

**DANIEL G. FEDERMAN, MD**

Department of Medicine, Section of General Medicine, Firm Chief, VA Connecticut Health Care System, West Haven, CT; Associate Professor of Medicine, Yale University School of Medicine, New Haven, CT

GINA R. BRESCIA, MD

Department of Medicine, Section of General Medicine, VA Connecticut Health Care System, West Haven, CT; Assistant Professor of Medicine, Yale University School of Medicine, New Haven, CT

JOHN P. MORIARTY, MD

Department of Medicine, Section of General Medicine, VA Connecticut Health Care System, West Haven, CT; Assistant Professor of Medicine, Yale University School of Medicine, New Haven, CT

SALLY G. HASKELL, MD

Department of Medicine, Section of General Medicine, Director of Women's Health, VA Connecticut Health Care System, West Haven, CT; Assistant Professor of Medicine, Yale University School of Medicine, New Haven, CT

RAJ KRISHNAMURTHY, MD

Department of Medicine, Section of General Medicine, Primary Care Service Line Manager, VA Connecticut Health Care System, West Haven, CT; Assistant Professor of Medicine, Yale University School of Medicine, New Haven, CT

ROBERT S. KIRSNER, MD, PhD

Associate Professor, Department of Dermatology, University of Miami School of Medicine, Miami, FL

Update in thrombosis: Answers to perplexing questions

■ ABSTRACT

Recent clinical trials are answering some of the perplexing clinical questions about venous thromboembolism (VTE), such as the length and intensity of anticoagulation needed to prevent recurrence. We review some of these clinical trials and their implications for physicians and patients.

■ KEY POINTS

Long-term conventional anticoagulation with warfarin appears superior to long-term low-intensity anticoagulation in preventing recurrent deep venous thrombosis (DVT).

Patients with either the factor V Leiden mutation or the prothrombin G20210A mutation are not at significantly increased risk for recurrent DVT.

Preliminary studies suggest an association between atherosclerotic disease and venous thrombosis.

It is not clear whether supplementation with folic acid for patients with elevated homocysteine levels will lead to a decrease in arterial or venous disease.

NEW INFORMATION from clinical studies is shedding light on some perplexing questions that commonly arise in the care of patients with or at risk for venous thromboembolism (VTE):

- How long should patients receive warfarin after a VTE event such as deep venous thrombosis (DVT)? Is extended therapy better than a shorter course of therapy?
- Is less-intense therapy as effective as standard therapy? Is it safer?
- When is the risk of VTE recurrence highest after warfarin is stopped?
- Are patients with the factor V Leiden mutation or the prothrombin G20210A mutation at increased risk for VTE recurrence after a first episode?
- Is there an association between venous and arterial disease?
- Does reducing homocysteine with supplemental folate decrease cardiovascular risk in patients with elevated homocysteine levels?

■ HOW LONG TO TREAT?

The optimal duration of therapy for patients with VTE is a three-way balance between the risks and the benefits of long-term anticoagulation and the risk of recurrence after anticoagulation is stopped.

Agnelli et al,¹ in a multicenter trial in Italy, randomized patients with a first episode of idiopathic DVT to receive oral anticoagulant therapy for either 3 or 12 months. Although fewer patients in the 12-month group had another episode while on active treatment than those who had already com-

pleted 3 months of treatment, the clinical benefit ended after the treatment was stopped.

These findings suggest that extending anticoagulant therapy indefinitely might extend its clinical benefit. Several studies have addressed this question.

Schulman et al² randomized patients who had had two episodes of VTE to receive oral anticoagulant therapy for either 6 months or indefinitely. The target international normalized ratio (INR) during therapy was 2.0 to 2.85. After 4 years, recurrent episodes had occurred in 23 (20.7%) of the 111 patients in the 6-month group, compared with only 3 (2.6%) of the 116 patients in the indefinite-therapy group. There were more major hemorrhages in the indefinite-therapy group, but the difference was not statistically significant.

