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Original Article

Targeted treatment of primary aldosteronism — The consensus of Taiwan Society of Aldosteronism

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Background/Purpose: Even with the increasing recognition of primary aldosteronism (PA) as a cause of refractory hypertension and an issue of public health, the consensus of its optimal surgical or medical treatment in Taiwan has not been reached. Our objective was to develop a clinical practice guideline that is feasible for real-world management of PA patients in Taiwan.
Methods: The Taiwan Society of Aldosteronism (TSA) Task Force recognized the above-mentioned issues and reached this Taiwan PA consensus at its inaugural meeting, in order to

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provide updated information of internationally acceptable standards, and also to incorporate our local disease characteristics and constraints into PA management.
Results: In patients with lateralized PA, including aldosterone producing adenoma (APA), laparoscopic adrenalectomy is the 'gold standard' of treatment. Mini-laparoscopic and laparoendoscopic single-site approaches are feasible only in highly experienced surgeons. Patients with bilateral adrenal hyperplasia or those not suitable for surgery should be treated by mineralocorticoid receptor antagonists. The outcome data of PA patient management from the literature, especially from PA patients in Taiwan, are reviewed. Mental health screening is helpful in early detection and management of psychopathology among PA patients.
Conclusion: We hope this consensus will provide a guideline to help medical professionals to manage PA patients in Taiwan to achieve a better quality of care.

Introduction

According to a nationwide study in Taiwan, the prevalence rates of hypertension are 25% in men and 18% in women with a prevalence rate of primary aldosteronism (PA) ranging from 5.5% in normotensive population to 16.4% in stage 3 hypertensive populations.[1,2] In addition, the diagnosis and treatment of PA usually require complex health care resources and facilities and consequently a treatment consensus or guideline is of help in the management of PA patients.

Several treatment guidelines for PA have been developed to fit the regional consensus and treatment/diagnosis requirements, such as the Japan Endocrine Society 2009 guidelines and the Endocrine Society Clinical Practice Guideline of 2008.[3,4] Unlike western PA cohorts, the Taiwanese PA cohort has a higher prevalence of somatic mutation carriers and no gender difference.[5] Moreover, the long-term surgical and medical treatment results also show significant discrepancy between the western and Taiwan PA cohorts.[6,7] Thus, a treatment consensus for PA is needed in improving the quality of health care in Taiwan.

In order to provide updated information on internationally acceptable standards and also to incorporate our local disease characteristics in the management of PA. We published the consensus in the case detection and diagnosis of PA in 2017.[8] Therefore, current work is focused on the targeted treatment for PA, Taiwan Society of Aldosteronism (TSA) has gathered a Task Force from among Taiwan PA professionals to reach a PA treatment consensus in Taiwan. The consensus is based on medical evidence and also recognizes the constraints of our real-world clinical practice in managing PA in Taiwan.

Method of development of evidence-based consensus

Task Forces used the best available research evidence to inform the recommendations, and both used consistent language and graphical descriptions of the strength of a recommendation and the quality of the evidence. The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were 'Level 1 to level 4. The 'strength of a recommendation' indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the grade A recommendation, and weak grade B recommendations use the phrase "we suggest". The levels of scientific evidence and the grades of the recommendation were weighed and graded according to The Scottish Intercollegiate Guidelines Network (SIGN), as outlined in Tables 1 and 2.

Treatment of choice

Once the diagnosis of PA is confirmed, its treatment of choice depends on the result of lateralization tests (as discussed in Wu V-C et al., Case detection and diagnosis of primary aldosteronism — The consensus of Taiwan Society of Aldosteronism).[8] Surgical treatment is recommended for a lateralized PA; whereas targeted pharmacological treatment is suggested if the diagnosis of PA is confirmed but the lateralization tests fail to localize the origin of excessive aldosterone from a certain side.

A 'lateralized PA' indicates that significantly higher secretion of aldosterone could be identified to a certain side of the adrenal glands. A typical example of the 'lateralized PA' is an aldosterone-producing adenoma (APA) that produces supernormal amount of aldosterone; i.e. APA is included in the broader term of 'lateralized PA'. We will use the term 'lateralized PA' in the later majority portion of this article, and only to mention APA if denoting specifically a well demarcated aldosterone hyper-secreting mass.

