Statins in primary prevention of cardiovascular disease –Is use based on real evidence or distorted evidence?

Distort: to give a false or misleading account of, misrepresent

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Over the last few years the statins has become the highest consumption therapeutic group within the Navarre Regional Health Service as well as in the rest of Spain. The increasing media impact on the population at large and on the medical profession has created an impression of illness where there is simply a risk factor. The Spanish epidemiology reality differs notably from the circumstances of actual clinical testing with statins. Critical appraisal of the different clinical trials in cardiovascular primary prevention with these drugs shows benefits of scant clinical relevance. The importance given to the reduction in relative risk in detriment to the reduction of absolute risk is especially criticized.

The scant relevance of the results obtained when shifted to a population such as Spain's, demands the use of cardiovascular risk charts before imposing a cholesterol-lowering treatment with statins so as to select the high-risk patients. The use of these drugs as primary prevention in women and the elderly is not justified if we consider the results found in clinical trials. Diabetic patients should not be classified systematically as secondary prevention patients but rather should have specific risk charts applied to their cases. Finally, the adverse effects of statins can be minimized in clinical tests through a bias in the selection of patients.

Introduction

According to a study made in cardio-health habits, 70% of the Spanish population believe that suffering from high cholesterol means having a serious illness[1]. This erroneous belief among the population is a consequence of the media barrage over the last years which both the food industry as well as the pharmaceutical one have carried out on public opinion. It is important to realize that health sells and the media portray medicine as an exact and omnipotent science where the social relevance of symptoms and illnesses is exaggerated. The use of medicines and interventional techniques is stressed while the importance of maintaining a healthy lifestyle is played down[2].

This campaign has not been carried out on barren ground, but rather on a population already alerted by the medical profession of the dangers of cholesterol. The pharmaceutical industry has taken it on themselves to define what exactly high cholesterol is, and through clinical trial after clinical trial, it has convinced the medical profession of the great importance of attaining low levels of cholesterol both in primary and secondary prevention. Health professionals are sending out messages from many sources: pharmacies, doctor's surgeries, patient associations, science societies and now even supermarkets, are all urging everyone over 30 years of age to control their cholesterol through "health campaigns."

In 1990 if American guidelines and recommendations were followed about cholesterol, some 13 million Americans would have received pharmaceutical treatment with statins. In 2001 a new panel of experts rewrote these guidelines in which some 36 million Americans should have taken this medication. In 2004 a new review of the recommendations on cholesterol would have some 40 million Americans taking this medication[3].

Nine experts were contracted by the United States Government for this latest review of recommendations with regard to cholesterol (NCEP). All of them were heads of influential medical groups, protago-

nists of prestigious congresses and they frequently published in the most influential journals. They were considered indisputable giants in their field. But all of them had something in common. Eight of the nine received money from the same companies whose cholesterol-lowering agents they had been recommending to millions of Americans. Moreover, two of them were shareholders in these companies. Two more began to work for these same companies soon after making the recommendations. Another adviser has worked with ten companies and is a board director of one of them. This fact created a big scandal in The United States and called into question these latest recommendations from the NCEP[4].

In Spain, according to present guidelines, 25% of patients (31% in some areas) that attend a medical consultation are dyslipaemics[5] and should be treated with medication. As we can see, the quantity of potential patients is immense and getting bigger as the "optimal" cholesterol figures are continually dropping. The magic figures of 200 mg/dL (5.2 mmol/L) of total cholesterol or 115 mg/dl (3.0 mmol/l) of LDL-c are converting healthy people into potentially ill patients, and consequently, into consumers of statins.

Therefore, although this paper is going to try to respond exclusively to the question whether the results obtained with statins in primary prevention can justify their use, and to look at the importance given to this therapeutic group (to the point where it is the single biggest resource consumed in Navarre and in the rest of Spain), it is worth considering a series of questions:

What is the real extent of the cholesterol problem? Are the academic viewpoints of many scientific groups and opinion factions the correct ones? Or do they reflect the power of the "cholesterol lobby"? Is all this undercurrent of opinion applicable to a population like Spain's? Are the present "agreed-by-consensus" levels of cholesterol in fact, arbitrary?

Epidemiology

In spite of the fact that the mean figures of total cholesterol and of LDL-c in the Spanish population are not low, the truth is that incidence of ischaemic cardiopathy is lower than that found in other countries. If we compare them with some countries from the north of Europe, incidence is four times lower in Spain[6] (Figure 1). Yet, the clinical trials that show the efficiency of statins in primary prevention have nearly all been carried out in

