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*

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Primary aldosteronism is a frequent cause of secondary hypertension requiring a specific pharmacological treatment with mineralocorticoid receptor antagonist or with unilateral adrenalectomy. These treatments have shown to reduce the excess of cardiovascular risk characteristically associated with this disease. In part I of this consensus, we discussed the procedures for the diagnosis of primary aldosteronism. In the present part II, we address the strategies for the differential diagnosis of primary aldosteronism subtypes and therapy. We also discuss the evaluation of outcomes and provide suggestions for follow-up as well as cardiovascular and metabolic complications specifically associated with primary aldosteronism. Finally, we analyse the principal gaps of knowledge and future challenges for research in this field.

Keywords: adrenal vein sampling, adrenalectomy, aldosterone, primary aldosteronism

Abbreviations: ACTH, adrenocorticotropic hormone; APA, aldosterone-producing adenoma; APCC, aldosterone-producing cell cluster; ARR, aldosterone-to-renin ratio; AVS, adrenal vein sampling; CLR, contralateral ratio; CT, computed tomography; LI, lateralisation index; MR, magnetic resonance; MRAs, mineralocorticoid receptor antagonists; RAAS, renin—angiotensin–aldosterone system; SI, selectivity index

INTRODUCTION

In part I of this consensus, we presented the genetic factors contributing to the pathogenesis of sporadic and familial forms of primary aldosteronism, we discussed the relatively high prevalence of primary aldosteronism in patients with hypertension and described the optimal strategies currently available for the diagnosis of primary aldosteronism, including screening and confirmation.

In this second part of the consensus, we discuss the most appropriate strategies for subtype differentiation, up-to-date therapies for primary aldosteronism, describe the most common cardiovascular and metabolic complications associated with primary aldosteronism and the assessment of treatment outcomes (medical and surgical). We also provide an overview of future challenges and directions of research in this field.

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At the end of each section, a statement summarizes the most important messages. An asterisk indicates the statements that require special attention from general practitioners and other nonspecialists.

Following confirmation of a diagnosis of primary aldosteronism, it is fundamental to distinguish between the main subtypes for therapeutic management, which is surgery for unilateral forms (mainly because of an aldosterone-producing adenoma, APA) or medical therapy for bilateral forms. The diagnostic flow-chart for primary aldosteronism diagnosis and subtype differentiation is provided in part I of this consensus.

SUBTYPE DIAGNOSIS

Adrenal imaging

Computed tomography (CT) scanning of the adrenal glands with contrast is considered the preferred imaging technique over MRI because of the lower spatial resolution obtained with magnetic resonance. Imaging techniques display unacceptable sensitivity for the detection of micro-APAs (less than 10 mm diameter) and low specificity for the distinction of APAs from nonsecretory adrenal adenomas as functional information is not provided [1]. CT scanning is also useful to exclude the presence of an extremely rare aldosterone-producing carcinoma (that should always be considered) and to provide information for the interventional radiologist on the location and anatomy of the adrenal veins [2,3].

The optimal approach to distinguish unilateral from bilateral primary aldosteronism is by adrenal vein sampling (AVS) performed by an expert radiologist (in some units, AVS is performed by an interventional endocrinologist or cardiologist, or a specialist in angiology) [1,4,5]. In a systematic review evaluating 950 patients from 38 studies, imaging techniques (either CT or MR) resulted in an incorrect diagnosis compared with AVS in 38% of cases (with 15% of patients classified as unilateral instead of bilateral and potentially incorrectly adrenalectomized; 19% of patients incorrectly classified as bilateral thereby missing the chance of a definitive surgical cure and 4% of cases with adrenalectomy performed on the wrong side) [6].

