# Vitamin D and the Heart

Although vitamin D supplementation appears to be a provocative intervention for reducing the risk of cardiovascular disease (CVD) and other chronic diseases, existing evidence of its benefits and risks is limited. Recruitment is now underway for the Vitamin D and Omega-3 Trial (VITAL; NCT01169259), the first large-scale, prospective, randomized clinical trial of these nutritional agents for the prevention of cancer and CVD. Thomas Wang, MD, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, USA, presented information on the VITAL Trial (NCT01169259) on behalf of JoAnn Manson, MD, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts, USA, primary investigator of the trial.

Risk factors for low vitamin D levels include advanced age, residence in northern latitudes, sun avoidance, dark skin pigmentation, obesity, low dietary intake, and various malabsorption syndromes. Some of these are also risk factors for CVD, cancer, and other chronic diseases and potentially confound outcomes in many studies.

Still, data suggest that vitamin deficiency is associated with increased risk of developing CVD. The Framingham Offspring Study [Wang TJ et al. *Circulation* 2008] followed 1739 men and women (mean age 59 years) without prior CVD for a period of 5.4 years. The study compared the incidence of CVD in subjects with a prespecified threshold serum 25-dihydroxyvitamin D level (25-OH D) of 37.5 nmol/L with subjects with lower 25-OH D levels. The multivariable-adjusted risk of CVD in individuals with 25-OH D <37.5 nmol/L was 1.62 times higher (95% CI, 1.11 to 2.36; p=0.01) than in those with higher levels of vitamin D.

The Health Professionals Follow-Up Study [Giovannucci E. *Arch Intern Med* 2008] prospectively evaluated 18,225 men aged 40 to 75 years for a period of 10 years. The study compared subjects with a low serum vitamin D level (<37.5 nmol/L) with those who possessed a more optimal level (>75 nmol/L). The incidence of CV events was 2.09 times higher (95% CI, 1.24 to 3.54; p=0.02) in men with low levels. Similar trends in both studies were observed in individuals with intermediary levels of vitamin D as compared with a more optimal level. A systematic review of prospective and randomized studies also found that vitamin D supplements at moderate to high doses may reduce CVD risk [Wang L. *Ann Intern Med* 2010].

The VITAL trial will aim to recruit 20,000 healthy men (≥60 years) and women (≥65 years) who are representative of the US population (www.vitalstudy.org). Participants will be randomized in a double-dummy, double-blinded manner to receive either 2000 IU of vitamin $D_3$ per day or placebo and further randomized to receive either 1 g per day of fish oil (combined eicsapentaenoic acid and docosahexaenoic acid) or placebo.

Mean treatment period will be 5 years, with blood collection for approximately 20,000 individuals. Primary outcome measures will be incidence of cancer (total) and CVD (myocardial infarction, stroke, CVD death). The trial is expected to conclude in June 2016.

With emerging evidence that indicates that vitamin D reduces CVD risk but no previous large-scale, randomized clinical trials of this agent in the primary prevention of CVD, VITAL has a strong rationale behind it. The growing use of these supplements underscores the need for more conclusive evidence on benefits and risks.

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