Media pressure is making an illness of cholesterol when it is only a risk factor

Figure 1. Coronary events rate in different populations (No cases / 100,000 persons-year). MONICA study (Lancet 1999;353:1547-1557)
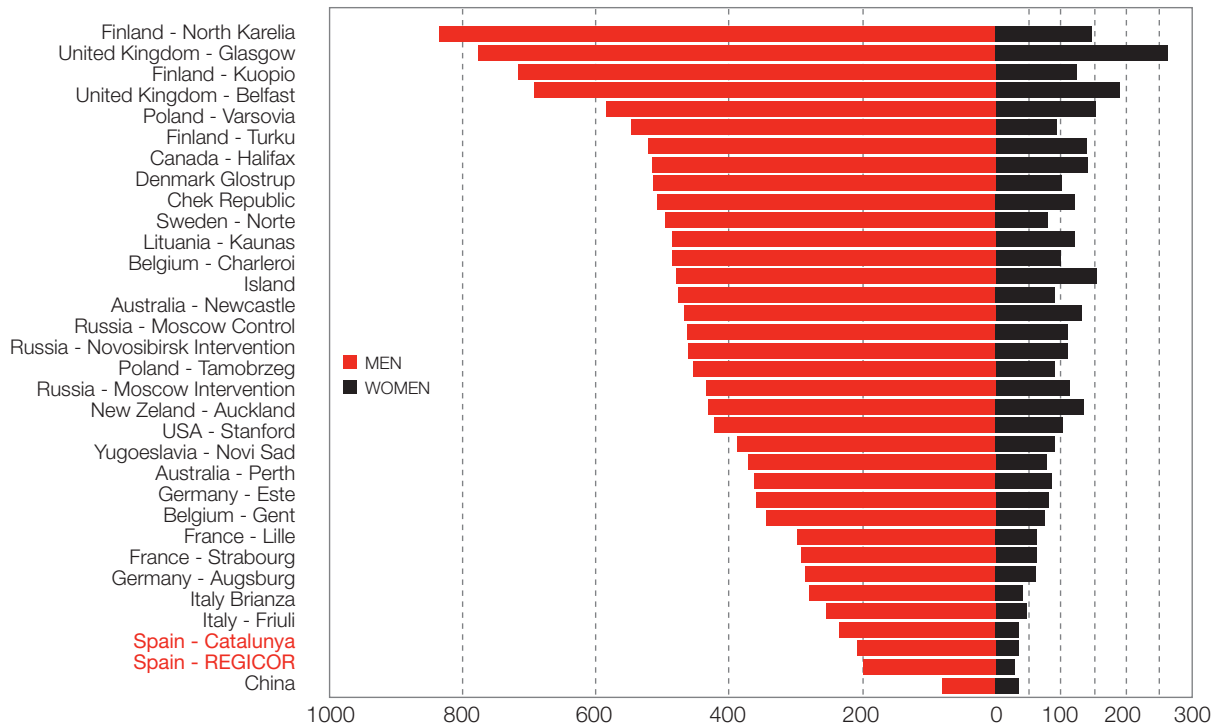
countries such as Scotland, The United States and the Nordic countries. The base risk of ischaemic cardiopathy in these countries is 3 or 4 times higher even when cholesterol figures are similar to Spain's (so-called Mediterranean paradox)[7]. To what extent are the proofs of these clinical trials comparable to our reality?

One clear example is the *Seven Countries* study which shows evidence of a 15% cardiovascular mortality for a concentration of 200 mg/dL (5.2 mmol/L) of total cholesterol in the Nordic countries and of a 3% in the southern Mediterranean countries after making adjustments for age, tobacco consumption and arterial blood pressure[7] (Fig. 2).

As regards mortality, Spain occupies a privileged place among the industrialized countries with regard to ischaemic cardiopathy, showing mortality rates for this illness which are among the lowest in the industrialized world[8]. For cerebro-vascular disease it shows an intermediate rate among these kinds of countries. Cerebro-vascular disease has been decreasing in Spain, as well as the whole group of cardiovascular illnesses, since the middle of the 1970's up to the present. This could be due, at least in part, to a better population control of blood pressure, such an important risk factor for this illness. The evolution of ischaemic cardio-

pathy is a little different in the sense that, since that same period of the mid 1970's, the rates have remained stable[9,10]. In spite of this favourable tendency and in spite of the relatively favourable position of Spain with regard to other countries, cardiovascular disease continues to be the principal cause of death in our country, in fact, responsible for 32% of deaths among males and 44% of deaths in females[10].

Several epidemiological studies have shown the relative importance of other risk factors such as tobacco, a sedentary lifestyle, obesity and hypertension and these are much greater than that of cholesterol, both in ischaemic cardiopathy as well as in cardiovascular deaths[11] (Fig. 3). The important role of hypertension in stroke stands out, es-

Smoking, sedentary life and hypertension are more important risk factors than cholesterol

Figure 2. Coronary mortality rates and total cholesterol levels after a 25-year follow up
(Kromhout D. European Heart Journal 1999;20:796-802)

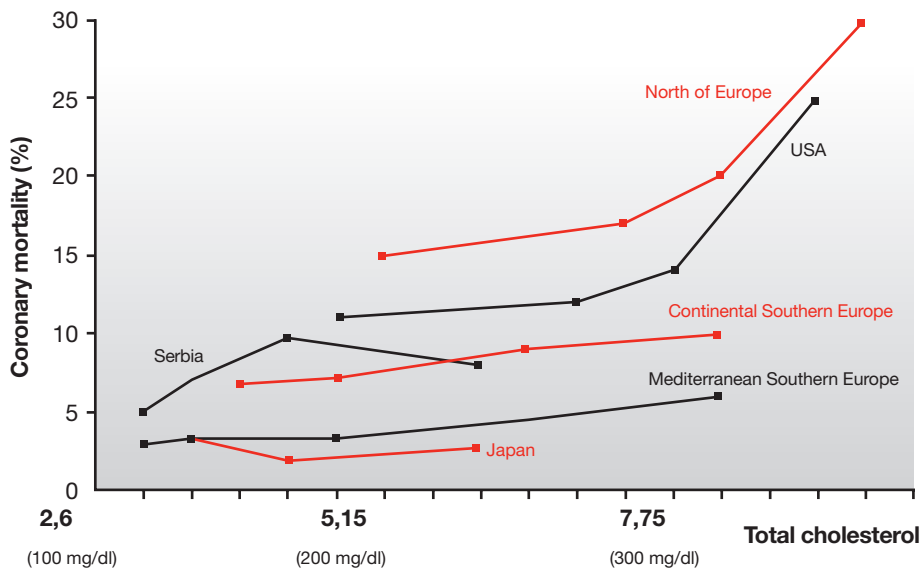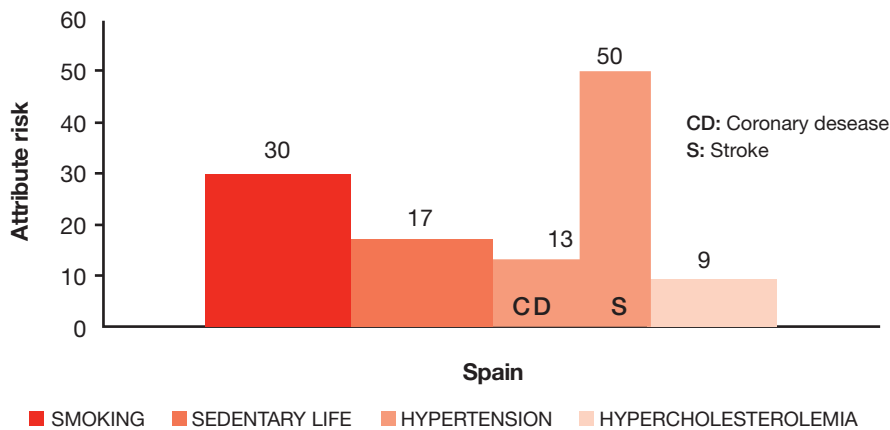### CORONARY MORTALITY RATES IN RELATION TO CHOLESTEROL LEVELS IN DIFFERENT POPULATIONS

