REYES & REYES
A B O G A D O S

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMI
E. S. D.

REF: **Expediente No. 11-163-910**

TÍTULO SOLICITADO: **"Cápsulas que comprenden eicosapentaenoato de etilo y una estatina"**

PUBLICACIÓN: **Gaceta 647 de 29/06/2012, Nº de publicación 839.**

PRIORIDAD: **US 61/173.759 de 29/04/2009**

SOLICITANTE: **AMARIN CORPORATION PLC**

APODERADO: **LUZ CLEMENCIA DE PAEZ**

TRÁMITE: **Pronunciamiento frente al Recurso de Reposición contra la Resolución 17840 de Marzo 19 de 2014, por la cual se niega una patente de invención.**

JOSÉ LUIS REYES VILLAMIZAR, conocido apoderado de la sociedad **TECNOQUÍMICAS S.A.** en el asunto de la referencia, de manera respetuosa, e invocando la defensa del orden jurídico en materia de Propiedad Industrial, me permito remitir información fundamentada, orientada a demostrar que el **Recurso de Reposición** interpuesto por el solicitante el 5 de mayo de 2014 contra la Resolución 17840 de Marzo 19 de 2014, carece de fundamento, y que por ello, la decisión de negación proferida en dicha resolución deberá mantenerse incólume.

I. RATIFICACION

Sírvase ratificar la negación del beneficio patentario a la solicitud contenida en el expediente 11-163-910, por incumplir los requisitos materiales de patentabilidad establecidos por el Título II, Capítulo I de la Decisión 486 de 2000. Lo anterior, con base en los argumentos, fundamentos y pruebas que dentro de los términos que oportunamente he presentado a ese Despacho, y en los argumentos que planteo en el presente memorial.

II. ARGUMENTOS SOBRE LOS FUNDAMENTOS DEL RECURSO Y MOTIVOS DE INCONFORMIDAD

El Recurso de Reposición contra la Resolución 17840 de Marzo 19 de 2014 por la cual se niega a la solicitud 11-163-910 el privilegio de patente de invención solicitado para el capítulo reivindicatorio de la invención titulada **"Composiciones farmacéuticas que contienen EPA y un agente cardiovascular y métodos para emplearlas"**, afirma que está en desacuerdo con el análisis de patentabilidad del Examinador y solicita la reconsideración de la negación por argumentos que no parecen aportar evidencia o demostrar que estas composiciones posean nivel inventivo:

D1 no indica que el activo sea estatina

Según el recurrente, D1 no revela el uso de la estatina en la composición:

> documento D1 establece que una composición incluyendo una grasa poliinsaturada puede incluir, *inter alia* "otros principios activos y/o drogas", pero no indica que el otro principio activo y/o droga pueda ser estatina, tal como lo reconoce el Examinador en la resolución pendiente.

Sin embargo, se observa que D1 indicaba que los ácidos grasos poliinsaturados podrían llegar a ser combinados con otros principios activos que tuvieran actividad complementaria o sinérgica:

> [0021] The drug suitable for use according to the present invention can also comprise other active principles and/or drugs, in association, possessing activity complementary to or synergic with that of the drug suitable for use according to the invention, and also at least one pharmaceutically acceptable vehicle and/or one diluent and/or one surfactant and/or one thickener and/or one binder and/or one lubricant and/or one aromatizer and/or one colorant and/or one stabilizer and the like, which can easily be selected by the expert of the art. Of the stabilizers, antioxidants such as vitamin E (tocopherol), ascorbyl palmitate, ascorbic acid, hydroxytoluene and the like, which can be easily selected by the expert of the art, are particularly preferred.

Por lo tanto, el Examinador eligió adecuadamente el documento como el más cercano, pues éste indicaba composiciones para realizar prevención primaria de eventos cardiovasculares que contenían ácidos poliinsaturados y que podían ser combinados con otros principios activos para lograr un efecto sinérgico.

Ahora bien, según D1, existen una serie de eventos cardiovasculares en las que son usados los ácidos grasos poliinsaturados como se ve a continuación:

> **[0015]** The use of polyunsaturated fatty acids of the w-3 series according to the invention is particularly indicated if the occurrence of a major event is predicted, such as an infarct, in particular of the myocardium, death from a cardiological cause, or sudden death, and where such an occurrence takes place in cardiopathic subjects affected, for example, by coronary ischemia, arrhythmia, atrial and/or ventricular fibrillation, electrical hyperexcitability of the myocardium cells, disorder of the diffusion of electrical excitement or of electrical conduction of the myocardium, or cardiac disorders of mechanical type, for example cardiac insufficiency or cardiac decompensation, possibly affected by diabetic pathology concomitant with the cardiopathy.

Teniendo en cuenta las indicaciones anteriores, la **combinación sinérgica** con estatinas era obvia pues en el estado del arte son ampliamente conocidos los efectos de las estatinas como se observa en el articulo siguiente: LaRosa JC, He J, Vupputuri S. Effect of Statins on Risk of Coronary Disease: A Meta-analysis of Randomized Controlled Trials. *JAMA.* 1999;282(24):2340-2346:

> IN A VERY IMPORTANT SENSE, THE CHOlesterol "controversy" is no more. A spate of recent clinical trials using 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) to lower low-density lipoprotein cholesterol (LDL-C) have demonstrated beyond reasonable doubt that coronary events, both morbid and mortal, can be prevented.[1-8] Post hoc analyses of these trials also strongly suggest that stroke rates may be reduced to about the same degree. Observational epidemiology has not identified hypercholesterolemia as a major risk factor for stroke,[9] although these data did not distinguish hemorrhage from atherothrombotic stroke.

Incluso, LaRosa et al., muestra que a la fecha de prioridad de la patente denegada el efecto de las estatinas sobre el colesterol total, LDL-C, triglicéridos y HDL-C ya era conocido:

Effects of Statins on Lipids

The net changes in lipids (percentage change in treatment group – percentage change in placebo group) among those attending follow-up for lipid measurements are shown in Table 1. The mean reduction (weighted by sample size) in total cholesterol, LDL-C, and triglyceride levels was –20%, –28%, and –13%, respectively, and HDL-C was increased by an average of 5% among the 5 trials. The estimates excluded participants who were lost to follow-up before the end of the trial, although those participants were still included in end-point analysis. Assuming that there were few differences in changes in serum lipids between treatment and control groups among dropouts, the differences in lipid changes between treatment and control groups among all participants were likely somewhat smaller than these estimates.

