Homocysteine-Lowering Therapy and Stroke Risk, Severity, and Disability

Additional Findings From the HOPE 2 Trial

Gustavo Saposnik, MD, MSc, FAHA; Joel G. Ray, MD, MSc; Patrick Sheridan, MSc; Matthew McQueen, MD, PhD; Eva Lonn, MD, MSc; the HOPE 2 Investigators*

Background and Purpose—Elevated total homocysteine is associated with a higher risk of cerebrovascular disease. It is not known whether lowering homocysteine impacts on stroke risk, both in terms of severity and ischemic vs hemorrhagic stroke subtypes. Our aim was to determine whether vitamin therapy reduces the risk of ischemic and hemorrhagic stroke, as well as stroke-related disability.

Methods—We analyzed stroke outcomes among participants of the Heart Outcomes Prevention Evaluation 2 (HOPE 2) trial that randomized 5522 adults with known cardiovascular disease to a daily combination of 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12, or matching placebo, for 5 years.

Results—Among 5522 participants, stroke occurred in 258 (4.7%) individuals during a mean of 5 years of follow-up. The geometric mean homocysteine concentration decreased by 2.2 μmol/L in the vitamin therapy group and increased by 0.80 μmol/L in the placebo group. The incidence rate of stroke was 0.88 per 100 person-years in the vitamin therapy group and 1.15 per 100 person-years in the placebo group (hazard ratio [HR], 0.75; 95% CI, 0.59–0.97). Vitamin therapy also reduced the risk of nonfatal stroke (HR, 0.72; 95% CI, 0.54–0.95) but did not impact on neurological deficit at 24 hours (P=0.45) or functional dependence at discharge or at 7 days (OR, 0.95; 95% CI, 0.57–1.56). In subgroup analysis, patients aged younger than 69 years, from regions without folic acid food fortification, with higher baseline cholesterol and homocysteine levels, and those not receiving antiplatelet or lipid-lowering drugs at enrollment had a larger treatment benefit.

Conclusions—Lowering of homocysteine with folic acid and vitamins B6 and B12 did reduce the risk of overall stroke, but not stroke severity or disability. **(*Stroke*. 2009;40:1365-1372.)**

Key Words: cardiovascular disease ■ folate ■ folic acid ■ homocysteine ■ primary stroke ■ randomized clinical trial ■ secondary stroke ■ stroke prevention ■ vitamin B12

Observational studies have detected higher levels of total plasma homocysteine in persons with acute cerebrovascular disease.[1–6] In the Vitamin Intervention for Stroke Prevention (VISP) trial, the only randomized clinical trial that exclusively recruited persons with previous nondisabling cerebral infarction, high-dose multivitamin therapy was no better than control in preventing recurrent stroke (RR, 1.0; 95% CI, 0.8–1.3); however, the control agent contained small doses of vitamins B6, B12, and folic acid, and the reduction in homocysteine levels was less than assumed in the study design, which impacted on the power of this key trial.[6] In the main report of the Heart Outcomes Prevention Evaluation 2 (HOPE-2) study, homocysteine-lowering B vitamin therapy was no better than placebo in terms of the primary composite outcome of cardiovascular death, myocardial infarction, and stroke (HR, 0.95; 95 CI, 0.84–1.07), but the risk of stroke was reduced (HR, 0.75; 95% CI, 0.59–0.97).[7,8]

At present, there are insufficient data to reliably exclude a clinically important effect of B vitamins in preventing stroke, especially according to patient subgroups and stroke subtypes. Moreover, it is not known whether homocysteine-lowering therapy has any impact on stroke severity or stroke-related disability. The present study greatly expands on the initial HOPE-2 paper by focusing on stroke types, stroke severity, and disability, and subgroup treatment–effect interactions.

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From Division of Neurology (G.S.), Departments of Medicine, and Health Policy Management and Evaluation, St. Michael's Hospital, University of Toronto, Toronto, Ontario; Departments of Medicine, Obstetrics, and Gynecology (G.S., J.G.R.), and Health Policy Management and Evaluation, St. Michael's Hospital, University of Toronto, Toronto, Ontario; Population Health Research Institute (P.S.), Hamilton General Hospital, McMaster University, Hamilton, Ontario; Department of Pathology and Molecular Medicine and Population Health Research Institute (M.M.), Hamilton General Hospital, McMaster University, Hamilton, Ontario; Population Health Research Institute (E.L.), Hamilton General Hospital, McMaster University, and the Department of Medicine, Division of Cardiology, Hamilton Health Sciences, Hamilton, Ontario.

*The HOPE-2 investigators are listed in the Supplemental Appendix, available online at http://stroke.ahajournals.org.