Surgical treatment of lateralized primary aldosteronism

According to our population based study published in 2016, adrenalectomy decreases long-term all-cause

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Table 1 Levels of scientific evidence.

1++	High-quality meta-analyses, high-quality systematic reviews of clinical trials with very little risk of bias.
1+	Well-conducted meta-analyses, systematic review of clinical trials or well-conducted clinical trials with low risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High-quality systematic reviews of cohort or case and control studies; cohort or case and control studies with very low risk of bias and high probability of establishing a causal relationship.
2+	Well-conducted cohort or case and control studies with low risk of bias and moderate probability of establishing a causal relationship.
2-	Cohort or case and control studies with high risk of bias and significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports and case series.
4	Expert opinion.

Table 2 Grades of treatment recommendation.

A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guideline, or a volume of scientific evidence comprising studies classified as 1+ and which are highly consistent with each other.
B	A body of scientific evidence comprising studies classified as 2++, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 1++ or 1+.
C	A body of scientific evidence comprising studies classified as 2+, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 2++.
D	Level 3 or 4 scientific evidence, or scientific evidence extrapolated from studies classified as 2+.

mortality independently from PA cure from hypertension in Taiwan.[6] The effect of PA on those who did not receive adrenalectomy to all-cause mortality is similar to subsequent major cardiovascular events. Our study generated the largest current study cohort of PA patients in the world, It calls for more attention on early diagnosis, early treatment (especially surgical treatment) for Taiwan PA patients.

Laparoscopic or/and robot-assisted endoscopic adrenalectomy

Laparoscopic adrenalectomy is the gold standard of care for APA/lateralized PA. (B, 1-)

Robot-assisted endoscopic adrenalectomy is a feasible alternative to conventional laparoscopic adrenalectomy for APA/lateralized PA. (C, 2++)

Rationale

Laparoscopic adrenalectomy has been accepted as the 'gold standard' approach for the treatment of benign adrenal tumors that require surgical extirpation, including APA. Although most treatment guidelines recommended the transperitoneal approach as the gold standard of treatment for lateraized PA, evidence proving the transperitoneal approach is better than a retroperitoneal approach remain scarce in the literature. A recent meta-analysis study that compared 1205 transperitoneal adrenalectomies and 688 retroperitoneoscopic adrenalectomies found no statistically significant differences between these two approaches in terms of operative time, blood loss, hospital stay, time to oral intake, overall and major morbidity, and mortality.[9] Therefore, it's not the transperitoneal approach itself that is better than the retroperitoneal one, but its surgical advantages such as easier access, larger working space and well-defined anatomical landmarks, make it popular for most surgeons and thus a well accepted standard of treatment. However, in cases when the transperitoneal approach is not suitable because of previous abdominal surgery or in laparoscopic single-site approach, the retroperitoneal approach is a preferred alternative.

Robotic adrenalectomy is another form of laparoscopic approach made with the aid of robotic systems. It is not surprising that robot-assisted laparoscopic adrenalectomy is also a feasible procedure for the treatment of adrenal tumors including APA. However, for surgeons with enough laparoscopic experience, there is no evidence to advocate that robot-assisted laparoscopic adrenalectomy will yield better peri- and post-operative outcomes as there are no prospective, randomized studies today.

Evidence

Even though there are no prospective randomized studies comparing laparoscopic versus open adrenalectomies, the obvious consensus is that laparoscopic adrenalectomies are associated with less postoperative pain, earlier recovery and similar long-term outcomes compared to open surgery. In a prospective randomized controlled study, trans-peritoneal and retro-peritoneal approaches had similar peri-operative outcomes in terms of blood loss, hospitalization, operative time, convalescence and analgesics requirements.[10]

The question of whether a robot is necessary for the treatment of lateralized PA cannot be answered by evidence-based medicine even though a recent meta-analysis to compare robot-assisted versus conventional laparoscopic adrenalectomy showed the two procedures did not make significant differences in peri-operative outcomes.[11]

Mini-laparoscopic adrenalectomy

Mini-laparoscopic adrenalectomy is an alternative to conventional laparoscopic approach with a faster recovery in patients with lateralized PA. (D, 2-)