A recent prospective study, set out to challenge the superiority of AVS and reported similar blood pressure outcomes in patients randomized to surgery on the basis of CT scanning or AVS results [7]. This study has been criticized for reasons of an inferior primary endpoint (improvement in blood pressure control instead of biochemical cure) and insufficient statistical power, such that the results should be interpreted with caution [5,8]. A subsequent retrospective study reported a six-time higher level of absent biochemical success, that is persistence of primary aldosteronism, in patients adrenalectomized on the basis of CT scanning than patients with AVS-based surgical management [9]. Furthermore, in the CT but not in the AVS group, an increased ARR was associated with absent clinical success after surgery [9]. Therefore, in agreement with available guidelines [1,10,11], unilateral primary aldosteronism should be diagnosed by AVS in all patients with primary aldosteronism who are potential candidates for adrenal surgery. The only exception to this recommendation could be for patients with primary aldosteronism younger than 35 years, with plasma aldosterone levels greater than 30 ng/dl, spontaneous hypokalemia and a CT scan showing a unilateral adenoma (>10 mm) with a normal appearing contralateral adrenal [1,5,9,11,12]. AVS should always be avoided in patients carrying germline mutations responsible for familial hyperaldosteronism as familial forms of the disease are bilateral. Selection of candidates for AVS may be available in the near future by measurements of 18 steroids or steroid profiling to identify patients likely to have an APA [13–16]. The use of PET-tracers to visualize APAs, such as ^{11}C-metomidate, ^{68}Ga-pentixafor and ^{18}F-CDP2230 [17–19], display inferior accuracy to AVS and are unsuitable for use in routine clinical practice.

Statement: CT scanning with contrast is the preferred method for adrenal imaging but as functional information is not provided, adrenal vein sampling is the only reliable method to select patients for surgery.*

Adrenal vein sampling procedure

The preparation of patients for AVS is well established and described elsewhere [4]. It should be emphasized that drugs activating the RAAS (particularly diuretics) should be avoided in the 4 weeks before AVS, as for the rest of the diagnostic work-up. Via fluoroscopy guidance, the left adrenal vein that drains into the left renal vein is cannulated successfully in most patients. The cannulation of the right adrenal vein is more challenging as it is shorter and narrower, and drains directly into the inferior vena cava [2]. AVS should be performed by an experienced and dedicated radiologist to increase the rate of successful procedures and to minimize complications [1,4,5,20]. Whenever performed by an expert, AVS has a low incidence of major complications [21,22], such as adrenal haemorrhage, that in most cases, despite the requirement of hospitalization for pain control, has no long-term detrimental effect on adrenal function [21].

AVS is performed by bilateral or sequential cannulation, under basal conditions or after cosyntropin stimulation. The theoretical advantage of simultaneous cannulation during unstimulated procedures, is to avoid confounding steroid measurements with oscillations of adrenal steroids potentially caused by a delay between successive cannulations of both adrenal veins (Supplemental Table 1, http://links.lww.com/HJH/B374). Simultaneous cannulation is more challenging and invasive and lateralization indices are not different for simultaneous bilateral and sequential AVS if between-cannulation time is no longer than 5 min [23]. This should be achievable with cannulation of the right adrenal vein first, allowing for the much easier cannulation of the left adrenal vein in usually less than 5 min. However, in expert hands, simultaneous cannulation can be achieved without an increase of complications [24]. The concordance between two simultaneous AVS procedures is not superior to that between simultaneous and sequential AVS. Further, lateralization results between simultaneous bilateral AVS procedures 5 min apart were discrepant in 10.6% of cases, indicating nonuniform fluctuation of steroid production between the two adrenals [23]. Therefore, we suggest that

the choice between the two techniques is left to the preference of the radiologist/centre.

Super-selective segmental AVS is a highly challenging technique in which the tributary veins of the central adrenal vein are cannulated with microcatheters [25]. This approach allows determination of the exact site of aldosterone production for nodulectomy instead of adrenalectomy in patients with bilateral APAs, in the presence of an adrenal nodule in a patient with previous adrenalectomy and in cases of simultaneous aldosterone-producing and cortisol-producing nodules [26]. This should be performed only in centres with highly experienced radiologists as it carries an additional potential risk of complications [25]. In centres with low success rates, the rapid cortisol assay, performed during AVS, allows self-training of the radiologist who can perform further attempts until successful adrenal vein cannulation is achieved [27,28]. The rapid cortisol assay has been used to increase the success rate of AVS and reduce the requirement to repeat the procedure and is considered routine in many centres [4,27–29]: this method should be particularly useful in centres with low cannulation success rates.

Statement: *Simultaneous or sequential, cosyntropin-stimulated or unstimulated AVS procedures are considered equivalent in terms of diagnostic accuracy. The rapid cortisol assay during AVS is helpful to increase successful cannulation of the adrenal veins.*

Cosyntropin stimulation

The discussion about pros and cons of the cosyntropin stimulation during AVS is available in the supplemental file, http://links.lww.com/HJH/B374 and supplemental Table 1, http://links.lww.com/HJH/B374.

