# Primary Aldosteronism; a growing challenge

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"We theorized that resistance to repletion of potassium was the result of an intracellular overabundance of sodium, being held by excessive activity of aldosterone and concluded that total adrenalectomy followed by substitution therapy should abolish the entire metabolic abnormality. To our surprise and delight, a cortical adenoma, 4 cm. in diameter was observed to be arising from the right adrenal gland."

by Jerome W. Conn

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## ABSTRACT

Primary aldosteronism (PA), caused by excessive aldosterone production, is a frequently overlooked cause of hypertension. Cardiovascular complications are more common in patients with PA than patients with essential hypertension. However, disease-specific treatment with either mineralocorticoid receptor antagonists (MRAs) or unilateral adrenalectomy, effectively reduces the risk for these complications. The aim with this thesis was to investigate several contentious issues related to epidemiology, subtype classification, and treatment of patients with PA. The key findings are summarized below.

The incidence of PA in Region Västra Götaland has increased from 2 patients per million in 1987–1996 to 17 patients per million in 2007–2016. Despite this, PA is still significantly underdiagnosed.

International guidelines postulate that adrenal venous sampling (AVS) is not necessary to confirm unilateral PA in young adults with visible adenoma on imaging. However, our review of 45 young patients (<40 years of age) who had undergone AVS at our institution showed that 20% of these patients would have received inappropriate treatment based solely on imaging studies.

A nationwide cohort study of 2419 patients with PA showed that mortality was increased compared to age- and sex-matched controls from the general population (HR 1.23, 95% CI 1.10–1.38), especially in patients with established cardiovascular disease or age >56 years at the time of diagnosis and in patients treated with low doses of MRAs, but not in patients treated with adrenalectomy. Patients with PA also had an increased risk of hip fracture (HR

1.55, 95% CI 1.18–2.03), especially women and patients diagnosed at an older age as well as patients treated with an MRA.

To conclude, PA is an underdiagnosed and undertreated condition that can lead to cardiovascular complications, hip fractures, and increased mortality. Early and targeted treatment improves patient outcome.

**Keywords**: hyperaldosteronism, incidence, mortality, hip fractures

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# SAMMANFATTNING PÅ SVENSKA

Högt blodtryck utgör en av de viktigaste riskfaktorerna för hjärtkärlsjukdom. Aldosteron har en central roll i reglering av blodtryck. Primär aldosteronism är en sjukdom som orsakas av överproduktion av aldosteron och leder till högt blodtryck och ofta lågt kalium, samt inflammation i blodkärlen som ytterligare ökar risken för hjärtkärlsjukdom. Sjukdomen är vanlig bland personer med högt blodtryck och ännu vanligare bland dem som inte svarar på blodtryckssänkande behandling. Läkemedel som blockerar aldosteronreceptorer (MRA) finns tillgängliga och har god effekt. Dessutom kan ungefär en tredjedel av alla patienter få kirurgisk behandling, vilket rekommenderas vid ensidig hormonproduktion.

Denna avhandling baseras på fyra studier där förekomst av primär aldosteronism i Sverige, betydelse av binjurevenskateterisering bland unga patienter och prognos vad det gäller långtidsperspektivet undersöktes.

Första studien visar att antalet individer som diagnostiseras med primär aldosteronism i Västra Götalands Regionen har ökat de senaste åren. Trots det är sjukdomen fortfarande kraftigt underdiagnostiserad.

Internationella riktlinjer postulerar att binjurevenskateterisering (BVK) inte är nödvändig för att bekräfta ensidig PA hos unga vuxna med synligt adenom på datortomografi. I vår genomgång av 45 unga patienter (<40 år) som genomgått BVK på vår institution visades motsatsen. En femtedel av patienterna hade fått fel behandling om endast fynd på datortomografi av binjurarna hade använts.

En nationell studie med över 2419 patienter med primär aldosteronism och 24189 kontrollpersoner med samma kön och ålder visade att primär aldosteronism tydligt ökar risken för död. Patienter som genomgick en adrenalektomi eller högre dos MRA än genomsnittet hade dock snarlik överlevnad med den i allmänna befolkningen. Patienter som löpte störst risk var framför allt personer med samexisterande hjärtsjukdom vid diagnos, lägre dos av MRA än genomsnitt eller ålder >56. Slutligen, löper patienter med primär aldosteronism ökad risk för höftfrakturer. Detta gäller särskilt kvinnor, patienter med hjärtsjukdom vid diagnos, patient som har fått diagnosen vid ålder >56 och patienter som fick MRA.

Sammanfattningsvis visar denna avhandling att primär aldosteronism är underdiagnostiserat och förknippat med ökad risk för allvarliga konsekvenser,

hjärtkärlsjukdom, höftfrakturer och dödlighet. Sjukdomen bör uppmärksammas så att patienter identifieras för att de ska få möjlighet att behandlas. Patienter bör erbjudas binjurevenskateterisering, vilket kan bidra till att förbättra den enskilde patientens prognos och detta gäller särskilt unga patienter. Det krävs en mer inriktad och individanpassad behandling, då kön, samsjuklighet, ålder och användning av MRA i rätt dos påverkar prognosen. Det är viktigt med framtida forskning med fokus på att fastställa patientrapporterade utfallsmått och identifiera patientgrupper som bör erbjudas adrenalektomi.

Studier har finansierats med hjälp av anslag från Avtal om Läkarutbildning och Forskning (ALF 971027), och Göteborgs Läkaresällskap.

# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

*I.* Gkaniatsa E, Ekerstad E, Gavric M, Muth A, Trimpou P, Olsson DS, Johannsson G, Ragnarsson O. **Increasing Incidence of primary aldosteronism in Western Sweden during 3 Decades – Yet An Underdiagnosed Disorder.** *J Clin Endocrinol Metab. 2021;106:e3603-e3610*

*II.* Gkaniatsa E, Sakinis A, Palmér M, Muth A, Trimpou P, Ragnarsson O. **Adrenal venous sampling in young patients with primary aldosteronism. Extravagance or irreplaceable?** *J Clin Endocrinol Metab. 2021;106:e2087-e2095*

*III.* Gkaniatsa E, Zverkova Sandström T, Rosengren A, Trimpou P, Olsson DS, Lind M, Muth A, Johannsson G, Ragnarsson O. **Mortality in patients with primary aldosteronism: a Swedish nationwide study.** *Hypertension. 2023;80:2601-2610*

IV. Gkaniatsa E, Sandström TZ, Rosengren A, Trimpou P, Muth A, Johannsson G, Ragnarsson O. **Hip fractures in patients with primary aldosteronism – a Swedish nationwide study.** *Osteoporos Int. 2024;35:1585-1593*

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# PREFACE

At least 1.8 million Swedish adults have hypertension, a major risk factor for stroke, heart attack, and heart failure.[1] Treatment of hypertension includes medication and lifestyle changes; however, many patients have poorly controlled blood pressure despite recent advances in molecular biology, genomics, and pharmacology. Primary aldosteronism is often the cause of poorly controlled hypertension and carries a risk of cardiovascular complications. When primary aldosteronism is diagnosed and treated correctly, blood pressure can be lowered and cardiovascular complications can be prevented.

This thesis focuses on the epidemiology, subtype distinction, and outcomes of primary aldosteronism in Sweden and the influence of treatment and other risk factors on morbidity and mortality. Using registries, we can track patient characteristics, treatment, and outcomes longitudinally in a real-world healthcare setting. This data allows us to identify areas for improvement and may support changes in our practices to optimize treatment. I hope this thesis contributes to the improvement of healthcare in patients with primary aldosteronism.

# ABBREVIATIONS

| | |
|---|---|
| 11β-HSD2 | 11β-hydroxysteroid dehydrogenase |
| ACTH | Adrenocorticotropic hormone |
| APA | Aldosterone-producing adenoma |
| ARR | Aldosterone-renin ratio |
| ATC | Anatomical Therapeutic Chemical Classification |
| AVS | Adrenal vein sampling |
| CI | Confidence interval |
| CT | Computed tomography |
| CVD | Cardiovascular disease |
| CYP | Cytochrome P450 |
| DDD | Defined daily dose |
| DHEA | Dehyrdroepiandrosterone |
| ENaC | Epithelial sodium channel |
| GRA | Glucocorticoid-remediable aldosteronism |
| HR | Hazard ratio |
| ICD | International Classification of Diseases |
| IQR | Interquartile range |
| LISA | Longitudinal Database of Health Insurance and Labour Market Studies |
| MR | Mineralocorticoid receptor |

| | |
|---|---|
| MRA | Mineralocorticoid receptor antagonist |
| MRE | Mineralocorticoid response element |
| MRI | Magnetic resonance imaging |
| NFκB | Nuclear factor kappa B |
| NPR | National Patient Register |
| OR | Odds ratio |
| PA | Primary aldosteronism |
| ROS | Reactive oxygen species |
| SD | Standard deviation |
| SIT | Saline infusion test |
| SSIT | Seated saline infusion test |

# DEFINITIONS IN SHORT

| | |
|---|---|
| Prevalence | The total number of cases of disease in a given timeframe |
| Incidence | The number of newly identified cases of disease during a specified timeframe |
| Mortality rate | The number of deaths due to a disease divided by the total population |
| Hazard ratio | A measure of how often a particular event happens in one group compared to how often it happens in another group over time. A hazard ratio of 1 means that there is no difference in the risk between the two groups. A hazard ratio of >1 or <1 means that the risk of the event is higher or lower in one of the groups, respectively. |

# 1 INTRODUCTION

## 1.1 HISTORY OF PRIMARY ALDOSTERONISM

The history of primary aldosteronism (PA) begins in 1952 when electrocortin, later named aldosterone, was discovered and isolated by Simpson and Tait.[2] In 1955, Jerome Conn described the clinical features of severe PA and published the first report of a person with an aldosterone-producing adenoma to be treated by adrenalectomy.[3] The patient was a 34-year-old woman who suffered from generalized muscular weakness and periodic paralysis attributed to remarkable hypokalemia. Severe hypertension and salt loss were the only clues to pinpoint that the adrenal glands were diseased with the production of excessive aldosterone. Conn considered bilateral adrenalectomy as a treatment choice due to the patient's severe functional impairment. The finding of an adrenal tumor exceeded all expectations and the patient made a full recovery after the tumor was removed. She left the clinic 227 days later with a resolution of all her symptoms.

