Localizador web
Artículo 61.737

Applicability to a Different Community (External Validity) of Studies of the Primary Prevention of Hypercholesterolemia

A. Hervás Angulo, U. Lacosta Ramírez, C. Brugarolas Brufau, and J. Díez Espino

Objectives. The main objective of this study was to determine the degree of similarity between large primary prevention trials of hypercholesterolemia and our population of patients with dyslipidemia, in order to evaluate the external validity of these studies and their applicability to the general population.
Design. Descriptive retrospective study.
Setting. Tafalla Health Center in Navarra (Northern Spain), serving a population of 11 500 inhabitants.
Participants. All patients older than 18 years assigned to our health center who had dyslipidemia with no antecedents of ischemic heart disease.
Results. The percentage of patients in our sample who satisfied the inclusion criteria used in large clinical trials ranged from 2.4% to 46%, depending on the study: AFCAPS/TexCAPS 1998, 46.2%; HPS 2002, 46.1%; WOSCOPS 1995, 10.9%; HHS 1987, 10.6%; LRC-CPPT 1984, 2.4%.
Conclusions. Many of our patients (54%-97%) with dyslipidemia would not have been eligible for inclusion in earlier studies of hyperlipidemia and primary prevention. The external validity (applicability to the general population) of these studies is questionable. Decision-making in clinical practice for the primary prevention of hypercholesterolemia should be based on the risk/benefit ratio of pharmacological treatment.

Key words: Hypercholesterolemia. Primary prevention. Coronary heart disease.

APLICABILIDAD EN UNA COMUNIDAD (VALIDEZ EXTERNA) DE LOS ESTUDIOS DE PREVENCIÓN PRIMARIA DE HIPERCOLESTEROLEMIA

Objetivos. El objetivo principal de nuestro estudio es determinar el grado de similitud de los grandes ensayos clínicos de prevención primaria e hipercolesterolemia y nuestra población de pacientes con dislipemia, para valorar su aplicabilidad a la población general y la validez externa de los mismos.
Diseño. Estudio descriptivo retrospectivo.
Emplazamiento. Centro de Salud de Tafalla (Navarra); población de 11.500 habitantes.
Participantes. Todos los pacientes dislipémicos, mayores de 18 años, sin antecedentes de cardiopatía isquémica, del centro de salud.
Resultados. El porcentaje pacientes de nuestra muestra que cumplen los criterios de inclusión de los grandes estudios varía del 46 al 2,4%. En el estudio AFCAPS/TexCAPS (1998) fue del 46,2%, en el estudio HPS (2002) del 46,1%, en el estudio WOSCOPS (1995) del 10,9%, en el estudio HHS (1987) del 10,6%, y en el estudio LRC-CPPT (1984) del 2,4%.
Conclusiones. Un gran número de nuestros pacientes (97-54%) con dislipemia no serían incluidos en los estudios de hiperlipidemia y prevención primaria. Comprobamos que la validez externa (aplicabilidad a la población general) de estos estudios es cuestionable. La toma de decisiones en la práctica clínica de la prevención primaria en la hipercolesterolemia deberá basarse en la relación riesgo/beneficio de la introducción de un fármaco.

Palabras clave: Hipercolesterolemia. Prevención primaria. Cardiopatía isquémica coronaria.

Spanish version available at
www.atencionprimaria.com/87.340

A commentary follow this article (pág. 514)

*Especialistas en Medicina de Familia y Comunitaria, Centro de Salud Tafalla, Navarra, Spain.

Correspondence:
Adolfo Hervás Angulo.
Paseo Enamorados, 4, 5.º C.
31014 Pamplona. Navarra. España.
E-mail: adolhervas@hotmail.com

This research was reported at the XXII National Congress of the Spanish Society of Family and Community Medicine, Madrid, 20-23 November 2002.

Highest Honors, II Research Prize in Primary Care, Navarra Society of Family Medicine and Primary Care (SNavMFAP).

Manuscript received 21 February 2003.
Manuscript accepted for publication 25 June 2003.

Introduction

Dyslipidemia is a well established risk factor for cardiovascular disease. In 1998, ischemic heart disease in Spain was the most frequent cause of death in men and the third most frequent cause of death in women.[1] Different studies have shown the treatment of dyslipidemia to be useful in the secondary prevention of ischemic coronary heart disease.

