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Risk factors for a major coronary event after myocardial infarction in the Scandinavian Simvastatin Survival Study (4S)

Impact of predicted risk on the benefit of cholesterol-lowering treatment

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Aims To analyse (1) the prognostic importance of clinical findings and lipids in patients with a previous myocardial infarction and (2) the relative and absolute benefit of simvastatin in patients at low, medium and high predicted risk.

Methods The 4S was a double-blind, randomized, clinical trial of long-term treatment with simvastatin or matching placebo in patients with myocardial infarction or angina pectoris, serum total cholesterol 5·5–8·0 mmol . l^{-1}, and serum triglycerides $\leq$2·5 mmol . l^{-1}. The present study only deals with those 3525 patients who had a previous myocardial infarction. End-points comprised coronary death, definite and probable hospital verified myocardial infarction, and resuscitated cardiac arrest. Because there were few women the primary analyses were performed among men.

Results A Cox model analysis in the placebo group identified the following independent predictors of coronary events: a history of hypertension (P=0·023), diabetes (P=0·0001), smoking after the myocardial infarction (P=0·010), total cholesterol (P=0·020), and HDL cholesterol (P=0·062). The relative reduction of risk by simvastatin treatment in patients at low, medium and high predicted risk was 38%, 39% and 42%, respectively, but the corresponding absolute benefit per 100 patients treated for 6 years increased from 7·9 to 16·2.

Conclusion In addition to serum lipids, clinical variables contributed significantly to prediction. The relative benefit from simvastatin treatment was independent of predicted risk, but the absolute benefit increased from low to high risk.

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Key Words: Myocardial infarction, prognosis, diabetes, hypertension, smoking, lipids.

See page 1065 for the Editorial comment on this paper

Introduction

Many risk factors for a first myocardial infarction are reported. It is well established that a series of factors related to the size of the index infarction and reduction of myocardial contractility are related to deteriorated prognosis after a myocardial infarction[1]. Other factors associated with worse prognosis are presence of angina pectoris[2,3], ventricular arrhythmias[4] as well as some

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*The participating investigators and centres have been listed in the main report of the Scandinavian Simvastatin Survival Study [13].

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factors known to increase the risk of a first myocardial infarction such as blood glucose level and diabetes[5–7], smoking habits after the infarction[8], hypertension[2,6,9,10] and increased total cholesterol[6,11,12].

The Scandinavian Simvastatin Survival Study (4S) is based upon a unique patient sample because a large number of Scandinavian patients with coronary heart disease (previous myocardial infarction or angina pectoris) and high serum total cholesterol levels were recruited with a standard collection of entry variables as well as careful follow-up and analysis of several lipid variables. In addition to the main report[13] there have been reports of prognosis in relation to age and gender[14], lipids and lipoproteins at baseline and during the trial[12,15,16], and prognosis in the subgroup with diabetes or elevated fasting plasma glucose levels[17,18]. The above mentioned reports dealt with men and women who had suffered a myocardial infarction, as well as those who were included in the study with angina pectoris but no myocardial infarction. Prognostic factors may differ between men and women as well as between angina and myocardial infarction patients.

The aim of the present paper was to evaluate the prognostic importance of clinical findings together with lipid variables in those 4S patients whose qualifying diagnosis was myocardial infarction. Another aim was to analyse the relative and absolute benefit of simvastatin treatment in patients with predicted low, medium and high risk. We decided to concentrate our study on patients with myocardial infarction, because the majority of 4S patients (79%) were recruited with this qualifying diagnosis. Furthermore, this study deals mainly with male patients with myocardial infarction, because more women than men entered the study without previous myocardial infarction. Therefore, the number of female patients with myocardial infarction available for prospective analysis was small. With regard to clinical baseline variables it has to be noted that standardized measurements of ejection fraction (or other measures related to infarct size) or information about the presence of ventricular arrhythmias, were not available in the 4S, because many patients were recruited from general practice and at varying intervals from the index infarction. At variance from previous reports from the 4S, we excluded silent myocardial infarctions (detected on the basis of annual ECGs only) as a coronary event end-point, because this end-point is not systematically evaluated in usual clinical practice.

Patients

4S was a double-blind, randomized, placebo-controlled, multicentre clinical trial of long-term simvastatin or matching placebo therapy in patients with coronary heart disease. The design of the trial and the main findings on mortality, morbidity, and long-term safety have been described previously[12,13,16,19]. The patients were men and women 35–70 years old (mean 58·7 years) with a history of myocardial infarction or angina pectoris. These patients were identified from hospital records and, if they did not have any of the exclusion criteria, they were then invited to a screening visit. As described in the 4S main report[13] and presented in previous publications, there were certain cardiological exclusion criteria such as myocardial infarction during the preceding 6 months, unstable angina pectoris, planned coronary bypass surgery or angioplasty, congestive heart failure requiring drug treatment, and arrhythmias requiring therapy, that led to exclusion of a relatively large number of patients. Patients with reduced life expectancy due to other serious diseases were also excluded. Thus, the prognosis of the 4S patients was somewhat better than for an unselected population of coronary patients.

