Homocysteine-lowering trials for prevention of cardiovascular events: A review of the design and power of the large randomized trials

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Background Dietary supplementation with folic acid and vitamin B_{12} lowers blood homocysteine concentrations by about 25% to 30% in populations without routine folic acid fortification of food and by about 10% to 15% in populations with such fortification. In observational studies, 25% lower homocysteine has been associated with about 10% less coronary heart disease (CHD) and about 20% less stroke.

Methods We reviewed the design and statistical power of 12 randomized trials assessing the effects of lowering homocysteine with B-vitamin supplements on risk of cardiovascular disease.

Results Seven of these trials are being conducted in populations without fortification (5 involving participants with prior CHD and 2 with prior stroke) and 5 in populations with fortification (2 with prior CHD, 2 with renal disease, and 1 with prior stroke). These trials may not involve sufficient number of vascular events or last long enough to have a good chance on their own to detect reliably plausible effects of homocysteine lowering on cardiovascular risk. But, taken together, these 12 trials involve about 52 000 participants: 32 000 with prior vascular disease in unfortified populations and 14 000 with vascular disease and 6000 with renal disease in fortified populations. Hence, a combined analysis of these trials should have adequate power to determine whether lowering homocysteine reduces the risk of cardiovascular events within just a few years.

Conclusion The strength of association of homocysteine with risk of cardiovascular disease may be weaker than had previously been believed. Extending the duration of treatment in these trials would allow any effects associated with prolonged differences in homocysteine concentrations to emerge. Establishing a prospective meta-analysis of the ongoing trials of homocysteine lowering should ensure that reliable information emerges about the effects of such interventions on cardiovascular disease outcomes. (Am Heart J 2006;151:282-7.)

The occurrence of premature atherothrombotic events in individuals with homocystinuria, a rare genetic disorder associated with greatly elevated blood concentrations of homocysteine, prompted the hypothesis that more modest elevations of homocysteine may be relevant to cardiovascular disease in the general population.[1] Individuals with homocystinuria have about 10-fold higher mean plasma homocysteine concentrations (ie, 100-300 μmol/L)[2] compared with levels among middle-aged individuals in the general population (ie, "normal" range of about 10-15 μmol/L).[3,4] Folic acid appears to be the most important dietary determinant of blood homocysteine concentrations,[3] and dietary supplementation with folic acid typically lowers plasma homocysteine concentrations by about 25%.[5] The introduction of mandatory folic acid fortification in North America during 1998 reduced the mean plasma homocysteine concentration in middle-aged individuals to about 8 to 10 μmol/L,[6] and additional B-vitamin supplementation in such fortified populations lowers homocysteine by only about 10% to 15%.[7]

In the late 1990s, several large-scale randomized trials in people with prior coronary heart disease (CHD), prior stroke, or renal disease were initiated to test the hypothesis that homocysteine lowering with folic acid (and other B vitamins) could reduce the risk of recurrent cardiovascular disease.[8] These trials were typically designed to detect 30% reductions in the risk of CHD or stroke, based on quantitative reviews of the observational epidemiologic studies published by the late 1990s.[9,10] However, an updated meta-analysis of such observational studies found that a 25% (or, typically, 3 μmol/L) lower blood homocysteine was associated with only about

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The study was supported in part by grants from the British Heart Foundation, London, England, and the Medical Research Council, London, England, and the European Union BIOMED Program (BMH4-98-3549), Brussels, Belgium.
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doi:10.1016/j.ahj.2005.04.025

Table I. Characteristics of the major homocysteine-lowering trials in people with prior CHD, prior stroke, or renal disease