However, questions have arisen regarding the usefulness of primary prevention in the general population.[2] Treatment for dyslipidemia in patients with no antecedents of coronary heart disease has been the subject of debate, and physiopathological, epidemiological, ethnicity and cost-effectiveness considerations have been used to argue in favor of and against such treatment.

Well-performed clinical trials have a high degree of internal validity, but their external validity for the general population has been questioned. The criteria used to select patients for large trials of the primary prevention of hypercholesterolemia have been highly restrictive in terms of age, lipid levels, sex, and concomitant diseases such as hypertension and diabetes mellitus.

Currently, the five most important trials of primary prevention of ischemic heart disease are the Lipids Research Clinics Coronary Prevention Trial (LRC-CPPT, 1984),[3] the Helsinki Heart Study (HHS, 1987),[4] the West Scotland Coronary Prevention Study (WOSCOPS, 1995),[5] the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS, 1998)[6] and the Heart Protection Study (HPS, 2002).[7] This latter trial included patients with and without coronary heart disease.

These studies have documented reductions of 19% to 37% in the risk of primary cardiovascular events or mortality from coronary heart disease as a result of lipid-lowering therapy in comparison to a placebo. However, the inclusion criteria in these studies are in general inappropriate for the general population, and are usually circumscribed to patients at high risk for cardiovascular disease. For example, women were included in only two of these trials (AFCAPS/TexCAPS[6] and HPS[7]).

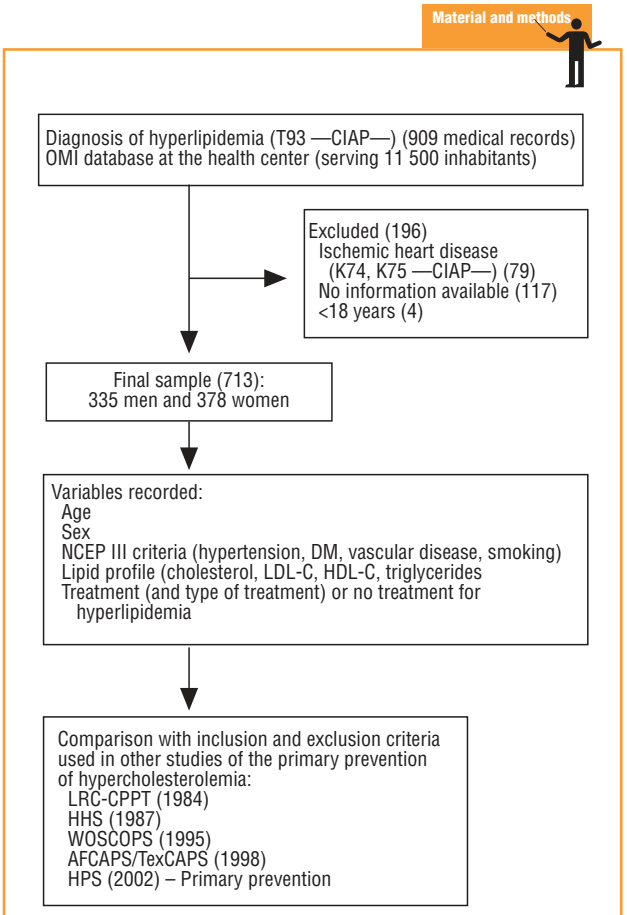
In one recent analysis (Lloyd-Jones, et al, 2001)[8] based on the population used in the Framingham[9] study, between 20% and 80% of the participants would not have been eligible for inclusion in any of the primary prevention studies done to date. Thus the applicability of the results of these studies to actual clinical practice is, to some extent, debatable.

The main objective of our study was to determine the degree of external validity of the clinical trials mentioned above for the population under our care, by determining the degree of similarity between the sample populations used in these studies and the population of persons with dyslipidemia in our setting.