Table 1 Original study sample in 4S and patients with myocardial infarction as qualifying diagnosis who constituted the present study sample

	Placebo		Simvastatin	
	n	%	n	%
Men	1803	(81)	1814	(82)
Women	420	(19)	407	(18)
Qualifying diagnosis				
Infarction	1766		1759	
Men	1490	(84)	1515	(86)
Women	276	(16)	244	(14)

For them to qualify for randomization, their serum total cholesterol had to be between 5·5 and 8·0 mmol . l^{-1} (213–310 mg . dl^{-1}) and serum triglyceride levels $\leq$2·5 mmol . l^{-1} (220 mg . dl^{-1}), after dietary advice 2 months previously. Due to these lipid inclusion criteria, the 4S population had truncated serum total cholesterol and triglyceride distributions, resulting in a somewhat higher mean cholesterol level and somewhat lower mean triglycerides than those for an unselected coronary patient population.

Patients were randomized to placebo or simvastatin 20 mg . day^{-1}, with titration to 40 mg simvastatin at 12 or 24 weeks in patients who did not reach the study target of a serum total cholesterol of 3·0 to 5·2 mmol . l^{-1} (116–201 mg . dl^{-1}) after 6 to 18 weeks. Clinic visits with lipid determination took place at 6 and 18 weeks and at 6 months, and thereafter every 6 months. All patients were accounted for at the end of the study. Medium follow-up time was 5·4 years (range 4·9 to 6·3 years). The number of men and women in the overall 4S cohort and the number of those with a previous myocardial infarction as the qualifying diagnosis randomized to placebo and simvastatin is shown in Table 1.

Methods

Age, sex, smoking at baseline, history of hypertension, history of intermittent claudication, diabetes, transitory

ischaemic attacks, previous PTCA/CABG were evaluated according to a pre-defined questionnaire. Presence of major Q waves in the baseline ECG was also assessed.

The following baseline variables were measured: body mass index, systolic and diastolic blood pressure, heart rate, total serum cholesterol, serum triglycerides, HDL-cholesterol, LDL-cholesterol, apolipoprotein-A1, apolipoprotein-B, as well as lipoprotein(a) and fasting plasma glucose. The baseline variables of lipids and apolipoproteins are means of two measurements from serum collected about 2 months after dietary advice, the first at the beginning of the single blind placebo period and the second 2 weeks later, on the day of randomization, except for apolipoprotein-A1, apolipoprotein-B and lipoprotein(a), which were measured only at randomization. Lipids measured according to the same protocol 1 year after baseline were also included in the present analyses.

Blood samples were collected after 12 to 14 h of fasting and left to coagulate for 1 to 2 h at room temperature. Serum was separated by centrifugation and divided into three aliquots. One tube was shipped unfrozen to the Central Laboratory the same day to be analysed for total cholesterol, and the two other tubes were frozen immediately at -20°C. The frozen serum was shipped in batches in isolated containers with dry ice to the Central Laboratory to be analysed within 3 months. Cholesterol and triglycerides were measured enzymatically by the method of Boehringer-Ingelheim. HDL-cholesterol was measured after precipitation of apolipoprotein-B containing lipoproteins by heparin-MnCl. LDL-cholesterol was calculated according to the Friedewald formula. Serum apolipoprotein-A1 and apolipoprotein-B were measured by immunoturbidometry by test kits with antisera and standards from Orion. Lipoprotein(a) measurements were conducted with a commercially available test kit for radio-immunoassay (Irma, Pharmacia Diagnostics, Uppsala). Details of this, as well as other analyses, have been published previously[15,16]. Plasma or blood glucose measurements were performed in local laboratories, converting for data analyses blood glucose to plasma glucose, as described elsewhere[18].

End-points

All end-points were classified by an independent end-point classification committee. The primary study end-point of the 4S was death from any cause. The secondary end-point was major coronary events which comprised coronary deaths, definite or probable hospital-verified non-fatal infarction, resuscitated cardiac arrest, and definite silent myocardial infarction verified by annual ECGs. In the present paper, silent myocardial infarction was, however, not included as an end-point. Major coronary events, as defined above but excluding silent myocardial infarction, are referred to as coronary events in the present paper. Only the first end-point event was included in the analysis. Among male patients with myocardial infarction as the qualifying diagnosis, there were 431 coronary events in the placebo group and 276 in the simvastatin group, respectively. The corresponding number of coronary events among female patients with myocardial infarction as the qualifying diagnosis was 56 and 37, respectively.

Statistical methods

The relationships between baseline variables and coronary events were first assessed individually for each baseline variable among men because of the low number of women with myocardial infarction (Table 1). Logistic regression was used to compare the proportions of patients with coronary events among the values of categorical variables. Continuous variables were considered in univariate analyses by tertiles using cut-off points defined for the entire patient series. Multivariate statistical analyses were performed using the original continuous variables. A Cox proportional hazard model with backward elimination was used to find a basic set of predictor variables. A 0·05 criterion for retention in the model was used. The following baseline variables were included in the initial models: age, angina, hypertension, claudication, diabetes, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, time since first myocardial infarction, number of previous myocardial infarctions, total cholesterol, triglycerides, HDL, LDL, lipoprotein(a) and fasting plasma glucose. A small number of patients had missing data for one or more of the continuous variables. When this occurred, in order to keep the patient in the analysis, the missing value was estimated by the median value of all patients of the same age and sex. Based upon the regression coefficients obtained from the proportional hazard model (Table 3) for the placebo group, estimated risks for patients in both treatment groups were calculated. The estimated risks were then ranked and divided into thirds to form the low, medium, and high risk groups. All significance tests were two-sided with alpha = 0·05.

