

Correspondence

To the editor:

Vitamin supplementation in the secondary prevention of venous thromboembolism: about the VITRO study

We read with great interest and expectation the article by den Heijer et al¹ on a randomized, placebo-controlled double-blind trial in the secondary prevention of venous thromboembolism. We point out some issues to be clarified by the authors, and a general comment.

(1) The authors do not give any information on the prevalence of thrombophilic polymorphisms, such as factor V Leiden and prothrombin G20210A, which are expected to be highly prevalent in these patients with no major acquired risk factors. (2) Were patients with venous thromboembolism on hormonal therapy equally distributed? The risk of recurrence in these patients is, in fact, different from those with 'true' idiopathic venous thrombosis. (3) In den Heijer,¹(Table 1) the range of geometric mean baseline homocysteine (Hcy) levels in the hyperhomocysteinemic group is reported to be 6.3 to 84.8 in the multivitamin group and 7.4 to 108.3 in the placebo group. Does this mean that patients with Hcy levels below the cut-off of hyperHcy were considered as hyperhomocysteinemic? On the other hand, the range of geometric mean baseline Hcy levels in the normohomocysteinemic group treated with multivitamins is reported to be 4.0 to 23.0. Does this mean that patients with Hcy levels above the reported cut-off were considered as normohomocysteinemic? (4) What was the renal function of patients enrolled? Also documented by Spence et al,² patients with significant renal impairment do not respond to vitamin therapy, in particular to vitamin B12.

A limitation of the trial, as of other published trials (eg, VISP³), is the level of Hcy chosen to diagnose and treat hyperHcy. Indeed, the 75th percentile of Hcy distribution in controls identifies a quite low level of Hcy in the population of the Netherlands of 12.6 $\mu\text{M/L}$, which is even lower in the population enrolled in Milan (10.6 $\mu\text{M/L}$) and Wien. Lowering Hcy concentrations has been shown to have a significant effect on reducing the cardiovascular disease risk in patients with homocystinuria.^{4,5} However, because

of this cut off level, we would probably miss, once again, the opportunity to know if the lowering of intermediate Hcy levels rather than levels of 8 to 12 $\mu\text{M/L}$ may be useful for reducing the recurrence rate.

The debate continues, and we still look forward to an adequately-sized study addressing patients not homocystinuric but with intermediate hyperHcy.

**Rossella Marcucci, Francesco Sofi, Anna Maria Gori,
Gian Franco Gensini, and Rosanna Abbate**

Correspondence: R. Marcucci, Department of Heart and Vessels, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy; e-mail: r.marcucci@DAC.UNIFI.IT.

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To the editor:

Vitamins and Thrombosis (VITRO) study—homocysteine lowering with B vitamins

Den Heijer et al¹ present their randomized, placebo-controlled, double-blind trial for homocysteine lowering with B vitamins as a measure for secondary prevention of deep vein thrombosis and pulmonary embolism. Of the 8 water-soluble B vitamins, they used folic acid (5 mg), cyanocobalmin (0.4 mg), and pyridoxine (50 mg).

In the context of the known genotype-phenotype relation between the *MTHFR* (OMIM [Online Inheritance in Man] *607093), the homocysteine level, and thrombophilia (OMIM #188050), there remain some problems and questions.

What is the share of patients homozygous for the *MTHFR* C677T genotype? This genetic variant renders this enzyme thermolabile and affects its noncovalent binding of its prosthetic group FAD.²⁻⁵ Vitamin B₂, or riboflavin, is the biosynthetic precursor of

FMN or FAD, the coenzymes or prosthetic groups of diverse oxidoreductases.

If there is a link between folate and riboflavin mediated by the *MTHFR*⁶⁻⁹ as a flavoprotein, what effect or benefit for the cohort of patients in that study could an additional riboflavin supplementation to the aforementioned vitamin B cocktail have? In most of the published studies for lowering homocysteine with B vitamins, riboflavin supplementation is neglected.

What are the scientific rationales for choosing the mentioned doses of the 3 vitamins used? Following Ames et al's proposal⁴ of high-dose vitamin therapy, it may be an underdosing. The *MTHFR* C677T is an FAD-responsive mutant,^{2,3} and this should guide future trials for homocysteine lowering by vitamin supplementation