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Secondary prevention of cardiovascular disease with statins. How far should we go?

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OBJECTIVES

To review the efficacy of statins in secondary cardiovascular prevention. An analysis is made of the evidence to justify the use of intensive therapy with statins, greatly advocated in the last few years, to attain lower low-density lipid cholesterol (LDL-c) levels (<70 mg/dL or 1.8 mmol/L). This review also addresses the question whether there exists a LDL-c level below which no cardiovascular benefit is obtained. In addition, we also review the role of cholesterol in cardiovascular disease and the efficacy of statins in secondary prevention of stroke.

MATERIAL AND METHODS

A bibliographical search of randomised clinical trials available in Medline (1966-February 2008) and UpToDate involving patients with cardiovascular disease was carried out.

CONCLUSIONS

The use of statins has shown a reduction in cardiovascular morbidity and mortality in patients with coronary and atherosclerotic disease for different levels of cholesterol. Intensive treatment with high dose statins to obtain low levels of LDL-c (70-80 mg/dL or 1.8-2.0 mmol/L) in patients with stable coronary disease has shown only scarce benefits in selected patients and in composite endpoints with dubious justification. These benefits are small and there is no improvement in survival of patients with coronary disease. Intensive therapy notably increases the risk of side effects and sets objectives for LDL-c levels that demand in many occasions intolerable doses for patients.

Recent recommendations for LDL-c levels <100 mg/dL (<2.6 mmol/L) or <70 mg/dL (<1.8 mmol/L) are extrapolations from studies and epidemiological data, and are not derived from the results of well designed clinical trials. Besides LDL-c, other lipid fractions should be taken into account, such as HDL-c, before initiating intensive treatment.

Though cholesterol is not a risk factor for stroke there is, however, a group of patients that benefit from statins. Nevertheless, statins should not be systematically recommended in all patients who have suffered from stroke.

Introduction

As seen in a previous edition of the BIT[1] on primary prevention of cardiovascular disease, only a small number of non-elderly men with high cholesterol levels benefited from treatment with statins. Selection of these patients should be carried out using cardiovascular risk prediction charts, and we recommend the REGICOR (already validated for the Spanish population)[2] rather than others like the SCORE. In any case, it is preferable to use any of the two charts than not to use any at all to calculate cardiovascular risk.

Cardiovascular secondary prevention refers to those steps taken to avoid a new cardiovascular event in patients who already have suffered from one. Secondary prevention is also considered in patients, who though not having suffered any cardiovascular event, have known atherosclerotic disease and a high cardiovascular risk. As we shall see, in secondary prevention statins have shown a reduction in the number of cardiovascular events and in overall mortality. This article aims to respond to, amongst others, the following questions:

· How effective is the treatment for secondary prevention in different patients (coronary disease, stroke, heart failure) or populations (women, elderly, etc.)?

· From a rational point of view, up to what levels should cholesterol be reduced to be beneficial and recommendable in patients with previous vascular disease (mainly coronary)? What doses of statins should be employed? Is intensive treatment with statins justified to attain low density lipid cholesterol (LDL-c) levels of <70 mg/dL (<1.8 mmol/L)?

· Are statins useful to prevent cerebrovascluar disease?

The majority of coronary patients should be treated with statins at standard doses

· What management approach using statins should be taken in patients with coronary disease?

· What recent information is available on the safety of statins?

Benefits of statins in coronary disease

There are three main studies that have analysed the effect of statins on outpatients with coronary disease [myocardial infarction or unstable angina] against placebo in secondary prevention. These studies confirmed a clear body of evidence, in the sense that statins at standard doses reduce overall mortality, mortality from coronary disease and cardiovascular morbidity in patients with coronary disease. This was seen in patients with a wide range of cholesterol levels, though a greater reduction in morbidity and mortality was observed with higher cholesterol levels (table 1 and figure 1).

4S Trial

The first of the studies was the Scandinavian Simvastatin Survival Study (4S)[3] which included 4,444 patients with a mean age of 58 years in men and 60 years in women (18.5% of all patients). Patients had a history of angina or previous myocardial infarction or mean cholesterol levels of 261 mg/dl (6.7 mmol/L) and a mean LDL-c level of 188 mg/dL (4.8 mmol/L). These patients were randomly given either simvastatin (20-40 mg) or placebo for 5.4 years. The results obtained were clearly favourable for the simvastatin group with an absolute reduction in all-cause mortality of 3.3% [RR = 0.70 (0.58-0.85)], a 3.5% [RR = 0.58 (0.46-0.73)] reduction in coronary mortality and a reduction of 6.7% [RR = 0.66 (0.59-0.75)] in coronary events amongst other positive results.

CARE Trial

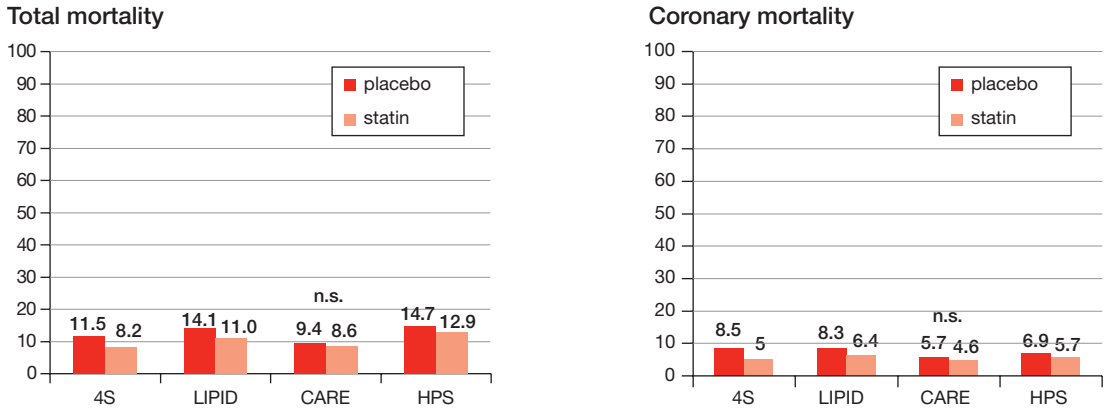
The second trial was the Cholesterol and Recurrent Events (CARE)[4] that compared pravastatin 40 mg vs placebo in 4,159 patients with a history of myocardial infarction in the previous two years and cholesterol levels <240 mg/dL (6.1 mmol/L), [mean 209 mg/dL (5.4 mmol/L)] and c-LDL levels between 115 and 174 mg/dL (2.9 and 4.5 mmol/L), mean, 139 mg/dL (3.6 mmol/L). An absolute re-

Table 1. Outcomes in the main clinical trials comparing statin use *vs* placebo in coronary patients.