Kearon et al³ conducted a similar study in patients with a *first* episode of idiopathic VTE. Patients received oral anticoagulant therapy (target INR 2.0–3.0) for 3 months and then were randomized to either continue active treatment for the next 24 months or to receive placebo. However, the study was terminated after an average follow-up of only 10 months, when a prespecified interim analysis showed there were 17 cases of recurrent VTE in the 83 patients in the placebo group (for a rate of 27.4% per patient-year) vs only 1 case in the 79 patients in the extended-therapy group (1.3% per patient-year). Though not statistically significant, there were 3 episodes of non-fatal major hemorrhage (3.8% per patient-year) in the extended-therapy group and none in the group receiving placebo.

■ IS LESS-INTENSE THERAPY AS GOOD AS STANDARD THERAPY?

Since these studies demonstrated that long-term anticoagulant therapy at standard intensity (a target INR of 2.0 to 3.0) decreased the rates of recurrent VTE, investigators wondered whether less-intense therapy (with a lower target INR) might be as effective while causing less bleeding.

Ridker et al, in the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial,⁴ studied men and women 30 years of age or older with idiopathic VTE who had completed full-dose anticoagulation for a

median of 6.5 months. The patients were randomized to receive either placebo or warfarin at a low intensity (target INR 1.5–2.0). Of note, some of the patients had the factor V Leiden mutation or the prothrombin G20210A mutation (see below). More than one third of them had two or more previous episodes of VTE. Those with known antiphospholipid antibody syndrome were excluded.

An independent data and safety monitoring board terminated the study early after it became apparent that the active therapy was beneficial. After follow-up of up to 4.3 years (mean 2.1), recurrent episodes of VTE had occurred in 37 of the 253 patients in the placebo group (7.2 episodes per 100 person-years) vs only 14 in the 255 patients in the warfarin group (2.6 per 100 patient-years), a risk reduction of 64%. The risk reduction was similar in all subgroups, including those with or without inherited thrombophilia and those with or without multiple previous episodes of VTE. Although not statistically significant, there were 2 major hemorrhages in the placebo group and 5 in the warfarin group.

These findings make it apparent that extended courses of standard-dose anticoagulation and low-dose anticoagulation decrease the risk of recurrent VTE. But which strategy is better?

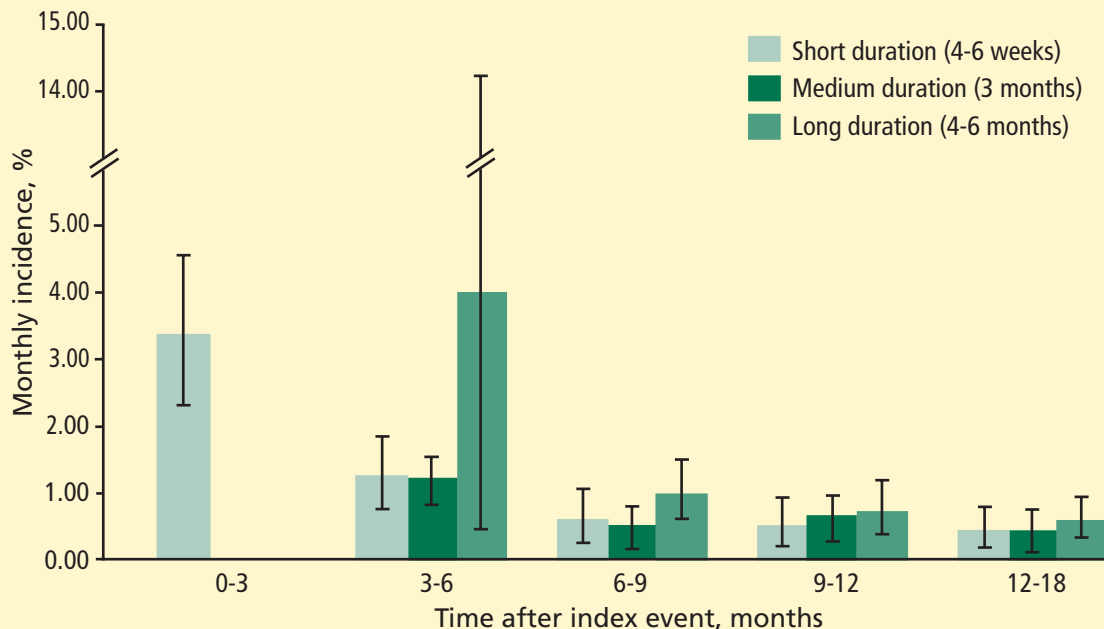
Kearon et al⁵ compared these two strategies in patients who had had one or more episodes of VTE, some of whom had the factor V Leiden mutation or the prothrombin G20210A mutation. After receiving warfarin at a conventional intensity for 3 or more months, the patients were randomized to continue to receive warfarin with a goal INR of either 1.5 to 1.9 (low intensity) or 2.0 to 3.0 (conventional intensity).