Correspondence to Gustavo Saposnik, Assistant Professor, Director, Stroke Research Unit, Department of Medicine, St. Michael's Hospital, University of Toronto, 55 Queen St E, Toronto, Ontario, M5C 1R6. E-mail saposnikg@smh.toronto.on.ca

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Methods and Design

The study design was described in detail previously.[7,8] In summary, HOPE-2 was a clinical trial that randomized participants to homocysteine-lowering therapy or placebo.[7,8] Safety and data quality were monitored by an independent monitoring board. The trial was approved by the research ethics review board of each participating center, and written informed consent was obtained from all study participants. The study sponsors were not involved in the design, execution, analysis, or reporting of the trial results. The study was registered as NCT00106886 (ClinicalTrials.gov) and ISRCTN14017017 (controlled-trials.com).

Study Participants

HOPE-2 included 5522 adults aged 55 years or older who had a history of coronary, cerebrovascular disease, or peripheral arterial disease, or diabetes mellitus and at least 1 additional cardiovascular risk factor, irrespective of baseline homocysteine concentration. Individuals using a daily vitamin supplement containing >0.2 mg of folic acid were excluded. Patients with a history of stroke, TIA with objective evidence of ischemic cerebrovascular disease, or with endarterectomy were eligible for trial participation. A complete list of inclusion and exclusion criteria are provided elsewhere.[7,8] All participants who were enrolled in HOPE-2 are included in the current analyses.

Study Centers

Individuals were recruited from 145 participating centers within 13 countries, including Canada (n=3568), the United States (n=414), Brazil (n=265), Western Europe (n=426), and Slovakia (n=849).

Study Intervention and Randomization

Participants were randomized (central randomization) to receive a once-daily supplement containing 2.5 mg of folic acid, 50 mg of vitamin B6, and

Table 1. Baseline Characteristics of Study Participants

Baseline Characteristics*	Homocysteine-Lowering Therapy (n=2758)	Placebo (n=2764)
General characteristics		
Mean (SD) age, yr	68.8 (7.1)	68.9 (6.8)
Female	796 (28.9)	763 (27.6)
Ethnicity, nonwhite	106 (3.8)	109 (3.9)
Living in North America	1988 (72.1)	1994 (72.1)
Cardiovascular risk factors		
Coronary artery disease	2285 (82.8)	2315 (83.8)
TIA	158 (5.7)	154 (5.6)
Stroke	241 (8.7)	251 (8.9)
TIA or stroke	341 (12.4)	343 (12.4)
Peripheral artery disease	216 (7.8)	169 (6.1)
Hypertension	1542 (55.9)	1497 (54.2)
Dyslipidemia	1524 (55.3)	1526 (55.2)
Diabetes mellitus	1122 (40.7)	1087 (39.3)
Current smoking	306 (11.1)	327 (11.8)
Baseline medication use		
Antiplatelet agent	2148 (77.9)	2224 (80.5)
Oral anticoagulant	227 (8.2)	193 (7.0)
Lipid-lowering agent	1627 (59.0)	1690 (61.1)
Estrogen replacement therapy among women	137 (17.2)	130 (17.0)
Multivitamin supplement	331 (12.0)	307 (11.1)
Baseline physical measures		
Mean (SD) heart rate, bpm	68.7 (11.2)	68.9 (11.5)
Mean (SD) systolic blood pressure, mm Hg	138.8 (21.7)	138.9 (23.4)
Mean (SD) diastolic blood pressure, mm Hg	77.4 (11.8)	77.5 (11.7)
Mean (SD) BMI, kg/m^2	29.6 (16.4)	29.7 (21.1)
Baseline biochemical measures		
Mean (SD) serum total cholesterol, mmol/L	4.83 (1.01)	4.78 (0.98)
Mean (SD) serum LDL cholesterol, mmol/L	2.73 (0.85)	2.68 (0.83)
Mean (SD) serum HDL cholesterol, mmol/L	1.21 (0.36)	1.18 (0.34)
Mean (SD) serum triglycerides, mmol/L	2.02 (1.35)	2.04 (1.29)
Mean (SD) serum glucose, mmol/L	7.15 (3.22)	6.97 (2.88)
Geometric mean (SD) plasma homocysteine concentration, μmol/l†	11.5 (0.80)	11.5 (0.80)

*Data are presented as a number (%) unless otherwise indicated.
†A total of 3306 participants underwent measurement of plasma homocysteine at baseline.
HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Stroke Outcomes Comparing Homocysteine-Lowering Therapy vs Placebo

Outcome*	N (Incidence Rate per 100 Person-Years)		HR (95% CI), Homocysteine-Lowering Therapy vs Placebo
	Homocysteine-Lowering Therapy (n=2758)	Placebo (n=2764)	
Any stroke	111 (0.88)	147 (1.15)	0.75 (0.59–0.97)
Ischemic stroke	79 (0.62)	98 (0.77)	0.81 (0.60–1.09)
Hemorrhagic stroke	8 (0.06)	10 (0.08)	0.80 (0.32–2.03)
Nonfatal stroke	84 (0.66)	117 (0.92)	0.72 (0.54–0.95)
Fatal stroke	27 (0.21)	30 (0.24)	0.91 (0.54–1.53)
Disabling stroke	26 (0.21)	41 (0.32)	0.64 (0.39–1.04)
Fatal or disabling stroke	48 (0.38)	63 (0.49)	0.77 (0.53–1.12)

*If a participant had >1 outcome during the study period, only the first event was included in this analysis.

