Approach to the Patient on Antihypertensive Therapy: Screen for Primary Aldosteronism

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Abstract

Primary aldosteronism is a condition that is still largely overlooked resulting in a significant burden of mortality and morbidity. This is despite decades of clinical and translational research on the deleterious effects of aldosterone on the cardiovascular system and the publication of several guidelines and consensuses on its diagnosis and treatment. One of the main reasons for the low rate of testing is the difficulty of screening patients under anti-hypertensive therapy that potentially interfere with aldosterone and renin levels and thus confound the interpretation of the aldosterone to renin ratio, the accepted and conventionally used screening test. To avoid interference, usually the therapies that affect the renin-angiotensin aldosterone system are withdrawn and substituted with non-interfering medications. However, in many cases the screening test can be confidently interpreted even when such therapies are not discontinued. In this review, we will evaluate the effects of anti-hypertensive therapies on the screening test for primary aldosteronism and suggest a practical approach for its interpretation.

Background

In recent decades, research in humans and animal models provided solid evidence that aldosterone excess, in the presence of high sodium, causes adverse effects to the cardiovascular system (1,2,3), at least partially independent from blood pressure levels. Patients with primary aldosteronism (PA) display an increased prevalence of cardio- and cerebrovascular and renal complications compared with patients with essential hypertension, even when they are matched for common risk factors including blood pressure levels and duration of hypertension (4,5). PA is a frequent cause of secondary hypertension and should be ruled out in most patients with hypertension since a specific pharmacological treatment is available for patients with bilateral PA and potentially curative surgery for unilateral forms (1,2). The prevalence of PA varies between around 5% in patients with hypertension in primary care and around 10% in referral hypertension centres (6-8).

The Endocrine Society Guideline and a European Society of Hypertension (ESH) consensus suggest screening patients with hypertension at a high risk of having PA (1,2) who represent more than 50% of patients with hypertension. The ESH consensus suggests screening patients with blood pressure values higher than 160/100 mmHg or resistant hypertension, patients with hypertension and hypokalemia (either spontaneous or diuretic-induced), hypertension and incidentaloma, hypertension and atrial fibrillation (not caused by an underlying cardiac disease), young patients with hypertension (less than 40 years) and in cases of a family history of PA (1). The Endocrine Society Guideline also suggests screening patients with hypertension and obstructive sleep apnea (2). By contrast, Japanese guidelines and some experts suggest that all patients with hypertension should be screened, regardless of pre-test probability (9-11). Despite these recommendations, in Europe and in the US (12-16), less than 5% of patients with hypertension are tested and this disappointingly low screening rate has not (13) or only marginally increased (14) compared with 20 years ago. Even when hypertension is associated with severe hypokalemia (potassium levels less than 3.0 mEq/L), the rate of PA screening is <4% (17). This is surprising since it has been shown that in patients with hypertension and severe spontaneous hypokalemia the probability of PA is higher than 70% (18). The Lancet Commission identified the lack or delayed diagnosis of secondary hypertension as one of the determining factors of global insufficient blood pressure control (19). All guidelines suggest screening with the aldosterone-to-renin ratio (ARR); renin can be measured as plasma renin activity (PRA) or as direct renin concentration (DRC). The most frequently adopted cut-off for screening is 30 (ng/dL/ng/mL/h) when PRA is measured (2), and around 2 (ng/dL/mU/L) when DRC is used (1). This is lower than the 3.7 cut-off suggested by the ES Guideline; the cut-off suggested by the ESH consensus is based on subsequent studies (20-22) that showed that the ARR displays the highest sensitivity between 1 and 2.7. Furthermore, a study in Chinese patients showed that using 3.7 instead of 2 as an ARR cut-off would miss 18% of patients with PA (23). However, it should be underlined that the ARR should be interpreted as a continuous rather than a categorical (yes/no) variable (24) and thus the higher the ARR the higher the probability of having PA (1,2,24). In some florid cases of positive ARR, for

example, when renin is below the detection limit, aldosterone is above 20 ng/dL and concomitant hypokalemia is present (potassium < 3.5 mEq/L), the diagnosis of PA is confirmed without the need for suppression testing (1,2).

One of the reasons for the low rate of PA screening is that clinicians are reluctant to leave the patient untreated or to withdraw potentially interfering anti-hypertensive therapy for the time necessary for screening and, when necessary, confirmation/exclusion testing. Furthermore, the patient is often under treatment with medication that can interfere with the levels of aldosterone and renin, making the interpretation of the screening test more difficult. However, in many cases, it is possible to interpret ARR results even under anti-hypertensive treatment by taking into account the specific effect of each interfering medication on the renin-angiotensin-aldosterone system (RAAS)(25-27).