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Evidence
Mini-laparoscopic adrenalectomy is defined as laparoscopic adrenalectomy using 2—3 mm working instruments. Two case series with large number of patients has revealed that mini-laparoscopic adrenalectomy is a feasible and safe technique which can be performed using either transperitoneal or retroperitoneal approaches.[12,13] However, only two retrospective studies focused on comparison of mini-laparoscopic and conventional laparoscopic approaches. In both of these studies, mini-laparoscopic adrenalectomy showed quicker convalescence than conventional laparoscopic adrenalectomy.[14,15]

Limitations
There are only 15 and 112 patients receiving mini-laparoscopic adrenalectomies in these two retrospective comparative studies, respectively.[12,14,15] Therefore, well-designed randomized control trials are required to confirm the outcomes of mini-laparoscopic adrenalectomy.

Remark
This recommendation requires the availability of a surgeon experienced in mini-laparoscopic adrenalectomy.

Laparoendoscopic single-site (LESS or single-port endoscopic) adrenalecomty

LESS adrenalectomy is a safe and feasible alternative to conventional laparoscopic adrenalectomy with a shorter length of hospital stay and lower post-operative pain in patients with lateralized PA. (B, 1-)

Evidence
According to a recent meta-analysis of LESS versus conventional laparoscopic adrenalectomy, which enrolled 10 comparative cohorts to date, LESS adrenalectomy is a safe approach in terms of peri-operative complication, estimated blood loss, risk of conversion and blood transfusion when compared with conventional laparoscopic approach.[16] In this review, LESS adrenalectomy revealed comparable peri-operative outcomes with conventional laparoscopic adrenalectomy. In addition, LESS approach offer the minor clinical benefits of better post-pain control and shorter hospital stay when compared with conventional laparoscopic approach. There is only one comparative trial reported the clinical outcome focus on treating APA thus far.[17] This retrospective cohort study confirms that LESS adrenalectomy achieved similar hypertension and disease control as conventional laparoscopic adrenalectomy for management of unilateral APA.

Limitations
However, current limitation of above evidence is that most enrolled trials are retrospective comparative studies comparing different approaches and none of them is a prospective randomized control trial.[16] In addition, the follow-up periods were relatively short in these early reports. Thus, a high-quality randomized control trial with long-term follow-up is needed in the near future.

In addition, LESS adrenalectomy is associated with significant technical challenges when compared with conventional multiport laparoscopic adrenalectomy for the following reasons: loss of instrument triangulation, instrument clashing, especially with straight instruments, and the mind-set of the operator and assistant relying on their prior experiences of multiport laparoscopic surgery. It also had been reported that a higher BMI, greater height, or a right side adrenal tumor were associated with significant challenges.[18] Thus, LESS adrenalectomy for APA is only suggested to be done by experienced surgeons.

Remark
This recommendation requires the availability of a surgeon experienced in LESS adrenalectomy.

Laparoscopic partial adrenalectomy for APA

Laparoscopic partial adrenalectomy may be an alternative option for patients with synchronous of metachronous bilateral APAs. (D, 2-)

Evidence
According to a meta-analysis of recurrence and functional outcomes of partial adrenalectomy, the overall recurrence rate was 8% (95% CI: 0.05—0.12) and the 85% (95% CI: 0.78—0.9) of the patients were steroid independent after partial adrenalectomy for all functioning adrenal lesions.[19] The specific recurrence rate for PA is 2% (95% CI: 0.01—0.05) and highest in open partial adrenalectomy 15% (95% CI: 0.07—0.28). The specific steroid independence rate for PA was 97% (95% CI: 0.85—0.99). On the other hand, Ishidoya et al. recommended total laparoscopic adrenalectomy over partial adrenalectomy in patients lateralized PA.[20] Of their 63 extirpated specimens 17 adrenals (27.0%) demonstrated multiple space occupying lesions along with the main aldosterone producing adenoma; suggesting that PA is highly associated with multiple adrenal space occupying lesions.

Limitations
The current evidence was mainly derived from retrospective studies, thus was subjected to selection bias with potential reporting on more patients with favorable outcomes. In addition, the heterogeneity due to different study population groups might contribute to the study bias. A prospective randomized control trial might be beneficial.