Results

Table 2 gives number and percent of baseline discrete characteristics and tertiles of continuous variables as well as number and percent with coronary events, relative risks (95% CI) in relation to the group with lowest event rate (=1·0) in male infarct patients in the placebo and simvastatin groups, respectively. The analysis summarised in Table 2 was intended to show the relationship of various baseline variables without adjustment for anything else. The purpose of the paper was to show which of these were independent risk factors. As seen in Table 2 the relationship of age with the risk of coronary events was different in the placebo and simvastatin groups. Furthermore, adjustment for age had no material effect on the results. Age is included in the multivariate analyses in Tables 3 and 4. In both the

Table 2 Total number of male patients with baseline variables as well as number and (%) with coronary events and relative risk (RR 95% CI) during follow-up in the placebo and simvastatin groups.* P*-values according to logistic regression are given

Variable	Placebo				Simvastatin			
	Total n	Event n (%)	RR (95% CI)	*P*	Total n	Event n (%)	RR (95% CI)	*P*
Years since diagnosis								
≤1 year	362	89 (25)	1	0·0011	387	54 (14)	1	0·004
2–5 years	679	183 (27)	1·10 (0·88, 1·36)		645	113 (18)	1·26 (0·93, 1·69)	
>5 years	449	159 (35)	1·44 (1·16, 1·79)		483	109 (23)	1·62 (1·20, 2·18)	
Number of MI								
1	1249	324 (26)	1	0·0001	1263	216 (17)	1	0·05
2	192	91 (47)	1·83 (1·53, 2·18)		209	49 (23)	1·37 (1·04, 1·80)	
≥3	49	16 (33)	1·26 (0·83, 1·90)		43	11 (26)	1·50 (0·89, 2·53)	
Q-wave								
No	813	225 (28)	1	0·24	868	162 (19)	1	0·60
Yes	677	206 (30)	1·10 (0·94, 1·29)		647	114 (18)	0·94 (0·76, 1·17)	
Chest pain								
No	714	170 (24)	1	0·0001	706	112 (16)	1	0·014
Heavy exertion	522	165 (32)	1·33 (1·11, 1·59)		526	95 (18)	1·14 (0·89, 1·46)	
On slopes	231	91 (39)	1·65 (1·35, 2·03)		263	62 (24)	1·49 (1·13, 1·96)	
Minimum exertion	23	5 (22)	0·91 (0·42, 2·00)		20	7 (35)	2·21 (1·19, 4·11)	
Any family history								
No	460	134 (29)	1	0·91	500	87 (17)	1	0·56
Yes	1030	297 (29)	0·99 (0·83, 1·18)		1015	189 (19)	1·07 (0·85, 1·35)	
Diabetes								
No	1427	398 (28)	1	<0·0001	1445	263 (18)	1	0·94
Yes	63	33 (52)	1·88 (1·46, 2·41)		70	13 (19)	1·02 (0·62, 1·69)	
Hypertension								
No	1134	311 (27)	1	0·024	1164	196 (17)	1	0·013
Yes	356	120 (34)	1·23 (1·03, 1·46)		351	80 (23)	1·35 (1·07, 1·71)	
Claudication								
No	1412	404 (29)	1	0·26	1425	247 (17)	1	0·001
Yes	78	27 (35)	1·21 (0·88, 1·66)		90	29 (32)	1·86 (1·35, 2·56)	
TIA								
No	1460	418 (29)	1	0·09	1488	265 (18)	1	0·006
Yes	30	13 (43)	1·51 (1·00, 2·30)		27	11 (41)	2·29 (1·43, 3·65)	
Prior PTCA/CABG								
No	1406	402 (29)	1	0·25	1399	254 (18)	1	0·83
Yes	84	29 (35)	1·21 (0·89, 1·64)		116	22 (19)	1·04 (0·71, 1·55)	
Smoking status								
Non-smoker	295	85 (29)	1	0·07	285	51 (18)	1	0·017
Ex-smoker	768	205 (27)	0·93 (0·75, 1·15)		848	137 (16)	0·90 (0·67, 1·21)	
Smoker	427	141 (33)	1·15 (0·92, 1·43)		382	88 (23)	1·29 (0·95, 1·75)	
Age (years)								
<57	558	159 (29)	1	0·72	527	90 (17)	1	0·014
57–62	449	127 (28)	0·99 (0·81, 1·21)		461	73 (16)	0·93 (0·70, 1·23)	
≥63	483	145 (30)	1·05 (0·87, 1·27)		527	113 (21)	1·26 (0·98, 1·61)	
BMI ($kg \cdot m^{-2}$)								
<24·5	518	133 (26)	1	0·13	529	92 (17)	1	0·61
24·5–27·0	493	158 (32)	1·25 (1·03, 1·52)		493	90 (18)	1·05 (0·81, 1·37)	
>27·0	479	140 (29)	1·14 (0·93, 1·39)		493	94 (19)	1·12 (0·85, 1·42)	
SBP (mmHg)								
≤129	452	130 (29)	1	0·21	478	76 (16)	1	0·16
130–145	591	174 (29)	1·02 (0·85, 1·24)		610	120 (20)	1·24 (0·95, 1·61)	
≥146	447	127 (28)	0·99 (0·80, 1·21)		427	80 (19)	1·18 (0·89, 1·57)	
DBP (mmHg)								
≤79	310	83 (27)	1	0·18	360	67 (19)	1	0·97
80–89	643	184 (29)	1·07 (0·86, 1·33)		637	114 (18)	0·96 (0·73, 1·26)	
≥90	537	164 (31)	1·14 (0·91, 1·43)		518	95 (18)	0·99 (0·74, 1·31)	