Recently, a clinical score (STOP-PA score) and a machine learning algorithm have been shown to efficiently predict the individual pre-test probability of having PA in patients with hypertension. This can potentially reduce the number of patients for screening by 33% without missing patients with unilateral PA (28).

We will discuss below some selected and illustrative cases in which the ARR is interpreted during interfering anti-hypertensive therapy and clinical decisions are taken in accordance with the expected effects of these drugs on the RAAS.

Clinical case 1

Patient 1 is a 50 year-old male under treatment with ramipril 10 mg and hydrochlorothiazide 25 mg, blood pressure (BP) levels of 150/100 mm/Hg, potassium (K^+) levels 3.4 mEq/L, left ventricular hypertrophy at echocardiography, body mass index (BMI) 24 kg/m^2. The patient is then visited by a hypertension specialist for a second opinion. The specialist prescribes an ARR test, but the patient is reluctant to interrupt therapy and undergoes ARR testing without changing medications. DRC is 20

mU/L (PRA 1.6 ng/ml/h) and aldosterone 30 ng/dL, ARR-DRC = 1.5 (ARR-PRA = 18.7); urinary sodium is 145 mEq/day.

The ARR test is negative, but not far from the cut-off for positivity. Notably, the patient is taking 2 medications that are potentially responsible for a false-negative ARR result (1,2,29,30). Both angiotensin-converting enzyme inhibitors (ACE-Is) and diuretics increase DRC and PRA levels, while diuretics increase and ACE-Is reduce aldosterone levels (Table 1). Therefore, we can hypothesize that the substitution of hydrochlorothiazide with a calcium channel blocker (DHP-CCB), such as amlodipine or verapamil, could result in a reduction of DRC and PRA and an increase of the ARR above the cut-off for positivity (2 with DRC ng/dL/mu/L and 30 with PRA ng/dL/ng/mL/h). Suspicion for PA in this patient is also raised by the diuretic-induced hypokalemia (which in turn can reduce the ARR giving false negative results) (29). The risk of having PA for this patient according to a recently validated pre-test clinical score is 41% (24% probability of unilateral PA) (28). Repetition of screening under ramipril and amlodipine gave positive results (DRC 8 mU/L, PRA 0.6 ng/mL/h, aldosterone 26 ng/dL, ARR-DRC= 3.2 and ARR-PRA= 43.3, respectively); K^+ levels were now 3.7 mEq/L. After confirmation, CT scanning and adrenal vein sampling, the patient underwent unilateral adrenalectomy with pathology showing an aldosterone-producing nodule (31) of 8 mm. After surgery the patient had complete clinical and biochemical success (32), that is, PA was cured and the patient became normotensive without therapy.

Clinical case 2

Patient 2 is a 55 year-old female under therapy with olmesartan 40 mg/amlodipine 10 mg, BP is 155/85 mmHg and K^+ 4.4 mEq/L. DRC is 25 mU/L (PRA 2 ng/ml/h), aldosterone 9 ng/dL, ARR-DRC= 0.36 (ARR-PRA= 4.5). This patient has a negative ARR. Theoretically, olmesartan can be responsible for a false-negative ARR (1,2,25,28,32) (Table 1). However, aldosterone levels are lower than the cut-off for a positive captopril-challenge test result and therefore, the probability that the ARR becomes positive after olmesartan withdrawal is very low and a diagnosis of PA canbe

excluded. The patient was tested again after substitution of the therapy with verapamil 240 mg and doxazosin 4 mg per day: DRC was 16 mU/L, PRA 1.2 ng/ml/h aldosterone 13.5 ng/dL, ARR-DRC= 0.84 and ARR-PRA= 11.5.

Clinical case 3

Patient 3 is a 60 year-old male under therapy with atenolol 100 mg and nifedipine 60 mg. BP is 155/90 mmHg and K^+4.6 mEq/L. DRC is 10 mU/L (PRA 0.7 ng/ml/h), aldosterone 13 ng/dL, ARR-DRC= 1.3 (ARR-PRA= 18.6).

This patient has a negative ARR under atenolol that can give a false-positive result (1,2,25,28,32,33) (Table 1) and therefore, a diagnosis of PA is excluded.

