

Homocysteine

The association with atherosclerotic vascular disease in older persons

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Plasma homocysteine is a risk factor for coronary artery disease, stroke, peripheral arterial disease, extracranial carotid arterial disease, aortic atherosclerosis, deep vein thrombosis, and possibly dementia and Alzheimer's disease in older persons. Randomized trials are in progress investigating whether multivitamin therapy with folic acid, vitamin B₁₂, and vitamin B₆ to reduce plasma homocysteine levels will reduce the risk for atherosclerotic vascular disease.

Aronow WS, Homocysteine: The association with atherosclerotic vascular disease in older persons. *Geriatrics* 2003; 58(Sept):22-28.

Key words: atherosclerotic vascular disease • multivitamin therapy homocysteine

Increased plasma homocysteine levels contribute to the development of atherosclerotic vascular disease by promoting arterial endothelial dysfunction.¹ High homocysteine levels are independently related to isolated systolic hypertension in older persons.² Other mechanisms of homocysteine contributing to vascular disease include enhancement of thromboxane A₂ formation and platelet aggregation, proliferation of smooth muscle cells, increased activation of factors V and X, increased fibrinogen levels, reduced serum antithrombin activity, and increased binding of lipoprotein (a) to fibrin. By increasing oxidative stress, impairing vascular endothelial function, inducing a

prothrombotic state, impairing vascular smooth muscle cell function, and changing extracellular matrix structure and function, homocysteine may cause atherosclerotic vascular disease.

This article will discuss the association of plasma homocysteine with atherosclerotic vascular disease in older persons. It also provides a look at potential treatments for elevated plasma homocysteine levels.

Coronary artery disease

A meta-analysis of 27 studies showed that, in general, the odds ratio for coronary artery disease (CAD) of a 5-mmol/L increase of homocysteine level was 1.6 for men and 1.8 for women.³ The odds ratio for cerebrovascular disease for a 5 mmol/L increase of homocysteine level was 1.5. When looking specifically at the older population, the evidence has shown that plasma homocysteine levels increase with age. In an older population of 347 women and 153 men, mean age 81 years, plasma homocysteine was a significant independent risk factor for the prevalence of

CAD, with an odds ratio of 1.21 for each 1 μmol/L increase in plasma homocysteine.⁴ Elevated plasma homocysteine levels (>17.0 μmol/L) were present in 43% of older men with CAD versus 18% of older men without CAD and in 37% of older women with CAD versus 12% of older women without CAD.⁴ At 31-month follow-up of this older population, elevated plasma homocysteine was a significant independent predictor of new coronary events (ie, MI or sudden cardiac death) in older persons with prior CAD (risk ratio = 1.07 for each 1 μmol/L increase) and in older persons without prior CAD (risk ratio = 1.11 for each 1 μmol/L increase).⁵

In postmenopausal women in the Women's Health Study, the adjusted relative risk for MI or stroke for women in the top quartile of plasma homocysteine level was 2.2 compared with women in the lowest quartile.⁶ At 9- to 11-year follow-up of 1,788 men and women, mean age 65, living in Jerusalem, elevated plasma homocysteine was a significant risk factor in both sexes for all-cause mortality, cardiovascular mortality, and CAD mortality.⁷

At 4.6-year median follow-up of 587 men and women, mean age 62 (15% ≥ age 70), with angiographically documented CAD, plasma homocysteine levels were a strong predictor of mortality.⁸ The mortality ratios were 1.0 for patients with homocysteine levels <9 μmol/L, 1.9 for homocysteine levels of 9.0 to 14.9 μmol/L, 2.8 for patients with homocysteine levels of 15.0 to 19.9