Como se ha demostrado hasta aquí, para un técnico medio en la materia habría sido obvio combinar los ácidos grasos poliinsaturados con las estatinas para conseguir una combinación

D2 no sugiere la combinación reclamada

En cuanto a D2, el recurrente dice que no motivaría al técnico versado en la materia a formular una composición como la reclamada:

> trámite de la presente solicitud, que las enseñanzas de D2 alejarían a una persona versada en la materia a combinar un ácido graso poliinstarurado y un segundo ingrediente medicinal dentro de un recubrimiento de una capsula. Sin embargo, el Examinador insiste que una persona versada en la materia a partir de las capsulas de D1 se vería motivada a adicionar el ingrediente activo estatina revelado en D1, con el fin de obtener el objeto de la presente invención y por lo tanto, concluye que la materia acá reivindicada se deriva de manera obvia u evidente a partir de las enseñanzas del estado de la técnica.

A partir de D2, se observa que efectivamente se sugiere en esta anterioridad la combinación de ácidos grasos con un segundo agente activo:

Means for Solving the Problems

[0010]

In order to solve the problems as described above, the present invention provides a jelly composition comprising a polyunsaturated fatty acid as a first pharmaceutical component; a second pharmaceutical component; an emulsifier; and a gelling agent.

Adicionalmente, D2 revela que el segundo activo podría ser un agente antihiperlipidémico(p.16):

alkaloid narcotics such as synthetic narcotics. Among these, the preferred are antihyperlipidemic agents,

que pueden ser estatinas:

[0018]

Exemplary antihyperlipidemic agents include statin drugs (HMG-CoA reductase inhibitors) such as pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin, cerivastatin, pitavastatin, and rosuvastatin; fibrates such as bezafibrate and fenofibrate; squalene synthase inhibitor (such as TAK-475); and cholesterol absorption inhibitor (such as ezetimibe). The preferred are statin drugs such as pravastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin.

De lo anterior, es claro que D2 si sugería al técnico medio en la materia la combinación de ácidos grasos con estatinas, siendo de este modo, capaz de afectar el nivel inventivo de la materia reclamada.

D2 sugiere gel o gelatina altamente viscosa

El recurrente dice que D2 no revela tabletas sino geles y gelatinas:

> No obstante, en contraste a lo señalado por el Examinador, el documento D2 expresamente enseña en contra de incorporar una combinación de un ácido graso poliinsaturado y un segundo ingrediente medicinal dentro de un caparazón de cápsula. Por ejemplo, el documento D2 establece en el párrafo [003] que varios gramos por día de la PUFA se administrarían típicamente, resultando "en los problemas de dificultad de tomar una cápsula grande, dificultad de tomar muchas cápsulas a la vez, y similares". El documento D2 luego explica que estos problemas son más relevantes cuando múltiples drogas son administradas al mismo tiempo (D2: párrafo [0004]). En estos casos "formas de dosis de preparaciones convencionales como las tabletas, **cápsulas**, polvos y gránulos no han sido siempre fáciles de tomar" y pueden resultar en complicaciones adicionales como neumonía y aspiración (D2: párrafos [0004] y [0005]) (énfasis añadido). En vez el documento D2 enseña que las combinaciones de PUFAs y un segundo ingrediente medicinal se deben administrar como un gel o gelatina altamente viscosa (D2: [0005]).

Sin embargo, se observa que D2 si mencionaba el uso de formas farmacéuticas sólidas y semisólidas en este tipo de composiciones. Por lo tanto, no es posible afirmar que D2 aleja a la persona versada en la materia de la creación o formulación de una forma farmacéutica sólida que contenga estos productos, pues la misma anterioridad menciona que puede prepararse en cualquiera de las preparaciones convencionales.

El efecto técnico: La reducción de triglicéridos sin aumento de LDL-C

En cuanto al efecto logrado por las composiciones reclamadas, el recurrente menciona que el Examinador no reconoce tal efecto como inesperado sino como parte del régimen de administración:

> Además, es importante resaltar que en la declaración del Dr. Paresh Soni presentada junto el memorial de respuesta a la acción oficial No. 17791, el declarante reconoce que de forma inesperada se encuentra que la administración de 2 g o 4 g por día de una capsula en donde EPA de etilo representa 96%-100% de los ácidos grasos encapsulados ("AMR101"), a sujetos en terapia con estatina resultó en la reducción de triglicéridos **mientras que inesperadamente no aumentó LDL-C.**
>
> De otro lado, de acuerdo con el Examinador, el efecto obtenido en la reducción de los triglicéridos sin incrementar el LDL-C no se debe a la composición farmacéutica sino al régimen de administración en un lapso de tiempo. A este respecto, mi representada desea

En este aspecto, se pone de presente que lo natural frente a las estatinas es que los triglicéridos y el LDL-C se reduzcan en los pacientes, como ya lo mostraba LaRosa et al.:

Table 1. Characteristics of 5 Randomized Controlled Cholesterol-Lowering Trials Using Statin Drugs*

Characteristics	4S[1] (1994)	WOSCOPS[3] (1995)	CARE[4,5] (1996)	AFCAPS/TexCAPS[7] (1998)	LIPID[8] (1998)
No. of participants	4444	6595	4159	6605	9014
Follow-up, mean, y	5.4	4.9	5.0	5.2	6.1
Study drug	Simvastatin	Pravastatin	Pravastatin	Lovastatin	Pravastatin
Baseline data					
Age, mean, y	59	55	59	58	62
Age ≥65 y, %	23	0	31	21	39
Women, %	19	0	14	15	17
History of myocardial infarction, %	79	0	100	0	64
Cholesterol level, mean, mmol/L†					
Total cholesterol	6.75	7.03	5.40	5.71	5.64
LDL-C	4.87	4.97	3.59	3.89	3.88
HDL-C	1.19	1.14	1.01	0.95	0.93
Triglycerides	1.50	1.84	1.76	1.78	1.58
Net change in lipid levels, mean, %					
Total cholesterol	−26	−20	−20	−19	−18
LDL-C	−36	−26	−28	−27	−25
HDL-C	+7	+5	+5	+5	+5
Triglycerides	−17	−12	−14	−13	−11