Figure 3. Role of different risk factors in the Spanish population

ATTRIBUTE RISK OF CORONARY HEART DISEASE ACCORDING TO THE MAIN CARDIOVASCULAR RISK FACTORS IN SPAIN

Banegas JR et al. Rev Epidemiol Santé Pub 1992;40:313-322

pecially in females (where the apportioned risk is near 50%)[12]. However, many epidemiological studies have failed to encounter a relation between cholesterol and stroke[13].

Efficacy of statins in primary prevention

Here are the six main clinical trials carried out in primary prevention with statins (Table 1). Of all the-se, only the MEGA study was carried out on a low risk population. Generally, the results of these studies have been given in values of a relative risk reduction. In this way, relative decreases of 25% or 30% only correspond to a total reduction of 1% or 2% (Fig. 4).

As we can see in Table 1, risk reduction was very low, in general terms. Even so, we must bear in mind that:

Figure 4. Comparison between Mediterranean and Anglo-Saxon populations. Though relative risk reductions are similar in both cases, absolute risk is 5-fold lower in the Mediterranean population.
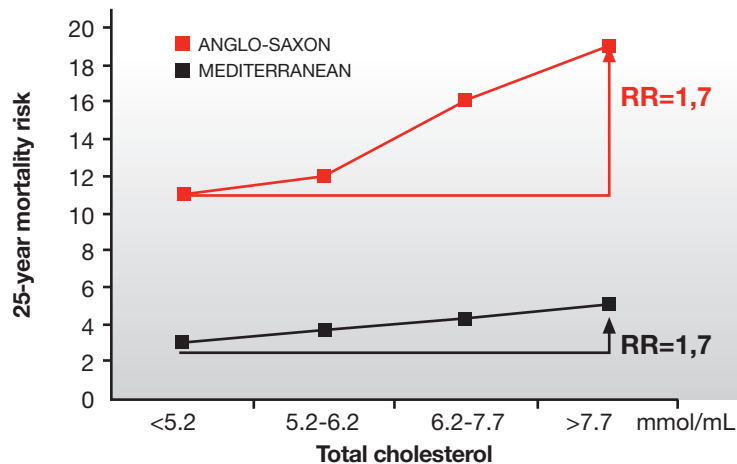

- The analysis of the evidence related to statins is frequently contaminated by four important out-of-focus features: pre-eminence of statistical significance to the detriment of clinical relevance, the privileged position of relative risk reduction as opposed to absolute reduction, the mixing of effects obtained in primary and secondary prevention and the estimated deduction of the effect are reached artificially[14].

- In none of the trials did the total mortality rate diminish in any significant way. Generally, the drop in the number of coronary events was significant, although not in all the trials, and this drop did not reach even 3% in absolute risk in any of the trials. Stroke incidence decrease was only significant in the ASCOT trial, but the clinical relevance was scant, as only an absolute risk reduction of 0.63% was produced.

- The presence in several of the trials of composite end-points makes it even more difficult to extract any assessment of the results to clinical practise. The combination of different end-points such as revascularization, non-fatal stroke, coronary death, hospital admission, etc. in order to achieve statistical significance very often raises the question of the validity of the same end-points. This would only be really valid if the following points are strictly adhered to:

  - The patients give the same importance to each of the components of the composite end-point.
  - Each component of the composite end-point, more or less important, occurs in similar frequency. If the number of events in any of the end-points included in the composite end-point is clearly higher than that in the others, then each component must be interpreted separately.

  - It is likely that the components of the composite end-point would have a similar reduction in the relative risk.
  - The components of the composite end-point have a similar physiological rationale.
  - The reductions of relative risk are similar among the components.
  - When there is a narrow confidence interval[15].

- The smaller the effect achieved in terms of risk, the more likely it is that, in practice, these findings observed in clinical trials will not arise in real life[16].

- Although the evolution and change in the LDL-c was not a primary end-point of the trials, the WOSCOP study shows that the cardiovascular benefits are similar in patients who had a baseline LDL-c<or>189 mg/dL (4.9 mmol/L), while in the AFCAPS trial no benefits are obtained when LDL-c <157 mg/dL (4.0 mmol/dL). In the PROSPER trial no benefits are obtained when LDL-c <158 mg/dL (4.0 mmol/dL) and in the ALLHAT trial no benefits were obtained in any of the cases, but there is a tendency towards an increase in the mortality rate when LDL-c<130 mg/dL. In the MEGA study, no benefit is obtained when LDL-c<155 mg/dL (4.0 mmol/dL).

