Author's response to reviews

Title: Impact of newly diagnosed abnormal glucose regulation on long-term prognosis in low risk patients with ST-elevation myocardial infarction: a follow-up study.

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Author's response to reviews: see over
Dear Emilie Aimé
MS: 1972093857529038

Please find enclosed the revised manuscript “Impact of newly diagnosed abnormal glucose regulation on long-term prognosis in low risk patients with ST-elevation myocardial infarction: a follow-up study”, which we resubmit for possible publication in BMC Endocrine Disorders.

First of all, we would like to thank the Editor for the opportunity to submit a revised manuscript and the Reviewers for helpful comments and suggestions. We have written a point-by-point reply to the Reviewers’ comments (see below) and the manuscript has been revised according to the reviewers’ suggestions.

All changes in the revised manuscript have been underlined.

We hope that the manuscript now will be deemed suitable for publication in BMC Endocrine Disorders. We are looking forward to hear from you.

On behalf of all authors,
Yours sincerely

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Reviewer: Mattie J Lenzen
Major concerns:

1. In the present study patients with a primary PCI treated ST-elevation myocardial infarction (STEMI) without previously known diabetes performed an oral glucose tolerance test (OGTT) in-hospital and at three-month follow-up. Only 54% of the patients remained in the same glucometabolic category after a repeated OGTT. These results are thoroughly discussed in a previous paper (Cardiovasc Diabetol 2009, 8:6, reference 10 revised paper). We have expanded the introduction section (page 3) in the revised manuscript with a brief discussion of these results and reference to the previous paper.

2. The following Table was published previously (reference 10, revised paper), showing that about 50% of our patient population changed glucometabolic category after a repeated OGTT. Due to small numbers, in the present paper we choose to studied the association between abnormal glucose regulation (sum of IFG, IGT and DM) classified acutely and at three-month, and clinical outcome.

<table>
<thead>
<tr>
<th></th>
<th>NGR (OGTT2)</th>
<th>IFG (OGTT2)</th>
<th>IGT (OGTT2)</th>
<th>DM (OGTT2)</th>
<th>Total (OGTT1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGR (OGTT1)</td>
<td>91</td>
<td>6</td>
<td>11</td>
<td>1</td>
<td>109</td>
</tr>
<tr>
<td>IFG (OGTT1)</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>IGT (OGTT1)</td>
<td>41</td>
<td>4</td>
<td>11</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>DM (OGTT1)</td>
<td>11</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Total (OGTT2)</td>
<td>151</td>
<td>11</td>
<td>29</td>
<td>10</td>
<td>201</td>
</tr>
</tbody>
</table>

Data are number of patients.
Observed reproducibility: 54%

3. The aims of the present study have been revised, emphasising that we were interested in:
1) The prognosis of the patient cohort independent of glucose status.
2) The impact of OGTT measurement and glucometabolic classification after STEMI on clinical outcome. A glucometabolic classification made very early compared to three-month follow-up, clearly identified different patient populations and may have different impact on prognosis. That is why we included two analyses; clinical outcome in a patient cohort defined according to the result of a very early OGTT measurement (in-hospital) and clinical outcome according to a classification performed during stable condition at follow-up. If clinical outcome had been evaluated according to the glucometabolic classification made at three-month only, we could had missed identification of patients at high-risk of early new cardiovascular events.
Minor concerns:

1. This was an observational study. The results of analyses of blood glucose, either fasting or during OGTT, were available for the treating physician at all time. Hyperglycaemia, if present, was treated at the physician’s decision. Under the Method section with the subheading “study population”, we have now given a more detailed explanation on how patients with a positive OGTT were followed and when glucose-lowering drugs were introduced if indicated (page 5, line 7-17).

2. We agree that the term “of whom” instead of “and” is more precise and we also agree that the use of percentage is somewhat confusing here. We have revised the manuscript (page 8, line 4-5, page 8, line 15-17) in order to clarify this issue. It is now stated “the prevalence of abnormal glucose regulation in-hospital was 47 % (n=105), of whom 24 patients (23 %), (or 11 % of the total population, n=224) were classified with newly detected type 2 diabetes” The prevalence of abnormal glucose regulation at three-month follow-up was 25 % (n=50), of whom 20 % (n=10) (or 5 % of the total population, n=201) were classified with newly detected type 2 diabetes.
Reviewer: Claudio Picariello
Major concerns:

1. We agree that the exclusion criteria (known diabetes, cardiogenic shock, heart failure, ongoing chest pain, severe renal failure and, persistent hyperglycaemia) have resulted in a selection bias with exclusion of patients with the most severe prognosis, and inclusion of a somewhat younger patient population. However, the patients population do not differ from a general STEMI population in Norway according to troponin T (TnT) values. According to data from our Registry of STEMI patients at Oslo University Hospital (not published data), mean TnT peak value was 5.48 ug/l vs. median 4.9 ug/l, in the present study corresponding to 5000 ng/l which is how the TnT values are presented today (in Norway, the TnT values were changed from ug/l to ng/l in 2009). We have, however, discussed the limitations of the study population more extensively (page 13, line 9-16,) in the revised manuscript.

2. The aims of the study published in 2009 were to elucidate the prevalence of abnormal glucose regulation three months after an acute STEMI in patients without previously known diabetes and to evaluate the reliability of a 75-g OGTT performed early after an acute STEMI to predict the presence of abnormal glucose regulation at three-month follow-up.

The aims of the present work are now clarified in the revised manuscript (Introduction) (page 4, line 2-6). The 2009 article concluded that an OGTT performed very early after a STEMI did not provide reliable information on long-term glucometabolic state (evaluated by a repeated test after three months) and should probably not be recommended. Instead, we concluded that the OGTT should be part of a post-infarction follow-up (during stable conditions) in order to identify patients with undiagnosed disease. However, present guidelines still recommend early testing before discharge in order to identify high-risk patients with a severe prognosis. Testing after three months may be too late. The 2009 article lacked information about possible impact of abnormal glucose regulation on new clinical event. The novelty of the present paper is that it provides such information and it indicate en excellent prognosis independent of glucose status.

3. This was an observational study. The results of analyses of blood glucose, either fasting or during OGTT, were available for the treating physician at all time. Hyperglycaemia, if present, was treated at the physician’s decision. Under the Methods section with the subheading “study population” (page 5, line 7-17), we have now given a more precise explanation on how patients with a positive OGTT were followed and when glucose-lowering drugs were introduced if indicated.

4. At page 12, line 20-23 in the revised manuscript we have included a brief discussion on management of hyperglycaemia in patients with acute MI. Recent literatures suggested by the Reviewer are referred to at page 10, line 15, page 12, line 9 and page 13, line13.
Minor concerns:

1. Table 1 has been changed. The revised Table 1 specify the two time-points “in-hospital” and “at three-month follow-up” inside the table.

2. The patients included in the study were hemodynamically stable and this has now been stated properly in the revised manuscript at page 4, line 13.

3. We followed the ESC guidelines on heart failure from 2008 and the respective reference is included in the revised manuscript on page 4, line 17.