Clinical case 4

Patient 4 is a 48 year-old male under therapy with chlortalidone 25 mg, valsartan 320 mg, amlodipine 10 mg. BP is 150/100 mmHg, K^+ 3.3 mEq/L. DRC is 15 mU/L (PRA 1 ng/ml/h), aldosterone 30 ng/dL, ARR-DRC= 2 (ARR-PRA= 30).

In this case we have a borderline positive ARR under an angiotensin-II receptor blocker (ARB) and a diuretic, which can both give false-negative results and hypokalemia that can result in the same alteration (1,2,26,29,33) (Table 1). Therefore, we should consider the patients to be affected by PA with a high probability and proceed with the diagnostic flow-chart (1,2). After adrenalectomy, the final diagnosis was a unilateral aldosterone-producing adenoma (15 mm diameter) and the patient displayed complete biochemical success and partial clinical success (normotension under amlodipine 5 mg per day) (32).

Clinical case 5

Patient 5 is a 76 year-old male, with hypertension since he was 50 years´ old, under therapy with nebivolol 5 mg and chlortalidone 25 mg. BP is 160/70 mmHg, K^+4.6 mEq/L, eGFR 45 ml/min/$m^{1.73}$. The patient was referred to a cardiologist to switch interfering therapy to non-interfering medication.

148 This patient has a low probability of being affected by PA (normokalemia under full-dose diuretic).
149 Furthermore, the age, the long-standing hypertension and the associated organ damage (arterial
150 stiffness as shown by the high pulse pressure, and reduced kidney function) indicate a low probability
151 of complete clinical success after adrenal surgery (32). Elderly patients often display high ARR
152 levels, due to decreased renin levels that parallel a reduction in kidney function, and due to
153 aldosterone levels that remain unsuppressed by potassium that is less efficiently eliminated in case of
154 renal failure(Table 1) (1,2,29). Therefore, it is suggested not to proceed to ARR measurement and
155 treat the patient empirically.

156 **Medications and conditions affecting renin and aldosterone levels**

157 Most medications display an effect on the RAAS thereby potentially interfering with ARR
158 interpretation. The drugs with a neutral effect on the RAAS that therefore can be used during the
159 screening and confirmation of PA are alpha-blockers (doxazosin, prazosin, terazosin), non-
160 dihydropiriridine calcium channel blockers (NDHP-CCB, verapamil and diltiazem) and moxonidine
161 (1,2,33,34). Also, DHP-CCB (such as amlodipine, lacidipine and lercanidipine) are used in most
162 centres to control blood pressure levels, although they can cause renin to increase due to sympathetic
163 activation and potentially a false negative ARR which, however, is observed in a very few cases
164 (2,29) (Table 1). Beta-blockers, clonidine and alpha-methyl dopa can cause false positive diagnoses,
165 especially if absolute levels of aldosterone are not taken into account (25,30,33,35). ACE-Is and
166 ARBs are potentially associated with a false-negative ARR by increasing DRC and PRA and reducing
167 aldosterone, and should be stopped whenever possible (1,2,30,33). However, as demonstrated by the
168 use of the captopril challenge test to confirm the diagnosis, aldosterone production in PA (especially
169 unilateral forms), is relatively independent from angiotensin-II stimulation and the ARR can be safely
170 interpreted and the florid forms of PA diagnosed even under treatment with ACE-I/ARB,. Recently,
171 it has been proposed a new screening test which uses the angiotensin-II over aldosterone ratio, both
172 measured by liquid chromatography and mass-spectrometry detection (36,37); this ratio seems to

provide results that are independent from the interference of ACE-Is treatment. Renin-inhibitors such as aliskiren, reduce PRA and aldosterone and increase DRC, resulting in potential false-positive ARR when renin is measured as PRA and false-negative when is measured as DRC. Thiazide and loop (potassium-wasting) diuretics increase both renin and aldosterone by inducing volume depletion and may result in false-negative ARR. This effect on ARR could be increased by the relative reduction of aldosterone secretion due to a concomitant diuretic-induced hypokalemia (29) (Table 1). Mineralocorticoid receptor antagonists (MRAs) block aldosterone effects and may determine false-negative ARR (1,2,38): these drugs should be stopped for at least 6-8 weeks before measuring ARR. However, in case of florid PA forms and low dose/short duration of MRA treatment, renin levels can be still suppressed and the ARR diagnostic for PA (39-41). It is suggested to repeat the ARR after MRA withdrawal when DRC or PRA levels are not suppressed and ARR negative. Similar effects on the ARR can be observed by potassium-sparing diuretics such as amiloride and triamterene especially when used at high dose (25).