1 mg of vitamin B12, or matching placebo, for 5 years. No request was made to unmask treatment allocation for any given participant.

Baseline Measures and Follow-Up

Baseline demographic data, medical history, and medication use, including current use of anticoagulant therapy, were recorded for all participants at study entry. History of stroke or TIA was also documented. After an overnight fast, blood was obtained for measurement of baseline plasma homocysteine from 3306 randomly selected participants. Homocysteine was measured using fluorescence polarization immunoassay (Abbott IMX; Abbott Laboratories, Inc). The distribution of homocysteine was statistically significantly skewed; thus, we log-transformed these measures and used inverse transformations to generate geometric mean values. At each 6-month interval, participants were assessed in the study clinics at each participating center. These assessments were directed primarily to ascertain study endpoints, side effects, and adherence. Adherence to treatment was assessed by interview and pill count. The trial used simple case report forms, which were faxed toll-free to the study coordinating office and read into a database using optical character recognition (DataFax software; Clinical DataFax Systems).

Neurological Outcomes

All stroke events, but not TIA, were centrally adjudicated by the Adjudication Committee using prespecified definitions of outcomes and all available supporting source documentation.[7,8] Accordingly, we separately evaluated the risk of any stroke, ischemic stroke, hemorrhagic stroke, nonfatal stroke, fatal stroke, disabling stroke, as well as fatal or disabling stroke. TIA was excluded from all stroke outcomes. A disabling stroke was based on a modified Rankin score of 3 to 5, equivalent to having moderate to severe disability (Supplemental Table I, available online at http://stroke.ahajournals.org).

A stroke was defined as a focal neurological deficit lasting >24 hours. Computed tomography or magnetic resonance cranial imaging was obtained for 92% of participants with an ischemic stroke.

Among persons with an incident stroke, the following symptoms were recorded at stroke onset and at 24 hours thereafter: change in the level of consciousness, ocular or visual symptoms (diplopia or amaurosis fugax), motor weakness, sensory symptoms, dysarthria or dysphasia, and dysphagia. A higher number of symptoms suggested a worse neurological deficit.

Separately, stroke-related disability at discharge from hospital or at 7 days after stroke (whichever came first) was determined using the modified Rankin scale, graded from 0 to 6, as described in Supplemental Table I.

Data Analysis

All analyses were by intention-to-treat, comparing the effect of homocysteine-lowering therapy against placebo. Binary stroke outcomes were analyzed by Cox proportional hazards regression models and risk estimates were expressed as a crude HR and 95% CI. Survival curves were estimated according to the Kaplan-Meier procedure and compared between treatment groups using a log-rank test. In the rare (<1%) circumstance that an individual could not be assessed at a clinic visit or contacted by telephone, the individual was considered to be free of a cerebrovascular event at that point in time. If lost to follow-up, then a participant was censored at the time of last contact. Censoring also occurred when a participant died or experienced any form of stroke, but not a TIA. We further assessed the risk of stroke in prespecified subgroups (Figure 2), including sex, those older and younger than the median age of the study participants, those with and without a history of hypertension, diabetes, smoking, coronary artery disease, TIA/stroke, cholesterol levels above/below the median of study participants, use of lipid-lowering therapy, use of antithrombotic agents, region (mandatory food fortification with folic acid vs nonfortified areas), and quartiles of homocysteine levels. In addition, we conducted posthoc analyses using a multivariable Cox proportional hazards models to evaluated the effect of homocysteine-lowering vitamin therapy on stroke adjusted for age, sex, and extended use of an antihypertensive, antiplatelet, and lipid-lowering agents (model 1) and age, sex, and geographic region (model 2).

Among persons with an incident stroke, the net mean difference in change in neurological deficit from initial presentation to that at 24 hours was compared between homocysteine-lowering therapy and placebo groups using a Wilcoxon rank sum test. The trend in the modified Rankin scores at hospital discharge (or 7 days after stroke onset) was assessed using a Mantel Haenzel χ^2 test. Modified Rankin scores were categorized into 2 levels of function: independence (a score between 0 and 2) and dependence (a score of 3–6). The risk of being functionally dependent after stroke was expressed as an OR and 95% CI, comparing persons who received homocysteine-lowering therapy to those assigned placebo.

Statistical significance was set at a 2-sided $P<0.05$ for all analyses, which were performed using SAS version 9.1 (SAS Institute Inc).

