STUDY PROTOCOL

Adrenal surgery for bilateral primary aldosteronism

Study Leaders

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Title	**Adrenal surgery to treat bilateral primary aldosteronism.**
Target population	Patients with sporadic bilateral primary aldosteronism.
Study design	International multicenter retrospective cohort study.
Targets of clinical testing	**Primary objective:** Investigate the performance of unilateral and bilateral adrenal surgery to treat bilateral primary aldosteronism. **Secondary objectives:** Evaluate the histopathology associated with bilateral primary aldosteronism.
Number of patients	All patients diagnosed with bilateral primary aldosteronism treated by adrenal surgery.
Inclusion criteria	• Male and female adult patients with bilateral primary aldosteronism diagnosed by adrenal venous sampling according to local criteria • Follow-up data for assessment of clinical and biochemical success of surgery (minimum requirement: assessment of clinical success) • All subjects with informed consent in accordance with local guidelines.
Exclusion criteria	• Patients with missing follw-up data for clinical outcome assessment. • Patients with unavailable formalin-fixed paraffin-embedded resected adrenals.

1. Adrenal surgery to treat bilateral primary aldosteronism

1.2 Scientific context

Primary aldosteronism (PA) is the most frequent cause of endocrine hypertension in which aldosterone production is inappropriately high relative to suppressed plasma renin levels (1). PA is usually classified into unilateral or bilateral forms of the disease according to the hypersecretion of aldosterone from one or both adrenal glands. Unilateral disease is optimally treated by curative adrenalectomy whereas pharmacotherapy with mineralocorticoid receptor antagonists is recommended to treat patients with bilateral PA (1-3). However, mineralocorticoid receptor antagonists are poorly tolerated at higher doses and are associated with unpleasant adverse effects.

2. Objectives of the study

2.1 Primary objective

The central hypothesis of this study is that adrenal surgery can be beneficial for selected patients with bilateral aldosterone hypersecretion. This hypothesis will be addressed in a multicentre international cohort by assessment of the success of surgical treatment for patients with a presurgical diagnosis of bilateral PA (4).

2.2 Secondary objective

The medical management of patients with bilateral PA limits available knowledge of the underlying histopathology. Our secondary objective is to evaluate the histopathology of bilateral PA according to the international HISTALDO consensus criteria (5).

3. Data management

- Individual patient data will be collected within the prospective registries of each participating centre. De-identified data will be transferred to the study leaders (TA Williams, M Reincke).
- Postsurgical outcomes will be assessed by Jacopo Burrello (Turin) and Tracy Williams (Munich)
- Haematoxylin-eosin staining and CYP11B2 immunohistochemistry will be performed in Munich. For this, centres will send 5 x 5 μm sections of each paraffin block corresponding to each resected adrenal
- Histopathology will be evaluated by Hironobu Sasano (Sendai), Tracy Williams (Munich) and Yuto Yamazaki (Munich).
- Statistical analyses will be perfomed by Jacopo Burrello (Turin) and Siyuan Gong (Munich)
- The first draft of the manuscript will be written by Martin Reincke and Tracy Williams

4. References

1. Stowasser M, Gordon RD. Primary aldosteronism: changing definitions and new concepts of physiology and pathophysiology both Inside and outside the kidney. *Physiol Rev.* 2016;96(4):1327-84.

2. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF Jr. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(5):1889-916.

3. Mulatero P, Sechi LA, Williams TA, Lenders JWM, Reincke M, Satoh F, Januszewicz A, Naruse M, Doumas M, Veglio F, Wu VC, Widimsky J. Subtype diagnosis, treatment, complications and outcomes of primary aldosteronism and future direction of research: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. *J Hypertens*. 2020;38(10):1929-1936.

4. Williams TA, Lenders JWM, Mulatero P, Burrello J, Rottenkolber M, Adolf C, Satoh F, Amar L, Quinkler M, Deinum J, Beuschlein F, Kitamoto KK, Pham U, Morimoto R, Umakoshi H, Prejbisz A, Kocjan T, Naruse M, Stowasser M, Nishikawa T, Young WF Jr, Gomez-Sanchez CE, Funder JW, Reincke M; Primary Aldosteronism Surgery Outcome (PASO) investigators. 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(9):689-699.

5. Williams TA, Gomez-Sanchez CE, Rainey WE, Giordano TJ, Lam AK, Marker A, Mete O, Yamazaki Y, Zerbini MCN, Beuschlein F, Satoh F, Burrello J, Schneider H, Lenders JWM, Mulatero P, Castellano I, Knösel T, Papotti M, Saeger W, Sasano H, Reincke M. International histopathology consensus for unilateral primary aldosteronism. *J Clin Endocrinol Metab*. 2021;106(1):42-54.