By the late 1960s, case reports proved the existence of another form of primary aldosteronism caused by bilateral hyperplasia of the adrenal glands. The efficacy of spironolactone, the first aldosterone antagonist launched in 1959, prompted physicians to reconsider potentially harmful bilateral adrenalectomy.[4] Subtype prediction proved difficult as patients with bilateral disease shared clinical features with Conn's original case.[5] To address this issue, angiographic techniques to localize adrenal tumors have been used since the 1960s.[6] Computed tomography (CT) scans were introduced in the 1970s. Decades later, it was acknowledged that nonfunctional adrenal tumors may coincide and undermine CT accuracy in diagnosing unilateral PA.[7]

Primary aldosteronism is not uncommon but until the early 1990s only clinically overt cases had come to light. Aldosterone-renin ratio (ARR), introduced in 1981, quickly became standard and greatly improved screening for PA.[8] The 1990s witnessed significant developments in laparoscopic surgery.[9,10] 1987 marked the identification of the mineralocorticoid receptor (MR) and opened the door to understanding molecular signaling pathways.[11] In the decades that followed, major aldosterone biosynthetic pathways were mapped[12,13] and insights into PA genetics were gained.[14-18] Through recent

advances in immunohistochemical methods[19] and genomics, our understanding of PA has improved (figure 1). [18,20,21]

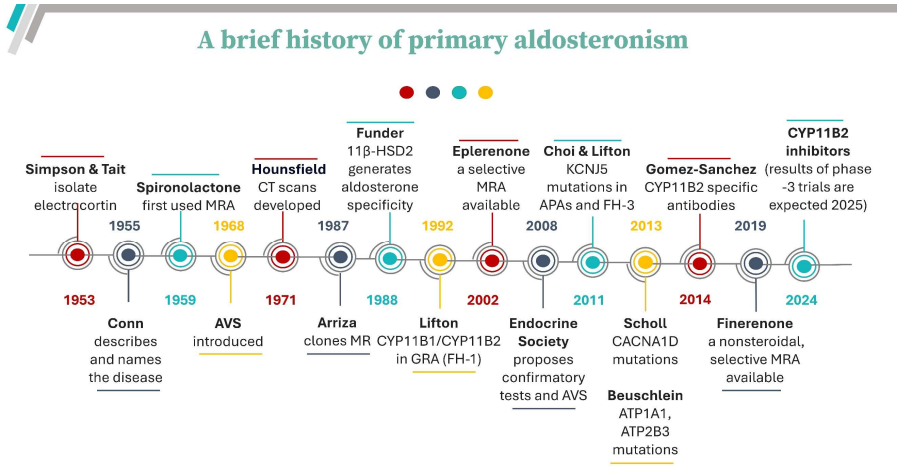


*Figure 1. Timeline highlighting key milestones for primary aldosteronism. Abbreviations: 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; APA, aldosterone-producing adenoma; AVS, adrenal vein sampling; CT, computed tomography; CYP, cytochrome P450; GRA, glucocorticoid-remediable aldosteronism; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist.*

## 1.2 PRIMARY ALDOSTERONISM – A GROWING CHALLENGE

Conn predicted the evolution of PA.[22] Comprehensive research suggests that PA is more common than previously thought.[23-27] Recent research has identified the heterogeneous nature of PA, ranging from clinically overt to normokalemic and normotensive patients that often go undetected.[28-30] Some experts argue that we need to be more pragmatic and target subgroups where PA has the most detrimental effects.[31-33] As the prevalence of PA is increasing,[27,34] more research is needed to guide clinicians on how to individualize PA treatment.[35]

## 1.3 ALDOSTERONE

The human adrenal glands are localized in the retroperitoneal space, near the upper poles of the kidneys. Macroscopically, each has an outer cortex and an

inner medulla. Aldosterone is a steroid hormone produced by the adrenal cortex. Aldosterone is the most physiologically important mineralocorticoid, widely known for its role in the kidney, where it interacts with the MR to regulate blood pressure (BP) by increasing sodium reabsorption (figure 2).[32,36] Aldosterone also has an important role in cell proliferation, cell differentiation, and macrophage infiltration.[37,38]

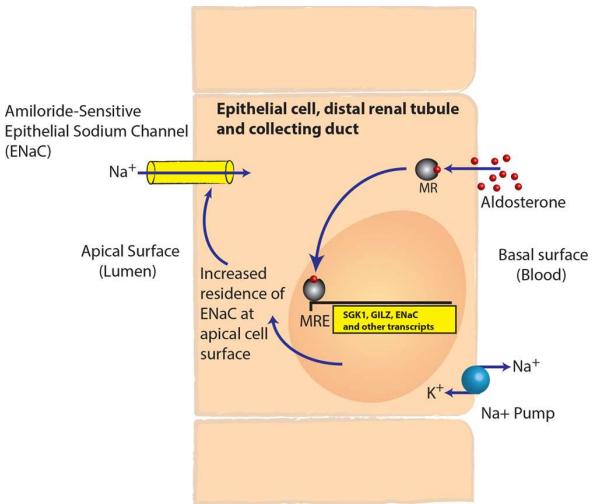


*Figure 2. Aldosterone, the specific MR ligand, regulates target gene expression. The predominant biological effect of aldosterone on renal epithelium is the transcription of ENaC. MRE is the specific aldosterone DNA response element. Abbreviations: ENaC, epithelial sodium channel; MR, mineralocorticoid receptor; MRE, mineralocorticoid response element. [Reproduced from Byrd et al.[32] with permission from ©Wolters Kluwer Health]*

The first steps of steroidogenesis from cholesterol are common for all steroid hormones. Steroidogenesis differs among the different adrenal cortex layers (zona glomerulosa, zona fasciculata, and zona reticularis) because of the presence of specific enzymes.[39] In the final steps of cortisol and aldosterone biosynthesis, the enzymes coded by CYP11B1 and CYP11B2 genes are required, respectively (figure 3). The zona glomerulosa, the outer layer of the adrenal cortex, is the only layer where CYP11B2 is expressed.[39] The organization of adrenal cortex layers and cell population differentiation is dynamic.[40] Dysregulation of cell differentiation can lead to adrenal gland pathologies such as adrenal tumors or overproduction of hormones.[41,42]

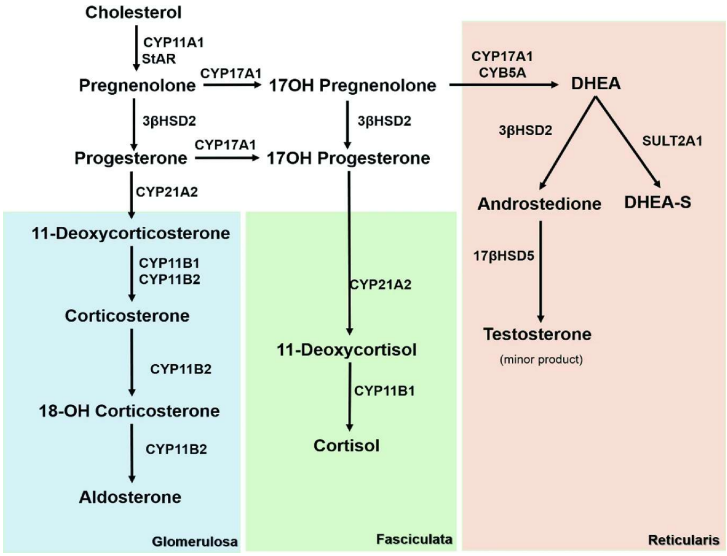


*Figure 3. Overview of steroidogenesis from the adrenal cortex. Abbreviations: 3βHSD2, 3β-hydroxysteroid dehydrogenase type 2; CYP, cytochrome P450; DHEA, dehyrdroepiandrosterone; SULT2A1, sulfotransferase 2A1. [Reproduced with permission from Pereira et al.[39] with permission from ©Springer]*

## 1.3.1 REGULATION OF ALDOSTERONE SECRETION

The zona glomerulosa cells regulate their secretion in response to angiotensin 2, changes in extracellular potassium, and to a lesser extent by adrenocorticotropic hormone (ACTH). Angiotensin 2, the main regulator of aldosterone synthesis, is part of the renin-angiotensin-aldosterone system. This complex hormone network is continually responding to changes in blood volume, vascular tone, and electrolyte levels. A decrease in the flow rate of filtered fluid through the kidney (sensed by the macula densa) or a drop in arterial BP (sensed by baroreceptors) triggers the release of renin. In circulation, released renin reacts with plasma angiotensinogen to form angiotensin 1, which is further converted by angiotensin-converting enzyme into angiotensin 2. Stimulation of aldosterone secretion by angiotensin 2 combined with vasoconstriction increases BP.

Recent research has shed light on the complex intracellular signaling pathways that modulate aldosterone secretion and their dynamics.[43] Angiotensin II receptor type 1, a membrane-bound G-protein-coupled receptor, allows angiotensin 2 to exert physiological regulation of aldosterone secretion. ACTH

causes transient increases in aldosterone synthesis by binding to the melanocortin 2 receptor.[44] Plasma potassium concentration has a direct effect on the electronegative potential of the zona glomerulosa cell membrane.[44] The cascade of aldosterone secretion responds to negative feedback loops to maintain fluid and electrolyte homeostasis. A rate-limiting step in the secretion of aldosterone from the zona glomerulosa cells of the adrenal cortex is the production of renin (figure 4A). The renin-angiotensin-aldosterone system adapts to sodium intake.[45,46] Thus, people with hypertension benefit from salt restriction.[46,47]

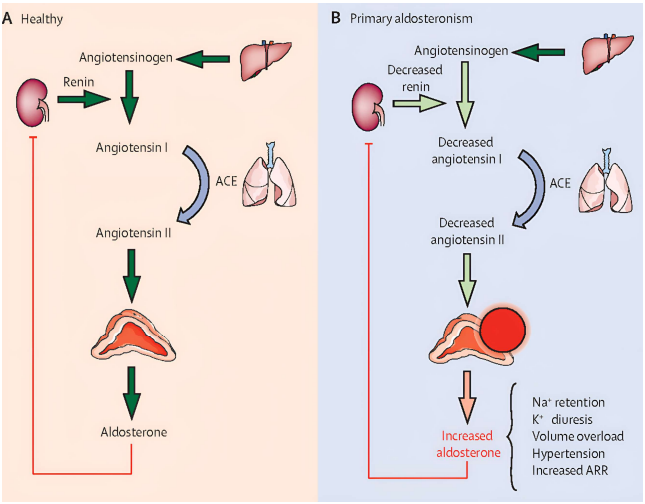


*Figure 4. A. Physiology of regulation of the renin-angiotensin-aldosterone system. B. Angiotensin-independent aldosterone secretion leads to volume overload, hypertension, and hypokalemia. This suppresses renin through negative feedback. ARR is often above the reference range. Abbreviations: ACE, angiotensin-converting enzyme; ARR, aldosterone-renin ratio. [Reproduced from Reincke et al.[48] with permission from ©Elsevier]*

## 1.3.2 EFFECTS OF MINERALOCORTICOID RECEPTOR OVERACTIVATION

The MR mediates the cellular response to aldosterone.[36] MRs regulate gene transcription across different tissues.[36] They are abundantly expressed in the renal nephron but are also present in the heart, vasculature, intestine, salivary glands, adipocytes, and bone.[39,49] The MR has a similar structure to the glucocorticoid receptor.[50] The concentration of circulating glucocorticoids is 1000-fold the concentration of aldosterone.[36] In target tissues, the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) inactivates cortisol to

cortisone, allowing aldosterone to bind to the MR.[12] When 11β-HSD2 is absent or inhibited (i.e. syndrome of apparent mineralocorticoid excess or licorice), the MR can be equally activated by glucocorticoids.[51]

In renal epithelial cells, MR overactivation increases the transcription of epithelial $Na^+$ channels and enhances the activity of the $Na^+/K^+$-ATPase pump in the basolateral membrane. This increases blood volume and BP since more sodium is transported from urine into peritubular capillaries, while water is retained with the osmotically active sodium.[32] Aldosterone also enhances the function of the $H^+$-ATPase pump in the intercalated cells of the distal kidney nephron, which recycles potassium into the urine in exchange for $H^+$ ions. Thus, aldosterone overproduction leads to hypertension, low potassium levels, and alkalosis (figure 4B).

