

Peer Review File

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Reviewer A

There are a number of issues which the authors need to address before the commentary can be reconsidered, as follows:

1. The authors' comment is on Vignaud et al (7) which is mentioned four times in the paper - on lines 55/92/102/108. These form a very minor part of the text; which in fact is concerned with a range on issues not mentioned in what has been labeled a commentary.

Reply: Thank you for your comment. Considering it, we have discussed in more detail the results of the Vignaud et al study, and we have removed other parts of the text that were no related to the Vignaud study.

Changes in the text:

We have added the following parts to the commentary:

“We read with great interest the results of the Vignaud et al. study [1], which showed that preoperative workup was consistent with guidelines for only 40% of the patients with primary aldosteronism (PA). In addition, they found that complete biological success was not sufficiently assessed after surgery, and no differences in surgical outcomes were observed between patients operated based on the results of adrenal CT scanning or adrenal venous sampling (AVS).”

“However, there is a gap between clinical guidelines recommendations and current clinical practice. In this regard, as it has been reported by Vignaud et al. [1], only 31% of the patients with PA underwent AVS before surgery and preoperative AVS was “adequately” performed in just 40% of the cases [2,3]. These results are in agreement with the described in the SPAIN-ALDO study, where only 35% of the patients had an available AVS [7]. The criteria for using AVS is quite heterogeneous across centers. For example, in the Vignaud series [1], some centers hardly ever used the procedure, others limited AVS use to specific situations such as bilateral lesions on imaging, small lesions on imaging or large number of preoperative antihypertensive treatments, and others followed strictly the French recommendations. Nonetheless, in this study, there was no correlation between complete clinical successful and the completeness of preoperative workup. These results are in line with the described in the unique prospective randomized study published comparing CT-based and AVS-based management [8]. However, we have to take into account that SPARTACUS study has several limitations, including that they selected the most severe group of patients with PA; the four cases in whom AVS failed were included in the CT cohort; the difficulties in reconciling CT diagnoses between cooperating institutions and the study was not generated to evaluate secondary endpoints

(hypertension cure and biochemical cure) [8].”

“Thus, it is essential to standardize the way of publishing the outcomes (Table 1) [13], which implies hormonal determination once the patient has undergone surgery, as well as a minimum follow-up time. The Outcomes after adrenalectomy for unilateral primary aldosteronism (PASO criteria) are the most widely used (Table 1) [13]. Based on them, complete clinical success is defined by normal blood pressure without antihypertensive medication after surgery. At the last follow-up, it was achieved in 31% of patients in the series of Vignaud [1]. These results are in accordance with the reported in our Spanish registry, of 38% [14]. Nevertheless, it should be noted that even biochemical cure without hypertension cure is associated with an improvement in the cardiometabolic risk and a major increase in health-related quality of life (HRQoL) after surgery. In this way, it has been recently described that correction of hypokalemia and control of diastolic blood pressure are essential factors contributing to the improvement in the HRQoL in patients with PA [15].”

2. The English needs to be thoroughly revised by a native English speaker. Example are line 13 Corresponding author; line 34 as a consequence, not consecutively; line 39 In terms of, not in relation to - and what, not which; line 40 nor, not neither...and so on.

Reply: Thank you for your comment. Considering your comment, the text was reviewed by a native English speaker.

Changes in the text: we have marked in red the changes that we have included in the manuscript.

3. Lines 39-87 contain only one reference to Vignaud et al, which is a sorry account over the previous decade of patients being subjected to very outdated treatment, sadly in agreement with the following sentence.

Lines 92-95 corroborate the results of Vignaud et. al. with 16% of 'cured' patients in fact with continuing PA.

Reply: Thank you for your comment. Considering it, we have shorted this paragraph and we have extended the text that refers to Vignaud et al.

Changes in the text:

“In terms of the preoperative work-up, no consensus exist about which aldosterone to renin ratio should be used for PA screening, nor what confirmatory test is the most reliable to confirm autonomous aldosterone secretion [2,3]. Nevertheless, as Vignaud et al [1] highlighted, the most challenging diagnostic step is the subtyping of PA since computed tomography (CT) and magnetic resonance imaging (MRI) are considered unreliable procedures to differentiate between unilateral and bilateral PA, with a reported discordance between these techniques and AVS of 38% [6]. Thus, last guidelines recommend that when surgical treatment is desired by the patient, an experienced radiologist should use an AVS to make the distinction between unilateral and bilateral disease [3]. The exceptions proposed by the guidelines for performing