Table 2 Continued

Variable	Placebo				Simvastatin			
	Total n	Event n (%)	RR (95% CI)	*P*	Total n	Event n (%)	RR (95% CI)	*P*
Heart rate (beats . min^{-1})								
≤59	419	108 (26)	1	0·06	458	72 (16)	1	0·07
60–69	658	191 (29)	1·13 (0·92, 1·38)		643	114 (18)	1·13 (0·86, 1·48)	
≥70	413	132 (32)	1·24 (1·00, 1·54)		414	90 (22)	1·38 (1·05, 1·83)	
Total cholesterol (mmol . l^{-1})								
≤6·40	540	138 (26)	1	0·025	559	94 (17)	1	0·24
6·41–7·00	488	149 (31)	1·19 (0·98, 1·45)		477	81 (17)	1·01 (0·77, 1·32)	
≥7·01	462	144 (31)	1·22 (1·00, 1·49)		479	101 (21)	1·25 (0·97, 1·62)	
Triglycerides (mmol . l^{-1})								
≤1·20	480	134 (28)	1	0·023	487	86 (18)	1	0·97
1·21–1·65	477	121 (25)	0·91 (0·74, 1·12)		537	106 (20)	1·12 (0·86, 1·44)	
≥1·66	533	176 (33)	1·18 (0·98, 1·43)		491	84 (17)	0·97 (0·74, 1·27)	
HDL (mmol . l^{-1})								
≤1·00	585	177 (30)	1·15 (0·94, 1·42)	0·08	548	112 (20)	1·23 (0·93, 1·63)	0·08
1·01–1·25	516	152 (30)	1·12 (0·91, 1·39)		600	103 (17)	1·03 (0·77, 1·38)	
≥1·26	389	102 (26)	1		367	61 (17)	1	
LDL (mmol . l^{-1})								
≤4·50	479	127 (27)	1	0·06	481	76 (16)	1	0·06
4·51–5·15	555	164 (30)	1·11 (0·92, 1·36)		560	107 (19)	1·21 (0·93, 1·58)	
≥5·16	456	140 (31)	1·16 (0·95, 1·42)		474	93 (20)	1·24 (0·94, 1·64)	
Apo-A1 (mmol . l^{-1})								
≥1·0	193	63 (33)	1·13 (0·90, 1·43)	0·54	196	49 (25)	1·49 (1·11, 1·99)	0·06
1·1–1·2	606	168 (28)	0·96 (0·81, 1·15)		591	105 (18)	1·06 (0·83, 1·34)	
≥1·3	677	195 (29)	1		713	120 (17)	1	
Apo-B (mmol . l^{-1})								
≤1·0	387	99 (26)	1	0·08	389	55 (14)	1	0·03
1·1–1·2	651	189 (29)	1·13 (0·92, 1·40)		680	126 (19)	1·31 (0·98, 1·75)	
≥1·3	438	138 (32)	1·23 (0·99, 1·53)		431	93 (22)	1·53 (1·13, 2·07)	
Lp(a) (mg . 100 ml^{-1})								
≥120	509	142 (28)	1	0·11	517	96 (19)	1	0·10
121–400	489	140 (29)	1·03 (0·84, 1·25)		490	78 (16)	0·86 (0·65, 1·13)	
≥401	492	149 (30)	1·09 (0·89, 1·32)		508	102 (20)	1·08 (0·84, 1·39)	
Fasting plasma glucose (mmol . l^{-1})								
<5·0	286	73 (26)	1	0·0003	276	53 (19)	1	0·26
5·0–5·9	790	220 (28)	1·09 (0·87, 1·37)		794	142 (18)	0·93 (0·70, 1·24)	
≥6·0	392	134 (34)	1·34 (1·05, 1·70)		430	78 (18)	0·94 (0·69, 1·29)	

MI=myocardial infarction; TIA=transitory ischaemic attack; BMI=body mass index; SBP/DBP=systolic/diastolic blood pressure; Apo=apolipoprotein; Lp(a)=lipoprotein(a).

placebo and simvastatin groups there were higher endpoint rates among men with longer time from their index myocardial infarction to inclusion into the trial as well as among men with more than one myocardial infarction. Presence of a Q wave in the baseline ECG was not associated with worse prognosis. Chest pain at lower levels of exertion was associated with worse outcome in both the placebo and simvastatin groups. Outcome was not related to family history of myocardial infarction.

