Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): Characteristics of a randomized trial among 12064 myocardial infarction survivors

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Background Cholesterol lowering with statins reduces the risk of vascular disease, but uncertainty remains as to whether more intensive statin therapy produces worthwhile benefits safely. Blood homocysteine level is an independent marker of vascular risk, but it is unknown whether this association is causal.

Methods and Results 12 064 myocardial infarction survivors have been randomized to more versus less intensive cholesterol-lowering treatment using simvastatin 80 mg versus 20 mg daily. Allocation to more intensive treatment has yielded average further low-density lipoprotein cholesterol reductions of 0.5 mmol/L at 2 months and 0.4 mmol/L at 5 years. In addition, using a factorial design, these patients have been randomized to homocysteine lowering with folic acid 2 mg plus vitamin B_{12} 1 mg daily versus matching placebo, yielding an average 3 to 4 μmol/L reduction in homocysteine. After 6 years of median follow-up, the annual overall rate of major vascular events is approximately 3%. Follow-up is scheduled to continue for a median of 7 years.

Conclusion SEARCH should provide reliable evidence about the efficacy and safety of prolonged use of more intensive cholesterol-lowering therapy and, separately, of folate-based homocysteine-lowering therapy in a high-risk population. (Am Heart J 2007;154:815-823.e6.)

More intensive cholesterol lowering: balance of benefits versus risks

There is a general agreement that blood cholesterol is an important cause of coronary heart disease (CHD). Observational studies indicate a continuous positive relationship between CHD risk and blood low-density lipoprotein cholesterol (LDL-C) level that extends well below the range currently seen in western populations, without any definite threshold below which a lower level is not associated with lower risk.[1,2] In the past decade, several large randomized trials of statin therapy have demonstrated unequivocally that lowering LDL-C reduces not only the risk of coronary events but also the risk of stroke and need for arterial revascularization.[3] The magnitude of the relative risk reduction in each of these trials was associated with the absolute reduction in LDL-C that was achieved. Furthermore, the benefits of statins were seen even in participants with below-average blood LDL-C levels before treatment.[3,4] These findings are consistent with the hypothesis that larger LDL-C reductions produce larger reductions in the risk of cardiovascular events.

Recently, 4 randomized trials have reported on the comparative effects on clinical endpoints of intensive versus standard statin regimens.[5-8] One trial randomized 4162 patients with acute coronary syndrome to atorvastatin 80 mg daily versus pravastatin 40 mg daily for 2 years.[5] The additional 0.9 mmol/L LDL-C reduction achieved with the atorvastatin regimen was associated with a significant 16% (95% confidence interval [CI] 5%-26%, $P = .005$) relative reduction in the primary end point of total mortality and cardiovascular events. Another trial randomized 4497 patients with acute coronary syndrome to simvastatin 40 mg daily for the first month followed by 80 mg daily for approximately 2 years versus placebo for 4 months followed by simvastatin 20 mg daily.[6] Overall, the more intensive regimen was associated with an LDL-C reduction of

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The study is funded by a grant to the University of Oxford, Oxford, United Kingdom, from Merck & Co, Inc, Whitehouse Station, NJ. It has, however, been designed and conducted, and will be analyzed and interpreted by the Clinical Trial Service Unit independently of this source of support.
Collaborators and participating hospitals are listed in Web-Appendix 4.
The Clinical Trial Service Unit has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry, except for reimbursement of costs to participate in scientific meetings.
Submitted October 13, 2006; accepted June 22, 2007.
0002-8703/$ - see front matter

doi:10.1016/j.ahj.2007.06.034

approximately 0.6 mmol/L and a nonsignificant 11% relative reduction in cardiovascular events (hazard ratio [HR] 0.89, 95% CI 0.76-1.04, $P = .14$). In a trial among 10 001 patients with CHD randomized to receive atorvastatin 80 mg versus 10 mg daily for a median of 4.9 years, the more intensive regimen was associated with an LDL-C reduction of 0.6 mmol/L and a significant 22% (95% CI 11-31%, $P < .001$) relative reduction in major cardiovascular events.[7] Finally, among 8888 patients with a previous myocardial infarction (MI) randomized to receive atorvastatin 80 mg versus simvastatin 20 mg daily for a median of 4.8 years, the more intensive regimen was associated with an LDL-C reduction of 0.6 mmol/L and a nonsignificant 11% relative reduction in major coronary events (MCEs) (HR 0.89, 95% CI 0.78-1.01, $P = .07$).[8]

However, higher statin doses have been associated with dose-related increases in blood levels of liver transaminases and muscle creatine kinase (CK).[9] The risk of the rare, but important, side effect of myopathy also appears to be dose related. In previous trials, more intensive regimens have been associated with more liver enzyme elevations (eg, alanine transaminase [ALT] elevations >3 times the upper limit of normal in 3.3% with intensive vs 1.1% with standard therapy, $P < .001$[5]; and consecutive rises in liver enzymes in 0.9% vs 0.4%, $P = .05$[6]; in 1.2% vs 0.2%, $P < .001$[7]; and in 1.0% vs 0.1%, $P < .001$[8]) and with more muscle-related adverse effects (eg, 9 [0.40%] myopathy cases among 2265 participants allocated simvastatin 80 mg daily compared with 1 [0.04%] among 2232 allocated 20 mg daily[6]). So, although these trials indicate that more intensive cholesterol lowering produces further reductions in the risk of major vascular events (MVEs),[10] the balance between the benefits and risks of this approach remains uncertain. Further large long-term direct randomized comparisons (such as the present SEARCH trial) are therefore needed to help assess this balance of efficacy and safety reliably.