Trial	Fortified population (−/+)	Prior disease	Actual/ scheduled number randomized	Scheduled/ actual median duration of treatment (y)	Homocysteine-lowering regimen (Daily doses in mg)			Observed/ estimated reduction in plasma homocysteine (%)	Estimated total number of vascular events*		
					Folic acid	B_{12}	B_6		MCE	Strokes	MVE
CHAOS-2†	–	CHD	1880	2	5.0	–	–	13	87	32	226
SU.FOL.OM3	–	CHD	2000	5	0.5	0.02	3	25	190	190	626
WENBIT	–	CHD	3000	3	0.8	0.4	40	25	209	77	563
NORVIT†	–	CHD	3750	3	0.8	0.4	40	25	606	94	1575
SEARCH	–	CHD	12064	7	2.0	1.0	–	25	1400	373	2800
HOPE-2	+/–	CHD	5522	5	2.5	1.0	50	20	718	276	1795
WACS	+	CHD	5442	7.4	2.5	1.0	50	20	268	134	850
SU.FOL.OM3	–	Stroke	1000	5	0.5	0.02	3	25	95	95	358
VITATOPS	–	Stroke	8000	3	2.0	0.5	25	25	321	951	1690
VISP†	+	Stroke	3680	2	2.5	0.4	25	15	221	288	504
FAVORIT	+	Renal	4000	5	2.5	0.4	20	33	480	220	1000
HOST	+	Renal	2056	5	40.0	0.5	100	33	247	113	514

*Major coronary events and major vascular events are designated as MCE and MVE, respectively. Event rates were provided for all but the WENBIT trial (which was estimated from the average of all trials in prior CHD) and the 2 trials in renal disease (which were estimated from registry data).
†Data for 3 trials were based on the actual number of events in the trials.

11% (95% CI 4%-17%) lower risk of CHD and 19% (95% CI 5%-31%) lower risk of stroke.[4] Moreover, a recent meta-analysis of 40 studies of a polymorphism in the gene encoding methylenetetrahydrofolate reductase found that the 2.5 μmol/L higher homocysteine levels among individuals with the TT genotype was associated with a 16% (95% CI 5%-28%) higher CHD risk than among those with the CC genotype[11,12] (although the results of these genetic studies were not entirely concordant). In the light of this recent evidence,[4,12] we have reexamined the likely statistical power of each of the large trials of B-vitamin supplements to detect any plausible reductions in vascular risk that might be produced by lowering blood homocysteine concentrations.

Methods

Data from ongoing or completed trials

We aimed to identify all randomized trials involving >1000 participants that were assessing the effects of folic acid supplements (with or without the addition of vitamins B_{12} or B_6) versus control without such supplementation on the incidence of vascular events.[13-19] Trials were identified by MEDLINE searches and by personal contact with relevant investigators. Investigators were asked to provide information about the number of people to be randomized, the details of the vitamin regimens, and the scheduled duration of treatment for their trial. Information was also sought on the achieved reductions in homocysteine levels and the expected vascular event rates in the trial population.

Observed or estimated vascular event rates

Major coronary events (MCEs) were defined as the first occurrence of nonfatal myocardial infarction or coronary death (including death due to heart failure and sudden or unexpected deaths that were assumed to be coronary in origin); stroke was defined as the first occurrence of either fatal or nonfatal stroke of any type (but not including transient cerebral ischemic attacks); coronary revascularization included coronary artery bypass grafting or coronary angioplasty; and noncoronary revascularization included carotid endarterectomy or carotid artery angioplasty, repair of aortic aneurysm, peripheral arterial surgery, or angioplasty. Major vascular events (MVEs) were defined as the first occurrence of any MCE, any stroke, or any coronary or noncoronary revascularization. The estimated event rates were provided by the investigators for all trials, with the exception of the WENBIT in prior CHD and the 2 trials in renal disease (Table I). In the absence of data on event rates in the WENBIT trial, the weighted average of the vascular event rates in the other trials in prior CHD was used. In the absence of data on event rates in trials in renal disease, registry data of people with end-stage renal disease[20-22] were used to estimate the likely event rates (although it is recognized that rates in a trial may be somewhat lower than in population studies because of the "healthy volunteer" effect). Estimated numbers of MCE, stroke, and MVE for each ongoing trial were calculated using the product of the event rates and the scheduled duration of treatment in each trial. Actual numbers of vascular events for completed trials were abstracted from published reports.[13,15]