History of previously diagnosed diabetes and elevated fasting plasma glucose were associated with worse prognosis in the placebo group but not in the simvastatin group. Patients with hypertension had a worse prognosis in both the placebo and the simvastatin groups.

Table 3 Multivariate analysis of baseline prognostic factors for a coronary event after a myocardial infarction in placebo men. Only significant (or close to significant) variables are listed

Variable	Parameter		*P*-value	Risk ratio
	Coefficient	SE		
Hypertension, yes/no	0·245	0·108	0·023	1·28
Diabetes, yes/no	0·696	0·181	0·0001	2·01
Smoking, yes/no	0·266	0·103	0·010	1·31
Total cholesterol, mmol . l^{-1}	0·168	0·072	0·020	1·18
HDL cholesterol, mmol . l^{-1}	− 0·353	0·189	0·062	0·70

Table 4 Multivariate analysis of 1-year lipid levels as well as information from history as prognostic factors for a coronary event in the simvastatin group. Only significant (or close to significant) variables are listed

Variable	Parameter		*P*-value	Risk ratio
	Coefficient	SE		
Age, 10 years	0·320	0·110	0·003	1·38
Hypertension, yes/no	0·380	0·163	0·020	1·46
Claudication, yes/no	0·531	0·265	0·045	1·70
Total cholesterol, mmol . l^{-1}	0·263	0·080	0·001	1·30
HDL-cholesterol, mmol . l^{-1}	− 0·762	0·279	0·0062	0·47
Lp(a), 100 × mg . 100 ml^{-1}	0·049	0·017	0·004	1·05
Smoking, yes/no	0·316	0·163	0·052	1·37

Lp(a)=lipoprotein(a).

Intermittent claudication as well as transitory ischaemic attacks prior to inclusion were associated with worse prognosis only in the simvastatin group (for transitory ischaemic attacks in the placebo group: $P=0·090$). Smokers had significantly more coronary events compared to non-smokers in the simvastatin group, and in the placebo group it was close to significance ($P=0·07$). When the analyses were repeated combining the two treatment groups these clinical criteria were all significant predictors. Prognosis was not related to prior PTCA or CABG in the two groups or in the combined groups.

Older patients had a significantly higher end-point incidence in the simvastatin group only. There was no significant association with body mass index, systolic or diastolic blood pressure in either group. A positive association between heart rate and end-point incidence was almost significant (placebo; $P=0·06$, simvastatin; $P=0·07$).

Among the lipid variables, high total cholesterol and triglycerides were significantly associated with higher end-point rate in the placebo group. Worse outcome was not significantly associated with higher LDL level (placebo; $P=0·062$, simvastatin; $P=0·059$) or low HDL level (placebo and simvastatin; $P=0·08$). Incidence was not significantly related to low apolipoprotein-A_1 in the simvastatin group ($P=0·064$). Worse outcome was significantly associated with high apolipoprotein-B in the simvastatin group ($P=0·03$), but not in the placebo group ($P=0·08$). Lipoprotein(a) was neither significantly associated with outcome in the simvastatin group ($P=0·10$) nor in the placebo group ($P=0·11$).

Multivariate regression analyses aiming to identify independent predictors of coronary events in the placebo group were carried out entering into the Cox models variables listed in the 'Statistical methods' section. Because of the associations between various lipids such as total cholesterol and LDL-cholesterol, etc. lipids were included, alternatively excluding other lipids that might affect the outcome. In general, all analyses came out with hypertension, diabetes and smoking after myocardial infarction as significantly associated with post-infarction coronary events (Table 3). Total serum cholesterol was also significant whereas HDL-cholesterol was close to significant ($P=0·062$). If LDL-cholesterol, HDL-cholesterol, triglycerides or lipoprotein(a) were included as single lipid variables none of them was significant. When the multivariate analysis shown in Table 3 was done, entering LDL-cholesterol instead of total cholesterol, the coefficient for LDL-cholesterol was 0·131 ($P=0·078$). Using the risk factors identified in Table 3 as covariates, the risk of coronary events in males with prior myocardial infarction was reduced 40% in the simvastatin group (95% CI 30% to 48%, $P<0·001$).