Lowering blood homocysteine, effects on cardiovascular events

In observational studies, 3-4 μmol/L lower blood homocysteine is typically associated with approximately 10% proportionally lower risk of CHD and 20% lower risk of cerebrovascular disease.[11] Studies of gene variants that affect homocysteine levels provide some support for these associations being causal.[12] A meta-analysis of randomized trials of vitamin supplementation indicated that supplementation with folic acid (at least 0.8 mg daily) and vitamin B_{12} reduces blood homocysteine levels by about one quarter (eg, from approximately 12 μmmol/L to approximately 9 μmmol/L).[13] Randomized trials have not yet, however, provided convincing evidence that lowering blood homocysteine with folic acid reduces cardiovascular events.[14]

In a recent meta-analysis of 12 randomized trials, there was no significant benefit of folic acid supplementation on the risk of CHD (HR 1.04, 95% CI 0.92-1.17) or stroke (relative risk 0.86, 95% CI 0.71-1.04), although stroke was only reported in 8 of these trials.[15] Even with nearly 17 000 participants with prior vascular disease, however, this meta-analysis had only approximately 80% power to detect a 10% reduction in cardiovascular disease. The largest randomized trial to have reported involved 5522 patients with vascular disease or diabetes allocated 2.5 mg folic acid, 1 mg vitamin B_{12}, and 50 mg vitamin B_6 daily versus placebo for an average of 5 years, which yielded an average of 3 μmol/L reduction in homocysteine levels.[16] The folate-based treatment was not associated with a significant reduction in the primary composite end point of stroke, MI, or cardiovascular death (HR 0.95, 95% CI 0.84-1.07), but there was a marginally significant reduction (HR 0.75, 95% CI 0.59-0.97, $P = .03$) in the secondary outcome of stroke (which is more strongly associated with homocysteine levels in observational studies[11]). Several large trials of folic acid supplementation are ongoing (including SEARCH), and a combined analysis based on more than 50 000 participants in these trials should have adequate power to determine whether lowering homocysteine reduces the risk of cardiovascular events.[14]

Methods

Aims

SEARCH aims to demonstrate reliably whether a more intensive cholesterol-lowering regimen using simvastatin 80 mg daily safely produces a greater reduction in cardiovascular risk than does a standard simvastatin 20 mg daily regimen. In addition, SEARCH aims to obtain reliable evidence about the effects on cardiovascular risk of homocysteine-lowering with folic acid 2 mg plus vitamin B_{12} 1 mg daily. 12 064 MI survivors aged between 18 and 80 years have been randomized to receive intensive versus standard cholesterol lowering and, separately, using a "2 × 2 factorial" design, to receive vitamin supplementation versus placebo.

Sample size and predicted number of events

Compared with simvastatin 20 mg daily, it was anticipated that simvastatin 80 mg daily would produce an average reduction in LDL-C levels of approximately 0.5 mmol/L. If this translated into a 15-20% further reduction in MCEs[17] (defined as nonfatal MI, coronary revascularization, or coronary death), then a study involving at least 1900 MCEs would have a good chance of demonstrating this effect (>90% power at 2 $P < .01$). The LDL-C difference observed during the first year of follow-up in SEARCH was approximately 0.5 mmol/L, but the average difference during median follow-up of 5 years was only approximately 0.4 mmol/L. Consequently, the steering committee decided in 2004 (blind to treatment-related results for clinical outcomes) that the trial should aim to be able to detect differences in risk of approximately 10% reliably, which requires at least 2800 events for 90% power at 2 $P < .05$. Similarly, if the

3-4-μmol/L reduction in blood homocysteine levels expected with the folate-based therapy being studied produces a 10-20% reduction in cardiovascular events,[11] then this too could be detected reliably.

Previous studies in patients with a history of MI had suggested that, in participants receiving the standard simvastatin 20 mg daily regimen, the annual MCE rate would be approximately 4%.[17] However, despite the baseline characteristics of patients in SEARCH being similar to those in previous statin studies,[4] the overall annual rate of MCE during the first 5 years of follow-up is only approximately 2.6%. Given this lower than anticipated event rate and the evidence from other trials that statin therapy also produces similar relative reductions in the risk of stroke and the need for noncoronary revascularization,[4,18] the steering committee decided (again, blind to treatment-related results) to change the primary outcome to MVE (defined as MCE, stroke, or noncoronary revascularization [any arterial bypass procedure or angioplasty of noncoronary arteries], including amputations). Based on the current overall MVE rate of approximately 3.5% per annum, it was estimated that 2800 MVEs should have occurred by approximately 7 years' median follow-up.

Planned comparisons of outcome

For cholesterol-lowering therapy, the primary comparison will be of MVEs during the scheduled treatment period among all those allocated simvastatin 80 mg daily versus all those allocated simvastatin 20 mg daily (ie, intention-to-treat analyses). Similarly, for the folate-based therapy, the primary comparison will be of MVEs during the scheduled treatment period among all those allocated folic acid plus vitamin B_{12} versus all those allocated placebo. No allowance will be made for multiple hypothesis testing in these 2 separate primary comparisons. Further details regarding secondary and other prespecified comparisons and statistical methods are provided in the data analysis plan (Web-Appendix 1).

Results

Identification and invitation of potentially eligible people to screening clinics

Medical collaborators from 88 UK hospitals supervised senior nurses who ran the local study clinics. Relevant ethics committee and regulatory agency approvals were obtained. Records of patient hospital discharges after MI were used to identify potentially eligible candidates. In accordance with the Data Protection Act, the coordinating center staff in the Clinical Trial Service Unit, University of Oxford, Oxford, UK, processed these data in confidence on behalf of the local hospitals. Having sought agreement from their general practitioners, letters were sent (in the name of the local collaborator) inviting potentially eligible people to attend screening appointments. In total, 83 237 people were invited to participate.

Screening clinic visit

Of those invited, 34 780 people attended a screening visit. Relevant past medical history, lifestyle information, other factors relevant to eligibility, height, weight, and blood pressure were recorded directly onto personal computer–based electronic screening forms (Web-Appendix 2), and inclusion and exclusion criteria were checked (Figures 1 and 2). Of 15 590 people who attended screening but did not enter the prerandomization run-in phase, 75% indicated that they would have difficulty attending study clinics or taking study medication regularly, or refused for other reasons; 7% had some life-threatening disease other than vascular disease or diabetes; 6% reported MI, hospitalization for angina, or coronary revascularization procedure within the previous 3 months, or had a coronary revascularization planned within the next 3 months; 5% were on a contraindicated drug; 3% denied a history of previous MI; and 5% were not eligible for some other reason (more than one reason may apply per person).

Run-in period prior to randomization

Of those attending screening, 19 190 people (55%) gave their written consent to participate and had a nonfasting blood sample taken. They were instructed to stop any current nonstudy statin therapy and given a run-in pack containing simvastatin 20 mg daily and placebo vitamin tablets. Blood samples were couriered to the central laboratory for assay of lipid profile (total cholesterol, high-density lipoprotein cholesterol [HDL-C], and triglycerides), liver enzymes, albumin, creatinine, and CK.[19] Participants who were found to have total cholesterol levels below the prespecified cut points (n = 2383, Figure 1) or significantly elevated liver enzymes (n = 343), creatinine (n = 105), or CK (n = 45) were advised to stop taking the run-in treatment and did not proceed to randomization. The local hospital collaborator and general practitioner were provided with the screening lipid profile and other relevant blood results of each of their patients who started run-in treatment, and asked to indicate those patients that they did not want to be randomized (eg, because their lipids might not be adequately controlled on study treatment).