Overactivation of the MR leads to endothelial dysfunction, cardiac remodeling, and kidney injury (figure 5).[52] Two early experiments in rats demonstrated the importance of MR overactivation in cardiac and renal disease. Aldosterone infusion along with a high-salt diet caused oxidative stress, myocardial and perivascular inflammation, accumulation of fibrillar collagen, and subsequent interstitial and perivascular fibrosis.[53] In another experiment, exogenous aldosterone infusion induced thrombotic microangiopathies causing glomerulosclerosis and proteinuria.[54]

Chronic overexposure to aldosterone can be caused by secondary factors such as renal artery stenosis, heart failure, or liver cirrhosis; therefore, inhibition of MRs is effective in treating these conditions.[55]

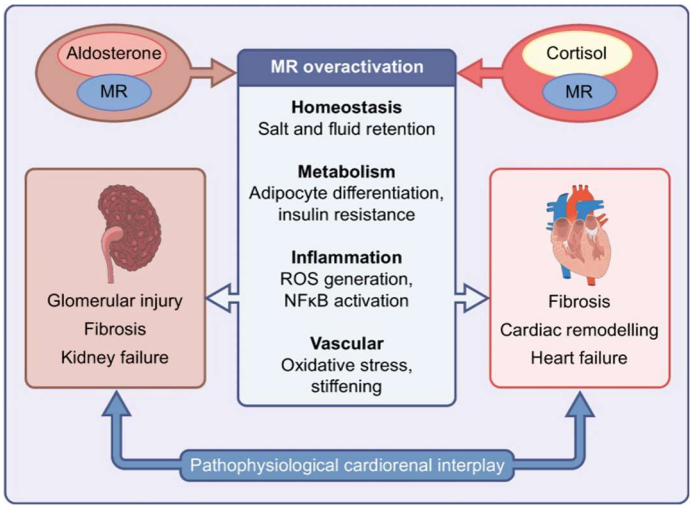


*Figure 5 Principal mechanisms by which MR overactivation may cause cardiac and renal injury. Abbreviations: MR, mineralocorticoid receptor; NFκB, nuclear factor kappa B; ROS, reactive oxygen species. [Reproduced from Savarese et al.[55] with permission from ©Springer Nature]*

# 1.4 PRIMARY ALDOSTERONISM

## 1.4.1 DEFINITION

The Endocrine Society defines PA as "a group of disorders in which aldosterone production is inappropriately high for sodium status, relatively autonomous of the major regulators of secretion (angiotensin II, plasma potassium concentration), and not suppressible by sodium loading."[56] The definition of PA covers a spectrum of normotensive and hypertensive people with autonomous aldosterone secretion.[30]

## 1.4.2 CLINICAL PRESENTATION

For most patients, the diagnosis of PA is made in their 50s but PA can occur at any age. Clinical presentation varies. Combined hypertension and hypokalemia are highly suggestive of PA, although not all patients present with these features.[57,58] Hypokalemia relates to disease duration and aldosterone levels, affecting up to 37% of all prevalent patients.[23,34] Patients with hypokalemia may experience muscle weakness and cramping, palpitations or arrhythmia, lack of energy, frequent urination, and constipation depending on severity.

## 1.4.3 EPIDEMIOLOGY OF PRIMARY ALDOSTERONISM

The prevalence of PA varies from 4% in individuals with mild hypertension to 20% in individuals with treatment-resistant hypertension.[59] Assessing the prevalence of PA in different patient populations has been challenging, at least in part due to variability in definitions and criteria used to define it.[24] In a meta-analysis of 42 510 patients,[24] the prevalence of primary aldosteronism was lower in primary care (range 3.2%–12.7%) than in referral centers (1%–29.8%). A regional study in Sweden estimated that 6% of patients with newly diagnosed hypertension (*n*=353) in specialized units (*n*=123) and primary care centers (*n*=230) had confirmed PA.[60] In primary care settings, the prevalence ranged from 1.6% to 5.5%.[61,62]

PA is underdiagnosed.[48,63,64] Screening rates for PA are reported to be low in the USA and Europe.[64-66] A contemporary study raises further concerns that current screening cut-offs fail to identify some patients with PA.[67] Clinical diagnostic accuracy remains suboptimal, even when hypokalemia is clinically manifest.[57]

## 1.4.4 HISTOPATHOLOGIC CLASSIFICATION OF PRIMARY ALDOSTERONISM

Historically, PA has been classified as unilateral or bilateral depending on whether adrenal adenomas were present on histopathology. In 2021, consensus classification of histopathological features of PA was updated by an expanded group of pathologists to achieve consistency in terminology.[68] Immunostaining for monoclonal antibodies against aldosterone synthase (CYP11B2), the enzyme needed for aldosterone synthesis, has served to identify the site-specific source of aldosterone production and subdivide PA into several categories.[19]

Aldosterone-producing diffuse hyperplasia is characterized by an uninterrupted strip of aldosterone synthase-positive cells.[21] The only difference between aldosterone-producing adenomas >10 mm and aldosterone-producing nodules <10 mm is their size. Aldosterone-producing micronodules, also known as microscopic aldosterone-producing cell clusters, are not visible by hematoxylin and eosin staining but stain positive for aldosterone synthase. Multiple aldosterone-producing micronodules may be present in single adrenal

gland. Nonfunctional adrenal tumors do not stain for aldosterone synthase (figure 6).

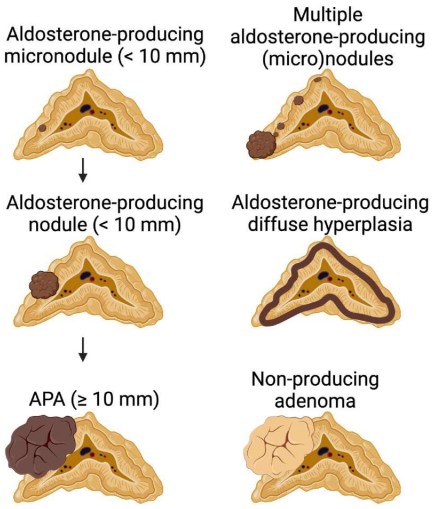


*Figure 6. Illustration of different histopathological types of primary aldosteronism. Abbreviation: APA, aldosterone-producing adenoma. [Reproduced from Scholl[18] with permission from ©Wolters Kluwer Health]*

Patients with bilateral disease rarely undergo surgery, so access to adrenal tissue specimens is limited. A study found that aldosterone-producing cell clusters were common in patients with bilateral PA in whom subtype was proven through adrenal vein sampling.[69]

Histopathology provides insights that the source of autonomous aldosterone secretion can be viewed as a continuum from unilateral to bilateral disease. Throughout this thesis, the terms unilateral and bilateral PA are used according to the framework provided in the current guidelines.[56]

### 1.4.5 SOMATIC AND GERMLINE MUTATIONS ASSOCIATED WITH PRIMARY ALDOSTERONISM

Genetics have provided important insights into the pathogenesis of PA. In most people, PA is not inherited. Somatic mutations in KCNJ5, CACNA1D, ATP1A1, ATP2B3, and CTNNB1 genes can lead to impaired aldosterone secretion and have been identified in more than 90% of aldosterone-producing adenomas.[15-18,21,70,71] These mutations do not fully explain the development of

an adrenal tumor.[21,42] The mechanisms underlying aldosterone-producing diffuse hyperplasia need to be better characterized.[21,42,72]

PA is rarely inherited (1%–5%). A full review of the genetics of familial forms (I–V) and management is beyond the scope of this thesis.[15,73,74] It is relevant from a clinical perspective to understand the genetic basis of glucocorticoid-remediable aldosteronism (GRA), which makes treatment with dexamethasone efficient. In GRA, combination of cortisol and aldosterone synthase genes in a chimeric gene result in upregulated aldosterone secretion, which is pathologically activated by ACTH. GRA has a prevalence of 0.7% among patients with PA.

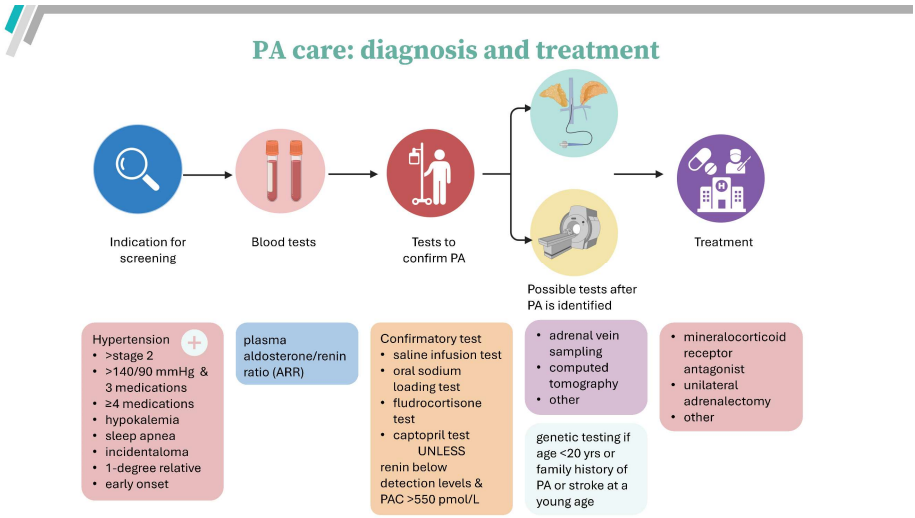


*Figure 7. Diagnostic work-up of primary aldosteronism. Abbreviations: PA, primary aldosteronism; PAC, plasma aldosterone concentration. Figure was created with BioRender.com*

## 1.5 ASSESSMENT AND DIAGNOSIS OF PRIMARY ALDOSTERONISM

The diagnosis of PA relies on biochemical evidence of angiotensin-independent aldosterone production. A combination of methods must be employed to accomplish a complete assessment (figure 7). In Sweden, national guidelines have been issued to help diagnose the different forms of PA and were updated in 2023.[75] They are in line with the guidelines from the Endocrine Society (updated 2016) and the consensus statement by European Society of

Hypertension (issued 2020).[56,76] The early diagnosis of PA is challenging due to nonspecific symptoms. Without testing, PA can go unnoticed. Screening for PA is currently recommended if a patient with hypertension has: a) sustained grade 2 hypertension (>150/100 mmHg); b) resistant hypertension (3 antihypertensive medications including diuretics and BP >140/90 mmHg or need of ≥4 antihypertensive medications); c) young age (<40 years); d) early-onset stroke; e) hypokalemia; f) incidentalomas (coincidental tumors in the adrenal glands); g) sleep apnea; and h) a first-degree relative with PA or stroke at a young age.

