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5. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010;303(18):1815-1822.

COMMENT & RESPONSE

Changes in Coronary Artery Plaque With Testosterone Therapy

To the Editor Dr Budoff and colleagues demonstrated that testosterone therapy compared with placebo in elderly men for 1 year increased noncalcified plaque volume in coronary arteries as measured by computed tomographic angiography. An analysis of the individual components revealed that the increase was confined to the fibrous component of the plaque, which provides for plaque stability. Fatty and necrotic portions, characterized by low attenuation and indicative of a vulnerable plaque, as well as calcified plaque volume did not alter. Thus, testosterone therapy may have resulted in stabilization of coronary plaques. This finding is consistent with retrospective reports of decreased major adverse cardiovascular events after testosterone therapy. The placebo group had greater calcification and noncalcified plaque volume at baseline. The adjusted mean change in fibrous plaque volume in the testosterone group was numerically higher than the change in median volumes between the 2 groups. Were the results driven by large changes in a few men who drove the mean but not the median? It would be informative if the authors could provide the number of participants who had an increase or a decrease in plaque volume.

It cannot be assumed that an increase in plaque volume would always result in a limitation of the vascular lumen. Expansive vascular remodeling may maintain luminal volume. The data could be reanalyzed including plaque volume as a percentage of vessel volume because after therapy the median plaque volume in the testosterone group was still less than the baseline plaque volume in the placebo group.

A longer-term trial to evaluate cardiovascular events after testosterone therapy should be undertaken. A change in surrogate markers, including an increase in the volume of the atherosclerotic plaque, would not obviate the need for such a trial.

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In Reply We do not agree with Dr Dhindsa and colleagues that the increase in noncalcified plaque volume was confined to the fibrous component. Changes in that component did reach statistical significance, but changes in the other noncalcified plaque components were also greater in the testosterone group, although they did not reach statistical significance (P values of .11 and .14). Thus, the results for all 3 components were consistent.

Dhindsa and colleagues also ask whether results were driven by large changes in plaque volume in a few men in the testosterone group. This was not the case. The proportion of men in the testosterone group whose noncalcified plaque volume increased during the 1 year of the trial was 70%, compared with 54% of men in the placebo group, whereas the proportions showing a decrease in noncalcified plaque volume were 27% in the testosterone group and 45% in the placebo group. Only 2 men in the testosterone group had larger changes than the largest change in the placebo group, and those changes were not markedly larger.

Reanalysis of plaque volume as a percentage of vessel volume is an interesting idea but was not a prespecified analysis. We agree that a larger and longer-term trial to evaluate clinical cardiovascular events is needed.

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Temporal Changes in Subsequent Malignancies Among Childhood Cancer Survivors

To the Editor Dr Turcotte and colleagues1 found that cumulative incidence rates of subsequent malignancies at 15 years after initial childhood cancer diagnosis were lower among survivors treated in more recent treatment eras and that lower risk was associated with reduced therapeutic radiation dose.

Although the authors analyzed maximum radiation treatment dose to any body region as well as median dose for chemotherapy agents, it is not clear how many children treated with hematopoietic cell transplantation (HCT) were included. Before autologous or allogeneic HCT, a myeloablative conditioning regimen is commonly used with higher doses of chemotherapy and radiation, including total body irradiation, in a shorter period than conventional chemotherapy. Such a conditioning regimen could influence the incidence of subsequent malignancies in the study population.

Furthermore, in the case of allogeneic HCT, previous studies have shown that chronic graft-vs-host disease (GVHD) can be an independent risk factor for all solid cancers, especially cancers of the oral cavity and gastrointestinal tract.2,3 Chronic GVHD causes chronic inflammation, and treatment requires prolonged immunosuppression, which can reduce antitumor immunity and thus may increase the risk of secondary malignancies. It is estimated that the overall incidence of secondary malignancies is 3% to 4% at 10 years and 10% to 12% at 15 years after allogeneic HCT—rates much higher than those in the current study.4,5 Secondary malignancies can be categorized into posttransplant lymphoproliferative diseases, leukemia or myelodysplastic syndrome, and solid cancers, and the risk of solid cancers is considered not to plateau over time.

Could the authors provide further subgroup analyses of children treated with conventional chemotherapy alone, myeloablative autologous HCT, or allogeneic HCT?

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In Reply Dr Tanimoto and colleagues query whether treatment with HCT was considered in our analysis of temporal changes in subsequent neoplasms in the Childhood Cancer Survivor Study (CCSS). They raise the point that treatment modalities used in the context of HCT, such as the dose and intensity of chemotherapy, total body irradiation, or both, are unique and also point out the potential importance of chronic GVHD as a risk factor for subsequent neoplasms.