Participants who, during run-in, had any apparent side effects to treatment, were noncompliant, or wished to drop out for any reason were not randomized. So, in addition to allowing the biochemical checks of eligibility, this run-in period allowed many potential dropouts to be excluded before becoming part of the randomized comparison, with a consequent improvement in statistical sensitivity.[20] Moreover, lipid profiles taken at the randomization visit after the 2-month run-in period reflect the use of simvastatin 20 mg daily by all patients (whereas values obtained at screening reflect variable statin use among the 72% of randomized patients who were already taking a statin, of whom 60% were on simvastatin, 18%

Figure 1

1. **Aged between 18 at 80** at the time of invitation for screening.*
2. **History of prior myocardial infarction** (but not eligible if MI, hospitalization for angina, CABG or PTCA occurred within the previous 3 months before screening appointment, or if a coronary revascularisation procedure is planned during the following 3 months).
3. **Current use of any HMG CoA reductase inhibitor ("statin"), or clear indication for statin therapy.**
4. **No clear indication for folic acid.**
5. **No clear contraindications to the study treatments:**
   - Screening plasma total cholesterol <3.5 mmol/l in a patient already on statin therapy, or <4.5 mmol/l in a patient not already on such therapy;
   - Chronic liver disease (i.e. cirrhosis or persistent hepatitis) or abnormal liver function (i.e. plasma ALT>1.5 x ULN);
   - Severe renal disease or evidence of renal impairment (i.e. plasma creatinine >2 x ULN);
   - Inflammatory muscle disease (such as dermatomyositis or polymyositis) or CK >3 x ULN);
   - Concurrent treatment with fibrates or high-dose (over 1g per day) niacin. (N.B. Patients on other cholesterol-lowering drugs or diets can still enter the trial, although they must be prepared to stop any non-study statin.);
   - Concurrent treatment with ciclosporin, nefazodone (Dutonin), methotrexate, systemic azole antifungals or systemic macrolide antibiotics;
   - Child-bearing potential (i.e. pre-menopausal woman who is not sterilised or using a reliable method of contraception).
6. **No other predominant medical problem:** The patient does not have some condition (other than CHD) that might limit compliance with 5 years of study treatment.

Eligibility for SEARCH. *The upper age limit was raised from 75 to 80 in a protocol amendment in June 2000.

on atorvastatin, 11% on pravastatin, 7% on cerivastatin, and 4% on fluvastatin).

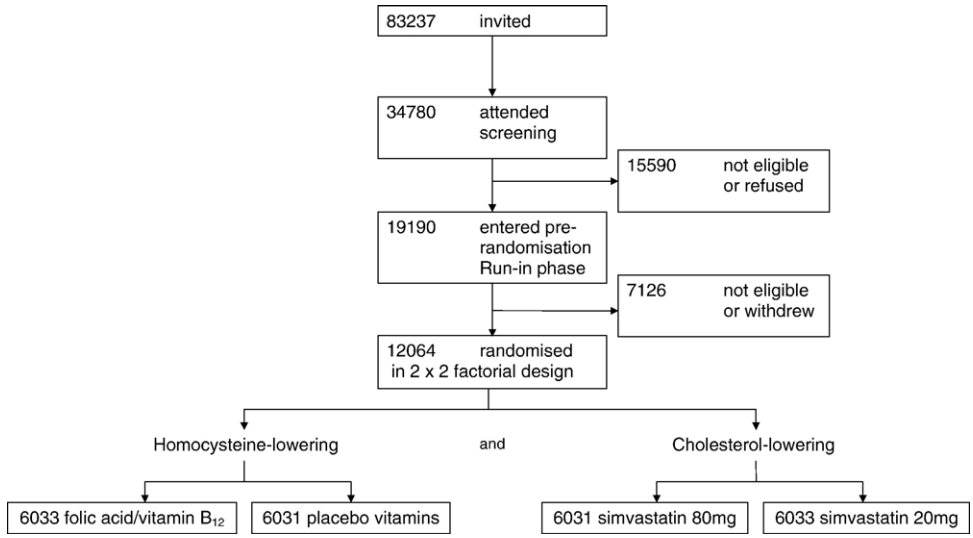
Randomization clinic visit

Approximately 2 months after the screening visit, participants attended a randomization appointment. Those who had not had an MVE or other problems during the run-in period were asked if they were willing to continue taking study treatment for at least the next 5 years. Of 7126 people who entered the run-in period but were not randomized, 39% had been excluded on the basis of blood results from the screening visit; 6% were excluded by their own doctor or local collaborator; 49% chose not to continue; 6% reported new unexplained muscle pain; and 4% were no longer eligible for other reasons (more than one reason may apply per person).

Participants who agreed to be randomized provided a nonfasting blood sample for central laboratory assay (liver enzymes, CK, total cholesterol and lipid fractions [including direct measurement of LDL-C and apolipoproteins A-I and B], plasma folate, vitamin B_{12}, homocysteine, full blood count, and glycated hemoglobin [HB/$A1_c$] in participants with diabetes) and for long-term storage of plasma and buffy coat aliquots. A central telephone service was contacted to confirm eligibility and randomize with minimization for important characteristics (in particular, age, sex, previous medical history, blood pressure, smoking, ethnic origin, prior statin use, and screening total cholesterol).[21]

A total of 12 064 people (10 012 men and 2052 women) with an average age of 64 years (SD 9) were randomized between September 1998 and October 2001 (Table I). All participants had a history of MI. In addition, 33% reported prior coronary revascularization, 7% had a history of cerebrovascular disease (previous stroke or transient ischemic attack), 2% reported previous noncoronary arterial bypass surgery or angioplasty, 11% had diabetes, and 42% had treated hypertension. Following the

Figure 2



Trial profile.