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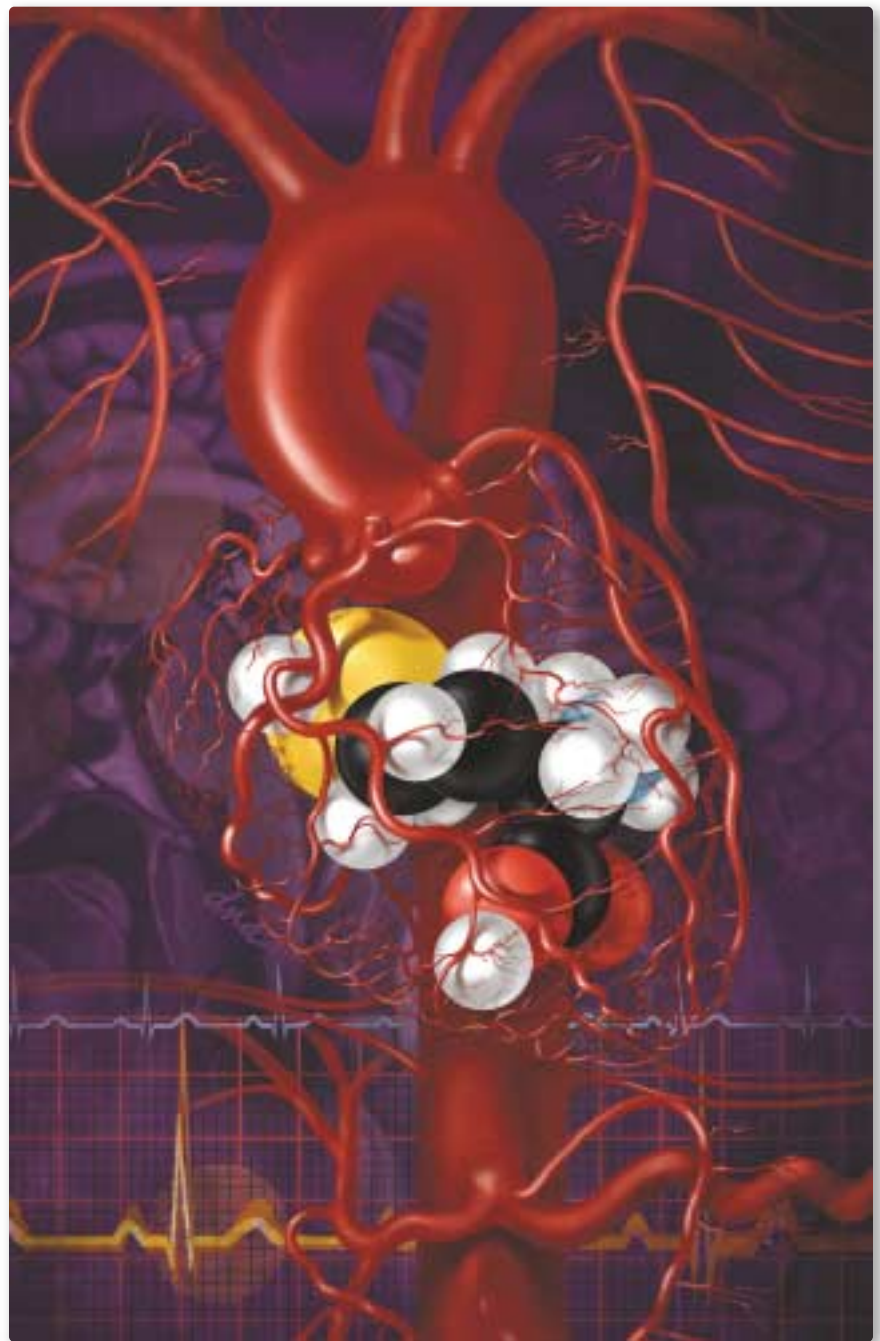
Disclosure: The author has no real or apparent conflicts of interest relating to the content presented here.

$\mu\text{mol/L}$, and 4.5 for patients with homocysteine levels $\geq 20.0 \mu\text{mol/L}$.⁸

At 5.3-year mean follow-up of 17,321 men and women in Western Norway age 40 to 42 or 65 to 67 at baseline, elevated plasma homocysteine level was a significant predictor of hospitalization for cardiovascular disease only in the older group, and especially among older individuals with pre-existing cardiovascular disease.⁹ In 304 men and women with CAD and 231 men and women without CAD, mean age 62, increased plasma homocysteine level was a risk factor for CAD, regardless of age and sex.¹⁰ In 631 men and women, mean age 61, who had coronary angiography performed (78 patients had no CAD), elevated plasma homocysteine level was not only significantly associated with the presence of CAD but was also significantly associated with the severity of CAD.¹¹

