Title
Changes in Coronary Artery Plaque With Testosterone Therapy—Reply

Journal
JAMA, 317(23)

ISSN
0098-7484

Authors
Budoff, Matthew J
Ellenberg, Susan S
Snyder, Peter J

Publication Date
2017-06-20

DOI
10.1001/jama.2017.6024

Peer reviewed

Mary R. Rooney, MPH
Lisa Harnack, DrPH, RD
Erin D. Michos, MD, MHS
Rachel P. Ogilvie, MPH
Christopher T. Sempos, PhD
Pamela L. Lutsey, PhD, MPH

Author Affiliations: Division of Epidemiology and Community Health, University of Minnesota, Minneapolis (Rooney, Harnack, Ogilvie, Lutsey); Division of Cardiology, Johns Hopkins University, Baltimore, Maryland (Michos); Office of Dietary Supplements, National Institutes of Health, Bethesda, Maryland (Sempos).

Accepted for Publication: March 27, 2017.

Corresponding Author: Pamela L. Lutsey, PhD, MPH, 1300 S Second St, Ste 300, Minneapolis, MN 55454 (lutsey@umn.edu).

Author Contributions: Ms Rooney and Ms Ogilvie had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Rooney, Michos, Sempos, Lutsey.
Acquisition, analysis, or interpretation of data: Rooney, Harnack, Ogilvie, Sempos, Lutsey.
Drafting of the manuscript: Rooney, Lutsey.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Rooney, Harnack, Ogilvie, Sempos, Lutsey.
Obtained funding: Lutsey.
Administrative, technical, or material support: Lutsey.
Supervision: Ogilvie, Lutsey.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Michos reports receiving personal fees from Siemens Healthcare Diagnostics. No other disclosures were reported.

Funding/Support: This research was supported by grants R01 HL103706 and T32-HL-007779 from the National Institutes of Health National Heart, Lung, and Blood Institute and grant R01 HL103706-S1 from the Office of Dietary Supplements.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institutes of Health or the US Department of Health and Human Services.

1. Ross CR, Taylor CL, Yaktine AL, et al. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011.

2. Manson JE, Bassuk SS. Vitamin D research and clinical practice: at a crossroads. *JAMA*. 2015;313(13):1311-1312.

3. Ahluwalia N, Dwyer J, Terry A, Moshfegh A, Johnson C. Update on NHANES dietary data: focus on collection, release, analytical considerations, and uses to inform public policy. *Adv Nutr*. 2016;7(1):121-134.

4. Schleicher RL, Sternberg MR, Lacher DA, et al. The vitamin D status of the US population from 1988 to 2010 using standardized serum concentrations of 25-hydroxyvitamin D shows recent modest increases. *Am J Clin Nutr*. 2016;104 (2):454-461.

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.

6. Wallace RB, Wactawski-Wende J, O'Sullivan MJ, et al. Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. *Am J Clin Nutr*. 2011;94(1):270-277.

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.[1] An analysis of the individual components revealed that the increase was confined to the fibrous component of the plaque, which provides for plaque stability.[2] Fatty and necrotic portions, characterized by low attenuation and indicative of a vulnerable plaque,[2] 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.[3] The placebo group had greater calcified 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.[4] 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.

Sandeep Dhindsa, MBBS
Michael F. Wilson, MD
Paresh Dandona, MBBS, DPhil, FRCP

Author Affiliations: Division of Endocrinology and Metabolism, Saint Louis University, St Louis, Missouri (Dhindsa); Division of Endocrinology and Metabolism, State University of New York at Buffalo, Buffalo, (Wilson, Dandona).

Corresponding Author: Sandeep Dhindsa, MBBS, Division of Endocrinology and Metabolism, Saint Louis University, 1402 S Grand Blvd, Schwitalla Hall, Fourth Floor, Room M-412, St Louis, MO 63104 (dhindsa@slu.edu).