Table I. Numbers of randomized patients subdivided by LDL-C at randomization, age, and other medical history

	Tertiles of LDL-C at randomization				
	≤2.2	>2.2 ≤2.7	>2.7	Total*	(%)
Age (y)					
<50	152	238	377	767	6
≥50 <60	706	1029	1263	2998	25
≥60 <70	1598	1652	1578	4828	40
≥70 <75	859	677	541	2077	17
≥75	691	437	266	1394	12
Other factors					
Cerebrovascular disease	314	265	258	837	7
Other arterial disease †	100	80	99	279	2
Diabetes	526	397	344	1267	11
Treated hypertension	1774	1706	1594	5074	42
Smokers	365	476	642	1483	12
Sex					
Male	3396	3365	3251	10012	83
Female	610	668	774	2052	17
Total	4006	4033	4025	12064	100

*Including 6 patients with no LDL values recorded at randomization who have arbitrarily been placed in the middle LDL group.
†History of noncoronary arterial bypass surgery or angioplasty.

Table II. Relevant nonstudy drug use at randomization and during follow-up

	% of patients (N = 12064)	
Treatment	At randomization (%)	At latest appointment (%)
Aspirin (or other antiplatelet)*	91	89
Warfarin	5	9
β-Blocker	48	54
Nitrate	44	47
Calcium channel blocker	27	29
ACE inhibitor	38	50
Angiotensin II receptor antagonist	4	10
Hypoglycemics (oral or insulin)	8	15

ACE, Angiotensin-converting enzyme.
*Percentage on other antiplatelet drugs but not aspirin: 1% at randomization and 7% at latest appointment.

2-month run-in period on 20 mg daily simvastatin, the mean blood level of total cholesterol was 4.2 mmol/L (SD 0.7) and of LDL-C was 2.5 mmol/L (SD 0.6), with 2464 participants (20%) having LDL-C <2.0 mmol/L. The mean blood level of triglycerides was 1.9 mmol/L (SD 1.2), of HDL-C was 1.0 mmol/L (SD 0.4), of apolipoprotein A-I was 135 mg/dL (SD 22), and of apolipoprotein B was 90 mg/dL (SD 17). Table II shows the principal nonstudy treatments being used at randomization (and subsequently during follow-up).

Postrandomization follow-up

After randomization, participants are seen for follow-up at 2, 4, 8, and 12 months, and then at 6-month intervals. By the end of 2006, the median follow-up was 6 years (range 62-99 months). Details are recorded of all hospital admissions and, in particular, of any possible MI, hospitalization for angina, stroke, vascular procedure, pulmonary embolus, cancer, or other serious adverse experience. In addition, any new unexplained muscle

Table III. Proportions of randomized patients reporting compliance with study treatment during follow-up

Scheduled follow-up (months)	No. of patients who completed follow-up	Taken >80%, study statin		Taken >80%, supplement	
2	11776	11425	97%	11485	98%
4	11827	11223	95%	11390	96%
8	11703	10815	92%	11080	95%
12	11647	10548	91%	10941	94%
18	11444	10188	89%	10647	93%
24	11276	9804	87%	10377	92%
30	11089	9490	86%	10142	91%
36	10895	9172	84%	9930	91%
42	10772	8887	83%	9728	90%
48	10626	8625	81%	9521	90%
54	10453	8351	80%	9296	89%
60	10269	8062	79%	9057	88%
66	9145	7069	77%	7997	87%
72	6235	4791	77%	5450	87%

pain or weakness is explicitly sought and recorded. At each of the scheduled follow-up times, approximately 6% of all participants report unexplained muscle pain or weakness, which is similar to the 6% on either placebo or simvastatin 40 mg daily who reported such symptoms during the Heart Protection Study.[4] A blood sample is taken for central laboratory assay of ALT and CK. All blood results are reviewed by a coordinating center clinician, and abnormalities requiring action are dealt with according to prespecified guidelines (Web-Appendix 1).

At each follow-up, compliance with study treatment is assessed and reasons for discontinuation recorded (with the option for more than one reason). Compliance with the study simvastatin fell to approximately 90% during the first year and has since fallen more slowly to approximately 80% by 5 years (Table III). The main reasons given for discontinuation are participant's wishes (43% of those stopping) and medical advice (45%). Patient's managing doctors may measure blood lipids and, if they believe levels are not adequately controlled, may change their statin therapy (or add some other lipid-lowering therapy, see below). In principle, this could unblind the treatment allocation, but there is considerable overlap between the lipid levels among those allocated simvastatin 20 or 80 mg daily. Moreover, central adjudication of end points remains blind to treatment allocation, minimizing the risk of any such bias.

Participants prescribed statins, fibrates, or high-dose niacin by their own doctors are required to stop their allocated study simvastatin. However, those who are given other cholesterol-lowering therapies (such as a resin or ezetimibe) may continue their study simvastatin. Amiodarone was not contraindicated when SEARCH started, but the trial found an increased risk of myopathy when it was combined with high-dose simvastatin. Consequently, in January 2003, the protocol was amended so that participants taking concurrent amiodarone are provided with simvastatin 20 mg daily (irrespective of their original allocation to 20 or 80 mg).

Participants who become unable to attend study clinics (10% of those stopping) are asked to discontinue the study simvastatin treatment because safety monitoring is not possible. Other reasons given for stopping the study statin include muscle symptoms (5%), gastrointestinal symptoms or diagnoses (6%), skin problems (1%), and concerns, either from participants' own doctors or study clinicians, about abnormal ALT or CK measurements (4%). For the folic acid plus vitamin B_{12} versus placebo tablets, compliance fell to approximately 95% during the first year and has since fallen more slowly to approximately 90% by 5 years. This higher level of compliance than for the simvastatin comparison chiefly reflects the option to continue study vitamins/placebo (but not study simvastatin) if participants are unable to attend the study clinic. Only 44 patients have stopped the vitamins/placebo while continuing the simvastatin treatment chiefly because of the use of an antifolate drug (such as methotrexate).

Effects of study treatments on blood lipids and homocysteine levels

To assess the overall effects of the study treatments on the lipid profile and on homocysteine levels in the different treatment groups, approximately 10% of all surviving participants are selected each year (irrespective of whether or not they are continuing to take the study treatments or attending follow-up clinics) for extensive analysis of their nonfasting blood samples. Compared with simvastatin 20 mg daily, allocation to 80 mg daily produced further reductions of approximately 0.6 mmol/L in blood total cholesterol, 0.5 mmol/L in LDL-C, and 0.2 mmol/L in triglycerides at 2 months (Table IV). However, the average reductions in blood lipids throughout the whole study period will be somewhat lower due to discontinuation of study treatment. Compared with plasma homocysteine levels of approximately 13 μmol/L among those allocated placebo supplement tablets, allocation to folic acid plus vitamin B_{12} is producing a sustained reduction of approximately 3-4 μmol/L (Table V).