STUDY	PATIENTS	PRIMARY ENDPOINT	OUTCOMES	NNT	SECONDARY ENDPOINTS	OUTCOMES
4S	4,444 patients with MI or angina Total chol = 6.7 ± 0.7 mmol/L LDL-c = 4.8 ± 0.6 mmol/L 19% women Mean age: 58 years Length: 5.4 years Scandinavian Countries	Total mortality	RRR: 30% (15-42) ARR: 3.3% p = 0.0003	30 (21-58)	Coronary mortality Cardiovascular mortality	RRR = 42% (27-54) ARR = 3.5% RRR = 45% (20-48) ARR = 3.2%
CARE	4,159 patients with MI Total chol = <6.1 mmol/L (mean, 5.4 mmol/L) LDL-c = 3.6 mmol/L 14% women Mean age = 59 years Length = 5 years USA and Canada	Coronary death or non-fatal myocardial infarction	RRR: 24% (9-36) ARR: 3% p = 0.003	32 (21-85)	Coronary mortality Total mortality	RRR = 20% (-5 a 39) n.s. ARR = 1.1% n.s. RRR = 9% (-12 a 26) n.s. ARR = 0.8% n.s.
LIPID	9,014 patients with MI or unstable angina Total chol = 5.6 mmol/L LDL-c = 3.8 mmol/L 17% women Mean age = 62 years Length = 6 years Australia and New Zeland	Coronary death	RRR: 24% (12-35) ARR: 1.9% p < 0.001	51 (35-101)	Cardiovascular mortality Total mortality	RRR = 25% (13-35) ARR = 2.3% RRR = 22% (13-31) ARR = 3.1%

RRR = relative risk reduction
ARR = absolute risk reduction
NNT = number needed to treat in order to prevent one additional bad outcome in the primary endpoint

Figure 1. Total mortality and coronary mortality in the 4S, LIPID, CARE and HPS trials.



* In the CARE trial no statistically significant differences were found in total mortality, nor in coronary mortality.

duction by 3% in the primary endpoint, death by coronary disease or non-fatal myocardial infarction [RR = 0,76 (0,64-0,91)]. Non-fatal myocardial infarction was reduced by 1.8% [RR = 0,77 (0,61-0,96)] in absolute terms while the risk of stroke by 1.2% [RR = 0,69 (0,48-0,97)]. No statistically significant reduction was observed in mortality due to coronary disease (5.7% vs 4.7%) cardiovascular disease (5.77% vs 5.38%) or in overall mortality (9.4% versus 8.64%).

LIPID Trial

The third study against placebo in chronological order was the Long term Intervention with Pravastatin in Ischemic Disease (LIPID)[5] study in which 9,014 patients with a mean age of 62 years were included. All the patients had suffered from myocardial infarction or unstable angina. Mean cholesterol levels were 218 mg/dL (5.6 mmol/L) and mean LDL-c was 150 mg/dL (3.8 mmol/L). Patients were randomly assigned either pravastatin 40 mg or placebo. The primary endpoint, coronary death was reduced by 1.9% in absolute terms [RR = 0.75 (0.65-0.87)]. Mortality due to cardiovascular disease was reduced by 2.3% [RR = 0.75 (0.65-0.87)] and overall mortality by 3.1%

[RR = 0.78 (0.69-0.87)]. There were no significant differences in coronary mortality or in the number of non-fatal myocardial infarctions in either the subgroup of women or patients over 70 years of age.

A rather special study... The HPS

The Heart Protection Study (HPS)[6] was designed to find out whether in a population of high cardiovascular risk patients, with a history or not of cardiovascular events, simvastatin 40 mg would reduce mortality and the number of clinical events. To do so 20,536 British adults between 40-80 years with coronary disease, or other occlusive arterial disease, or diabetes were randomly assigned to either receive simvastatin 40 mg or placebo. The mean total cholesterol levels were 228 mg/dL (5.8 mmol/L) and LDL-c was 132 mg/dL (3.4 mmol/L).

A statistically significant reduction was observed in overall mortality (primary endpoint) of 1.8% in absolute terms [RR = 0.87 (0.81-0.94)]. In addition, there was an absolute reduction in cardiovascular mortality of 1.5% [RR = 0.83 (0.75-0.91)]. The reduction in the number of coronary events was 3.1% [RR = 0.73 (0.67-0.79)] and general vascular events were reduced from 25.2% to 19.8% [RR = 0.76 (0.72-0.81)] (the majority of the events were either coronary or non-coronary revascularizations). Cardiovascular events were reduced significantly in both sexes, and in patients both over and under 70 years (table 2).

The authors concluded that high risk patients (coronary, vascular, high risk diabetic patients) of both sexes, and independent of age and even with low cholesterol levels, would benefit from a reduction in the number of vascular events when treated with simvastatin. Even patients with LDL-c levels <116 mg/dL (<3.0 mmol/L) showed a lower number of coronary events.

However the HPS has some points that are worth clarifying or at least should be taken into account when making conclusions.

· Of those patients selected in the first screening, 36% (11,609 patients) were rejected in the prerandomisation phase for various reasons. These include non compliance with treatment, elevation of liver enzymes, creatinine and creatinine-phosphokinase (CPK), lowering the external validity of the study and certainly minimising the communication of adverse effects during the trial.

· The measurement of LDL-c levels. In the earlier studies LDL-c was calculated using the Friedewald equation, while in this trial levels were measured directly. This means that 15% more should be added to the values obtained (as acknowledged by the NCEP) in the HPS trial to be comparable to other studies that measure LDL-c either di-

Table 2. Main outcomes in the HPS trial.

STUDY	PATIENTS	PRIMARY ENDPOINT	OUTCOMES	NNT	SECONDARY ENDPOINTS	OUTCOMES
HPS	20,356 high risk patients (with and without coronary disease) Total chol = 5.9 mmol/L Women: 25% Age: 40-80 years 52% older than 65 years Length = 5 years United Kingdom	Total mortality	RRR = 13% (6-19) ARR = 1.8%, p = 0.0003	53 (36-114)	Coronary mortality Cardiovascular mortality	RRR = 17% (8-25) RRA = 1.2% RRR = 17% (9-25) RRA = 1.5%, p < 0.0001

RRR = relative risk reduction
ARR = absolute risk reduction
NNT = number needed to treat in order to prevent one additional bad outcome in the primary endpoint

rectly or indirectly[7,8]. In most common practice LDL-c is measured with the Friedewald equation.

· There is another difference with the rest of the trials concerning secondary prevention. The introduction of the endpoint "non-coronary revascularization" under cardiovascular events means there is an increase in the number of cardiovascular events with respect to other trials, 20% in the placebo group and 22% in the simvastatin group.

· The high mortality in the placebo group (14.7%) implies that participants in the HPS trial should be considered very high cardiovascular risk patients. Therefore conclusions made from the trial in patients with no cardiovascular event cannot be extrapolated to primary prevention.

· Patients were recruited from hospitals, thus exposing the trial to the Bergson bias (results extracted from patients that are more severely ill than in the general population) and potentially affecting its external validity.

Integrating the evidence from the 4 trials we can conclude the following:

· The great majority of patients with coronary disease on outpatient treatment should take standard doses of statins (table 3). There is evidence to show a reduction in cardiovascular morbidity and mortality in patients with different ranges of cholesterol levels.
· Statins at standard doses reduce overall mortality in patients with established atherosclerotic disease and/or high cardiovascular risk.

Table 3. Standard statin doses that produce a reduction of 30-40% in LDL-c levels.

Lovastatin	40 mg
Simvastatin	20 mg
Fluvastatin	80 mg (prolib)
Atorvastatin	5-10 mg
Pravastatin	40-80 mg

Efficacy in women

Current evidence on the role of statins in secondary prevention in women is limited due to the low number of female patients included in trials[9]. These drugs have shown a reduction in the number of

Table 4. Statin efficacy in the secondary prevention of cardiovascular disease in women.