Results

Baseline Characteristics, Adherence, and Homocysteine Levels

Of the 5522 study participants, 2758 were randomly assigned to homocysteine-lowering therapy and 2764 to placebo. Baseline characteristics were well-balanced in the 2 treatment groups (Table 1). The mean participant age was 69 years and 28% were women. Overall, 8.8% had a history of stroke. A total of 3982 persons (72%) originated from North America, where universal folic acid flour fortification was in place before the start of the trial.

Adherence to treatment was similar between active and placebo groups at 1 year (95% vs 96%), 2 years (94% vs 93%), 3 years (92% vs 92%), 4 years (91% vs 90%), and 5 years (91% vs 88%). A total of 21 participants in the active arm and 16 in the placebo arm were lost to follow-up or withdrew from the study,

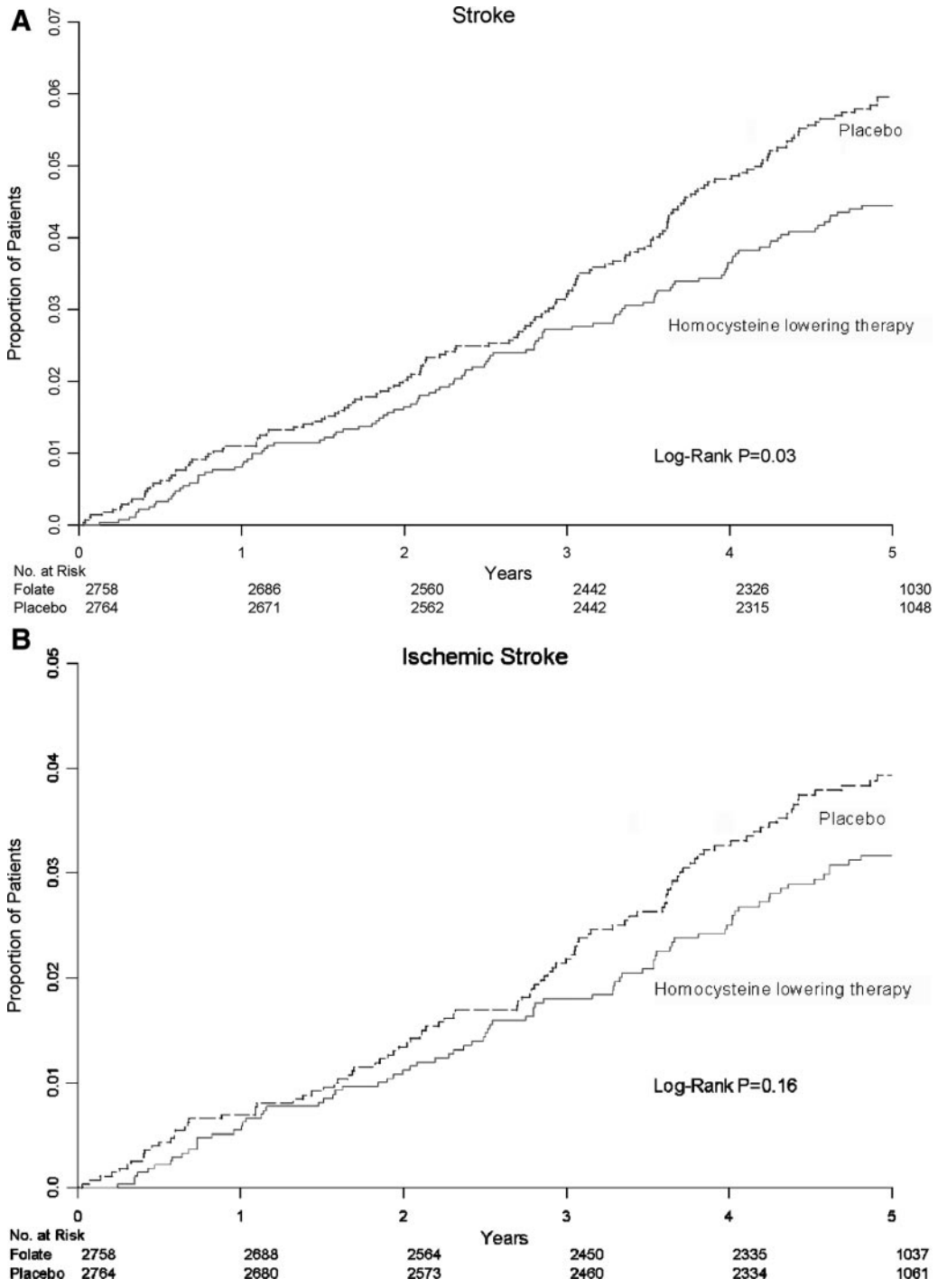

Figure 1. Kaplan-Meier estimates of the probability of any stroke (A), ischemic stroke (B), disabling stroke (C), or fatal or disabling stroke (D) according to receipt of homocysteine-lowering therapy vs placebo among all participants. The relative risk of any stroke in the active-treatment group, as compared with the placebo group, was 0.76 (95% CI, 0.59–0.97; $P=0.03$ by the log-rank test). There was a nonsignificant reduction in ischemic stroke, disabling stroke, or fatal or disabling stroke.

but all were enrolled for at least 2 years and were included in the final analysis, censored for duration of observation.

