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Outcomes of drug-based and surgical treatments for primary aldosteronism

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Abstract

Treatments for primary aldosteronism (PA) aim to correct or prevent the deleterious consequences of hyperaldosteronism: hypertension, hypokalemia and direct target organ damage. Patients with unilateral PA considered fit for surgery can undergo laparoscopic adrenalectomy, which significantly decreases blood pressure and medications in most cases, and cures hypertension in about 40%. Mineralocorticoid receptor antagonists (MRA) are used to treat patients with bilateral PA and those with unilateral PA if surgery is not possible or not desired. Spironolactone is more potent than eplerenone, but high doses are poorly tolerated in men. MRA can be replaced or complemented with epithelial sodium channel blockers, such as amiloride. Thiazide diuretics and calcium channel blockers are used when the first-line drugs are insufficient to control blood pressure. Dietary sodium restriction should be implemented in all cases, because the deleterious consequences of hyperaldosteronism are dependent on salt loading. Several studies comparing the results of surgery and MRA have reported no differences in terms of blood pressure, serum potassium concentration or cardiovascular and renal outcomes, although the benefits of treatment tend to be observed sooner with surgery. PA patients display relative glomerular hyperfiltration, which is reversed by specific treatment, revealing chronic kidney disease in 30% of patients. However, further kidney damage is prevented by the treatment of PA.

Clinical summary

- The goals of treatment are the normalization of serum potassium concentration, blood pressure control and prevention of the direct effects of excess aldosterone on target organs.

- The non-surgical treatment of PA is based on mineralocorticoid receptor antagonists and dietary sodium restriction.
- Epithelial sodium channel blockers are used when mineralocorticoid receptor antagonists are not well tolerated; thiazide diuretics and calcium channel blockers are used when blood pressure control is insufficient with the first-line treatment.
- Laparoscopic adrenalectomy is safe and decreases BP and medication requirements in patients with unilateral PA; drug-based treatments are appropriate in cases in which surgery is inappropriate or not desired.

Keywords

Hyperaldosteronism; Adrenalectomy; Mineralocorticoid receptor antagonists; Epithelial sodium channel blockers; Chronic kidney disease.

Introduction

Primary aldosteronism (PA) is the state of autonomous aldosterone overproduction by one or both adrenal glands.[1] Activation of the mineralocorticoid receptor increases the number of epithelial sodium channels (ENaC) and sodium chloride cotransporters (NCC) on the epithelial cell membrane of distal tubules and collecting ducts.[2] This leads to sodium reabsorption and potassium secretion, resulting in an increase in plasma volume and hypokalemia. However, sodium availability in the distal tubule must exceed a certain amount for these consequences to occur. Hypertension results partly from an increase in plasma volume and partly from the aldosterone-mediated vasoconstriction of systemic arteries.[3] Target organ damage is mostly due to hypertension, but aldosterone also promotes oxidative stress, inflammation and fibrosis in the kidney and other organs (heart, vessels, adipose tissue). These effects are also dependent on salt loading and may be partly independent of the mineralocorticoid receptor.[4–6]

Treatment aims to decrease the morbidity and mortality associated with PA and to improve the quality of life of patients. Economic constraints make it necessary to achieve these ends at the lowest possible cost. The most logical way to achieve these goals is to normalize aldosterone secretion. This is possible in patients with unilateral PA, through removal of the offending adrenal gland. Aldosterone synthase inhibitors are currently being developed but are not yet used in clinical practice.

Mineralocorticoid receptor antagonists (MRAs) counteract most, but not all the biological effects of hyperaldosteronism. However, they yield clinical results comparable to those achieved by adrenalectomy. ENaC blockers impede only some of the many pathways leading to target organ damage, but are useful adjunctive treatments, together with dietary sodium

restriction, for controlling blood pressure (BP) and hypokalemia. Non-specific antihypertensive agents are often required in addition to these specific treatments, to control hypertension.

We will begin by describing the principal treatments for PA — surgery and antihypertensive drugs — and reviewing their outcomes. We will then discuss the most appropriate uses of these treatments according to PA subtype, and the clinical circumstances and individual preferences of patients.