Rates of fatal and nonfatal events

The coordinating center seeks further details from the participant's general practitioner (plus, if necessary, from hospital records) about all reports from follow-up that might relate to MVEs and from the UK national registries about cancers and the certified causes of any deaths. All such information is reviewed by coordinating center clinical staff, blind to study treatment allocation, and events are coded according to prespecified criteria (Web-Appendix 3). Based on events reported and confirmed during a median of 6 years of follow-up, the estimated

Table IV. Nonfasting blood lipid differences (SE) with allocation to 80 mg simvastatin versus 20 mg simvastatin (data from annual random samples)

Scheduled follow-up (months)	No. of samples	Total cholesterol (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	Triglycerides (mmol/L)	Apolipoprotein A-I (mg/dL)	Apolipoprotein B (mg/dL)
2	437	0.63 (0.07)	0.50 (0.06)	0.02 (0.04)	0.23 (0.11)	2.93 (2.19)	12.59 (1.59)
4	428	0.62 (0.08)	0.50 (0.06)	–0.09 (0.03)	0.37 (0.11)	–2.55 (2.14)	13.63 (1.66)
8	636	0.52 (0.06)	0.40 (0.05)	–0.01 (0.03)	0.24 (0.09)	0.61 (1.78)	11.47 (1.46)
12	412	0.46 (0.08)	0.40 (0.06)	–0.03 (0.04)	0.18 (0.11)	–1.45 (2.30)	10.29 (1.75)
18	719	0.48 (0.06)	0.41 (0.05)	–0.02 (0.03)	0.20 (0.08)	–0.24 (1.82)	10.00 (1.37)
24	496	0.42 (0.07)	0.36 (0.06)	–0.03 (0.04)	0.17 (0.09)	–2.53 (2.30)	9.43 (1.69)
30	760	0.43 (0.06)	0.34 (0.05)	0.02 (0.03)	0.17 (0.07)	2.46 (1.80)	7.99 (1.37)
36	557	0.32 (0.07)	0.31 (0.06)	–0.05 (0.03)	0.05 (0.10)	–0.93 (2.13)	8.69 (1.63)
42	762	0.38 (0.06)	0.28 (0.05)	0.06 (0.03)	0.14 (0.08)	4.41 (1.75)	6.98 (1.43)
48	551	0.39 (0.07)	0.34 (0.06)	–0.05 (0.04)	0.19 (0.12)	–0.96 (2.11)	9.75 (1.75)
54	411	0.34 (0.09)	0.30 (0.07)	0.01 (0.04)	–0.02 (0.15)	1.07 (2.42)	6.94 (2.10)
60	579	0.31 (0.07)	0.30 (0.06)	–0.04 (0.03)	0.18 (0.08)	–1.17 (1.92)	6.21 (1.71)
66	596	0.30 (0.06)	0.30 (0.05)	–0.03 (0.03)	0.03 (0.09)	–1.92 (1.96)	5.83 (1.62)
72	287	0.43 (0.10)	0.39 (0.08)	–0.02 (0.04)	0.06 (0.14)	–1.34 (2.49)	6.63 (2.33)

Figures are (mean value for patients allocated 20 mg simvastatin) – (mean value for patients allocated 80 mg simvastatin). Missing values are imputed using the respective randomization value.

Table V. Plasma homocysteine difference (SE) between those allocated folic acid/vitamin B_{12} supplements versus matching placebo (data from annual random samples)

Scheduled follow-up (months)	No. of samples	Plasma homocysteine difference (μmol/L)
2	437	2.77 (0.40)
4	428	4.15 (0.46)
8	636	4.18 (0.30)
12	412	3.90 (0.33)
18	719	3.61 (0.28)
24	496	4.17 (0.34)
30	760	4.11 (0.31)
36	557	3.48 (0.30)
42	762	3.92 (0.34)
48	551	3.13 (0.36)
54	411	3.46 (0.43)
60	579	3.59 (0.34)
66	596	2.69 (0.32)
72	287	4.12 (1.23)

Figures are (mean value for patients allocated placebo) – (mean value for patients allocated folic acid + vitamin B_{12}). Missing values are imputed using the respective randomization value.

overall annual rate of MCEs is approximately 2.5% and of MVEs is approximately 3.5%.

Discussion

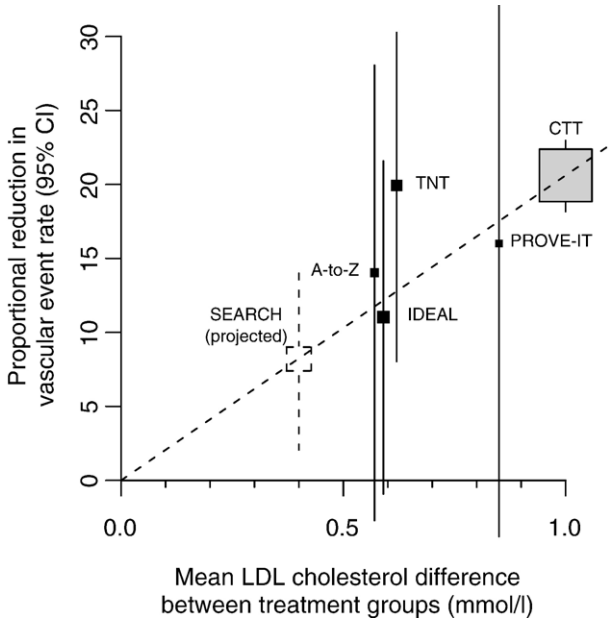
Need for reliable assessment of benefits versus risks of intensive lipid lowering

Statin therapy is now widely recommended for both primary and secondary prevention of vascular disease in high-risk groups.[22,23] However, there is uncertainty about the value of more intensive cholesterol-lowering therapy. Most current guidelines recommend targets for treatment, typically aiming for LDL-C <2 mmol/L.[22] Evidence from observational studies and from randomized trials is generally consistent with lower LDL-C levels being associated with lower risks of vascular disease.[1,3] Four recent trials have directly compared the effects of intensive versus standard statin regimens.[5-8] When considered together,[10] those trials indicate that intensive cholesterol lowering produces further reductions in vascular disease risk (Figure 3). SEARCH is the largest trial to assess directly the effects of more intensive statin therapy. Its prolonged duration and large number of vascular and nonvascular events provide good statistical power to detect as little as a 10% reduction in MVEs while also providing a reliable assessment of the safety of more intensive LDL lowering.