### 1.5.1 ALDOSTERONE AND RENIN MEASUREMENTS

Screening involves measuring aldosterone and renin plasma concentrations. The diagnosis of PA is confirmed if a patient has a severe phenotype, i.e. high aldosterone levels >550 pmol/L and inappropriately low or suppressed renin (according to the local laboratory reference values) along with hypokalemia.[56,77] Patients with a high ARR and a less severe phenotype need a confirmatory test.[56] Due to the potential for false negative screening, repeated testing may be required.[67] In up to 31% of patients, aldosterone levels vary on consecutive aldosterone measurements.[78]

Several physiological factors and medications have the potential to interfere with aldosterone and renin concentrations.[56,76,79] Discontinuation of interfering medications causes distress and side effects.[80] Interpretation without discontinuing treatment seems to be the best approach.[33] Recent guidelines outline how to optimize testing conditions and how to interpret ARR in patients with interfering drugs.[56,75] To avoid false-negative ARR, hypokalemia should be identified and corrected before screening. If a patient is on an MRA medication and renin is not suppressed, it will be necessary to discontinue treatment at least 4 weeks before screening.[56]

It is important that clinicians know about the assays used at their institution and interpret results accordingly. Most centers have replaced plasma renin activity, which measures the amount of angiotensinogen I generated over time, with direct renin concentration,[81] which is less sensitive to poor sample handling and can be measured with a fully automated mass spectrometry analyzer.[81,82]

## 1.5.2 CONFIRMATORY TESTS

Recommended second-line tests to confirm PA include oral or intravenous sodium loading, fludrocortisone inhibition test, or captopril challenge test.[56] Intravenous sodium loading (or saline infusion test, SIT) is primarily used in Västra Götaland County. Aldosterone, renin, and potassium levels are measured before and after saline infusion. Adequate suppression is defined as an aldosterone concentration ≤140 pmol/L when SIT is performed in a recumbent position (saline infusion test, SIT).[56] An SIT in a seated position (seated saline infusion test, SSIT) does not compromise accuracy when a cut-off is set at 165 pmol/L and aldosterone is measured by tandem liquid chromatography-mass spectrometry.[83] Since SSIT does not require admission, this approach has gained popularity in more recent years.[83] In a validation study of SSIT,[84] aldosterone >171 pmol/L measured by immunoassay was 95.4% sensitive but incorrectly identified 20% of unaffected individuals as having PA. As demonstrated, cut-offs should be interpreted according to the assay used. Patients with unilateral disease have higher aldosterone levels after an SSIT.[85] Confirmatory testing is contraindicated in patients with severe uncontrolled hypertension, kidney failure, arrhythmia, or pronounced hypokalemia.

## 1.5.3 ASSESSING THE ETIOLOGY OF PRIMARY ALDOSTERONISM

Several diagnostic tools, often combined, are used to assess the underlying cause of PA including imaging studies, AVS, and genetic tests. When assessing the etiology of PA, it may be relevant to consider the potential benefits of a unilateral adrenalectomy.

### 1.5.3.1 GENETIC TESTS

Genetic testing should be performed when PA is diagnosed before the age of 20 years as well as in patients with early-onset stroke and PA, as familial forms require specific therapies (e.g. cortisol) that are not used in patients with nonfamilial forms of PA.[74] Currently, genomic sequencing to detect sporadic mutations is confined to research purposes.

### 1.5.3.2 ADRENAL IMAGING

CT scanning is central in the evaluation of newly diagnosed patients with PA. Although the most common causes of PA are benign, adenocarcinoma is a rare culpable cause of PA that should be ruled out.[86] CT is the imaging of choice to detect and characterize large adrenal masses but cannot establish endocrine

activity. Conversely, CT and likewise magnetic resonance imaging (MRI) carry the risk of identifying coincidental nonfunctional adrenal lesions. In about 33% of patients with a unilateral adenoma visualized on CT scans, the diagnosis is bilateral disease when AVS is performed.[7] In a Swedish cohort comprising 130 aldosterone-secreting adenomas,[87] the mean (standard deviation [SD]) diameter was 15.4 (7.3) mm. Small adenomas <1 cm may not be differentiated from focal adrenal enlargement.[88] Thus, normal CT scans do not exclude unilateral PA.

Studies on functional imaging such as $^{11}$C-metomidate positron emission tomography show promise in localizing the source of aldosterone secretion.[89] However, the use of this technique is limited due to the need for an on-site cyclotron facility because the radiotracer that binds to adrenal enzymes has such a short half-life. Other radiotracers are under investigation.[89,90]

#### 1.5.3.3 ADRENAL VEIN SAMPLING

AVS is currently the gold standard for the diagnosis of lateralized PA in patients ≥35 years of age who are candidates for adrenalectomy regardless of radiological findings.[56,91-94] Lateralized PA refers to the functional dominance of one adrenal gland compared to the other. This term is gaining traction, reflecting a better understanding of disease pathology. In this context, patients with marked asymmetric aldosterone hypersecretion benefit from surgery. AVS is more accurate than CT scans for diagnosing lateralized PA.[56,93,95] In centers that perform AVS, approximately 35% of all patients show lateralization.[96]

Performing adrenal vein catheterization is a technically difficult procedure that requires an experienced and dedicated physician.[97,98] To determine whether there is a gradient in aldosterone secretion, it is important to catheterize both adrenal veins and take samples for measurement of aldosterone and cortisol levels. Hence, the distinction between unilateral and bilateral disease only makes sense if a patient is willing to proceed to surgery.

Successful adrenal vein catheterization is determined by comparing cortisol levels in the adrenal veins and the inferior vena cava. If the aldosterone-to-cortisol ratio is significantly higher on one side compared to the other (reported as the lateralization index), it indicates unilateral aldosterone excess. Finally, to assess if the contralateral gland is suppressed due to autonomous aldosterone secretion, the contralateral suppression index is calculated by dividing the lower aldosterone-to-cortisol ratio by that of the inferior vena cava.

Lateralizing criteria are not consensual among different centers.[99] When stimulation with ACTH is used, a lateralization index >4 indicates unilateral aldosterone excess. Lateralization index in the range of 3 to 4 is indeterminate and indicates unilateral aldosterone production if the contralateral suppression index is <0.5 (figure 8).[97,99]

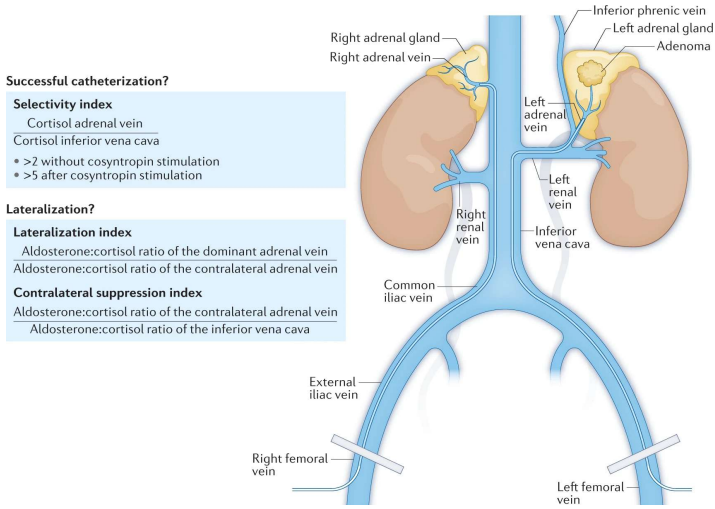


*Figure 8. Adrenal vein sampling in primary aldosteronism. [Reproduced from Turcu et al.[35] with permission from ©Springer Nature]*

AVS measures adrenal activity in real time; however, it is not indisputable. Factors such as timing of testing (due to circadian rhythm), interfering medications, and cortisol co-secretion may affect the results of AVS. ACTH stimulation can overcome some of these problems and enhance accuracy.[100]

# 1.6 TREATMENT AND OUTCOME OF PRIMARY ALDOSTERONISM

## 1.6.1 SURGERY

Unilateral adrenalectomy performed laparoscopically is a potentially curative treatment for PA and is therefore preferred when feasible in patients with unilateral disease. Treatment success is determined by clinical and biochemical outcomes postoperatively.[101] When guided by AVS, aldosterone and renin return to normal in most patients (96%–100%) but sustained hypertension is common and additional medications may be needed depending on age,

hypertension duration, and phenotype.[102] In a Swedish study of 190 patients with PA treated by adrenalectomy,[87] 92% of the patients were biochemically cured after adrenalectomy and 7% had improved potassium levels at follow-up. Of note, 34% of the patients became normotensive without the need for medication, while 60% experienced improvement in hypertension. No fatal events were reported in this cohort with the majority of patients treated with a minimally invasive approach. Following adrenalectomy, transient adrenal hormone deficiencies may occur in up to 5% of patients.[103] In some patients, this may be related to cortisol co-secretion.[104] A biochemical re-assessment should be performed 6 months after surgery.[101] Histological features of the resected gland determine how long a patient needs to be followed biochemically. Despite histopathology evaluations showing hyperplasia, some patients are cured.[105,106] Immunohistochemical staining for CYP11B2 is recommended to determine the functionality of resected adrenals but is not yet widely used.[19,107] Adrenalectomy is generally not considered an option in most patients with bilateral disease but some experts argue that it might be an option for selected patients under certain circumstances.[108,109] Some patients may benefit from selective adenoma removal, although the level of evidence is weak.[110,111]

### 1.6.2 MINERALOCORTICOID RECEPTOR ANTAGONISTS

An MRA is the established treatment for patients with primary aldosteronism who have bilateral disease, limited access to an accurate lateralization procedure, or who cannot undergo surgery.[56] MRAs are effective in treating a range of medical conditions linked to mineralocorticoid overactivation. The two most used MRAs are spironolactone and eplerenone. Spironolactone is the most widely used but has more side effects.[112,113]

