CLINICAL FOCUS **THERAPY UPDATE**

A GP guide to primary aldosteronism

Increased awareness and active screening for this condition in the primary care setting are key to timely diagnosis and improved patient outcomes

10 minutes to read | 16th September 2021

By Dr Renata Libianto, Dr Jun Yang

0

Need to know:

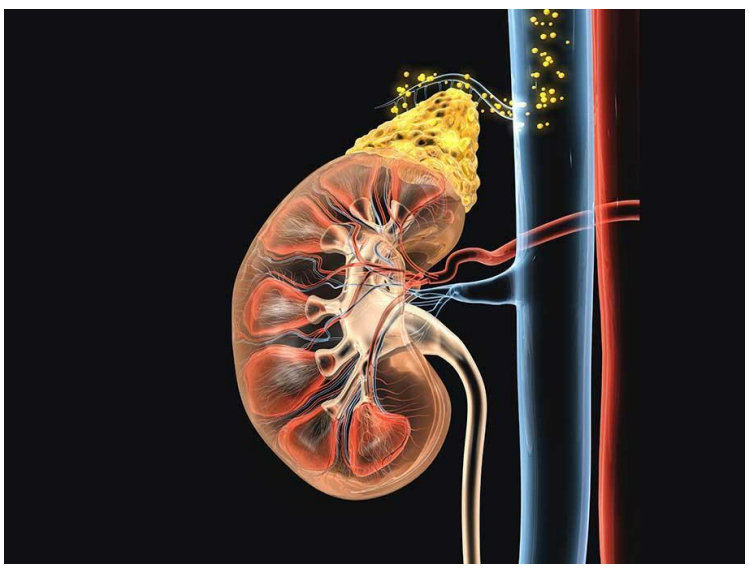
- Primary aldosteronism is a common secondary cause of hypertension.
- Untreated primary aldosteronism is associated with worse cardiovascular outcomes than blood pressure-matched essential hypertension.
- The best screening test for primary aldosteronism is an aldosterone to renin ratio, measured in the morning around two hours after getting up.
- Antihypertensive medications that interfere with the aldosterone to renin ratio should ideally be stopped or switched to non-interfering medications before testing.
- There are targeted and highly effective treatments for primary aldosteronism in the form of mineralocorticoid receptor antagonists, such as spironolactone, or surgical resection of aldosterone-producing adrenal adenoma.

Hypertension is the most common diagnosis made in Australian general practice and is a leading risk factor for chronic disease.[1]

In 2014-2015, close to six million adults in Australia were affected; 4.1 million of these had uncontrolled or untreated hypertension.[2]

The 2016 Lancet Commission on Hypertension found that missing a diagnosis of secondary hypertension was one of the most important reasons for the unacceptably low control rate of blood pressure.[3]

A common but substantially underdiagnosed secondary cause of hypertension is primary aldosteronism.



Resources:

- **Endocrine Society primary aldosteronism treatment guideline**
- **Hormones Australia website with consumer information about primary aldosteronism**

Pathophysiology

Also known as Conn syndrome, primary aldosteronism is characterised by autonomous secretion of aldosterone by the adrenal gland(s) that is independent of renin and angiotensin II.[4]

Hence, the aldosterone concentration does not respond to usual regulatory mechanisms, such as sodium loading.

The two most common causes of primary aldosteronism are aldosterone-producing adrenal adenoma (usually unilateral) and adrenal hyperplasia (usually bilateral).

The former accounts for around 30% of cases and the latter for the remaining 60-70%.

Less commonly, adrenal carcinoma or inherited conditions of familial hyperaldosteronism can also be the cause.

Epidemiology

Primary aldosteronism is the most common endocrine cause of hypertension.