The geometric mean homocysteine concentration at baseline, measured among 3306 participants, was 11.5 μmol/L in both groups (Table 1). In the active group, the mean concentration was 2.1 μmol/L lower in countries with folic acid food fortification than in those without fortification; in the placebo group, this difference at baseline was 2.3 μmol/L. At the end of the trial, the mean homocysteine concentration was 9.3 μmol/L in the vitamin therapy group and 12.3 μmol/L in the placebo group, indicating a decrease of 2.2 μmol/L and an increase of 0.80 μmol/L, respectively.

Stroke Risk

Overall, there were 258 (4.7%) strokes in total. One hundred eleven (4.0%) patients in the homocysteine-

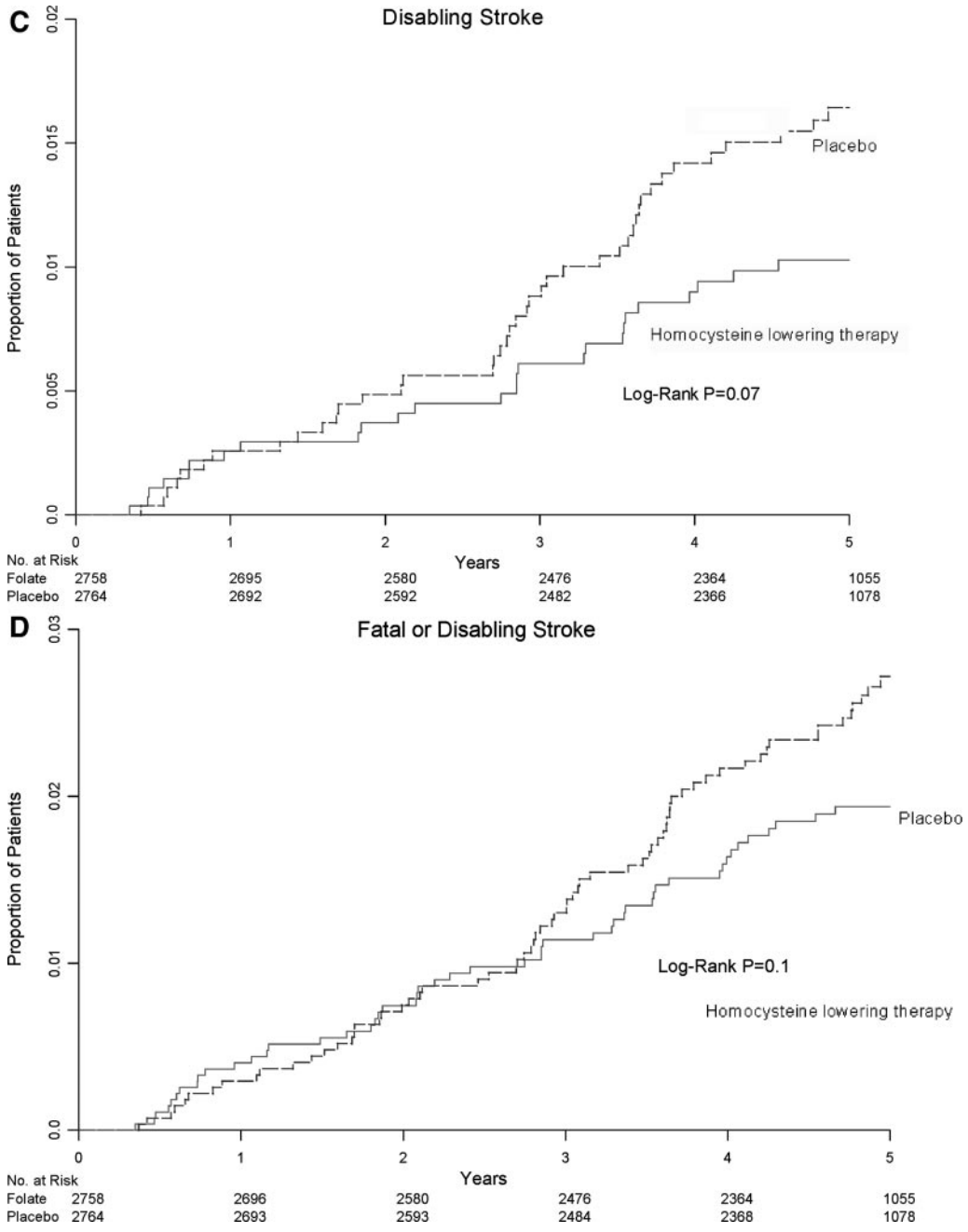

Figure 1 (Continued).

lowering group and 147 (5.3%) in the placebo group had a stroke (HR, 0.75; 95% CI, 0.59–0.97; absolute risk reduction, 1.3%; Table 2, Figure 1A). The corresponding risk of ischemic stroke (HR, 0.81; 95% CI, 0.60–1.09; Figure 1B) and hemorrhagic stroke (HR, 0.80; 95% CI, 0.32–2.02) tended to favor vitamin therapy, but not significantly so (Table 2). The relative risk of stroke was most reduced among those who baseline homocysteine concentration was in the highest quartile (Figure 2). There were no significant differences in baseline characteristics between stroke patients with and without imaging (data not shown).