Statement: *The use of cosyntropin carries pro and cons for the interpretation of AVS results. In most cases the diagnosis obtained with or without cosyntropin is the same.*

Adrenal vein sampling interpretation criteria

Despite efforts of two groups of experts towards standardization and uniformity [4,20], most centres still use criteria for AVS interpretation that are widely diverse [6]. Several ratios can be calculated after AVS (supplemental Table 2, http://links.lww.com/HJH/B374 [30]). The selectivity index, is used to demonstrate correct cannulation of the adrenal veins; it has been shown that higher selectivity index is more reliable and the obtained results more accurate and reproducible [31,32]. Therefore, we suggest to interpret with caution procedures in which the selectivity index is less than 2 for unstimulated and less than 5 for stimulated procedures [4,5], even if this causes a lower number of conclusive AVS procedures.

The lateralization index is used to identify the source of aldosterone production. There is no agreement on the ideal cut-off to select a patient for adrenalectomy and it is probable that there is a grey zone between unilateral and bilateral primary aldosteronism, with asymmetrical bilateral conditions or when an APA is associated with bilateral APCCs or cortical hyperplasia [33,34].

Ideally, the optimal lateralization index should be assessed from prospective studies in which all patients with a lateralization index greater than 1 are operated and the biochemical outcome is evaluated postoperatively [35]. Such a study cannot be performed for ethical reasons, and thus the only approach to identify the optimal lateralization index is using data from retrospective studies.

Traditionally, the lateralization index cut-off has been considered to be different between stimulated and unstimulated procedures with a suggested lateralization index under basal conditions lower than that under cosyntropin [4,20]. However, considering the potential reduction of lateralization index during cosyntropin stimulation, we suggest a cut-off of 4 under both conditions, instead of a lower lateralization index for unstimulated procedures (Supplemental Table 2, http://links.lww.com/HJH/B374). In agreement with our suggestion, 40 patients with hypertension but without primary aldosteronism underwent AVS: lateralization index was observed to be between 1 and 2 in 32 patients and between 2 and 4 in eight patients. None of the patients had a lateralization index at least 4 [36]. AVS in which lateralization index are between 2 and 4 could be candidates for surgery in some cases when other parameters and clinical data are taken into account, such as the presence of contralateral suppression, lack of response to medical therapy, side effects, and so forth [33,37].

Other ratios used for AVS interpretation are the ipsilateral ratio and the contralateral ratio (CLR) (Supplemental Table 2, http://links.lww.com/HJH/B374). CLR, also called contralateral suppression index, has been used as an ancillary indicator of unilateral primary aldosteronism [38] but does not seem to be a requisite for surgery [39]. We suggest it can be used in cases of controversy, when the LI is in the grey zone or when only the adrenal vein contralateral to an adrenal nodule is detected.

AVS interpretation can be more difficult in patients with concomitant hypercortisolism, a condition which is not so rare in some series [40,41]. Therefore, subclinical hypercortisolism should always be evaluated before AVS [4]. When this condition is observed, a stimulated procedure is suggested and/or metanephrine instead of cortisol concentrations should be used to correct aldosterone for dilution and calculate the lateralization index [42]. The extremely rare association of primary aldosteronism and pheochromocytoma should be excluded before AVS because of associated procedural risks in these patients.

Statement: *Adrenal vein sampling can be interpreted only when selectivity indices demonstrate correct cannulation of the adrenal veins; stricter criteria for cannulation and lateralization provide more reproducible diagnoses.*

COMPLICATIONS

Initial descriptions of patients with primary aldosteronism had a reported low incidence of cardiovascular events [43]

and this form of hypertension was considered relatively benign. This assumption reflected the primacy ascribed to elevated levels of angiotensin II in terms of deleterious cardiovascular effects, and the fact that in primary aldosteronism, the renin–angiotensin axis is suppressed by aldosterone-induced body fluid expansion. Evidence subsequently accumulated over a few decades to indicate clearly that primary aldosteronism causes a variety of cardiovascular, renal, metabolic, and bone complications that are relatively independent of blood pressure increase [44]. The majority of these detrimental effects of aldosterone are related to the action of the hormone on multiple cell types, cellular mechanisms and molecules that are involved in regulation of tissue responses [45] that lead to hypertrophy, remodeling and fibrosis. Primary aldosteronism is frequently associated with high grade and resistant hypertension [46] that may itself be associated with more severe organ damage and with obstructive sleep apnea [47], another potential contributor to cardiovascular events. A comprehensive discussion of cardiovascular, renal and metabolic complications in patients with primary aldosteronism is available in the supplemental file (Supplemental Figure 1, http://links.lww.com/HJH/B374 and Figure 2, http://links.lww.com/HJH/B374).