*4S indicates Scandinavian Simvastatin Survival Study; WOSCOPS, West of Scotland Coronary Prevention Study; CARE, Cholesterol and Recurrent Events trial; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; LIPID, Long-term Intervention With Pravastatin in Ischaemic Disease trial; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.
†To convert total cholesterol, HDL-C, and LDL-C from mmol/L to mg/dL, divide by 0.02586. To convert triglycerides from mmol/L to mg/dL, divide by 0.01129.

Por lo tanto, contrario a lo que dice el recurrente:

> La declaración establece claramente que la falta de aumentos en LDL -C en los sujetos que recibieron las cápsulas de la prueba fue inesperado. En consecuencia, no entendemos por qué el Examinador concluye que la declaración no establece que la

según los documentos de la anterioridad, era de esperarse que **no aumentara el LDL-C en presencia de las estatinas**, más aún, cuando éstas se encuentran en combinación con los ácidos grasos.

D1 y D2 no enseñan o sugieren las composiciones reveladas

El recurrente menciona que ni D1 ni D2 anticipaban o sugerían el efecto técnico logrado por las composiciones reclamadas:

> ésteres (ver , por ejemplo , los párrafos [0004] a [0009]) . Sin embargo, D1 no proporciona enseñanza o sugerencia en relación con que sus composiciones puedan reducir los triglicéridos sin aumentar el LDL - C .
>
> Asimismo, D2 no enseña o sugiere que las composiciones allí reveladas son capaces de reducir los niveles de triglicéridos sin aumentar el LDL - C . En contraste, D2 se limita a afirmar que " El paciente que está tomando EPA -E para la hiperlipidemia a menudo sufren de complicaciones con otras enfermedades. . . . " (ver párrafo [0004] de

En el caso de D2, el recurrente menciona que no revela ninguna indicación para modificar la solución:

> solución al problema técnico". Como se demostró anteriormente el documento D2 no solamente no divulga la solución de la invención reivindicada sino que además sus enseñanzas se alejan de esta, es decir, no existe en el documento D2 ninguna indicación para modificar la solución y luego combinarla con el documento D1 a fin de llegar a la invención reivindicada, por lo que se concluye que la presente solicitud no es obvia (ver pág. 70 del Instructivo).

Frente a lo anterior y como se ha venido argumentando en el presente escrito, el Señor Examinador eligió correctamente las anterioridades D1 y D2, pues estos documentos si revelaban la combinación de ácidos grasos poliinsaturados con estatinas para obtener composiciones sinérgicas frente a eventos cardiovasculares.

En efecto, una persona medianamente versada en la materia si habría encontrado sugerencias suficientes en D1 y D2 para llegar a la composición denegada; adicionalmente, no hay efectos inesperados en lo presentado por el recurrente, pues la LaRosa et al., mencionaban el efecto reductor de las estatinas sobre los lípidos (colesterol total, LDL-C)

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que el Despacho decrete además de la ratificación de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. PRUEBAS

Ruego que se tengan como pruebas de este pronunciamiento, además de los documentos mencionados en el texto del mismo, todos ellos aportados por el suscrito en sus escritos de oposición y sustentación, la siguiente:

- LaRosa JC, He J, Vupputuri S. Effect of Statins on Risk of Coronary Disease: A Meta-analysis of Randomized Controlled Trials. *JAMA*. 1999;282(24):2340-2346.

Señor Superintendente,

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Effect of Statins on Risk of Coronary Disease
A Meta-analysis of Randomized Controlled Trials

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Suma Vupputuri, MPH

Context Lowering low-density lipoprotein cholesterol (LDL-C) is known to reduce risk of recurrent coronary heart disease in middle-aged men. However, this effect has been uncertain in elderly people and women.

Objective To estimate the risk reduction of coronary heart disease and total mortality associated with statin drug treatment, particularly in elderly individuals and women.

Data Sources Trials published in English-language journals were retrieved by searching MEDLINE (1966–December 1998), bibliographies, and authors' reference files.

Study Selection Studies in which participants were randomized to statin or control treatment for at least 4 years and clinical disease or death was the primary outcome were included in the meta-analysis (5 of 182 initially identified).

Data Extraction Information on sample size, study drug duration, type and dosage of statin drug, participant characteristics at baseline, reduction in lipids during intervention, and outcomes was abstracted independently by 2 authors (J.H. and S.V.) using a standardized protocol. Disagreements were resolved by consensus.

Data Synthesis Data from the 5 trials, with 30 817 participants, were included in this meta-analysis. The mean duration of treatment was 5.4 years. Statin drug treatment was associated with a 20% reduction in total cholesterol, 28% reduction in LDL-C, 13% reduction in triglycerides, and 5% increase in high-density lipoprotein cholesterol. Overall, statin drug treatment reduced risk 31% in major coronary events (95% confidence interval [CI], 26%-36%) and 21% in all-cause mortality (95% CI, 14%-28%). The risk reduction in major coronary events was similar between women (29%; 95% CI, 13%-42%) and men (31%; 95% CI, 26%-35%), and between persons aged at least 65 years (32%; 95% CI, 23%-39%) and persons younger than 65 years (31%; 95% CI, 24%-36%).

Conclusions Our meta-analysis indicates that reduction in LDL-C associated with statin drug treatment decreases the risk of coronary heart disease and all-cause mortality. The risk reduction was similar for men and women and for elderly and middle-aged persons.

