs 1.1%). In the IDEAL[27] study, was 8 to 10 times more frequent with 80 mg / d of atorvastatin thant with 20 mg / d of simvastatin (0.97% vs. 0.11%) and in the A to Z[29] study, this side effect was 2 times higher with high doses than with low doses of simvastatin (0.9% vs 0.4%). A recent meta-analysis found a relative risk of elevated transaminases of 3.10 (95% CI 1.72 to 5.58) for high vs low statin dose with absolute risk of 1.5% vs 0.4 %[33]

Dose of 80 mg / d of simvastatin used in the study A to Z[29] increased 9 times the rate of myopathy, with 3 cases of rhabdomyolysis. This incidence of 0.4% is compatible with the 0.6% found in a meta-analysis of muscle adverse effects of this dose drug.[34] On the other hand, no significant increase in muscle adverse effects in studies using doses of 80 mg / d of atorvastatin was found. [26 -28]

If we use statin in general population, we should expect a higher incidence of adverse effects in relation to those found in clinical trials since patients from these studies have been

specially selected with exclusion of other comorbidities and concomitant treatments, hence the risk it is expected to increase when drugs are use in the general community.[35]

Costs

In the GREACE study, targeting LDL-C to less than 100 mg / dl requires a mean dose of atorvastatin of 24 mg / d and only 3% required the maximum dose of 80 mg / d.[24] In contrast, to achieve the C-LDL goal of less than 80 mg / dl in the ALLIANCE study a median dose of 40.5 mg / d of atorvastatin was needed and 45% of patients used the maximum dose. [25] Therefore, the target LDL-C chosen also determines the statin dose to be used and the corresponding increase in costs.

The problem is accentuated by the systematic use of maximum doses vs usual doses of statins, where the benefits are questionable and, therefore, the cost-effectiveness less favorable, compromising the continuity of treatment.

Furthermore, since the effectiveness of standard dose of different statins analyzed in this paper is similar, final seleccción drug depend on the local cost of the dose equivalents. [36]

LDL-C goals in secondary prevention

The ATP III proposed a target LDL-C less than 100 mg / dl in secondary prevention and drug use if it exceeded 130 mg / dl, leaving optional medication for values between 100 and 129 mg / dl. [15] An update of this guideline proposed medication to all exceeding 100 mg / dl and considered a new target LDL-C below 70 mg / dl for patients with high cardiovascular risk, described as prior vascular disease plus other risk factors.[16]

In the following years, many opinions have been published for and against this proposal. [35,37-41] A review concluded that for patients with baseline LDL-C less than 130 mg / dl there was no high-quality degree clinical evidence to suggest that of LDL-C response to statins independently predict the degree of cardiovascular risk reduction.[41]

As the HPS shows the benefit of statin use even with baseline LDL-C of 100 mg / dl or less, it is concluded that all patients with coronary disease should be treated with at least a standard dose of statins.[20]

However, the use of a high fixed dose of statin has not consistently shown significant additional benefit over the standard dose. In tthree of the five trials exploring this point[27,29,30]

there were no significant changes in the primary endpoint. In PROVE-IT, the benefit analysis according to baseline LDL-C showed that is practically zero with values less than 100 mg / dl.[28,31,38-42] As already noted, there is no detailed information as LDL-C baseline in the study TNT.[32]

In addition, it should be noted that both the PROVE-IT and TNT average LDL-C values in the control group were close to 100 mg / dl, indicating that about 50% of these coronary patients were not meeting ATP III target LDL-C less than 100 mg / dl; then from these data cannot be concluded that this goal should be changed, but rather that must be achieved in all patients.

Although there is considerable individual variability in the LDL-C response to dietary and drug treatments, the use of LDL-C levels goals still can aid doctor's job in terms of secondary coronary disease risk reduction. It is judged likely that a goal approach may facilitate adherence to treatment. For all these reasons many groups like the European Task Force retains a goal approach to lipid management and treatment goals are defined, tailored to the cardiovascular risk level. Anyhow, it is well evidenced that lowering LDL-C beyond the goals is associated with less secondary cardiovascular risk. Therefore, it seems appropriate to reduce LDL-C as low as possible, at least in patients at very high CV risk.

In Summary

• All patients in secondary prevention of cardiovascular events should receive at least a standard dose of statin, irrespective of C-LDL levels.

• The systematic use of maximum doses of statins is not recommended, nor an increase in the dose after reaching LDL-C goal of less than 100 mg / dl.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest with respect to any of the specific issues addressed in this work.

REFERENCES

1. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. Predicting coronary heart disease in middle aged and older persons. The Framingham study. JAMA, 1977; 238: 497-499.
2. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. J Chron Dis, 1978; 31: 201-306.
3. Goldbourt U, Holtzman E, Neufeld HN. Total and high density lipoprotein cholesterol in the serum and risk of mortality: evidence of a threshold effect. Br Med J, 1985; 290: 1239-1243.
4. Grundy SM, Greenland P, Herd A, Huebsch JA, Jones RJ, Mitchell JH, et al. Cardiovascular and risk factor evaluation of healthy American adults. Circulation, 1987; 75: 1340A-1362A.
5. Neaton JD, Kuller LH, Wentworth D, Borhani NO. Total and cardiovascular mortality in relation to cigarette smoking, serum cholesterol concentration, and diastolic blood pressure among black and white males followed up for five years (MRFIT). Am Heart J, 1984; 108: 759-769.
6. Gómez-Barrado, JJ; Ortiz C; Gómez Turégano M; Gómez Turégano P; Garcipérez de Vargas FJ; Sánchez Calderón P. Lipid control in patients with coronary artery disease in a healthcare area in Cáceres (Spain): LIPICERES study. Clin Investig Arterioscler, 2017; 29(1): 13-19.
7. Kotseva K et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. European Journal of Preventive Cardiology, 2015; 23(6): 636 – 648.
8. Lipid Research Clinics Program. The Lipid Research Clinics coronary primary prevention trial results. JAMA 1984; 251: 351-364.
9. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med, 1987; 317: 1237-1245.
10. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet, 1994; 344: 1383-1389.
11. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med, 1995; 333: 1301-1307.

12. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med, 1996; 335: 1001-1009.
13. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med, 1998; 339: 1349-1357.
14. Downs JR, Clearfield M, Wels S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol level. Results of AFCAPS/TexCAPS. JAMA, 1998; 279: 1615-1622.
15. Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Programa (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA, 2001; 285: 2486-2497.
16. Grundy SM, Cleeman JI, Merz NB, Brewer HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation, 2004; 110: 227-239.
17. Nishimura RA. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017; 135(17): 1-59. https://doi.org/10.1161/CIR.0000000000000503
18. Catapano AL et al. European Association for Cardiovascular Prevention and European Atherosclerosis Society Guidelines about dislipemia treatment. Rev Esp Cardiol, 2017; 70(2): 115.e1-e64.
19. Sackett DL, Richardson WS, Haynes RB, et al. Evidence-based medicine: how to practice and teach EBM. London: Churchill-Livingstone, 1996.
20. MRC/BHF Heart Protection Study of cholesterol lowering with Simvastatin in 20536 high risk individuals: a ramdomized placebo controlled trial Lancet, 2002; 360: 7-22.
21. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet, 2002; 360: 1623-1630.
22. Kjekshus J et al. Rosuvastatin in older patients with systolic heart failure. CORONA Trial. N Engl J Med, 2007; 357(22): 2248-61.

23. Serruys PWJC, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention. JAMA, 2002; 287: 3215-3222.
24. Athyros VG, Mercouris BR, Symeonidis AM, et al. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) Study. Current Medical Research and Opinion, 2002; 18: 220-228.
25. Koren MJ, Hunninghake DB, on behalf of the ALLIANCE Investigators. Clinical outcomes in managed care patients with coronary heart disease treated aggressively in lipid lowering diseases management clinics. Journal of the American College of Cardiology, 2004; 44: 1772-1779.
26. LaRosa J, Grundy SM, Waters D, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med, 2005; 352: 1425-1435.
27. Pedersen TB, Faergeman O, Kastelein JJP, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction. JAMA, 2005; 294: 2437-2445.
28. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med, 2004; 350: 1495-1504.
29. Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes. JAMA, 2004; 292: 1307-1316.
30. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. Lancet, 2010; 376(9753): 1658-1669. doi:10.1016/S0140-6736(10)60310-8.
31. Cannon CP, Braunwald E. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med, 2004; 351: 716-717.
32. Southern E. Intensive lipid lowering with atorvastatin in coronary disease. N Engl J Med, 2005; 353: 93-96.
33. Argo, C. K., Loria, P., Caldwell, S. H. and Lonardo, A. Statins in liver disease: A molehill, an iceberg, or neither? Hepatology, 2008; 48: 662–669. doi:10.1002/hep.22402
34. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA, 2003; 289: 1681-1690.

35. Nissen SE. High-dose statins in acute coronary syndromes. Not just lipid levels. JAMA, 2004; 292: 1365-1367.
36. Ong HT. Evidence-based prescribing of statins: a developing world perspective. PloS Medicine, 2006; 3(3): e50.
37. Topol EJ. Intensive statin therapy – A sea change in cardiovascular prevention. N Engl J Med, 2004; 350: 1562-1564.
38. Cannon CP. The IDEAL cholesterol: lower is better. JAMA, 2005; 294: 2492-2494.
39. Pitt B. Low-density lipoprotein cholesterol in patients with stable coronary heart disease: Is it time to shift our goals? N Engl J Med, 2005; 352: 1483-1484.
40. Ravnskov U, Rosch PJ, Sutter MC, Houston MC. Should we lower cholesterol as much as possible? BMJ, 2006; 332: 1330-1332.
41. Hayward RA, Hofer TP, Vijan S. Narrative review: Lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. Ann Intern Med, 2006; 145: 520-530.
42. Dale KM, White MC, Henyan NN, Kluger J, Coleman CI. Impact of statin dosing intensity on transaminase and creatine kinase. Am J Med, 2007; 120: 706-712.
43. Hosomi N, Nagai Y, Kohriyama T, Ohtsuki T, Aoki S, Nezu T, et al. The Japan Statin Treatment Against Recurrent Stroke (J-STARS): A Multicenter, Randomized, Open-label, Parallel-group Study. EBioMedicine. 6 de agosto de, 2015; 2(9): 1071-8.
44. Leibowitz M, Karpati T, Cohen-Stravi CJ et al. Association Between Achieved Low-Density Lipoprotein Levels and Major Adverse Cardiac Events in Patients With Stable Ischemic Heart Disease Taking Statin Treatment. JAMA Intern Med, 2016; 176(8): 1105-1113.