

Letter to the Editor

Letters to the Editor will be published, if suitable, as space permits. They should not exceed 1000 words (typed double-spaced) in length and may be subject to editing or abridgment.

Response by Glisic et al to Letter Regarding Article, “Associations of Endogenous Estradiol and Testosterone Levels With Plaque Composition and Risk of Stroke in Subjects With Carotid Atherosclerosis”

In Response:

We appreciate the comments by Drs Scarabin and Scarabin-Carre on our recent publication.¹ In this population-based study among postmenopausal women and elderly men, we identified sex differences in the association between estradiol, carotid plaque composition, and risk of stroke in men and women with carotid atherosclerosis. Our main findings indicate that circulating estradiol is associated with, both, presence of vulnerable carotid plaque and risk of stroke in postmenopausal women. Previously, we have, also, found that high levels of estradiol are associated with increased risk of type 2 diabetes mellitus in postmenopausal women and adverse cardiovascular profile, providing additional evidence on potential harmful effects of estradiol on cardiometabolic health in elderly women.^{2,3} In line with the findings from the Three City Cohort,⁴ our group has reported previously that estrogen receptors, especially estrogen receptor β , might play an important role in mediating estradiol effects in the female cardiovascular system.⁵ Therefore, it would be of interest for future studies to investigate the role that estrogen receptors have in mediating the effects of estradiol in elderly women and whether targeting only one of the estrogen receptors could be a better treatment approach than using untargeted hormone therapy in these women.

In our study, we found no consistent association between testosterone and plaque composition and risk of stroke in either sex. In the Three City Cohort, low plasma testosterone was related to elevated carotid intima-media thickness only in men with increased CRP (C-reactive protein),⁶ therefore, Scarabin-Carre and Scarabin argue that low-grade inflammation may interact with low serum testosterone in determining stroke risk in the men within our study population. Thus, they suggested a stratified analysis by inflammatory status to be performed within the Rotterdam Study.

In the sensitivity analysis in our article,¹ we adjusted for CRP as continuous variable, and results did not differ from the main estimates. In our study population, median CRP level was 1.5 mg/L (25th–75th quartile, 0.6–3.29 mg/L) in men. Now, we additionally tested the interaction term between testosterone and CRP in our population among men, and it was not significant. Also, in the stratified analysis by median CRP results did not differ from the overall findings from our study as previously described (Table). Because of small number of stroke cases (57 in women and 56 in men), we were limited to run the Cox regression

analysis using hormones as continuous variables only. Therefore, comparison of extreme low testosterone levels and normal testosterone levels in regard of the stroke risk would not be feasible within the Rotterdam Study in subjects with underlying carotid atherosclerosis. However, to investigate whether a nonlinear relationship was present in this population, we tested a quadratic term and used splines.⁷ No evidence of nonlinearity was found in either sex. Future studies with larger sample size and more stroke events might provide more insights on whether extreme testosterone levels are associated with risk of stroke and investigate if ageing, inflammation, and comorbidities (carotid atherosclerosis) may play a role in modifying this association.

Disclosures

None.

Marija Glisic
Oscar H. Franco
Taulant Muka
Department of Epidemiology
Erasmus Medical Center
Rotterdam
The Netherlands

References

1. Glisic M, Mujaj B, Rueda-Ochoa OL, Asllanaj E, Laven JSE, Kavousi M, Ikram MK, Vernooij MW, Ikram MA, Franco OH, Bos D, Muka T. Associations of endogenous estradiol and testosterone levels with plaque composition and risk of stroke in subjects with carotid atherosclerosis. *Circ Res*. 2018;122:97–105. doi: 10.1161/CIRCRESAHA.117.311681.
2. Jaspers L, Dhana K, Muka T, Meun C, Kieffe-de Jong JC, Hofman A, Laven JS, Franco OH, Kavousi M. Sex steroids, sex hormone-binding globulin and cardiovascular health in men and postmenopausal women: the Rotterdam study. *J Clin Endocrinol Metab*. 2016;101:2844–2852. doi: 10.1210/je.2016-1435.
3. Muka T, Nano J, Jaspers L, Meun C, Brammer WM, Hofman A, Dehghan A, Kavousi M, Laven JS, Franco OH. Associations of steroid sex hormones and sex hormone-binding globulin with the risk of type 2 diabetes in women: a population-based cohort study and meta-analysis. *Diabetes*. 2017;66:577–586. doi: 10.2337/db16-0473.
4. Scarabin-Carré V, Brailly-Tabard S, Ancelin ML, Maubaret C, Guiochon-Mantel A, Canonico M, Scarabin PY. Plasma estrogen levels, estrogen receptor gene variation, and ischemic arterial disease in postmenopausal women: the three-city prospective cohort study. *J Clin Endocrinol Metab*. 2014;99:E1539–E1546. doi: 10.1210/jc.2013-4472.
5. Muka T, Vargas KG, Jaspers L, et al. Estrogen receptor β actions in the female cardiovascular system: a systematic review of animal and human studies. *Maturitas*. 2016;86:28–43. doi: 10.1016/j.maturitas.2016.01.009.
6. Soisson V, Brailly-Tabard S, Empana JP, Féart C, Ryan J, Bertrand M, Guiochon-Mantel A, Scarabin PY. Low plasma testosterone and elevated carotid intima-media thickness: importance of low-grade inflammation in elderly men. *Atherosclerosis*. 2012;223:244–249. doi: 10.1016/j.atherosclerosis.2012.05.009.
7. Berry WD, Feldman, S. *Multiple Regression Analysis in Practice*. Sage University Papers Series on Quantitative Applications in the Social Sciences, series no. 07-050. Newbury Park, CA: Sage. 1985.

Table. Association Between Testosterone and Risk of Stroke by Inflammatory Status in Men With Carotid Atherosclerosis From the Rotterdam Study

Men (n=1124)†	HR (95% CI)*	P Value
Testosterone		
CRP ≤1.5 mg/L	0.97 (0.53–1.8)	0.93
CRP >1.5 mg/L	1.2 (0.72–2.02)	0.49

Model 2: Age, body mass index (BMI), sex hormone-binding globulin, total serum cholesterol (continuous), statin use (yes vs no), prevalent diabetes mellitus (yes vs no), systolic blood pressure (continuous), antihypertensive medication (yes vs no), prevalent cardiovascular disease before the date of hormone measurement, smoking status (yes vs no), and alcohol consumption (continuous). CRP indicates C-reactive protein. *Results are presented as hazard ratio (HR) and 95% confidence interval (CI 95%) per 1SD of testosterone increase. †Analysis is done in men diagnosed with carotid atherosclerosis using ultrasonography, and during the follow-up period, 56 stroke cases were identified.

Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Response by Glisic et al to Letter Regarding Article, "Associations of Endogenous Estradiol and Testosterone Levels With Plaque Composition and Risk of Stroke in Subjects With Carotid Atherosclerosis"

Marija Glisic, Oscar H. Franco and Taulant Muka

Circ Res. 2018;122:e69-e70

doi: 10.1161/CIRCRESAHA.118.312977

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2018 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circres.ahajournals.org/content/122/8/e69>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation Research* is online at:
<http://circres.ahajournals.org/subscriptions/>