At an average follow-up of 2.4 years, there had been 16 episodes of recurrent VTE in the 369 patients in the low-intensity group (1.9 per 100 person-years) vs only 6 in the conventional-intensity group (0.7 per 100 person-years). There were 9 episodes of major bleeding in the low-intensity group and 8 in the conventional-intensity group. The authors concluded that long-term conventional-intensity therapy prevents recurrent episodes of VTE better than long-term low-dose therapy, and it does not cause more major bleeding.

Standard-dose warfarin was more effective than low-dose warfarin



Monthly incidence of recurrent venous thromboembolism after stopping oral anticoagulation



WITH PERMISSION FROM VAN DONGEN CJJ, VINK R, HUTTEN B, ET AL. THE INCIDENCE OF RECURRENT VENOUS THROMBOEMBOLISM AFTER TREATMENT WITH VITAMIN K ANTAGONISTS IN RELATION TO TIME SINCE FIRST EVENT. ARCH INTERN MED 2003; 163:1286-1293.

FIGURE 1. Monthly incidence and 95% confidence intervals of recurrent venous thromboembolism after stopping oral anticoagulation in a meta-analysis of 18 trials that included 3,186 patients.

Conclusions:

Long-term conventional therapy appears superior to long-term low-intensity therapy

Long-term conventional anticoagulant therapy appears superior to long-term low-intensity anticoagulant therapy in preventing recurrent VTE.

Of note, however: although these studies profess to offer guidance about the merits of “long-term” anticoagulation, they were not powered to detect differences in the incidence of hemorrhage, and they included only patients at low risk for bleeding. Furthermore, follow-up was relatively short; one can assume that if therapy were continued longer, major hemorrhage would become more prevalent.

Linkins et al⁶ performed a meta-analysis that included 33 studies and 4,374 patient-years of oral anticoagulant therapy. They found that major bleeding occurred at a rate of 7.22 per 100 patient-years and fatal bleeding at a rate of 1.31 per 100 patient-years.

Practicing clinicians should keep these studies in mind when deciding whether to keep individual patients on long-term anticoagulant therapy to prevent recurrent VTE.

■ WHEN IS VTE RISK HIGHEST AFTER STOPPING WARFARIN?

The risk of VTE recurrence after stopping anticoagulant therapy is most affected by the patient’s underlying risk factors and the circumstances surrounding the index event. Hirsch and Lee⁷ and Kearon⁸ have developed risk-stratification systems to help guide therapeutic decisions. Transient risk factors such as major surgery, medical illness, or leg trauma predict a low risk of recurrence after anticoagulation is stopped.^{9,10} Patients without an identifiable risk factor^{1,3,11} and patients with active malignancies^{8,12} have high rates of recurrence after stopping.