Unilateral adrenalectomy

The vast majority of adrenal lesions causing unilateral PA are small and benign, and are therefore ideal candidates for laparoscopic adrenalectomy, for which morbidity is lower and hospital stays are shorter than for open surgery.[7,8] Several surgeons have advocated partial adrenalectomy as a safe and feasible way of removing single aldosterone-producing adenomas (APA).[9,10] However, the benefits of this adrenal gland-sparing approach are questionable in PA, because contralateral tumors requiring subsequent adrenalectomy are very rare. Moreover, 10 to 25% of patients with unilateral PA have multiple adjacent nodules that may be missed on preoperative adrenal imaging, and the largest lesion is not necessarily the lesion responsible for PA.[11] Several percutaneous alternatives for the destruction of APAs have been proposed, including ethanol injection, arterial embolization, cryoabalation and radiofrequency ablation.[11,12] These techniques are less invasive than surgery, but the long-term outcome and risks are uncertain. They should therefore be used only within the confines of a study protocol.

Surgeons may opt for a transperitoneal or for a retroperitoneal approach. Both approaches have drawbacks and advantages. The lateral transperitoneal laparoscopic approach exposes the adrenal gland to a greater extent, whereas the retroperitoneal approach avoids facing adhesion in patients who have previously undergone intra-abdominal surgery, and potentially reduces the duration of the patient's stay in hospital.[13] Laparoscopic adrenalectomy usually requires three to four ports for the introduction of the instruments, but a single-port transumbilical approach is possible.[14,15] Robot-assisted laparoscopic adrenalectomy is feasible and safe but more expensive, and its advantages over conventional laparoscopy have yet to be definitively demonstrated.[15–17]

The mean operating time for laparoscopic adrenalectomy performed by experienced surgeons in major series is between one and two hours, and mean hospital stay is about three days.[18,19] Conversion to open surgery is required in less than 5% of cases.[8] Perioperative mortality is less than 0.5%, non-fatal complications occur in 5% to 15% of cases and most of them are benign (temporary relaxation and/or hypoesthesia of the abdominal wall).[7,8,18] Fewer than 2% of patients experience severe complications: hemorrhage requiring transfusion, cardiac or respiratory destabilization.[7,8,18] However, cases of major complications have been reported outside of referral centers.[20] Surgery should be performed by an experienced surgeon at an institution with a high volume of such interventions. In such settings, outpatient laparoscopic adrenalectomy is possible in selected cases: patients under the age of 65 years, tumors of less than 6 cm in diameter, no significant cardiorespiratory disease, first case of the day to be managed in the surgical program, residence less than 30 minutes from the hospital by car, and treatment with no more than three antihypertensive agents.[21–23]

Patients should be treated with a MRA and potassium supplements to lower BP and to correct hypokalemia before surgery. Preoperative mineralocorticoid receptor blockade for a few weeks before surgery may also decrease the risk of postoperative hypoaldosteronism due to the chronic suppression of aldosterone secretion in the contralateral gland. Nonetheless, postoperative hyperkalemia is seen in up to 30% of patients.[24,25] It is usually mild and transient, but MRA treatment and potassium supplements should be discontinued at the time of surgery, to minimize the risk, and serum potassium concentrations should be monitored closely, particularly in patients with chronic kidney disease (CKD).[25] In addition to the restriction of potassium-rich food, fludrocortisone has been used in rare cases of persistent hyperkalemia due to postoperative hypoaldosteronism.[24] Hormonal studies should be carried out for patients with high BP after surgery, to distinguish between persistent PA and associated essential hypertension.

Outcomes of adrenalectomy in unilateral PA

We discuss here the findings of a systematic review of large surgical series published since 2000.[11] This time limit was set to correspond to current outcomes of laparoscopic surgery in patients with unilateral PA diagnosed with current protocols. This evidence base is nonetheless limited by the lack of comparison with drug-based treatment and medium-term evaluations of mostly intermediate outcomes (BP, serum potassium, subclinical target organ damage).

By definition, unilateral adrenalectomy should normalize aldosterone secretion in all cases of unilateral PA. However, 5 to 10% of patients display residual autonomous aldosterone production after surgery, even if hypertension is cured[26] and adrenal venous sampling (AVS) is used in the diagnostic process. Hypokalemia, when present, resolves in more than 95% of

cases, in all series. The mean rate of hypertension cure is 40%, with a high variability between series. Patients with persistent hypertension nonetheless experience a clinically significant decline in BP (of between 20 and 40 mmHg for systolic BP) and a decrease in the number of antihypertensive drug classes used (one or two fewer). Less than 25% of patients experience no apparent BP benefit from surgery.