Uncertainty as to whether lowering blood homocysteine reduces vascular events

No randomized trial has clearly shown that lowering blood homocysteine reduces the risk of cardiovascular events. This may reflect a lack of adequate statistical power to detect plausible effects due to relatively small numbers of vascular events and/or short duration of treatment in previous trials,[14-16] particularly since the association between blood homocysteine and vascular disease in observational studies appears to be weaker than had previously been thought.[24] SEARCH is expected to involve at least 2800 confirmed MVEs (including approximately 500 strokes and 2200 MCEs) and a 3-4 μmol/L reduction in blood homocysteine during a median of 7 years. If such a homocysteine reduction produces a 10-20% reduction in cardiovascular events (which would be consistent with the observational

Figure 3



Relation between the proportional reduction in vascular event rate and mean absolute LDL-C difference. Gray square represents summary result for MVEs from Cholesterol Treatment Trialists' (CTT) collaborative meta-analysis of effect of 1 mmol/L LDL-C reduction in randomized trials of statin versus no statin.[3] Sloping line plotted through zero and CTT result. Solid squares represent individual trials comparing more versus less intensive statin therapy,[5-8] with data derived from published meta-analysis.[10] (Directly comparable outcome is not available for these trials, so endpoint of "CHD death or MI" is plotted.) Average achieved LDL difference for A-to-Z is based on aggregate of achieved differences during month 1, months 2 to 4, and thereafter.[6] Open square represents projected result for SEARCH, based on primary outcome of MVE and estimated average LDL-C difference of 0.4 mmol/L between intensive and standard statin groups. The area of each square is proportional to the amount of statistical information in trial or meta-analysis. Vertical lines are 95% CIs.

epidemiology[11]), then SEARCH should have good statistical power. Even if the cardiovascular benefits are somewhat smaller or confined to stroke (as suggested by one trial[16]), then a planned collaborative meta-analysis may still be able to detect these effects.[14] In either case, the implications for public health would be important because widespread folic acid supplementation is readily achieved (eg, through fortification of flour).

Conclusion

SEARCH has randomized 12064 heart attack survivors and currently has median follow-up of more than 6 years. During 2008, it should provide a reliable and relevant assessment of whether lowering LDL-C more with intensive simvastatin therapy safely produces further benefits. By also randomizing these patients to B-vitamin therapy or placebo, SEARCH will also generate uniquely reliable evidence about the causal nature of the association between blood homocysteine and cardiovascular disease, and about the public health value of B-vitamin supplementation.

The most important acknowledgement is to the participants in the SEARCH study and to the collaborators and steering committee listed in Web-Appendix 4.

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Web-Appendix 1. Data analysis plan (revised, December 2004, blind to treatment-related results for clinical outcomes)

1. Comparisons of simvastatin 80 mg versus 20 mg daily

For the cholesterol-lowering comparison with the different simvastatin doses, it is hypothesized that the more substantial reduction in low-density lipoprotein cholesterol (LDL-C) produced by simvastatin 80 mg daily than by simvastatin 20 mg daily will reduce the incidence of nonfatal and fatal occlusive vascular events without adversely affecting the incidence of other nonfatal or fatal serious adverse events (in particular, hemorrhagic strokes and cancers), and that the same absolute reduction in LDL-C will be associated with similar proportional reductions in vascular risk throughout the blood cholesterol range studied. All simvastatin dose comparisons will involve comparing outcome among all those patients allocated at randomization to receive simvastatin 80 mg daily versus all those allocated to receive simvastatin 20 mg daily (ie, intention-to-treat analyses[1]).

1.1. Primary comparison. The primary comparison for the simvastatin dose allocation will be of "major vascular events" (MVE) during the scheduled study treatment period.

1.2. Secondary comparisons. The secondary comparisons for the simvastatin dose allocation will be of the following:

1. MVEs separately in the first year after randomization (when little difference is anticipated) and in the later years of the scheduled treatment period;
2. MVEs among patients subdivided into 3 similar-sized groups with respect to blood LDL-C levels at the end of the prerandomization run-in period on simvastatin 20 mg daily (with the hypothesis that the same absolute reduction in LDL-C will be associated with similar proportional reductions in vascular risk in each of these groups);
3. MVEs in the presence and in the absence of the allocated study folic acid plus vitamin B_{12} (with the hypothesis that the effects will be similar);
4. major coronary events; and
5. total strokes.

1.3. Tertiary comparisons. The tertiary comparisons for the simvastatin dose allocation will be of the effects during the scheduled treatment period on the following:

1. total mortality;
2. cause-specific mortality (ie, considering, separately, deaths from vascular causes [ICD10 I20-I99] and from nonvascular causes);
3. vascular mortality excluding the first year after randomization (when little difference is anticipated);
4. coronary and noncoronary revascularizations;
5. confirmed hemorrhagic and other strokes considered separately;
6. pulmonary embolus;
7. total and site-specific cancers;
8. hospitalizations for various causes; and
9. possible adverse effects of treatment, including, in particular, evidence of liver function abnormalities (defined as 2 or more consecutive elevations of alanine transaminase [ALT] > 4 × upper limit of laboratory normal [ULN]) and evidence of muscle abnormalities (defined as any elevation of creatine kinase [CK] > 10 × ULN).

2. Comparisons of folic acid plus vitamin B_{12} versus placebo

For the assessment of folic acid plus vitamin B_{12}, it is hypothesized that this treatment will reduce the incidence of nonfatal and fatal occlusive vascular events without adversely affecting the incidence of other nonfatal or fatal serious adverse events, and that the same absolute reduction in homocysteine will be associated with similar proportional reductions in vascular risk throughout the blood homocysteine range studied. All folate-based therapy comparisons will involve comparing outcome among all those patients allocated at randomization to receive folic acid 2 mg plus vitamin B_{12} 1 mg versus all those allocated to receive placebo (ie, intention-to-treat analyses[1]).

2.1. Primary comparison. The primary comparison for the folate-based therapy allocation will be of MVEs during the scheduled study treatment period.

2.2. Secondary comparisons. The secondary comparisons for the folate-based therapy allocation will be of the following:

1. MVEs separately in the first year after randomization (when little difference is anticipated) and in the later years of the scheduled treatment period;
2. MVEs among patients subdivided into 3 similar-sized groups with respect to (*a*) plasma folate levels and (*b*) blood homocysteine levels at the end of the prerandomization run-in period on placebo vitamins (with the hypothesis that the same absolute reduction in homocysteine will be associated with similar proportional reductions in coronary heart disease risk in each of these groups);
3. MVEs in the presence and in the absence of each of the simvastatin dose regimens (with the hypothesis that the effects will be similar);
4. major coronary events; and
5. total strokes.