Incidence of major bleeding with warfarin: 7.2%/year
Fatal bleeding: 1.3%/year

The incidence rate of recurrent VTE has been estimated at 9% per year in the first 2 years after stopping therapy and 4% per year over 8 years.¹³ Therefore, the risk must wane over time. But does the clock start with the index event or when therapy is stopped? Given that the rate of major bleeding with vitamin K antagonists such as warfarin remains constant over time,⁶ this information would be helpful for clinicians in deciding when patients could stop taking warfarin.

Van Dongen et al¹⁴ performed a meta-analysis of randomized controlled trials and prospective cohort studies in which detailed follow-up data were present. The target INRs were mostly in the range of 2.0 to 3.0. About two thirds of the studies included only patients with DVT, and one third also included patients with pulmonary embolism. The 3,186 patients were heterogeneous in underlying risk factors, with varying rates of cancer, immobility, surgery, trauma, and idiopathic VTE. Recurrent VTE events were sorted by the duration of therapy and by the length of time after therapy was stopped.

The results (FIGURE 1) confirm a period of increased risk for recurrence of about 3% to 4% per month in the first 3 months after stopping treatment, falling to about 0.5% to 0.72% per month by 9 months after stopping, regardless of the initial treatment duration.

This meta-analysis was hampered by a lack of sufficient studies. Of 135 potentially eligible studies, only 18 met the stringent inclusion criteria; 83 were excluded because they lacked sufficiently detailed data on the timing of recurrent VTE events. There were subsequently insufficient numbers to determine if any duration of anticoagulant therapy is more effective in preventing recurrences after stopping. Confidence intervals were wide, including the data for the two small studies in which treatment had been given for a short or medium duration.^{15,16} Most importantly, the inclusion of patients with temporary risk factors (immobilization, surgery, trauma), permanent risk factors (cancer, factor V Leiden, antiphospholipid antibodies), and idiopathic VTE, all believed to have differing risk of recurrence, may have also contributed to the lack of clear benefit of a specific duration of anticoagulation.

Hutten et al,¹⁷ in a recent Cochrane Systematic Review, included only randomized controlled clinical trials that compared different durations of anticoagulation in patients with symptomatic VTE. This meta-analysis did not demonstrate an excess of recurrent events after prolonged anticoagulation was stopped. Again, the patient populations were heterogeneous, including both idiopathic VTE and second episodes of VTE.

Conclusions: Risk linked to time after stopping treatment

The risk of recurrence seems to be determined in part by the time from cessation of anticoagulation rather than time from the index VTE event. For a subset of patients with reversible risk factors, time-limited anticoagulation therapy appears to be appropriate. For patients with ongoing risk factors, there does not appear to be an absolute time period of risk. Defining more precisely who is at ongoing risk of recurrent VTE and the magnitude of that risk is of greater importance.

DO MUTATIONS INCREASE THE RISK OF RECURRENCE?

Recent advances in the understanding of thrombophilia have led to an increased understanding of the etiology of venous thromboembolism in cases that heretofore would have been unexplained. Several excellent reviews have described newly discovered inherited and acquired causes of thrombophilia.^{18–20}

The factor V Leiden mutation and the prothrombin G20210A mutation are common inherited thrombophilic disorders. As many as 5% of the general population is heterozygous for the factor V Leiden mutation, which confers up to a seven times higher risk of a first episode of VTE.²¹ Approximately 2% of the population is thought to harbor the prothrombin G20210A mutation, and their risk of a first episode is thought to be increased by a factor of 2.8 to 3.8.²²

Factor V Leiden mutation

Whether these mutations confer an increased risk of recurrent VTE is less certain, but two early prospective observational studies report-

Up to 5% of people carry the factor V Leiden mutation and have up to 7 times the risk of VTE



ed a higher risk of a second VTE in patients heterozygous for factor V Leiden compared with controls.

Ridker et al²³ followed 77 patients in the Physicians Health Study who had suffered a first episode of idiopathic DVT or pulmonary embolism. Of those who were heterozygous for the factor V Leiden mutation, 28.6% had a second event compared with 11.1% of those without the mutation.