The absolute risk of stroke was higher among certain patient groups, such as those with a history of stroke or TIA, those from regions without folic acid food fortification, with a history of hypertension, with higher baseline cholesterol and homocysteine levels, and those not receiving antiplatelet and lipid-lowering drugs at study enrollment (Figure 2). There were no statistically significant differences among the subgroups examined with regards to the effect treatment on stroke risk. However, we observed trends, suggesting a possibly larger treatment benefit for patients aged younger than 69 years, those from regions without folic acid food fortification, with higher baseline cholesterol and homocysteine levels and those not receiving antiplatelet or lipid-lowering drugs at enrollment (Figure 2). In countries without folic acid food fortification, the HR was 0.67 (95% CI, 0.46–0.97), which was however not significantly different in the presence of background fortification (HR, 0.82; 95% CI, 0.59–1.14). Vitamin therapy attained the largest reduc-

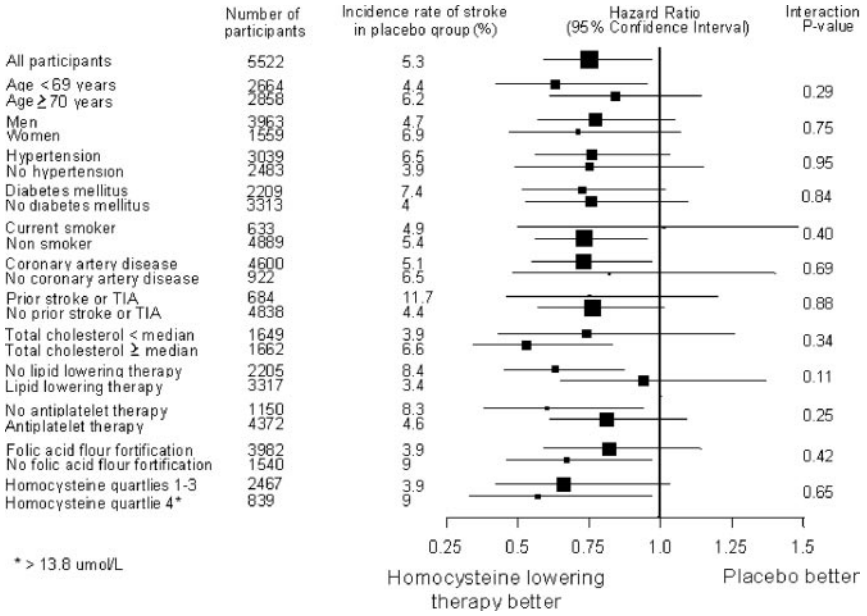

Figure 2. Risk of any stroke according to baseline participant characteristics, comparing homocysteine-lowering therapy vs placebo. The size of each symbol is proportional to the number of patients in each subgroup.

tion in the HR for stroke in patients with a baseline homocysteine concentration in the highest quartile (>13.8 μmol/L; HR, 0.57; 95% CI, 0.33–0.97; absolute risk reduction, 4.1%; Figure 2).

Post hoc, we evaluated the effect of homocysteine-lowering therapy on the risk of any stroke, while further adjusting for age, sex, and extended use of an antihypertensive, antiplatelet, or lipid-lowering agent. The adjusted HR for stroke was 0.71 (95% CI, 0.56–0.91). In a second multivariable model that included age, sex, and geographic region, the benefit of homocysteine-lowering therapy was similar (adjusted HR, 0.76; 95% CI, 0.59–0.97).

Functional Status

Among all participants in HOPE-2, the risk of disabling stroke (HR, 0.64; 95% CI, 0.39–1.04) and combined fatal or disabling stroke (HR, 0.77; 95% CI, 0.53–1.12) was lower among recipients of homocysteine-lowering therapy, but not significantly so (Table 2, Figure 1C, 1D).

Among the 258 participants with any form of stroke newly diagnosed, there was no significant difference between vitamin and placebo groups in the change in neurological deficit at stroke onset vs 24 hours (P=0.45; Table 3). Whereas a higher percentage of stroke victims in the vitamin group (15.7%) than placebo group (9.6%) had full recovery at hospital discharge or day 7, the overall trend was not significant (P=0.62; Table 4). The risk of poor function or death (ie, a modified Rankin score of 3–6) after any stroke was not significantly different among vitamin and placebo recipients (OR, 0.95; 95% CI, 0.57–1.56; Table 4).

