Medical treatment of primary aldosteronism

Authors: Benjamin Lechner, MD[1]; Katharina Lechner, MD[2]; Daniel Heinrich, MD[1]; Christian Adolf, MD[1]; Finn Holler, MD[1]; Holger Schneider, MD[1]; Felix Beuschlein, MD[1,3], Martin Reincke, MD[1]*

Author affiliations

[1] Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Ludwig-Maximilian University of Munich, Munich, Germany

[2] Department of Prevention, Rehabilitation and Sports Medicine, Technical University of Munich, Munich, Germany

[3]Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, Universitätsspital Zürich, Zürich, Switzerland.

Corresponding author

* Prof. Dr. Martin Reincke

Medizinische Klinik und Poliklinik IV

Klinikum der Universität München

Ziemssenstr. 1, 80336 München, Germany

E-Mail: martin.reincke@med.uni-muenchen.de

Word count 2266 (without abstact, references, tables, figures)

Keywords: primary aldosteronism, spironolactone, eplerenone, renin, hypertension

Figures: 1 **Tables**: 1

Abstract

In patients with primary aldosteronism specific treatment provides prognostic benefit over optimal antihypertensive therapy and is therefore crucial to reduce mortality and morbidity in this subgroup of patients with hypertension. Prognostic relevance has been shown for adrenalectomy in unilateral disease, and for medical treatment with mineralocorticoid receptor antagonists in bilateral adrenal hyperplasia. Collectively, evidence points to the superiority of surgical treatment compared to medical treatment. The causal approach of removing the mineralocorticoid excess, as well as the often-accompanying glucocorticoid excess, might provide one biologically plausible explanation for the observation of slightly better outcomes with surgical therapy.

However, in patients living with primary aldosteronism, medical treatment is often insufficient for three major reasons. First and foremost, no marker of sufficient aldosterone blockade has yet been established and therefore adequate treatment of the aldosterone excess is often dismissed as a treatment goal. Second, side effects often limit patient compliance. Third, as recommendations differ from other indications like heart failure, drug dosing is often inadequate.

The aim of this review is first to provide an overview over medical treatment options, and second to review potential markers for treatment surveillance in patients with primary aldosteronism.

Introduction

Primary aldosteronism is the most common cause of surgically curable secondary hypertension. The estimated prevalence is 4-6% in patients living with hypertension in primary care, around 10% in specialized hypertensive clinics, and reaches 20% in patients with refractory hypertension (1). Primary aldosteronism is characterized by inappropriately high plasma aldosterone concentrations relative to suppressed plasma renin activity (2). A growing body of sound evidence suggests that the

aldosterone excess poses a significantly increased risk of cardiometabolic disease via activation of the mineralocorticoid receptor (1, 3). This provides biologic plausibility for the observation that several studies have shown higher morbidity rates in patients with primary aldosteronism compared to matched patients with essential hypertension (4-8).

Early specific medical or surgical treatment decreases the risk associated with primary aldosteronism and therefore has the potential to impact prognosis (9, 10).

Of note, recent data suggests that in patients with resistant hypertension, despite the exclusion of primary aldosteronism, spironolactone and amiloride are superior to other antihypertensive medication in lowering blood pressure (11). This has been explained by their potential to counteract the increased salt retention in resistant hypertension, which is likely due to mild inappropriate aldosterone secretion.

Types of primary aldosteronism and treatment options

Primary aldosteronism is classified into unilateral and bilateral forms of the disease. These conditions must be distinguished because of different treatment approaches (1). While in unilateral disease, surgical treatment via adrenalectomy is considered the gold standard, in bilateral disease, medical treatment with mineralocorticoid receptor antagonists is the therapy of choice (1).

Although there is controversy over whether adrenalectomy is superior to adequate medical treatment with regard to cardiovascular outcomes, lines of recent evidence from observational studies speak to the superiority of surgical treatment in unilateral disease (9, 12-16). For example, Rossi et al. showed a higher risk of atrial fibrillation in medically treated versus adrenalectomized PA patients (17) and in a study done by Strauch et al. arterial stiffness was reduced significantly by adrenalectomy but not after 1 year of spironolactone treatment (14). Moreover, a nationwide survey in Japan showed greater improvement of hypertension and hypokalemia in surgically treated PA

