EDITORIAL COMMENT
To C or Not to C, That Is the Question!* 

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In this issue of the Journal, Osganian et al. (1) in Dr. Walter Willett’s group at Harvard University report that women in the Nurses’ Health Study who took vitamin C supplements had a significantly lower risk of incident coronary heart disease (CHD) than women who did not take vitamin C supplements. The risk reduction with vitamin C supplement use was 28% after adjusting for age, smoking, and several other coronary risk factors, vitamins, and dietary antioxidants such as vitamin E and carotenoids. In contrast, vitamin C from dietary intake alone was not significantly associated with a reduced CHD risk. After all the controversy and overall disappointing results with beta-carotene and vitamin E supplementation for secondary prevention of CHD, could vitamin C be the saving grace for a cardioprotective role of antioxidant vitamins?

The totality of evidence from past population-based studies suggests that low or deficient intakes of vitamin C are associated with an increased CHD risk and that a modest intake of about 100 mg/day is sufficient for maximum reduction of CHD risk by vitamin C among non-smoking men and women (2). This conclusion is buttressed by several studies showing no benefit of higher vitamin C intakes in well-nourished populations consuming close to 100 mg/day in the lowest quintile and no CHD risk reduction among vitamin C supplement users (2). The 100-mg threshold for maximum CHD benefits also seems reasonable in light of pharmacokinetic data showing that this dose of vitamin C is associated with near-saturation of circulating cells and, thus, presumably tissues and the vitamin C body pool in both men (3) and women (4).

One notable exception for a lack of effect of vitamin C supplementation on CHD risk is the First National Health and Nutrition Examination Study (NHANES I) Epidemiologic Follow-up Study (5). This study found a 45% and 25% reduced CHD risk in men and women, respectively, consuming >50 mg/day of vitamin C from the diet and taking regular supplements, corresponding to a total vitamin C intake of about 300 mg/day (6). The study of Osganian et al. (1) appears to confirm the conclusion of the NHANES I study (5) that vitamin C supplementation lowers CHD risk in women by about 25%. However, an important difference is that the NHANES I study, unlike the present study, did not adjust for vitamin E intake or supplementation, which may contribute to the primary prevention of CHD (7).

The finding that vitamin C intake from diet alone, in contrast to vitamin C supplements, was not associated with a reduced CHD risk (1) raises at least two intriguing issues. First, it implies that the amounts of vitamin C derived from the diet, even in this well-nourished cohort of female nurses with a median dietary vitamin C intake of 209 mg/day in the highest quintile, is not sufficient to provide protection against CHD. In contrast, a vitamin C intake of >359 mg/day from diet plus supplements or supplement use itself was associated with a significant 27% to 28% reduction in risk (1). The recently revised recommended dietary allowance for vitamin C in women is 75 mg/day (8), far from providing cardioprotective benefits if the current data are confirmed.

Based on detailed pharmacokinetic data of vitamin C in healthy young women (4), the dietary intake range in Osganian’s study (61 to 209 mg/day of vitamin C, median intake in lowest vs. highest quintile) encompasses the steep portion of the dose-response curve for plasma vitamin C levels, in contrast to the median vitamin C intake in non-supplement users (132 mg/day) and supplement users (672 mg/day) (Fig. 1). Thus, on the basis of these pharmacokinetic data (4) and the above-mentioned threshold of about 100 mg/day for near-saturation of cells, one might expect to find a stronger association of CHD risk with dietary intake of vitamin C than with vitamin C supplementation. This apparent incompatibility of the pharmacokinetic (4) with the observational data (1) could be explained by differences in the subjects studied, such as age, menopausal status, or lifestyle, and by the inherent difficulties of accurately assessing vitamin C intake in epidemiologic studies (as described later). On the other hand, the vitamin C pharmacokinetic study (4) also showed that plasma (Fig. 1) and circulating cells only fully saturate at a daily dose of 400 mg of vitamin C. Consequently, the cardioprotective effect of vitamin C may become manifest only when plasma and cells, and presumably tissues, are completely saturated with the vitamin, thus making the two studies potentially compatible (1,4).

Second, the fact that vitamin C intake from diet alone, in contrast to vitamin C supplements, was not associated with a reduced CHD risk (1) implies that vitamin C itself is beneficial. Most previous studies that found an inverse association between dietary intake or plasma levels of vitamin C and CHD risk interpreted these results as an indication of a protective role of fruit and vegetable consumption (2,9). Similar to beta-carotene, vitamin C was presumed to be a marker of fruit and vegetable intake, rather than the cardioprotective component itself. This notion turned out to be largely correct with respect to beta-
carotene, as beta-carotene supplementation in randomized, placebo-controlled clinical trials, both for primary (10) and secondary prevention (11), exerted no CHD benefits. However, corresponding data from clinical trials of vitamin C supplementation are currently unavailable.

An alternative interpretation of the lower CHD incidence rates in vitamin C supplement users versus nonusers is that supplement use may reflect other healthy behaviors. Indeed, the vitamin C supplement users compared with non-users had higher intakes of numerous other vitamins derived from both diet and supplements, were more physically active and less likely to smoke, and took more aspirin (1). Despite adjustment for these and other known coronary risk factors, residual confounding can never be excluded in any observational study.