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Dhindsa reported receiving speaker's honoraria and research support from AbbVie. Dr Dandona reported receiving grants and personal fees from AbbVie, Novo Nordisk, GlaxoSmithKline, Merck, Novartis, and Takeda; personal fees from Eli Lilly and Co and Sanofi; and a grant from Solvay Pharmaceuticals. No other disclosures were reported.

1. Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. *JAMA*. 2017; 317(7):708-716.

2. Ahmadi A, Stone GW, Leipsic J, et al. Prognostic determinants of coronary atherosclerosis in stable ischemic heart disease: anatomy, physiology, or morphology? *Circ Res*. 2016;119(2):317-329.

3. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J*. 2015;36(40):2706-2715.

4. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987;316(22):1371-1375.

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.

Matthew J. Budoff, MD
Susan S. Ellenberg, PhD
Peter J. Snyder, MD

Author Affiliations: Los Angeles Biomedical Research Institute, Torrance, California (Budoff); Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia (Ellenberg); University of Pennsylvania, Philadelphia (Snyder).

Corresponding Author: Peter J. Snyder, MD, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104 (pjs@mail.med.upenn.edu).

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Budoff reported receiving grants from the National Institutes of Health and General Electric. Dr Ellenberg reported receiving grants from the National Institutes of Health and AbbVie. Dr Snyder reported being a consultant to Watson Laboratories.

Temporal Changes in Subsequent Malignancies Among Childhood Cancer Survivors

To the Editor Dr Turcotte and colleagues[1] 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?

Tetsuya Tanimoto, MD
Kenji Tsuda, MD
Jinichi Mori, MD, PhD

Author Affiliations: Jyoban Hospital of Tokiwa Foundation, Fukushima, Japan (Tanimoto, Mori); Teikyo University Chiba Medical Center, Chiba, Japan (Tsuda).

Corresponding Author: Tetsuya Tanimoto, MD, Jyoban Hospital of Tokiwa Foundation, 9728322 Fukushima, Japan (tetanimot@yahoo.co.jp).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Tsuda reported receiving grants to his institution from Yakult Honsha, Mitsubishi Tanabe Pharma, Chugai Pharmaceutical, Japan Blood Products Organization, Mochida Pharmaceutical, Sumitomo Dainippon Pharma, Ono Pharmaceutical, Kyowa Hakko Kirin, and Bristol-Myers Squibb; receiving payments for lectures from Janssen Pharmaceutical, Takeda Pharmaceutical, Celgene, and Pfizer; receiving payment for manuscript preparation from Pfizer, Kyowa Hakko Kirin, Celgene, Janssen Pharmaceutical, Astellas Pharma, Eisai, Bristol-Myers Squibb, Asahi Kasei Pharma, and Nippon Shinyaku; and holding stock in Takeda Pharmaceutical. No other disclosures are reported.

1. Turcotte LM, Liu Q, Yasui Y, et al. Temporal trends in treatment and subsequent neoplasm risk among 5-year survivors of childhood cancer, 1970-2015. *JAMA*. 2017;317(8):814-824.

2. Majhail NS, Brazauskas R, Rizzo JD, et al. Secondary solid cancers after allogeneic hematopoietic cell transplantation using busulfan-cyclophosphamide conditioning. *Blood*. 2011;117(1):316-322.

3. Tanaka Y, Kurosawa S, Tajima K, et al. Increased incidence of oral and gastrointestinal secondary cancer after allogeneic hematopoietic stem cell transplantation [published online February 13, 2017]. *Bone Marrow Transplant*. doi:10.1038/bmt.2017.4

4. Inamoto Y, Shah NN, Savani BN, et al. Secondary solid cancer screening following hematopoietic cell transplantation. *Bone Marrow Transplant*. 2015;50(8):1013-1023.

5. Clark CA, Savani M, Mohty M, Savani BN. What do we need to know about allogeneic hematopoietic stem cell transplant survivors? *Bone Marrow Transplant*. 2016;51(8):1025-1031.

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.