Routine Screening for Primary Hyperaldosteronism in Hypertensive Patients: Yes or No?

27

Konstantinos P. Economopoulos and Carrie C. Lubitz

Abstract

Primary hyperaldosteronism is the most common cause of secondary hypertension and endocrine-related hypertension and is characterized by autonomous, inappropriately elevated serum aldosterone, arising from either an aldosterone producing adenoma or bilateral adrenal hyperplasia. In comparison to matched patients with primary (essential) hypertension, patients with both subtypes of primary hyperaldosteronism have increased odds of stroke, non-fatal heart attack and atrial fibrillation. Moreover, patients with primary hyperaldosteronism have worse psychosocial and quality of life scores when compared to patients with primary hypertension. Although treatment guidelines for primary hyperaldosteronism vary, diagnosis is usually focused on identifying serum hyperaldosteronism and subsequently by differentiating between unilateral and bilateral disease with imaging (CT or MRI) and/or adrenal-venous sampling. Most patients with aldosterone producing adenoma can be managed successfully with laparoscopic adrenalectomy, not only by curing their hypertension, but also by reversing cardiovascular and renal complications. Moreover, primary hyperaldosteronism patients diagnosed with bilateral-adrenal hyperplasia can likewise have improvement in hypertension and downstream cardiovascular outcomes with appropriate mineralocorticoid-receptor antagonist treatment.

Keywords

Primary hyperaldosteronism · Secondary hypertension · Screening · Adrenal venous sampling · Adrenalectomy · Mineralocorticoid receptor antagonists

K. P. Economopoulos
Department of Surgery, Duke University, Durham, NC, USA

C. C. Lubitz (✉)
Department of Surgery, Massachusetts General Hospital, Boston, MA, USA

Institute for Technology Assessment, Boston, MA, USA
e-mail: CLUBITZ@mgh.harvard.edu

P. Angelos, R. H. Grogan (eds.), *Difficult Decisions in Endocrine Surgery*,
Difficult Decisions in Surgery: An Evidence-Based Approach,
https://doi.org/10.1007/978-3-319-92860-9_27

What Is the Public Health Impact of Hypertension?

Hypertension (HTN; see table 1 for most commonly used abbreviations) is the leading cause of heart disease, stroke and death and costs the U.S. over 46 billion annually [1]. Seventy-six million Americans and one billion people worldwide suffer from the disease [2]. The primary goals of treatment of HTN, as these are listed by the Joint National Committee on prevention, evaluation, and treatment of high blood pressure are: (1) Targeting modifiable lifestyle risk factors, (2) Treating end-organ damage, and (3) Identifying the cause of the disease.

Resistant hypertension (RH), defined as failure to meet goal BP with a three-drug antihypertensive regimen, including a diuretic, in a compliant patient, is estimated between 12 and 30% of the hypertensive population [3–5]. Morbidity and death are even greater with RH. As outlined by expert and commonly practices, a work-up for secondary causes of hypertension is postponed until standard treatment for primary hypertension has failed [3, 6–8]. The clinical approach to these patients is a matter of debate and on-going research. We argue that earlier approaches to subtype differentiation and treatment of potentially curable causes of hypertension are of paramount public health concern.

Why Should We Screen for Primary Hyperaldosteronism?

Primary hyperaldosteronism (PA) is the most common cause of secondary HTN and is characterized by autonomous, inappropriately elevated serum aldosterone, arising from either an aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia (BAH) [9–14]. Recent reports indicate a higher prevalence of PA than previously thought. This may be attributable to improvements in our diagnostic armamentarium (e.g. increased use of screening with aldosterone-renin ratio) and increased use and quality of abdominal imaging. Best estimates of the prevalence of PA in hypertensive population are approximately 10% [15]; the prevalence of PA in the resistant hypertensive population is more than two times higher, almost 23% [3, 16–18]. Most patients with aldosterone producing adenoma (APA) can be managed successfully with laparoscopic adrenalectomy. Depending on the definition of “cure”, 33–77% are cured or benefited by surgery [19–23]. It has been shown that treatment of aldosterone excess results in vascular remodeling, reversal of ventricular hypertrophy and reverses cardiovascular and renal complications [21, 24].