Conditions in which PA is associated with activation of the RAAS may be associated with false-negative screening tests: these include malignant or renovascular hypertension (29,42) and pregnancy (43,44) (Table 1). Conditions associated with potentially false-positive ARR include elderly patients, patients with familial hyperkalemic hypertension, women under estrogen-containing contraceptive agents and patients treated with non-steroidal anti-inflammatory drugs (Table 1). Elderly patients display a progressive reduction of renin levels that parallel the reduction of the kidney function; by contrast, aldosterone production is maintained by the stimulus of potassium that is less efficiently eliminated by the kidney (45). Familial hyperkalemic hypertension is a genetic condition characterized by hypertension, hyperkalemia and hyperchloremic acidosis (45,46,47). In affected patients, volume expansion determines suppression of renin levels whereas aldosterone levels are variable but generally not suppressed because of the direct renin-independent stimulus of the associated hyperkalemia on aldosterone secretion, resulting in an increased ARR. Women under

198 estrogen-containing pills may have a false-positive ARR when renin is measured as DRC (49,50). I
199 In women, the ARR can also result falsely elevated during the luteal phase of the menstrual cycle
200 (51). These effects are due to the negative feedback on renin levels determined by the stimulation of
201 angiotensinogen production by estrogens (30). Finally, non-steroidal anti-inflammatory drugs can
202 reduce renin more than aldosterone resulting in an increased ARR (29,52).

203 Ideally, ARR should be measured from blood samples collected in the morning after patients have
204 been out of bed for at least 2 hours and after they have been seated for few minutes (2).

205 **Suggested flow-chart in case of screening under anti-hypertensive therapy**

206 Considering the different effects of anti-hypertensive drugs on the RAAS, a pragmatic and operative
207 flow-chart can be designed to screen patients under potentially interfering therapies (Figure 1).
208 Patients under ACE-Is or ARBs, associated or not with CCBs, when they have a positive ARR should
209 undergo confirmatory testing since they have a high probability of PA (some authors could consider
210 PA as confirmed since one of the confirmatory tests, the captopril challenge test, uses an ACE-I). If
211 the ARR value is very low (for example ARR<10 with PRA, measured in ng/mL/h, and <0.5 with
212 DRC, measured in mU/L) and/or absolute aldosterone values are low (for example < 10 ng/dL or
213 below the value considered as cut-off for a confirmatory test) (23), the patient can be confidently
214 considered as not having PA. When ARR is negative but close to the cut-off (for example ARR
215 between 10 and 30 with PRA or between 0.5 and 2 with DRC) the ARR should be repeated after 2-3
216 weeks of withdrawal of the ACE-I/ARB that should be substituted with an alpha-blocker (such as
217 doxazosin) or moxonidine to maintain blood pressure control (Figure 1) (1,2).

218 A negative ARR under beta-blockers, with or without a CCB, can confidently exclude PA. If the
219 ARR result is positive, beta-blockers should be withdrawn (33,35) and if necessary, substituted with
220 a non-DHP-CCB that could be associated with doxazosin instead of giving also a DHP-CCB to the
221 patient (Figure 1).

CCBs and/or alpha-blockers do not affect the RAAS, hence it is possible to proceed with the diagnostic flow-chart according with the ARR values, i.e. performance of confirmatory test or PA exclusion (Figure 1) (1,2).

If the ARR result is positive under treatment with thiazide/loop diuretics or low-dose MRA with or without ACE-I/ARBs and with or without CCBs, than the patient has a very high probability of having PA and should proceed with the diagnostic work-up (1,2,25); on the contrary a negative ARR, warrants to stop diuretics for 4 weeks (8 weeks for MRA especially if at high doses or for long duration of time) and to repeat the ARR (diuretics should be substituted with other non-interfering drugs) (figure 1). This is not the case if the ARR is low, but aldosterone is below the cut-off for a confirmatory test (for example aldosterone < 10 ng/dL) or if renin levels are very high under low doses of thiazide diuretic (for example DRC >30 mU/L or PRA > 3ng/mL/h under 12.5 mg of hydrochlorothiazide).

When the patient is under treatment with both a beta-blocker and a thiazide diuretic the interpretation of the ARR result is complex: ideally, the beta-blocker should be substituted with a non-DHP CCB and the diuretic with doxazosin. However, the clinician may choose to only substitute the drug that is supposed to have a higher impact on the ARR result, that is the beta-blocker in case of a positive ARR and the diuretic in case of a negative ARR (Figure 1) and repeat the hormone measurements.

