Reviewer's report

Title: Unilateral cause of primary hyperaldosteronism is usual and adrenal vein sampling is mandatory in the diagnosis. Results from screening to histopathology in a Swedish population

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Reviewer: Teresa Maria Seccia

Reviewer's report:

This study was performed by Sigurjonsdottir and coll. with the aim of assessing the prevalence of PA in a Swedish population consisting of both selected and non selected hypertensive patients. Moreover, the Authors established the percent rate of unilateral forms of PA and, among them, of APA and IHA.

The study was focused on an interesting issue. Nevertheless, there is a number of methodological points that seriously weaken the weight of the study.

Major Compulsory Revisions

Identification of the cutoffs of ARR and S-aldosterone for PA. I appreciated the willingness of establishing local cutoff values, but the sample is too small to provide solid data. Moreover, ROC curves and Youden index should be shown.

Screening for PA. It was based on S-aldosterone and ARR measured in patients also assuming antihypertensive drugs that can interfere with the renin-angiotensin system, as shown in Table 1. The second measurements of S-aldosterone and ARR after withdrawal of interfering drugs were used to confirm PA.

1. The values obtained after appropriate pharmacological wash-out (which the Authors identified as follow-up visit), not the values obtained under unrestricted drug treatment, should be used for case detection of PA. Thus, the values obtained at follow-up visit should be shown in the Table.

2. It is not clear how long was the wash-out period before the follow-up visit. This is a crucial issue.

3. Use of S-aldosterone in conjunction with ARR should be discussed. Use of a 'formal' cutoff of S-aldosterone for case detection of PA is debated, as also reported in the 2008 Guidelines.

4. PRA values lower than 0.2 ng/ml/h are conventionally set to 0.2 to avoid inflation of ARR. Did the Authors adopt this strategy?

5. Was hypokalaemia corrected before measuring ARR?

AVS. A rapid determination of cortisol was done in RAV before catheterization of LAV. It is of utmost relevance mention the interval time elapsing from the collection of plasma in RAV and collection in LAV. Moreover, what method was
used for the rapid measurement of cortisol?

Histology. The boundary between adenoma and hyperplasia can be difficult to establish. A more detailed description of the criteria used for discriminating the two forms is needed. This is a crucial issue to understand why the Authors found a high percentage of unilateral hyperplasia.

Statistical analysis.
1. Two methods were used for PRA measurement. Comparison between methods needs Bland-Altman based approach.
2. How the correction factor was calculated?
3. Were aldosterone levels log transformed before being analysed?
4. It is not clear why a non parametric test was used also for variables with a normal distribution.

Cutoff value for s-aldosterone. The value 0.44 mmol/L is too high to be as cutoff. Please check aldosterone units throughout the text.

Identification of PA subtype. AVS was not performed in 2 of 20 PA patients with ‘negative’ CT. It is well known that very small APAs may be not detected with CT or RM. Hence, these two patients might have unilateral, not bilateral, form of PA.

Primary from secondary aims should be distinguished. Moreover, when describing aims, the object of the screening work-up, i.e. the local population of Sweden, should be specified.

Reference for cosyntropin dose and time of infusion should be added.

Please add a reference for the lateralization criteria and explain why you used these criteria. Could the high per cent rate of hyperplasia be related to the choice of these criteria or the criteria adopted for case detection?

Minor Essential Revisions
Some references were erroneously reported. E.g.: the paper quoted in ref 15 was published in JACC, not Hypertension.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

NO conflict of interest