Remark

1. This recommendation requires the availability of a surgeon experienced in laparoscopic partial adrenalectomy.
2. Recent data reveal that PA is highly associated with multiple adrenal space occupying lesions, thus recurrence of PA might be a significant risk after partial adrenalectomy in the long-run; this option should only be offered to very selective PA patients, and should not be offered to PA patients with a contralateral normal adrenal gland.

Imaging-guided ablation of APA

Even though laparoscopic adrenalectomy is the standard of care for lateralized PA, some patients might pose higher surgical risks because of their medical co-morbidities, and

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the rates of postoperative persistent hypertension have been reported to be 33%–70% after adrenalectomy.[21–26] Image-guided therapy could offer some alternative under such conditions.

Imaging-guided percutaneous radiofrequency ablation (RFA)

Imaging-guided percutaneous RFA is a promising treatment option for APA with comparable short-term success to surgery. (D,2-)

Evidence

Imaging-guided percutaneous radiofrequency ablation (RFA) is a promising treatment options for lateralized PA.[27] It is ideal for poor surgical candidates due to its minimal-invasiveness with local anesthesia and intraprocedural moderate sedation. RFA creates an alternating current through radiofrequency pulses, which results in friction-induced heating and resultant ablation effects.[28,29] The perirenal fat around the adrenal gland is a natural heat insulator to prevent thermal injury to adjacent organs and inadequate ablation due to heat sink phenomenon. Moreover, ablative track seeding is not a concern since almost all APAs are of a benign nature. RFA could achieve short-term treatment success in 96% of patients,[29] and sustainable long-term treatment success for hypertension in 56% of patients, with the major complication rate of 3%.[27] However, RFA is contraindicated for adrenal lesions suspicious for malignancy and caution to avoid the adjacent major vasculatures needs to be exerted.

Imaging-guided ablative agent injection

Imaging-guided Ethanol injection is a safe alternative in APA patients who are not feasible for surgical intervention. (D,3)

Evidence

Ethanol injection is another emerging treatment option for treatment of APA, which is performed with transcatheter or percutaneous techniques. Pilot studies showed that the technical success rate was 82% using transarterial technique.[30,31] However, up to 61% of patients require a repeat procedure 2–4 weeks after ethanol injection, as shown in study by Inoue et al.[30] Complication of transarterial ethanol injection is not common, but pleural effusion was observed in around 20% of patients when ethanol was injected into the inferior phrenic artery.[31] Percutaneous ethanol injection has been demonstrated to have comparable survival rates with surgical resection for small hepatocellular carcinoma.[32] Application of percutaneous ethanol injection to endocrine glandular lesions, such as thyroid, parathyroid, and adrenal glands, has also been proposed recognized as an alternative therapy. The ethanol would induce tissue coagulative necrosis as well as vascular thrombosis. Besides ethanol as the injective agent for ablation, acetic acid is another commonly used agent for chemical ablation.[33,34] Despite extensive experience among liver, endocrine tumors and other viscera, only small series regarding the efficacy of percutaneous ethanol injection for APA was available in the literature with generally good short-term outcome.[32–35] Further investigation is warrant to define its role among other ablative treatments and laparoscopic adrenalectomy.

Pre-intervention management (including adrenalectomy and image-guided ablation)

Both hypertension and hypokalemia should be well under control before adrenalectomy. MR antagonist may be indicated for the patients with refractory hypokalemia or resistant hypertension before surgery.

Postoperative management (including adrenalectomy and image-guided ablation)

To avoid hyperkalemia, potassium replacement and spironolactone should be discontinued immediately after adrenalectomy unless serum potassium levels remain very low (i.e., $<$3.0 mmol/L).[36]

To avoid tissue hypoperfusion secondary to hypotension, antihypertensive medications should be reduced appropriately by monitoring the blood pressure frequently.[37]

We suggest evaluation of adrenal function including plasma aldosterone concentration, plasma renin activity, ACTH, and cortisol level in the morning after adrenalectomy. After surgery, steroid replacement may be indicated if adrenal insufficiency occurs in the patient with aldosterone- and cortisol-co-secreting adrenal tumors.[38]

Pharmacological treatment of PA

In PA patients with bilateral adrenal disease or lateralized PA patients with no desire for surgical treatment, we recommend medical treatment with a (mineralocorticoid receptor) MR antagonist (C++);

We suggest that spironolactone be used as the first choice of medical treatment for PA patients, while eplerenone be the alternative in cases of side effects from spironolactone or pregnancy.