Observed or estimated magnitude of homocysteine lowering

The observed plasma homocysteine reduction by allocated treatment in each trial population was used (if available). In the absence of data on the homocysteine difference within a trial, the reduction in blood homocysteine levels was estimated from a previous meta-analysis of randomized trials of the effects of folic acid and other B vitamins on plasma homocysteine concentrations.[5] That meta-analysis demonstrated that the proportional reductions in homocysteine concentrations

produced by folic acid supplements were greater at higher pretreatment concentrations of homocysteine and lower pretreatment blood folate concentrations, but did not differ with doses between 0.5 and 5 mg daily.[5] Dietary supplementation with folic acid doses of at least 0.5 mg daily reduced blood homocysteine concentrations by 25% (95% CI 23%-28%) in populations with pretreatment mean blood homocysteine levels of 12 μmol/L (which is the approximate average level for most populations before the introduction of folic acid fortification) and by 16% (95% CI 11%-20%) in populations with pretreatment blood homocysteine levels of 8 μmol/L (which is the approximate average level for populations after the introduction of folic acid fortification).[6] In this meta-analysis, vitamin B_{12} (mean 0.5 mg daily) supplementation produced an additional 7% (95% CI 4%-11%) reduction in homocysteine concentrations, whereas vitamin B_6 supplementation (mean 16.5 mg daily) had no significant effect on fasting or basal homocysteine levels. More recently, 2 other trials that assessed the effects of folic acid and vitamin B_{12} supplementation on homocysteine levels after the introduction of folic acid fortification reported homocysteine reductions of about 15%,[7,20] which is consistent with the findings of the meta-analysis. All participants in the WACS in North America are female and the proportional reduction in homocysteine concentrations associated with folic acid appears to be about 20% to 25% greater in women compared with men (Homocysteine Lowering Trialists' Collaboration, unpublished data on 2596 people in 25 trials), and only two thirds of the participants in the HOPE-2 trial were recruited from a fortified population, so the homocysteine reduction for both of these trials was estimated to be 20%. Individuals with renal disease have persistently elevated homocysteine concentrations despite fortification, and these can be reduced by as much as 33% with a multivitamin-containing folic acid, vitamin B_{12}, and vitamin B_6.[23]

Estimation of plausible effects on cardiovascular risk of lowering homocysteine levels

The estimated reduction in cardiovascular risk associated with a prolonged difference in blood homocysteine concentrations was obtained from a recent meta-analysis of observational studies of homocysteine and risk of CHD or stroke.[4] To minimize the possibility of reverse causality (due to homocysteine levels being altered by prior cardiovascular disease), the chief emphasis in that meta-analysis was on the analysis of prospective studies involving people who had no history of prior vascular disease. In prospective studies, a 25% lower homocysteine was associated with 11% (95% CI 4%-17%) lower CHD risk and 19% (95% CI 5%-31%) lower stroke risk after adjustment for cigarette smoking, systolic blood pressure, and total cholesterol levels and correction for regression dilution.[4] Hence, the statistical power for the randomized trials to detect 10%, 15%, or 20% reductions in first occurrence of vascular events during the scheduled treatment periods was estimated by log-rank comparisons of 2 survival curves.[24] The risk reductions associated with folic acid–based vitamin supplements were assumed to be directly proportional to the observed or estimated proportional differences in homocysteine concentrations for each trial and, hence, if B-vitamin supplementation in an individual trial (ie, a 20% reduction in homocysteine concentrations was assumed to yield 20/25 of the risk reduction associated with a 25% reduction in homocysteine concentrations).