2.3. Tertiary comparisons. The tertiary comparisons for the folate-based therapy allocation will be of the

effects during the scheduled treatment period on the following:

1. total mortality;
2. cause-specific mortality (ie, considering, separately, deaths from vascular causes and from nonvascular causes);
3. vascular mortality excluding the first year after randomization (when little difference is anticipated);
4. coronary and noncoronary revascularizations;
5. confirmed hemorrhagic and other strokes considered separately;
6. pulmonary embolus;
7. total and site-specific cancers;
8. fractures of any kind and osteoporotic fractures (ie, hip, wrist, or spine combined), excluding, in both cases, those due to road traffic accidents;
9. cognitive impairment (ie, <22 for modified Telephone Interview of Cognitive Status [TICS-m] score) at final follow-up;
10. hospitalizations for various causes; and
11. possible adverse effects of treatment.

3. Details of analyses

3.1. Methods of analysis. The fundamental assessments of efficacy will involve comparisons among all randomized patients in their originally allocated treatment group, irrespective of compliance, during the scheduled treatment period (ie, intention-to-treat analyses[1]). All time-to-event analyses will be based on the first relevant event and will use log-rank methods[1] to calculate *P* values and Cox regression analyses[2,3] to calculate odds ratios and confidence intervals. Comparisons of the overall proportions of affected individuals, irrespective of time, will involve standard Mantel-Haenszel methods[4] for the analysis of contingency tables.

The main assessment of the effects of different doses of simvastatin will involve comparing outcome among all patients allocated simvastatin 80 mg daily versus outcome among all those allocated simvastatin 20 mg daily, without stratification for the folate-based therapy allocation or other factors. Similarly, the main assessment of the effects of folic acid plus vitamin B_{12} will involve unstratified comparison of outcome among all patients allocated folic acid plus vitamin B_{12} versus outcome among all those allocated matching placebo. Use of a factorial design instead of a simple 2-way design is anticipated to have little or no effect on the statistical sensitivity with which the overall benefits of different simvastatin doses or of folic acid plus vitamin B_{12} can be assessed, or on the size of the study.[1]

3.2. Allowance for multiplicity of comparisons. No allowance will be made for multiple hypothesis testing in the primary comparison of each of the 2 separate treatment modalities being assessed (different cholesterol-lowering regimens and folate-based therapy) in this 2 × 2 factorial study. For secondary and, particularly, tertiary comparisons, allowance will be made for multiple hypothesis testing,[1] taking into account the nature of events (including timing, duration, and severity) and evidence from other studies. In addition to the prespecified comparisons, many other analyses will be performed, with due allowance for their exploratory and, perhaps, data-dependent nature. Conventionally, 2-sided *P* values (2*P*) <.05 are often described as "significant." However, the larger the number of events on which a comparison is based and the more extreme the *P* value (or, analogously, the further the lower limit of the confidence interval is from zero) after any allowance has been made for the nature of the particular comparison (ie, primary, secondary, or tertiary; prespecified or exploratory), the more reliable the comparison and, hence, the more definite any finding will be considered.

3.3. Tests for heterogeneity of effects. The large number of vascular events expected in this study may allow reasonably reliable direct assessment of the effects of treatment in some subcategories of patient (eg, baseline levels of plasma cholesterol or homocysteine) or of vascular events (eg, fatal vs nonfatal). However, when a number of different subgroups are considered, chance alone may lead to there being no apparent effect in several small subgroups in which the effect of treatment really is about the same as is observed overall. In such circumstances, "lack of direct evidence of benefit" is not good "evidence of lack of benefit," and clearly, significant overall results would provide strong indirect evidence of benefit in some small subgroups where the results, considered in isolation, are not conventionally significant (or, even, perhaps, slightly adverse).[1,5] Hence, unless the proportional effect in some specific subcategory is clearly different from that observed overall, the effect in that subcategory is likely to be best estimated indirectly by applying the proportional effect observed among all patients in the trial to the absolute risk of the event observed among control patients in that category.[5] Tests for heterogeneity of the proportional effect on particular outcomes in specific subgroups will be used (with allowance for multiple comparisons and for other differences between the subgroups) to determine whether the effects in those subgroups are clearly different from the overall effect.[6] If, however, such subgroups can be arranged in some meaningful order (eg, baseline cholesterol subdivided into 3 similar sized groups of low, medium, and high), then assessment of any trend in the proportional effects on outcome will also be made.

4. Analyses of adverse events or biochemical abnormalities

4.1. Adverse events. Only those adverse events that are serious (defined as resulting in death or life-

threatening, produce a persistent or significant disability, require inpatient hospitalization or the prolongation of existing hospitalization, are cancer or congenital abnormality, or are judged to jeopardize the patient or to require intervention to prevent any of these listed outcomes), which lead to discontinuation of study treatment, or that are believed with a reasonable probability to be due to study treatment are to be recorded systematically during follow-up. Comparison of the incidence of these adverse events between the randomly allocated treatment groups will be made using the Mantel-Haenszel method.[4]

Statistical hypothesis testing of differences in adverse events must be interpreted cautiously because this is essentially a screening exercise. Hence, in interpreting these results, substantial allowance will be made for multiple hypothesis testing, the data-derived nature of the exercise, the nature of the events (including timing, duration, and severity), and evidence from other studies.

4.2. Biochemical abnormalities. Blood samples are scheduled to be taken from all randomized patients at 2, 4, 8, and 12 months after randomization, and then at 6-month intervals, as well as at additional clinic visits if any problems (including biochemical abnormalities) are thought to have arisen. On each occasion, ALT and CK will be measured. For ALT, elevations of more than twice the ULN will result in an early recall visit for repeat sampling, and 2 or more consecutive elevations of >4× ULN will be defined as an adverse event. For CK, elevations of >5× ULN will result in an early recall visit for repeat sampling, and a single elevation of >10× ULN will be defined as an adverse event. Comparisons of the incidence of such elevations of ALT and of CK between patients allocated simvastatin 80 mg and those allocated simvastatin 20 mg will be made using the Mantel-Haenszel method without stratification, and estimates made of the absolute differences and their SDs. Proportional and absolute differences between the randomly allocated treatment groups in mean ALT, CK, vitamin B_{12}, and various aspects of the full blood count measured during follow-up will also be calculated with their SDs.