Table 5 gives incidence of events among men in tertiles of predicted low, median and high risk, relative and absolute benefit of simvastatin treatment as well as the number of men needed to treat based upon Kaplan–Meier 6-year survival estimate. It is evident that the relative benefit is similar in the different tertiles of predicted risk, whereas the absolute benefit doubles from the lowest to the highest tertile of predicted risk. If only lipid variables were used in the stratification into low, medium and high risk tertiles, the difference in the

Table 5 Incidence of events, relative risk (95% CI), predicted absolute benefit per 100 patients during 6 years and number needed to treat to prevent one coronary event by tertile of predicted multivariate risk in placebo and simvastatin groups

	Multivariate risk (tertile)		
	Low	Medium	High
Incidence of events			
Placebo	106/483 (21·9%)	139/497 (28%)	186/510 (36·5%)
Simvastatin	74/519 (14·3%)	91/505 (18·0%)	111/491 (22·6%)
Relative risk (95% CI)	0·62 (0·46, 0·83)	0·61 (0·47, 0·80)	0·58 (0·46, 0·73)
Significance, *P*	0·0016	0·0003	0·0001
Kaplan-Meier 6-year estimate (95% CI) of survival without coronary event			
Placebo	0·773 (0·735, 0·812)	0·713 (0·672, 0·755)	0·596 (0·543, 0·649)
Simvastatin	0·852 (0·821, 0·884)	0·808 (0·772, 0·845)	0·758 (0·713, 0·803)
Absolute benefit per 100 pts (95% CI) during 6 years	7·9 (2·9, 12·9)	9·5 (4·0, 15·0)	16·2 (9·2, 23·1)
Number needed to treat (95% CI) during 6 years	13 (8, 34)	11 (7, 25)	6 (4, 11)

predicted risk, and consequently differences in absolute benefits of simvastatin treatment were much smaller than those obtained, including also clinical variables. Thus, using baseline total cholesterol alone, the absolute benefit of simvastatin treatment per 100 patients during 6 years in the low, medium and high tertile was 9·8 (95% CI 4·4, 15·2), 10·9 (95% CI 4·8, 16·9), and 13·3 (95% CI 7·4, 19·2), respectively.

Table 4 includes those variables that were significant or close to significant in multivariate analysis when 1-year lipid levels in the simvastatin group were used instead of baseline lipids. Age, hypertension, claudication, total cholesterol, HDL-cholesterol, lipoprotein(a) were significant, and smoking was almost significant ($P=0·052$). Results were similar if LDL-cholesterol was exchanged for total cholesterol.

The same type of analysis using 1-year lipid levels was performed in the placebo group. Only hypertension and diabetes were significantly associated with outcome, but the lipid variables were not.

The female myocardial infarction patients were analysed regarding prognosis in the same way as men. In the placebo group hypertension ($P=0·01$) and chest pain at lower levels of exertion ($P=0·04$) were significantly associated with end-points. In multivariate analysis only hypertension was significantly associated with end-points in women ($P=0·01$). In the simvastatin group, there were no significant associations in univariate analysis, but the trends did not differ from those among men.

Discussion

There were some selections in the present paper because patients with impending high mortality risk were excluded as were those with total cholesterol levels below 5·5 mmol . l^{-1} and above 8·0 mmol . l^{-1} This is because the study wished to avoid randomizing patients with a low cholesterol level to a lipid lowering drug and similarly placebo treatment to patients with high cholesterol levels. Therefore, the 4S population most probably had a lower than usual immediate mortality risk and a narrower than usual distribution of lipid levels. Nevertheless there were still relationships as presented above.

The present analyses differ from those previously published from the 4S trial because only patients with a previous myocardial infarction as a qualifying diagnosis were included. Furthermore, in contrast to previous reports, silent myocardial infarctions were not included as an end-point. Only patients who had suffered their myocardial infarctions more than 6 months before were recruited into the 4S study in order to avoid early mortality due to myocardial factors that were not expected to be affected by lipid-lowering therapy. Patients randomized more than 5 years after their index infarction turned out to have the highest end-point incidence. This finding is probably not explained by their older age, because there was no consistent relationship with age in the placebo group or in the two groups combined. However, it may be due to survival bias, because myocardial infarction patients with worse early prognosis may have died earlier after their index infarction and were not included in this study. Thus, patients who had survived for more than 5 years after their myocardial infarction may represent a subgroup with postponed manifestations of coronary events.

In accordance with several previous studies, coronary events were more common among patients who had had more than one infarction, had a history of hypertension and among those who continued to smoke after their index infarct. Recently, results from the Framingham study, including patients who entered the study with myocardial infarction, angina pectoris and coronary insufficiency (211 men and 160 women) were reported[20]. Their findings were similar regarding diabetes, smoking, and high systolic blood pressure as significant predictors among men and women. The log transformed ratio between total cholesterol and HDL-cholesterol was also significant. These results again indicate the importance of clinical variables in determining prognosis after an infarction. In accordance with several previous studies, univariate analyses of our data showed that the risk of coronary events was increased among patients with multiple infarctions, those with a history of hypertension and those who continued to smoke after their infarction. A history of diabetes and elevated fasting glucose had in univariate analyses a strong negative influence on prognosis in the placebo group and in the combined treatment groups but not in the simvastatin group. However, in multivariate analyses, adjusting for the impact of other factors, history of diabetes was a statistically significant independent predictor of the risk of coronary events in both the placebo group and the simvastatin group, although its predictive value was stronger in the placebo group. Fasting glucose level did not, however, come out as an independent risk predictor in multivariate models which included the history of diabetes. The prevalence of diabetes among the 4S patients was only 4·4%, much lower than the about 20% prevalence usually observed among unselected male post-infarction patients[21]. This low prevalence is explained mainly by the exclusion of patients with triglycerides >2·5 mmol . l^{-1}, but also by the cardiological exclusion criteria, because diabetic patients more often have severe cardiovascular complications than non-diabetic patients.