patients compared to medical treatment with spironolactone (13). In the prospective SPARTACUS trial, which compared adrenal vein sampling with CT scan to determine treatment in primary aldosteronism, blood pressure was similar in surgically versus medically treated patients. However, patients who underwent adrenalectomy needed less (non-MRA) antihypertensive medication after 6 and 12 months and showed higher quality of life compared to medically treated patients (18, 19). Of note, adrenalectomy results in clinical blood pressure remission in 17 to 62 % and in biochemical remission of aldosterone excess in 93 to 100 % (1, 15). Another layer of complexity is added by the emerging evidence that glucocorticoid co-secretion is very common in aldosterone producing adenomas as well as in bilateral hyperplasia (20, 21). This has been linked to the increased cardiovascular morbidity and mortality in primary aldosteronism, and could provide a biologically plausible explanation for the observation that adrenalectomy, which removes the glucocorticoid and aldosterone excess, has shown more favorable outcomes than medical treatment (9, 13, 14). Glucocorticoid co-secretion is associated with body mass index (BMI), insulin resistance (20), left ventricular hypertrophy (21) and impaired glucose tolerance (22).

Of note, surgical candidates with primary aldosteronism have a higher rate of persistent hypertension after adrenalectomy if preoperative plasma renin levels are not suppressed (23). This clinically unfavorable escape of renin from suppression by excess aldosterone has been explained by more severe renal damage and altered intra-glomerular hemodynamics leading to less favorable outcomes after treatment. Other factors that predict clinical success after adrenalectomy are known duration of hypertension, sex, antihypertensive medication dosage, body mass index, target organ damage, and size of the largest nodule as depicted by imaging (15).

Noteworthy, a recently published study by Hundemer et. al. sheds new light on the treatment with mineralocorticoid receptor antagonists (3). In this retrospective analysis the authors compared data of 602 medically treated patients with primary aldosteronism with 41853 essential hypertension patients. Data were sourced from the Brigham and Women's, the Massachusetts General and affiliate partner hospitals and included patients seen over a 25-year period (1991-2016). Patients

whose baseline laboratory data were inconsistent with the diagnosis of primary aldosteronism (defined as aldosterone-to-renin-ratio <555 pmol/l per µg/l per h or plasma renin activity ≥1 µg/l per h or negative confirmatory testing) as well as patients with primary aldosteronism who underwent adrenalectomy, had a previous cardiovascular event or were not treated with MR antagonists were excluded from the analysis. The groups were matched by decade of age at study entry. Mean age (58 years in the PA group, 57 years in the essential hypertension group) and BMI values (31.1 kg/m^2 in the PA group, 29.8 kg/m^2 in the essential hypertension) were quite high and the sex balance was fairly even (45% female in the PA group, 51% in the essential hypertension group).

The results show an almost doubled incidence of cardiovascular events in patients with primary aldosteronism compared to the essential hypertension group during a follow-up of 7 years for patients with PA and 8.8 years for those with essential hypertension. Of note, in a subgroup analysis of 201 primary aldosteronism patients in whom plasma renin was measured at least 1 month after starting MR antagonists, there was a strong correlation between plasma renin activity and cardiovascular outcomes: those 67 patients with unsuppressed plasma renin activity (≥1 µg/l per h) showed an identical risk profile as the essential hypertension group, whereas those 134 patients with suppressed plasma renin activity had a risk profile almost three times higher, despite the fact that mean blood pressure did not differ between the groups (3, 24). The authors thus concluded that plasma renin activity might be a predictor of cardiovascular outcomes and may serve as a potential marker for treatment response.

However, as John W. Funder pointed out in an accompanying editorial, there are several limitations that should provide caution against oversimplified inference (24). First, sodium plays a major role in renin regulation. With dietary sodium restriction, renin tends to rise whereas with sodium excess, renin is suppressed. This may be a confounder, because dietary sodium restriction has been linked to more favorable cardiovascular outcomes in PA (25), a parameter which was not available in the aforementioned study. Second, non-compliance, which leads to suppressed renin activity, is very common, particularly in men treated with spironolactone. Therefore, it may be hypothesized that

non-compliance was overrepresented in the suppressed renin activity group (24). Another reason for non-suppressed renin levels could be simply a sloppy diagnosis of primary aldosteronism. It is worth mentioning that the aldosterone to renin ratio as a screening test is notoriously imprecise (26). The diagnostic criteria for primary aldosteronism used in this study were rather loose (3, 24), since confirmatory testing was only performed in 72%, and adrenal vein sampling in only 55%. In such a scenario, non-suppressed renin levels could also indicate presence of essential hypertension, which would explain the better cardiovascular long-term outcome.