In patients with heart failure, treatment with spironolactone or eplerenone prevents hospitalizations and reduces mortality.[114,115] In patients with hypertension, studies show that MRA treatment improves BP and left ventricular hypertrophy.[116-119] In patients with resistant hypertension (on 3 medications including a diuretic), spironolactone is the most effective fourth medication to consider.[120] In patients with primary aldosteronism, the effectiveness of MRA treatment in patients with primary aldosteronism goes beyond reducing BP. MRA treatment has the potential to reduce left ventricular mass,[117] improve metabolic complications,[121] reverse albuminuria and renal complications,[121-123] prevent cardiovascular events,[124,125] reduce

mortality,[121] and improve quality of life in patients with primary aldosteronism.[126,127]

Key considerations when choosing the type of MRA should be tolerability issues, which often lead to undertreatment.[116,128] Spironolactone has an inhibitory effect on the testosterone receptor and an agonistic effect on the progesterone receptor, and is therefore associated with gynecomastia and menstrual irregularities. Eplerenone is a selective antagonist that does not share spironolactone's adverse effects but is costly and therefore considered a second-line treatment in primary aldosteronism. Since eplerenone has a relatively short half-life, it should be taken twice daily. Eplerenone may be preferred in premenopausal women as many patients discontinue spironolactone due to safety concerns before attempting pregnancy.[129,130] A typical starting dose consists of spironolactone 25 mg once daily or eplerenone 25 mg twice daily. In order of importance, regular re-evaluation is essential to monitor clinical and biochemical responses and adjust the dose accordingly.

### 1.6.3 MORBIDITY ATTRIBUTABLE TO PRIMARY ALDOSTERONISM

The association between untreated PA and cardiovascular morbidity is well established, emphasizing the need for early diagnosis and effective treatment to improve the prognosis.

Diagnostic delay may lead to a broad spectrum of coexisting disorders. PA is associated with increased odd ratios (ORs) for stroke (2.58, 95% CI [confidence interval] 1.93–3.45), coronary artery disease (1.77, 1.10–2.83), atrial fibrillation (3.52, 2.06–5.99), and heart failure 2.05 (1.11–3.78) compared to patients with essential hypertension.[131]

Patients with PA may also experience renal impairment,[132] albuminuria,[133] metabolic complications,[121] and impaired quality of life.[126] Renal damage in PA is more prominent than in patients with essential hypertension and it affects kidney function independently of BP.[122,132,133] In a German study of disease severity,[132] plasma aldosterone and serum potassium were independent predictors of a lower glomerular filtration rate. Treatment with adequate doses of an MRA or adrenalectomy can potentially reverse renal impairment and albuminuria.[122,132]

Aldosterone excess has been associated with increased diabetes prevalence, occurring in up to 23% of patients, almost 2-fold than in hypertensive controls, as reported in a German study.[134] Overall, aldosterone excess inhibits insulin secretion and increases insulin resistance, leading to impaired glucose tolerance and diabetes.[135,136]

Aldosterone has a negative influence on calcium metabolism (increasing calcium) as shown by hypercalciuria and a secondary rise in parathyroid hormone.[137] This may result in secondary osteoporosis with vertebral fractures being common in patients with PA compared to patients with hypertension, as seen in three studies.[138-140]

It has been recognized that patients with PA at long-term follow-up still have a worse cardiovascular risk profile than that of hypertensive controls.[125]

## 1.7 CHALLENGES IN THE DIAGNOSIS AND INDIVIDUALIZED TREATMENT OF PRIMARY ALDOSTERONISM

Despite important advances, the diagnosis of PA remains a daunting task.[48,63] Screening for PA is considered cost-effective only in high-risk populations.[141] Lack of symptoms leads to missed opportunities for early intervention.[63,64,141] Both screening and confirmatory tests have diagnostic caveats, as provided earlier. The necessity for confirmatory testing and interpretation of tests by unfamiliar physicians affect the number of patients identified and prevalence estimates. Ultimately, improving screening efficiency is the greatest challenge of modern times.[63]

Setting reasonable treatment expectations and explaining what defines a successful outcome is essential when counseling individual patients. Optimal management requires an understanding of four aspects:

i. Accurate subtype differentiation is necessary for the avoidance of unnecessary surgical procedures. AVS is the key diagnostic tool for selecting surgical candidates but it is not possible for all patients and may be subject to sampling error.[142,143] The availability of AVS remains a clinical problem that affects treatment decisions and outcomes for patients with primary aldosteronism.

ii. Not all patients with unilateral disease can be clinically cured of hypertension after surgery.[87] This is evidenced by the fact that up to 60% of patients may require additional treatment after adrenalectomy, as shown in a recent study from Sweden.[87]

iii. Available data suggests that surgery has a more favorable effect on cardiovascular complications than medical therapy in patients with PA.[144,145] However, the evidence is not substantial. An ongoing randomized trial is evaluating whether eplerenone is as efficient as adrenalectomy in patients with unilateral disease.

iv. The appropriate dose of MRAs is a contentious issue between clinicians. It was previously recommended that patients who are not eligible for surgery should be given a low-dose MRA as a first-line antihypertensive in PA.[146] It has since been shown that patients achieving normal renin levels after treatment initiation have better outcomes.[121] Although consensus has not yet been reached, normalization of renin levels appears to be a reasonable goal.[147]

## 1.8 GAPS OF KNOWLEDGE

Several questions about the epidemiology, diagnosis, and complications of PA remain unanswered.

First, the incidence of PA is unclear. PA is the cause of hypertension in 1%–6% of patients in Sweden depending on the population tested,[60-62] although it is unknown how screening strategies perform in real-world settings. The number of people diagnosed with PA who are currently in care is undetermined. A population-based study of PA incident rates in Sweden will potentially be useful in capacity management and allocation of resources to ensure optimal performance for the healthcare system.

AVS is best practice to determine disease laterality irrespective of radiological findings.[56,91,92,97] However, according to Endocrine Society guidelines from 2016, AVS is not deemed necessary in young patients with confirmed primary aldosteronism and a solitary adrenal adenoma on imaging.[56] Seeking to justify this exception, we found that the original argument was based on small sample size studies.[94] Since young patients have a greater chance of being clinically cured,[101] it is particularly important that they receive a correct diagnosis. Paper II explores whether conventional imaging is reliable to assess laterality in young patients with PA. We hypothesize that relying on imaging alone can lead to wrong treatment decisions, as it may misclassify subtypes.

Another long-standing question relates to long-term consequences after treatment for PA and mortality.[145,148] Previous studies have reported potential links between PA and mortality,[121,148-150] but a meta-analysis of six studies (*n*=3039) of patients with PA suggested that mortality risk may decline over time.[151] Several limitations were acknowledged, such as enrollment of limited patients from large referral centers, short follow-up, and inadequate adjustment for disparities. A nationwide study using data from register linkage can provide valuable insights into treatment effects, enabling control for some important factors that may have influenced mortality outcomes in earlier studies. A comprehensive understanding of the association between morbidity, mortality, and primary aldosteronism, and furthering the influence of treatment can help guide individual approaches.

Aldosterone excess might have a larger clinical impact on bone health than is currently recognized. Previous studies have linked PA with a higher prevalence of radiographic vertebral fractures than in patients with hypertension.[138-140] However, determining the age of a vertebral fracture is difficult and fractures found through densitometric morphometry or lateral radiographs do not always correlate with clinical symptoms.[152] A study of 2533 patients with PA and 3684 hypertensive controls matched on propensity score found increased fracture risk in PA but did not specify site-specific fractures.[153] As a result of uncertain causality, we tested the hypothesis that patients with PA have an increased risk of hip fractures in our nationwide cohort. We picked hip fracture because it is a robust outcome, which is associated with impaired quality of life, reduced life expectancy, and high economic costs.[154,155]

# 2 AIM

The present thesis aims to address unanswered questions concerning epidemiology, diagnostic methods, treatment, and long-term outcomes in patients with PA. The specific aims were:

I. To estimate the incidence of PA in Western Sweden (Västra Götaland County) over three decades (1987–2016).
II. To evaluate whether young patients (up to 40 years of age) with PA need to undergo AVS to determine the subtype before treatment strategy is decided.
III. To study all-cause and cause-specific mortality in patients with PA as well as the impact of factors such as age, sex, treatment modality, and cardiovascular comorbidity in a large population-based study.
IV. To investigate the risk of hip fracture in patients with PA compared to the general population.

# 3 PATIENTS AND METHODS

*Table 1. Overview of each paper.*

| | Aim | Study design | Population | Results |
|---|---|---|---|---|
| Paper I | Incidence of PA | Retrospective review of medical records of patients identified with diagnostic codes in the NPR | Patients registered with a diagnostic code for PA in the NPR 1987–2016 (*n*=570) | Incidence rates of PA increased. However, PA is still underdiagnosed |
| Paper II | Role of AVS in guiding therapy in young patients with PA | Cross-sectional study | Consecutive patients aged ≤40 years who underwent AVS at Sahlgrenska Hospital 2005–2019 (*n*=45) | One-fifth of young patients with PA would have received inappropriate treatment if based on imaging studies alone and not AVS |
| Paper III | Investigate mortality in PA | Linkage of national registries | Patients registered with a diagnostic code for PA in the NPR 1997–2019 (*n*=2419) | Patients with PA have increased mortality compared to general population controls during the study period (1997–2020) |
| Paper IV | Investigate the incidence of hip fractures in patients with PA | Linkage of national registries | Same as in paper III | The risk of hip fracture is increased in PA during the study period (1997–2019) compared to the general population |

*Abbreviations:* AVS, adrenal venous sampling; NPR, National Patient Register; PA, primary aldosteronism.