Material and methods

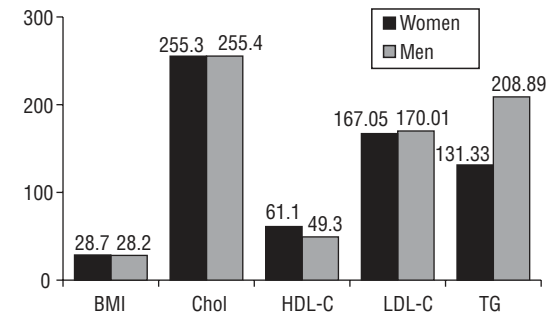
The study was done in the Tafalla basic health care area (Navarra province, Northern Spain), which serves a population of approximately 11 500.

We selected patients older than 18 years with a diagnosis of hyperlipidemia (Clasificación Internacional de Atención Primaria [CIAP] code T93) and registered in the OMI database of clinical histories, who had no personal antecedents of cardiovascular disease, i.e., acute myocardial infarction (CIAP code K74) or angina (CIAP code K75), and who were therefore eligible for primary prevention. When necessary, clinical histories recorded on paper only were used. The two exclusion criteria were any car-



General scheme of the study

Descriptive, retrospective study to evaluate the applicability of large, previously published studies of primary prevention and hypercholesterolemia in a different population.



*Mean values are shown for each group
BMI: body mass index (kg/m^2).
Chol: total cholesterol (mg/dL).
HDL-C: HDL-cholesterol (mg/dL).
LDL-C: LDL-cholesterol (mg/dL).
TG: triglycerides (mg/dL).

FIGURE 1 Distribution of lipid profiles in men and women.*

TABLE 1 NCEP-ATP III criteria

Hypertension
(Blood pressure ≥140/≥90 or antihypertensive treatment)
Diabetes mellitus
Vascular disease
Aortic aneurysm
Intermittent claudication
Peripheral artery disease
Symptomatic carotid artery disease
Smoking

diovascular event (AMI or angina) before dyslipidemia had been diagnosed, and unavailability of lipid profile data obtained before treatment was begun.

Sociodemographic data were noted for age, sex, year of birth, and year of diagnosis of hyperlipidemia. Clinical data were recorded for total, HDL-C and LDL-C, triglycerides, weight, height and body mass index (BMI, kg/m^2). We also recorded whether pharmacological treatment was prescribed to lower cholesterol levels, and the drug used (simvastatin, lovastatin, pravastatin, atorvastatin, fluvastatin, fibrates, other).

The risk factors chosen for analysis were based on NCEP III[10] criteria (Table 1), currently considered the most reliable for clinical decision-making.

For patients whose cholesterol levels were being treated pharmacologically, we recorded as the lipid profile values the earliest results entered in the medical record before treatment was begun. For patients who were not taking any lipid-lowering medication, we recorded the most recent values obtained during the previous 6 months.

A specially-designed database was used to compare the inclusion criteria in 5 earlier studies of the primary prevention of ischemic heart disease: LRC-CPPT (1984),[3] HHS (1987),[4] WOSCOPS (1995),[5] AFCAPS/TexCAPS (1998),[6] HPS(2002)[7] (Table 2). For all statistical analyses we used version 10 of the SPSS.

Results

We reviewed 909 medical records and included 713 in the analysis. Of the 196 records we excluded, 79 recorded at least one cardiovascular event, 117 lacked data on cholesterol levels before treatment was begun, and 4 were for patients younger than 18 years. Of the 731 records included, 335 were for men (47%) and 378 (53%) were for women. Mean age±SD was 61±13.7 years.

TABLE 2 Criterios de inclusión de los estudios de prevención primaria

	LRC-CPPT 1984	HHS 1987	WOSCOPS 1995	AFCAPS/TexCA 1998	HPS 2002
Molecule	**Cholestyramine**	**Gemfibrozil**	**Pravastatin**	**Lovastatin**	**Simvastatin**
Profile lipidic, mg/dL and other factors	Total cholesterol 265; LDL-C 190; TG 300	LDL-C 200	Total cholesterol 254; LDL-C 155 (triplicate analysis; one 174)	Total cholesterol 180-264; LDL-C 130-190; LDL-C 125-129 if AI>6; HDL-C or 45 or 47; TG 400	Total cholesterol* 135. Associated elevated risk CV disease at 5 years Heart disease. Artery disease. DM2 or HT
Sex	Men	Men	Men	Men; women	Men; women
Age, years	35-39	40-55	45-64	45-73; 55-73	40-80

Chol indicates cholesterol; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; TG, triglycerides; AI, atherothrombotic index; CV, cardiovascular; DM: diabetes mellitus; HT, hypertension.