Simioni et al²⁴ evaluated the cumulative risk of recurrent DVT after an initial episode of idiopathic or secondary DVT in 38 patients with the factor V Leiden mutation and 186 patients without this abnormality. The relative risk for a second clot in factor V Leiden carriers was 2.4 compared with controls.

Importantly, in both of these studies, the average duration of anticoagulant therapy that patients received after their first event was only 3 months. Several other studies have shown conflicting results.

Eichinger et al²⁵ in a multicenter trial, evaluated 380 patients who received 6 months of anticoagulant therapy after a first or recurrent episode of VTE. Twelve months after stopping therapy, the rate of recurrence among carriers of the factor V Leiden mutation was 6.0%; among noncarriers it was 7.6%. At 24 months, the rates were 10.6% and 12.4%, respectively. Neither difference was statistically significant.

Variations in study design and patient populations were thought to explain some of the differences in outcomes between trials. Some of the studies were relatively small. Eligibility criteria varied, with some studies enrolling only patients with a first idiopathic DVT and others including those with secondary or recurrent events. Patients with pulmonary embolism, calf clots, or upper extremity clots were included in some studies but not in others. There was also variation with respect to which other thrombophilic disorders were tested for and excluded. Furthermore, the duration of preceding anticoagulant therapy was inconsistent between studies.

Eichinger et al²⁶ readdressed this question in a more defined cohort: 287 patients completing anticoagulant therapy for a first episode of spontaneous proximal DVT or pul-

monary embolism. Of these, 83 (29%) were heterozygous for factor V Leiden and 204 were without the mutation. Homozygotes for factor V Leiden and patients with natural inhibitor deficiencies or lupus anticoagulant were excluded. After 6 years, the relative risk of recurrence was 0.9 for carriers. Findings were unchanged after controlling for the G20210A mutation, hyperhomocysteinemia, and high factor VIII levels.

Prothrombin G20210A mutation

Fewer studies have looked at the relationship between the prothrombin G20210A mutation and recurrent venous thrombosis. Available data are conflicting, and comparison is difficult due to differences in study design and inclusion and exclusion criteria.

Simioni et al²⁴ observed 24 patients with the prothrombin mutation and 186 without and reported an increased hazard ratio of 2.4 for subsequent recurrent VTE in carriers.

Lindmarker et al²⁷ on the other hand, prospectively followed 456 Swedish patients with first episodes of DVT or pulmonary embolism for 48 months. Patients with deficiencies of protein C, protein S, or antithrombin were excluded. In this study, 13% of noncarriers and 14% of heterozygotes for the prothrombin G20210A mutation had objectively documented recurrences; the difference was not statistically significant. There were no significant differences between the groups with regard to family history of thrombosis, type of initial thrombosis (pulmonary embolism, proximal DVT, or distal DVT), or percentage of initial thromboses that were idiopathic.

Carriers of both mutations

Few studies have attempted to determine the risk of recurrent VTE in patients heterozygous for both factor V Leiden and the prothrombin mutation.

DeStefano et al²⁸ evaluated patients with a first episode of idiopathic or secondary DVT and found a relative risk of recurrence of 2.6 in heterozygous carriers of both mutations compared with those with factor V Leiden alone, and a relative risk of 2.7 compared with those with neither mutation.

Margaglione et al²⁹ found similar results in a retrospective study of 542 men and

Risk of recurrent VTE seems to be the same with or without the factor V Leiden mutation

women with unilateral DVT referred for thrombophilia evaluation. Twenty-two patients were positive for both factor V Leiden and the prothrombin gene mutation, and of these, 36% had recurrent DVT compared with 13% of those possessing neither defect.

Conclusions: Single mutations do not increase the risk of recurrent VTE

At present there are no conclusive data to suggest that patients with either factor V Leiden or the prothrombin G20210A mutation are at increased risk of recurrent VTE. Available data do suggest that patients who carry both mutations are at increased risk. More studies are needed to confirm this and determine if long-term anticoagulation is warranted.

■ IS VTE ASSOCIATED WITH ATHEROSCLEROSIS?