Just recently a meta-analysis was published (Table 2) which includes primary prevention patients enrolled in the above-mentioned trials as well as those patients who had not suffered any cardiovascular events from the HPS trial[18] (more than 80% were in secondary prevention) and the patients from the CARDS trial[19] (diabetics in primary prevention) which will be commented on later. The authors affirm that statin therapy could reduce the absolute risk of coronary events during the next 4.3 years in a 0.75% in low-risk patients (NNT= 133), in a 1.63% (NNT=61) in moderate-risk pa-

Table 1. Outcomes of different clinical trials in cardiovascular primary prevention with statins

TRIAL	PATIENS (Inclusion criteria)	PRIMARY END-POINTS	OUTCOMES	NNT	SECONDARY END-POINTS	OUTCOMES
WOSCOP[14] 1995	Pravastatin 40 mg n=6,595; 45-64 years Follow up= 4,9 years Scotland Tot chol>6.5 mmol/mL LDLc>4.0 mmol/mL	Non-fatal MI or coronary death	RRR= 31% (17-43) ARR=2.4% p<0.001	53 (30-75)	Stroke Cardiovascular death Total mortality	RRR=11% (-33 to 40) ARR=0.16% p=0.57 RRR=32% (3-53) ARR=0.70 p=0.033 RRR=22% (0-40) ARR=0.89 p=0.051
AFCAPS[15] 1998	Lovastatin 20-40 mg N=6,605; 45-73 years California and Texas Tot chol>4.6-6.8 mmol/mL LDLc>3.4-4.9 mmol/mL	Fatal or not MI, unstable angina or sudden death	RRR= 37% (21-50) ARR=2.3% p<0.001	49 (37-86)	Coronary events Fatal coronary events Cardiovascular mortality	RRR=25% (9-38) ARR=2.79% p=0.006 ARR=0.12% p=n.a. ARR=0.25% p=n.a.
PROSPER[16] 2002	Pravastatin 40 mg N=3,229; 70-82 years Scotland, Ireland and Holland 44% secondary prev. Tot chol>4.0-9.0 mmol/mL	Coronary death, non-fatal MI or fatal or not stroke	RRR=15% (3-26) ARR=2.1% p=0.014	42 (24-206)	Coronary death or non-fatal MI Fatal or not stroke	RRR=19% (6-31) ARR=2.1% p=0.006 RRR= -3% p=0.81
ASCOT-LLA[17] 2003	Atorvastatin 10 mg N=10,305; 40-79 years Follow up=3.3 years Great Britain, Ireland and Nordic Countries 9.70% secondary prev. Tot chol<6.5 mmol/mL	Non-fatal MI or fatal coronary disease	RRR=36% (17-50) ARR=1.1% p=0.0005	94 (60-215)	Total mortality Cardiovascular mortality Stroke	RRR=13% (-6 a 29) ARR=1.7 p=0.16 RRR=10% (-23 to 34) ARR=0.5 p=0.50 RRR= 27% (4-44) ARR=0.63 p=0.023
ALLHAT-LLT[18] 2002	Pravastatin 40 mg N=10,355; >55 years Follow up=4,8 years USA, Canada and Puerto Rico 14% secondary prev. LDLc=3.0-4.9 mmol/mL	Total mortality	RRR=1% (-11 to 11) ARR=0% p=0.88	n.s.	Fatal or not coronary events Stroke	RRR=9% (-4 to 21) ARR=0% p=0.16 RRR=9% (-9 to 25) ARR=0% p=0.31
MEGA[19] 2006	Pravastatin 10-20 mg vs diet N=7,832 Follow up=5.3 years Japan Tot chol>5.7-7.0 mmol/mL	Coronary events	RRR= 33% (8-51) ARR=0.84% p=0.01	120 (78-438)	Stroke Total mortality	RRR=17% (-21 to 43) ARR=0.27% p=0.33 RRR=28% (-1 to 49) ARR=0.57 p=0.055

RRR: Relative risk reduction.　　n.a.: Not available.
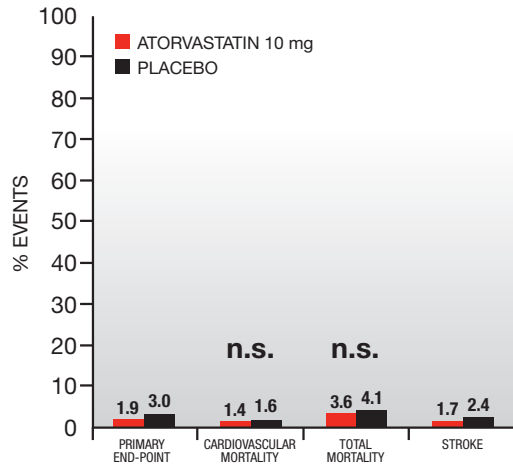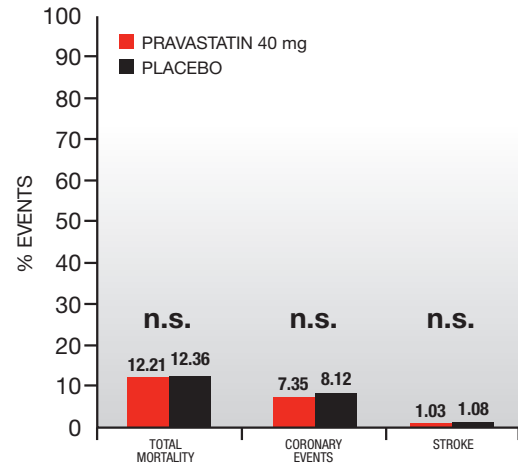ARR: Absolute risk reduction.　　n.s.: Not signifficant.
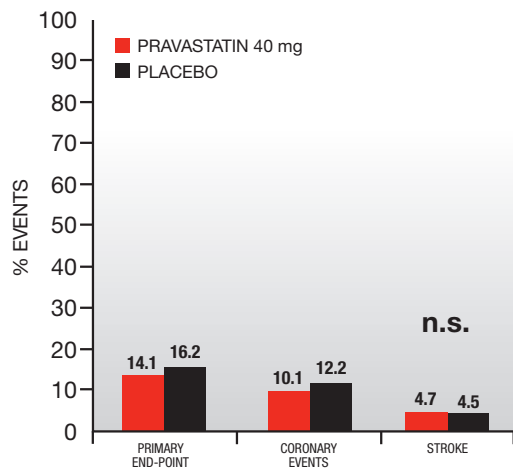