An increase in markers of oxidative stress is observed more frequently in patients with PA than in patients with essential hypertension, and the levels of these markers decrease significantly after adrenalectomy in patients with unilateral disease.[27]

Patients with PA have higher cardiovascular morbidity and greater subclinical organ damage than expected on the basis of their BP.[28] Many studies have shown that left ventricular mass decreases and that aortic pulse wave velocity and carotid intima-media thickness improve after adrenalectomy.[29–35] A prospective study compared cardiovascular events in 54 PA patients treated by adrenalectomy (unilateral disease) or with spironolactone (unilateral or bilateral disease) with 323 patients with essential hypertension.[36] The composite endpoint was myocardial infarction, stroke, any type of revascularization procedure, and sustained arrhythmia. Its incidence over a mean follow-up of 7.4 years did not differ between patients with treated PA and their controls (who achieved similar BP levels throughout follow-up). A study with a similar design found the incidence of cardiovascular events — acute coronary events, stroke, sustained arrhythmia, hospitalization for heart failure — to be slightly higher in 270 PA patients after specific treatment than in 810 matched patients with essential hypertension over a median follow-up period of 12 years.[37] These discrepancies may be due to the higher rate of incident hospitalization for heart failure in PA patients than in controls in the second study, this outcome not being considered in the first study.

A worsening of kidney function after adrenalectomy was first reported one year after Jerome Conn described the first APA.[38] By contrast to otherwise similar patients with essential hypertension, patients with PA display relative glomerular hyperfiltration, defined as a high estimated glomerular filtration rate (eGFR) and low-grade albuminuria.[39] These changes are associated with lower intrarenal arterial resistance and higher rates of blood flow in the kidney.[40] They are most marked in patients with unilateral PA[41,42] and are reversed within one month of adrenalectomy (Figure 1).[40,43–55] Hemodynamic stress and hyperaldosteronism *per se* lead to chronic structural damage in the long run.[45,56]

PA patients have been reported to display a certain level of insulin resistance, which may improve after adrenalectomy.[57,58] However, PA patients have the same likelihood of clinically defined glucose and lipid metabolism disorders at diagnosis as similar patients with essential hypertension, and adrenalectomy does not improve their clinical metabolic profile.[37,59,60]

One study suggests that the subjective well being of patients with unilateral PA, which is lower at baseline than that of the general population, significantly improves after adrenalectomy.[61]

Drug-based treatment for PA

As the deleterious consequences of hyperaldosteronism depend on salt loading, dietary salt reduction is a cornerstone of medical treatment. A strict low-salt diet as the sole intervention in patients with PA reduces BP, restores the nocturnal dip in BP and lessens hypokalemia.[62–64] Moreover, dietary salt reduction greatly potentiates the effect of spironolactone.[65] However,

strict compliance with a low-salt diet is as difficult to achieve in PA patients as in other subjects.

Spironolactone is a potent, cheap but non-selective MRA. The usual daily dose of spironolactone required to achieve normokalemia and a significant decrease in BP in patients with PA ranges from 50 mg to 200 mg, and the published evidence was obtained from studies involving daily doses of 100 mg or more.[66] However, adverse effects of this drug, due to its anti-androgenic and anti-progesterone activity, limit the use of such doses in many men and some women. Doses below 50 mg/day are usually well tolerated,[67] but are not always sufficient to correct PA completely. Eplerenone, a selective MRA, is an appealing alternative in settings where its use for PA is approved.[68] However, double the dose is required to achieve an efficacy similar to that of spironolactone for lowering BP, and the ceiling effect appears to occur sooner: a 10 mmHg decreased in systolic BP at most, versus 25 mmHg for spironolactone.[69] Moreover, eplerenone must be administered twice daily to ensure activity throughout the day and is currently more expensive than spironolactone.