MR antagonist is administered to block the effect of excessive aldosterone to stop either hypokalemia or hypertension, and to attenuate organ damages such as vascular inflammation, myocardial injury, vascular stiffness, atherosclerosis, endothelial dysfunction, and glomerular proteinuria.[39–43]

MR antagonists

Spironolactone

In the early 1960's, spironolactone (Aldactone) was developed and approved to treat PA, essential hypertension, and the edema associated with congestive heart failure and liver cirrhosis.[44]

The first-generation spironolactone displays strong potency as a MR antagonist, but it lacks specificity for the mineralocorticoid receptors. It is also an androgen receptor (AR) antagonist which leads to the development of gynecomastia and impotence in men.[45,46] Gynecomastia resulting from spironolactone therapy is dose-related and

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reversible. It has been reported that such incidence after 6 months of therapy was at 6.9% for a dose <50 mg/d and at 52.2% for a dose >150 mg/d.[63] It acts as an agonist of the progesterone receptor (PR) to cause disturbance of the menstrual cycle in pre-menopausal women.[47] Spironolactone is a potassium-sparing diuretic, thus it could cause life-threatening hyperkalemia.[44]

Although spironolactone has a very short half-life (1.4 h), the major metabolites resulting from its rapid metabolization in the liver have much longer half-lives. 7-α-(thiomethyl) spironolactone (TMS), one of the major metabolites which accounts for 80% of the potassium sparing effect of the parent compound spironolactone, has a half-life of 13.8 h. Another active metabolite, canrenone, has a half-life of 16.5 h.[48,49] In view of the half-lives of these metabolites, spironolactone can only be administered once daily. It takes several days for all its active metabolites to reach steady plasma levels and the maximal hypotensive effect is attained after 3–4 weeks of treatment.[48,49]

After the discontinuance of spironolactone, the effects on renin secretion may persist for several weeks. It is always recommended that the spironolactone treatment be suspended for at least 4 weeks before the patient takes a biochemical assessment for PA.[36]

Spironolactone is very effective for the control of potassium and blood pressure. Despite the fact that there are no randomized placebo-controlled trials in patients with PA,[50] there are, however, several observational studies with various numbers of patients and varying duration of treatment. In the recently updated guideline on PA, a data summary of spironolactone treatment on 122 BAH (bilateral adrenal hyperplasia) patients, with doses varying from 50 to 400 mg/day, reported reductions in patients' systolic and diastolic blood pressures of 25% and 22%, respectively.[36] In another study of 28 PA patients with no detectable adenomas on adrenal CT scan, low-dose spironolactone therapy (25–50 mg/d) reduced systolic BP by 15 mmHg (from a mean of 161 to 146 mmHg) and diastolic BP by 8 mmHg (from a mean of 91 to 83 mm Hg); About half of the patients were treated with spironolactone monotherapy and 48% of patients were able to achieve a BP <140/90 mm Hg.[49,51]

Eplerenone

Eplerenone is a second-generation MRA that has been available for clinical use since 2002. Compared to spironolactone, Eplerenone has a 50–75% blood pressure-lowering potency in vivo but is a much more selective antagonist for the MR receptor.[49,52,53] It has a half-life of 4–6 h (Table 1), therefore its starting dose is recommended at 25 mg twice daily.

Besides the fact that eplerenone is more selective than spironolactone for mineralocorticoid receptors, eplerenone does not affect metabolic parameters such as glucose and cortisol.

Finerenone

Finerenone (BAY 94-8862) is a third-generation MRA that is still in clinical trial. It is a novel non-steroidal MRA (developed from dihydropyridine, CCBs) that could have both the advantages of high potency (similar to spironolactone) and high selectivity (greater than eplerenone) and could improve end-organ protective activity. Finerenone has a lower risk for hyperkalemia than spironolactone in many clinical trials for congestive heart failure, chronic renal disease, and diabetes patients (ARTS, ARTS-DN).[47] However the clinical use of finerenone on PA is of limited experience.