TABLE 3 **Characteristics of the population we studied in comparison to the Framingham study and primary prevention studies**

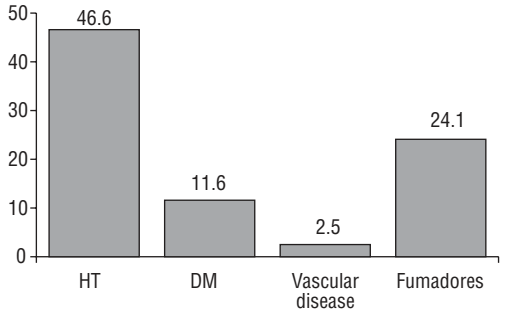
	Men							Women			
Characteristics	**FHS**	**Tafalla**	**LRC-CPPT**	**HHS**	**WOSCOPS**	**AFCAPS/ TexCAPS**	**HPS***	**FHS**	**Tafalla**	**AFCAPS/ TexCAPS**	**HPS***
Mean age, range	48 (30-74)	57 (26-90)	47 (35-59)	47 (40-55)	55 (45-64)	58 (45-73)	55 (40-80)	49 (30-74)	65 (27-92)	58 (55-73)	55 (40-80)
Cholesterol, mg/dL	213±40	255±41	279±35	289±32	272±23	221±21	227±38	218±45	255±34	222±21	227±38
HDL, mg/dL	45±12	49±14	45±10	47±11	44±10	36±5	41±13	58±16	61±16	40±5	41±13
Smokers, %	40,5	38,8	Excluded	36,2	44,0	12,4	3,6	37,6	11,1	12,4	3,6
Diabetes mellitus, %	5,2	11,3	Excluded	2,6	1,0	3,6	13,1	3,9	11,9	3,6	13,1
Hypertension, %[a]	35,8	40,0d	Excluded	14,0[b]	15,7[c]	21,9	10,4	29,8	52,5[d]	21,9	10,4

Table based on Lloyd-Jones et al[8]
Data are shown for both sexes together. This was a combined primary and secondary prevention study.
FSH indicates Framingham Heart Study;[9] LRC-CPPT, Lipids Research Clinics Coronary Prevention Trial;[3] HHS, Helsinki Heart Study;[4] WOSCOPS, West Scotland Coronary Prevention Study;[5] AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study;6 HPS, Heart Protection Study[7]. [a]HT≥140/≥90 mm Hg. [b]HT>170 mm Hg or diastolic >105 or receiving treatment. [c]History of HT or treatment. [d]HT≥140/≥90 mm Hg or treatment.

TABLE 4 **Percentage of the sample population that satisfied inclusion criteria for studies of the primary prevention of dyslipidemia**

LRC-CPPT 1984	HHS 1987	WOSCOPS 1995	AFCAPS/TexCAPS 1998	HPS 2002
Cholestyramine	**Gemfibrozil**	**Pravastatin**	**Lovastatin**	**Simvastatin**
2.4%	4.0%	10.6%	46.2%	46.1%

Total cholesterol level (mean±SD) was 255.04±37.4 mg/dL, with no significant difference between men and women (Figure 1). HDL-C level (mean±SD) was 55.7±16.2 mg/dL, and was higher in women (61.1±16 mg/dL). Notably, the HDL-C level was higher than 50 mg/dL in 60.4% of our sample. The LDL-C level (mean ±SD) was 168.4±35.1 mg/dL, with no significant difference between sexes. Triglyceride levels (mean±SD) were higher in men (208.9±177.2 mg/dL) than in women (131.33±72 mg/dL).



HT: hypertension (blood pressure ≥140/≥90 mm Hg or antihypertensive treatment).
DM: diabetes mellitus.

FIGURE 2 Percentages of risk factors according to NCEP-ATP III criteria in our sample.

Of the patients with a diagnosis of hyperlipidemia, 38.8% were taking lipid-lowering drugs. The most frequently used drug was atorvastatin (27.4%), followed by simvastatin (22.4%) and lovastatin (20.2%).