JAMA. 1999;282:2340-2346 www.jama.com

IN A VERY IMPORTANT SENSE, THE CHOlesterol "controversy" is no more. A spate of recent clinical trials using 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) to lower low-density lipoprotein cholesterol (LDL-C) have demonstrated beyond reasonable doubt that coronary events, both morbid and mortal, can be prevented.[1-8] Post hoc analyses of these trials also strongly suggest that stroke rates may be reduced to about the same degree. Observational epidemiology has not identified hypercholesterolemia as a major risk factor for stroke,[9] although these data did not distinguish hemorrhage from atherothrombotic stroke.

Most subjects in these studies have been middle-aged men. This led to the suggestion that while elevated LDL-C is a risk factor in women as well as in men and in older as well as in middle-aged individuals, the data from these trials cannot be extrapolated to groups other than middle-aged men. It has been further suggested that, in the absence of such sex- and age-specific data, cholesterol screening is optional except in middle-aged men.[10] This has encouraged some insurers, including Medicare, to refuse funding for cholesterol screening in older individuals. While it is difficult to prove, lack of support even for screening may contribute to the rather poor frequency of prescription of cholesterol-lowering regimens even for women with established coronary disease.[11]

With 1 exception,[3] the major statin cholesterol-lowering trials with clinical event end points have included women and those aged 65 years or older. All have reported similar effects in women vs men and in younger vs older subjects. Two trials have issued expanded reports of their findings.[2,5,6]

Meta-analysis of these studies can provide a more accurate and precise estimate of subgroup effects than can be derived from individual trials.[12] It also provides the opportunity to examine, in the aggregate, the effect of statin-induced cholesterol lowering in men and women across a wide age spectrum.

METHODS

Study Selection

A literature search of the MEDLINE database (1966–December 1998), using the Medical Subject Headings *hydroxymethyl-glutaryl-CoA reductase inhibitors*, *simvastatin*, *lovastatin*, *pravastatin*, *coronary disease*, and *myocardial infarction* as well as the key words *statin*

Author Affiliations: Office of the President, State University of New York Health Science Center at Brooklyn, Brooklyn, NY (Dr LaRosa); and the Department of Epidemiology, Tulane University Medical Center, New Orleans, La (Dr He and Mr Vupputuri).
Financial Disclosure: Dr LaRosa is chairman of the steering committee of the Treating to New Targets Study, a Parke-Davis/Pfizer study of atorvastatin-induced cholesterol lowering in patients with coronary artery disease; he has also received occasional honoraria for speaking or consulting from Bristol-Myers Squibb, Merck & Co, Novartis, and Bayer.
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and *coronary heart disease* was performed. The search was restricted to studies published in English-language journals, conducted in human subjects, and classified as clinical trials in the MEDLINE database. A manual search was also performed using the authors' reference files and reference lists from original communications and review articles.[13-15] The contents of 182 abstracts or full-text manuscripts identified during our literature search were reviewed to determine whether they met the criteria for inclusion. Of these abstracts and manuscripts, 29 statin drug treatment trials were identified. Other publications included reviews, letters to the editor, subgroup analysis, and secondary analysis of data from the 29 published trials.

For inclusion, a study had to meet the following criteria: (1) random allocation of study participants to statin or a placebo control group; (2) no intervention difference, other than use of a statin, between the treatment and control groups; (3) intervention duration of at least 4 years; and (4) clinical disease or death as the primary end point. The mean intervention duration in all outcome trials was more than 4 years. Five trials met these criteria and were included in the meta-analysis.[1-8]

Major reasons for exclusion of studies were intervention duration of less than 4 years[16-36] and trial primary end points that were not clinical events.[16-38] Additional reasons for exclusion of studies included comparison of different statin drugs[33] and comparison of aggressive or moderate cholesterol lowering with statin drug treatment.[39]

Data Abstraction

All data were abstracted in duplicate using a standardized protocol and reporting form. Disagreements were resolved by consensus. We did not contact authors to request additional information. Study characteristics recorded were as follows: (1) first author's name, year of publication, and country of origin; (2) number of participants; (3) mean age and age and sex distributions of participants; (4) presence of preexisting myocardial infarction; (5) baseline mean total, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels; (6) net changes in lipids during intervention; (7) type and dosage of statin drug; and (8) intervention duration.

Major coronary events during treatment were abstracted as the primary outcome. They included coronary death, nonfatal myocardial infarction, silent myocardial infarction, or resuscitated cardiac arrest in the Scandinavian Simvastatin Survival Study (4S)[1]; coronary death or nonfatal myocardial infarction in the West of Scotland Coronary Prevention Study (WOSCOPS),[3] the Cholesterol and Recurrent Events Trial (CARE),[4,5] and the Long-term Intervention With Pravastatin in Ischaemic Disease (LIPID) trial[8]; and fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).[7] In addition, data were abstracted on fatal coronary heart disease, cardiovascular disease deaths, noncardiovascular deaths, and all-cause deaths during treatment.

Statistical Analysis

Both proportional (1 – odds ratio [OR]) and absolute risk reduction were used to measure the effect of statin drug treatment on clinical outcomes. The numbers of various outcomes for both the statin and placebo groups were recorded for each study using 2×2 tables. The Peto method was used to calculate pooled ORs of outcomes associated with statin therapy.[40] For each trial, the number of individuals in the treatment group in whom an end point of interest was observed (O) was compared with the number that would, if treatment had no effect, have been expected (E) on the basis of the overall experience in the treatment and control groups combined. If treatment was beneficial, then O – E would tend to be negative. The O – E values from each trial were summed and z statistics were used to test whether the total of O – E values differed from 0. Odds ratios were calculated by using $[(O - E)/V]$, where V was the variance of the O – E total.[40] To calculate the pooled absolute risk, each study was weighted by its sample size $(N_t \times N_c)/(N_t + N_c)$, where N_t and N_c were sample sizes for statin therapy and control groups, respectively. The number needed to treat was calculated by taking the reciprocal of the absolute risk reduction. This represents the number of patients who would have to be treated to prevent 1 outcome event.