A history of claudication, and similarly, a history of transitory ischaemic attacks had a statistically significant adverse influence on prognosis in the simvastatin group only. The difference in outcome between the two treatment groups in relation to these clinical variables might be due to small numbers. When the analyses were repeated in the two treatment groups together these clinical criteria were significantly associated with end-points.

Regarding continuous variables, higher age, as expected, was associated with worse prognosis only in the simvastatin group and with an increase in risk ratio

of only 2·2% per year. High body mass index, which is a risk factor for a first myocardial infarction, was not related to worse prognosis which is compatible with earlier reports on post-infarction prognosis[22,23]. As mentioned above, a history of hypertension before the infarction denoted worse prognosis, but blood pressure measured after the infarction did not. The latter finding may be due to differences in measurement of blood pressure between centres, but may also be a real finding. It is well known that blood pressure falls with a myocardial infarction, and the amount of decline in blood pressure is related to infarct size and to prognosis[24]. Thus, there may well be a mixture of blood pressure findings post myocardial infarction. Patients entered the study at varying times after the index infarction; some patients may have returned to their pre-infarction blood pressures, others still being below their pre-infarction levels.

Other studies have demonstrated a positive relationship between heart rate and the risk of coronary events in post-infarct patients[25,26]. In our study this association did not quite reach the level of statistical significance. The reason may be the varying inclusion times after the index infarction, and loss of patients who died before inclusion, but also treatment with beta-adrenergic blockers given to 57% of the patients.

High serum total cholesterol and triglycerides were associated with higher rates of coronary events in the placebo group only, whereas LDL-cholesterol, HDL-cholesterol and lipoprotein(a) had borderline significance in the univariate analyses in any groups and HDL-cholesterol in the multivariate analysis (Table 3). While these findings have the same directional relationship, the strengths of the relationships are different from previously reported results with regard to several lipid variables in this study[12,15,16]. Possible explanations for these differences are the different patient populations and end-points — in the present study only male infarct patients were included (prognosis in angina patients may be more strongly related to lipids) — and the smaller sample size in this subgroup.

In the placebo group, the beta-coefficient for serum total cholesterol was 0·168, corresponding to an approximately 17% increase in risk with 1 mmol . l^{-1} increase in serum cholesterol. This is similar to the beta-coefficient found in prospective studies in post myocardial infarction patients[2,6] but smaller than those found in prospective population studies; from 0·151 to 0·316, median 0·270, for a 1 mmol increase in total cholesterol[27]. In a prospective study including healthy men, men with angina pectoris, and post-infarction patients, relative risks (95% CI) were 1·29 (1·19, 1·39), 1·34 (1·13, 1·60) and 1·12 (0·94, 1·35), respectively[28], which confirms the smaller relative risk in post-infarction patients than in the healthy population.

It is noteworthy that in the simvastatin group, serum total cholesterol and LDL cholesterol measured after the first year of simvastatin therapy showed a strong association with the risk of coronary events. This association was even stronger than that observed between these lipid variables and the risk in the placebo group, the beta-coefficient for serum total cholesterol being 0·263. Because in this analysis, patients with coronary events within the first year were excluded, this may have led to bias with removal of patients whose events were unrelated to lipid levels. This would leave to further follow-up preferentially patients whose risk was more strongly dependent on cholesterol. Furthermore, it is possible that during the subsequent trial years, patients who did not respond to simvastatin treatment with a good reduction in cholesterol level were at increased risk, leading to a steepening of the relationship between cholesterol and risk. Our results showed that in the simvastatin group a number of demographic and clinical variables, including age, hypertension, claudication and smoking (close to significance) were associated with risk of coronary events (Table 4).

It was also demonstrated that the relative benefit of cholesterol-lowering treatment with simvastatin was similar in post-infarct patients with low, medium and high risk, using tertiles of multivariate risk for stratification including hypertension, diabetes, smoking, total cholesterol and HDL cholesterol. Importantly, however, the absolute benefit of simvastatin treatment doubled from the lowest to the highest tertile of risk. Consequently, the number of men needed to treat for 6 years to save one major coronary event was 13 in the lowest and 6 in the highest risk tertile.

Conclusions

Among the 4S patients with a previous myocardial infarction and high or relatively high serum total cholesterol levels, clinical variables, such as history of hypertension, history of diabetes, and smoking after myocardial infarction, contributed significantly, in addition to serum lipid levels, to the multivariate prediction of the risk of coronary events. The relative benefit from simvastatin treatment was independent of the level of predicted risk, but the absolute benefit increased from low to high risk.

