

Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal



Journal of Clinical and Basic Cardiology 2001; 4 (4), 261-264

Homocysteine and Risk of Cardiovascular Disease

Auer J, Berent R, Eber B

Homepage:

www.kup.at/jcbc

**Online Data Base Search
for Authors and Keywords**

Homocysteine and Risk of Cardiovascular Disease

J. Auer, R. Berent, B. Eber

Homocysteine is a sulphhydryl-containing amino acid derived from demethylation of methionine. Nutritional deficiencies in the vitamin cofactors (folate, vitamin B12, and vitamin B6) required for homocysteine metabolism may promote hyperhomocysteinaemia.

Multiple prospective and case-control studies suggested that a moderately elevated plasma homocysteine concentration is an independent risk factor for atherothrombotic vascular disease. Homocysteine concentrations are consistently higher in patients with peripheral, cerebrovascular, and coronary artery disease than in those without such diseases. Homocysteine seems to promote atherothrombogenesis by a variety of mechanisms; however, it is not yet clear whether homocysteine itself or a related metabolite or cofactor is primarily responsible for the atherothrombotic effects of hyperhomocysteinaemia *in vivo*. Before advocating wide spread screening of patients with atherosclerotic vascular disease, we must have a clearer understanding of the clinical efficacy of potential therapeutic interventions.

Vitamin supplementation decreases or even normalizes plasma homocysteine concentrations in most cases. Prospective, randomized clinical trials, however, will be necessary to determine the effect of vitamin supplementation on cardiovascular morbidity and mortality. The use of pills containing low dose B vitamins as a primary or secondary preventive measure against vascular disease remains unproved, although they are definitely cheap, probably innocuous, and may help prevent acute vascular episodes. *J Clin Basic Cardiol 2001; 4: 261-4.*

Key words: homocysteine, cardiovascular disease, folate, pathophysiology, therapy

Homocysteine is a sulfur-containing amino acid derived from the metabolic demethylation of dietary methionine, which is abundant in animal protein. Homocysteine is metabolized by one of two pathways: remethylation and transsulfuration. It is present in plasma in four forms: as circulating free thiol (1 %); disulphide-bound to plasma proteins, chiefly albumin (70–80 %); and combinations with itself to form the dimer homocysteine or with other thiols, including cysteine, with which it forms the homocysteine-cysteine mixed disulphide (20–30 %). The term “total plasma (or serum) homocysteine” (tHcy) refers to the combined pool of all four forms of homocysteine.

Homocysteine and Vascular Disease – Introduction

In 1969, McCully [1] made the clinical observation linking elevated plasma homocysteine concentrations with vascular disease. Subsequent investigations have confirmed this hypothesis. For about two decades, moderately raised concentrations of total homocysteine (tHcy) have been correlated with an increased risk of atherothrombotic vascular events [2, 3], but only recently has evidence mounted to suggest that the association may be causal. The association is independent of other known risk factors and it is consistent across many studies. Furthermore, it is strong and dose-related, and it is biologically plausible. Although the molecular mechanism by which homocysteine or a related metabolite promotes atherothrombosis is unknown, the epidemiologic evidence of the association of hyperhomocysteinaemia with atherothrombotic vascular disease seems to be convincing.

However, the evidence needs to be strengthened by a systematic review of all comparable studies and the demonstration, in randomised trials, that lowering tHcy is followed by a significant reduction in atherothrombotic vascular disease. In addition, the measurement of tHcy needs to be standardised.

If these can be achieved then tHcy measurement will become another useful marker of vascular risk, multivitamin

therapy will be another therapeutic option for people at risk of atherothrombotic vascular disease, and fortification of food with folic acid will rise high on the political and public health agenda.

Only about two-thirds of all episodes of symptomatic atherothrombotic vascular disease in developed countries can be attributed to established genetic and environmental vascular risk factors [4]. An additional causal vascular risk factor may be raised plasma levels of homocysteine (hyperhomocysteinaemia). Mild hyperhomocysteinaemia occurs in approximately 5 to 7 percent of the general population [5, 6]. Patients with mild hyperhomocysteinaemia are typically asymptomatic until the third or fourth decade of life when premature coronary artery disease develops, as well as recurrent arterial and venous thrombosis. Although 30 years have elapsed since hyperhomocysteinaemia was first associated with an increased risk of atherothrombotic vascular disease, it is only recently that sufficient evidence has mounted to suggest that the association is independent and dose-related, and it remains to be established whether it is causal and modifiable.