We are still left with a conundrum: why did most previous studies observe a reduced CHD risk within the dietary vitamin C intake range and maximal beneficial effects at an intake of about 100 mg/day, but not with vitamin C supplementation (2,9)? One possible explanation is that the semiquantitative food frequency questionnaire used by Osganian et al. (1) is not sensitive enough to detect small differences in CHD risk. Indeed, investigators of the EPIC-Norfolk Prospective Study (9) found a strong inverse association between CHD mortality and plasma vitamin C levels or vitamin C intake assessed by a seven-day diet diary, but not with a semiquantitative food frequency questionnaire. Thus, a significant association in the present study (1) may have been observed for supplemental vitamin C only because supplemental intake is relatively easy to assess (i.e., it is possible for subjects to remember the dose of supplements and the frequency of their use). In contrast, assessment of dietary intake by food frequency questionnaire is less precise and does not take into account loss of vitamin C during food storage or preparation. Nevertheless, the current data (1) suggest that vitamin C itself has a beneficial effect on CHD risk and is not just a marker of fruit and vegetable intake (9).

Although the degree of protection and the required dose of vitamin C are debatable, one clear finding of Osganian’s study is that vitamin C supplementation does not increase CHD risk. One recent study has suggested that combined treatment with vitamin C (1,000 mg/day) and vitamin E (800 IU/day) increases the risk of death and nonfatal myocardial infarction in postmenopausal women, although the only significant effect of supplementation was on deaths from all causes combined (12). This is most likely a chance finding, given the small number of subjects (n = 423) and the much smaller number of deaths during the 4.5 years of the study (16 in the active group vs. 6 in the placebo group). In contrast, the current study prospectively followed 85,118

Figure 1. Steady-state vitamin C plasma concentrations as a function of dose in women. Fifteen healthy nonsmoking women (ages 19 to 27 years, body mass index 22.3 ± 2.7 kg/m²) living in a hospital ward were depleted of vitamin C, and then repleted in succession with daily vitamin C doses of 30, 60, 100, 200, 400, 1,000, and 2,500 mg. Doses through 200 mg daily were received by 15 subjects, through 1,000 mg by 13 subjects, and through 2,500 mg by 10 subjects. Median vitamin C intakes from the diet in the lowest and highest quintile, as well as median vitamin C intakes in users and non-users of vitamin C supplements in the study by Osganian et al. (1) are also shown, with multivariate-adjusted relative risk (RR) for coronary heart disease. *Statistical significance (confidence interval 0.61 to 0.86). Adapted from ref. 4.
female nurses for 16 years with 1,356 incident cases of CHD (1).

What might be the mechanism by which vitamin C lowers CHD risk? In addition to acting as the first line of antioxidant defense in plasma (13) and effectively inhibiting low-density lipoprotein oxidation (14), and thus potentially atherosclerotic lesion formation (2), vitamin C has been shown to play a pivotal role in maintaining normal endothelial function. In particular, endothelial synthesis of nitric oxide (NO) is impaired in patients with CHD or coronary risk factors, and NO is known to cause vasodilation and inhibit platelet aggregation and thrombus formation, thus inhibiting clinical expression of CHD (15). A large number of clinical trials has demonstrated that vitamin C treatment, either orally or by intravenous infusion, increases NO bioactivity in patients with CHD or coronary risk factors, as measured by brachial or coronary artery vasodilation (2). The underlying mechanism by which vitamin C enhances endothelial NO synthase activity is by maintaining its essential cofactor, tetrahydrobiopterin, in the reduced, and thus active, form (16).

Is vitamin C ready for prime time in randomized, placebo-controlled clinical trials? Even though this latest study is encouraging, a number of questions remain unanswered. What is the effective dose? Does vitamin C itself protect? Which populations will benefit the most from vitamin C supplements? Is vitamin C effective in primary prevention only, as suggested by the current study, or will the data hold up in secondary prevention, especially if combined with standard drug therapy for CHD? The effects of vitamin C supplementation should be tested in populations that have low or deficient dietary vitamin C intakes in the lowest quantile, to make sure the subjects are not already saturated with vitamin C and to provide adequate statistical power for the study. A supplement of 500 mg/day seems reasonable to ensure that plasma and tissues in all subjects will become fully saturated. Plasma vitamin C levels, in vivo markers of oxidative stress, and possibly NO bioactivity need to be monitored before, during, and at the conclusion of the study, to identify those subjects that may benefit the most from antioxidant supplementation and to confirm that the treatment had the intended effects. Although results from such well-designed secondary prevention trials may be forthcoming, we may never know with certainty whether vitamin C supplementation is of benefit in the primary prevention of CHD, as such long-term trials may be prohibitively expensive and impractical. What we know with certainty, however, is that a healthy diet and lifestyle lowers the risk of CHD (17), and this is what we should advocate to CHD patients and healthy people alike. An additional multivitamin/multimineral supplement as a “health insurance” also is sensible advice (18), as may be a vitamin C supplement to help lower CHD risk.

REFERENCES