Results

Trials in patients with prior CHD

Table I provides selected details of the number randomized, treatment duration, vitamin regimen, plasma homocysteine reductions, and vascular event rates in each trial involving >1000 people. Among the 7 large randomized trials in people with prior CHD, 5 involve 22 694 people in European populations without systematic fortification of food with folic acid and 2 involve 11 022 people predominantly recruited in North America with mandatory folic acid fortification. All trials use daily doses of folic acid of ≥0.8 mg, except one that uses 0.56 mg of 5-methyltetrahydrofolate,[18] and all except one include additional vitamin B_{12}. The CHAOS-2 trial of 1882 people with prior CHD was terminated prematurely after a median treatment period of 1.7 years because of a perceived lack of power to address the hypothesis. The 13% reduction in homocysteine concentrations observed in the CHAOS-2 trial was lower than in other trials in unfortified populations (possibly due to poor compliance with instructions to take the allocated study treatment) and had no effect on any vascular outcome. In contrast with all other trials, participants in the NORVIT trial were recruited during hospitalization for acute myocardial infarction, so the vascular event rates were higher than in other trials of prior CHD. The scheduled duration of treatment has been extended in some trials and currently varies from 2 to 7.4 years.

Table II provides the estimated statistical power to detect 10%, 15%, or 20% reductions in the risk of MCE, stroke, and MVE in the individual trials of people with prior CHD and in all these trials combined. If a 25% lowering in homocysteine concentrations was associated with at least a 20% lower risk of MVE, as was assumed when the trials were designed, then several of the individual trials in unfortified populations would have reasonable statistical power. But if a 25% lowering in homocysteine levels is associated with only a 10% lower risk of MVE, then few individual trials would have adequate power even in unfortified populations. Moreover, because folic acid lowers blood homocysteine concentrations by only about 15% to 20% in fortified populations, the power for trials conducted in these populations is even more limited. On the other hand, for a 10% difference in risk at $2P < .05$, a combined analysis of all 7 trials involving 33 658 people with prior CHD would have 86% power for MCE and 99% power for MVE; although, it would still only have 94% power to detect a 20% reduction in stroke.

Table II. Estimated power of the individual trials and combinations of these trials in people with prior CHD, prior stroke or renal disease to detect reductions in risk of 10%, 15% or 20% for MCEs, stroke and MVEs

			10% Reduction in risk			15% Reduction in risk			20% Reduction in risk		
			Approximate power (%) at $2P < .05$			Approximate power (%) at $2P < .05$			Approximate power (%) at $2P < .05$		
Population/trial	**Fortified population (−/+)**	**n***	**MCE**	**Stroke**	**MVE**	**MCE**	**Stroke**	**MVE**	**MCE**	**Stroke**	**MVE**
CHD											
CHAOS-2	−	1880	5	4	7	7	5	11	9	6	17
SU.FOL.OM3	−	2000	12	12	36	22	22	69	36	36	**92**
WENBIT	−	3000	12	7	28	23	11	57	38	17	**83**
NORVIT	−	3750	29	7	**79**	59	12	**99**	**85**	19	**99**
SEARCH	−	12064	55	18	**89**	**90**	36	**99**	**99**	59	**99**
Subtotal: unfortified	−	22694	**78**	31	**99**	**99**	61	**99**	**99**	**87**	**99**
HOPE-2	+/−	5522	22	11	58	45	19	**91**	70	32	**99**
WACS	+	5442	10	7	26	19	11	53	31	17	**79**
Subtotal: fortified	+	11022	28	14	69	56	26	**97**	**82**	43	**99**
All CHD	−/+	33658	**86**	39	**99**	**99**	74	**99**	**99**	**94**	**99**
Stroke											
SU.FOL.OM3	−	1000	8	8	24	13	13	49	21	21	**75**
VITATOPS	−	8000	16	41	68	32	**76**	**96**	53	**95**	**99**
Subtotal: unfortified	−	9000	19	44	**78**	39	**80**	**99**	64	**97**	**99**
VISP	+	3680	7	8	11	11	13	21	16	20	34
All stroke		12680	21	46	**78**	43	**81**	**99**	69	**97**	**99**
Renal disease											
FAVORIT	+	4000	37	18	72	71	38	**98**	**94**	63	**99**
HOST	+	2056	21	12	45	44	22	**81**	71	37	**97**
All renal		6056	52	26	**88**	**87**	53	**99**	**99**	**80**	**99**
All trials	+/−	52394	**96**	**79**	**99**	**99**	**99**	**99**	**99**	**99**	**99**

Bolded text is used to distinguish trials with statistical power of 75% or greater.
*Number randomized or (scheduled to be randomized).