Statement: Suboptimally treated primary aldosteronism is associated with an increased risk of developing cardiac, renal and vascular damage and major cardiovascular events than essential hypertension.*

TREATMENT

Similar to all forms of hypertension, the mandatory goal of treatment in patients with primary aldosteronism is the prevention of organ damage in order to decrease the rate of complications. The established treatment for unilateral disease is adrenalectomy, whereas mineralocorticoid receptor antagonists (MRA) are used to manage patients with bilateral disease. Although primary aldosteronism is considered correctable, in many cases, hypertension persists after treatment and less than half of treated patients have their blood pressure normalized without the use of additional antihypertensive agents.

Surgical treatment

Laparoscopic adrenalectomy is recommended for patients with evidence of unilateral primary aldosteronism [1]. This treatment is preferred over other interventions because of substantial benefits in terms of resolution of hypokalemia, reduction of blood pressure with a higher probability of hypertension cure, a reduction in the requirement for concurrent antihypertensive medications and improved quality of life. These benefits largely outweigh any risks of surgery. Alternatively, if patients are unwilling or unable to undergo surgery, treatment with MRA is a second choice alternative option. This also applies to patients in whom evidence of lateralized aldosterone hypersecretion cannot be reliably obtained. Laparoscopic adrenalectomy should be performed in an appropriate surgical setting, and is associated with shorter hospital stays and a lower rate of complications than laparotomic adrenalectomy [48]. Blood pressure and serum potassium should be under appropriate control before surgery, and this might require the use of MRAs and other antihypertensive agents if needed. Potassium supplementation, MRAs and other antihypertensive agents should be withdrawn immediately after surgery [49] and blood pressure and serum electrolytes should be closely monitored as hyperkalemia and hyponatremia could ensue because of transient hypoaldosteronism. Hypoaldosteronism may persist in a very small percentage of patients requiring use of fludrocortisone [50].

Another rare consequence of unilateral adrenalectomy is adrenal insufficiency [40,51]: it is associated with glucocorticoid co-secretion from the APA and requires transient standard glucocorticoid replacement therapy postoperatively to prevent adrenal crisis in 1% of patients [53].

Statement: Laparoscopic adrenalectomy is the treatment of choice for patients with primary aldosteronism and evidence of unilateral adrenal disease.*

Medical treatment

Medical treatment is the choice for patients with primary aldosteronism and bilateral adrenal disease, patients with unilateral disease who are unable or unwilling to undergo surgery, and patients in whom evidence of lateralized aldosterone hypersecretion cannot be reliably obtained. In addition to salt restriction that should be recommended to all patients with primary aldosteronism, treatment should always include the use of MRAs.

Spironolactone and its principal pharmacologically active metabolite canrenoate have been the agents of choice for decades. Both compounds have long lasting biological effects allowing once per day or even every other day administration [52,53]. Observational studies and extensive clinical experience clearly demonstrate that spironolactone effectively reduces blood pressure and corrects hypokalemia in patients with primary aldosteronism. Use of spironolactone at daily doses from 50 to 400 mg induced an average blood pressure reduction of 25% for systolic and 22% for diastolic [54]. Effective reduction in blood pressure was also obtainable with lower doses (25–50 mg/day) of spironolactone, thereby limiting the sex-steroid-related side effects of this compound. About half of patients with bilateral adrenal disease are effectively managed with these low doses of spironolactone as monotherapy [55]. The downside of spironolactone use is related to its antiandrogenic effect because of its affinity for the androgen receptor and its progesterone receptor agonist effects [56]. These effects may cause a variety of side effects in men, including breast engorgement with painful nipples up to true gynecomastia, decreased libido, and erectile dysfunction. The drug is much better tolerated in women and menstrual irregularities are relatively infrequent.