	PLACEBO		INTERVENTION		RR (95% CI)
	Events	Women	Events	Women	
Total mortality					
4S	25	420	27	407	1.11 (0.66-1.87)
LIPID	78	760	74	756	0.95 (0.71-1.29)
Coronary mortality					
4S	17	420	13	407	0.79 (0.39-1.60)
CARE	14	290	11	286	0.80 (0.38-1.71)
LIPID	50	760	39	756	0.79 (0.52-1.18)
Non-fatal MI					
4S	83	420	53	407	0.66 (0.48-0.90)
CARE	28	290	14	286	0.51 (0.27-0.94)
LIPID	61	760	54	756	0.89 (0.63-1.26)
Revascularization					
4S	42	420	21	407	0.52 (0.31-0.86)
CARE	65	290	56	286	0.82 (0.64-1.20)
LIPID	103	760	77	756	0.66 (0.50-0.87)
Coronary events					
4S	91	420	60	407	0.68 (0.51-0.91)
CARE	80	290	46	286	0.60 (0.37-0.97)
LIPID	104	760	90	756	0.87 (0.67-1.13)
HPS	282	1638	237	1628	0.85 (0.72-0.99)

Adapted from Walsh JM, Pinone M. Drug Treatment of Hypelipidemia in Women. JAMA 2004;291:2243-2252.

Women and the elderly can also benefit from secondary prevention with statins

cardiovascular events, but have not demonstrated a reduction in either cardiovascular mortality or overall mortality (table 4). Probably this lack of effect is related to a reduced sample size and a lower absolute risk of women, rather than a lack of efficacy of these drugs in secondary prevention in women.

Efficacy in the elderly

In contrast to what occurs in primary prevention, where therapy with statins did not show any benefits1, elderly patients with coronary disease do benefit from treatment. A recent meta-analysis[10] shows that in patients over 65 years with coronary disease, there is a statistically significant reduction in overall mortality and coronary mortality, the number of non-fatal infarctions, the need for revascularization, and the number of strokes. In the PROSPER study (the only one carried out in elderly patients) significant benefits were seen only in secondary prevention (fundamentally due to the lower number of non-fatal myocardial infarctions) while no benefit was observed in primary prevention (figure 2).

Efficacy in the Acute Coronary Syndrome (ACS)

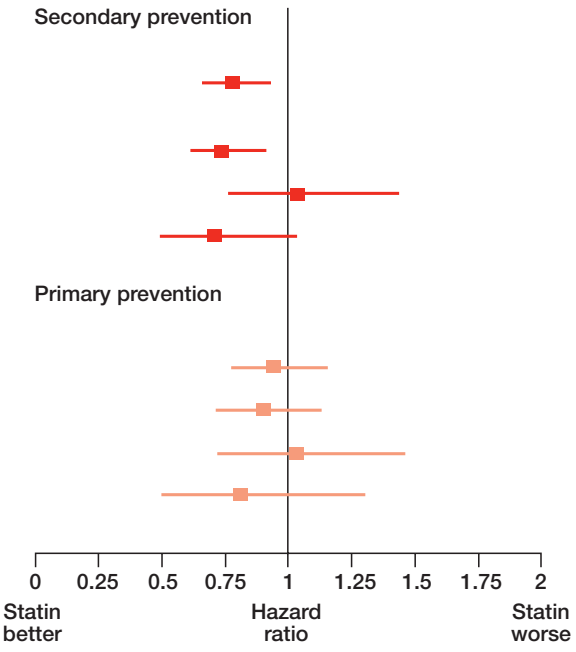
The term ACS includes all clinical manifestations of a progressive physio-pathological process that determines the apparition of stable angina, non-Q (subendocardial) myocardial infarction or transmural myocardial infarction.

The above trials (4S, LIPID, CARE) were carried out months after the patients had suffered from the coronary event. This was because it was thought that cholesterol lowering agents did not have any effect on coronary death, or infarction caused by ventricular arrhythms, heart failure or on the high instability of the atherosclerotic plaque common in the first few days after a coronary event. To find out whether statins could reverse this situation, several studies were designed to compare them with placebo:

Figure 2. Major cardiovascular outcomes in the PROSPER trial, according to primary or secondary status of participants.

Secondary prevention	Pravastatin (n=1306)	Placebo (n=1259)
CHD death, non-fatal MI and fatal or non-fatal stroke	227	273
CHD death, non-fatal MI	166	211
Fatal or non-fatal stroke	74	69
TIA	47	64
Primary prevention	**(n=1585)**	**(n=1654)**
CHD death, non-fatal MI and fatal or non-fatal stroke	227 181	273 200
CHD death, non-fatal MI	126	145
Fatal or non-fatal stroke	61	62
TIA	30	38

CHD = coronary heart disease
MI = myocardial infarction
TIA = transient ischaemic attack.



From Shepherd J et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623-30.

MIRACL Trial[11]

A total of 3,086 hospital patients with unstable angina or non-Q myocardial infarction randomly received atorvastatin 80 mg or placebo 24-96 hours after admission to hospital for 16 weeks. The primary endpoint was the combination of death, non-fatal infarction, cardiac arrest with resuscitation or symptoms of recurrent ischemia that required admission to hospital. The primary endpoint was 14.8% in the atorvastatin group and 17.4% in the placebo group [RRR= 16% (0-30)] at the limit of statistical significance. LDL-c levels in the trial were between 124 mg/dL (3.2 mmol/L) and 135 mg/dL (3.5 mmol/L) in the placebo group and between 124 and 72 mg/dL (3.2 and 1.8 mmol/L) in the atorvastatin group. Besides a reduction of 42% in LDL-c, treatment with atorvastatin did not reduce mortality, cardiac arrest with resuscitation, myocardial infarction or the need for revascularization (bypass or angioplasty). A significant reduction was found only in recurrent ischemic symptoms that required urgent hospital admission. More so, atorvastatin did not show any modification in the rapid accumulation of coronary events that occurred in the first 5 weeks (70% of the total)[12].

FLORIDA Trial[13]

A total of 540 patients with previous myocardial infarction and total cholesterol <251 mg/dL (6.4 mmol/L) were randomly assigned to receive either fluvastatin 80 mg or placebo. Treatment commenced in the first 14 days after infarction. primary endpoint was a combination of cardiovascular death, non cardiovascular death, recurrent myocardial infarction and recurrent ischemia that required admission to hospital or revascularization. After one year of treatment, no significant differences were found between the two groups neither in the primary endpoint nor in other endpoints such as major vascular events. LDL-c levels which initially were 135 mg/dL (3.5 mmol/L) in the fluvastatin group were reduced by 21% by the end of the study period. In the placebo group LDL-c initially was 139 mg/dL (3.6 mmol/L) and increased by 9% at the end of the year.

Therefore, only short term marginal benefits are obtained with early treatment with statins in patients with ACS and non-elevated cholesterol levels.

Intensive therapy in secondary prevention? "Primum non nocere"

As commented earlier, the ability of statins, especially at high doses, to produce a marked reduction in LDL-c cholesterol has won them a principal role in secondary prevention. In the last 4 years, various trials have been published comparing results obtained in terms of reduction in cardiovascular events, with low or high doses of statins (intensive treatment) (table 5 and figure 3). The "evidence obtained" from these trials has convinced many specialists to recommend reducing LDL-c levels to under 70 mg/dL (1.8 mmol/L) and many guidelines and consensus have incorporated these recommendations.