When patients with a high ARR undergo confirmatory testing, they should be treated with drugs with minimal effects on the RAAS (1,2). In particular, drugs that increase aldosterone and renin levels should be avoided since they can cause a false positive diagnosis of PA. Similarly, drugs that activate RAAS should not be administered during adrenal vein sampling since they could stimulate aldosterone production from the adrenal gland contralateral to an aldosterone-producing adenoma, causing a false diagnosis of bilateral PA and exclude patients from curative surgery (1,2).

Conclusions

In conclusion, in many cases, when withdrawal of a drug or its substitution with another with a neutral effect on the RAAS is considered unsafe or complex, ARR can be confidently interpreted in many cases even when the patient is under treatment with two or more classes of anti-hypertensive drugs. Therefore, this should not represent a major issue to discourage general practitioners or clinicians from measuring the ARR in patients with hypertension that are candidates for PA screening. Experimental and clinical findings demonstrated that diagnosis and targeted treatment of PA is of fundamental importance and when it is not possible to switch therapy to drugs with minimal interference with RAAS activity, it is highly suggested to screen the patients under their usual medications, rather than not screening at all. Appropriate diagnosis and treatment of PA, either with adrenalectomy for unilateral forms or with sufficient doses of MRAs for patients with bilateral forms, determines a marked reduction of the risk of cardio- and cerebrovascular events (53,54). This opportunity cannot be missed for the 5-6% of the patients with hypertension that are seen by general practitioners or cardiologists if the reason is the difficulty of ARR interpretation under interefering therapy.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study

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Figure Legend

Legend to Figure 1. Suggested flow-chart for patients with hypertension under anti-hypertensive treatment that should be screened for primary aldosteronism.

Suggested practical approach to patients with hypertension and high risk of PA, which should be screened with ARR but are under potentially interfering anti-hypertensive therapy. Boxes with a thick outline indicate patients for whom a decision can be reached, either PA highly probable thus they should undergo confirmatory testing and/or subtype diagnosis (grey boxes) or PA can be confidently excluded and they should be considered as affected by essential hypertension (white boxes).

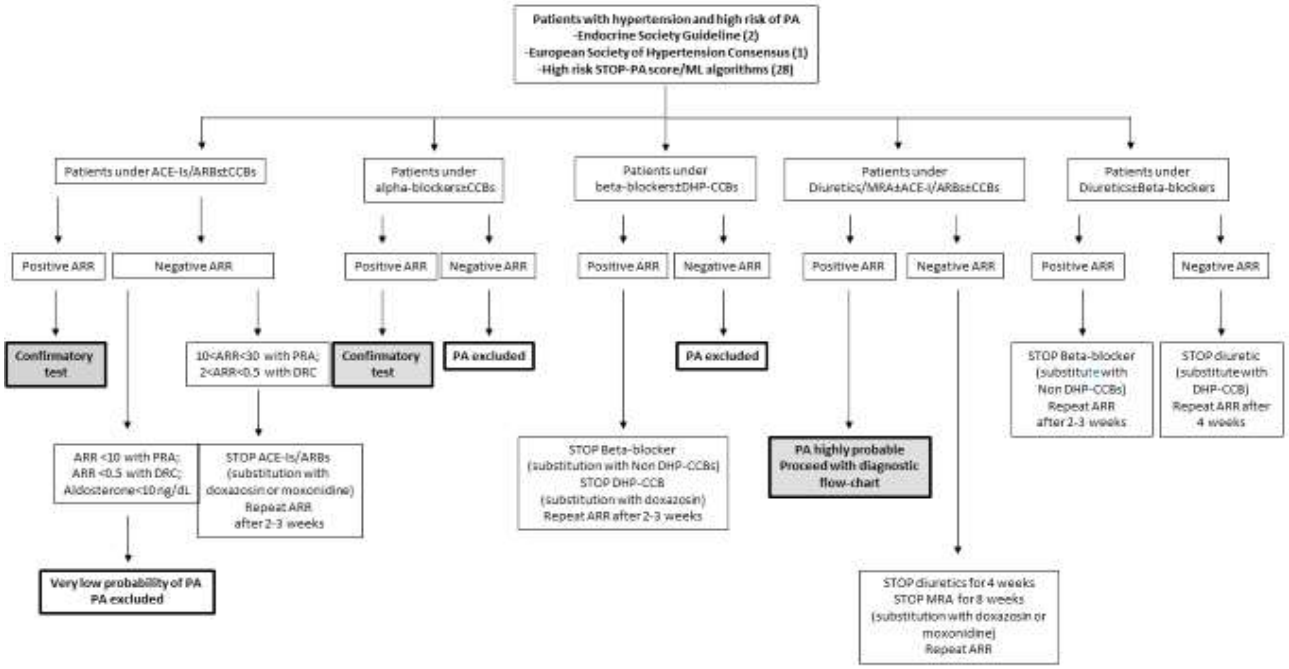
STOP-PA: Score To Predict Primary Aldosteronism; ML: machine learning; PA: primary aldosteronism; ARR: aldosterone renin ratio; PRA: plasma renin activity; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; DRC: direct renin concentration; DHP-CCB: di-hydropyridin calcium channel blocker; MRA: mineralocorticoid receptor antagonist.