Given 1/8 of the hypertensive population has resistant hypertension, approximately 1/5 of patients with resistant hypertension have PA, and half of patients with PA have unilateral disease, we estimate over a million hypertensive patients in the U.S. could be potentially cured with surgery [13, 25, 26]. Not only could we potentially cure those patients with unilateral disease with screening, we can also identify those patients with bilateral adrenal hyperplasia likely to benefit from disease-targeted mineralocorticoid-receptor antagonists. Disease-specific therapy—either medical or surgical is more effective [26–33]. In comparison to primary hypertensive patients matched for blood pressure, patients with PA have four times increased

odds of stroke, seven times increased odds of non-fatal myocardial infarction, and 12 times increased odds of atrial fibrillation [14]. Moreover, it has been consistently shown length of time with hypertension is correlated with failure of cure following surgery for APA [22, 23].

Are Clinical Signs and Symptoms of Primary Hyperaldosteronism Helpful?

Patients with PA are difficult to distinguish from patients with primary hypertension. Frequently, HTN is the only clinical sign of PA, making its diagnosis extremely challenging. Because of this, PA is frequently over-looked and under-diagnosed. PA is characterized by inappropriately elevated plasma aldosterone, non-suppressible with sodium, which causes serum hypernatremia, hypokalemia, metabolic alkalosis, and suppression of renin [10]. Given that many patients with all forms of hypertension are on a number of anti-hypertensive medications that can affect the renin-angiotensin system, minor electrolyte abnormalities often go unnoticed. In rare instances, patients can present with muscle weakness, muscle cramping, myalgia and tremor which are the signs and symptoms of hypokalemia. While hypokalemia is commonly referenced as a distinguishing feature of patients with PA, it is present in <40% of patients with the disease [34]. Even more rarely, patients may be diagnosed during biochemical and/or hormonal evaluation of an adrenal incidentaloma with early-onset HTN or stroke [35]. Age nor gender is helpful in distinguishing PA within the hypertensive population with a mean age of diagnosis of PA of 52 years old and close to equivalent rate between men and women [36]. Moreover, there is no increased race or ethnicity-specific incidence of PA [36]. In sum, a high index of suspicion and systematic screening for patients with PA are the only clear way to identify potentially curable disease.

Who Should We Screen for Primary Hyperaldosteronism and How?

There is no consensus among experts on who should be screened for PA and currently there are no guidelines recommending the screening of all primary hypertensive patients for PA [11, 12, 36, 37]. However, it is agreed in the field that patients who fail to have their blood pressure corrected following concurrent administration of three antihypertensive medications with one diuretic (i.e. resistant hypertension), should be screened for secondary causes of hypertension [3, 7, 8]. Other possible entities causing secondary hypertension and their biochemical profiles should be considered while screening these patients (Table 27.1).

Serum potassium levels were historically used to be the only screening tool for the diagnosis of PA. However, hypokalemia is currently known to occur in less than 38% of the PA population, rendering it an inappropriate screening test for PA [15]. While hypokalemia is not a sensitive screening test, in a patient with

Table 27.1 Biochemical profiles of different causes of secondary hypertension

Disease	Potassium	Aldosterone	Renin
Aldosterone-producing adenoma	50%↓↓	↑↑	↓
Bilateral adrenal hyperplasia	17%↓	↑↑	↓
Loop-diuretic therapy	↓	↓	↑
Renal artery stenosis	↓	↑	↑
Congenital adrenal hyperplasia	↓	↓	↓
Cushing's syndrome	↓	↓	↓
Familial hyperaldosteronism			
Type I or GRA	Normal	↑↑	↓
Type II	↓	↑	↓
Type III	↓	↑	↓

difficult-to-control hypertension, hypokalemia is predictive of PA and other secondary etiologies of hypertension. Patients with hypertension and hypokalemia should be screened for iatrogenic causes (e.g. loop-diuretic therapy, exogenous steroids), anatomic abnormalities (e.g. renal artery stenosis), as well as other congenital and acquired pathologies (APA, BAH, congenital adrenal hyperplasia, familial hyperaldosteronism, ectopic ACTH production and Cushing's disease). Patients with an incidentaloma found on abdominal imaging should undergo a hormonal and biochemical diagnostic work-up.