Aggressive goals in LDL-c levels provide scarce clinical benefits and increase adverse effects

Patients with stable coronary disease

TNT Trial[14]

A total of 10,002 patients with stable coronary disease were randomly given atorvastatin 10 or 80 mg. All patients (after the treatment phase) had LDL-c levels below 130 mg/dL (3.3 mmol/L), the average in both groups, 98±18 mg/dL (2.5±0.5 mmol/L). The study period was 4.9 years. Women accounted for 19% of the study group. The mean age was 61±8.8 years. The primary endpoint was the combination of coronary death, non-fatal myocardial infarction that did not require intervention, resuscitation after fatal or non-fatal cardiac arrest and stroke (in the BIT on primary prevention we discussed the inconveniences of certain composite endpoints). This endpoint occurred in 10.9% and 8.7% of the atorvastatin 10 mg and 80 mg groups, respectively [HR = 0.78 (0.69-0.89)], [NNT = 46 (33-93)]. This signifies that there was an absolute reduction by 2.2% in the primary endpoint. The levels of LDL-c reached were 77 mg/dL (2.0 mmol/L) and 101 mg/dL (2.6 mmol/L) in the atorvastatin 80 mg and 10 mg groups respectively.

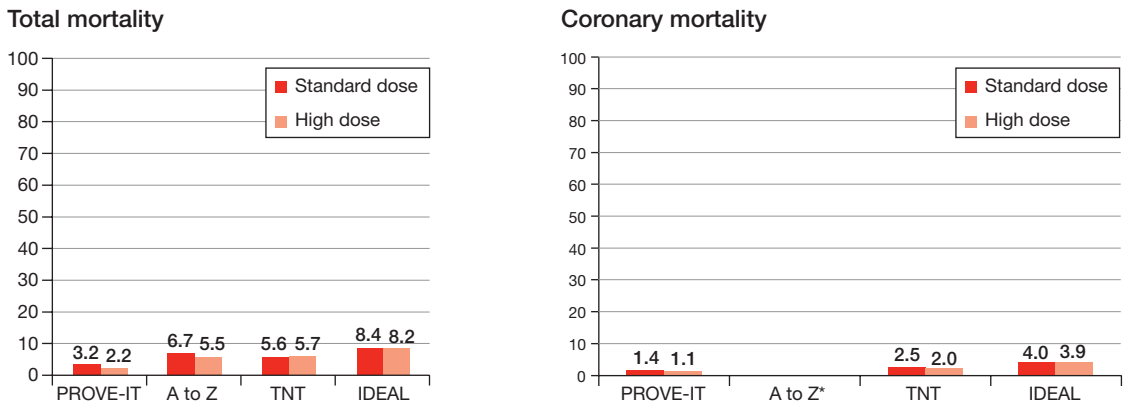
There were significant differences in adverse effects, 8.1% in the atorvastatin 80 mg group and 5.8% in the atorvastatin 10 mg group. There were also significant differences in patients abandoning treatment due to adverse effects, 7.2% vs 5.3% ($p<0.001$). In 1.2% of the cases under atorvastatin 80 mg, there was an elevation in liver enzymes

Table 5. Major cardiovascular outcomes of high-dose statin treatment in the main clinical trials.

STUDY	PATIENTS	STATIN	PRIMARY ENDPOINT	OUTCOMES	NNT	SECONDARY ENDPOINTS	OUTCOMES
TNT	10,001 patients with stable coronary disease LDL-c = 2.5±0.5 mmol/L 19% women Age: 61±8.8 years Length = 4.9 years Patients from all continents	Ator. 10 mg Ator. 80 mg	Coronary death, non-fatal myocardial infarction that did not require intervention, resuscitation after fatal or non-fatal cardiac arrest or stroke	RRR = 22% (11-31) ARR = 2.2% p<0.001	46 (33-93)	Total mortality Coronary mortality Any coronary event Any cardiovascular event	RRR = -1% (-19 al 15) ARR = -0.1% n.s. RRR = 20% (-3 al 39) ARR = 0.5% n.s. RRR = 21% (14-27) ARR = 4.9% RRR = 19% (13-25) ARR = 5.4%
IDEAL	8,888 patients with myocardial infarction LDL-c = 3.1 mmol/L 20% women Age = 61.7±9.5 years Lenght = 4.8 years North Europe	Sim. 20 mg Ator. 80 mg	Coronary death, myocardial infarction, or resuscitation after cardiac arrest	RRR = 11% (-1 a 22) ARR = 1.1% n.s.	97 (n.s.)	Total mortality Coronary mortality Any coronary event Any cardiovascular event	RRR = 2% (-13 al 15) ARR = 0.2% n.s. RRR = 1% (-22 al 20) ARR = 0.1% n.s. RRR = 16% (8-24) ARR = 3.6% RRR = 16% (9-22) ARR = 4.2%
PROVE-IT	4,162 patients admitted with ACS LDL-c = 2.7 (2.2-3.3) mmol/L 22% women Age = 58.3±11.3 years Length = 2 years Canada, UK, USA and Australia	Prav. 40 mg Ator. 80 mg	All-cause mortality, myocardial infarction, unstable angina that required admission to hospital, revascularization, or stroke	RRR = 16% (5-26) ARR = 3.9 %	31 (19-102)	Total mortality Coronary mortality Myocardial infarction Revascularization	RRR = 28% n.s. ARR = 1% n.s. RRR = 30% n.s. ARR = 0.3% n.s. RRR = 13% ARR = 0.8% n.s. RRR = 14% ARR = 2.6%
A to Z	4,497 patients with ACS LDL-c = 2.8 mmol/L 25% women Age = 61 (52-69) Length = 24 months Patients from all continents	Sim. 40-80 mg Sim. 20 mg	Cardiovascular death, non-fatal myocardial infarction, readmission due to acute coronary syndrome, or stroke	RRR = 11% (-4 al 24) ARR = 2.3% n.s.	65 (n.s.)	Total mortality Cardiovascular mortality Myocardial infarction	RRR = 21% (-2 al 39) ARR = 1.2% n.s. RRR = 25% (0 al 43) ARR = 1.3% p=0,05 RRR = 4% (-21 al 23) ARR = 0.3% n.s.

RRR = relative risk reduction
ARR = absolute risk reduction
NNT = number needed to treat in order to prevent one additional bad outcome in the primary endpoint

Figure 3. Total mortality and coronary mortality with statin treatment (standard *vs* high doses) in the main clinical trials.



(*) Coronary mortality data not available.

compared to 0.2% in the atorvastatin 10 mg (p<0,001). For certain, in this study the NNT to avoid a cardiovascular event was 46 (33-93) and the NNH to observe an adverse event related to atorvastatin 80 mg was 42 (30-74).

IDEAL Trial[15]

Just after the publication of the TNT trial, the IDEAL study was published. This trial carried out over 4.8 years with 8,888 outpatients who had suffered from myocardial infarction. Twenty percent of the patients were women. The mean LDL-c levels were 121 mg/dL (3.1 mmol/L) at the onset of the study and the mean HDL-c levels was 46 mg/dL (1.2 mmol/L). Mean total cholesterol was 196 mg/dL (5.0 mmol/L). The patients were randomly assigned to receive either simvastatin 20 mg or atorvastatin 80 mg. The primary endpoint was the occurrence of a coronary event (coronary death, myocardial infarction, or resuscitation after cardiac arrest). Once completed, this trial showed no significant differences in the primary endpoint [HR = 0.83 (0.71-1.01)].

Neither were there significant differences in mortality due to vascular origin, nor in overall mortality. The mean values of LDL-c at the end of the trial were 99.8 and 80 mg/dL (2.6 and 2.0 mmol/L) in the simvastatin and atorvastatin groups respectively. The percentage of adverse effects that supposed a suspension of treatment was 4.2% in the simvastatin group and 9.6% in the atorvastatin group (p<0.001), with significant differences in the apparition of myalgias, diarrhoea, abdominal pain, nauseas and liver enzyme elevation. The results of this trial did not coincide with those of the TNT trial and meant a setback in the aggressive approach in treatment against hypercholesterolemia. Moreover, it was made clear that in these patients aggressive therapy to control cholesterol levels provided only marginal benefits and more adverse effects.