Nearly half (46.6%) of the patients in our analysis had hypertension (≥140/≥90 mm Hg) or were taking medication to lower blood pressure (Figure 2); 52.2% of these patients were women. Diabetes mellitus (DM) was recorded in 11.6% of the sample. Vascular disease was recorded in 2.5% of the medical records we reviewed. About one-fourth (24.1%) of the patients were smokers, 7.2% were ex-smokers and 51.2% had never been smokers; no information on smoking habit was recorded in the remainder of the medical records we reviewed. About three-fourths (72.5%) of the patients were overweight, with a mean BMI±SD of 28.5±4.3 kg/m^2.

The characteristics of our sample were compared with those of the population from the Framingham study[9] and earlier primary prevention studies (Table 3). Of note was the higher percentage of men with hypertension in our sample (40.0%) in comparison to other studies, the higher percentage of persons with DM (11.3%) in our sample, and the higher mean level of HDL-C. Among women included in the samples we compared, mean age was higher in our sample (65 years), as was total cholesterol level (mean±SD, 255±34 mg/dL), HDL-C (61±16 mg/dL), the percentage of women with DM (11.9%) and the percentage of women with hypertension (52.5%).

The percentage of our sample that satisfied the inclusion criteria used in each of the earlier primary prevention studies is shown in Table 4. This percentage was highest for the AFCAPS/TexCAPS study[6] (46.2%), followed in decreasing order by the HPS[7] (46.1%), the WOSCOPS[5]

Discussion
Key points

What is known about the subjec

- In 1998, ischemic heart disease in Spain was the most frequent cause of death in men, and the third most frequent cause of death in women.
- Primary prevention trials of dyslipidemia have documented reductions in the risk of a first cardiovascular event or death from coronary heart disease.
- The inclusion criteria used in different studies have usually been circumscribed to patients at high risk for cardiovascular disease.
- Well-performed clinical trials have a high degree of internal validity, but their external validity for the general population is questionable.

What this study contributes

- Many patients in our sample (54%-97%) with dyslipidemia would not have been included in any of the large studies of hyperlipidemia.
- The degree of external validity of large studies of primary prevention and hypercholesterolemia is low for our Spanish population.
- The indication for lipid-lowering pharmacological therapy should be evaluated on an individual basis in accordance with cardiovascular risk, and should not be based exclusively on cholesterol values.

(10.9%), the HHS[4] (10.6%), and the LRC-CPPT study[3] (2.4% of the population).

Discussion

The selection criteria used in different primary prevention studies of hypercholesterolemia published to date do not reflect the realities of daily practice for patients seen in our primary care service. In other words, the internal validity (degree to which the results of a given study reflect the actual status of the population under study) has been well established. However, the external validity (degree to which the results of a given study can be generalized to other individuals) is questionable.

Of the large trials published to date, those that come closest to reflecting the characteristics of the population of patients with dyslipidemia in our setting are the AFCAPS/TexCAPS[6] and the HPS,[7] for which we found a concordance of 46%. The other studies (WOSCOPS[5], HHS[4] and LRC-CCPT[3]) yielded a concordance of only 2% to 10%. These figures are similar to the results reported by Lloyd-Jones, et al[8] in their analysis of the population used for the Framingham study[9]. These authors found that 40% of the men and 80% of the women with dyslipidemia were missed by these large hyperlipidemia studies.

It should be recalled that in large studies of primary prevention and hyperlipidemia, the participants included for analysis were generally persons who had not yet had any cardiovascular event, although they were at high risk for such events. In other words, the most frequently chosen participants were middle-aged men (usually between 45 and 65 years old) with at least one associated cardiovascular risk factor (e.g., smoking, mild-to-moderate hypertension or well-controlled diabetes mellitus). However, in our sample women made up approximately 50% of the patients with dyslipidemia, a major cardiovascular risk factor. Of the large primary prevention trials published to date, only the AFCAPS-TexCAPS[6] and HPS[7] studies included women, but the degree of similarity between these studies and our sample was nonetheless only about 45%.