5. Data and safety monitoring

5.1. Interim analyses by the Data Monitoring Committee. During the period of the study, unblinded interim analyses of mortality, of vascular events, and of any other information that is available on major events (including serious adverse events), along with any other analyses requested, will be supplied at least annually, in strict confidence, to the chairman of the independent Data Monitoring Committee. In the light of these analyses and the results of any other relevant trials, the Data Monitoring Committee will advise the Steering Committee if, in their view, the randomized comparisons in SEARCH have provided both (1) "proof beyond reasonable doubt"* that for all patients, or for some specific types, really prolonged use of higher-dose simvastatin or of folate-based therapy is clearly indicated or clearly contraindicated in terms of a net difference in mortality or major morbidity, and (2.) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of any other main trial results. The Steering Committee can then decide whether to modify the study (or to seek extra data).

Unless this happens, the Steering Committee, the collaborators, Merck & Co., Inc, and the coordinating center staff (except those who supply the confidential analyses) will remain ignorant of the interim unblinded results on mortality and major morbidity until the study is terminated. Collaborators and all others associated with the study may write (preferably through the Oxford coordinating center) to the chairman of the Data Monitoring Committee, drawing attention to any worries they may have about the possibility of particular adverse effects, or about particular categories of patient requiring special consideration, or about any other matters that may be relevant. (Minutes of all Data Monitoring and Steering Committee meetings will be kept, and these will be available for consideration at the end of the study.)

5.2. Monitoring of any serious adverse events believed to be due to study treatment. Throughout the trial, all serious adverse events believed with a reasonable probability to be due to study treatment are to be reported immediately by telephoning the 24-hour Freefone service at the Oxford coordinating center. These reports will be reviewed promptly by one of the clinical coordinators blind to treatment allocation, and any further information required will be sought urgently. Confirmed reports will be promptly forwarded "unblinded" to the chairman of the Data Monitoring Committee and "blinded" to the chairman of the South Thames Multicentre Research Ethics Committee, to medical collaborators and, by facsimile, to Merck Sharp & Dohme (MSD), UK. The company will notify the coordinating center if any further information is needed (including unblinding) and will then forward relevant reports to drug regulatory agencies.

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* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but in general, a difference of at least 3 SDs in an interim analysis of a major end point would be needed to justify halting, or modifying, such a study prematurely, especially if the comparison was based on relatively few events (eg, <100). If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed.[1]

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Web-Appendix 2. SEARCH electronic data entry

Participant data are recorded at each study appointment by nurses using a secure electronic data capture system ("Sentry") developed at the SEARCH coordinating center (Clinical Trial Service Unit, University of Oxford, UK). This enables research nurses conducting participant interviews to enter trial data directly onto remote off-line laptop computers using "intelligent" electronic Case Report Forms (eCRFs) and then to transfer these data electronically to the coordinating center in a secure way. Sentry ensures that only relevant questions are displayed on eCRFs, and warning boxes appear when unusual or out-of-range values are entered. It is not possible to answer questions out of sequence, thus, eliminating the possibility of questions being missed. Where appropriate, "pick lists" have been provided to allow automatic coding (eg, of nonstudy treatment). Checks are made within and between eCRFs to minimize the likelihood of contradictory answers being given. The Sentry system checked each individual's eligibility during the screening and randomization visit, thus, helping to ensure that ineligible patients were not randomized and that eligible ones were not inappropriately excluded.

On completion of an eCRF, the research nurse electronically "signs" the form, and the data are saved to a database on the laptop's hard disk. This database is password protected and encrypted in a way that cannot be accessed or changed by the laptop user except by entering data through Sentry. Measures have been taken to protect the database against a binary-level examination of the installed programs. Sentry allows users to view, but not alter, eCRFs completed on previous occasions. Encrypted data can be transferred to the SEARCH coordinating center either via a dial-up Internet connection or by sending floppy diskettes by mail or courier. Data sent via a dial-up connection are received onto a dedicated computer at the coordinating center, which is protected by the coordinating center's firewall, and acknowledgements are sent back. The study site's laptop continues to resend data during each transfer until it receives a specific acknowledgment that the data have been incorporated in the central system. Authorized coordinating center administrative staff run a program to import new eCRF data from the dedicated computer, or from floppy diskettes, and decrypt it into tables within the Clinical Trial Service Unit firewall.

Web-Appendix 3. Criteria for confirmation of myocardial infarction and stroke in SEARCH

The coordinating center seeks further details from the participant's general practitioner (plus, if necessary, from any relevant hospital records) about all reports that might relate to major vascular events and from the UK national registries about the sites of any registered cancers and the certified causes of any deaths. All such information is reviewed by the coordinating center clinical staff blind to the study treatment allocation, and events are coded according to the prespecified criteria. The diagnosis of definite myocardial infarction (MI) requires information about either (1) the presence of 2 or more of (*a*) typical ischemic chest pain, pulmonary edema, syncope, or shock; (*b*) development of pathologic Q-waves and/or appearance or disappearance of localized ST-elevation followed by T-wave inversion in 2 or more of 12 standard electrocardiograph leads; and (*c*) increase in concentration of serum enzymes consistent with MI (eg, CK > 2 × ULN or raised troponins consistent with MI); or (2) necropsy findings of MI of an age corresponding to the time of onset of symptoms.[1] Deaths attributed to MI, other coronary disease (including heart failure due to coronary disease), and sudden or unexpected deaths (without postmortem evidence of another cause) are classified as coronary death. For any strokes reported, information is sought for review to help establish the likely etiology and severity. The diagnosis of stroke requires a rapid (or uncertain) onset of focal or global neurologic deficit, lasting more than 24 hours or leading to death. (The following are not included in the definition of a stroke: traumatic intracranial hemorrhage, neurologic deficit due to major metabolic disturbance or hemodynamic disturbance, venous sinus thrombosis, and cerebral tumor.)

Currently, the required criteria have been met by approximately 80% of the reported nonfatal heart attacks and 70% of the reported nonfatal strokes (94% ischemic, 2% hemorrhagic, and 4% unknown etiology), with 16% of the reported transient ischemic attacks also meeting the criteria for stroke. Most of the reported revascularizations are confirmed: 100% for coronary artery bypass grafting, 94% for percutaneous transluminal angioplasty (with or without stenting), and 70% for other arterial revascularizations (including amputations).

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Appendix D. Web-Appendix 4:

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Independent Data Monitoring Committee

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