In the last few years a novel approach has been emphasized to reach lower levels of LDL-c, precisely with the aim to avoid increasing doses of statins and to avoid their adverse effects. This novel approach involves the use of ezetimibe. Ezetimibe[16] is a drug that reduces LDL-c acting upon the microvilli of the small intestine inhibiting the absorption of cholesterol through a molecular mechanism which remains still unknown. Cardiovascular morbidity and mortality has not been as yet evaluated through any trial and cases have been reported through drug surveillance of high creatine phosphokinase levels and of myalgias and rhabdomyolysis, just as with statins[17,18]. Recently a controversy broke out in the USA regarding the ENHANCE[19] trial in which a comparison was made between the use of ezetimiba plus simvastatin and simvastatin alone in patients with familial hypercholesterolemia. Despite a reduction in LDL-c levels by 58% in the ezetimibe group vs 41% in the simvastatin only group (p<0.01), the thickness of the intima-media layers of the carotid artery did not alter after 2 years of treatment. These results and the company's interest to conceal them has created an enormous scandal in the USA and a warning on the part of the FDA[20].

Ezetimibe has not shown a reduction in cardiovascular morbidity and mortality

Intensive treatment in Acute Coronary Syndrome (ACS)

PROVE-IT Trial[21]

This trial involved 4,162 hospitalised patients with ACS and compared pravastatin 40 mg with atorvastatin 80 mg. Basal LDL-c values were 106 (87-128) mg/dL [2.7 (2.2-3.3) mmol/L]. The primary endpoint was the combination of all-cause mortality, myocardial infarction, unstable angina that required admission to hospital, revascularization and stroke. Twenty-two percent of the participants were women and the mean age was 58.3±11.3 years. The duration of the study was 2 years. The primary endpoint was reduced by 3.9% in absolute terms and by 16% (5-26) in relative terms in the simvastatin group. There were no significant differences in coronary death, or by any cause. The mean LDL-c values reached 95 mg/dL (2.4 mmol/L) in the pravastatin group (interquartile range, 79-113 mg/dl or 2.0-2.9 mmol/L) and 62 mg/dL (1.6 mmol/L) (interquartile range, 50-79 mg/dL or 1.3-2.0 mmol/L). The percentages of patients abandoning treatment were 21.4% and 22.8% for pravastatin and atorvastatin, respectively, in the first year and 33% and 30.4%, respectively, in two years. In the atorvastatin group, 3.3 % of the patients suffered from muscular pain or CPK elevation while in the pravastatin group the incidence reached 2.7%. Elevation of liver enzymes was significantly greater in the atorvastatin group (atorvastatin 3.1% vs pravastatin 1.1%, p<0.001).

A to Z Trial[22]

This trial compared the early initiation of intensive treatment, with a more conservative approach with lower doses in patients with ACS. The complexity in the design and methodology of the study gives it only very little relevance to extract any evidence. The study involved randomly assigning 4,497 patients with either simvastatin 40 mg for one month followed by 80 mg per day up to the end of the trial (3 years) vs the use of placebo for 4 months initially followed by simvastatin 20 mg up to the end of the trial. The primary endpoint was the combination of cardiovascular death, non-fatal myocardial infarction, readmission due to acute coronary syndrome, and stroke. There were no significant differences in the primary endpoint [HR= 0.89 (0.76-1.04)] nor in the secondary endpoints such as overall mortality, cardiovascular mortality, stroke and myocardial infarction. There were higher incidences in elevated liver enzymes and myopathies in the high dose group (with significant differences).

Intensive therapy with high dose statins to reach low values of LDL-c (70-80 mg/dL or 1.8-2.0 mmol/L) in patients with stable coronary disease has only shown scarce benefits in composite endpoints in selected patients. These benefits are small and survival does not improve in patients with coronary disease. Intensive therapy notable increases adverse effects and proposes objectives for LDL-c values that demand high doses of statins that are intolerable for patients.

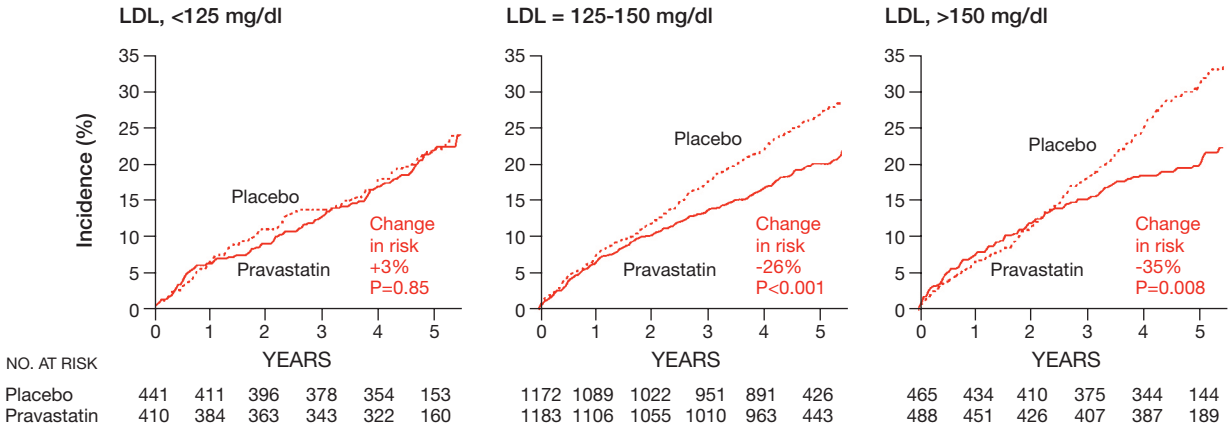
What goals should be set for LDL-c levels?

Even though the 4S study did not stratify the benefits by levels of cholesterol, a later study was carried out though with LDL-c levels >170 mg/dL (>4.4 mmol/L)[23]. By then, cholesterol values were not the ones considered today. A further study analysed the reduction in coronary risk for each unit of cholesterol reduced, concluding that for each percentage of reduction in LDL-c values there was a 1.7% decrease in risk. The authors however, could not respond to the question whether there is a basal total cholesterol value or LDL-c value below which there would be no benefit from treatment[24].

In the CARE study a non-linear correlation between coronary events and treatment was found, such that no benefit was obtained in patients whose LDL-c levels were <125 mg/dL (3.2 mmol/L) (figure 4).

In the LIPID trial, the results of the analysis of subgroups with LDL-c levels <135 mg/dL (3.5 mmol/L) did not reveal any cardiovascular benefit. In a substudy of the LIPID trial[25], patients with LDL-c levels <140 mg/dL (3.6 mmol/L) and HDL-c values of <40 mg/dL (1.0 mmol/L) showed significant differences in the number of coronary events, coronary death and overall mortality, the last two in the limits of statistical significance. In no case was there any advantage in patients with LDL-c values <116 mg/dL (3.0 mmol/L).

Figure 4. Outcomes in the primary endpoint of the CARE trial, according to base-line LDL-c level.



From Sacks F M et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001-9.

However, in the HPS trial a significantly lower incidence of vascular events was observed in patients with LDL-c <116 mg/dL (3.0 mmol/L) and total cholesterol <193 mg/dL (5.0 mmol/L). At the same time, similar data in patients with LDL-c values <100 mg/dL (2.6 mmol/L) who also presented low HDL-c levels was observed. Moreover, there was also a reduction in coronary events in patients with LDL-c levels <116 mg/dL (3.0 mmol/L). It should be noted that the LDL-c levels should be at least 15% higher than those compared to in other trials.

