Author’s response to reviews

Title: Prophylactic anticoagulation in nephrotic syndrome prevents thromboembolic complications

Authors:

Sarah Kelddal (sarah.kelddal@midt.rm.dk)
Karen Nykjær (karen.marie.nykjaer@vest.rm.dk)
Jon Gregersen (jonwgregersen@gmail.com)
Henrik Birn (hb@biomed.au.dk)

Version: 1 Date: 08 Mar 2019

Author’s response to reviews:

Sarah Kelddal, MD

Department of Renal Medicine, Aarhus University Hospital
Palle Juul-Jensens Boulevard 35, Aarhus N, Denmark
sarah.kelddal@midt.rm.dk

March 7th, 2019

Dear Suceena Alexander and Mario Eduardo Alamilla

Attached please find the revised version of our manuscript entitled “Prophylactic anticoagulation in nephrotic syndrome prevents thromboembolic complications”, ID BNEP-D-19-00036, which we hope you will reconsider for publication in BMC Nephrology. We thank for the reviewers thoughtful comments, and the manuscript has been revised accordingly.
The following pages outline our point-to-point response to the reviewers comments. Additionally, every change in the manuscript is trackable in the resubmitted manuscript.

On behalf of the authors

Yours sincerely,

Sarah Kelddal

Responds to Suceena Alexander (Reviewer 1) comments to author:

Comment 1.
In the table for baseline characteristics, information on 24-hour urine protein and the underlying GN diagnoses in both the groups to be included.

• Unfortunately, 24-hour urine protein excretion was not reported in all patients since inclusion was based on urine protein secretion greater than 3.5 g/day or urinary albumin secretion greater than 2.2 g/day. Only the presence of one of these inclusion criteria was recorded. We believe that, given the presence of nephrotic syndrome, plasma albumin is the most significant risk factor for thromboembolic events.

• We have included information on the histopathological diagnosis in the text (Line 113-116).
Comment 2.

Please explain criteria used for treating patients with low versus high dose of LMWH. How were the patient monitored?

• Local guidelines recommend LMWH as initial treatment with dosing as by physician’s discretion and according to general recommendation for the use of these drugs in patients with kidney disease. It was not common clinical practice at the time of study to monitor the biochemical effects of LMWH. This information is now included in the manuscript (Line 85-87).

Comment 3.

What was the monitoring protocol while using oral- anticoagulation?

• Unfortunately, we do not have the results of all INR measurements.

Comment 4.

Why did 11 patients receive antiplatelet therapy and 4 received combined therapy?

• Aspirin was not used as PAC, but patients treated with aspirin prior to the diagnosis of NS continued the treatment when initiated on LMWH and/or warfarin. Aspirin was in general prescribed to prevent cardiovascular disease; however, the exact indication in these 11 patients was not recorded.
Comment 5.

Did Viborg Regional Hospital refrain from anti-coagulation for all NS irrespective of serum albumin?

- In general Viborg Regional Hospital was restrictive to prescribe PAC in patients with NS irrespective of plasma albumin levels. Two patients from Viborg Regional Hospital received anticoagulation treatment with plasma-albumin levels of 16 g/L and 23 g/L respectively (Line 124-126).

Comment 6.

Male patients were more in number in the group treated with anti-coagulation (tending to be significant). This could have resulted in greater risk reduction while using anti-coagulation and needs to be highlighted as one of the limitations.

- Thank you for pointing this out. This have now been included in the Discussion (Line 185-187).

Responds to Mario Eduardo Alamilla (Reviewer 2) comments to author:

Some observations:

- There is no decision-making algorithm for the use of prophylactic anticoagulation.
- Unfortunately, it can not be excluded that a percentage of patients could have presented a subclinical pulmonary thromboembolism.
- Due to the retrospective design, long-term follow-up of patients is not available.
- The number of events is very small, probably related to the small sample size.
• Thank you for your time in reviewing the manuscript and acknowledging our work. We appreciate your valuable comments. We do agree that the addressed observations are questionable but unfortunately the dataset do not permit the issues to be corrected.

- I suggest adding the dose of anti-platelets used.

• The antiplatelet treatment is Aspirin 75 mg daily and is now included in table 2 (Line 128)