Advantages and disadvantages of different drugs

Medical treatment options for PA are very limited. Treatment of choice are mineralocorticoid receptor antagonists, the most commonly used agents being spironolactone and eplerenone. In case of contraindications against MRA-therapy, potassium sparing diuretics like amiloride or triamteren are recommended, which are less effective (1, 27).

In many countries including Germany, only spironolactone, a non-selective MR-antagonist which has been clinically applied since the early 1960s, has been approved for the therapy of primary aldosteronism (28). Upon administration spironolactone is rapidly dethioacetylated to its principal pharmacologically active metabolite canrenone. Recent data suggests that spironolactone as well as canrenone undergo further metabolization by adrenal enzymes (CYP11B1 and CYP11B2) into hydroxylation products with different pharmacological properties (28). Due to the extended metabolization the half-life of spironolactone is quite long (24-58 hours). Therefore, a one-time per day or even every other day administration has proven to be efficacious. An important downside to be considered with spironolactone is its anti-androgenic action due to its affinity to the androgen receptor. This causes a variety of dose-dependent adverse effects, especially in men which include painful gynecomastia and erectile dysfunction. This might be one of the explanations for the commonly observed non-compliance (29). In the SPARTACUS trial the authors observed a high rate of

antiandrogenic adverse events in both sexes: Gynecomastia, mastopathy, menstrual disturbances, erectile dysfunction, and decreased libido were present in 1% in the adrenalectomy group, but in 57% of the spironolactone group. In consequence, 34% of patients were switched to eplerenone.

The more selective MR-antagonist eplerenone, which at the right dose, has been proven to be equally efficacious as spironolactone, is not yet approved for the treatment of PA in many countries including Germany. However, its common use in heart failure makes it easily available and off-label-use is common. The advantage of eplerenone over spironolactone is its relative selectiveness on the mineralocorticoid receptor, with no adverse anti-androgenic effects (29). In this context, eplerenone is a viable option to consider in patients with anti-androgenic complications under spironolactone treatment. In contrast to spironolactone, eplerenone is not converted into active metabolites (28). Therefore, eplerenone has a significantly shorter half-life of only 3-4 hours. This requires a twice daily administration (29). Moreover, this pharmacological agent is hepatically eliminated by CYP3A4, and therefore prone to interact with other pharmacological, and non-pharmacological agents. In clinical practice, eplerenone is administered at higher doses than spironolactone, since it has been shown to be inferior in lowering blood pressure in primary aldosteronism in a randomized head to head comparison (30) (see Table 1).

Drug titration in medically treated PA patients

Optimal medical therapy is crucial to prevent the complications of PA. As there is not a “one size fits all” therapy regimen in PA, individualized treatment is key for optimal patient benefit. In addition to normotensive blood pressure, causally targeting the aldosterone excess by pharmacological MR receptor blockade constitutes an important treatment goal and conveys prognostic superiority over optimal blood pressure control in PA (1).

For optimal disease control, regular follow up visits, including blood pressure monitoring and surveillance of serum potassium levels are of utmost importance (see flow chart 1). MR antagonists

should be administered at a low starting dose (e.g. 25 mg spironolactone per day) with a slow uptitration according to blood pressure. In our outpatient clinic, we re-evaluate the patients after 4 weeks to amend the spironolactone dose. Although hyperkalemia rarely limits up-titration because of the underlying hyperaldosteronism favoring hypokalemia, serum potassium levels should be monitored frequently in the beginning. It is our experience that 50 mg per day of spironolactone are often sufficient. Higher doses are not well tolerated, particularly in males because of the anti-androgenic actions leading to painful gynecomastia, erectile dysfunction and loss of libido. In females, spironolactone can be used in higher doses, but doses above 100 mg often induce menstrual irregularities. If blood pressure control is suboptimal despite maximum tolerated MRA dose, further antihypertensive drugs should be added (1).

Plasma renin activity might constitute an additional marker to evaluate successful aldosterone blockade (3). In case of persistent renin suppression, increasing the MRA dose might be considered, provided that there are no contraindications (e.g. antiandrogen side effects, elevated serum potassium levels or hypotension). Another alternative, or adjunct, might be dietary sodium restriction (24). In our experience, primary aldosteronism patients tend to spontaneously consume a very high salt diet often exceeding 10 g per day, potentially because of a shift in the sensory salt perception (Adolf et al., manuscript under review).