WOSCOP TRIAL
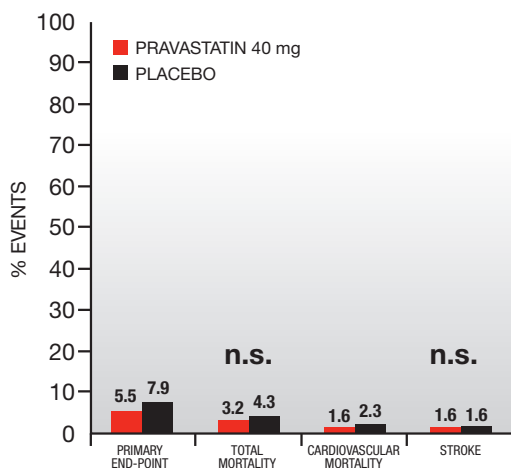
AFCAPS/TEXCAPS TRIAL
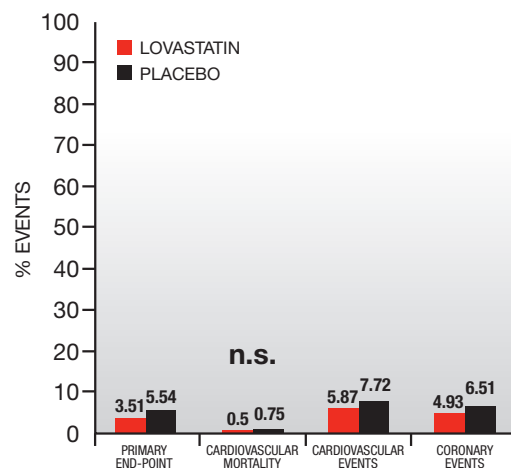
ASCOT-LLA TRIAL

ALLHAT-LLT TRIAL

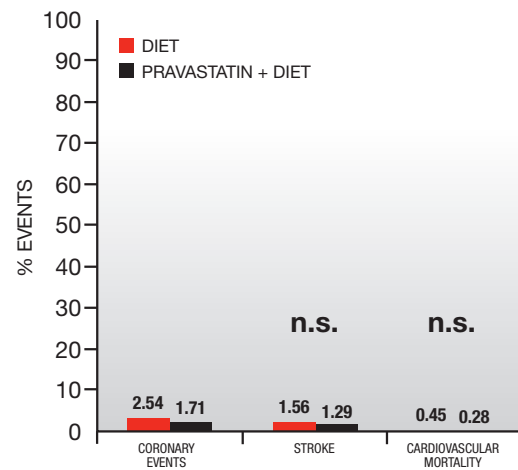## PROSPER TRIAL

MEGA TRIAL

Table 2. Outcomes of a meta-analysis carried out by Thavendiranathan et al. (Arch Intern Med 2006;166:2307-2313)

End-Point	Relative risk reduction (%)	Absolute risk reduction (%)	NNT
Primary coronary events	29,2	1,66	60 (45-106)
Stroke	14,4	0,37	268 (169-1.482)
Non-fatal MI	31,7	1,65	61 (50-74)
Revascularization	33,8	1,08	93 (76-133)
Coronary mortality	22,6*		
Total mortality	8*		

(*) not statistically significant differences

tients and in a 2.51% (NNT=40) in high-risk patients. They also conclude that it could be cost-effective in patients with an absolute risk over 20% of having a coronary event in the following 10 years. It would not be cost-effective in patients with a risk <10%, and its use would be controversial in the risk-group of 10-20%.

Primary prevention in women

As it is shown in fig 1, the risk of ischaemic cardiopathy is noticeably less in woman than in men. In fact, in the clinical trials carried out in primary prevention, the proportion of women has been quite lower.

In 2004 a meta-analysis was published in which the efficiency in primary prevention of women with high cholesterol was evaluated. Neither in total mortality, nor in cardiovascular mortality or myocardial infarction, nor in cardiovascular events was there any difference in comparison with placebo[20].

The authors of the AFCAPS study include in their conclusions women as beneficiaries of lovastatin treatment, although in this group there were no significant differences in the coronary events. This is a clear example of over-interpretation since, even if the relative reduction of risk is 47%, these differences were not statistically significant.

In the MEGA study where women represented 69% of the patients, no significant difference could be observed in coronary events (HR=0.71; 0.44-1.14). Thus, at present we have no compelling evidence that treating dyslipaemic women in primary prevention could be even minimally effective in preventing cardiovascular morbimortality. Women show a much lower risk of dying from cardiovascular disease than men and the baseline risk, as stated above, will determine the efficiency of statins.

Primary prevention in elderly patients

Of the trials carried out in primary prevention, just one of them was specifically carried out on elderly patients – the PROSPER study. This trial could almost be considered a study in secondary prevention as it includes 44% of patients with previous cardiovascular events. All the patients were over 70 years of age and with high cardiovascular risk. The primary end-point (coronary death, or non-fatal MI, or fatal or not stroke) was reduced in a 2.1% in absolute terms (p=0.014). If the data is extracted only from the aged in primary prevention, no significant differences are found between pravastatin and placebo nor in major coronary, cardiovascular, nor cerebro-vascular events. A significant 25% more cancer was indeed found in the actively treated group in comparison with placebo [HR=1.25 (CI 95%, 1.04-1.51)]. A later analysis of the PROSPER study suggests that the HDL-c could be a risk predictor in these patients and that the therapy with statins should only be used when the LDL-c is high and HDL-c <44, 5 mg/dL (1.15 mmol/mL) or at a relation LDL-c/HDL-c >3.3[21].