Another difference was that our patients with alterations in their lipid profile were older, on average, than the participants in earlier trials. In primary prevention studies, mean age of the selected patients (with the exception of the AFCAPS-TexCAPS[6] and HPS[7] studies) was usually 70 years at most. Aging of the population, and improvements in quality of life in older and oldest old patients, has meant that the percentage of older persons with hypercholesterolemia tends to increase. Pharmaceutical companies are now actively engaged in primary and secondary prevention studies in older patients. An example of such research is the PROSPER (PROSpective Study of Pravastatin in the Elderly Risk) study,[11] begun in 1999, which selected only patients aged 70 to 82 years and followed them for 3.5 years.

We can therefore say that many of our patients with dyslipidemia would not have been included in any of the large primary prevention studies of hyperlipidemia. According to the results of our analyses, these studies would have excluded from 54% to 97% of our patients.

Another factor that should be considered in evaluations of external validity is adherence to treatment, with a greater degree of commitment and control, at least initially, in clinical trials. The rate of chronic noncompliance with treatment in patients with dyslipidemia is said to be between 50% and 60%.[12,13]

To these considerations must be added the fact that the large studies used here for comparison were carried out in populations different from the one in our setting, with different dietary habits and a higher incidence of ischemic heart disease than in our setting. Consequently, the applicability of earlier findings to our population, and the risk/benefit ratio of the introduction of statins, need to be

weighed against other measures (such as public health or dietary interventions) that can be used for the primary prevention of hypercholesterolemia.[14]

Conclusions

The findings for our population sample suggest that the degree of external validity of large studies of primary prevention and hypercholesterolemia is low. Many of our patients (54%-97%) with dyslipidemia would not have been included in these large studies. We believe that in the primary prevention of coronary heart disease, the decision to use pharmacological treatment to reduce lipid levels should be based on individual factors that determine cardiovascular risk, rather than on cholesterol values alone.

References

1. Llacer A, Fernández Cuenca R, Martínez Aragón MV. Mortalidad en España en 1998. Evolución en la década 1989-1998 (I). Principales causas de muerte y de años potenciales de vida perdidos. Boletín Epidemiológico Semanal 2001;9:242-8.
2. Primary prevention of Coronary Heart Disease. Where do we go from here? [Editorial] Arch Intern Med 2001;161:922-4.
3. Lipids Research Clinics Program. The Lipids Research Clinics Coronary Prevention Trial results (I). Reduction in incidence of coronary heart disease. JAMA 1984;251:351-64.
4. Frick MH, Elo O, et al. Helsinki Heart Study: Primary Prevention Trial with Gemfibrozil in Middle-Aged Men with Dislipemia. N Engl J Med 1987;317:1237-45.
5. Sheperd J, Cobbe SM, Ford I, et al. for the West Scotland Coronary Prevention Study. Prevention of Coronary Heart Disease with Pravastatin in Men with Hipercholesterolemia. N Engl J Med 1995;333:1301-7.
5. Downs JR, Clearfield M, Weis S, et al. Primary Prevention of Acute Coronary Events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998;279:1615-22.
7. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of Antioxidant Vitamin Supplementation in 20,536 High-Risk Individuals: a Randomised Placebo-Controlled Trial. Lancet 2002;360:7-22.
8. Lloyd-Jones D, O'Donnell J, Dágostino R, Massaro J, Silbershatz H, Peter WF, et al. Applicability of cholesterol-lowering primary prevention trials to a general population. Arch Intern Med 2001;161:949-54.
9. Dawberg TR. Estudio Framingham. The Framinghan Study. The Epidemiology of Arteriosclerotic Disease. Cambridge: Harvard University Press, 1980.
10. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
11. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, et al. The Design of a Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. Prospective Study of Pravastatin in the Elderly at Risk. Am J Cardiol 1999;84:1192-7.
12. Piñeiro F, Gil VF, Pastor R, Donis M, Torres MT, Merino J. Factores implicados en el incumplimiento del tratamiento farmacológico de las dislipemias. Aten Primaria 1998;21:425-30.
13. García Navarro MD, Orozco Beltrán D, Gil Guillén V, Carratalça Munuera C, Terol Moltó C, Merino Sánchez J. Relación entre cumplimiento farmacológico y grado de control, en pacientes con hipertensión, diabetes o dislipemia. Med Clin (Barc) 2001;116(Supl 2):141-6.
14. Capella D, Bosch M. Estatinas ¿beneficio o riesgo? Med Clin (Barc) 2002;118:335-6.