Aldosterone-to-renin ratio (ARR) has been proposed as the gold standard initial diagnostic tool for PA in hypertensive patients by most endocrine and cardiovascular societies. However, published guidelines on threshold ratios (conventional threshold ARR $\geq$ 20) and subsequent steps in management substantially differ among different societies (Table 27.2) [3, 7, 8, 38]. Given the obscure clinical picture of PA and the disagreement in the optimal diagnostic method, some experts recommend use of a combination of tests. The American Heart Association and American Association of Clinical Endocrinologists (AACE)/American Association of Endocrine Surgeons (AAES) guidelines use an absolute serum aldosterone level $\geq$ 15 ng/dL in addition to an ARR $\geq$ 20 for diagnosis of PA. An ARR > 30 and a serum aldosterone >20 ng/dL was shown to have both sensitivity and specificity >90% in diagnosing APA [39]. Rossi et al. developed a model with superior diagnostic accuracy using a combination of plasma renin activity, potassium, and either serum aldosterone or captopril-suppressed aldosterone [40]. The threshold value utilized by a clinician may also vary depending on the lateralization strategy at that institution. Knowledge and application of testing characteristics (i.e. using a higher threshold increased false-negatives) is essential to guide clinical decision making.

Although ARR is the best screening test we have for the diagnosis and differentiation of PA, its accuracy depends on many factors, such as age, posture, time of day, medications, serum electrolyte levels and cause of hypertension [8]. It is essential that the clinician is aware of how the aforementioned factors affect the ARR results (Table 27.3). Confirmatory testing is recommended with either administration of oral or intravenous saline, captopril, or fludrocortisone as the specificity of

Table 27.2 Consensus guideline recommendations for PA screening

Guidelines	Criterion for screening	Suggested ARR threshold	Confirmatory test	Imaging	AVS
AACE/AAES Guidelines for the Management of Adrenal Incidentalomas [35]	Incidental adrenal nodules + HTN, new HTN, HTN + hypokalemia, resistant HTN	ARR ≥ 20 + plasma aldosterone ≥ 15 ng/dL	Oral salt loading or saline infusion testing	CT	Yes, in all except age < 40 + unilateral 1 cm nodule on CT (directly to surgery)
American Heart Association Guidelines for Resistant Hypertension [3]	Resistant hypertension	ARR 20–30 (using minimum renin 0.5 ng/mL/h) ± plasma aldo ≥ 15 ng/dL	–	–	–
Endocrine Society clinical practice guidelines [8]	JNC 7 [7] stage 2, resistant HTN, hypokalemia, incidentalomas, family history	ARR 20–40	Oral sodium, saline infusion, captopril, or fludrocortisone suppression testing	CT	Yes, in all surgical candidates
ESH/SSC Guidelines for the management of arterial hypertension	Incidental adrenal nodules + HTN, new HTN, HTN + hypokalemia, resistant HTN	ARR ≥ 20 + plasma aldosterone ≥ 15 ng/dL	Oral salt loading or saline infusion testing	CT	Yes, in all except age < 40 + unilateral 1 cm nodule on CT

AACE American Association of Clinical Endocrinologists, *AAES* American Association of Endocrine Surgeons, *ARR* plasma renin to aldosterone ratio, *ESH* European Society of Hypertension, *ESC* European Society of Cardiology

Table 27.3 Factors that affect the aldosterone-renin ratio (ARR)

Factor	Effect on ARR
Increased age	FP
Hypokalemia	FN
Hypernatremia	FP
Pregnancy	FN
Renal failure	FP
Resistant hypertension	FN
Drugs	
Diuretics	FN
ACE inhibitors	FN
ARBs	FN
β-blockers	FP
CCB	FN

FP false-positive (FP), decreased specificity, *FN* false-negative, decreased sensitivity

screening tests are low. Oral load of 5 g sodium diet for 3 days is followed by a 24 h urinary aldosterone level; when urinary aldosterone is greater than 12 μg the diagnosis of PA is confirmed. Also, intravenous load of 2 L saline infused over 4 h is followed by quantification of serum aldosterone; serum aldosterone >10 ng/dL confirms PA. However, confirmatory suppression testing could be potentially dangerous, especially for patients with exacerbation of congestive heart failure [37, 41]. For the most accurate measurements of confirmatory testing: (1) hypokalemia should be corrected, (2) hypertension should be controlled and (3) patients should not be under treatment with a mineralocorticoid receptor antagonist, such as spironolactone or eplerenone, for 6 weeks prior to testing. On the contrary, screening with ARR has been shown to still be useful without withdrawing anti-hypertensive medications and should be utilized in cases where discontinuation of medications may be harmful [8, 17, 36].