A series of prestated subgroup analyses was performed to examine the effect of statin drug treatment on major coronary events. First, the risk reductions of major coronary events and deaths were compared between 2 primary prevention trials[3,7] and 3 secondary prevention trials.[1,4,8] Furthermore, the risk reductions of major coronary events were calculated by sex and age groups. Four of the 5 trials included participants who were women or aged at least 65 years.[1,4,7,8] Three of these trials planned subgroup analyses by sex and age group (≥65 years) in their original proposal.[1,4,8] One trial[7] only reported subgroup analysis by median age, which was 57 years for men and 62 years for women.

A sensitivity analysis was conducted to explore the impact of excluding small nonoutcome trials with short intervention duration (<4 years) on risk estimates. Twelve trials that were excluded from the primary analysis and reported at least 1 major coronary event were included in this analysis.[16-20,23,25,27-30,37]

RESULTS

Study Design and Participants

Study design and participant characteristics for the 5 randomized, placebo-controlled, double-blind trials included in our meta-analysis are presented in TABLE 1. A total of 30 817 participants were included in these trials. Mean follow-up time was 5.4 years and mean age was 59 years. Only men younger than 65 years were included in WOSCOPS, while women and participants who were aged 65 years or older were included in the remaining 4 trials. Three trials (4S, CARE, and LIPID) were conducted in patients with

a history of coronary heart disease (secondary prevention trials) and 2 trials (WOSCOPS and AFCAPS/TexCAPS) were conducted in a healthy population (primary prevention trials).

In 4S, patients with serum total cholesterol levels of 5.5 to 8.0 mmol/L (213-309 mg/dL) and triglyceride levels of 2.5 mmol/L (221 mg/dL) or less while following a lipid-lowering diet were eligible for participation.[1] In WOSCOPS, men with serum LDL-C levels of at least 4.0 mmol/L (155 mg/dL) at screening visits (at least 1 LDL-C measurement of ≥4.5 mmol/L [174 mg/dL] and 1 of ≤6.0 mmol/L [232 mg/dL]) while following a lipid-lowering diet were eligible for participation.[3] In CARE, patients with total serum cholesterol levels of less than 6.2 mmol/L (240 mg/dL), LDL-C levels between 3.0 and 4.5 mmol/L (116-174 mg/dL), and triglyceride levels of less than 4.0 mmol/L (354 mg/dL) were eligible.[4] Total cholesterol levels between 4.65 and 6.82 mmol/L (180-264 mg/dL), LDL-C levels between 3.36 and 4.91 mmol/L (130-190 mg/dL), and HDL-C levels of 1.16 mmol/L (45 mg/dL) or less for men and 1.22 mmol/L (47 mg/dL) or less for women were used as entry criteria in AFCAPS/TexCAPS.[10] A broad range of serum total cholesterol levels (4.0-7.0 mmol/L [155-271 mg/dL]) and triglyceride levels of less than 5.0 mmol/L (443 mg/dL) were used as entry criteria for LIPID.[8] Mean baseline levels of serum lipids in the 5 trials reflected these inclusion criteria.

Effects of Statins on Lipids

The net changes in lipids (percentage change in treatment group − percentage change in placebo group) among those attending follow-up for lipid measurements are shown in Table 1. The mean reduction (weighted by sample size) in total cholesterol, LDL-C, and triglyceride levels was −20%, −28%, and −13%, respectively, and HDL-C was increased by an average of 5% among the 5 trials. The estimates excluded participants who were lost to follow-up before the end of the trial, although those participants were still included in end-point analysis. Assuming that there were few differences in changes in serum lipids between treatment and control groups among dropouts, the differences in lipid changes between treatment and control groups among all participants were likely somewhat smaller than these estimates.

Effects of Lipid Reduction on Coronary Disease and Mortality

Overall, 2042 major coronary events and 748 coronary deaths occurred in participants assigned to placebo and 1490 events and 543 deaths occurred in those allocated to active treatment (TABLE 2). When the results from the 5 trials were pooled, a significant reduction in the odds of major coronary events and coronary deaths ($P<.001$ for both) was observed among the participants allocated to active treatment. The reduction in coronary events was 31% (95% confidence interval [CI], 26%-36%) and the reduction in fatal coronary disease was 29% (95% CI, 20%-36%). Compared with control groups, active treatment was associated with an absolute risk reduction in coronary disease of 36 events and 13 deaths per 1000 patients. The number needed to treat was 28 to prevent a major coronary event and 75 to prevent a death from coronary disease.

Overall, 1297 deaths (868 from cardiovascular disease and 429 from noncardiovascular disease) occurred in control participants and 1046 (646 from cardiovascular disease and 400 from noncardiovascular disease) occurred in those assigned to active treat-

Table 1. Characteristics of 5 Randomized Controlled Cholesterol-Lowering Trials Using Statin Drugs*

Characteristics	4S[1] (1994)	WOSCOPS[3] (1995)	CARE[4,5] (1996)	AFCAPS/TexCAPS[7] (1998)	LIPID[8] (1998)
No. of participants	4444	6595	4159	6605	9014
Follow-up, mean, y	5.4	4.9	5.0	5.2	6.1
Study drug	Simvastatin	Pravastatin	Pravastatin	Lovastatin	Pravastatin
Baseline data					
Age, mean, y	59	55	59	58	62
Age ≥65 y, %	23	0	31	21	39
Women, %	19	0	14	15	17
History of myocardial infarction, %	79	0	100	0	64
Cholesterol level, mean, mmol/L†					
Total cholesterol	6.75	7.03	5.40	5.71	5.64
LDL-C	4.87	4.97	3.59	3.89	3.88
HDL-C	1.19	1.14	1.01	0.95	0.93
Triglycerides	1.50	1.84	1.76	1.78	1.58
Net change in lipid levels, mean, %					
Total cholesterol	−26	−20	−20	−19	−18
LDL-C	−36	−26	−28	−27	−25
HDL-C	+7	+5	+5	+5	+5
Triglycerides	−17	−12	−14	−13	−11

*4S indicates Scandinavian Simvastatin Survival Study; WOSCOPS, West of Scotland Coronary Prevention Study; CARE, Cholesterol and Recurrent Events trial; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; LIPID, Long-term Intervention With Pravastatin in Ischaemic Disease trial; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.
†To convert total cholesterol, HDL-C, and LDL-C from mmol/L to mg/dL, divide by 0.02586. To convert triglycerides from mmol/L to mg/dL, divide by 0.01129.

ment (Table 2). Compared with controls, those receiving active treatment had a 21% reduction in the odds of total mortality (95% CI, 14%-28%; $P<.001$) and a 27% reduction in the odds of cardiovascular mortality (95% CI, 19%-34%; $P<.001$). Active treatment was also associated with an absolute risk reduction of 16 deaths from all causes and 14 deaths from cardiovascular disease per 1000 patients. The number needed to treat was 61 to prevent a death from all causes and 69 to prevent a death from cardiovascular disease. Noncardiovascular mortality was similar in active treatment and control groups (OR, 0.93; 95% CI, 0.81-1.07; $P = .29$).