The prevalence among hypertensive patients is between 5% and 10% in primary care settings and up to 30% in referral centres.[5-7]

> **Despite the high published prevalence of primary aldosteronism among hypertensive patients, it is substantially underdiagnosed in practice.**

A survey of GPs in Victoria found fewer than 0.1% of 7000 hypertensive patients had a diagnosis of primary aldosteronism.[8]

Similar findings were reported in Italy and Canada, where 1-2% of all patients expected to have the condition were actually investigated and diagnosed.[9,10]

The BEACH (Bettering the Evaluation And Care of Health) dataset, collected from more than 15,000 GPs in Australia over 16 years, revealed only 57 cases of primary aldosteronism out of 1.5 million GP-patient encounters.[8]

During that time, aldosterone was only measured 66 times. In a European study, only 7% of GPs had ever ordered renin and aldosterone measurements.[11]

Without active screening using a blood test, it is difficult to diagnose primary aldosteronism based on the history and examination, as there are few distinguishing features.

Clinical features

Hypertension is the predominant feature of primary aldosteronism.

This condition is responsible for approximately 20% of cases of resistant hypertension, defined as blood pressure greater than 140/90mmHg despite three antihypertensive agents or controlled blood pressure on four or more antihypertensive medications.[12]

However, primary aldosteronism can be present at any stage of hypertension, having been reported in 4-15% of patients with stage 1 hypertension and 10-20% of patients with stage 2 hypertension.[6,13]

> **Young age and hypokalaemia have traditionally been considered hallmarks of the condition. However, the mean age of patients with primary aldosteronism identified in primary care studies is around 50.[6,7,14]**

The prevalence of hypokalaemia in patients with the condition is variable, ranging between 0% and 37.5% in the primary care setting and up to 57.1% in the tertiary care setting.[5,15]

Patients with primary aldosteronism caused by aldosterone-producing adenomas are more likely to present with florid disease, including hypokalaemia and be diagnosed at a younger age than those with bilateral disease.

However, in most cases, patients with primary aldosteronism present in a similar way to those with essential hypertension, and neither age nor serum potassium levels can reliably distinguish the two.

Consequences of untreated primary aldosteronism

Above and beyond hypertension, primary aldosteronism confers a higher risk of cardiovascular complications.

A meta-analysis reported an increased risk of stroke (odds ratio [OR] 2.58), coronary artery disease (OR 1.77), AF (OR 3.52) and heart failure (OR 2.05) among patients with primary aldosteronism compared with patients with essential hypertension — independent of their blood pressure.[16]

The higher risk has been attributed to aldosterone per se, which mediates pro-inflammatory and pro-fibrotic tissue injury by activating the mineralocorticoid receptor in the heart, blood vessels and immune cells.[17]

In recent years, there has been a growing appreciation of the wider effects of aldosterone excess beyond the cardiovascular system.

Primary aldosteronism has been associated with diabetes and the metabolic syndrome.[18]

In one study, the prevalence of primary aldosteronism in patients with newly diagnosed type 2 diabetes and hypertension was at least 19%.[19]

Suggested mechanisms include decreased insulin secretion and insulin sensitivity.[20]

Primary aldosteronism has also been associated with obstructive sleep apnoea, the severity of which is attenuated by the treatment of primary aldosteronism.[21]

Furthermore, patients with primary aldosteronism have a higher risk of osteoporosis that is possibly related to aldosterone-mediated hypercalciuria and parathyroid disorders.[22]

In a metabolic bone clinic, primary aldosteronism was observed in 26.1% of patients with the concomitant presence of osteoporosis, hypertension and hypercalciuria.[23]

As we gain a better understanding of the effects of aldosterone and activation of the mineralocorticoid receptor outside the renal tubules, primary aldosteronism may become increasingly relevant for clinicians across different areas of medicine.

It is crucial to diagnose primary aldosteronism and treat it appropriately — not only to control blood pressure but also to prevent these aldosterone-mediated complications.