Discussion

In this randomized clinical trial, combined folic acid and vitamins B6 and B12 reduced the risk of stroke by ≈25% (an absolute risk reduction of 1.3%). A fair duration of treatment (ie, ≥3 years) was required for this effect to become apparent. Homocysteine-lowering therapy also reduced the risk of nonfatal stroke among all study participants, along with a nonsignificant reduction in functional disability or death at 7 days among persons with a stroke, but there was no difference in the number of neurological deficits at 24 hours. The positive impact of vitamin therapy on overall stroke risk was most pronounced among subgroups of persons younger than age 70 years, with untreated hyperlipidemia, those not receiving an antiplatelet agent, and in persons with hyperhomocystinemia or residing in a country without folic acid food fortification.

Table 3. Change in Neurological Deficit at the Onset of Stroke Symptoms and at 24 Hours Thereafter, Comparing Homocysteine-Lowering Therapy vs Placebo

	Mean (SD) Neurological Deficit Score*						
	At Initial Onset of Stroke Symptoms		At 24 Hours After Onset of Stroke Symptoms		Change Between 24-Hour and Stroke Symptoms at Initial Onset		
Stroke Type	Homocysteine-Lowering Therapy	Placebo	Homocysteine-Lowering Therapy	Placebo	Homocysteine-Lowering Therapy	Placebo	P†
Any stroke	2.2 (1.4)	2.3 (1.5)	1.4 (1.4)	1.5 (1.4)	−0.85 (1.4)	−0.77 (1.4)	0.45
Ischemic	2.4 (1.3)	2.5 (1.5)	1.4 (1.2)	1.6 (1.4)	−0.96 (1.4)	−0.93 (1.5)	0.69
Hemorrhagic	1.6 (1.9)	2.2 (1.6)	1.4 (1.9)	1.8 (1.3)	−0.25 (0.89)	−0.4 (1.3)	1.00

*Defined by the number of symptoms as follows: (1) change in level of consciousness; (2) ocular or visual symptoms; (3) motor weakness; (4) sensory symptoms; (5) dysarthria or dysphasia; and (6) dysphagia. A higher score indicates a greater neurological deficit.

†Wilcoxon rank sum test comparing the net mean difference in the change in the neurological deficit score between homocysteine-lowering therapy vs placebo.

Table 4. Stroke-Related Functional Status and Dependence at Hospital Discharge or at 7 Days After Stroke Onset, Comparing Homocysteine Lowering Therapy vs Placebo

	Overall Modified Rankin Score*				Modified Rankin Score, Divided According to Functional Dependence†			
		N (%) With Given Score‡				N (%) With Given Score		OR (95% CI) for Functional Dependence, Homocysteine-Lowering Therapy vs Placebo
Stroke Type	Modified Rankin Score	Homocysteine-Lowering Therapy	Placebo	*P* for Trend	Modified Rankin Score	Homocysteine-Lowering Therapy	Placebo	
Any	0	17 (15.7)	14 (9.6)	0.62	0–2	57 (52.8)	75 (51.4)	0.95 (0.57–1.56)
	1	19 (17.6)	28 (19.2)					
	2	21 (19.4)	33 (22.6)					
	3/4	18 (16.7)	25 (17.1)		3–6	51 (47.2)	71 (48.6)	
	5	8 (7.4)	16 (11.0)					
	6	25 (23.2)	30 (20.6)					
Ischemic	0	14 (18.2)	11 (10.7)	0.50	0–2	46 (59.7)	55 (56.1)	0.86 (0.47–1.58)
	1	14 (18.2)	20 (19.4)					
	2	18 (23.4)	24 (23.3)					
	3/4	14 (18.2)	19 (19.4)		3–6	31 (40.3)	43 (43.9)	
	5	5 (6.5)	10 (10.2)					
	6	12 (15.6)	14 (14.3)					
Hemorrhagic	0	0 (0.0)	0 (0.0)	0.58	0–2	2 (25.0)	4 (40.0)	2.00 (0.26–15.4)
	1	1 (12.5)	2 (20.0)					
	2	1 (12.5)	2 (20.0)					
	3/4	2 (25)	2 (20.0)		3–6	6 (75.0)	6 (60.0)	
	5	1 (12.5)	1 (10.0)					
	6	3 (37.5)	3 (30.0)					

*0 indicates full recovery from all symptoms; 1, persistent symptoms, which do not limit functional status; 2, slight disability but able to manage all activities independently; 3/4, moderate disability (ie, requires help to perform everyday activities); 5, severe disability (ie, incapacitated, unable to perform everyday activities even with help); 6, dead.

†A score of 0–2 denotes functional independence, whereas a score of 3–6 denotes dependence on others or death.

‡Data were unavailable for 3 participants in the homocysteine-lowering therapy group and 1 participant in the placebo group.