In a study of 243 patients, mean age 59, with non-Q-wave MI or unstable angina pectoris, high plasma homocysteine levels were associated with an increased intracoronary thrombus burden and with increased myocardial injury.¹² In a study of 205 patients, mean age 62, presenting with acute MI and of 185 patients, mean age 59, presenting with unstable angina pectoris, elevated plasma homocysteine levels were associated with a higher risk of ischemic myocardial injury.¹³ In a study of 440 patients with acute MI (n=236) or unstable angina pectoris (n=204) (94 patients >70 and 154 patients age 60 to 70), patients with homocysteine levels in the upper two quintiles ($>12.2 \mu\text{mol/L}$) had a 2.6 increased risk of a cardiac event at 2.5-year follow-up.¹⁴ A high plasma homocysteine level was also an independent risk factor for atherosclerotic complications in 176 dialysis patients, mean age 56.¹⁵

Of 553 patients undergoing coronary angiography, 272 patients, mean age 63, were randomized to receive 1 mg/d folic acid, 400 $\mu\text{g/d}$ vitamin B₁₂, and 10 mg/d vitamin B₆ for 6 months, and 281 patients, mean age 62, were randomized to receive placebo. At 11-month follow-



Homocysteine contributes to atherosclerotic vascular disease by promoting arterial endothelial dysfunction, increasing oxidative stress, inducing a prothrombotic state, impairing vascular smooth muscle cell function, and changing extracellular matrix structure and function.

Illustration for Geriatrics by Alexandra Baker

up, the composite endpoint of death, nonfatal MI, and need for repeat coronary revascularization was significantly reduced by 32% (primarily due to a reduced rate of target lesion revascularization) in patients taking homocysteine-lowering therapy with folic acid, vitamin B₁₂, and vitamin B₆.¹⁶

Until the results of ongoing intervention trials are completed, routine screening for homocysteine levels is not recommended.¹⁷ However, the American Heart Association recommends that a fasting plasma homocysteine level be determined for certain individuals (table).

continued

Table A fasting plasma homocysteine level should be obtained for:*

Patients with coronary artery disease without conventional risk factors

Patients at high risk for plasma homocysteine levels, including those with:

- Impaired renal function
- Malnutrition
- Malabsorption
- Hypothyroidism
- Systemic lupus erythematosus
- Recurrent deep vein thrombosis
- Pernicious anemia

Patients taking select pharmaceuticals, such as:

- Nicotinic acid
- Levodopa
- Tamoxifen
- Bile acid sequestrants
- Phenytoin
- Theophylline
- Methotrexate
- Anticonvulsants
- Fibrin acid derivatives

*An optimal level for plasma homocysteine is thought to be <10 μmol/L.

Source: Prepared for Geriatrics by Wilbert S. Aronow, MD, based on information in reference 15.

All persons should have an adequate intake of folate, vitamin B₆, and vitamin B₁₂ by eating vegetables, fruits, fish, and fortified grains and cereals. High risk persons may warrant supplemental vitamin therapy with folic acid, vitamin B₆, and vitamin B₁₂.

Stroke

Four prospective studies have demonstrated that elevated plasma homocysteine is an independent risk factor for stroke.¹⁸⁻²¹ The Framingham Study reported that plasma homocysteine is a significant independent risk factor for stroke in 1,947 men and women, mean age 70.¹⁸ Compared with persons in the lowest quartile (4.13 to 9.25) of plasma homocysteine level, the relative risk of new stroke was 1.82 for the highest quartile (14.24 to 219.84) of plasma homocysteine, 1.44 for the second highest quartile (11.44 to 14.23) of plasma homocysteine, and 1.32 for the third highest quartile (9.26 to 11.43) of plasma homocysteine.¹⁸ At 31-month follow-up of 500 men and women, mean age 81, elevated plasma homocysteine was a significant independent risk factor of new stroke (risk ratio = 1.08 for each 1 μmol/L increase of plasma homocysteine).²¹ A study among British men, mean age 54, and a study among the Hopkins Lupus Cohort also support this finding.

However, two prospective studies did not find an association between plasma homocysteine and stroke.^{22,23} These two studies included a study of Finnish men and women age 40 to 64,²² and a study of U.S. male physicians responding to a survey.²³ The two negative studies were characterized by modest stroke event rates (11.1 for stroke patients vs 10.6 for controls²³) and overall exposure to lower total homocysteine levels (mean levels were 9.99 for male cases vs 9.82 for male controls and 9.58 for female cases vs 0.24 for female controls²²).