Therefore with respect to the question whether there exists a limit below which LDL-c values in patients with coronary disease do not benefit from treatment, the first three trials provide indirect information, while making room to propose new hypothesis:

· If the values of cholesterol are high [188 mg/dL (4.8 mmol/L) of LDL-c in the 4S trial, and 150 mg/dL (3.8 mmol/L) in the LIPID study] in patients with coronary disease (infarction or angina), treatment with statins reduce overall mortality and mortality due to coronary disease.

· If the levels are slightly lower [139 mg/dL (3.6 mmol/L) of LDL-c in the CARE trial], the number of clinical events is reduced but neither is the overall mortality, nor that due to coronary disease or cardiovascular disease decreased.

· Below LDL-c values of 125 mg/dL (3.2 mmol/L), no reduction whatsoever in clinical events is observed in patients who do not have low HDL-c values.

But then the "evidence" extracted from the subgroups of the HPS trial inform us that in patients with atherosclerotic disease and/or very high cardiovascular risk, those individuals with LDL-c values <116 mg/dL (<3.0 mmol/L) also benefit from statin therapy in terms of coronary and vascular morbidity and mortality. Although these conclusions are extracted from the analysis of subgroups (with all the precautions that should be taken) it seems clear that patients with coronary disease and high risk vascular disease should be treated with statins at standard doses [which would be reached with in a high proportion of patients with LDL-c values <116 mg/dL (<3.0 mmol/L)]. Now, what cannot be made more specific from the available information from clinical trials are the target levels of LDL-c to be attained.

The American NCEP[26] is the forerunner of all existing guidelines and recommendations. The European guidelines and other guidelines have adopted these recommendations and objectives in cholesterol values in secondary prevention of cardiovascular patients. We should not forget the fact that the NCEP is a consensus of experts. The current review of 2004, goes far beyond the objectives set for secondary prevention, recommending desirable levels of LDL-c of ≤ 70 mg/dL (1.8 mmol/L) in high risk patients. In fact the latest recommendations focus nearly exclusively on the LDL-c values[27]. The NCEP uses the PROVE-IT trial to establish the recommendation of LDL-c values ≤ 70 mg/dL (1.8 mmol/L) in patients with ACS. Despite the solidity which currently characterises the acceptance of these recommendations in clinical practice, a few reflections concerning the validity of the guidelines above the purely academic and theoretical propositions can be made.

· In contrast to what occurs with diabetes and hypertension, none of the trials carried out up to now responds to the question on the values of LDL-c to be reached with treatment with statins. Trials with statins use fixed doses that can be increased following a protocol, but in no case have the results been compared to when different values of total cholesterol or LDL-c have been reached. The different results from subgroups that appear frequently in trials are post hoc analysis, with the consequent error incurred as we do not know if the groups are balanced and, in some cases, do not even appear in the initial protocol.

The recent recommendations of the goals for LDL-c levels <100 mg/dL (2.6 mmol/L) or <79 mg/dL (2.0 mmol/L) are nothing but extrapolated data from the trials and epidemiological data, rather than conclusions based on evidence from clinical trials[28].

· Other lipid fractions should be taken into account besides LDL-c, given that the latter should not be an exclusive marker. In fact, in some of the trials reviewed, statins were only useful in terms of reduction of clinical events in patients who besides a low LDL-c count also showed low HDL-c values.

In any case, the clinician needs the guidelines and values that could orient daily clinical practice. From the data reviewed it seems reasonable to fix the objectives for LDL-c values to <100 mg/dL (2.6 mmol/L) in patients who have suffered from a coronary event or have a high cardiovascular risk profile. It should be noted that the value <100 mg/dL (2.6 mmol/L) is more of an indirect inference from some of the clinical trials and thus fruit of consensus rather than clear evidence from a specifically designed clinical trial. The use of high doses of statins to reach LDL-c levels of <70 mg/dL

(1.8 mmol/L) only reaps marginal benefits in selected groups of patients and notably increases adverse effects.

Stroke, statins and cholesterol. The SPARCL study

Given a clear correlation between blood pressure and cerebrovascular events, the relationship between cholesterol levels and stroke has not been demonstrated. We could just as say that what has been demonstrated is that there is no relationship. In 1995 an epidemiological study was published[29] in which a clear relation was confirmed between hypertension and stroke in all ages, cholesterol levels only had a slight correlation with stroke in younger ages.

Recently another trial[30] was published that clearly showed again the relation between stroke and cholesterol occurred in middle ages (40-58 years). This relationship was not consistent, given that the relation is weak and observed in patients with low blood pressure. In hypertensive patients >60 years there is a negative correlation between mortality from stroke and hemorrhagic stroke. That is to say that the lower the cholesterol, the higher the mortality due to stroke. Just as in other epidemiological studies[31], cholesterol in hypertensive patients over 60 years is a protective factor against hemorrhagic stroke. In 2005 a case-control study[32] was published based on the cohort of the PROGRESS trial. It was concluded that, in patients with cerebrovascular disease, levels of plasma lipids could predict myocardial infarction but not stroke.

In the clinical trials (patients with coronary disease in secondary prevention or high risk patients) a slight reduction in the number of cerebrovascular events has been observed. Nevertheless this reduction has in no case been greater than 1.5% in terms of absolute risk reduction and involves a high NNT. It is worth noting that, in the HPS trial, the subgroups with a high frequency of strokes (patients with previous stroke), statin therapy did not have any effect and, in patients with no history of stroke, there was a reduction in cerebrovascular accidents (table 6).

Various meta-analysis have reflected the positive effect of statins in the prevention of stroke in patients with coronary disease, specifically one which was published this year. This was an analysis of 42 trials involving statins to evaluate the number of strokes. The results of the meta-analysis showed a positive effect [RR = 0.84 (0.79-0.91)] in the total number of strokes when comparing patients under statin treatment vs placebo[33].

Table 6. Efficacy of statin treatment in stroke in coronary patients.

TRIAL	ENDPOINT	OUTCOMES	NNT	RELATIVE RISK
4S	Stroke + TIA	Placebo: 4.6% Statin: 3.4% ARR = 1.2%	73 (46-544)	RR = 0.70 (0.52-0.96)
	Stroke			
CARE	Stroke	Placebo: 3.8% Statin: 2.6% ARR =1.2%	85 (51-878)	RR = 0.69 (0.48-0.97)
LIPID	Stroke	Placebo: 4.5% Statin: 3.7% ARR = 0.8%	117 (66-∞)	RR = 0.81 (0.66-1.00)
HPS	Stroke	Placebo: 5.7% Statin: 4.3% ARR = 1.4%	71 (52-117)	RR = 0.75 (0.66-0.85)
	Stroke (in patients without previous stroke)	Placebo: 4.8% Statin: 3.2% ARR = 1.6%	64 (50-95)	RR = 0.67 (0.58-0.78)
	Stroke (in patients with previous stroke)	Placebo: 10.4% Statin: 10.3% ARR = 0.1% 71 (52-117)	n.s.	n.s.

The SPARCL trial[34] was designed to determine the role of statins in patients with no coronary disease, but with a history of stroke. The trial recruited a selection of 4,731 patients with previous stroke or transient ischemic attack (TIA). They were randomly assigned to receive either placebo or atorvastatin 80 mg. The primary endpoint was the occurrence of fatal and non-fatal stroke. This endpoint was reduced by 1.9% in absolute terms [HR = 0.84 (0.71-0.99)]. Stroke or TIA was reduced by 4.2% [HR = 0.77 (0.67-0.88)]. Despite the reduction in the number of cerebrovascular events, overall and cardiovascular mortality did not change significantly.