Table 1. Drugs and conditions that interfere with the interpretation of the ARR

FALSE POSITIVE SCREENING TEST	FALSE NEGATIVE SCREENING TEST

Anti-Hypertensive Drugs that Frequently Cause False-positive ARR*				**Anti-Hypertensive Drugs that Frequently Cause False-negative ARR***			
	Renin	**Aldo**	**ARR**		**Renin**	**Aldo**	**ARR**
Beta-Blockers	↓↓	↓	↑	MRAs and ENaC blockers	↑↑	↑	↓
Clonidine/Alpha-Methyl Dopa	↓↓	↓	↑	Thiazides and Loop Diuretics	↑↑	↑	↓
Aliskiren#	↓↓	↓	↑	**Anti-Hypertensive Drugs that May Cause False-negative ARR**			
Other Conditions				ACE-Is, ARBs and Aliskiren§	↑	↓	↓
Advancing age/reduced renal function	↓↓	↓	↑	**Other Conditions**			
FHH	↓↓	↓↔	↑	Hypokalemia	↔	↓	↓
Women under estrogen contraceptive agents§	↓	↑	↑	Concomitant Malignant or RVH	↑↑	↑	↓
Anti-inflammatory drugs	↓↓	↓	↑	Pregnancy	↑↑	↑	↓

ARR: aldosterone renin ratio; ENaC: epithelial sodium channel; PRA: plasma renin activity; ACE-Is: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; DRC: direct renin concentration; Aldo: aldosterone; FHH: familial hyperkalemic hypertension; MRA: mineralocorticoid receptor antagonist; RVH: renovascular hypertension; # when renin is measured as PRA; §when renin is measured as DRC) *ARR is intended false-positive (or false negative) when interfering drugs determine an increase (or a decrease) of the ARR above (or below) the cut-off for positive (or negative) test, for example 30 when renin is measured as PRA in ng/mL/h and aldosterone in ng/dL or 2 when renin is measured as DRC in mU/L and aldosterone in ng/dL. In many centres a minimum aldosterone level is required to consider the ARR as positive, that is > 10 ng/dL in our unit (>15 ng/dL or higher than the cut-off of the confirmatory tests in others)(1,2,24).


Patients with hypertension and high risk of PA
-Endocrine Society Guideline (2)
-European Society of Hypertension Consensus (1)
-High risk STOP-PA score/ML algorithms (28)
Patients under ACE-Is/ARBs±CCBs
Patients under alpha-blockers±CCBs
Patients under beta-blockers±DHP-CCBs
Patients under Diuretics/MRA±ACE-I/ARBs±CCBs
Patients under Diuretics±Beta-blockers
Positive ARR
Negative ARR
Positive ARR
Negative ARR
Positive ARR
Negative ARR
Positive ARR
Negative ARR
Positive ARR
Negative ARR
Confirmatory test
10<ARR<30 with PRA; 2<ARR<0.5 with DRC
Confirmatory test
PA excluded
PA excluded
STOP Beta-blocker (substitute with Non DHP-CCBs) Repeat ARR after 2-3 weeks
STOP diuretic (substitute with DHP-CCB) Repeat ARR after 4 weeks
ARR <10 with PRA; ARR <0.5 with DRC; Aldosterone<10 ng/dL
STOP ACE-Is/ARBs (substitution with doxazosin or moxonidine) Repeat ARR after 2-3 weeks
STOP Beta-blocker (substitution with Non DHP-CCBs) STOP DHP-CCB (substitution with doxazosin) Repeat ARR after 2-3 weeks
PA highly probable Proceed with diagnostic flow-chart
STOP diuretics for 4 weeks STOP MRA for 8 weeks (substitution with doxazosin or moxonidine) Repeat ARR
Very low probability of PA PA excluded

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