Epithelial sodium channel blockers

Amiloride and triamterene are the two Epithelial sodium channel blockers that have been reported to have anti-aldosterone activity.[54–56] Limited available data indicate that Epithelial sodium channel blockers are less effective as antihypertensive monotherapy in PA patients as compared to MRAs.[57] Therefore, Epithelial sodium channel blockers -blockers could be used as second-line drugs for the treatment of PA. In cases where the side effects of spironolactone or eplerenone are to be avoided, Epithelial sodium channel blockers may be added to MRAs to reduce the dosage of MRAs and thus the side effects.[49,58]

Mineralocorticoid receptor antagonists and management of PA during pregnancy

Mineralocorticoid receptor antagonists (MRAs) are the most effective drugs to treat hypertension and hypokalemia in patients with PA. However, spironolactone (FDA pregnancy category C) might have the adverse effects on sex differentiation of the male during embryogenesis due to its anti-androgenic effect. In the FDA report, studies on spironolactone with carcinogenic, mutagenic and teratogenic effects on mice, rats, and rabbits are mentioned (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/012151s072lbl.pdf 2014). Although the data of its effect on human are very limited, treatment with spironolactone during pregnancy is not recommended. Eplerenone (FDA pregnancy category B) is a selective MRA without anti-androgenic potential. In animal models, no teratogenic effects were observed (FDA report Inspra Eplerenone, http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021437s006lbl.pdf). If MRA treatment is required in pregnancy, eplerenone appears to be a safe and effective alternative. Laparoscopic adrenalectomy is a therapeutic option in the second trimester of pregnancy if the pharmacological treatment fails to control hypertension and hypokalemia.[59]

Glucocorticoid treatment of familial hyperaldosteronism type 1 (FH-1)

Familial primary aldosteronism type 1 (FH-1) is due to an aberrantly formed chimeric gene product that combines the glucocorticoid-responsive promoter of the 11-beta-hydroxylase gene (CYP11B1) with the coding region of the aldosterone synthetase gene (CYP11B2). The aldosterone synthase is thus controlled by an ACTH-responsive promotor.[49,60] Dexamethasone, which suppresses ACTH, could normalize blood pressure and aldosterone levels. The starting dose of dexamethasone in adults is 0.125–0.25 mg/d.

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Psychosomatic assessment and intervention

Patients with PA are prone to have psychosomatic symptoms which include anxiety, depression, and somatization.[61] Also, PA patients are more likely to have formal psychiatric diagnoses of anxiety disorders, and usually, require integrative care with mental health professionals.[62] The psychopathology has been reported to be widely prevalent among PA patients across their natural course, no matter they are untreated, under mineralocorticoid antagonist therapy, or after adrenalectomy.[63]

Like other psychiatric and cardiovascular comorbidity, the mechanism underlying the PA and anxiety/depression comorbidity is still undetermined.[64] In addition to the emotional reaction of suffering from a chronic illness, the renin–angiotensin–aldosterone-system might play a role in the psychosomatic comorbidity.[65]

The anxious PA patients are sensitive to medical uncertainty. They worry about the prognosis, the possible side effect of invasive diagnostic procedures, the choice of treatments, and the interpretation of laboratory data. Establishing a supportive relationship is helpful for PA patients to cope with their anxiety. The good therapeutic alliance also facilitates a shared medical decision of an optimal treatment plan. It is suggested that mental health screening in the routine medical assessment is helpful to early detection of psychopathology among the patients with endocrinological diseases, but the screening should be coupled with an adequate system for diagnosis and aftercare.[66,67]

Non-pharmacological treatments for anxiety disorders include cognitive-behavioral therapy, relaxation training, mindfulness training, and supportive psychotherapy.[68] A full range of psychotropic medications which included tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, calcium channel modulators, and benzodiazepines, were recommended for anxiety disorders.[69] In the future, researchers may elaborate the targeted interventions for the PA related psychiatric syndrome. The PA patients may become less anxious while they have sufficient visit length, optimal follow-up frequency, an experienced case manager, and through psychoeducation. The stigma of mental health problems is a barrier to referring PA patients with distressing psychopathology to the psychiatrists or the clinical psychologists. To have liaison with mental health professionals in the treatment team would be an effective way to deliver a holistic bio-psycho-social care to PA patients.