Treatment Effects in Primary and Secondary Prevention Trials

Two primary prevention trials with 13 200 participants and 3 secondary prevention trials with 17 617 participants were included in this meta-analysis. Active treatment was associated with a 34% risk reduction (95% CI, 23%-43%; $P<.001$) in major coronary events in the 2 primary prevention trials and a 30% risk reduction (95% CI, 24%-35%; $P<.001$) in the 3 secondary prevention trials. Compared with controls, active treatment was associated with a lower risk of coronary disease mortality (OR, 0.73; 95% CI, 0.51-1.05; $P = .09$), cardiovascular mortality (OR, 0.68; 95% CI, 0.50-0.93; $P = .01$), and all-cause mortality (OR, 0.87; 95% CI, 0.71-1.06; $P = .18$) in the 2 primary prevention trials. Likewise, active treatment was associated with a lower risk of coronary disease mortality (OR, 0.71; 95% CI, 0.63-0.80; $P<.001$), cardiovascular mortality (OR, 0.73; 95% CI, 0.66-0.82; $P<.001$), and all-cause mortality (OR, 0.77; 95% CI, 0.70-0.85; $P<.001$) in the 3 secondary prevention trials. Active treatment was not significantly associated with change in noncardiovascular mortality in the 2 primary prevention trials (OR, 1.04; 95% CI, 0.80-1.35; $P = .75$) or in the 3 secondary prevention trials (OR, 0.89; 95% CI, 0.75-1.04; $P = .15$).

Table 2. Overall Risk Reduction for Major Coronary Events and Deaths From Coronary Disease, Cardiovascular Disease, and All Causes*

	No. of Events		Proportional Risk Reduction, % (95% CI)†	Absolute Risk Reduction per 1000 (95% CI)	No. Needed to Treat (95% CI)	P Value
	Placebo	Statin				
Major coronary events‡	2042	1490	31 (26 to 36)	36 (29 to 43)		<.001
4S,[1] 1994	622	431	38 (29 to 46)	86 (61 to 111)		<.001
WOSCOPS,[3] 1995	248	174	31 (16 to 44)	23 (11 to 34)		<.001
CARE,[4,5] 1996	274	212	25 (10 to 38)	30 (10 to 49)	28 (23-34)	.002
AFCAPS/TexCAPS,[7] 1998	183	116	38 (21 to 50)	20 (10 to 30)		<.001
LIPID,[6] 1998	715	557	25 (16 to 34)	35 (21 to 50)		<.001
Coronary deaths	748	543	29 (20 to 36)	13 (9 to 18)		<.001
4S	189	111	43 (38 to 55)	35 (20 to 50)		<.001
WOSCOPS	52	38	27 (−10 to 52)	4 (−1 to 10)		.13
CARE	119	96	20 (−5 to 39)	11 (−2 to 25)	75 (56-112)	.11
AFCAPS/TexCAPS	15	11	27 (−58 to 66)	1 (−2 to 4)		.44
LIPID	373	287	25 (12 to 36)	19 (8 to 30)		<.001
Cardiovascular deaths	868	646	27 (19 to 34)	14 (10 to 19)		<.001
4S	207	136	36 (20 to 49)	32 (16 to 48)		<.001
WOSCOPS	73	50	32 (3 to 52)	7 (0 to 14)		.03
CARE	130	112	15 (−11 to 34)	9 (−5 to 23)	69 (52-103)	.23
AFCAPS/TexCAPS	25	17	32 (−25 to 63)	2 (−1 to 6)		.22
LIPID	433	331	25 (14 to 36)	23 (11 to 34)		<.001
Noncardiovascular deaths	429	400	7 (−7 to 19)	2 (−2 to 6)		.29
4S	49	46	6 (−41 to 38)	1 (−7 to 10)		.76
WOSCOPS	62	56	10 (−29 to 38)	2 (−5 to 8)		.57
CARE	66	68	−3 (−45 to 27)	−1 (−12 to 10)	. . .	.87
AFCAPS/TexCAPS	52	63	−21 (−76 to 16)	−3 (−10 to 3)		.30
LIPID	200	167	17 (−2 to 33)	7 (−1 to 16)		.08
All-cause deaths	1297	1046	21 (14 to 28)	16 (11 to 22)		<.001
4S	256	182	31 (16 to 44)	33 (16 to 51)		<.001
WOSCOPS	135	106	22 (0 to 40)	9 (0 to 18)	61 (45-95)	.05
CARE	196	180	9 (−12 to 26)	8 (−10 to 25)		.38
AFCAPS/TexCAPS	77	80	−4 (−43 to 24)	−1 (−8 to 6)		.81
LIPID	633	498	24 (14 to 33)	30 (17 to 44)		<.001

*CI indicates confidence interval; see footnote to Table 1 for expansion of study names; ellipses, data not applicable.
†Woolf χ^2 tests for heterogeneity were not significant for major coronary events or coronary, cardiovascular, noncardiovascular, or all-cause deaths (P for all ≥.95).
‡Major coronary events included coronary death, nonfatal myocardial infarction, silent myocardial infarction, or resuscitated cardiac arrest in 4S; coronary death or nonfatal myocardial infarction in WOSCOPS, CARE, and LIPID; and fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death in AFCAPS/TexCAPS.