Amiloride is an ENaC blocker that opposes the reabsorption of sodium in exchange for potassium in the distal tubules and collecting ducts. In most countries, it is available in the form of 5 mg tablets, although the usual daily dose required to correct hyperaldosteronism effectively is 10 to 40 mg.[70] Its half life is 8 hours, and twice-daily intake is therefore required for an optimal effect. Triamterene is another ENaC blocker.[71,72] In many countries, triamterene is only available in combination with thiazide diuretics. Amiloride (or triamterene) can be used to complement the highest well tolerated dose of spironolactone: as a rule of thumb, 10 mg amiloride or 100 mg triamterene prevent potassium wastage as effectively as 25 mg spironolactone.[70,72]

The long-term use of potassium supplements is undesirable. They are costly and cause gastrointestinal discomfort. Slow-release tablets are better tolerated but may cause esophageal and gastrointestinal ulcerations. Appropriate doses of spironolactone or amiloride are always sufficient to correct hypokalemia. Serum potassium concentration should be monitored 7 to 15 days after each change in the dose of potassium-sparing diuretics (MRAs, ENaC blockers).

MRAs, even if used in combination with ENaC blockers, are often insufficient to control BP. The most logical adjunctive treatments are thiazide diuretics and calcium channel blockers (CCB). Thiazide diuretics potentiate natriuresis, helping to decrease plasma volume. They act in synergy with spironolactone and ENaC blockers.[65,71] In patients with low eGFR, they can be replaced by loop diuretics. Several dihydropyrine calcium channel antagonists weakly antagonize the mineralocorticoid receptor or inhibit key enzymes of aldosterone biosynthesis (most notably CYP1B2).[73,74] Nifedipine, nitrendipine and felodipine are the available molecules with the greatest antialdosterone potency. Nifedipine has been tested as a monotherapy in 10 PA patients, and was shown to have a significant effect on BP, serum potassium and aldosterone concentrations at four weeks.[75] Beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and aliskiren are probably not the best choices for decreasing BP in PA patients, because renin activity is chronically suppressed in these patients.[76] However, ARBs may be beneficial in some patients with bilateral hyperplasia or angiotensin-responsive adenoma.[77,78]

Finerenone, a new non-steroidal and highly potent MRA, has been studied in patients with chronic heart failure and mild CKD; it seems to decrease BNP and albuminuria as efficiently as spironolactone.[79,80] Aldosterone synthase inhibitors are currently in clinical development.

For instance, LCI699 has been tested in patients with PA, with mixed results: aldosterone secretion was decreased, but this did not translate into a lowering of BP. Moreover, the drug induced a blunted glucocorticoid response to ACTH of uncertain clinical significance.[81,82]

Outcomes of drug-based treatment

No randomized study has compared the BP outcome of adrenalectomy with that of specific drugs in patients with unilateral PA. However, drug-based treatment in 24 patients with unilateral PA led to normokalemia in all patients and long-lasting BP decreases of a magnitude similar to that observed in surgical series.[83] Moreover, a prospective study showed that the BP-lowering effect of high-dose spironolactone was similar to, or even slightly greater than that of subsequent adrenalectomy in 44 patients.[84]

Spironolactone may appear to be less potent than adrenalectomy for improving left ventricular hypertrophy, but studies with long-term follow-up have shown that the same improvement is ultimately achieved, even though the regression of left ventricular mass is slower with spironolactone than with adrenalectomy.[29,34,85] The benefits of PA treatment were similar for specific drugs and surgery in both studies comparing the incidence of cardiovascular events in treated PA patients and matched controls with essential hypertension.[36,37]

The relative glomerular hyperfiltration and microalbuminuria of PA patients are corrected on specific drugs (Figure 1).[40,44–46,50,51,53–55] Spironolactone was found to be less effective than surgery for achieving this end in one study using a fixed low dose (50 mg/day).[50] Five other studies, with spironolactone uptitrated as needed and tolerated, revealed effects no different from those of surgery.[44–46,48,53,55]

PA patients treated with spironolactone or amiloride experience an improvement in well-being similar to that observed after adrenalectomy, although these effects appear to be established more slowly.[86]

Treatment choice as a function of PA subtype

Adrenal carcinomas are very rare (1-2/million subjects/year) and present as isolated PA in less than 5% of cases. Carcinomas are often irregular and exceed 40 mm in size; their spontaneous density on adrenal CT is > 10 UH, with heterogeneous enhancement and slow contrast washout, and they may infiltrate surrounding tissues and invade adjacent organs.[87] Resection by open surgery is the cornerstone of treatment, except for carcinomas with distant metastases.