Diagnosis

There are three key steps to diagnosis: screening, confirmatory testing and subtyping (see figure 1).[24]

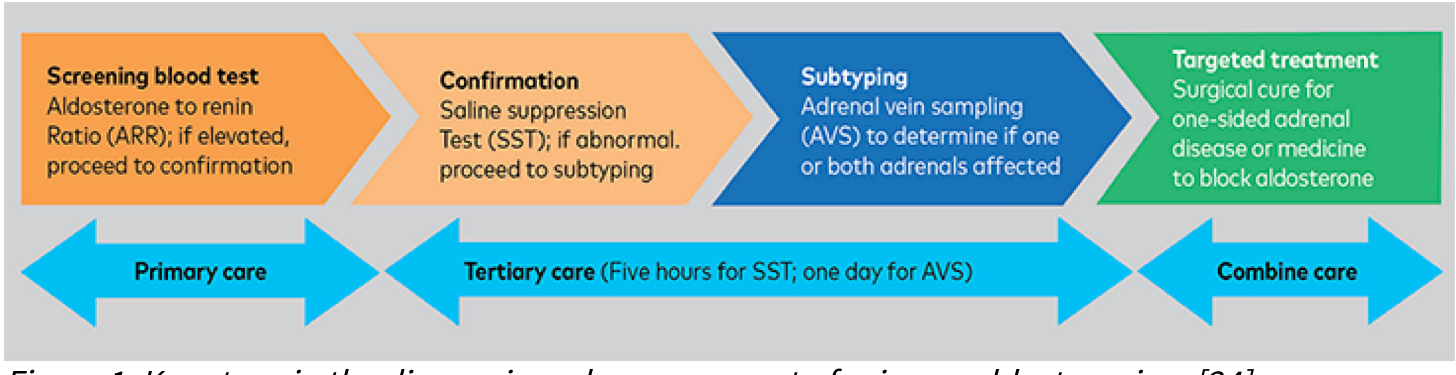


Figure 1. Key steps in the diagnosis and management of primary aldosteronism.[24]

Screening involves the measurement of aldosterone and renin concentration in the blood, which are expressed as the aldosterone to renin ratio (ARR).

This is measured via a standard blood test, which is best done in the morning around two hours after getting up.

An abnormal screening test is defined as an elevated ARR above a set threshold, which differs between different centres but is commonly considered abnormal if greater than 70 (where aldosterone is measured in pmol/L and renin concentration is measured in mU/L).

The renin concentration is typically suppressed or low, while the aldosterone concentration is often within the normal range or elevated.

The most commonly used antihypertensive medications can affect the ARR (see table 1).[25]

Table 1. Antihypertensive medications that can alter aldosterone, renin and the aldosterone to renin ratio (ARR)

	Aldosterone	Renin	ARR
Medications that may cause a false-positive result			
Beta blockers	↓	↓↓	↑
Alpha-methyldopa	↓	↓↓	↑
Clonidine	↓	↓↓	↑

Medications that may cause a false-negative result			
Loop and thiazide diuretics	↓	↑↑	↓
Mineralocorticoid receptor antagonists	↓	↑↑	↓
ACEIs	↓	↑↑	↓
ARBs	↓	↑↑	↓
Dihydropyridine calcium-channel blockers	↓	↑	↓

Where possible, they should be stopped or switched to non-interfering agents — including verapamil, prazosin, moxonidine or hydralazine — 4-6 weeks prior to the ARR test.

Hypokalaemia can also lead to false-negative results; hence, potassium should be normalised before measuring the ARR.

An elevated ARR alone is not diagnostic of primary aldosteronism.

Confirmation requires the demonstration of at least partly autonomous aldosterone production during interventions to suppress aldosterone, including saline infusion, oral salt loading, fludrocortisone administration or captopril challenge.

The most commonly used confirmatory test in Australia is the seated saline suppression test, in which an aldosterone concentration greater than 170pmol/L after infusion of 2L of normal saline confirms the diagnosis of primary aldosteronism.[26]

Confirmatory testing may be bypassed in hypertensive patients with spontaneous hypokalaemia who also have an elevated plasma aldosterone concentration above 550pmol/L and renin below 2.5mU/L.

These patients almost certainly have primary aldosteronism.[27]

> **Once the diagnosis is confirmed, the patient would normally proceed to adrenal CT and adrenal venous sampling (AVS) for subtyping as either unilateral or bilateral primary aldosteronism.**

Unilateral primary aldosteronism — where aldosterone excess is caused by pathology in one adrenal gland — is potentially curable by adrenalectomy, while bilateral disease requires lifelong medical treatment.