In case of poor blood pressure control, low serum potassium and suppressed renin activity despite high doses of MRA medication, non-compliance must be considered (1).

If eplerenone is used for PA treatment, an important consideration is the significantly shorter half-life compared to spironolactone. For an adequate aldosterone antagonism administration at least twice daily is necessary. In case of an insufficient response, a three times per day administration should be considered. In general, eplerenone must be dosed twice as high as spironolactone for therapeutic equivalence (29).

Conclusion

Early diagnosis, and specific treatment, have prognostic relevance in primary aldosteronism. In unilateral disease, the standard of care remains surgical treatment via adrenalectomy. This causally addresses aldosterone excess, as well as potentially accompanying hypercortisolemia.

In bilateral disease, medical treatment with MR-antagonists is the gold standard. Slow drug titration under regular supervision improves adherence, and disease control. Primary markers of adequate treatment are potassium levels in the upper normal range and optimal blood pressure control. Plasma renin activity has been suggested as an adjunct marker that might provide additional information. In case of persistently suppressed plasma renin activity, adjustment of the MRA therapy should be considered, provided the absence of contraindications. It is important to not draw precipitous conclusions from the Hundemer et al. study. More data from larger populations is needed to confirm these results, especially in the context of salt consumption and compliance.

Declaration of conflicting interests

The authors declare that they have no conflict of interest to disclose with respect to this manuscript.

Funding:

This work was supported by the Else Kröner-Fresenius Stiftung in support of the German Conns Registry-Else-Kröner Hyperaldosteronism Registry (2013_A182 and 2015_A171 to MR), the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No [694913] to MR), by the Deutsche Forschungsgemeinschaft (DFG)

(within the CRC/Transregio 205/1 “The Adrenal: Central Relay in Health and Disease” to AR, FB and MR).

Author contribution:

All authors contributed to the review. Benjamin Lechner did the literature search and drafted the manuscript. Martin Reincke and the other authors reviewed and edited the manuscript. All authors approved the final version of the manuscript.

References:

1. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism. 2016;101(5):1889-916.
2. Conn JW. Plasma renin activity in primary aldosteronism: Importance in differential diagnosis and in research of essential hypertension. JAMA. 1964;190(3):222-5.
3. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: a retrospective cohort study. The lancet Diabetes & endocrinology. 2018;6(1):51-9.
4. Mulatero P, Monticone S, Bertello C, Viola A, Tizzani D, Iannaccone A, et al. Long-term cardio- and cerebrovascular events in patients with primary aldosteronism. The Journal of clinical endocrinology and metabolism. 2013;98(12):4826-33.
5. Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. Archives of internal medicine. 2008;168(1):80-5.
6. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. Journal of the American College of Cardiology. 2005;45(8):1243-8.
7. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. The lancet Diabetes & endocrinology. 2018;6(1):41-50.
8. Williams TA, Reincke M. MANAGEMENT OF ENDOCRINE DISEASE: Diagnosis and management of primary aldosteronism: the Endocrine Society guideline 2016 revisited. European journal of endocrinology. 2018;179(1):R19-r29.
9. Catena C, Colussi G, Lapenna R, Nadalini E, Chiuch A, Gianfagna P, et al. Long-term cardiac effects of adrenalectomy or mineralocorticoid antagonists in patients with primary aldosteronism. Hypertension (Dallas, Tex : 1979). 2007;50(5):911-8.