Familial hyperaldosteronism type 1 or glucocorticoid-remediable aldosteronism (GRA) is also very rare. Patients with this disorder have a chimeric gene, placing aldosterone synthase transcription under the control of ACTH, causing bilateral PA. Autosomal dominant inheritance results in familial clusters of cases. Low-dose dexamethasone (0.125 to 0.25 mg/day) or low-dose prednisone (2.5 to 5 mg/day) at bedtime efficiently suppresses ACTH secretion, thereby decreasing the ACTH-dependent hyperaldosteronism.[88] The following characteristics of patients should lead to genetic testing: early primary aldosteronism (< 30 years old) or early cerebrovascular events (< 50 years old), in the patient or a close relative.[89]

For the more common causes of PA, treatment options depend on lateralization: unilateral PA is amenable to adrenalectomy, whereas bilateral PA generally is not. Adrenal venous sampling (AVS) is recommended to compare the aldosterone secretion of the two adrenal glands.[88,90,91] AVS is invasive, performed only at referral centers and its use is based on a

pathophysiological rationale rather than solid clinical evidence.[42,92] However, the rate of complications is low and no better supported alternative has yet been identified.[93] Guidelines have recently been published, with the aim of decreasing the heterogeneity of AVS protocols and interpretation criteria, although the evidence supporting the recommendations is weak.[94]

Subtype diagnosis, and hence AVS, is required only if surgery is being considered. Some factors are significantly associated with persistent hypertension after surgery:[11] being male, advanced age, familial hypertension, longer duration and higher grade of hypertension, higher body mass index, higher serum potassium concentration, lower glomerular filtration rate, higher 24h urinary aldosterone secretion, subclinical target organ damage. However, none of these predictors has been consistently confirmed in all published series. Moreover, their predictive value at the individual level is limited. Typically, a patient with an unfavorable profile still has a 25% chance of being cured of hypertension by adrenalectomy[95] and, even if hypertension persists, the patient will experience a significant decrease in BP and/or treatment requirements.[92] Moreover, the normalization of aldosterone secretion probably has BP-independent benefits. Factors predictive of the persistence of hypertension after adrenalectomy should not, therefore, be used as arguments for or against surgery in individual cases.

Surgery should be considered an option in all patients without contraindication who are willing to undergo AVS, followed by adrenalectomy if lateralization is demonstrated. Unlike the drugs currently available, surgery normalizes aldosterone secretion, thereby preventing all the effects of aldosterone overproduction. However, as we have seen above, this theoretical advantage does not translate into a proven clinical advantage over specific drug treatment.

The most consistent argument for surgery in unilateral PA is that it eliminates or decreases the need for drug treatment and the economic and psychological burden that such drug treatment entails. A primitive cost-effectiveness analysis found that adrenalectomy, with a 35% cure rate and a 85% improvement rate, was a cost-saving option for 50-year-old PA patients, as it eliminated the need for lifelong drug therapy.[96] Another more thorough cost-effectiveness analysis suggested that, for PA patients with a life expectancy of more than 25 years, performing AVS in all patients and adrenalectomy in those displaying lateralization would be cheaper than not carrying out AVS and providing lifelong drug treatment for all patients.[97] However, the assumptions of the model (cure rate; cost of medical treatment, AVS and surgery) may not extend to all settings.

Younger patients have a longer life expectancy and therefore derive greater benefit from surgery. The risk of anesthesia is also smallest in this group of patients. The early diagnosis of unilateral PA is therefore important. Patients with resistant hypertension may also derive a significant benefit from surgery, particularly if compliance is an issue or if spironolactone is ineffective or not well tolerated. The benefit-risk ratio is less positive in older patients, particularly if there are compelling indications for antihypertensive drugs, which must be continued irrespective of BP levels. This is the case for beta-blockers for coronary artery disease and for ACE inhibitors and spironolactone for heart failure.