But the doubts and lack of evidence in the use of statins in the aged goes further than this. Different studies point, although not in a very consistent way, to an inverse relationship between low concentrations of cholesterol in aged patients and an increase in cancer. The trial which has raised most controversy is a cohort study carried out in Honolulu (patients aged 71-93 years) as part of the Honolulu Heart Program. A higher mortality rate was found in patients with a low level of cholesterol. But this effect has not only been found in Japanese patients. In a Dutch cohort over a ten-year period it was observed that in patients of more than 85 years, a high concentration of cholesterol was associated with a longer life span, basically due to less deaths from cancer and infection[23]. Whether this association can be really shown, what is surprising in itself in this study is that patients with high concentration of cholesterol did not mean a high cardiovascular risk factor.

A recent meta-analysis[24] has shown an inverse relation between total cholesterol and total mortality in persons over 80 years of age. In this meta-analysis the possibility is suggested that a reduction of cholesterol in this group would be really prejudicial.

Last year a cohort study carried out in the North of Italy was published[25]. The relationship between total or cardiovascular mortality and LDL-c levels, showed a J-shaped curve in such a way that same mortalities were observed with either high or low LDL-c levels. There was no relationship between the incidence of stroke and LDL-c levels neither in men nor in women. In men, LDL-c>150 mg/dL (3.9 mmol/mL) was related to a higher incidence of myocardial infarction, whereas LDL-c<112 mg/dL (2.9 mmol/mL) in men and LDL-c<139 mg/dL (3.6 mmol/mL) in women was associated with an increase in total mortality (Fig. 5).

In conclusion, there is no evidence to treat elderly patients with high LDL-c levels with statins in primary prevention. Severe reduction in the cholesterol levels could be counter-productive and the risk

[*Primary prevention in women and elderly people is not justified*]

Figure 5. Total and cardiovascular mortality in both male and female elderly people related to their LDL-c levels
(Tikhonoff V et al. J Am Geriatr Soc 2005;53:2159-64)
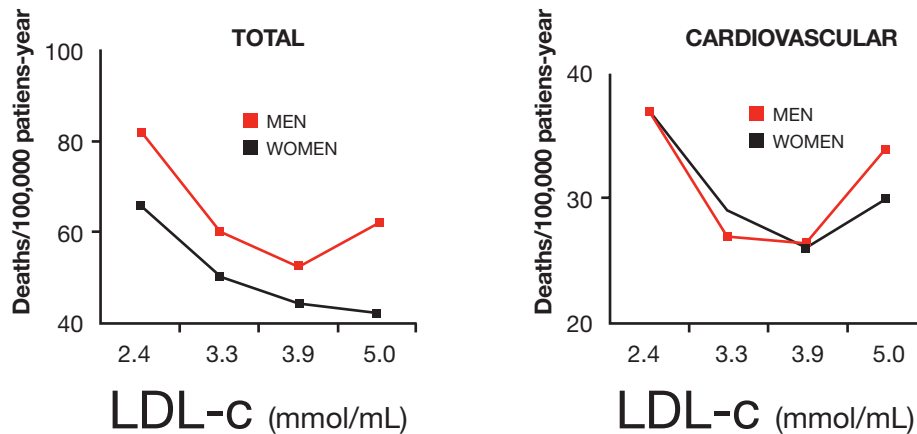
charts do not take into consideration patients older than 65 or 70 years of age.

Diabetics in primary prevention

For quite a while now, controversy has existed on whether or not diabetic patients should be considered as primary prevention patients or as secondary prevention ones[26,27]. In the trials in primary prevention the proportion of diabetics has been variable, swinging between 2.3% of the AF-CAPS/TexCAPS study up to 24.6% of the ASCOT-LLA study, which means that no clear conclusions can be drawn. In 2004 the CARDS study was published which graded the diabetic type 2 with atorvastatin as a primary prevention patient. An added condition was the fact that these diabetics did not have high cholesterol yet an inclusion criterion was LDL-c<160 mg/dL (4.1 mmol/mL).

In this study the primary end-point (coronary events, revascularization and stroke) was reduced 3.2% in absolute terms, the coronary events in a 1.9% and the stroke in a 1.3%. There were no significant differences in total mortality. The analysis of this study was the object of an article in the BIT[28], last year. This article basically criticizes the fact that the efficiency results of the trial are modest and that the authors have magnified their importance. In addition, these results are only applicable to diabetic patients with another associated risk factor and with an estimated risk of coronary events in the following ten years around 15%. Hence the importance of using specific risk charts for diabetics[29].

In July 2006, the ASPEN trial[30] was published. In this study, a total of 2,410 diabetic patients were randomly given atorvastatin 10 mg or placebo.

From this total of patients, 21% were in secondary prevention. Just as in the CARDS trial, LDL-c levels were normal or moderately increased, that is LDL-c<160 mg/dL (4.1 mmol/mL). Baseline LDL-c was 113±25 mg/dL (2.9±0.6 mmol/mL). The primary end-point was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, revascularization, coronary bypass surgery, resuscitated cardiac arrest and worsening or unstable angina needing hospitalization. This composite end-point occurred in a 13.7% in the atorvastatin group vs 15% in the placebo group [HR=0.90 (0.73-1.12), p=0.34]. Consequently, there were no significant differences in the primary end-point, but neither was there any in the secondary end-points (fatal myocardial infarction, fatal or non fatal stroke, bypass surgery and hospitalization due to angina). LDL-c was reduced by 30.48% in primary prevention patients and 29.65% in secondary prevention patients.

If we only examine the diabetic patients in primary prevention, 10.4% of atorvastatin patients and 10.8% of placebo patients underwent some kind of event considered in the composite end-point. According to this study, a 30.48% reduction in LDL-c in diabetic patients without any previous cardiovascular event and normal or moderately elevated baseline LDL-c does not serve any use at all in terms of cardiovascular morbimortality. Of

Statins efficacy in primary prevention is of scant relevance

the 505 patients in secondary prevention, the primary end-point was observed in 26.2% of the atorvastatin group and 30.8% in the placebo group and here too there were no significant differences [HR=0.82 (0.59-1.15)]. The results of this study does not confirm that obtained from the CARDS trial. The authors contend that this difference in the results can be explained by the fact that in CARDS trial the patients were more elderly, there were more hypertensive individuals, more males and more smokers.