## 3.1 PATIENTS AND STUDY DESIGN

### 3.1.1 DATA SOURCES AND ETHICAL CONSIDERATIONS

This work consists of four observational studies (table 1). Each study included in this thesis was reviewed and approved by the Swedish Ethics Review Board: Papers I, III, and IV (Dnr 029-17) and Paper II (Dnr 826/16). Study II was based on existing data from patients who performed AVS investigations at Sahlgrenska Hospital, which is the tertiary referral center in Västra Götaland County. The data used in Papers I, II, and III was collected from the following

national registries and databases held by the Swedish National Board of Health and Welfare, and Statistics Sweden (figure 9). Data linking was possible because of the universal use of the nationwide personal identification number by health care, private, and official authorities.[156]

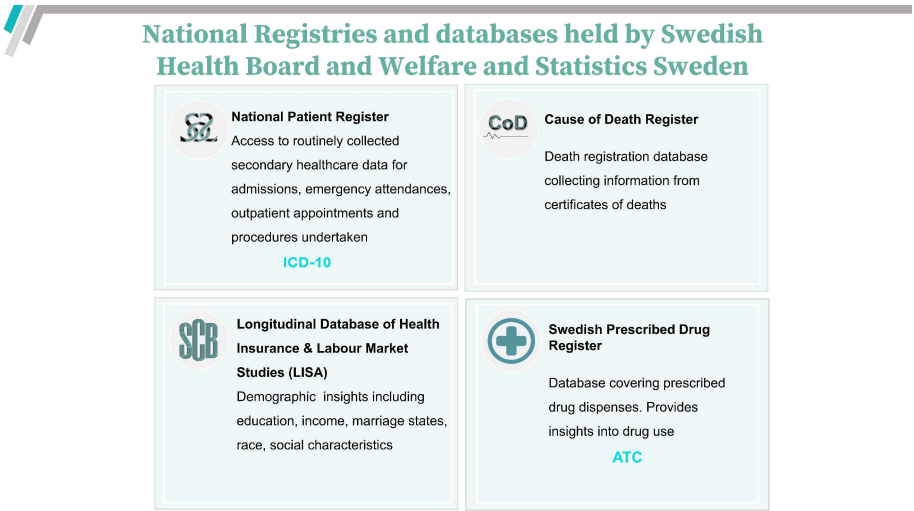


*Figure 9 Data sources for Papers II, III, and IV. Abbreviations: ATC, Anatomical Therapeutic Chemical Classification; ICD, International Classification of Diseases*

- The Swedish National Patient Register (NPR) is a nationwide registry that collects diagnostic codes from hospital discharges since 1987 and specialist outpatient care since 2001 following the International Classification of Diseases (ICD). Procedures are coded according to the Nordic Classification of Surgical Procedures. The registry does not contain data on primary care. The Health Data Register Act (1998:543) and the associated regulation (2001:707) support the National Board of Health and Welfare and oblige healthcare providers to provide information to the Patient Register.[157]
- The Swedish Causes of Death Register covers all deaths that occurred in Sweden, including deaths of non-Swedes. It also includes deaths of Swedes who have died abroad.[158]
- The Swedish Prescribed Drug Register "contains all prescribed drugs as dispensed in pharmacies" from July 2005 onwards according to Anatomical Therapeutic Chemical Classification (ATC) codes.[159]
- The Swedish Population Register contains demographic data for all Swedish residents.[160]

- The Longitudinal Database of Health Insurance and Labour Market Studies (LISA) held by Sweden Statistics integrates data from the labor market, education, and social sector, and offers insight into supply and demand and the economy in general.[160]

All registries contain sensitive personal data protected by the General Data Protection Regulations. To validate the PA diagnosis (Study I), the Swedish National Board of Health and Welfare provided the personal identifier for patients diagnosed between 1987 and 2016 in Västra Götaland County. To reduce the identification risk in Studies III and IV, identification numbers were replaced with serial numbers by the Swedish National Board of Health and Welfare. We followed laws and regulations governing data storage, access, and sharing rules. Since none of these studies involved direct contact with study participants and did not alter their management, the Swedish Ethics Review Board waived the requirement for obtaining informed consent.

### 3.1.2 PAPER I – INCIDENCE OF PRIMARY ALDOSTERONISM

This study aimed to assess the incidence of primary aldosteronism in the Västra Götaland County between 1987 and 2016. A data file of individuals assigned with a diagnostic code for PA in the NPR (i.e. ICD-9 255.B or ICD-10 E260) was provided by the Swedish National Board of Health and Welfare. Available medical reports were reviewed and clinical, biochemical, imaging, and histopathological data was assessed to validate PA diagnosis. The incidence and prevalence of PA were calculated by using the number of residents in the Västra Götaland County as reference. Register coverage was assessed using a dataset of patients who underwent AVS at Sahlgrenska University Hospital, the tertiary center for subtype investigation in the County.

### 3.1.3 PAPER II − ADRENAL VEIN SAMPLING IN YOUNG PATIENTS WITH PRIMARY ALDOSTERONISM

This was a cross-sectional, single-center study of 45 consecutive young patients diagnosed with PA at Sahlgrenska University Hospital between 2005 and 2019. The study aimed to evaluate CT/MRI performance compared to AVS for classifying PA as unilateral or bilateral in young patients (≤40 years of age at the time of AVS) with PA. Based on the re-evaluation of imaging data by two experienced radiologists, the study estimated how many patients

would have been given inappropriate treatment if the decision had been based solely on imaging studies.

### 3.1.4 PAPER III − MORTALITY IN PRIMARY ALDOSTERONISM

This was a nationwide, register-based, matched cohort study. Data covers all patients with PA >18 years of age who were newly diagnosed between 1997 and 2019 in Sweden. Patients were identified by search of ICD-10 diagnoses for PA in the NPR. To distinguish between prevalent and incident patients, we identified and excluded patients diagnosed from 1987 to 1996. Statistics Sweden randomly selected 10 controls from the general population for each case matching them by age, sex, and country of residence. The study included 2419 patients with PA and 24 187 age- sex- and residential area-matched controls from the general population. The study aimed to study mortality in PA and determine how age and cardiovascular comorbidity at diagnosis, sex, and treatment mode impact outcome.

Record linkage with the Cause of Death Register allowed identification of all deaths and causes of death. Causes of death were subdivided by ICD codes into: deaths from any cause (all-cause mortality), cardiovascular diseases (CVDs) (ICD-10 I10–I99), coronary heart disease (ICD-10 I20–I25), stroke (ICD-10 I61–I64), and other causes of death (all codes not listed above). Patients treated with adrenalectomy were identified by searching for diagnostic codes for adrenal resection (BCA20) or unilateral adrenalectomy (BCA30, BCA31) according to the Nordic Classification of Surgical Procedures. Data on MRA use was collected from the Swedish Prescribed Drug Registry, for which data was available since 2006. MRA users were those patients who had received an MRA (spironolactone or eplerenone) from pharmacies at least twice annually during follow-up and were not treated by adrenalectomy. The average MRA dose was defined in defined daily dose (DDD) units according to the World Health Organization. One DDD for spironolactone (ATC code C03DA01) is 75 mg and one DDD for eplerenone (ATC code C03DA04) is 50 mg.[161] Patients receiving an average daily dose of MRA that was lower or higher than the median MRA dose among all users were further classified as low- or high-dose MRA users, respectively. Patients who could not be classified as surgically treated or MRA users were considered untreated. Detailed information on patients' comorbidity before diagnosis was obtained from the NPR and socioeconomic factors from LISA including level of education, marital status, income, and country of birth. Sex was inferred by

gender. Comorbidity was based on ICD codes I20–I25 (ischemic heart disease), I21 (myocardial infarction), I48 (atrial fibrillation or flutter), (I50 (heart failure), and I61–I64 (stroke), and E10–E14 (diabetes mellitus).

### 3.1.5 PAPER IV − HIP FRACTURES IN PRIMARY ALDOSTERONISM

This nationwide observational study used the same population as in Study III to assess the association between primary aldosteronism and hip fracture risk. Hip fractures were identified in the NPR from 1997 to 2019 based on ICD codes S72.0, S72.1, and S72.2 (femoral neck fracture, intertrochanteric fracture, and subtrochanteric fracture, respectively). Adjustments included all covariates assessed in Study III and additional risk factors for hip fracture, including CVD comorbidity at baseline (defined as in Study III), osteoporosis (M80–M82), hyperparathyroidism (E21), and prior fracture at any site (ICD-10 S02, S12, S22, S32, S42, S52, S62, S72, S82, and S92) assigned before the index date.

## 3.2 STATISTICAL ANALYSIS

Baseline characteristics of subjects included in Studies I–IV were presented as mean (SD) when continuous variables were normally distributed or as median (interquartile range; IQR) when variables were not normally distributed. Categorical variables are presented as numbers with percentages.

In Study I, the incidence and prevalence of PA were calculated by using the number of residents in the Västra Götaland County as reference. To compare patients' characteristics diagnosed in earlier and later periods a t-test or the Mann-Whitney U-test was used for continuous variables depending on data distribution. To compare frequencies, Fisher's exact test or Pearson's chi-squared test was used.

In Study II, the results of AVS and imaging were treated as ordinal data (unilateral and bilateral) for concordance analysis. Inconclusive data was presented separately. We reported the number of concordant and discordant pairs (AVS *vs* CT/MRI). Cohen's kappa was used to assess agreement between readers.

In Study III, the general population cohort was considered the reference cohort to study mortality in PA. To present and compare survival graphically in

different treatment groups, we used Kaplan-Meier survival plots. The plots describe the relationship between survival probability and follow-up time. Notably, the Kaplan-Meier method does not allow adjustments for confounders and depicts crude all-cause mortality. We used Cox regression analysis, which allows adjustment for confounding factors, to compare all-cause mortality and cause-specific mortality in patients with PA and matched controls. The results from regression analysis are presented as hazard ratio (HR) with 95% CI. CI provides information about the precision of estimates. For the patient group, survival time is calculated from the date of diagnosis. For the reference group, survival time is calculated from the diagnosis date of their matching. Individuals who survived to the end of follow-up were censored. To utilize Cox regression analysis, we ensured that the proportional hazards assumption applied to the data.

The association of PA and mortality was assessed in the following models. The first model adjusted for sex and age at diagnosis of PA. In the second model, further adjustments were made for socioeconomic factors at study entry (level of education, marital status, income, and country of birth) as well as diabetes mellitus. In stratified (subgroup) analysis, we compared survival in different patient groups and corresponding controls from the general population. These groups were *a priori* categorized based on the median age of the cohort, sex, and treatment category (adrenalectomy, MRA, low-dose MRA, high-dose MRA, or no specific treatment) and by CVD (yes/no) at study entry. Definitions of these terms are explained in the Methods section. Two sensitivity analyses were performed to assess the robustness of the hazard estimates. The first sensitivity analysis aimed to increase the validity of the PA diagnosis by including only patients with multiple diagnostic codes. The second sensitivity analysis aimed to assess whether the results would change when different identification sources were used to adjust for diabetes mellitus. (i.e. clinical codes or dispensed drugs used to treat diabetes, a variable that captures all patients with diabetes regardless of their health provider). Because CVD comorbidity is a mediator of the association between PA and mortality, we only adjusted for CVD comorbidities at baseline, along with diabetes in a within-PA cohort analysis, to assess the independent influence effect of age, sex, and treatment underlying increased mortality risk among patients with PA.