AVS is an invasive procedure performed by interventional radiologists in tertiary settings and should only be done if the patient is an appropriate surgical candidate and agrees to potential surgery.

Adrenal CT is usually performed to rule out an adrenal carcinoma as a cause of primary aldosteronism.

However, it is important to remember that the presence of an adrenal adenoma does not equate to unilateral aldosterone production as non-functioning adrenal incidentalomas are common.

AVS is necessary to differentiate non-functioning from aldosterone-producing adenomas, as well as between unilateral and bilateral primary aldosteronism.[28]

Management

Laparoscopic adrenalectomy is the treatment of choice for patients with unilateral disease.

Prior to surgery, a mineralocorticoid receptor antagonist, such as spironolactone, should be prescribed to normalise renin and potassium levels and to stablise blood pressure.

After surgery, the mineralocorticoid receptor antagonist can be stopped, but other antihypertensive medications may need to be continued.

Plasma aldosterone and renin concentration should be measured around three months postoperatively to confirm a biochemical cure.

Hypokalaemia usually resolves rapidly, so mineralocorticoid receptor antagonist and potassium supplementation should be stopped immediately after surgery and serum potassium monitored.

Hypertension caused by primary aldosteronism typically resolves in 1-6 months, but residual hypertension due to vascular remodelling and/or concurrent essential hypertension is not uncommon and requires additional antihypertensive treatment.

The cure rates of hyperaldosteronism are high at 83-100%, but long-term cure rates of hypertension range from 17% to 62%.[29]

Bilateral primary aldosteronism is treated with mineralocorticoid receptor antagonists, such as spironolactone (12.5mg - 100mg daily), as the first choice.

Spironolactone directly blocks the actions of aldosterone and protects the cardiovascular and renal systems from aldosterone-mediated injury.

However, spironolactone also acts on the androgen and progesterone receptors and is associated with dose-dependent adverse effects, such as gynaecomastia and impotence in men and menstrual disturbance in women.

A more selective mineralocorticoid receptor antagonist, eplerenone (25mg-100mg twice a day), has fewer side effects but is less potent and requires twice daily dosing because of a short half-life.

The dose of spironolactone or eplerenone should be increased until the plasma renin concentration is normal ('unsuppressed') to achieve cardiovascular benefits.[30]

- **Want to share cases and discuss hot topics? Join our Cardiology Group**

It is important to anticipate a decline in eGFR following targeted treatment of mineralocorticoid receptor as a result of reversal of aldosterone-mediated glomerular hyperfiltration and unmasking of underlying renal disease.[31]

Once the dose of mineralocorticoid receptor antagonist is optimised, other antihypertensives may be required to optimally control blood pressure.

If spironolactone is not tolerated and eplerenone is not available, then amiloride, an epithelial sodium-channel antagonist, may be considered.

It targets the distal tubular epithelial sodium channels that are upregulated by aldosterone but does not antagonise the mineralocorticoid receptor elsewhere in the body.

Unfortunately, amiloride will no be longer available in Australia from October 2021 and can only be obtained via the Special Access Scheme.

The following is an example of a medical treatment regimen for bilateral primary aldosteronism:

1. Commence spironolactone 12.5-25mg daily or eplerenone 25mg twice daily if spironolactone is not tolerated.

2. Increase spironolactone to 50-150mg daily or eplerenone to 50-100mg twice daily until normokalaemia is achieved without potassium supplementation and renin is fully unsuppressed (plasma renin concentration above 12mU/L).

3. Use amiloride (2.5-10 mg daily) if spironolactone or eplerenone are not tolerated or unavailable.

4. Add ACEIs, angiotensin II receptor blockers, other diuretics (for example, hydrochlorothiazide) or calcium-channel blockers to optimise blood pressure control.

Summary

Prompt diagnosis and targeted treatment of primary aldosteronism significantly improve blood pressure control, reduce polypharmacy, reverse target organ damage and ameliorate associated cardiovascular risk in the affected patients.[14,30,32]

Increased awareness and active screening for this condition in the primary care setting are key to a timely diagnosis and improved patient outcomes.