Extracranial carotid arterial disease

Two studies document that elevated plasma homocysteine is a risk factor for extracranial carotid arterial disease (ECAD) in older persons. In 1,041 older persons in the Framingham Study, the odds ratios for ECAD were 2.0 in persons in the highest quartile (≥ 14.4) of plasma homocysteine and 1.6 in persons in the second highest quartile (11.4 to 14.3) of plasma homocysteine compared with persons in the lowest quartile (≤ 9.1) of plasma homocysteine.²⁴

In 400 older men and women, mean age 81, increased plasma homocysteine was associated with an increased risk of ECAD. Increased plasma homocysteine

levels were found in 45% of older men with 40 to 100% ECAD versus 20% of older men with 0 to 39% ECAD and in 40% of older women with 40 to 100% ECAD versus 18% of older women with 0 to 39% ECAD.²⁵

Peripheral arterial disease

Several studies have identified plasma homocysteine as a significant independent risk factor for peripheral arterial disease (PAD). In 520 older persons, mean age 81, the odds ratio for the prevalence of PAD was 1.13 for each 1 μmol/L increase in plasma homocysteine. Increased plasma homocysteine levels were found in 49% of older men with PAD versus 18% of older men without PAD and in 46% of older women with PAD versus 15% of older women without PAD.²⁶

Aortic atherosclerosis

Plasma homocysteine levels were significantly and independently correlated with the degree of atherosclerosis in the thoracic aorta measured with transesophageal echocardiography in 156 patients, mean age 69.²⁷ Plasma homocysteine levels were also a marker of severity of thoracic atherosclerosis diagnosed by transesophageal echocardiography in 81 patients.²⁸

Type 2 diabetes mellitus

In 2,484 men and women age 50 to 75, the odds ratio for 5-year mortality was 1.56 for hyperhomocysteinemia (plasma homocysteine >14 μmol/L), 2.51 for diabetic patients with hyperhomocysteinemia, and 1.34 for nondiabetic patients with hyperhomocysteinemia.²⁹

Deep vein thrombosis

In 269 patients with deep vein thrombosis and in 269 age-matched and sex-matched controls, high plasma homocysteine levels were a risk factor for deep vein thrombosis with an odds ratio of 2.5.³⁰ The association between elevated plasma homocysteine levels and deep venous thrombosis was stronger among women than among men and increased with age.

continued

Dementia and Alzheimer's disease

At 8-year follow-up of 667 women and 425 men, mean age 76, without dementia at baseline in the Framingham Study, dementia developed in 111 persons, including a diagnosis of Alzheimer's disease in 83 persons.³¹ In this study, an increased plasma homocysteine level was a strong independent risk factor for the development of dementia and Alzheimer's disease.

Therapy

Studies are underway to determine whether multivitamin therapy to reduce plasma homocysteine levels—in particular, a combination of folic acid, vitamin B₁₂, and vitamin B₆—will reduce the incidence of cardiovascular disease. One potential hazard of folic acid therapy is progressive neurologic damage (ie, subacute combined degeneration of the spinal cord) in patients with subclinical vitamin B₁₂ deficiency in whom treatment with folic acid may mask the development of the hematologic signs of vitamin B₁₂ deficiency. This can be avoided by supplementing folic acid therapy with at least 400 µg/d of vitamin B₁₂. The minimum effective daily dose of folic acid for maximally reducing plasma homocysteine levels is 400 µg/d. Higher daily doses are not more effective except in patients with renal failure. Moderate hyperhomocysteinemia should also be treated with vitamin B₆ 10 to 50 mg/d.³²

Conclusion

Plasma homocysteine, which is dependent on several physiologic determinant (figure), is a risk factor for CAD, stroke, ECAD, PAD, aortic atherosclerosis, deep vein thrombosis, and possibly for dementia and Alzheimer's disease in older persons. Randomized trials are in progress investigating whether multivitamin therapy to reduce plasma homocysteine levels will reduce the risk for cardiovascular disease. If these studies demonstrate that decreasing elevated homocysteine levels by a combination of folic acid, vi-

Figure Physiologic determinants of total homocysteine levels



Source: <http://www.homocysteine.net/pages/homocysteine/1/aboutncy.html>. Last accessed 8/26/03. © Axis-Shield plc 2003.

tamin B₁₂, and vitamin B₆ are effective in reducing the incidence of cardiovascular disease, we will have a safe, inexpensive, easily administered treatment to decrease the incidence of cardiovascular disease. **□**

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