Patients with atherosclerosis have higher levels of platelet activation, blood coagulation, and fibrin turnover, which may lead to thrombotic complications in both the venous and arterial circulations.^{30–32}

Case-control and prospective studies have found an association between venous thromboembolic disorders and arterial atherosclerotic disease.

Libertiny and Hands,³³ in a prospective study, performed ultrasonography in patients admitted for arteriography, angioplasty, or arterial reconstruction. DVT was more common in patients with peripheral vascular disease than in patients admitted for general surgical procedures.

Prandoni et al,³⁴ in a recent case-control study, performed ultrasonography of the carotid arteries in 299 patients with DVT of the legs without symptomatic atherosclerosis and in 150 control subjects. At least one carotid plaque was detected in 47.1% of the 146 patients with spontaneous thrombosis, 27% of those with secondary thrombosis, and 32% of controls (odds ratio 2.3 comparing patients with spontaneous thrombosis vs the other groups).

Whether cardiovascular risk factors predispose to venous thromboembolic disease has also been investigated in several studies.

The Nurses Health Study³⁵ prospective-

ly followed 112,822 women, age 30 to 55 years, for 16 years. There were 280 cases of pulmonary embolism, 125 of which were classified as primary (no antecedent risk factor could be identified). In multivariate analysis, cigarette smoking, obesity, and hypertension were found to be independent predictors of pulmonary embolism.

Tsai et al³⁶ obtained conflicting results in another large prospective study. In 19,293 men and women from six US communities, there were 215 validated venous thromboembolic events. Cigarette smoking, hypertension, dyslipidemia, physical inactivity, and alcohol consumption were not associated with increased risk of DVT. The age-adjusted hazard ratios were 1.4 for men vs women, 1.6 for blacks vs whites, and 1.7 per decade of age. Increased risk was also associated with a body mass index (BMI) greater than 25 and diabetes mellitus.

Vaya et al³⁷ investigated whether hyperlipidemia is a risk factor for VTE in a case-control study of 143 patients with DVT lacking thrombophilic risk factors and 194 age-matched and sex-matched controls. After adjustment for potential confounding factors, BMI was the only variable that remained significant. However, subjects with idiopathic DVT were older and had higher cholesterol levels than did those with secondary DVT.

Conclusions: Atherosclerosis may be linked to venous thrombosis

Several studies have shown an association between atherosclerotic disease (or risk factors for it) and venous thrombosis. Since atherosclerosis is associated with platelet activation and blood coagulation, a role of the prothrombotic state in promoting venous thrombosis is at least plausible. None of these studies established a causative role, but further investigation is warranted.

■ SHOULD ELEVATED HOMOCYSTEINE BE TREATED?

Elevated levels of homocysteine are associated with both venous and arterial disease. The mechanism by which homocysteine could induce vascular disease is not known, but hyperhomocysteinemia has been shown to

Plausibly,
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cause smooth muscle proliferation, impair endothelium-dependent vasodilatation, and promote vascular thrombosis.^{38,39} Treatment with folic acid decreases plasma homocysteine levels by one fourth to one third.⁴⁰ Few trials have tested if lowering levels of homocysteine with folic acid has an impact on vascular outcomes, however.

Several small studies have shown that treatment with folic acid can improve endothelial function in patients with hyperhomocysteinemia.

Woo et al⁴¹ studied 17 healthy adults with elevated serum homocysteine levels. Treatment with high doses of folic acid (10 mg daily) led to a significant improvement in flow-mediated endothelial-dependent dilatation.

Title et al⁴² also found a similar improvement in endothelial function with supplemental folic acid in a study of 75 patients with established coronary disease and elevated homocysteine levels.

Although similar improvements in endothelial function have been seen in studies of HMG-CoA reductase inhibitors (statins) and angiotensin-converting enzyme (ACE) inhibitors, it is not clear if treatment with folic acid to lower homocysteine levels will lead to reductions in cardiovascular end points similar to those with statins and ACE inhibitors.