Long-term outcomes of PA targeted treatment

The importance of PA is not only its prevalence and refractory high blood pressure, but also because of patients with PA have higher cardiovascular morbidity and mortality than patients with essential hypertension (EH), independent of age, gender and blood pressure level.[70,71] Target treatment with unilateral adrenalectomy or MRA can improve the outcomes of patients with PA. Although currently unilateral adrenalectomy is the preferred treatment in lateralized PA patients, the benefits of long-term outcomes between medical treatment and unilateral adrenalectomy in patients with APA were still controversial.[6,7,72,73] Cohort studies revealed that APA patients treated with unilateral adrenalectomy had better long-term outcomes than patients who received medical treatment only.[6,74] Additional benefits of adrenalectomy in patients with lateralized PA were also found in recent studies, including decrease of glucocorticoid secretion, less osteoporosis, attenuation of adverse metabolic risks and improving the quality of life.[38,75–77]

The effect on cardiovascular complications by aldosterone excess is partly independent of high blood pressure, and had been demonstrated by several studies. Hyperaldosteronism could increase left ventricular dimensions and mass.[79,80] It could also resulted in vascular

Table 3 The six criteria of clinical and biochemical outcomes.

Outcome measure	Definition	
	Clinical outcome	Biochemical outcome
Complete success (remission)	Normal BP without the aid of antihypertensive medication	Correction of hypokalemia (if present pre-surgery) and normalization of the ARR. In patients with an elevated ARR, aldosterone secretion should be suppressed in a post-surgery ***confirmatory test***.
Partial success (improvement)	The same BP with less antihypertensive medication ***or*** A reduction in BP with either the same amount or less antihypertensive medication	Correction of hypokalemia (if present pre-surgery) and an elevated ARR with one or both of the following (compared to pre-surgery): 1. ≥50% decrease in baseline plasma aldosterone level 2. Abnormal but improved post-surgery ***confirmatory test*** result
Absent success (persistence)	Unchanged or increased BP levels with either the same amount or an increase in antihypertensive medication	Persistent hypokalemia (if present pre-surgery) and/or persistent elevated ARR with failure to suppress aldosterone secretion with a post-surgery ***confirmatory test***.

Abbreviation: ARR, aldosterone-to-renin ratio; BP, blood pressure.

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comorbidities, including increased small resistant arteries fibrosis,[81] intima-mediate thickness,[82,83] femoral pulse wave velocity[84] and more endothelial dysfunction.[85] The pathophysiology of cardiovascular complications beyond blood pressure may because of hyperaldosteronism related proinflammatory cytokines release[86] and generation of oxidative stress.[87,88]

Higher risk of cardiovascular complications in patients with PA was also noted in clinical outcome studies. PA patients had higher rate of arrhythmias, cerebrovascular events, coronary artery disease and all-cause mortality than EH patients during long term follow-up.[70,72,89] In addition, PA patients had more prominent renal damage than EH patients.[90,91] In the general population, plasma aldosterone levels could be a predictor for hypertension development in normotensive people.[92]

Higher cardiovascular mortality was noted in patients with PA under target treatments, however, there was no difference of all-cause mortality between patients treated for PA and EH patients.[72] In recent study,[75] patients with lateralized PA who underwent adrenalectomy had reduced risk for all-cause of mortality, compared with matched hypertensive controls.

To evaluate the outcomes after surgical treatment, the Primary Aldosteronism Surgical Outcome (PASO) study reached expert consensus for 6 criteria of clinical and biochemical outcomes (Table 3).[93] Regular follow-up after surgery was also recommended. In this study, female and younger patients had higher clinical benefits after unilateral adrenalectomy and the results indicated that the expectations following surgery may based on age and sex. However, further investigations are needed for the clinical applications.

Conclusion

Laparoscopic adrenalectomy is the gold standard of care in lateralized PA patients if they are reasonable anesthetic candidates. Robot assisted endoscopic, mini-laparoscopic, or LESS adrenalectomy are feasible alternatives to conventional laparoscopic adrenalectomy. Imaging-guided percutaneous RFA is a promising treatment option for APA with comparable short-term success to surgery. In PA patients with bilateral adrenal disease or lateralized PA patients with no desire for surgical treatment, we recommend medical treatment with an MR antagonist. Cohort studies revealed that APA patients treated with unilateral adrenalectomy had better long-term outcomes thanpatients who received medical treatment only; however, further investigations are needed for the outcome measurement.

Disclosure statement

The authors have nothing to disclose.

Conflict of interest

There is no conflict of interest.

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