How Do We Identify Appropriate Patients for Adrenalectomy?

The next step after confirming a serological diagnosis of PA is to identify if this is due to unilateral (APA or unilateral hyperplasia) or bilateral adrenal disease (BAH). The great majority of patients with unilateral disease treated with adrenalectomy have improvement if not cure from their hypertension [42]. Given that most aldosteronomas are benign and fewer than two centimeters, nearly all tumors can be removed laparoscopically. Although it has been noted that APA patients have higher systolic blood pressure, lower serum potassium and higher aldosterone levels compared to BAH patients on average, there is no single diagnostic test to successfully differentiate the two pathologic entities [43–45]. This is mainly because APA, BAH and primary hypertension could all present with systolic blood pressure and spontaneous hypokalemia while on numerous antihypertensive medications and varying clinical settings in which the blood pressure is assessed [18]. Prior to pursuing

lateralization, a thorough discussion with the patient about the risks and benefits of surgery as well as the benefits and potential side effects of medical therapy (i.e. mineralocorticoid receptor antagonists) is needed.

Identifying the right candidates for adrenalectomy remains challenging. Frequently, the first step in assessing unilateral versus bilateral aldosterone-excess is by non-invasive imaging techniques (traditionally with CT scan). The major drawback of CT scan is that it does not provide us with any information regarding the functionality of the adrenal tumors. Also, aldosteronomas are frequently small tumors, thus increasing the false-negative rates and decreasing the sensitivity of CT scan. Rossi et al. reported on 1125 PA patients and found that 17% of them had tumors <1 cm, while 45% had tumors <2 cm [18]. In addition, non-functional adenomas increase with age, leading to high-false positive rates and decreased specificity of CT scan in the elderly. Magill et al. reported an accuracy rate of CT of 37% when is directly compared to adrenal venous sampling (AVS) [45]. Young et al. performed a direct comparison of AVS and CT scan lateralization results on 194 PA patients. In their study, 41% of patients who had negative CT scans had positive AVS results, CT identified the wrong adrenal gland in 21% of the patients and AVS falsely diagnosed four patients with bilateral adrenal hyperplasia [46]. However, CT scan is particularly helpful in assessing for large adrenal tumors, with tumors larger than 4 cm raising the suspicion for aldosterone-secreting adrenocortical carcinoma. Due to the aforementioned weaknesses of CT, we believe that AVS should be performed in all patients willing to undergo surgery (Fig. 27.1). Because incidental non-functional adrenal nodules in patients younger than 40 years old are rare, the AACE/AAES experts recommend proceeding with adrenalectomy without AVS when CT scan shows a unilateral microadenoma (with clear ARR elevation) [35].

Adrenal venous sampling is a costly and difficult procedure that is not available in all hospitals and clinics, but it remains one of the best diagnostic tools for

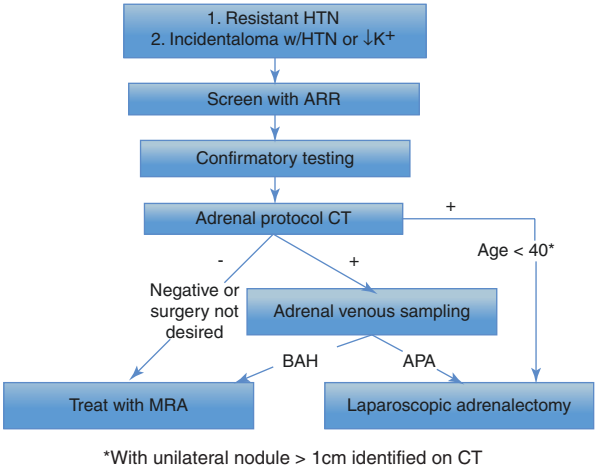

Fig. 27.1 Algorithm for diagnosis and treatment of surgically-correctable primary aldosteronism

lateralization of PA patients to date. It requires cannulation of both adrenal veins and inferior vena cava (IVC) and comparison of aldosterone and cortisol levels in these specific regions of venous circulation. ACTH stimulation is used to amplify potential laterality by reducing stress-induced fluctuations during cannulation and sampling, assisting in differentiating IVC versus right adrenal vein cannulation (adrenal to IVC cortisol ratio greater than 5 indicates proper placement in the right adrenal vein) and maximizing aldosterone secretion [46, 47]. Cortisol measurements are used to normalize aldosterone levels and cortisol-adjusted aldosterone lateralization ratio greater than 4 is indicative for adrenalectomy with a sensitivity ranging from 78 to 98% [45, 46, 48].

