What is the Significance of an Elevated Homocysteine Level on my Blood Test?

I have written before about the possible role of elevated homocysteine levels in causing vascular events. Folic acid and B vitamins do lower homocysteine levels and many believed that this would lower the cardiovascular risk. Supplemental folic acid and B vitamins do not lower the risk for important vascular events in women at high risk for such events, even though they lower homocysteine levels, found the Women's Antioxidant and Folic Acid Cardiovascular Study. The randomized, double- blind, placebo-controlled trial (RCT) conducted in Boston evaluated whether a combination of supplemental folic acid (2.5 mg/d), vitamin B6 (50 mg/d), and vitamin B12 (1 mg/d) reduces the risk of cardiovascular events in high-risk women, over 7.3 years of follow-up. The trial began in 1998 when the B vitamin component was added to the Women's Antioxidant Cardiovascular Study and 5,442 women were randomized to receive folic acid and B vitamins (n = 2,721) or matching placebo (n = 2,721). The women were aged 40 years and older (mean age, 62.8 y) and had a history of cardiovascular disease (CVD; 64.2% of participants) or at least three cardiac risk factors. CVD was defined as myocardial infarction (MI), stroke, coronary or peripheral revascularization, angina pectoris, or transient ischemic attack. Risk factors were hypertension, high cholesterol, diabetes, parental history of premature MI, obesity, and cigarette smoking. The primary outcome measure was a combined endpoint of cardiovascular morbidity and mortality. Secondary endpoints were the individual components of total MI, total stroke, and total coronary heart disease events (MI, coronary revascularization, and death from coronary heart disease). During the 7.3 years, there was a similar incidence of CVD events between groups, with 406 women in the treatment group and 390 in the placebo group experiencing at least one There were also similar risks between groups for the secondary outcomes of MI, stroke, and CVD mortality.

I am not sure how many studies it will take to quiet the doubters, but the null effect of B-complex vitamins and folic acid to reduce CVD clinical events despite significantly lowering homocysteine levels in this well-done should be the final one. The findings are identical to those seen in the Heart Outcomes Prevention Evaluation trial, the Norwegian Vitamin Trial, and the Vitamin Intervention for Stroke Prevention trial, among others (which enrolled mostly men), even though the therapy is successful in reducing homocysteine levels. Numerous observational, epidemiological studies have confirmed that elevated homocysteine is a predictor of cardiovascular risk. Thus logic, which so often fails in predicting the body's response to therapies, suggested B-complex and folic acid directed at reducing homocysteine would lower events significantly.

Maybe the answer lies in why patients with elevated homocysteine are at risk for CVD. There has never been a definite, accepted reason explaining the CVD risk seen in patients with high homocysteine. Is homocysteine the atherogenic culprit or is it simply a marker of some other process going on in the body? It has been proposed that homocysteine is simply indicative of impaired kidney function, a major CVD risk factor, and perhaps treatment should be directed at the kidney and not the homocysteine level.

It is speculative at best to predict what therapeutic manipulation of a given risk factor will do until it is subjected to properly designed, prospective, blinded outcome trials. It took many years before homocysteine was accepted as a risk factor and it took a decade of excellent clinical trials to prove that treating it with B-vitamin and folic acid is

no longer justified. As usual, most of the previous data was from studies of men, but now we also have the answer in women. Therefore, if B-vitamin and folic acid therapy is null, screening patients with expensive homocysteine assays and following the levels over time is no longer justified.