Eplerenone is much more selective than spironolactone for the MR, thus obviating the sex hormone-related effects [56]. Eplerenone has shorter half-life (3–6 h) and is inferior to spironolactone in lowering blood pressure in patients with primary aldosteronism [57], requiring the use of higher

daily doses (50–100 mg/day) and twice daily administration. The drug is contraindicated in patients with severe hepatic dysfunction and is not registered for use in primary aldosteronism in many countries so that its use is very often prescribed off-label.

Other agents to be considered as possible substitutes of MR antagonists if contraindicated or as additional treatment in order to limit side effects of spironolactone are the epithelial sodium channel blockers amiloride and triamterene. Whenever used alone, these drugs are less effective than spironolactone in reducing blood pressure [58] and may not block all mineralocorticoid receptor- mediated nonepithelial effects of aldosterone. Calcium-channel blockers and thiazide/thiazide-like diuretics can be added to MR antagonist therapy when target blood pressure is not reached [59]. In patients with uncontrolled blood pressure under MR antagonist therapy, ACE inhibitors or angiotensin II receptor blockers could also be considered to counteract the effects of the activation of the renin–angiotensin system when the MR is successfully blocked.

Statement*: MR antagonists are the treatment of choice for primary aldosteronism in patients with bilateral adrenal disease or unilateral disease that cannot be surgically treated. Treatment should be initiated with low-dose spironolactone and progressively uptitrated according to plasma potassium concentrations and blood pressure response. In the event of side-effects, eplerenone or amiloride/triamterene can be considered as substitutes. If blood pressure control is not adequate despite the maximum tolerated dose, addition of calcium channel blockers and/or low doses of thiazides/thiazide-like diuretics should be the preferred choice.*

OUTCOMES OF TREATMENT FOR PRIMARY ALDOSTERONISM

Outcomes after unilateral adrenalectomy

The PASO (Primary Aldosteronism Surgical Outcome) investigators developed an international consensus for the assessment of outcomes after unilateral adrenalectomy to treat unilateral primary aldosteronism [60]. The PASO consensus defines three levels of clinical and biochemical success (complete, partial and absent) and provides recommendations for the time and interval of follow-up. Clinical success was defined by blood pressure measurements and antihypertensive medication usage, biochemical success was determined by biochemical and hormonal parameters (Supplemental Table 3, http://links.lww.com/HJH/B374). Biochemical success of adrenalectomy was assessed separately from clinical success as a patient with primary aldosteronism can have the correct biochemical diagnosis and successful treatment but remain hypertensive after successful adrenalectomy. Application of these criteria to an international cohort of patients determined complete clinical success in 37% and significant clinical benefits (complete and partial clinical success combined) in 84% of 705 patients. Younger age and female sex were associated with an increased likelihood of complete clinical success (clinical remission) [60]. Thus, in the 12 centers participating to the study, those with lower levels of complete clinical success tended to have older cohorts of patients and/or a higher proportion of men. In support of this, the Japan Primary Aldosteronism Study (JPAS) group reported a higher incidence of persistent hypertension, hyperkalemia and renal impairment after unilateral adrenalectomy in elderly patients than the nonelderly with comparable levels of biochemical cure between the two groups [61].

For patients who do not want to pursue the surgical option with unilateral adrenalectomy, available evidence indicates that there is no difference in the reduction of left ventricular hypertrophy with surgical treatment of primary aldosteronism and medical treatment with MRAs [62]. However, a more rapid reduction of left ventricular hypertrophy has been observed at 1 year after surgery compared with medically treated patients with primary aldosteronism [63]. Further, in a cohort of 339 patients with unilateral primary aldosteronism, the JPAS group reported improved clinical and biochemical outcomes achieved with adrenalectomy (276 patients) compared with MRA therapy (63 patients) [64].

Complete biochemical success (biochemical remission) provides a measure of the correct diagnosis and appropriate treatment by unilateral adrenalectomy and was achieved in 94% of 699 patients in the PASO study [60]. The remaining 6% of patients with partial and absent biochemical success constitute those with persistent aldosteronism (or conceivably recurrence) despite successful adrenal venous sampling with lateralization of aldosterone production (with a lateralization index ranging from 4.4 to 10) and total adrenalectomy to remove the overactive adrenal [60]. It is likely that patients with persistence or recurrence of primary aldosteronism had asymmetrical bilateral primary aldosteronism with dominant secretion on one side, and therefore, a positive lateralization index at AVS. CYP11B2 immunohistochemistry of the resected adrenals is useful for the final histopathologic diagnosis and to identify, which patients are likely to require close postsurgical follow-up [34,65,66].

