Author's response to reviews

Title: Increased incidence of kidney diseases in general practice after a nationwide albuminuria self-test program

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Author's response to reviews: see over
July 27, 2011

Dear Sir / Madam,

Please find enclosed the revised manuscript ‘Increased incidence of kidney diseases in general practice after a nationwide albuminuria self-test program’. We would like to thank the reviewers for the valuable suggestions, which improved the quality of the manuscript. A point-by-point response to the concerns of the referees is added to this cover letter. All changes in the revised manuscript are marked in blue.

We hope that you will find the manuscript suitable for publication, and look forward to hearing from you.

Yours sincerely, also on behalf of the co-authors

Mark Nielen, PhD
Reviewer: Anteo Di Napoli

I am still perplexed about the choice of using Cox regression analysis. The authors have added a paragraph in Methods section where they stated the three reasons to prefer Cox regression analysis above logistic regression analyses:

1) In this study a dynamic population is used, including patients with incomplete follow-up. Cox regression makes it possible to include these patients, which not only results in a more precise estimate of the effect, but also prevents selection bias.

2) Cox regression makes it possible to compare the number of newly detected cases with the time of occurrence.

3) With Cox regression Hazard ratio’s are calculated, which can be interpreted as an Incidence Rate Ratio. This makes it possible to compare the output of the regression analyses with the incidence rate ratio’s calculated in the second analysis.

However, my questions are:

1) How did the authors define the time-to-event? Did they consider the whole study period (except for the patients with an incomplete follow-up) or the time to diagnosis? This issue is not clear for me.

2) How did they define the start point for survival time analysis? Did they define a start point for each patient (which one?) or did they assume for all the patients the date of 1 September 2005 (for the pre-period) and 1 November 2006 (for the post-period)? This issue is not clear for me.

3) Thus, if the authors did not use defined start, end and censoring points, how did they model the time-to-event? This issue is not clear for me.

My perplexities are supported by the observation that the results of incidence rates of kidney diseases/urinary complaints (table 2) are nearly identical to the results of Cox regression about the risk of being newly diagnosed (table 3). I suggest that the authors could better clarify these issues.

Although we still think that Cox regression analysis is the most accurate way to analyze these data, we have used logistic regression analyses instead of Cox regression analyses in the revised manuscript. We agree with the reviewer that Cox regression is not the most commonly used technique with these kind of data. As expected, based on the low incidence of kidney diseases and the low drop out rate in this study, there were only small differences between the two techniques (see table).

<table>
<thead>
<tr>
<th></th>
<th>Cox regression analyses</th>
<th>Logistic regression analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICPC U07: Urine symptoms / complaint</td>
<td>1.1 (1.0 - 1.2)</td>
<td>1.1 (1.0 - 1.3)</td>
</tr>
<tr>
<td>ICPC U14: Kidney symptoms / complaint</td>
<td>1.6 (1.3 - 1.9)</td>
<td>1.7 (1.4 - 2.0)</td>
</tr>
<tr>
<td>ICPC U27: Fears of urinary disease</td>
<td>1.0 (0.9 - 1.1)</td>
<td>1.0 (0.9 - 1.2)</td>
</tr>
<tr>
<td>ICPC U29: Urinary symptoms / complaint</td>
<td>1.1 (0.8 - 1.4)</td>
<td>1.2 (0.9 - 1.5)</td>
</tr>
<tr>
<td>ICPC U98: Abnormal urine test</td>
<td>2.8 (2.3 - 3.4)</td>
<td>3.0 (2.4 - 3.6)</td>
</tr>
<tr>
<td>ICPC U99: Urinary disease</td>
<td>2.0 (1.8 - 2.2)</td>
<td>2.1 (1.9 - 2.3)</td>
</tr>
</tbody>
</table>

Since the differences between the two techniques are very small, we have decided to prefer logistic regression analysis above Cox regression analysis. Logistic regression analysis is a more popular regression technique and is easy to understand for readers. The description of the technique is less complicated, which improves the quality of the methods section of the manuscript. In the revised manuscript, the methods section is rewritten and, where needed, the results are changed.

Following the comments of the reviewer about the results in table 2, we have recalculated the incidence rates and incidence rate ratios. The overall incidence rate ratios were not calculated correctly and, where needed, we have made corrections to table 2. However, this did not change the conclusions of the manuscript.
Reviewer: Susan Lynn Hogan

Overall the questions posed by the authors are well defined and this is a clearly written manuscript assessing the increased incidence of kidney disease diagnoses in general population practices after a nationwide self-test program for albuminuria in The Netherlands. The methods are much better described in response to reviewers’ comments. The data appear to be sound and are reported in a relevant and standard way. The addition of incidence rate ratios and their associated 95% confidence intervals per another reviewer’s suggestion has added significantly to the interpretability of the data. The rewording and additions where requested have also been carefully attended to, with one exception; the abstract does not appear to be revised to match the changes described and made in the manuscript.

Minor Essential Revision
The abstract needs to be updated. Specifically, the abstract needs to incorporate and emphasize the major results of the incidence rate ratios and 95% confidence intervals.

Following the reviewers comment, we have added 95% confidence intervals to the reported ORs in the abstract. We decided not to add the incidence rate ratios, because we prefer to report adjusted ORs above non-adjusted IRRs. Reporting both would not be informative given the slight influence of the confounders.