Successful catheterization of both adrenal veins ranges from 95% to 97% in experienced centers [43, 46]. However, in low volume centers with minimal experience with the procedure this rate could drop as low as 10% [49]. Complications due to AVS and adrenal vein rupture are seen in less than 3% and 1%, respectively, in high-volume centers [43, 46].

The main limitation of AVS is the variation in indication, technique and diagnostic cut-off values proposed by different research groups [43, 45, 46, 50]. Limited access to the procedure, technical difficulty, high cost and potential complications (such as hematoma, adrenal infarction and aortic dissection) are cited as arguments against using AVS regularly [51]. Successful categorization of PA patients in APA and BAH subtypes ranges from 63% to 97% in the literature [45, 52, 53].

Given the inaccuracies of CT and relatively low morbidity of AVS, we recommend AVS when available. Whether or not utilizing AVS in every case is a cost-effective approach has not been evaluated to date.

Routine Screening for Primary Hyperaldosteronism in Hypertensive Patients?

Yes. PA is a prevalent and under-diagnosed disease. While the screening tests for PA and lateralization strategies are imperfect, the benefits of definitive treatment are clear. Prevalence estimates have recently increased, mainly due to successful screening. The more we are looking, the more we are finding. Hypertension is epidemic and PA is the main etiology in at least 10% of this population. Given that approximately half of those patients (i.e. 5% of the hypertensive population) have unilateral disease, we have the potential to help a large group of patients by screening and targeted treatment of patients with PA, especially in the subgroup of patients with high-risk RH. Furthermore, AVS and laparoscopic adrenalectomy are safe procedures and length of stay following surgery and loss of productivity are minimal.

The financial impact of a screening strategy has been less well studied and is forthcoming. Reimel et al. found surgical treatment to be cost-effective compared to medical therapy alone in PA patients [54]. Our group presented our finding that screening all patients with resistant hypertension for PA is cost-effective at accepted willingness to pay thresholds (American Association of Endocrine Surgeons, Boston MA, 2013). It is less clear if screening the primary hypertensive population at large to identify and treat PA patients is cost-effective and is a key focus of on-going work.

In summary, we believe that the health benefits of targeted intervention for the significant portion of PA patients within the primary hypertensive population warrant early screening, especially in those patients with poorly controlled hypertension, those with concomitant hypokalemia, or known adrenal nodules.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29–322.
2. Rodriguez F, Foody J. Primary prevention of cardiovascular disease. In: Stergiopoulos K, Brown DL, editors. Evidence-based cardiology consult. London: Springer; 2014. p. 149–58.
3. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association professional education Committee of the Council for high blood pressure research. Circulation. 2008;117(25):e510–26.
4. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation. 2011;124(9):1046–58.
5. Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. Hypertension. 2011;57(6):1076–80.
6. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth joint National Committee (JNC 8). JAMA. 2014;311(5):507–20.
7. Green L. JNC 7 express: new thinking in hypertension treatment. Am Fam Physician. 2003;68(2):228, 30.
8. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(9):3266–81.
9. Fagugli RM, Taglioni C. Changes in the perceived epidemiology of primary hyperaldosteronism. Int J Hypertens. 2011;2011:162804.
10. Fardella CE, Mosso L, Gomez-Sanchez C, Cortes P, Soto J, Gomez L, et al. Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology. J Clin Endocrinol Metab. 2000;85(5):1863–7.
11. Gordon RD, Stowasser M. Primary aldosteronism: the case for screening. Nat Clin Pract Nephrol. 2007;3(11):582–3.
12. Lim PO, Rodgers P, Cardale K, Watson AD, MacDonald TM. Potentially high prevalence of primary aldosteronism in a primary-care population. Lancet. 1999;353(9146):40.
13. Strauch B, Zelinka T, Hampf M, Bernhardt R, Widimsky J Jr. Prevalence of primary hyperaldosteronism in moderate to severe hypertension in the Central Europe region. J Hum Hypertens. 2003;17(5):349–52.
14. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol. 2005;45(8):1243–8.
15. Mulatero P, Stowasser M, Loh KC, Fardella CE, Gordon RD, Mosso L, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. J Clin Endocrinol Metab. 2004;89(3):1045–50.
16. Eide IK, Torjesen PA, Drolsum A, Babovic A, Lilledahl NP. Low-renin status in therapy-resistant hypertension: a clue to efficient treatment. J Hypertens. 2004;22(11):2217–26.
17. Gallay BJ, Ahmad S, Xu L, Toivola B, Davidson RC. Screening for primary aldosteronism without discontinuing hypertensive medications: plasma aldosterone-renin ratio. Am J Kidney Dis. 2001;37(4):699–705.

18. Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol. 2006;48(11):2293–300.
19. Rutherford JC, Stowasser M, Tunny TJ, Klemm SA, Gordon RD. Laparoscopic adrenalectomy. World J Surg. 1996;20(7):758–60. discussion 61.
20. Lo CY, Tam PC, Kung AW, Lam KS, Wong J. Primary aldosteronism. Results of surgical treatment. Ann Surg. 1996;224(2):125–30.
21. Rossi GP, Cesari M, Cuspidi C, Maiolino G, Cicala MV, Bisogni V, et al. Long-term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism. Hypertension. 2013;62(1):62–9.
22. Letavernier E, Peyrard S, Amar L, Zinzindohoue F, Fiquet B, Plouin PF. Blood pressure outcome of adrenalectomy in patients with primary hyperaldosteronism with or without unilateral adenoma. J Hypertens. 2008;26(9):1816–23.
23. van der Linden P, Steichen O, Zinzindohoue F, Plouin PF. Blood pressure and medication changes following adrenalectomy for unilateral primary aldosteronism: a follow-up study. J Hypertens. 2012;30(4):761–9.
24. Rossi GP, Bolognesi M, Rizzoni D, Seccia TM, Piva A, Porteri E, et al. Vascular remodeling and duration of hypertension predict outcome of adrenalectomy in primary aldosteronism patients. Hypertension. 2008;51(5):1366–71.
25. Calhoun DA. Hyperaldosteronism as a common cause of resistant hypertension. Annu Rev Med. 2013;64:233–47.
26. Judd E, Calhoun DA. Apparent and true resistant hypertension: definition, prevalence and outcomes. J Hum Hypertens. 2014;28(8):463–8.
27. Ahmed AH, Gordon RD, Sukor N, Pimenta E, Stowasser M. Quality of life in patients with bilateral primary aldosteronism before and during treatment with spironolactone and/or amiloride, including a comparison with our previously published results in those with unilateral disease treated surgically. J Clin Endocrinol Metab. 2011;96(9):2904–11.
28. Vaclavik J, Sedlak R, Plachy M, Navratil K, Plasek J, Jarkovsky J, et al. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension. 2011;57(6):1069–75.
29. Gaddam K, Corros C, Pimenta E, Ahmed M, Denney T, Aban I, et al. Rapid reversal of left ventricular hypertrophy and intracardiac volume overload in patients with resistant hypertension and hyperaldosteronism: a prospective clinical study. Hypertension. 2010;55(5):1137–42.
30. Waldmann J, Maurer L, Holler J, Kann PH, Ramaswamy A, Bartsch DK, et al. Outcome of surgery for primary hyperaldosteronism. World J Surg. 2011;35(11):2422–7.
31. Pang TC, Bambach C, Monaghan JC, Sidhu SB, Bune A, Delbridge LW, et al. Outcomes of laparoscopic adrenalectomy for hyperaldosteronism. ANZ J Surg. 2007;77(9):768–73.
32. Catena C, Colussi G, Lapenna R, Nadalini E, Chiuch A, Gianfagna P, et al. Long-term cardiac effects of adrenalectomy or mineralocorticoid antagonists in patients with primary aldosteronism. Hypertension. 2007;50(5):911–8.
33. Rossi GP, Pitter G, Bernante P, Motta R, Feltrin G, Miotto D. Adrenal vein sampling for primary aldosteronism: the assessment of selectivity and lateralization of aldosterone excess baseline and after adrenocorticotropic hormone (ACTH) stimulation. J Hypertens. 2008;26(5):989–97.
34. Young WF Jr. Minireview: primary aldosteronism--changing concepts in diagnosis and treatment. Endocrinology. 2003;144(6):2208–13.
35. Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D, et al. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocr Pract. 2009;15(Suppl 1):1–20.
36. Schwartz GL, Chapman AB, Boerwinkle E, Kisabeth RM, Turner ST. Screening for primary aldosteronism: implications of an increased plasma aldosterone/renin ratio. Clin Chem. 2002;48(11):1919–23.
37. Mulatero P, Dluhy RG, Giacchetti G, Boscaro M, Veglio F, Stewart PM. Diagnosis of primary aldosteronism: from screening to subtype differentiation. Trends Endocrinol Metab. 2005;16(3):114–9.

38. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31(7):1281–357.
39. Weinberger MH, Fineberg NS. The diagnosis of primary aldosteronism and separation of two major subtypes. Arch Intern Med. 1993;153(18):2125–9.
40. Rossi GP, Rossi E, Pavan E, Rosati N, Zecchel R, Semplicini A, et al. Screening for primary aldosteronism with a logistic multivariate discriminant analysis. Clin Endocrinol (Oxf). 1998;49(6):713–23.
41. Mulatero P, Milan A, Fallo F, Regolisti G, Pizzolo F, Fardella C, et al. Comparison of confirmatory tests for the diagnosis of primary aldosteronism. J Clin Endocrinol Metab. 2006;91(7):2618–23.
42. Stowasser M, Gordon RD. Primary aldosteronism--careful investigation is essential and rewarding. Mol Cell Endocrinol. 2004;217(1–2):33–9.
43. Rossi GP, Sacchetto A, Chiesura-Corona M, De Toni R, Gallina M, Feltrin GP, et al. Identification of the etiology of primary aldosteronism with adrenal vein sampling in patients with equivocal computed tomography and magnetic resonance findings: results in 104 consecutive cases. J Clin Endocrinol Metab. 2001;86(3):1083–90.
44. Blumenfeld JD, Sealey JE, Schlussel Y, Vaughan ED Jr, Sos TA, Atlas SA, et al. Diagnosis and treatment of primary hyperaldosteronism. Ann Intern Med. 1994;121(11):877–85.
45. Magill SB, Raff H, Shaker JL, Brickner RC, Knechtges TE, Kehoe ME, et al. Comparison of adrenal vein sampling and computed tomography in the differentiation of primary aldosteronism. J Clin Endocrinol Metab. 2001;86(3):1066–71.
46. Young WF, Stanson AW, Thompson GB, Grant CS, Farley DR, van Heerden JA. Role for adrenal venous sampling in primary aldosteronism. Surgery. 2004;136(6):1227–35.
47. Doppman JL, Gill JR Jr. Hyperaldosteronism: sampling the adrenal veins. Radiology. 1996;198(2):309–12.
48. Satoh F, Abe T, Tanemoto M, Nakamura M, Abe M, Uruno A, et al. Localization of aldosterone-producing adrenocortical adenomas: significance of adrenal venous sampling. Hypertens Res. 2007;30(11):1083–95.
49. Vonend O, Ockenfels N, Gao X, Allolio B, Lang K, Mai K, et al. Adrenal venous sampling: evaluation of the German Conn's registry. Hypertension. 2011;57(5):990–5.
50. Nishikawa T, Omura M. Clinical characteristics of primary aldosteronism: its prevalence and comparative studies on various causes of primary aldosteronism in Yokohama Rosai Hospital. Biomed Pharmacother. 2000;54(Suppl 1):83s–5s.
51. Stewart PM, Allolio B. Adrenal vein sampling for Primary Aldosteronism: time for a reality check. Clin Endocrinol (Oxf). 2009;72(2):146–8.
52. Young WF Jr, Stanson AW, Grant CS, Thompson GB, van Heerden JA. Primary aldosteronism: adrenal venous sampling. Surgery. 1996;120(6):913–9. discussion 9–20.
53. Sheaves R, Goldin J, Reznek RH, Chew SL, Dacie JE, Lowe DG, et al. Relative value of computed tomography scanning and venous sampling in establishing the cause of primary hyperaldosteronism. Eur J Endocrinol. 1996;134(3):308–13.
54. Reimel B, Zanocco K, Russo MJ, Zarnegar R, Clark OH, Allendorf JD, et al. The management of aldosterone-producing adrenal adenomas--does adrenalectomy increase costs? Surgery. 2010;148(6):1178–85. discussion 85.