In Study IV, we used Cox regression analysis to estimate the HR for hip fracture in PA (overall, by sex, age, and CVD at baseline) and by treatment. HRs were adjusted for history of any prior fracture, osteoporosis, primary hyperparathyroidism, presence of CVD comorbidities (ischemic heart disease,

atrial fibrillation or flutter, congestive heart failure, and stroke), diabetes mellitus, and socioeconomic factors. As in Study III, a sensitivity analysis was performed that was restricted to patients who received the diagnostic code for PA in the NPR on two or more occasions.

## 3.3 METHODOLOGICAL CONSIDERATIONS

Accurate diagnostic methods and a representative reference population are crucial to produce accurate incidence and prevalence estimates. In Study I, the use of ICD codes for case identification is a limitation. Miscoding would bias our estimates: therefore, case ascertainment by review of medical records was a strength. Overall, healthcare services in Sweden perform similarly across counties and the study area is the second most populated county. Hence, we consider the study population representative. It is important to understand that the true incidence of PA cannot be captured for three reasons: a) chronic diseases develop gradually and patients are likely screened at different stages, b) varying screening tests and cut-offs; and c) increased awareness of PA, which may lead to increased recognition of prevalent patients. The value of our approach is that it shows how screening strategies perform in a real-world setting.

The main limitation of Study II, which evaluated the diagnostic reliability of adrenal imaging to assess disease laterality in young patients, is the small patient sample based on data availability rather than statistical power calculations. A reliable conclusion can be reached by pooling data from relevant reports.[162] A further limitation is potential selection bias. During the study period, four young patients proceeded to surgery based on imaging alone. Available information on their treatment outcomes was provided. Limitations of AVS, which is used as the reference test, are discussed in the Introduction. Strengths related to the methods are the use of a well-established AVS protocol, along with the success rate, and the detailed description of the patients' characteristics and outcomes. Another strength is that we considered the possibility of different readings and obtained independent assessments by two readers for each imaging study.

Studies III and IV utilized data from national registries and databases. The studies take advantage of the large sample size, long and almost complete follow-up, and the unselected and representative population of patients provided. On the other hand, several barriers exist when obtaining data from registries and databases for research purposes (see as follows).

First, validation of registry data is essential since the validity of our results is closely linked to the quality of the data provided. Validation of the PA diagnosis in the NPR was necessary to address misclassification, i.e. the possibility that individuals without PA were miscoded as diseased. It has been shown that 85%–95% of diagnoses in the NPR are correct but, when it comes to endocrine diseases, miscoding is a concern.[163,164] To assess completeness, we searched and identified a subset of patients who underwent AVS in our institution in the NPR. Notwithstanding that individuals with suspected PA are referred to secondary healthcare services for confirmatory testing, most patients with confirmed PA were included. Second, it was important to choose outcomes that could be reliably assessed through administrative health data. In validation studies of the Cause of Death Register, a cause of death was provided for 97% of all deaths and agreed with medical records in 77%–98% of patients, with higher levels of agreement seen for CVD deaths.[165] In Study IV, we relied on the NPR to assess the risk of hip fractures. Since most patients with hip fractures require specialized care and hospitalization, the NPR covers 97% of patients with hip fractures.[166] Third, the NPR does not capture data from primary care. Patients with diabetes may be inadequately represented in the NPR, as most of these patients are followed by general practitioners A sensitivity analysis was conducted to address imbalances in diabetes prevalence, utilizing information from the Drug Register as an alternative to ICD codes.

An important limitation that applies to retrospective and register-based studies is that data was not collected specifically for our research purposes. This makes it difficult to fully address potentially confounding factors. In Study I, the validation process was confined to earlier definitions and practices and limited in many cases due to missing data. In Study II, cortisol co-secretion and surgical outcome could not be assessed in a few patients. In Studies III and IV, adjustment for several socioeconomic factors that influence long-term outcomes was possible and the cohort was large enough for multivariable adjustments and stratification. However, it was not possible to study the independent role of hypertension, which partly mediates the development of complications in PA.[131] Another missing variable of interest was renin levels, which limited individual assessments of dose adequacy in MRA users. In Study IV, we could not adjust for risk factors such as bone mineral density, glucocorticoid therapy, smoking, body mass index, and heredity, all of which might add to the risk of hip fracture.[167] While the nationwide cohort had a large number of patients with PA, the number of events can be small in the subgroup

analysis. For this reason, the low number of hip fractures in men may lead to type II errors when assessing their fracture risk.

Finally, when interpreting associations, it is important to be aware that the design cannot establish cause-effect relationships. Importantly, the observed variations in the subgroup analysis (e.g. by age, sex, or presence of comorbidities) depend on different baseline hazards and do not imply a differential treatment effect. In this context, a comparison between MRA and surgery would not be fair due to limited control over several risk factors and selection bias. The ideal setting to assess treatment effects comparatively would be a randomized trial. To help guide whether these results can be extrapolated to other populations, it is important to consider differences in demographic characteristics, disease severity, genetic characteristics, or sodium intake.

# 4 RESULTS

## 4.1 PAPER I – INCIDENCE OF PRIMARY ALDOSTERONISM

In Study I, we determined the incidence of PA from 1987 to 2016 in Västra Götaland County. Results are summarized in figure 10. The total number of individuals assigned an ICD-9 (255.B) or ICD-10 code for PA (E260) in the NPR was 570. Out of the 553 individuals identified with available records, 473 (83%) were classified as having PA and 17 (3%) as probable PA. A common reason for misdiagnosis was that patients were coded as diseased at referral, as 31 of 63 incorrectly diagnosed patients had undergone a confirmatory test that ruled out PA. Among individual patients registered with ICD-10 E260 (since 1997), 87% were confirmed PA patients and 94% were assigned ICD-10 for PA more than once for confirmed PA. Additionally, 97% of patients in whom AVS investigation was performed at Sahlgrenska University Hospital were registered in the NPR. Patients with confirmed PA ($n$=416) had a mean (SD) age of 56 (12) years at diagnosis and about 40% ($n$=168) were women. Potassium supplementation was required in 80% of the patients with confirmed PA. Results of an SIT were available in half of the patients diagnosed between 1997 and 2006. The diagnosis of PA was corroborated with an SIT in 87% of patients diagnosed between 2007 and 2016. This trend may relate to changes in recommendations for screening. There has been an increase in the number of patients who have undergone AVS since 1997 (46% in 1998–2006 *vs* 80% in 2007–2016), leading to an increasing number of patients receiving adrenalectomy. Among all patients, 43% received adrenalectomy: seven patients between 1987 and 1996, 48 between 1997 and 2006, and 121 between 2007 and 2016.

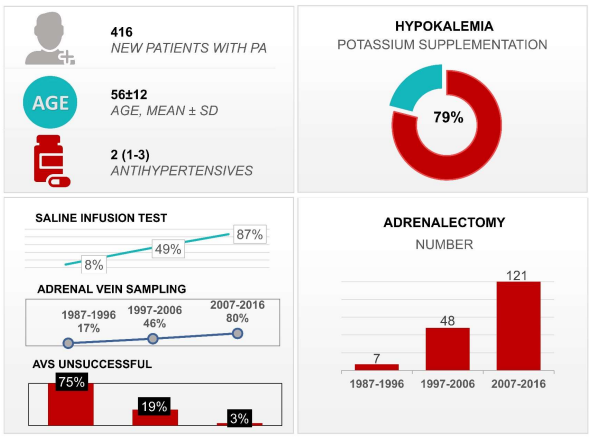


*Figure 10. Background characteristics, investigations, and treatment by time period. Significant difference was found between 1997–2006 and 2007–2016 for saline infusion tests and AVS along with success rates but not in indicators of disease severity such as hypokalemia and number of antihypertensive drugs. Abbreviations: AVS, adrenal vein sampling; PA, primary aldosteronism.*

For incidence analysis, 416 patients (60% men and 40% women) diagnosed with PA between 1987 and 2016 were eligible. The median (IQR) annual incidence of PA was estimated to be 2 (1–2) patients per million between 1987 and 1996, 6 (4–9) patients per million between 1997 and 2006, and 17 (12–24) patients per million between 2007 and 2016 (figure 11). At the end of the study (December 31, 2016), 386 patients with confirmed PA were still alive and living in Västra Götaland County, resulting in a prevalence of 231 patients per million (0.022%). The expected number of patients should have been 3500–20 000 based on previous prevalence studies.[60-62] Thus, only a small proportion of hypertensive patients are being diagnosed with PA.

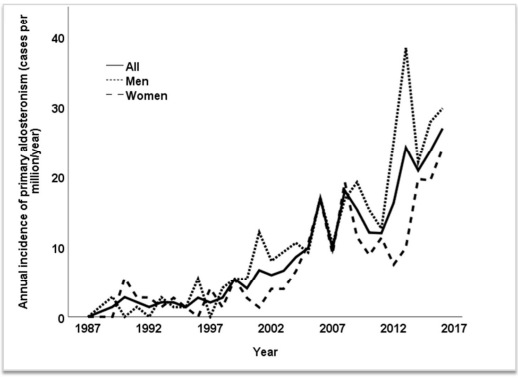


*Figure 11. Incidence of primary aldosteronism in Western Sweden over 3 decades. [Reproduced from Gkaniatsa et al.[168] with permission from ©Oxford University Press]*

## 4.2 PAPER II – ADRENAL VEIN SAMPLING IN YOUNG PATIENTS WITH PRIMARY ALDOSTERONISM

Study II, designed to compare CT/MRI scanning and AVS, included 45 consecutive patients with PA 26–40 years of age who underwent AVS in addition to imaging studies at Sahlgrenska University Hospital between 2005 and 2019. Sixteen patients were ≤35 years of age and 34 were women. At referral, 60% required potassium supplements and median post-infusion aldosterone level was 552 pmol/L.

Results are summarized in figure 12. Comparison of the radiological diagnosis with AVS results unexpectedly revealed that 20% (*n*=9) of young patient with PA had an inaccurate prediction of laterality based on imaging studies. In total, 22 patients had unilateral PA considering AVS as the criterion standard. Of these, two patients had a lateralization index between 3 and 4 but suppressed contralateral CL. AVS demonstrated that four of 25 patients with either normal or bilateral abnormal adrenal glands on imaging had unilateral aldosterone production, while five of 20 with solitary adrenal nodules had bilateral disease. Two patients with bilateral disease according to AVS and discordant imaging proceeded to adrenalectomy. Partial biochemical success was observed in one

patient and negative biochemical success was seen in the other. Only one of the patients who was lateralized on AVS showed features of nodularity on histology but showed complete clinical success.