10. Catena C, Colussi G, Di Fabio A, Valeri M, Marzano L, Uzzau A, et al. Mineralocorticoid antagonists treatment versus surgery in primary aldosteronism. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2010;42(6):440-5.
11. Williams B, MacDonald TM, Morant SV, Webb DJ, Sever P, McInnes GT, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. The lancet Diabetes & endocrinology. 2018;6(6):464-75.
12. Rossi GP, Bolognesi M, Rizzoni D, Seccia TM, Piva A, Porteri E, et al. Vascular remodeling and duration of hypertension predict outcome of adrenalectomy in primary aldosteronism patients. Hypertension (Dallas, Tex : 1979). 2008;51(5):1366-71.
13. Miyake Y, Tanaka K, Nishikawa T, Naruse M, Takayanagi R, Sasano H, et al. Prognosis of primary aldosteronism in Japan: results from a nationwide epidemiological study. Endocrine journal. 2014;61(1):35-40.
14. Strauch B, Petrak O, Zelinka T, Wichterle D, Holaj R, Kasalicky M, et al. Adrenalectomy improves arterial stiffness in primary aldosteronism. American journal of hypertension. 2008;21(10):1086-92.
15. 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. The lancet Diabetes & endocrinology. 2017;5(9):689-99.
16. Calhoun DA. Medical Versus Surgical Treatment of Primary Aldosteronism. Hypertension (Dallas, Tex : 1979). 2018;71(4):566-8.
17. Rossi GP, Maiolino G, Flego A, Belfiore A, Bernini G, Fabris B, et al. Adrenalectomy Lowers Incident Atrial Fibrillation in Primary Aldosteronism Patients at Long Term. Hypertension (Dallas, Tex : 1979). 2018;71(4):585-91.
18. Reincke M. Anxiety, Depression, and Impaired Quality of Life in Primary Aldosteronism: Why We Shouldn't Ignore It! The Journal of clinical endocrinology and metabolism. 2018;103(1):1-4.
19. Velema M, Dekkers T, Hermus A, Timmers H, Lenders J, Groenewoud H, et al. Quality of Life in Primary Aldosteronism: A Comparative Effectiveness Study of Adrenalectomy and Medical Treatment. The Journal of clinical endocrinology and metabolism. 2018;103(1):16-24.
20. Arlt W, Lang K, Sitch AJ, Dietz AS, Rhayem Y, Bancos I, et al. Steroid metabolome analysis reveals prevalent glucocorticoid excess in primary aldosteronism. JCI insight. 2017;2(8).
21. Adolf C, Kohler A, Franke A, Lang K, Riester A, Low A, et al. Cortisol Excess in Patients With Primary Aldosteronism Impacts Left Ventricular Hypertrophy. The Journal of clinical endocrinology and metabolism. 2018;103(12):4543-52.
22. Gerards J, Heinrich DA, Adolf C, Meisinger C, Rathmann W, Sturm L, et al. Impaired Glucose Metabolism in Primary Aldosteronism is Associated With Cortisol Co-Secretion. The Journal of clinical endocrinology and metabolism. 2019.
23. Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, et al. Relationships of plasma renin levels with renal function in patients with primary aldosteronism. Clinical journal of the American Society of Nephrology : CJASN. 2007;2(4):722-31.
24. Funder JW. Primary aldosteronism and cardiovascular risk, before and after treatment. The lancet Diabetes & endocrinology. 2018;6(1):5-7.
25. Funder JW. Primary aldosteronism and salt. Pflugers Archiv : European journal of physiology. 2015;467(3):587-94.
26. Tanabe A, Naruse M, Takagi S, Tsuchiya K, Imaki T, Takano K. Variability in the renin/aldosterone profile under random and standardized sampling conditions in primary aldosteronism. The Journal of clinical endocrinology and metabolism. 2003;88(6):2489-94.
27. Lim PO, Young WF, MacDonald TM. A review of the medical treatment of primary aldosteronism. Journal of hypertension. 2001;19(3):353-61.
28. Schiffer L, Muller AR, Hobler A, Brixius-Anderko S, Zapp J, Hannemann F, et al. Biotransformation of the mineralocorticoid receptor antagonists spironolactone and canrenone by human CYP11B1 and CYP11B2: Characterization of the products and their influence on

mineralocorticoid receptor transactivation. The Journal of steroid biochemistry and molecular biology. 2016;163:68-76.
29. Colussi G, Catena C, Sechi LA. Spironolactone, eplerenone and the new aldosterone blockers in endocrine and primary hypertension. Journal of hypertension. 2013;31(1):3-15.
30. Parthasarathy HK, Menard J, White WB, Young WF, Jr., Williams GH, Williams B, et al. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. Journal of hypertension. 2011;29(5):980-90.

336

337 **Table 1:** Comparison of the pharmacological profiles of MR antagonists.