Trials in patients with prior stroke

Among the 3 large randomized trials that are ongoing in people with prior stroke, 2 trials involving about 9000 people are being carried out in nonfortified populations.[16,18] In a fortified population, the VISP study of 3680 people who had had a nondisabling cerebral infarct was terminated after 2 years when the interim analyses were interpreted as indicating little possibility of demonstrating an effect on vascular events. Participants in VISP were allocated to either a "high-dose" multivitamin containing 2.5 mg folic acid, 25 mg vitamin B_6, and 400 μg vitamin B_{12} daily or "low-dose" multivitamin containing 0.2 mg folic acid, 0.2 mg vitamin B_6, and 6 μg vitamin B_{12} daily.[14,15] Despite the high-dose B-vitamin supplement being associated with a 2 μmol/L difference in plasma homocysteine concentrations compared with the low-dose B-vitamin group, no significant reduction in the risk of stroke, myocardial infarction, or vascular death was observed. The VITATOPS trial is still ongoing and has reasonable power to detect a 15% to 20% difference in MVE, but more limited power for stroke or MCE (Table II). A combined analysis of all 3 trials involving 12680 people with prior stroke would have reasonable power to detect a 15% to 20% difference in stroke risk (but still limited power for plausible effects on MCE).

Trials in patients with renal disease

Two trials are assessing the relevance of homocysteine lowering in patients with renal disease. Both of these studies are being conducted in North America, but a 25% to 33% reduction in homocysteine with B-vitamin supplementation may still be anticipated despite fortification because of their high baseline concentrations. Assuming that the trials accrue the predicted number of events over the scheduled treatment period, the combined analysis of both trials involving 6056 people with renal disease should have reasonable power to detect a 10% reduction in the risk of MVE, 15% reduction in MCE, and 20% reduction in stroke (Table II).

Discussion

Combined analyses of previous observational epidemiologic studies suggest that a 25% lowering in homocysteine levels is associated with about 10% lower risk of CHD and 20% lower risk of stroke.[4] If these epidemiologically predicted differences in risk of

10% to 20% are reversible at least within a few years, then the implications for public health of decreasing population homocysteine concentrations could be substantial. Several large-scale randomized trials are assessing whether lowering homocysteine levels with B-vitamin supplements can reduce the risk of cardiovascular disease, but these trials were set up when the associations were believed to be stronger. Reliable demonstration of any more modest effects on vascular risk of lowering homocysteine levels may require larger trial evidence to have sufficient power to detect plausible differences in risk at convincing levels of significance.

The statistical power of the randomized trials is likely to depend on a number of factors, including the number of vascular events; the difference in homocysteine levels between the B-vitamin–treated and control groups; and the differences in risk associated with a particular difference in homocysteine concentration, the speed of any reversal in risk, and the duration of the trial. Collection of data on revascularization events in addition to myocardial infarction and stroke may help to increase the power of these trials to detect any difference in the risk of vascular events associated with B-vitamin supplements (assuming that such effects on revascularization are comparable with those observed for myocardial infarction and stroke, as is the case for the cholesterol-lowering trials[25]). In addition, extending the duration of treatment in individual trials may increase their statistical power by increasing the number of vascular events that accrue and by allowing a longer period for any benefits to emerge. A meta-analysis of all 12 trials involving 52 000 participants (32 000 with prior vascular disease in unfortified populations and 14 000 with vascular disease and 6000 with renal disease in fortified populations) should have adequate power to determine whether lowering homocysteine by about 20% to 25% reduces the risk of cardiovascular disease by at least 10% within just a few years. The results of these trials would help to guide national public health policy in many countries about the benefits (or any hazards) of altering the population mean blood homocysteine and folate concentrations by mandatory folic acid fortification.

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Appendix A

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