Treatment Effects by Sex and Age

Odds ratios of major coronary events associated with statin treatment from individual trials stratified by sex are given in the FIGURE, top. In all trials, the odds of coronary events were reduced for those assigned to active treatment compared with controls, and the risk reduction was statistically significant in 2 of 4 trials in women and all 5 trials in men. The overall proportional risk reduction was similar for women (29%; 95% CI, 13%-42%; $P<.001$) and men (31%; 95% CI, 26%-35%; $P<.001$) (TABLE 3). The absolute risk reduction was also similar in women (33 per 1000; 95% CI, 13-52 per 1000) and men (37 per 1000; 95% CI, 29-44 per 1000).

In all trials, the odds of coronary events were reduced in active treatment compared with controls stratified by age group (Figure 1, bottom). The risk reduction was statistically significant in all 4 trials among persons aged at least 65 years and in 4 of 5 trials among persons younger than 65 years. The overall proportional risk reduction was similar for persons aged at least 65 years (32%; 95% CI, 23%-39%; $P<.001$) and persons younger than 65 years (31%; 95% CI, 24%-36%; $P<.001$) (Table 3). The absolute risk reduction, however, was slightly higher in persons aged at least 65 years (44 per 1000; 95% CI, 30-58 per 1000) compared with persons younger than 65 years (32 per 1000; 95% CI, 24-40 per 1000).

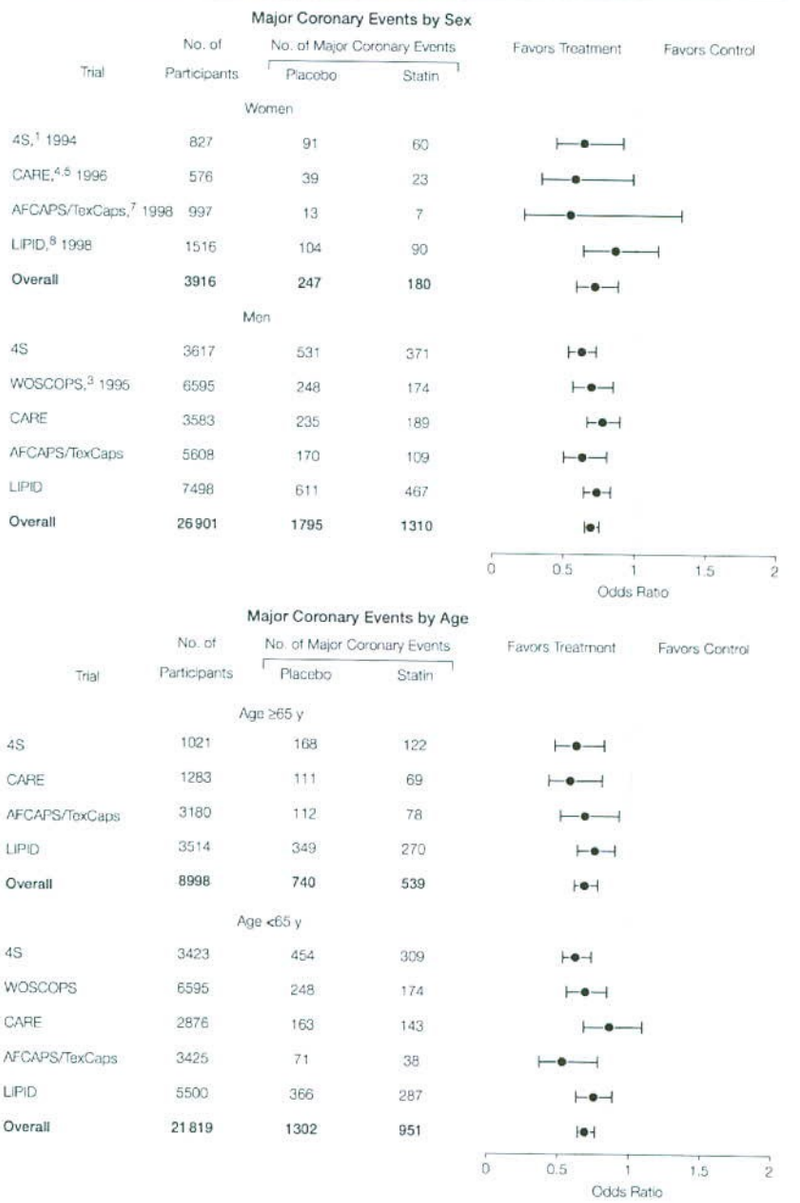
Sensitivity Analysis

After including 12 small nonoutcome trials, estimates for risk reduction were virtually unchanged. Among 17 trials, 19 597 participants were allocated to placebo and 24 601 to active treatment. Of those, 2159 and 1618 developed major coronary events, 776 and 589 died from coronary heart disease, 905 and 697 died from cardiovascular disease, 447 and 410 died from noncardiovascular disease, and 1352 and 1107 died from all causes for the control and active treatment groups, respectively. The corresponding proportional risk reduction was 31% (95% CI, 26%-35%; $P<.001$) for major coronary events, 28% (95% CI, 19%-35%; $P<.001$) for fatal coronary disease, 27% (95% CI, 19%-34%; $P<.001$) for cardiovascular disease mortality, and 22% (95% CI, 15%-28%; $P<.001$) for all-cause mortality. The mortality from noncardiovascular disease was not significantly different between placebo and treatment groups (OR, 0.91; 95% CI, 0.80-1.04; $P = .18$).

Safety

Overall, 1021 cancer cases occurred in participants who were allocated to placebo and 1009 in participants who were

Figure. Relative Odds of Major Coronary Events Associated With Statin Treatment From Individual Trials and Overall by Sex and Age



Error bars indicate 95% confidence intervals; see footnote to Table 1 for expansion of study names.

allocated to active treatment (OR, 0.99; 95% CI, 0.90-1.08; $P = .76$). Forty study participants had asymptomatic episodes of elevated creatine kinase concentrations (>10 times the upper reference limit) in the control group compared with 50 in the active treatment group (OR, 1.25; 95% CI, 0.83-1.89; $P = .29$). Two hundred fifty-eight participants had increased aspartate or alanine aminotransferase levels (>3 times the upper reference limit) in the control group compared with 290 in the active treatment group (OR, 1.13; 95% CI, 0.95-1.33; $P = .17$).