AVS are to suspect an adrenocortical carcinoma, cortisol cosecretion or an age <35 years old and clear unilateral adrenal nodule in CT/MRI [2,3]. However, there is a gap between clinical guidelines recommendations and current clinical practice. In this regard, as it has been reported by Vignaud et al. [1], only 31% of the patients with PA underwent AVS before surgery and preoperative AVS was “adequately” performed in just 40% of the cases [2,3]. These results are in agreement with the described in the SPAIN-ALDO study, where only 35% of the patients had an available AVS [7]. The criteria for using AVS is quite heterogeneous across centers. For example, in the Vignaud series [1], some centers hardly ever used the procedure, others limited AVS use to specific situations such as bilateral lesions on imaging, small lesions on imaging or large number of preoperative antihypertensive treatments, and others followed strictly the French recommendations. Nonetheless, in this study, there was no correlation between complete clinical successful and the completeness of preoperative workup. These results are in line with the described in the unique prospective randomized study published comparing CT-based and AVS-based management [8]. However, we have to take into account that SPARTACUS study has several limitations, including that they selected the most severe group of patients with PA; the four cases in whom AVS failed were included in the CT cohort; the difficulties in reconciling CT diagnoses between cooperating institutions and the study was not generated to evaluate secondary endpoints (hypertension cure and biochemical cure) [8].”

4, Reference 12 - Dekkers et al) is fatally flawed in a variety of ways and should never be quoted.

Reply: Thank you for your comment. Considering it, we have highlighted the potential limitations of the Dekkers study.

Changes in the text:

“For example, in the Vignaud series [1], some centers hardly ever used the procedure, others limited AVS use to specific situations such as bilateral lesions on imaging, small lesions on imaging or large number of preoperative antihypertensive treatments, and others followed strictly the French recommendations. Nonetheless, in this study, there was no correlation between complete clinical successful and the completeness of preoperative workup. These results are in line with the described in the unique prospective randomized study published comparing CT-based and AVS-based management [8]. However, we have to take into account that SPARTACUS study has several limitations, including that they selected the most severe group of patients with PA; the four cases in whom AVS failed were included in the CT cohort; the difficulties in reconciling CT diagnoses between cooperating institutions and the study was not generated to evaluate secondary endpoints (hypertension cure and biochemical cure) [8].”

Reviewer B

Araujo-Castro & García Sanz discuss the problems surrounding diagnosis and treatment of primary aldosteronism, in response to a recent French paper reporting low curation rates of hypertension after adrenalectomy for PA. There are still many uncertainties, which are mentioned in this short review, but the paper misses focus

Major

- There is an important distinction between cure of hypertension and cure of aldosteronism. The latter is associated with a major increase in QOL for example (see followup data from SPARTACUS), there is no mention at all of this.

This is also important regarding the french paper they are referring to, since the endocrine/biochemical cure is not mentioned there either.

Reply: Thank you for your comment. Considering it, we have included a paragraph about this aspect.

Changes in the text:

“The Outcomes after adrenalectomy for unilateral primary aldosteronism (PASO criteria) are the most widely used (Table 1) [13]. Based on them, complete clinical success is defined by normal blood pressure without antihypertensive medication after surgery. At the last follow-up, it was achieved in 31% of patients in the series of Vignaud [1]. These results are in accordance with the reported in our Spanish registry, of 38% [14]. Nevertheless, it should be noted that even biochemical cure without hypertension cure is associated with an improvement in the cardiometabolic risk and a major increase in health-related quality of life (HRQoL) after surgery. In this way, it has been recently described that correction of hypokalemia and control of diastolic blood pressure are essential factors contributing to the improvement in the HRQoL in patients with PA [15].”

- A lot of factors surrounding diagnostic difficulties are summed up, but they are not weighed against each other

Reply: Thank you for your comment. Considering it, and the comments of the other reviewers, we have shorted this paragraph and we have extended the discussion of the paragraph discussion the findings of the Vignaud T study.