Therefore, it is a global risk valuation which should effect the treatment of a type 2 patient with statins, as well as their level of cholesterol. Likewise, the results of this trial question the figures of LDL-c=100 mg/dL (2.6 mmol/mL), denoted as the objective in diabetic patients, given that the placebo group [baseline LDL-c=114± 26 mg/dL (2,9±0.7 mmol/mL)] did not experience more cardiovascular events than the atorvastatin group in spite of this group reduced the LDL-c by 30%. The results of the ASPEN trial have not been released by the Drug Company among professionals, while the results of the CARDS trial, as well as that of ASCOT trial, have been the object of professional meetings, talks and many promotional gatherings.

In a meta-analysis[31] published this same year, the efficiency of primary and secondary prevention with statins is analyzed in both the diabetic and non-diabetic patient. In none of the trials analyzed in this meta-analysis in primary prevention was there any significant differences in diabetic patients treated with statins and those not treated with statins. Only in an analysis of diabetic patients in the HPS trial[32] were differences found in favour of those treated with statins. In this substudy, 27% of the patients included in the analysis of primary prevention of coronary events, as well as being diabetics, had another cardiovascular disease which was not coronary. In spite of including this study, the difference of absolute risk in primary prevention of coronary disease among the diabetics treated or not treated with statins in the meta-analysis was 0.02 [(0.04-0.00) p=0.1]. Inexplicably, the authors center their conclusions in those positive results (secondary prevention and relative risks) and ignore this data.

Consequently, there is not enough evidence to recommend widespread primary prevention of car-

diovascular disease with atorvastatin for diabetics with not very high levels of cholesterol. Diabetic patients will benefit from statin treatment depending on their cardiovascular risk. On the other hand, global measures of cardiovascular prevention should be generalized for the diabetic, i.e. diet, exercise, weight control, smoking withdrawal, strict control of blood pressure and good glucose control[28].

Footnote: The genetic forms of hypercholesterolaemia (heterozygous familial hypercholesterolaemia and others) would be outside the valuations and conclusions reached in this article.

## Results in health with primary prevention with statins

As we have been able to see up to now, the results of the clinical trials must be considered as discreet, when not insignificant. One of the problems related to the chronic use of drugs in healthy patients is treatment compliance. Statin withdrawal in the clinical trials swings between 6-30% at the end of five years. However, in the environment outside the hospital this is noticeably higher. It seems that the proportion of patients that abandon the therapy increases rapidly during the first months and then continues to increase at a more moderate rate after that. In the USA, it is estimated that only 50% of patients continue with the treatment after six months and 30%-40% after one year[34]. In Australia and Great Britain studies have been published with very similar figures35,36. In Spain the data on therapy non-compliance with statins shows similar percentages, close to 50% after a year's treatment[37].

According to the clinical trials we have seen, more than 97% of the population treated will not benefit in any of the cases in terms of morbimortality. If we add to this fact that the populations under study in the trials had a baseline risk notably higher to that of the Spanish population and the compliance therapy in these drugs does not surpass 50%, we can get some idea of what the result will be in normal circumstances. The reduction of cardiovascular events in absolute risk would not reach 0.25% in practise.

Two articles were published last year that tried to explain the drop in mortality from coronary disease which took place in England and Wales between 1981 and 2000[38,39]. Of the total of deaths evaded, the authors attribute 58% of them to changes in the risk factors. Of these, the main cause was tobacco. The decline in the smoking habit was some 35% which meant 29,715 less deaths. The drop in blood pressure caused 7,755 less deaths, of which 5,865 were attributed to a long-term tendency in the drop of blood pressure (both in pri-

Diabetic patients should not be systematically considered as coronary patients

Figure 6. Role of different risk factors in the reduction of mortality rates
(Unal B et al. BMJ doi:10.1136/bmj.38561.633345.8F)
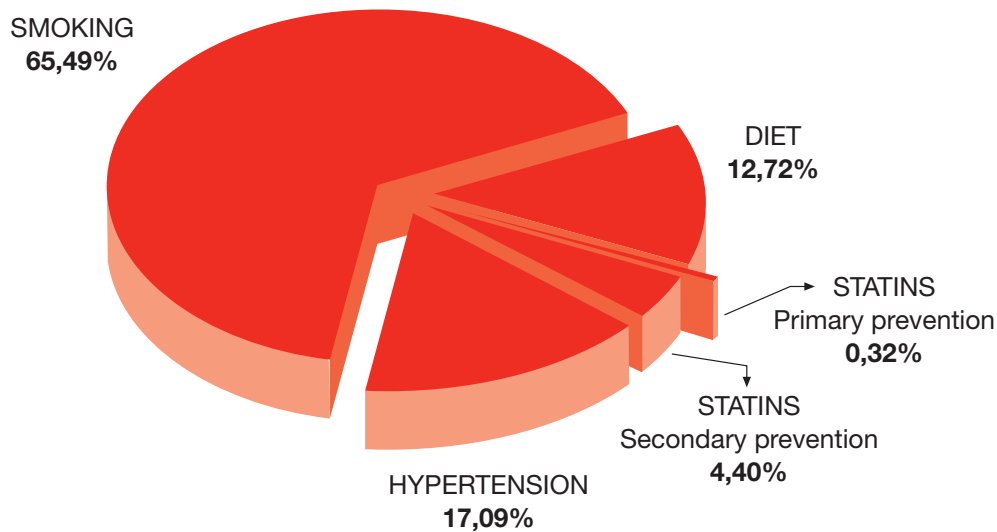
mary prevention as well as secondary) and 1,890 due to treatment in some seven million people. The reduction in cholesterol was attributed to 7,900 less deaths, 5,770 less due to diets and 2,135 were due to treatment with statins, of which only 145 would come from primary prevention (Fig. 6).