References

[1] Peterson ED, Shaw LJ, Califf RM. Clinical Guideline: Part II. Risk stratification after myocardial infarction. Ann Intern Med 1997; 126: 561–82.
[2] Ulvenstam G. Deaths and recurrences after myocardial infarction — occurrence and risk factors. MD Thesis, Göteborg University, Göteborg, 1984.
[3] Haider AW, Davies GJ. Preinfarction angina as a major predictor of left ventricular function and long-term prognosis after a first Q wave myocardial infarction. J Am Coll Cardiol 1996; 27: 954–5.
[4] Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation 1984; 69: 250–8.
[5] Ulvenstam G, Åberg A, Bergstrand R, *et al*. Long-term prognosis after myocardial infarction in men with diabetes. Diabetes 1985; 34: 787–92.

[6] Wong ND, Cupples LA, Ostfeld AM, Levy D, Kannel WB. Risk factors for long-term coronary prognosis after initial myocardial infarction: the Framingham Study. Am J Epidemiol 1989; 130: 469–80.
[7] Behar S, Boyko V, Reicher-Reiss H, Goldbourt U. Ten-year survival after acute myocardial infarction: comparison of patients with and without diabetes. SPRINT Study Group, Secondary Prevention Reinfarction Israeli Nifedipine Trial. Am Heart J 1997; 133: 290–6.
[8] Wilhelmsen L. Effects of cessation of smoking after myocardial infarction. J Cardiovasc Risk 1998; 5: 173–6.
[9] Herlitz J, Bang A, Karlsson BW. Five-year prognosis after acute myocardial infarction in relation to a history of hypertension. Am J Hypertens 1996; 9: 70–6.
[10] Gustafsson F, Køber L, Torp-Pedersen C, Hildebrandt P, Ottesen MM, Sonne B, Carlsen J on behalf of the TRACE study group. Long-term prognosis after acute myocardial infarction in patients with a history of arterial hypertension. Eur Heart J 1998; 19: 588–94.
[11] Ulvenstam G, Bergstrand R, Johansson S, *et al*. Prognostic importance of cholesterol levels after myocardial infarction. Preventive Medicine 1984; 13: 355–66.
[12] The Scandinavian Simvastatin Survival Study Group. Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). Lancet 1995; 345: 1274–5.
[13] The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–9.
[14] Miettinen TA, Pyörälä K, Olsson AG *et al.* Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation 1997; 96: 4211–8.
[15] Berg K, Dahlen G, Christophersen B, Cook T, Kjekshus J, Pedersen T. Lp(a) lipoprotein level predicts survival and major coronary events in the Scandinavian Simvastatin Survival Study. Clin Genet 1997; 52: 254–61.
[16] Pedersen TR, Olsson AG, Faergeman O, *et al*., for the Scandinavian Simvastatin Survival Study Group. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation 1998; 97: 1453–60.
[17] Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G, for the Scandinavian Simvastatin Survival Study (4S) Group. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. Diabetes Care 1997; 20: 614–20.
[18] Haffner SM, Alexander CM, Cook TJ *et al*. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. Arch Intern Med 1999; 159: 2661–7.
[19] Pedersen TR, Berg K, Cook TJ *et al.* Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. Arch Intern Med 1996; 156: 2085–92.
[20] D'Agostino RB, Russell MW, Huse DM *et al*. Primary and subsequent coronary risk appraisal: New results from the Framingham Study. Am Heart J 2000; 139: 272–81.
[21] EUROASPIRE Study Group. A European Society of Cardiology survey of secondary prevention of coronary heart disease: Principal results. Eur Heart J 1997; 18: 1569–82.
[22] Åberg A, Bergstrand R, Johansson S *et al*. Cessation of smoking after myocardial infarction. Effects on mortality after 10 years. Br Heart J 1983; 49: 416–22.
[23] Hosoda S, Kimata S, Tamura K *et al*. Follow-up of 2,733 Japanese patients with myocardial infarction. Jpn Circ J 1995; 59: 121–9.
[24] McCall M, Elmfeldt D, Vedin A, Wilhelmsson C, Wedel H, Wilhelmsen L. Influence of a myocardial infarction on blood pressure and serum cholesterol. Acta Med Scand 1979; 206: 477–481.
[25] Hjalmarson A, Gilpin EA, Kjekshus J *et al*. Influence of heart rate on mortality after acute myocardial infarction. Am J Cardiol 1990; 65: 547–553.
[26] Copie X, Hnatkova K, Staunton A, Fei L, Camm AJ, Malik M. Predictive power of increased heart rate versus depressed left ventricular ejection fraction and heart rate variability for risk stratification after myocardial infarction. Results of a two-year follow-up study. J Am Coll Cardiol 1996; 27: 270–6.
[27] Dobson AJ, Evans A, Ferrario M *et al*. for the WHO MONICA Project. Changes in estimated coronary risk in the 1980s: data from 38 populations in the WHO MONICA Project. Ann Med 1998; 30: 199–205.
[28] Rosengren A, Wilhelmsen L, Hagman M, Wedel H. Natural history of myocardial infarction and angina pectoris in a general population sample of middle-aged men: a 16 year follow-up of the Primary Prevention Study, Göteborg, Sweden. J Intern Med 1998; 244: 495–505.