Ongoing research is an essential step to improving the detection and management of primary aldosteronism, particularly in the primary care setting.

The authors are conducting projects that seek to engage any GPs who are interested in being involved in primary care research into this subject.

The projects are designed to integrate into routine clinical practice.

For more information about research projects with the Endocrine Hypertension Group, visit the **Centre for Endocrinology and Metabolism here** or contact **Dr Jun Yang**.

Practical tips from the authors

- Primary aldosteronism is common if you actively look for it by checking the aldosterone to renin ratio (ARR).
- If the patient is taking medications that interfere with the ARR, give them a medication titration chart so that they can stop the interfering medications and gradually self-titrate the non-interfering medications (for example, prazosin starting at 0.5mg daily, verapamil 180mg ½ daily or moxonidin 400µg ½ nocte) based on their home blood pressure measurements before you recheck their ARR in 4-6 weeks.
- Refer the patient with a positive screening test to an endocrine hypertension clinic for streamlined assessment, including confirmatory testing and subtyping.
- If the patient cannot tolerate medication changes or the full diagnostic process, or will never entertain the idea of adrenal surgery, then empiric treatment with spironolactone starting at 12.5mg daily may be a good idea following an abnormal ARR test.
- Spironolactone takes a few weeks to achieve its full effect, so do not up-titrate in a rush. Monitor blood pressure and serum potassium and renin concentration during the titration process and do not be disappointed if the patient needs additional antihypertensives for blood-pressure lowering even after a cure of hyperaldosteronism.

Dr Renata Libianto is an endocrinologist at Monash Health who is currently undertaking a PhD in primary aldosteronism.

Dr Jun Yang is an endocrinologist at Monash Health, head of the Endocrine Hypertension Group at Hudson Institute of Medical Research and research fellow in the School of Clinical Sciences at Monash University, Melbourne, Victoria.

References:

 # Tags Endocrinology Cardiology Vascular Screening Antihypertensive Medicines management

AUSTRALIAN DOCTOR **NEWS**

Accreditation: RACGP wants practices to undergo random spot checks

16th September 2021

A "continuous" approach to GP practice accreditation with random spot checks should be trialled to help modernise the scheme...

READ MORE

0 **2** minutes to read

AUSTRALIAN DOCTOR **NEWS**

COVID-19 group says it's instructed 200 Aussie doctors on prescribing ivermectin

16th September 2021

An organisation claiming to represent doctors who are prescribing ivermectin for COVID-19 has come out against the TGA's ban...

READ MORE

0 **3** minutes to read

AUSTRALIAN DOCTOR **NEWS**

GP gets longest practice ban ever imposed on a doctor in Australia

16th September 2021

The GP who tried to murder a pharmacist after she reported him to AHPRA has been barred for 25 years - the longest practice...

READ MORE

0 **3** minutes to read

AUSTRALIAN DOCTOR **NEWS**

Your comments of the week: Media abuse of doctors, the Taliban and ivermectin

16th September 2021
Each week, Australian Doctor readers post hundreds of comments in response to our articles. Below, whether medical colleges...

READ MORE

0 **3** minutes to read

SPECIALIST UPDATES **WOMEN'S HEALTH**

Outcomes after major postpartum transfusion 'similar across hospitals'

16th September 2021
Outcomes for women requiring large volume blood transfusions for postpartum haemorrhage at public hospitals are similar...

READ MORE

0 **2** minutes to read

SPECIALIST UPDATES **WOMEN'S HEALTH**

Tailored gynaecological surgical strategies 'beneficial' in Lynch syndrome

16th September 2021
Having different strategies to reduce the risk of gynaecological cancers in women with Lynch syndrome, based on the...

READ MORE

0 **2** minutes to read

6MINUTES **NEWS**

GPs 'pressured' by anti-vaxxers demanding medical exemptions

15th September 2021
GPs are coming under pressure from anti-vaxxers seeking medical exemptions to COVID-19 vaccines "on a daily basis", the...

READ MORE

14 **2** minutes to read