- The partial biochemical success in the table seems a bit arbitrary to me

Reply: we have included the definition proposed by the PASO criteria: Reference: Williams TA, Lenders JWM, Mulatero P, Burrello J, Rottenkolber M, Adolf C, et al. Outcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort. *Lancet Diabetes Endocrinol* 2017;5:689–99. [https://doi.org/10.1016/S2213-8587\(17\)30135-3](https://doi.org/10.1016/S2213-8587(17)30135-3). Nevertheless, considering

your comment we have specified better this criterion in Table 1:

Change in the table 1: for the definition of partial biochemical success, we use the following definition:

1. Correction of hypokalemia (if present before surgery) and increased postoperative ARR

And at least one of the following (compared with presurgical):

2. Decreased $\geq 50\%$ in basal aldosterone levels

or

3. Abnormal but improved postoperative aldosterone during confirmatory testing

Minor:

- **Sentence 1: aldosteronism is technically not the most common cause of secondary arterial hypertension (I would say obesity is).**

Reply: thank you for your comment. Considering it we have changed a little this sentence

Change in the text:

“It is known that primary aldosteronism (PA) is the most frequent cause of endocrine arterial hypertension and it is associated with a higher cardiometabolic risk than primary hypertension”

- **No references are given for the statements on PET imaging (N59 and metomidate)**

Reply: we have included the reference to PET imaging: **Ren X, Cheng G, Wang Z. Advances in the molecular imaging of primary aldosteronism. Ann Nucl Med 2023;37:433–41. <https://doi.org/10.1007/S12149-023-01851-Y>.**

Reviewer C

I do agree on the conclusion (line 109 -117), however the “discussion” from line 59 needs rewriting. Your arguments should be presented in a more stringent way.

Reply: Thank you for your comment. Considering it, we have written the commentary, and we have removed from the text several parts not related to the results described in the Vignaud T et al study. All changes have been marked in red.

Change in the text: “In terms of the preoperative work-up, no consensus exist about which aldosterone to renin ratio should be used for PA screening, nor what confirmatory test is the most reliable to confirm autonomous aldosterone secretion [2,3]. Nevertheless, as Vignaud et al [1] highlighted, the most challenging diagnostic step is the subtyping of PA since computed tomography (CT) and magnetic resonance imaging (MRI) are considered unreliable procedures to differentiate between unilateral and bilateral PA, with a reported discordance between these techniques and AVS of 38% [6]. Thus, last guidelines recommend that when surgical treatment is desired by the patient, an experienced radiologist should use an AVS to make the distinction between unilateral and bilateral disease [3]. The exceptions proposed by the guidelines for performing AVS are to suspect an adrenocortical carcinoma, cortisol cosecretion or an age <35 years old and clear unilateral adrenal nodule in CT/MRI [2,3]. However, there is a gap between clinical guidelines recommendations and current clinical practice. In this regard, as it has been reported by Vignaud et al. [1], only 31% of the patients with PA underwent AVS before surgery and preoperative AVS was “adequately” performed in just 40% of the cases [2,3]. These results are in agreement with the described in the SPAIN-ALDO study, where only 35% of the patients had an available AVS [7]. The criteria for using AVS is quite heterogeneous across centers. For example, in the Vignaud series [1], some centers hardly ever used the procedure, others limited AVS use to specific situations such as bilateral lesions on imaging, small lesions on imaging or large number of preoperative antihypertensive treatments, and others followed strictly the French recommendations. Nonetheless, in this study, there was no correlation between complete clinical successful and the completeness of preoperative workup. These results are in line with the described in the unique prospective randomized study published comparing CT-based and AVS-based management [8]. However, we have to take into account that SPARTACUS study has several limitations, including that they selected the most severe group of patients with PA; the four cases in whom AVS failed were included in the CT cohort; the difficulties in reconciling CT diagnoses between cooperating institutions and the study was not generated to evaluate secondary endpoints (hypertension cure and biochemical cure) [8].”

Present one argument for each point 1), 2) 3) and make them understandable for the readers. For instance, line 64 -65: “4) should we routinely use a rapid cortisol assay or a C-arm CT.” It’s actually unclear to the readers what you want to tell us.

Reply: we have removed the last sentence and we have discussed the other 3 points.

Changes in the text:

“Other factors that may justify the existence of a heterogenous use of AVS is the lack of consensus about which is the best approach in the AVS: 1) some authors defend the use of adrenocorticotrophic hormone (ACTH) stimulation during AVS since its use results in a higher proportion of successful samples, while other authors found that its use may lead to an inversion of the lateralization index to the wrong side [9]; 2) adrenal venous samples might be obtained simultaneously or sequentially; but, although with simultaneous sampling thought to potentially avoid problems related with ACTH fluctuation, simultaneous sampling increased technical difficulty of the AVS; 3) discontinuing renin angiotensin-system-interfering medications is not always feasible, so some authors have proposed the possibility of continuing some of these medications such as mineralocorticoid receptors antagonist during the procedure as long as renin levels remained unsuppressed [10].”

In line 68 you present a p-value. In a commentary you don't do that.

The arguments and the references are there, however you have to work one the text.

Reply: we have modified the text following the reviewer's recommendations. P value has been deleted.