Definition of Hyperhomocysteinaemia and Measurement of Plasma Homocysteine

An abnormal “total plasma (or serum) homocysteine” (tHcy) is defined by an arbitrary cut-off in the distribution of concentrations found in the “normal population”, in much the same way as other more common vascular risk factors like hypertension and hypercholesterolaemia have been defined. For example, after methionine-loading, hyperhomocysteinaemia is defined as a tHcy of more than 2 standard deviations (SD) above the mean [7]. Among fasting individuals, “normal” tHcy commonly ranges from 5 to 15 $\mu\text{mol/L}$ [8, 9] and higher fasting values are classified as moderate (16–30), intermediate (31–100), and severe ($>100 \mu\text{mol/L}$) hyperhomocysteinaemia [10] on the basis of concentrations measured during fasting.

The majority of the clinical studies involving homocysteine have relied on the measurement of total plasma homo-

From the 2nd Medical Department/Cardiology and Intensive Care, General Hospital Wels

Correspondence to: Johann Auer, MD, 2nd Medical Department, Division of Cardiology and Intensive Care, General Hospital Wels, Grieskirchnerstraße 42, A-4600 Wels, Austria; e-mail: johann.auer@khwels.at

cysteine, which includes homocysteine, mixed disulfides involving homocysteine, homocysteine thiolactone, free homocysteine, and protein-bound homocysteine. Protein-bound homocysteine accounts for 70 to 80 percent of the total pool. An oral dose of methionine (100 mg per kilogram of body weight) can be given to persons with suspected hyperhomocysteinaemia who have normal homocysteine concentrations during fasting.

Plasma homocysteine concentrations are determined before the methionine challenge and between four and eight hours afterward.

Hyperhomocysteinaemia is considered to be present if the homocysteine concentration after methionine challenge is more than 2 SD above the mean [11]. The prognostic value of the methionine-challenge test has recently been discussed controversially [8]. In contrast to a weak association between plasma homocysteine concentrations after methionine challenge and premature coronary heart disease in persons with the thermolabile variant of N,N-methylenetetrahydrofolate reductase, there was a significant association between plasma homocysteine concentrations during fasting and premature coronary heart disease. In conclusion, this enzyme regulates basal homocysteine concentrations, and thus, its activity cannot be adequately assessed by a methionine-challenge test. By contrast, however, enzymes in the transsulfuration pathway are responsible for reversing transient, postprandial increases in the homocysteine concentration, and their activities can be evaluated by a methionine-challenge test.

Homocysteine Metabolism

Homocysteine is a sulphhydryl-containing amino acid derived from the metabolic demethylation of methionine. Homocysteine is metabolized by remethylation or transsulfuration. In the remethylation cycle, homocysteine is salvaged by the acquisition of a methyl group in a reaction catalyzed by methionine synthase. Vitamin B12 (cobalamin) is an essential cofactor for methionine synthase, N-methyltetrahydrofolate is the methyl donor in this reaction, and N,N-methylenetetrahydrofolate reductase acts as a catalyst in the remethylation process [12] (Figure 1). Under conditions with an excess of methionine or when cysteine synthesis is required, homocysteine enters the transsulfuration pathway. In this pathway, homocysteine condenses with serine to form cystathionine in a reaction catalyzed by the vitamin B6-dependent enzyme cystathionine (beta)-synthase.

Nutritional Factors and Homocysteine Metabolism (Table 1)

Nutritional deficiencies in the vitamin cofactors (folate, vitamin B12, and vitamin B6) required for homocysteine metabolism may promote hyperhomocysteinaemia.

Markedly elevated homocysteine concentrations have been observed in patients with nutritional deficiencies of the essential cofactor vitamin B12 [13] and the cosubstrate folate [14]. It has been suggested that about two-thirds of hyperhomocysteinaemia is due to inadequate blood levels of one or more of these vitamin cofactors [15, 16].

Inadequate plasma concentrations of one or more B vitamins are contributing factors in approximately two thirds of all cases of hyperhomocysteinemia. Vitamin supplementation can normalize high homocysteine concentrations, however, it remains to be determined whether normalizing homocysteine concentrations will improve cardiovascular morbidity and mortality.

Hyperhomocysteinaemia Caused by Other Factors

Renal impairment commonly causes hyperhomocysteinaemia. Fasting tHcy rises as serum creatinine rises, not because of impaired urinary excretion but because of impaired metabolism of homocysteine by the kidney, the major route by which homocysteine is cleared from plasma. In contrast, urinary excretion is a very minor route for direct homocysteine clearance [17]. Total homocysteine levels are considerably higher in patients with chronic renal disease than

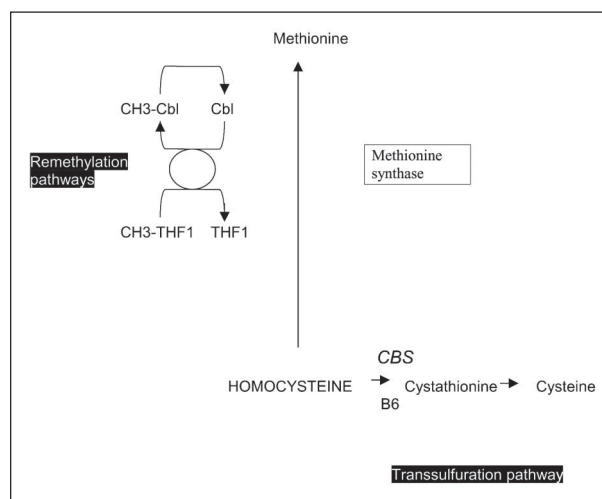


Figure 1. Pathways of homocysteine metabolism (CBS = cystathionine-β-synthase; Cbl = cobalamin; THF1 = monoglutamated form of tetrahydrofolate; B6 = vitamin B6; CH3 = Methyl). Homocysteine is metabolized either by transsulfuration to cysteine (in a reaction catalyzed by cystathionine-β-synthase [(CBS] with vitamin B6 as cofactor) or by remethylation to methionine. Remethylation is catalyzed by methionine synthase (and 5,10 methylenetetrahydrofolate reductase). Methionine synthase is dependent upon cobalamin (vitamin B12) as cofactor and folate as cosubstrate. An alternative remethylation pathway (not shown in the figure) uses the cobalamin independent betain-homocysteine methyltransferase.

Table 1. Factors influencing homocysteine metabolism (factors increasing homocysteine levels)

Nutritional deficiencies in vitamin cofactors	
Folate	
Vitamin B6 (pyridoxine)	
Vitamin B12 (cobalamin)	
Genetic defects in homocysteine metabolism	
CBS	
MTHFR	
Methionine synthase	
Medications/toxins	
Folate antagonists (methotrexate, phenytoin, carbamazepine)	
Vitamin B6 antagonists (theophylline, azarabine, oestrogen-containing oral contraceptives, cigarette smoking)	
Age/sex	
Increasing age	
Male sex	
Menopause	
Diseases	
Malignancy: acute lymphoblastic leukaemia; carcinoma of the breast, ovary and pancreas	
Severe psoriasis	
Pernicious anaemia	
Renal impairment	
Hypothyroidism	

the moderately raised concentrations commonly found in patients with atherothrombotic vascular disease, and this may contribute to the high incidence of vascular complications in patients with chronic renal failure. Values are higher in patients undergoing haemodialysis compared to peritoneal dialysis. The exact mechanisms for the raised levels of the amino acid seen in these patients remain unclear but reduced systemic clearance of homocysteine, lower circulating folate, and folate inhibition are probably major determinants.

A number of reports have linked hyperhomocysteinaemia to hypothyroidism, suggesting a potential mechanism for the higher incidence of vascular disease observed in patients with hypothyroidism. Hyperhomocysteinaemia has also been reported in patients with pernicious anaemia and it is unclear whether these patients are at increased risk for vascular events.

Elevated homocysteine concentrations have been reported in association with several types of carcinoma, including breast, ovarian, and pancreatic cancer [18]. Several drugs and toxins increase plasma homocysteine concentrations. Methotrexate depletes folate, the cosubstrate for methionine synthase, and causes a transient increase in plasma homocysteine concentrations. Phenytoin, Theophylline (interference with the synthesis of pyridoxal phosphate) and cigarette smoking interact with homocysteine metabolism. Cyclosporin may impair renal function and it has been associated with hyperhomocysteinaemia.

It has been reported that smokers have significantly lower pyridoxal phosphate concentrations than non-smokers [19]. These results suggest another important mechanism whereby smoking may promote atherogenesis. Homocysteine concentrations rise with age in both sexes. Women in general have lower concentrations than men, and concentrations rise after menopause. A high intake of caffeine or alcohol, and a sedentary lifestyle are associated with raised homocysteine.

Pathophysiologic Mechanisms of Association Between Hyperhomocysteinaemia and Atherosclerosis

Clinical and experimental studies suggest that high homocysteine concentrations may cause the atherogenic and thrombotic tendencies of homocystinuric and hyperhomocysteinaemic patients. Experimental evidence suggests that the atherogenic propensity associated with hyperhomocysteinaemia results from endothelial dysfunction and injury followed by platelet activation and thrombus formation [20, 21]. Although the exact mechanism of endothelial dysfunction is unknown, there is growing evidence that homocysteine exerts its effects by promoting oxidative damage. Superoxide-dependent formation of the hydroxyl radical has been shown to initiate lipid peroxidation [22], an effect that occurs at the level of the endothelial plasma membrane and within lipoprotein particles [23]. Homocysteine auto-oxidation has been shown to support the oxidation of low-density lipoprotein through the generation of the superoxide anion radical [24]. Homocysteine alters the normal antithrombotic phenotype of the endothelium by enhancing the activities of factor XII and factor V and depressing the activation of protein C [25]. All of these effects ultimately facilitate the formation of thrombin and create a prothrombotic environment. The production of endothelial-derived nitric oxide is also adversely affected by homocysteine [26]. In conclusion, it is clear that there is no one unifying hypothesis of the mechanism, if any, of homocysteine induced vascular damage although at present the endothelium is the most likely candidate.

Homocysteine as a Risk Factor for Vascular Disease

In an European multicentre investigation of 750 cases and a similar number of controls, a high homocysteine concentration conferred a risk equal to that of hypercholesterolaemia, smoking or hypertension [27]. Some, but not all, prospective (or nested case control) studies have confirmed these findings. In the multiple risk factor intervention trial (MRFIT), for example, the homocysteine concentrations in serum samples from men who subsequently suffered a myocardial infarction were not different from those in controls [28].

In another recent prospective study by Folsom and colleagues, higher homocysteine concentrations added to the risk of incident coronary artery disease in women but not in men [29]. In patients with coronary disease, higher homocysteine concentrations are related to lower circulating B vitamin concentrations. Indeed, in one study, as the concentration of folate fell, the levels of both homocysteine and cardiovascular risk rose [30]. Similarly, there is an increased vascular risk associated with lower levels of vitamin B6 [31].

Therapeutic Considerations of Hyperhomocysteinaemia

The treatment of hyperhomocysteinaemia varies with the underlying cause; however, vitamin supplementation (with folic acid, pyridoxine (vitamin B6), and vitamin B12) is generally effective in reducing homocysteine concentrations. The minimal effective doses of folic acid and pyridoxine have not yet been determined. In most patients, small doses of folate (0.4 to 5 mg per day) rapidly decrease homocysteine concentrations [32]. Whether doses lower than 400 µg are effective has not been adequately explored. Patients with renal impairment require much higher doses. A meta-analysis of data from 1114 individual participants in 12 randomised controlled trials of the effects of folic-acid-based supplements on basal tHcy found that the proportional and absolute reductions in tHcy produced by folic acid were greater at higher pretreatment tHcy and at lower pretreatment blood folate levels [33]. Folic acid alone, folic acid combined with vitamins B12 and B6, and vitamins B6 and B12 have all been shown to reduce homocysteine concentrations [34]. Because the response to homocysteine-lowering therapy is not uniform, and is dependent on factors such as genotype for enzymes involved in the metabolism of homocysteine, vitamin status, and nutritional needs [13], multivitamin doses required for the treatment of hyperhomocysteinaemia may vary according to individual patient requirements.

Normalization of the plasma homocysteine concentration usually occurs within four to six weeks after the initiation of therapy, but may occur in as little as two weeks. Interestingly, the reduction in mortality from cardiovascular causes since 1960 has been correlated with the increase in vitamin B6 supplementation in the food supply [11]. A potential hazard of folic acid therapy is progressive neurological damage (subacute combined degeneration of the spinal cord) in people with subclinical vitamin B12 deficiency in whom folic acid therapy may mask the development of the haematological manifestations of the B12 deficiency.

This can be avoided by either excluding B12 deficiency before starting folic acid or by supplementing folic acid therapy with vitamin B12. At least 400 µg per day of vitamin B12 is suggested as a supplement because the recommended daily intake of this vitamin is about 2 µg per day but only 1–3% of oral vitamin B12 is absorbed by simple diffusion.

Table 2. Trials of homocysteine-lowering therapy in vascular disease

- Vitamins in Stroke Prevention (VISP) Trial; Bowman Gray School of Medicine, USA
- Norwegian Study of Homocysteine Lowering with B-vitamins in Myocardial Infarction (NORVIT); University of Tromsø, Norway
- Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH); Clinical Trial Service Unit, Oxford, UK
- Women's Antioxidant and Cardiovascular Disease Study (WACS); Harvard Medical School, USA
- Bergen Vitamin Study; University of Bergen, Norway
- Cambridge Heart Antioxidant Study (CHAOS-2); University of Cambridge, UK
- Heart Outcomes Prevention Evaluation (HOPE-2) Study; McMaster University, Canada
- Prevention with A Combined Inhibitor and Folate in Coronary Heart Disease (PACIFIC) Study; University of Sydney, Australia
- Vitamins TO, Prevent Stroke (VITATOPS) Study; Stroke Unit, Royal Perth Hospital, Western Australia

The major potential hazard of vitamin B6 is a sensory peripheral neuropathy with use over months to years at doses of vitamin B6 usually at least 400 mg daily. However, most doses for the treatment of moderate hyperhomocysteinaemia are only 10–50 mg per day. In patients with severe hyperhomocysteinaemia due to CBS deficiency effective homocysteine-lowering therapy does reduce the risk of cardiovascular disease during long-term follow-up [35]. However, although the combination of folic acid 25 mg, vitamin B6 25 mg, and vitamin B12 250 µg per day reduces the progression of atherosclerosis, as measured by carotid plaque area [36], it remains to be confirmed that homocysteine-lowering therapy will prevent important atherosclerotic vascular events in patients with moderate hyperhomocysteinaemia. Several large randomised clinical trials are addressing this issue (Table 2).

Remaining Questions

Many important questions remain – for example, is a high circulating homocysteine concentration causal in the pathogenesis of coronary disease and other atherosclerotic and thrombotic vascular diseases, or is it merely an epiphenomenon? Is the high homocysteine level a reflection of lower B vitamin status which is itself (directly or indirectly) linked to atherosclerosis? Or is it a reflection of diminished renal function so often seen in patients with vascular disease [37]? What, if any, is the mechanism by which homocysteine may induce atherosclerosis? In other clinical circumstances such as following organ transplantation, or in the presence of hypothyroidism or inflammatory bowel disease, does high homocysteine predict increased vascular risk?

References

1. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *Am J Pathol* 1969; 56: 111–28.
2. Ueland PM. Homocysteine species as components of plasma redox thiol status. *Clin Chem* 1995; 41: 340–42.
3. Kang SS, Wong PW, Malinow MR. Hyperhomocysteinemia as a risk factor for occlusive vascular disease. *Ann Rev Nutr* 1992; 12: 279–98.
4. Stampfer MJ, Malinow MR, Willett WC, Newcomer LM, Upson B, Ullmann D, Tishler PV, Hennekens CH. A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians. *J Am Med Assoc* 1992; 268: 877–81.
5. Whisnant JP. Modeling of risk factors for ischemic stroke: the Willis lecture. *Stroke* 1997; 28: 1839–43.
6. Ueland PM, Refsum H. Plasma homocysteine, a risk factor for vascular disease: plasma levels in health, disease, and drug therapy. *J Lab Clin Med* 1989; 114: 473–501.
7. Ueland PM, Refsum H, Stabler SP, Malinow MR, Andersson A, Allen RH. Total homocysteine in plasma or serum: methods and clinical applications. *Clin Chem* 1993; 39: 1764–79.
8. Dudman NP, Wilcken DE, Wang J, Lynch JF, Macey D, Lundberg P. Disordered methionine/homocysteine metabolism in premature vascular disease: its occurrence, cofactor therapy, and enzymology. *Arterioscler Thromb Vasc Biol* 1993; 12: 1253–60.
9. Still RA, McDowell IF. Clinical implications of plasma homocysteine measurement in cardiovascular disease. *J Clin Pathol* 1998; 51: 183–8.
10. Refsum H, Fiskerstrand T, Guttormsen AB, Ueland PM. Assessment of homocysteine status. *J Inher Metab Dis* 1997; 20: 286–94.
11. Kang SS, Wong PW, Malinow MR. Hyperhomocysteinemia as a risk factor for occlusive vascular disease. *Ann Rev Nutr* 1992; 12: 279–98.
12. McCully KS. Homocysteine and vascular disease. *Nat Med* 1996; 2: 386–9.
13. Malinow MR, Nieto FJ, Kruger WD, Duell PB, Hess DL, Gluckman RA, Block PC, Holzgang CR, Anderson PH, Seltzer D, Upson B, Lin QR. The effects of folic acid supplementation on plasma total homocysteine are modulated by multivitamin use and methylenetetrahydrofolate reductase genotypes. *Arterioscler Thromb Vasc Biol* 1997; 17: 1157–62.
14. Brattstrom L, Israelsson B, Lindgarde F, Hultberg B. Higher total plasma homocysteine in vitamin B12 deficiency than in heterozygosity for homocystinuria due to cystathionine (beta)-synthase deficiency. *Metabolism* 1988; 37: 175–8.
15. Stabler SP, Marcell PD, Podell ER, Allen RH, Savage DG, Lindenbaum J. Elevation of total homocysteine in the serum of patients with cobalamin or folate deficiency detected by capillary gas chromatography-mass spectrometry. *J Clin Invest* 1988; 81: 466–74.
16. Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *J Am Med Assoc* 1993; 270: 2693–8.
17. Bostom AG, Lathrop L. Homocysteinemia in end-stage renal disease: prevalence, etiology, and potential relationship to arteriosclerotic outcomes. *Kidney Int* 1997; 52: 10–20.
18. Mayer EL, Jacobsen DW, Robinson K. Homocysteine and coronary atherosclerosis. *J Am Coll Cardiol* 1996; 27: 517–27.
19. Vermaak WJ, Ubbink JB, Barnard HC, Potgieter GM, van Jaarsveld H, Groenewald AJ. Vitamin B6 nutrition status and cigarette smoking. *Am J Clin Nutr* 1990; 51: 1058–61.
20. Harker LA, Slichter SJ, Scott CR, Ross R. Homocystinemia: vascular injury and arterial thrombosis. *Engl J Med* 1974; 291: 537–43.
21. James TN. The spectrum of diseases of small coronary arteries and their physiologic consequences. *J Am Coll Cardiol* 1990; 15: 763–74.
22. Rowley DA, Halliwell B. Superoxide-dependent formation of hydroxyl radicals in the presence of thiol compounds. *FEBS Lett* 1982; 138: 33–6.
23. Loscalzo J. The oxidant stress of hyperhomocyst(e)inemia. *J Clin Invest* 1996; 98: 5–7.
24. Heinecke JW, Rosen H, Suzuki LA, Chait A. The role of sulfur-containing amino acids in superoxide production and modification of low density lipoprotein by arterial smooth muscle cells. *J Biol Chem* 1987; 262: 10098–103.
25. Rodgers GM, Conn MT. Homocysteine, an atherogenic stimulus, reduces protein C activation by arterial and venous endothelial cells. *Blood* 1990; 75: 895–901.
26. Stamler JS, Osborne JA, Jaraki O, Rabbani LE, Mullins M, Singel D, Loscalzo J. Adverse vascular effects of homocysteine are modulated by endothelium-derived relaxing factor and related oxides of nitrogen. *J Clin Invest* 1993; 91: 308–18.
27. Graham IM, Daly LE, Refsum HM, et al. Plasma homocysteine as a risk factor for vascular disease. The European concerted action project. *J Am Med Assoc* 1997; 277: 1775–81.
28. Evans RW, Shaten BJ, Hempel JD, Cutler JA, Kuller LH. Homocyst(e)ine and risk of cardiovascular disease in the Multiple Risk Factor Intervention Trial. *Arterioscler Thromb Vasc Biol* 1997; 17: 1947–53.
29. Folsom AR, Nieto FJ, McGovern PG, Tsai MY, Malinow MR, Eckfeldt JH, Hess DL, Davis CE. Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 1998; 98: 204–10.
30. Pancharuniti N, Lewis CA, Sauberlich HE, Perkins LL, Go RC, Alvarez JO, Macaluso M, Acton RT, Copeland RB, Cousins AL. Plasma homocysteine, folate, and vitamin B12 concentrations and risk for early-onset coronary artery disease. *Am J Clin Nutr* 1994; 59: 940–8.
31. Robinson K, Arheart K, Refsum H, Brattstrom L, Boers G, Ueland P, Rubba P, Palma-Reis R, Meleady R, Daly L, Wittman J, Graham I. Low circulating folate and vitamin B6 concentrations: risk factors for stroke, peripheral vascular disease, and coronary artery disease. European COMAC Group. *Circulation* 1998; 97: 437–43.
32. Brattstrom LE, Israelsson B, Jeppsson JO, Hultberg BL. Folic acid – an innocuous means to reduce plasma homocysteine. *Scand J Clin Lab Invest* 1988; 48: 215–21.
33. den Heijer M, Brouwer IA, Bos GMJ, et al. Vitamin supplementation reduces blood homocysteine levels: a controlled trial in patients with venous thrombosis and healthy volunteers. *Arterioscler Thromb Vasc Biol* 1998; 18: 356–61.
34. Saltzman E, Mason JB, Jacques PF, Bostom AG, Wilson PW, Rosenberg IH. B vitamin supplementation lowers homocysteine levels in heart disease. *Clin Res* 1994; 42: 172A.
35. Wilcken DEL, Wilcken B. The natural history of vascular disease in homocystinuria and the effects of treatment. *J Inher Metab Dis* 1997; 20: 295–300.
36. Peterson JC, Spence JD. Vitamins and progression of atherosclerosis in hyperhomocysteinemia. *Lancet* 1998; 351: 263.
37. Robinson K. Homocysteine, B vitamins, and risk of cardiovascular disease. *Heart* 2000; 83: 127–30.

Mitteilungen aus der Redaktion

Besuchen Sie unsere zeitschriftenübergreifende Datenbank

[Bilddatenbank](#)

[Artikeldatenbank](#)

[Fallberichte](#)

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

[Bestellung e-Journal-Abo](#)

Haftungsausschluss

Die in unseren Webseiten publizierten Informationen richten sich **ausschließlich an geprüfte und autorisierte medizinische Berufsgruppen** und entbinden nicht von der ärztlichen Sorgfaltspflicht sowie von einer ausführlichen Patientenaufklärung über therapeutische Optionen und deren Wirkungen bzw. Nebenwirkungen. Die entsprechenden Angaben werden von den Autoren mit der größten Sorgfalt recherchiert und zusammengestellt. Die angegebenen Dosierungen sind im Einzelfall anhand der Fachinformationen zu überprüfen. Weder die Autoren, noch die tragenden Gesellschaften noch der Verlag übernehmen irgendwelche Haftungsansprüche.

Bitte beachten Sie auch diese Seiten:

[Impressum](#)

[Disclaimers & Copyright](#)

[Datenschutzerklärung](#)