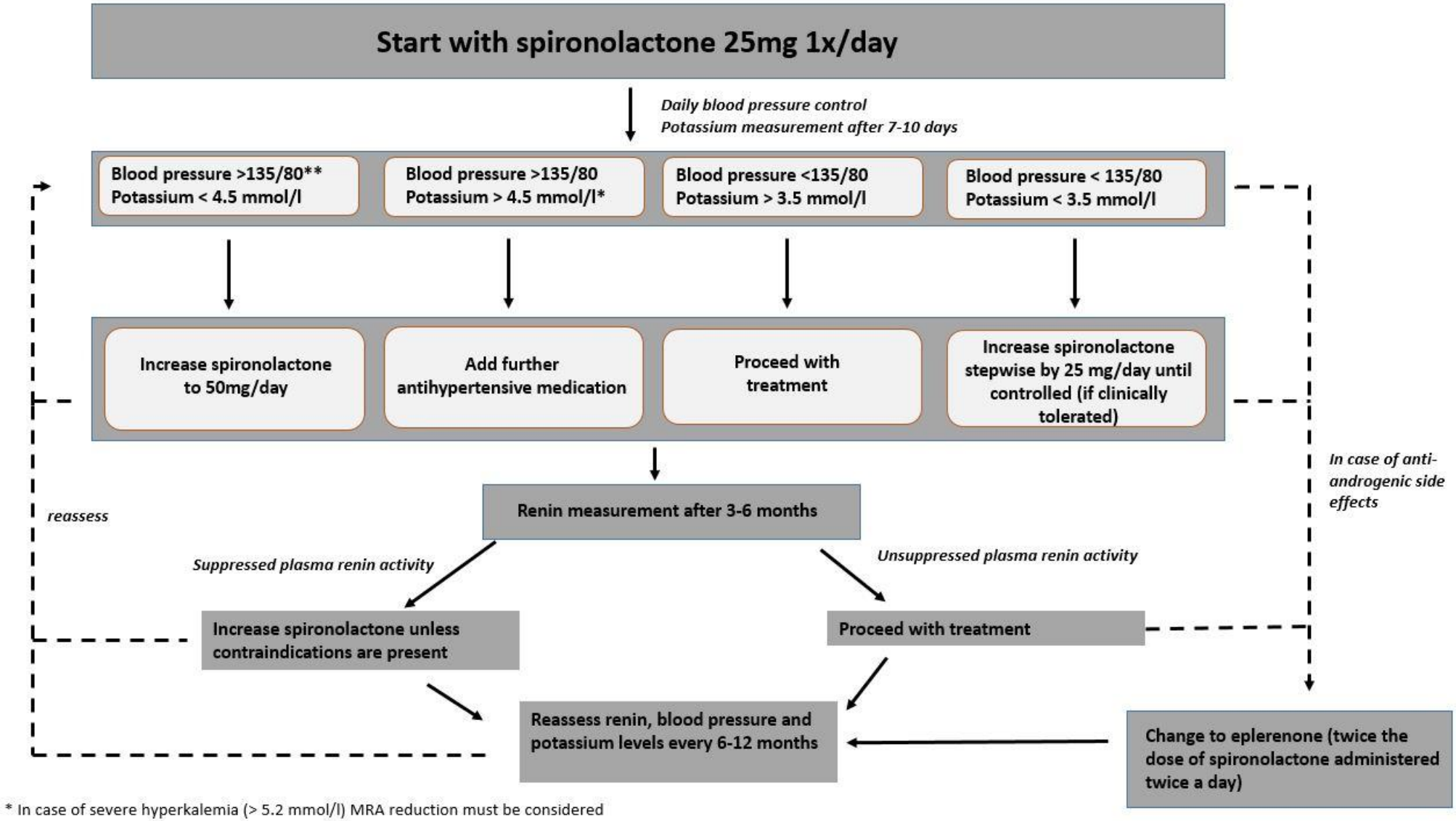
338 *Status is country-dependent

	spironolactone	**eplerenone**
Approved for PA treatment	yes	No*
Half-life (h)	24-58	3-4
Active metabolites	yes	no
Hepatic elimination (drug interaction)	no	yes
Administration	1x/d	2-3x/d
Starting Dose	25mg – 0 – 0	25mg – 0 – 25mg
Anti-androgenic side effects	yes (painful gynecomastia, erectile dysfunction, loss of libido, menstrual irregularities)	no

339

340

Flow chart 1: MRA dose titration



* In case of severe hyperkalemia (> 5.2 mmol/l) MRA reduction must be considered

** According to the 2018 ESC/ESH Guidelines for the management of arterial hypertension