However, the resources used for the treatment of cholesterol in primary prevention are enormous. In some areas of Navarre, more than 10% of the population over 16 years take statins every day, which meant an expenditure of more than 11 million euros for the Navarre Health Service in 2006.

Benefit from statin treatment in primary prevention

Statins has only proved to be beneficial in males of very high risk and in patients with additional cardiovascular risk factors. If we have seen that only 2% of patients at best (in Spain almost certainly less) can benefit from primary prevention with statins, an efficient use of the resources makes it necessary to center treatment efforts precisely in this risk group. The way to identify the risk patients is by using risk charts. They are a resource utility in taking therapeutic decisions, but not the final or the only resort in decision-making. At present, according to the different recommendations and protocols, the percentage of the treated population could go from 6% to 40%[40].

In the computerized clinical record in Navarre, both the European SCORE charts and the REGI-

COR (Framingham charts adapted for the Spanish population) are available for General Practitioneers. Nevertheless, while both of these have advantages and disadvantages, there are a series of aspects which it is important to be aware of and which, in our opinion, make the REGICOR charts more useful than the SCORE ones when it comes to using them in deciding whether cholesterol-lowering treatment should be given in a population of low risk such as the Spanish one is.

- REGICOR classifies the patient as low coronary risk (< 5% events in the following 10 years), light (5-9%), moderate (10-19%), high (20-39%). SCORE classifies its patients in accordance with their cardiovascular mortality risk in the next 10 years, taking into consideration all those who have a risk higher than 5% as high risk.

- SCORE identifies many patients as high risk in comparison with REGICOR, since it embraces the risk towards women of advanced age, non-smokers and with moderately high cholesterol levels to the detriment of middle-aged males with high cholesterol. Also it classifies patients according to cerebro-vascular risk, which is basically connected with blood pressure and is not preventable with statins[14].

- SCORE has no specific charts available for diabetics, which obliges it to consider them, for treatment purposes, as coronary patients, something which is, at the very least, questionable[41,42].

- The application of the SCORE charts to elderly males triples the number of subjects classified as high risk in comparison with REGICOR[14].

[*Risk charts should be used before prescribing statins for cardiovascular primary prevention*]

In spite of these arguments, there are also many voices in favour of SCORE rather than REGICOR. At present, the Spanish Family Medicine Association has accepted the SCORE charts as selection charts in line with the European Associations and with the Spanish Interdisciplinary Committee for Cardiovascular Prevention. In addition, recently, some publications have appeared comparing the two charts[43]. This comparison has been made with the aim of evaluating which of the two charts best fits in with cardiovascular reality. The REGICOR utility underestimated coronary risk while SCORE overestimated cardiovascular death risk. Nevertheless, if the aim is to not only evaluate cardiovascular risk but rather to detect the patient in risk that can benefit from statin treatment, we still believe that REGICOR is the best selection for those reasons which were outlined above.

In any case, the fact of using either one of the two charts will always be a better option than prescribing a statin simply on based on an analysis.

Statins safety

In general, statins are well tolerated if the proper doses are used. The most common side effects are gastro-intestinal upsets, headaches, insomnia and rash. Statins have also been associated with myopathy, including clinically important myositis and rabdomiolisis. The risk of rabdomiolisis could be exasperated by several factors such as hepatic or renal impairment, diabetes, hypothyroidism and concomitant medication such as fibrates[44]. The frequency of rabdomiolisis seen with atorvastatin has been estimated in 4.2 cases/100.000 patients-year[45]. The most serious case was that of cerivastatin, withdrawn in 2001, and where the FDA registered 31 deaths directly associated with its consumption.

Although it is generally assumed that statins are safe drugs, some doubts do remain, especially after seeing the data of some clinical trials. In the PROSPER trial, for example, the significant increase in the number of cancer cases neutralized the scant cardiovascular benefits. In the CARE trial[46] (secondary prevention) a significant increase in breast cancer was found.

In November last year, the IDEAL trial[47] was published in which atorvastatin 80 mg was compared to simvastatin 20 mg in secondary prevention. At least 90% of the patients in either of the two groups underwent some adverse effects, where half of these cases were of some importance, so much so that nearly 10% of the atorvastatin group had to abandon the treatment. In addition, a significantly higher incidence of myalgia, diarrhoea, stomach ache and transaminase increase was found in the group with a high dose of statins. How was it possible that to have such a high difference of adverse effects in comparison with other studies? It is very likely due to a bias in selection process. In the IDEAL trial, 91% of the patients previously recruited were eventually included in the study while in the TNT trial only 54% of those did so. It is common in these trials not to select patients who are susceptible to an increase in transaminase levels with low doses of statins or who have cancer, renal or hepatic impairment, heart failure, high triglyceride levels, etc. This diminishes the external validity of the study and minimizes the adverse effects, thus creating a false sense of safety. So, the adverse effects in clinical trials with statins are usually understated[48].

Conclusions

There is a lot of media pressure stimulated by the pharmaceutical industry in order to overrate the role of LDL-c in cardiovascular disease, with the aim of converting healthy patients in "ill" consumers of statins.

Some Mediterranean countries such as ours show rates of ischaemic cardiopathy which can be as much as four times lower than in some Anglo-Saxon Countries.

Results obtained with statins from clinical trials in primary prevention are of scant relevance when not totally nil

When a population such as the Spanish one is extrapolated, only a small percentage of high-risk males can benefit from the treatment.

Mortality rates will not be affected and the maximum reduction of cardiovascular events expected is not higher than 2%.

It has not been demonstrated that statins are efficient in women or in the over 70's in primary prevention.

The diabetic should not be systematically considered as a coronary patient.

The risk charts should be used to select patients that can get some benefit from statin treatment.

Adverse side effects from statins are minimized in clinical trials, generally through a bias in patients' selection process.

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