Response to Letter Regarding Article “Plasma Bilirubin and UGT1A1*28 Are Not Protective Factors Against First-Time Myocardial Infarction in a Prospective Nested Case-Referent Setting”

Dr Kono remarks in his letter about our article in the August paper of Circulation: Cardiovascular Genetics that the model for risk association between bilirubin and myocardial infarction, including body mass index, systolic blood pressure, smoking, Apo B/Apo A1, UGT-genotypes, high sensitivity C-reactive protein, and albumin was not presented. The significant risk associations seen are no longer evident in this model (Table). Adjusting the model only for UGT-genotypes had almost no effect on the results.

The apparent protective effect of bilirubin, reported by earlier studies, is reproduced in our material on myocardial infarction and recently also for ischemic stroke. However, the main conclusion of both our prospective studies is that bilirubin was not a causative risk factor. This conclusion is based on the concept of mendelian randomization, as UGT-genotypes (resulting in elevated bilirubin levels throughout life) were not associated with risk. As Kronenberg points out, this is analogous to the conclusion that C-reactive protein is not a causative risk factor for ischemic vascular disease, as a risk association was found for C-reactive protein but not for the genotypes elevating C-reactive protein.

In an attempt to find the reason to lower bilirubin among cases, we included both univariate and multivariate associations between bilirubin and several variables in our data set to show the multitude of variables affecting bilirubin levels.

In his editorial, Kronenberg discussed the issue of excluded subjects in our study. In total, 45 cases were excluded due to previous myocardial infarction, stroke, or cancer. Some of these had multiple reasons for exclusion. It is unlikely that this has biased our results on 618 cases of myocardial infarction.

We agree that further prospective studies are needed on the issue on bilirubin, UGT1A1*28, and the risk of myocardial infarction. We also think efforts should be made to find other factors, acting both on risk for myocardial infarction and bilirubin levels.

Disclosures

None.

References


Table. Risk for Myocardial Infarction, Odds Ratios, and 95% Confidence Intervals for Bilirubin Quartiles

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P_trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full study group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>Ref 0.71 (0.53–0.95)</td>
<td>0.49 (0.35–0.68)</td>
<td>0.44 (0.31–0.63)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>Ref 0.77 (0.57–1.05)</td>
<td>0.49 (0.35–0.70)</td>
<td>0.42 (0.28–0.63)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Adjusted†</td>
<td>Ref 0.89 (0.60–1.32)</td>
<td>0.63 (0.39–1.01)</td>
<td>0.67 (0.40–1.14)</td>
<td>0.062</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for UGT-genotypes.
†Adjusted for body mass index, systolic blood pressure, smoking, Apo B/Apo A1, UGT-genotypes, high-sensitivity C-reactive protein, and albumin.
Response to Letter Regarding Article "Plasma Bilirubin and UGT1A1*28 Are Not Protective Factors Against First-Time Myocardial Infarction in a Prospective Nested Case-Referent Setting"

Kim Ekblom, Stefan L. Marklund, Jan-Håkan Jansson, Pia Osterman, Göran Hallmans, Lars Weinehall and Johan Hultdin

Circ Cardiovasc Genet. 2011;4:e2
doi: 10.1161/CIRCGENETICS.110.958603

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

http://circgenetics.ahajournals.org/content/4/1/e2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Genetics 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: Cardiovascular Genetics is online at:
http://circgenetics.ahajournals.org/subscriptions/