Early studies on this subject have focused on surrogate markers for vascular disease and subclinical end points.

Hackman et al⁴³ treated 101 patients with vascular disease and hyperhomocysteinemia with folic acid 2.5 mg along with vitamins B₁₂ and B₆ and followed the rate of progression of carotid atherosclerosis by duplex ultrasonography. After treatment, there was a statistically significant regression in carotid plaque. However, this study was not randomized, post-treatment homocysteine levels were not available, and clinical events were not studied.

Vermeulen et al⁴⁴ in a similar trial, studied the development of subclinical atherosclerosis as estimated by exercise electrocardiography, the ankle-brachial index, and ultrasonography of the carotid and femoral arteries. In this study, 158 healthy siblings of 167 patients with premature atherosclerosis and hyperhomocysteinemia were randomized to treatment

with folic acid and vitamin B₆ for 2 years. The mean age of participants was 45, and the mean homocysteine level was 14.7 $\mu\text{mol/L}$.

Treatment with folate and vitamin B₆ was associated with a significantly lower rate of abnormalities on exercise electrocardiography, with an odds ratio of 0.4 (0.17–0.93). There was no significant effect on the findings on ultrasonography or on the ankle-brachial index.

Although these two small trials did show some benefit in markers for vascular disease, they were not designed to evaluate clinical end points such as stroke and myocardial infarction.

The Swiss Heart study⁴⁵ was an initial attempt to study clinical outcomes in patients treated with folic acid. In this trial, 553 patients who had undergone successful angioplasty were randomized to receive folic acid and vitamins B₁₂ and B₆ or placebo for 6 months after angioplasty. The primary end point was a composite of death, nonfatal myocardial infarction, and need for repeat revascularization. Noninvasive stress testing was performed at 1 year or at 6 months, or earlier if symptoms developed. After a mean of 11 months, the primary end point had occurred in 15.4% of the folate-treated group and 22.8 % in the placebo-treated group, a relative risk of 0.68 (0.48–0.96). This was largely due to a decreased need for target lesion revascularization, as subgroup analysis revealed no significant difference in death or nonfatal myocardial infarction.


A subset of 205 patients from the Swiss Heart Study was randomized to undergo angiography at 6 months.⁴⁶ The primary end point in this study was restenosis of more than 50% in the target lesion at 6 months. Secondary end points included cardiovascular death, nonfatal myocardial infarction, and the need for revascularization. The primary end point occurred in 19.6% of the folate-treated group and in 37.6% of the placebo group. This correlated with a relative risk of 0.52 (0.32–0.86) and a number needed to treat of 5.6 to prevent one restenosis. There were no significant differences in the rate of fatal or nonfatal myocardial infarction, and there was no difference in the rate of restenosis in patients who received a coronary stent.

Most studies of treating elevated homocysteine used surrogate end points

Lange et al,⁴⁷ in a study of patients undergoing coronary stenting randomized to treatment with folic acid and vitamins B₆ and B₁₂ or placebo, likewise found a significant increase in restenosis in the active treatment group.

Toole et al⁴⁸ more recently performed a randomized double-blind trial in patients with recent nondisabling stroke and found that supplementation with folic acid and vitamins B₆ and B₁₂ had no effect on the outcome measures of stroke, coronary heart disease events, or death after 2 years of follow-up.

Conclusions: Not enough evidence for homocysteine-lowering treatment

Although elevated levels of homocysteine have been linked to cardiovascular outcomes, it is still not clear if using folic acid to lower homocysteine levels will lead to a reduction in myocardial infarction, thromboembolism, or death. We anxiously await the results of ongoing randomized controlled trials examining whether supplementation with folic acid reduces vascular events in patients with hyperhomocysteinemia. 

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ADDRESS: Daniel G. Federman, MD, VA Connecticut (11ACSL), 950 Campbell Avenue, West Haven, CT 06516; e-mail daniel.federman@med.va.gov.