In contrast to cardiac ischemia, there is no correlation between cholesterol levels and stroke

Hemorrhagic stroke increased by 0.9% in absolute terms [HR = 1.6 (1.09-2.59)]. This increase was significant, especially in males and elderly patients and in those with previous hemorrhagic stroke. Only 2% of the initial patients before the onset of the trial had suffered from a previous hemorrhagic stroke. The inclusion or not of these patients was left to the investigators criteria to determine which patients were at risk of an ischemic stroke or if they had coronary disease. However, approximately 20% of the strokes observed during the trial were hemorrhagic (table 7).

As for adverse effects, atorvastatin produced an increase in liver enzymes (transaminases) in 2.2% of the patients while a 0.5% increase was seen in the placebo group, ($p<0.001$). There were also significant differences in the number of patients who abandoned treatment due to the adverse effects, 17.5% and 14.5% in the atorvastatin and placebo groups, respectively.

How can we integrate all this evidence? What is the external validity of this study?

After age and high blood pressure, cardiac disease is the third most important risk factor for stroke, specially the presence of atrial fibrillation. By excluding these patients to evaluate secondary prevention in patients with no cardiac disease, this data cannot be extrapolated to all patients with ischemic stroke or previous TIA. In 15-20% of cases of ischemic stroke, the origin is cardio embolic, in which 50% are represented by the presence of atrial fibrillation[35,36].

Therefore on a whole, we have a series of factors to consider before making any judgement: cholesterol is not a risk factor for stroke (especially for patients >60 years); plasmatic levels of lipids do not predict stroke; there is no improvement in mortality with high dose atorvastatin in patients with previous stroke but no previous coronary disease (although it is so in the number of events); there is an associated increase in hemorrhagic stroke (as seen in other studies) and adverse effects occur in a significantly higher proportion of patients taking atorvastatin than those with placebo.

Given the above, can the systematic prescription of atorvastatin 80 mg be justified for all patients who suffer from a stroke? The answer is clearly no. There would be a group of patients however who could benefit from treatment (patients with carotid atherosclerotic disease, for example) but, in general, the systematic therapy with atorvastatin in all stroke or TIA patients is unjustified.

However, the authors of the SPARCL trial recommend the prescription of atorvastatin 80 mg as early as possible to all patients suffering from either stroke or TIA. They do not take into account that in clinical practice there will be an important proportion of patients suffering from stroke of cardioembolic-origin or haemorragic stroke.

On the other hand, the benefits obtained from the use of statins have not been shown in other lipid-lowering drugs. This could support the hypothesis that statin benefits might have something to do with their antiatherothrombotic action rather than with their ability to lower cholesterol levels. In so-

Table 7. Outcomes in ischaemic stroke and haemorrhagic stroke in the SPARCL trial.

	Placebo	Atorvastatin	RR
Ischaemic stroke	274	218	RR=0.78 (0.66-0.94)
Haemorrhagic stroke	33	55	RR=1.66 (1.08-2.55)

me studies statins have demonstrated an improvement in vascular function[37], antiplatelet effects[38] and antiarrhythmic properties in patients suffering from atrial fibrillation[39]. Although the clinical relevance of all these effects has not been clearly established, some authors suggest that part of the benefits observed in clinical trials might have to do more with the actions above mentioned than with their effects on LDL-c.

Statins and heart failure

In general patients with systolic heart failure have been excluded from trials involving statins. This is mainly because the benefit derived from therapy is related to the prevention of myocardial infarction and the incidence of infarction in patients with heart failure is not usually high. Moreover low levels of cholesterol have been associated with a poor outcome in these patients[40,41]. However, as some epidemiological studies[42] and other small-size studies[43] have shown some benefits, it was necessary to carry out a specifically designed clinical trial vs placebo to evaluate these patients.

The only clinical trial that compares the use of statins against placebo in patients over 60 years is the CORONA trial[44]. In this study, 5,011 patients (24% women) were randomly assigned either rosuvastatin 10 mg (commercially unavailable in Spain) or placebo during a mean period of 2.7 years. Of all patients, 60% had suffered from a previous myocardial infarction (>6 months). The patients did not have hypercholesterolemia [mean total cholesterol = 206 ± 41 mg/dL (5.3 ± 1.0 mmol/L) and LDL-c = 137 ± 36 mg/dL (3.5 ± 0.9 mmol/L)]. The primary endpoint was a combination of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. The primary endpoint reduced by 29.3% and 27.5% [HR = 0,92 (0.83-1.02)] in the placebo and rosuvastatin groups respectively. Neither were there significant differences in overall mortality [HR = 0.95 (0.86-1.05)], nor in coronary events [HR = 0.92 (0.82-1.04)]. Thus, statins have not shown any significant benefit in terms of morbidity and mortality in patients with heart failure and non-elevated cholesterol levels.

Recent information on the safety of statins

In the BIT on primary prevention and statins a comment was made on the most common adverse effects of statins, and the fact that they were undervalued in the majority of clinical trials. This was because the patients selected had shown good tolerance to treatment beforehand. The most common adverse effects include elevation of liver enzymes (transaminases) and myopathies. The latter have been undervalued in clinical trials, because so far the indication for adverse effect was an increase in serum cretinine kinase levels, obviating the fact that there is a considerable number (as seen in one study) of patients with muscle weakness and myalgias with no increase in creatinine kinase values[45].

There are still some doubts remaining regarding trials with statins that have not been satisfactorily dealt with. These questions turn up when some controversial results regarding a higher incidence of cancer appear in some clinical trials (PROSPER[46], CARE) and a trend of higher all-cause mortality, specially in trials involving high dose statin therapy (TNT, SPARCL). Two meta-analyses[47,48] sought to evaluate the relation of cancer and statins and found a null effect. However in July 2007 a study was published[49] which included the adverse effects of statins of the majority of patients in trials involving statins (23 trials with 309,506 patient-years). Amongst the multiple information recollected it is worth taking note of the following:

· When high doses of statins were employed, for each 10% reduction in LDL-c the rate of increase in liver transaminases was significant.

· An inverse relation between the incidence of cancer and LDL-c levels reached was observed, that is, the lower the values of LDL-c the higher the incidence of cancer. There was no relation with the percentage of reduction obtained nor in absolute reduction.

How are statins employed in Navarre (Spain)?

In May 2008, an investigation was carried out of the data from 323 quotas of patients in primary care in Navarre. To do so, a computer based tool (ISIS) was employed to exploit the information from the electronic medical records. The analysis determined the number of patients with a history of a cardiovascular event who were under therapy with statins. It also identified those patients treated with statins for primary prevention. Consultation of medical records of patients was made to verify whether their cardiovascular risk profile had been calculated.

· A 64±14.6% of the cases of patients with coronary disease were treated with statins. The number of patients of this kind who are treated with statins

has increased notably, but there still is remains an important margin for improvement given the available evidence. As seen in the table, there exists considerable variability in treatments among centres, which is difficult to explain and requires urgent measures to be taken. Only 38% of the patients with peripheral arteriopathy (PA) are treated with statins, which shows there is a lot of room for improvement. There is also an ample variability among centres.

· Of the patients that are treated with statins, 53% had no history of coronary disease, stroke, arteriopathy or diabetes. Only 20% of them had a calculated cardiovascular risk score. It is most probable that a greater proportion of patients were evaluated for cardiovascular risk, but this was not registered in the electronic medical record.