As study strengths, HOPE-2 was the first large randomized, masked, placebo-controlled trial using adequate doses of vitamin B12. It included high-risk participants with and without history of cerebrovascular disease, originating from countries with and without folic acid food fortification, and with a sufficient duration of follow-up. Stroke outcomes were centrally adjudicated, and neuroimaging was commonly performed. Patients were also assessed for neurological deficits and functional recovery, an important feature of any stroke trial.

As a study limitation, only ≈12% of participants had a history of stroke or TIA. Nevertheless, the trial a fairly large number of stroke events. Also, because the mechanisms for ischemic stroke were not captured, we cannot comment whether homocysteine-lowering therapy may differentially impact on large vs small artery disease. The nonsignificant reduction in disability at 7 days/discharge is not surprising, because stroke recovery often requires weeks rather than days, and this would lower our ability to detect a clinically important difference, especially given the statistical power of only 30% for ischemic stroke and 42% for disabling stroke in the current trial. The original HOPE-2 trial was designed and powered to detect a proportional reduction in the risk of cardiovascular death, myocardial infarction, and stroke, rather than just stroke or 1 of its subtypes. Approximately two-thirds of the study patients were recruited from countries with folate food fortification, which may impact on the ability of the study intervention to further lower homocysteine levels. However, compared to the placebo group, homocysteine levels at study end were ≈25% lower in the active treatment group. Finally, we acknowledge that the results of this secondary analysis of the HOPE-2 trial may only be applicable to adults older than 55 with atherosclerosis.

The effect of multivitamin supplementation for preventing vascular events has been subject to much debate in the past decade. In a meta-analysis of randomized clinical trials by Bazzano et al,[9] comprising 16 958 participants with preexisting vascular disease (including persons in the HOPE-2 trial), folic acid supplementation did not impact on the risk of cardiovascular disease (RR, 0.95; 95% CI, 0.88–1.03) or all-cause mortality (RR, 0.96; 95% CI, 0.88–1.04). More recently, Wang et al[10] focused on a subset of 7 of 12 randomized studies included in the previous metaanalysis, and added a randomized trial from China, to assess the efficacy of folic acid supplementation in stroke prevention. They found that folic acid supplementation significantly reduced the risk of stroke by 18% (95% CI, 68–100). However, some studies were not included in this meta-analysis and some included therein did not use vitamin B6 or B12.

Previous studies failed to show a benefit from homocysteine-lowering therapy on coronary heart disease, but stroke and

myocardial infarction are biologically different, with the former having several pathogenic mechanisms and the latter mostly arising in the setting of local plaque rupture and in situ thrombosis[11]. As argued by Spence et al,[12] vitamin B12 may play an important efficacy role in homocysteine-related vascular disease, especially in the presence of folic acid food fortification.

Our data suggest that the detection of an effect from folic acid-containing therapy on stroke risk may be limited to countries without folic acid food fortification (ie, those outside of North America). As originally posited by Bostom et al[13] and reiterated by Wang et al,[10] the presence of folic acid food fortification may attenuate one's ability to detect a therapeutic difference between active treatment and placebo groups. The finding herein that vitamin therapy only significantly reduced the risk of stroke in persons whose plasma homocysteine was in the highest quartile adds weight to this argument, especially given that the mean concentration of homocysteine at baseline was 2.1 μmol/L lower in countries with vs those without folic acid food fortification. However, we did observe ≈3 μmol/L lower plasma homocysteine concentration in the active vs placebo groups by the end of the trial. However, it remains possible that we may have underestimated any real effect of multivitamin therapy in preventing cerebrovascular disease.

The current report greatly expands on the initial HOPE-2 article by focusing on stroke types, stroke severity, and disability, and subgroup treatment–effect interactions (Figure 2). Moreover, in the post hoc analysis in which we adjusted for the use of medications known to be protective against ischemic stroke, the beneficial effect of homocysteine-lowering therapy on stroke prevention was slightly more pronounced, with a decline in the HR from 0.76 to 0.71.

The present study is the first to provide evidence that homocysteine-lowering therapy may lower the incident risk of disabling stroke, but may not alter stroke severity at discharge. However, the effect on therapy on stroke severity and disability related to stroke requires further evaluation. Although we observed a significant reduction in stroke risk among those participants younger than 70 years and those not receiving antiplatelet or lipid-lowering therapy, the best test of validity regarding the benefit of multivitamin therapy in specific subgroups will be through other ongoing trials, such as the Vitamins to Prevent Stroke (VITATOPS) and Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) studies, and the planned individual patient data meta-analysis of all homocysteine-lowering trials.[14–16]

In conclusion, combined daily administration of 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12 for 5 years had a modest but beneficial effect on stroke prevention or fatal stroke among a population at high risk for cardiovascular disease. Ongoing clinical trials should help determine whether folic acid and B vitamin supplements are efficacious in reducing stroke risk and severity and which patient subsets are most likely to derive benefit from this treatment.

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Disclosures

None.

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Gustavo Saposnik, Joel G. Ray, Patrick Sheridan, Matthew McQueen, Eva Lonn and the HOPE 2 Investigators

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