COMMENT

A clear and consistent effect of statin-induced LDL-C lowering in significantly reducing the risk of coronary events, independent of sex or age, has been demonstrated in the individual studies and the meta-analysis presented here. A roughly 30% decline in coronary events is seen in all sex and age groups studied. There are insufficient data from published results (except in CARE and 4S)[2,5,6] to draw any conclusion about sex- or age-specific mortality. Ongoing trials will provide additional information on the effects of LDL-C lowering by statins by sex and age.[41-43]

It is clear that there is no effect of these interventions on noncardiovascular mortality. Neither those studies whose participants had initially high cholesterol levels (4S, LIPID, and WOSCOPS) nor those whose initial cholesterol levels were lower (CARE and AFCAPS/TexCAPS) reported any increase in noncardiovascular mortality. Because these studies were limited for approximately 5 years, they cannot offer information other than the possible effects of longer exposure to statins or cholesterol lowering. Some of the guidelines and policies that resulted from an unwillingness to extrapolate earlier reported data to women and the elderly should be revisited. Policies designed to limit screening in women and elderly persons[10] make no sense and, in fact, are potentially harmful because they diminish in the eyes of both the public and the practicing physician the importance of cholesterol interventions in these groups.

The recent results of the Heart and Estrogen/Progestin Replacement Study (HERS)[44] failed to demonstrate benefit on cardiovascular events with a regimen of conjugated equine estrogen and medroxyprogesterone (in dosages of 0.625 and 2.5 mg/d, respectively). At this point, therefore, hormone replacement therapy should not be looked on as an alternative to vigorous interventions to lower LDL-C levels in women, who make up two thirds of the population aged 65 years or older.[45]

Finally, currently available data do

Table 3. Overall Risk Reduction for Major Coronary Events by Sex and Age: Results From 5 Randomized Controlled Trials*

	No. of Events		Proportional Risk Reduction, % (95% CI)†	Absolute Risk Reduction per 1000 (95% CI)	Number Needed to Treat (95% CI)	*P* Value
	Placebo	Statin				
Sex						
Women	247	180	29 (13 to 42)	33 (13 to 52)		<.001
4S,[1] 1994	91	60	37 (10 to 56)	69 (17 to 122)		.01
CARE,[4,5] 1996	39	23	43 (3 to 66)	54 (4 to 104)	31 (19-75)	.04
AFCAPS/TexCAPS,[7] 1998	13	7	46 (−31 to 78)	12 (−5 to 29)		.17
LIPID,[8] 1998	104	90	15 (−15 to 37)	18 (−16 to 51)		.30
Men	1795	1310	31 (26 to 35)	37 (29 to 44)		<.001
4S	531	371	38 (28 to 47)	90 (62 to 118)		<.001
WOSCOPS,[3] 1995	248	174	31 (16 to 44)	23 (11 to 34)		<.001
CARE	235	189	22 (5 to 36)	26 (5 to 47)	27 (23-34)	.02
AFCAPS/TexCAPS	170	109	37 (20 to 50)	22 (10 to 33)		<.001
LIPID	611	467	27 (17 to 36)	39 (23 to 55)		<.001
Age‡						
≥65 y	740	539	32 (23 to 39)	44 (30 to 58)		<.001
4S	168	122	38 (19 to 53)	98 (43 to 154)		<.001
CARE	111	69	42 (20 to 57)	65 (27 to 103)	23 (17-33)	<.001
AFCAPS/TexCAPS	112	78	32 (8 to 49)	21 (5 to 38)		.01
LIPID	349	270	25 (11 to 37)	42 (17 to 67)		.001
<65 y	1302	951	31 (24 to 36)	32 (24 to 40)		<.001
4S	454	309	38 (27 to 47)	83 (55 to 110)		<.001
WOSCOPS	248	174	31 (16 to 44)	23 (11 to 34)		<.001
CARE	163	143	14 (−9 to 32)	14 (−8 to 37)	31 (25-41)	.21
AFCAPS/TexCAPS	71	38	47 (22 to 63)	19 (8 to 31)		.001
LIPID	366	287	25 (12 to 37)	31 (13 to 48)		<.001

*CI indicates confidence interval; see footnote to Table 1 for expansion of study names. Major coronary events included coronary death, nonfatal myocardial infarction, silent myocardial infarction, or resuscitated cardiac arrest in 4S; coronary death or nonfatal myocardial infarction in WOSCOPS, CARE, and LIPID; and fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death in AFCAPS/TexCAPS.

†Woolf χ^2 tests for heterogeneity were not significant for major coronary events or coronary, cardiovascular, noncardiovascular, or all-cause deaths (P for all >.95).

‡Age older than 57 years in men and older than 62 years in women were used in AFCAPS/TexCAPS.

not allow us to draw any conclusions about the effects on total mortality in these sex and age groups beyond those that are already published. It would, however, be wrong to conclude that an effect on morbidity has no implications for the potential effects on mortality. The prevention of a morbid event also prevents that individual from graduating into a much higher risk category for subsequent mortality.

In fact, the benefits of LDL-C lowering on morbidity, particularly in older age groups, have been underappreciated. Prevention of morbid events results in lower prevalence of congestive heart failure, angina, significant arrhythmia, and debilitating strokes. Such interventions are likely to have a beneficial effect on both the quality of life for the individual patients and the cost of caring for older subjects imposed on families and society. By placing undue attention on mortality alone as a measure of the success or failure of an intervention, clinicians fail to account for the importance of avoiding such disabilities. It is irrational to deny the demonstrable benefits of LDL-C lowering by sex and age while we await more definitive information about mortality, particularly given the lack of evidence that statin-induced LDL-C lowering in any way increases noncardiovascular morbidity or mortality.[15]

In summary, the benefits of LDL-C lowering induced by statins appear to be universal, not defined by sex or age. It is important now to work to extend these benefits to all who are at risk for atherosclerotic cardiovascular disease.

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