Only the few patients at high surgical risk and those with a short life expectancy should be advised against surgery. However, patients should not be coerced into considering surgery if they prefer not to undergo the procedure, given that there is reasonable evidence to suggest that lifelong treatment with mineralocorticoid antagonists is a valid alternative to surgery. Treatment choice should therefore also be driven by the preferences of the patient. Candidates

for surgery should be told that the presence of an APA poses no risk in terms of cancer. They should also be informed that the clinical outcomes of surgery and medication are similar, that hypertension is cured by surgery in only 40% of cases but that medication levels and BP are lowered even in those not cured, and that, in the absence of surgery, medication is lifelong and not always well tolerated. Patients may opt for a trial period on spironolactone before deciding whether to consider surgery and, therefore, to undergo AVS.

Patients with bilateral PA and those who refuse or have a contraindication for surgery should be treated with spironolactone, beginning with a dose of 25 mg/day, with uptitration until kalemia and blood pressure are normalized. Dietary sodium restriction should be actively promoted, because the deleterious consequences of hyperaldosteronism depend on salt loading. If spironolactone is poorly tolerated, the highest accepted dose should be complemented with amiloride, starting at a dose of 5 mg twice daily, with uptitration as required. Eplerenone can be used instead of this spironolactone-amiloride combination in settings in which it is approved for the treatment of hypertension, provided that the patient can afford it. We favor the spironolactone-amiloride combination over eplerenone because a beneficial impact on clinical events has been shown with spironolactone but not yet with eplerenone. If BP remains uncontrolled despite potassium-sparing diuretics, thiazide or loop diuretics and CCB should be added, as required. Unilateral adrenalectomy has been performed in a few patients with presumed bilateral disease refractory to drug treatment or unable to tolerate optimal medical management.[98] Hypertension was cured or improved in about one third of these patients, particularly those with mild PA or one dominant adrenal gland on AVS, even though the lateralization criterion was not met.

CKD affects the clinical profile of patients with PA and the effectiveness and risk associated with treatment options; it must therefore be taken into account when clinical decisions are made (Table 1).

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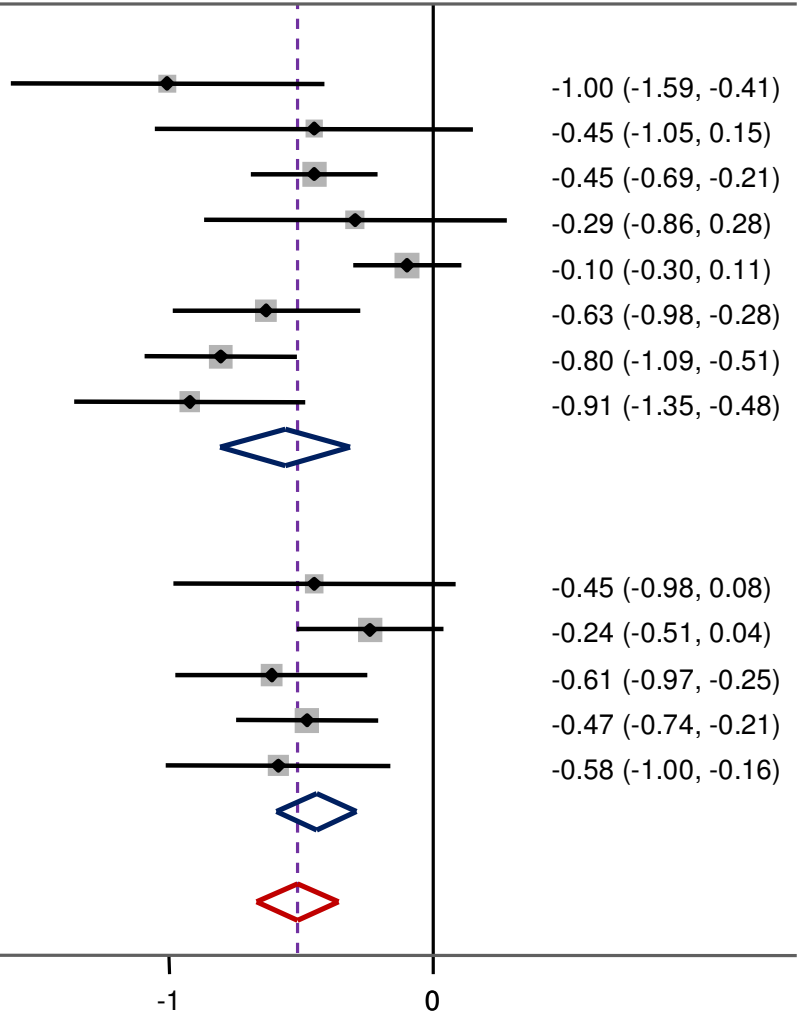
Table 1. Particularities of primary aldosteronism (PA) treatment in patients with chronic kidney disease (CKD)