COMMENTARY

External Validity of Studies on Primary Care Prevention of Hypercholesterolaemia

C. Brotons
EAP Sardenya, Servei Català de la Salut, Barcelona, Spain.

One of the limitations of clinical trials lies in the difficulty of extrapolating their results to populations other than the one investigated initially. There are two main limitations: the first arises when the inclusion and exclusion criteria are so strict that a non-negligible number of patients in daily clinical practice would not be eligible, for one reason or another, to take part in the trial. The second limitation lies in the extrapolation of the results to a population within a community whose epidemiological characteristics differ from those of the community chosen for the initial trial.
One example, now widely debated in the medical literature on the extrapolation of the results to other communities, is the case of clinical trials of the primary prevention of cardiovascular disease with lipid-lowering drugs.

Key points

- Primary prevention trials have been based mainly on populations of white men up to 79 years of age.
- For a given level of total cholesterol, the risk of dying from coronary heart disease can be up to five-fold as high in Northern Europe as in Mediterranean countries.
- New studies of lipid-lowering drugs are focussed differently: treatment aims to reduce risk levels rather than cholesterol levels.
- New evidence regarding secondary prevention suggests that all patients might benefit from statins, whereas evidence from primary prevention studies has not shown clearly that all patients at high risk — regardless of their cholesterol level — benefit from lipid-lowering treatment.

The first problem that raises concerns about the external validity of these clinical trials is age-bias and sex-bias. In an analysis of clinical trials of primary prevention published in the last 10 years, we found 4 studies (Table 1) that involved a total of 14 557 randomly assigned patients, with a mean age of 56.9 years. The WOSCOPS[1] and AFCAPS[2] trials included the largest numbers of participants. The WOSCOPS and KAPS[3] trials recruited men only; in the AFCAPS trail 85% of the participants were men, and women (48%) were best represented in the ACAPS[4] trial. Overall, of the 14 557 participants, 13 129 (90%) were men. The WOSCOPS and AFCPAS trials were the only ones to yield significant findings; the latter included patients up to 73 years of age. Information on ethnicity was included only in the reports of the ACAPS and AFCAPS trials. Both were carried out in the USA, and white persons made up 92% and 89% of the population, respectively.

Primary prevention trials have therefore been based on populations consisting predominantly of white males — a feature that makes it difficult to extrapolate the findings to populations of older persons, women, and non-white persons. A meta-analysis of primary prevention studies with statins confirmed the lack of benefit in terms of overall mortality, probably because the reduction in coronary heart disease was too small to influence overall mortality.
The WOSCOPS trial was the first to find net benefits of statins for primary prevention. The AFCAPS trial confirmed the benefits and extended them to persons at lower risk (mean cholesterol 5.7 mmol/L). The number needed to treat (NNT) to prevent 1 myocardial infarction was 42 in the WOSCOPS study, and 50 in the AFCAPS trial. A study that simulated the application of the results of the WOSCOPS trial in a Spanish population estimated that if the trial had been carried out in Spain, and assuming the same reduction in relative risk (RRR 31%), the NNT would be 161, or four-fold as high as in the original study, because the baseline risk for the Spanish population is much lower than in Scotland, where the WOSCOPS trial was done.[5] Moreover, cohort studies such as the Seven Countries Study showed that for a given cholesterol level, the risk of death from coronary heart disease varied in different countries[6]. Specifically, for a cholesterol level of 5.2 mmol/L the risk of death from coronary causes was five-fold as high in Northern Europe as in Mediterranean countries (15% vs 3%). This was the origin of the so-called «French paradox» (probably also applicable to Spain), which showed that with an equally unfavorable risk profile (for example, a mean level of total cholesterol of 6.1 mmol/L in men and 6.5 mmol/L in women in France from 1985 to 1990, and practically identical values in the UK), the rate of ischemic heart disease in France was around 25% the rate found in the UK.
More recent studies with lipid-lowering drugs[7,8] have been carried out in high-risk populations that included patients with a history of cardiovascular disease or other risk factors without a history of disease. The MRC/BHF Heart Protection Study and Anglo-Scandinavian Cardiac Outcome Trial-Lipid Lowering Arm represent a new approach to the design of trials with lipid-lowering drugs, as