The approach for differentiating unilateral from bilateral primary aldosteronism has an impact on outcomes after unilateral adrenalectomy. The likelihood of cure of primary aldosteronism when subtype differentiation is based on adrenal venous sampling is higher relative to surgery based on adrenal CT scanning [9]. Further, persistent aldosteronism was a potential factor that contributed to the absent clinical outcomes in patients with surgical management based on CT scanning but not with AVS [9]. This is important as long-term aldosterone excess has detrimental effects independent of blood pressure control with an increased risk of cardiovascular, cardiometabolic events and death relative to patients with essential hypertension [60,67,68]. This highlights that biochemical remission is by itself clinically important and supports the recommendation of long-term yearly follow-up with both clinical and biochemical assessment in surgically treated patients for primary aldosteronism [60,67].

Statement*: Outcomes after adrenalectomy for unilateral primary aldosteronism should be assessed according to the standard PASO criteria with separate evaluation of clinical and biochemical outcomes.*

Prediction of clinical cure after unilateral adrenalectomy

Baseline factors associated with clinical outcomes will be discussed in the supplemental file.

Statement: *Predictive scores can be useful in a clinical setting to differentiate patients who are likely to achieve clinical cure after surgery from those requiring close postsurgical follow-up for persistent hypertension.*

Outcomes after medical treatment

Longitudinal observational studies have indicated that long-term outcomes of medical treatment for primary aldosteronism are associated with plasma renin activity levels. Thus, when plasma renin activity levels remain suppressed with medical treatment (<1 μg/l per h), patients with primary aldosteronism have an increased risk of cardiovascular events and mortality compared with patients with essential hypertension whereas this elevated risk was absent in MRA-treated patients with unsuppressed plasma renin activity (≥1 μg/l per h) [67].

In a prospective study, a higher rate of incident atrial fibrillation was observed in medically treated relative to surgically treated patients with primary aldosteronism and compared with a control group with hypertension [69]. An observational retrospective study reported that it is the MRA-treated patients with sustained renin suppression with a higher risk of atrial fibrillation relative to surgically treated patients with primary aldosteronism and age-matched and blood pressure-matched patients with essential hypertension. In contrast, medically treated patients with unsuppressed renin levels and surgically treated patients display a similar risk profiles of atrial fibrillation relative to patients with essential hypertension [70].

A large retrospective cohort study demonstrated the increased risk of developing chronic kidney disease in patients with primary aldosteronism treated with MRA therapy ($n = 400$) compared both with surgically treated patients with primary aldosteronism ($n = 120$) and with age-matched and estimated glomerular filtration rate-matched patients with essential hypertension (n = 15 474) [71]. At long-term follow-up (5.2 years), the incidence of end-stage renal disease was similar in treated patients with primary aldosteronism and with essential hypertension. The group of patients treated with unilateral adrenalectomy displayed better long-term outcomes with a decreased incidence of end stage renal disease and mortality relative to patients with essential hypertension but this benefit was absent from the MRA group [67].

Growing evidence supports the superiority of surgical treatment with unilateral total adrenalectomy compared with medical therapy with MRAs for primary aldosteronism even in the context of equivalent reductions of blood pressure [72]. The most likely cause for this difference is inadequate blockade of the MR to ablate the effects of aldosterone excess. This may be overcome by up-titration of MR antagonist dosages such that plasma renin levels are unsuppressed [67] and highlights the importance of follow-up assessment of biochemical and not just clinical parameters. When side-effects do not allow MR antagonist increase, addition of amiloride and a further reduction of salt-intake are recommended.

Statement*: *The optimal management of patients with bilateral primary aldosteronism is lifelong treatment with MRAs. Plasma potassium concentrations and renal function should be monitored with periodical assessment of renin measurements to evaluate therapy efficacy.*

FUTURE DIRECTION OF RESEARCH

Despite the tremendous progress over the past few decades, there remain many significant gaps in our knowledge of the pathophysiology, clinical diagnosis and management of primary aldosteronism. Some areas of future research directed at these areas are outlined in the supplemental file, http://links.lww.com/HJH/B374.

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Conflicts of interest

There are no conflicts of interest.

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