Surgical treatment
• Contrast nephropathy is a specific concern when planning to perform adrenal venous sampling in CKD patients to identify those who could undergo adrenalectomy. However, complications are rare with appropriate hydration and the smallest possible amount of a low-osmolar contrast medium (less than 50 ml).[99] • Patients with CKD are at risk of hyperkalemia after adrenalectomy. Mineralocorticoid receptor antagonist treatment and potassium supplements should be discontinued immediately after surgery and serum potassium concentrations should be monitored closely.[25] • Adrenalectomy also unmasks postoperative eGFR below 60 ml/min/1.73m² in 30% to 40% of patients with unilateral PA.[52,54,55] It is more likely in patients who have a preoperative eGFR that is already close to this threshold.[54]
Drug-based treatment
• The pharmacokinetics of spironolactone and eplerenone are unaffected in patients with CKD.[100] Amiloride is partly excreted in the urine and its half-life is longer in patients with CKD, so lower doses and once-daily intakes can be used. Triamterene crystallizes in the urine, causing nephrolithiasis and acute kidney injury. It should not be used in patients with CKD. • Patients with CKD are prone to hyperkalemia with potassium-sparing diuretics (mineralocorticoid receptor and epithelial sodium channel blockers). However, patients with CKD are likely to require higher doses of mineralocorticoid blockers, due to their antiproteinuric and antifibrosing effects.[101] The initiation of treatment at a low dose and slow upward titration are advised.[100] Serum potassium concentration should be monitored within 7 days of each change in the dose of potassium-sparing diuretics. • Several drugs potentiate potassium retention and should be used with caution: beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aliskiren, nonsteroidal anti-inflammatory drugs, heparins, trimethoprim, and calcineurin inhibitors. Loop diuretics and low-potassium diet can help to control hyperkalemia in patients with advanced CKD who are taking potassium-sparing diuretics. • Finerenone, a new non-steroidal mineralocorticoid receptor antagonist seems to be as effective as spironolactone and results in lower levels of hyperkalemia in patients with mild CKD.[79]

Figure 1. Kidney function decline after the specific treatment of primary aldosteronism

*standardized mean differences are expressed as the number of observed standard deviations

		Estimated glomerular filtration rate mean (standard deviation), ml/min/1.73m²		Standardized mean difference* (95% confidence interval)
Adrenalectomy	N	Before	After	
Ribstein (2005)[43]	25	102 (15)	87 (15)	-1.00 (-1.59, -0.41)
Sechi (2006)[44]	22	102 (27)	89 (31)	-0.45 (-1.05, 0.15)
Reincke (2009)[46]	137	73 (22)	64 (18)	-0.45 (-0.69, -0.21)
Pimenta (2010)[49]	24	139 (51)	124 (48)	-0.29 (-0.86, 0.28)
Wu (2011)[51]	185	85 (27)	83 (27)	-0.10 (-0.30, 0.11)
Wu (2011)[50]	65	106 (33)	84 (36)	-0.63 (-0.98, -0.28)
Iwakura (2014)[55]	102	81 (20)	65 (20)	-0.80 (-1.09, -0.51)
Tanase-Nakao (2014)[54]	45	85 (21)	67 (18)	-0.91 (-1.35, -0.48)
Subtotal				
Drug-based treatment	N	Before	After	
Sechi (2006)[44]	28	105 (31)	92 (27)	-0.45 (-0.98, 0.08)
Wu (2011)51	101	87 (27)	81 (27)	-0.24 (-0.51, 0.04)
Wu (2011)[50]	62	101 (31)	82 (31)	-0.61 (-0.97, -0.25)
Iwakura (2014)[55]	111	79 (21)	69 (21)	-0.47 (-0.74, -0.21)
Tanase-Nakao (2014)[54]	45	85 (21)	74 (18)	-0.58 (-1.00, -0.16)
Subtotal				
Overall