· Elderly patients (>75 years) accounted for 29% of those under statin therapy. Of the elderly patients treated, 70% did not have coronary disease or peripheral arteriopathy and 42% did not have either coronary disease, diabetes, stroke or peripheral arteriopathy.

· Women accounted for half of the patients under treatment (though in the clinical trials, their participation was no more than 20%). Primary prevention with statins was carried out in 62.6% of the women (no coronary disease, nor diabetes, nor stroke, nor peripheral arteriopathy).

· The variability in the results in the different quotas of patients assigned to each physician, both in primary and in secondary prevention, is important as shown in the box diagram.

Table 8. Statin use in the secondary prevention of cardiovascular disease in different conditions. Navarre Regional Health Service in Spain.

Condition	Total No patients*	Patients taking statins	Mean	SD	PERCENTIL		
					25	50	75
Coronary heart disease	13,635	8,726	63.8%	14.6%	56.3%	65.6%	72.5%
Diabetes Mellitus	28,407	11,760	41.4%	12.1%	33.3%	42.1%	49.4%
Stroke	9,601	4,167	43.4%	14.5%	33.3%	44.1%	53.1%
Peripheral arteriopathy	6,367	2,432	38.2%	18.4%	27.0%	38.0%	50.0%

* Some patients may have more than one condition each

Table 9. Proportion of women and elderly people under statin treatment. Navarre Regional Health Service in Spain.

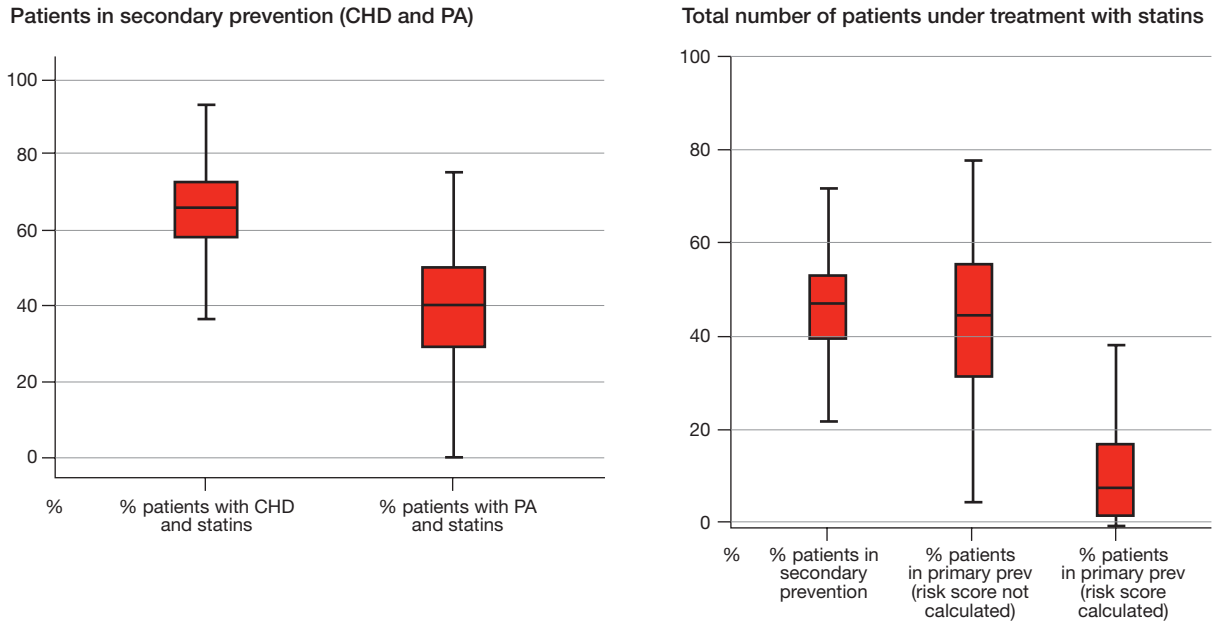
Patients treated with statins	Mean	SD	PERCENTIL		
			25	50	75
> 75 years	29.0%	9.8%	22.3%	29.0%	35.4%
Women	49.2%	7.3%	44.7%	49.2%	53.3%

Table 10. Patients taking statins according to different variables.

	n	%
Patients taking statins	**44,089**	**100.00%**
Primary prevention (no CHD, nor DM, nor PA, nor stroke)	23,632	53.60%
Cardiovascular risk score calculated	4,762	
Cardiovascular risk score not calculated	18,870	
Secondary prevention (CHD or DM or PA or stroke)	20,457	46.40%
Secondary prevention (CHD or PA)	9,700	22.00%
Men in primary prevention (no CHD, nor DM, nor PA, nor stroke)	9,898	22.45%
Cardiovascular risk score calculated	2,042	
Cardiovascular risk score not calculated	7,856	
Women in primary prevention (no CHD, nor DM, nor PA, nor stroke)	13,734	31.15%
Cardiovascular risk score calculated	2,720	
Cardiovascular risk score not calculated	11,014	
Elderly (>75 years)	12,802	29.03%
Elderly in primary prevention (no CHD nor PA)	8,974	20.35%
Elderly in primary prevention (no CHD, nor DM, nor PA, nor stroke)	5,326	12.08%

CHD = Coronary Heart Disease
PA = Peripheral Arteriopathy
DM = Diabetes Mellitus

Figure 5. Patients under treatment with statins. Variability according to the different quotas of patients in primary care in Navarre (Spain).



Conclusions

Statins have demonstrated effectiveness in preventing overall mortality and coronary death in secondary prevention of patients with coronary disease with high cholesterol levels.

Statins have also shown to reduce overall mortality in very high risk patients or atherosclerotic disease. In these patients there is a reduction in vascular and coronary events even with LDL-c levels <116 mg/dL (3.0 mmol/L).

Women also benefit from statins in secondary prevention (indirect data, given that women participation was small). A reduction in events was observed, but not in mortality.

Elderly patients with coronary disease benefit from statin therapy in terms of both morbidity and mortality.

Systematic prescription of statins in all patients with stroke or TIA should not be done. To base treatment on levels of cholesterol is even less sensible as no correlation exists between cholesterol and stroke.

Intensive therapy with high dose statins to obtain low levels of LDL-c (<80 mg/dL or <2.0 mmol/L) in patients with stable coronary disease has shown only scarce benefits in selected patients and in composite endpoints. This approach is hardly justified as the benefits are scarce and there is no improvement in survival of patients with coronary disease. Intensive therapy notably increases the incidence of adverse effects and the set goals for LDL-c levels to be attained demand high doses of statins that are frequently not tolerated by patients.

The use of ezetimibe has not demonstrated a reduction in cardiovascular morbidity and mortality. Lately there are doubts about the effectiveness of the ezetimibe-statin combination with the intention of reducing the doses of the latter, despite the reduction in LDL-c values.

Statins have not shown any significant benefit in terms if morbidity and mortality in patients with heart failure and low cholesterol levels.

Statins at high doses increase the incidence of adverse effects. The incidence of these in clinical trials is undervalued because patients selected for the trials had previously shown good tolerance to these agents. The possible association between cancer and statins warrants further study.

In Navarre, there is an ample margin for improvement of treatment with statins. Approximately 36% of patients with coronary disease should be treated with statins and are not. In addition, there are more patients treated with statins for primary prevention than for secondary prevention, a situation which is absolutely inefficient. In primary prevention many patients under statin therapy do not have a calculated cardiovascular risk profile. A considerable number of these patients can expect only a small benefit, if any, from this treatment.

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