TABLE 1 **Characteristics of clinical trials of statins for primary prevention**

Name and year	Pacients	Follow-up (months)	Mean age	Range	Men (%)	Reduction LDL (%)	Significant findings	Ethnicity
ACAPS, 1994	910	34	62	40-79	52	28	No	92% White
WOSCOPS, 1995	6595	57	55.3	45-64	100	26	Reduction MI and death	Not reported
KAPS, 1995	447	36	57	44-65	100	27	No	Not reported
AFCAPS, 1998	6605	62	58	45-73	85	25	Reduction MI	89% White 3% Black 7% Hispanic

the aim of treatment was not to reduce cholesterol levels, but to reduce risk. The HPS[7] trial enrolled more than 20 000 persons in the UK, and subgroup analyses were possible for age, sex, total cholesterol level and previous history of coronary heart disease. Although the benefits were spectacular in practically all subgroups, analysis of the application of the results in clinical practice is more complex than for the «pure» clinical trials of primary prevention measures noted above. For example, if we wished to compare patients without previous coronary disease assigned to receive simvastatin or placebo, we have no information on the number of patients with non-coronary vascular diseases who were included in each subgroup. Likewise, if we wished to compare the results in the subgroup of women, or the subgroup of participants more than 70 years old, no information is available on the proportion of these participants who had a previous history of coronary heart disease. These subgroups probably contained patients with prior vascular disease, given that 41% of the entire study population had a previous history of myocardial infarction, and 24% had a history of other coronary heart disease. Of the remaining 35% — participants with no history of coronary heart disease — 25% had a history of cerebrovascular disease, and 38% had a history of peripheral vascular disease. Consequently, about 87% of the population in the study had one or more cardiovascular diseases, meaning that the HPS trial should perhaps be considered a secondary prevention study. The results of the HPS trial showed that all patients who had a vascular event probably benefited from treatment with a statin regardless of their cholesterol level.

The ASCOT[8] study enrolled patients in the UK and Scandinavian countries with hypertension who were at high risk for cardiovascular disease but who did not have a prior history of coronary heart disease. This study can thus be considered a test of the primary prevention of coronary heart disease (but not of cardiovascular disease, as nearly 20% of the patients in both the group assigned to receive atorvastatin and the placebo group had antecedents of some other cardiovascular disease).

In the ASCOT study a cholesterol level below 6.5 mmol/L (approximately 260 mg/dL) was the criterion, with mean values of 5.5 mmol/L (approximately 220 mg/dL) in both groups. These values were slightly lower than those obtained in the AFCAPS trial described above.

The ASCOT study reported a significant 36% reduction in the combined endpoint of death and myocardial infarction after 3.3 years´ follow-up in a population aged 40 to 79 years. However, it is notable that no significant differences were found in certain subgroups such as women, patients with diabetes, or patients with a prior history of vascular disease.

Thus it is that some issues raised by now classical studies of primary prevention, such as the benefits for women or for persons older than 75 years, remain unresolved. The questions surrounding the benefits that would be expected if these trials had been done in populations with a lower baseline risk, such as the inhabitants of Mediterranean areas, also remain unanswered.

References

1. Furberg CD, Adams HP, Applegate WB, Byington RP, Espeland MA, Hartwell T, et al. Effect of lovastatin on early carotid artherosclerosis and cardiovascular events. Circulation 1994;90:1679-87.
2. Sheperd J, Cobbe SM, Ford I, Isles CG, Lormier AR, Macfarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1301-7.
3. Salonen R, Nyyssonen K, Porkkala E, Rummkainen J, Belder R, Park J, et al. A population based primary prevention trial of the effect of LDL lowering on atherosclerotic progresión in carotid and femoral arteries. Circualtion 1995;92:1758-64.
4. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol level. JAMA 1998;279:1615-22.
5. Brotons Cuixart C. Implicaciones en la práctica clínica de los megaestudios sobre prevención primaria con estatinas. Rev Esp Cardiol 1997;50:295-9.
6. Kromhout D. On the waves of the Seven Countries Study. A public health perspective on cholesterol. Eu H J 1999;20:796-802.
7. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.
8. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfied M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcome Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial.