



## Clinical Guide - Hyperhomocysteinemia (October 2006)

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### Background

Elevations of plasma homocysteine concentration are statistically associated with the risk of vascular events, both arterial [1] and venous [2]. The risk associated with higher homocysteine adds to or even multiplies the risk conferred by factors such as smoking, hypertension, diabetes, and lipid disorders (for arterial disease) and Factor V Leiden (for venous thromboembolism) [3]. Even mild elevations of plasma homocysteine increase risk.

Despite the statistical association of homocysteine with vascular events, a causal association is unproven [4], and there is no convincing biological mechanism by which small elevations of homocysteine would promote vascular disease. Moreover, the mandated folate fortification of staple foods in North America and many other jurisdictions has raised levels in the population. This may have attenuated the importance of homocysteine.

Homocysteine levels are influenced by diet, as homocysteine is produced from metabolism of methionine, and cleared by metabolic pathways that require folic acid, vitamin B6, and vitamin B12 as cofactors. Low levels of these vitamins are therefore associated with hyperhomocysteinemia. A common genetic variant in an enzyme involved in the recycling of folate, methylene tetrahydrofolate reductase (MTHFR 677C->T), causes modest elevation in plasma homocysteine concentrations in the face of limited folate intake. Congenital deficiencies of this and other enzymes in these metabolic pathways are causes of more striking elevations, as is renal failure.

### Screening

There is no evidence to support routine measurement of homocysteine in patients with arterial or venous disease.

Fasting plasma or serum homocysteine concentrations may be measured as a part of the investigation of selected patients with venous thromboembolism, particularly those with idiopathic thrombosis, recurrent thrombosis, and thrombosis at a young age or at an unusual site (see guideline on Investigation of Suspected Hypercoagulable States). The finding of elevated homocysteine by itself would not influence management, as it is a relatively weak risk factor for thrombosis and has not been shown to increase the risk of recurrence. The rationale for its measurement is that the risk associated with elevated homocysteine augments the risk associated with other thrombophilic disorders such as Factor V Leiden, and a longer duration of anticoagulation may be warranted in patients with multiple thrombophilias.

Attention to proper sample handling is essential to obtaining valid results; plasma should be separated from red cells within an hour of collection.

### Treatment

Vitamin B12 deficiency and renal disease should be excluded in all patients found to have elevated homocysteine levels.

Although homocysteine levels are readily lowered in most patients by folate-containing vitamin therapy [5], there is no evidence that such treatment will reduce vascular or thrombotic events. Three large and statistically powerful randomised controlled trials of vitamin therapy have failed to demonstrate a benefit in prevention of arterial events [6-8]. One of these trials also evaluated venous thromboembolism as a secondary endpoint, and found no benefit [7]. We therefore do not recommend vitamin therapy for moderate hyperhomocysteinemia, apart from therapeutic correction of vitamin B12 deficiency.

Patients with severe hyperhomocysteinemia (>30-50  $\mu\text{mol/L}$ ) who do not have renal failure or deficiency of vitamin B12 should be suspected to have an inborn error of metabolism and should be referred for further advice.

### References

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