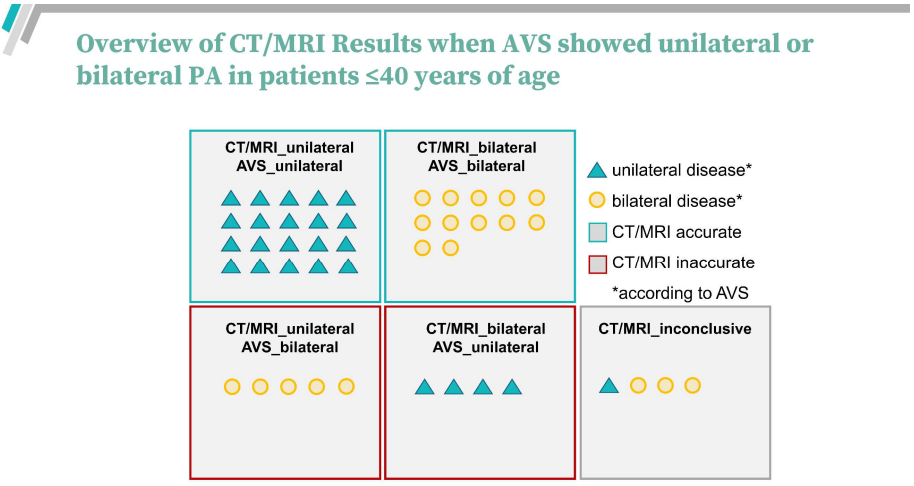


*Figure 12. Simplified overview of results in Paper II.[169] Abbreviations: AVS, adrenal vein sampling; CT, computerized tomography; MRI, magnetic resonance imaging; PA, primary aldosteronism.*

Re-evaluation of the same images by two experienced radiologists showed that inter-rater agreement of imaging studies in patients with PA was excellent (k=0.90) for detecting adrenal lesions >1 cm and substantial (k=0.71) for detecting lesions 0.8–1 cm in diameter. The only exceptions where different interpretations involved adrenal lesions >1 cm were a patient with a unilateral 11-mm lesion classified as focal hyperplasia by one reviewer and a patient with a unilateral adenoma and a benign extra-adrenal lesion that confused the two readers. In this case, MRI was more informative than CT scanning.

## 4.3 PAPER III – MORTALITY IN PRIMARY ALDOSTERONISM

Our population-based register study followed 2419 people >18 years of age who were diagnosed with PA between 1998 and 2019, and 24 187 unaffected people matched (1:10) for sex, birth year, and county of residence. Mean age was 56 years and 44.4% were women. Patients with PA had a higher prevalence of CVD comorbidities and diabetes compared to controls at

baseline. Cohorts were followed for a median duration of 8.1 *vs* 8.2 years, respectively, during the period from 1 January 1997 to 31 December 2020 (figure 13).

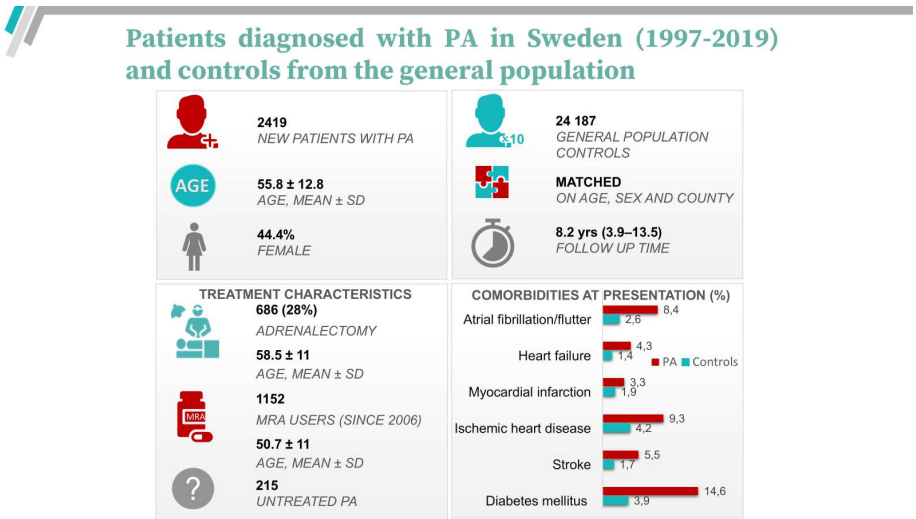


*Figure 13. Baseline characteristics of the study population in Paper III. Abbreviations: MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism; SD, standard deviation; yr, year.*

Mortality results are summarized in figure 14. In total, 345 patients and 2736 controls (14% *vs* 11%) died during the study period. On average, we found that patients with PA had a 20% greater risk of all-cause mortality (HR 1.23, 95% CI 1.10–1.38) and mortality due to CVD (1.57, 1.30–1.89) after adjustment for age, sex, diabetes, and socioeconomic variables. Mortality was increased in both women (1.36, 1.14–1.63) and men (1.17, 1.01–1.35) but varied according to age at diagnosis. When considering only patients diagnosed before the age of 56 years, mortality was not increased compared to corresponding controls without PA (0.98, 0.73–1.31). In stratified Cox proportional hazards models adjusted for age, sex, diabetes, and socioeconomic variables, the highest HRs were observed in the following subgroups: patients with PA and CVD at diagnosis (1.53, 1.26–1.85), age >56 years at diagnosis (1.28, 1.13–1.45), and those treated with a low-dose MRA (1.30, 1.02–1.66), all compared to corresponding controls. Conversely, in patients treated by adrenalectomy and patients receiving a higher dose of MRA than average, no excess mortality was observed. Patients who were not treated by adrenalectomy and were not MRA

users had an HR of 2.51 (1.72–3.67) compared to matched controls, accounting for socioeconomic factors and diabetes.

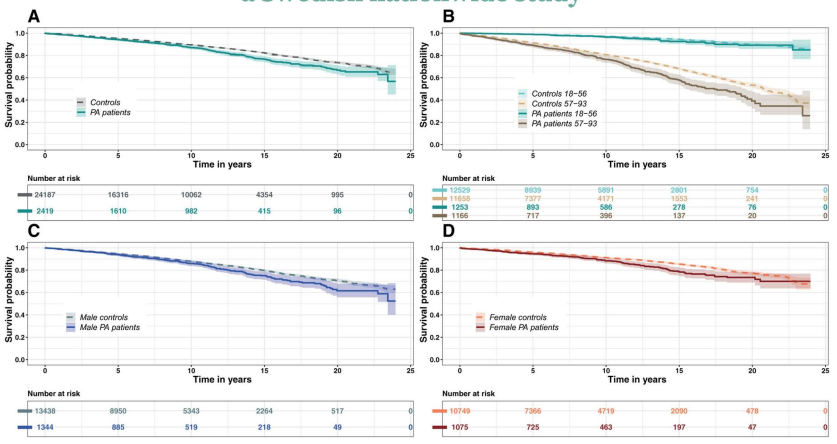


*Figure 14. Kaplan-Meier plots of overall survival throughout the study period in patients with primary aldosteronism (solid line) and corresponding controls (dotted line) for A) the entire cohort, B) by age group, C) men with PA, and D) women with PA. P-values are from log-rank tests. Abbreviation: PA, primary aldosteronism. Reproduced from Gkaniatsa et al.[170] with permission from ©Wolters Kluwer Health]*

## 4.4 PAPER IV – HIP FRACTURES IN PRIMARY ALDOSTERONISM

In Study IV, we explored hip fracture risk in patients with PA. The cohort of patients was the same as in Study III (*n*=2419) as was the matched general population control cohort (*n*=24 187). Hip fractures were assessed during the study period 1997–2019 (figure 15). During a mean (SD) follow-up of 8 (5) years, 64 (2.6%) patients had a hip fracture after being diagnosed with PA compared to 401 (1.7%) controls. Cox regression analysis showed that the risk of hip fracture was increased in PA compared to controls (HR 1.55, 95% CI 1.18–2.03) after adjustment for history of any prior fracture, osteoporosis, primary hyperparathyroidism, diabetes mellitus, and socioeconomic factors. Patients at highest risk were women (1.76, 1.24–2.52), patients >56 years of age at the time of diagnosis (1.62, 1.21–2.17), and patients with CVD at diagnosis (2.15, 1.37–3.37). No increased risk of hip fractures overall was seen

in patients treated by adrenalectomy (0.84, 0.35–2.0), while patients treated with MRAs retained a greater risk (1.84, 1.20–2.83).

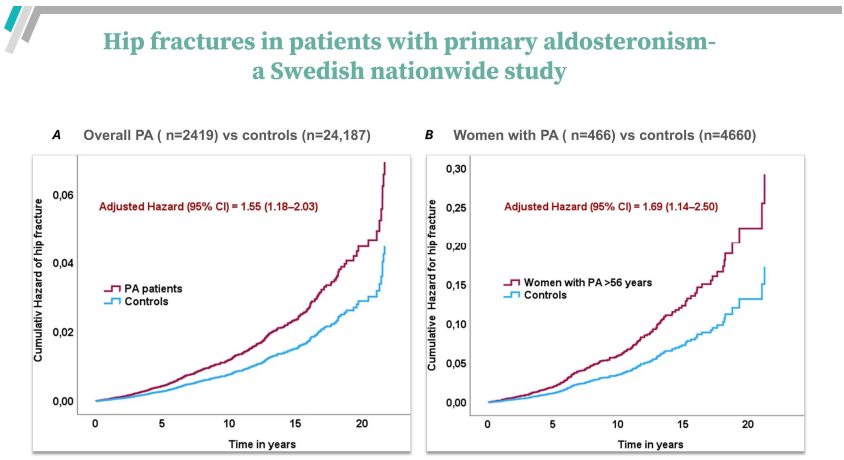


*Figure 15. Cumulative risk for hip fracture in patients with PA and controls matched by age at diagnosis, sex, and county of residence adjusted for socioeconomic factors, prior fractures, diabetes mellitus, osteoporosis, hyperparathyroidism, and cardiovascular disease for A) the entire cohort and B) women with PA. Results from Cox regression. Abbreviations: CI, confidence interval; PA, primary aldosteronism. [Reproduced from Gkaniatsa et al.[171] with permission from ©Springer]*

# 5 DISCUSSION

## 5.1 KEY FINDINGS

The thesis has uncovered several key findings.

i. PA remains under-diagnosed. The notified incidence of PA is increasing. Without capacity, these trends will probably strain the healthcare system.
ii. Conventional imaging compromises diagnostic accuracy and leads to inappropriate treatment in a substantial number of young patients. Recommendations to omit AVS in patients with a solitary adenoma and age under 35 years are not supported by our data.
iii. Long-term mortality is increased in PA. The major contributors appear to be older age and comorbidities at the time of diagnosis and undertreatment, stressing the importance of early disease identification and adequate treatment.
iv. Patients with PA are at an increased risk for hip fractures. For the outcome of the risk of hip fracture, women and patients with established comorbidity are most vulnerable as are patients treated with an MRA.

Overall, this thesis provides valuable insights into the long-term consequences of PA in various patient populations, highlighting a need for improvement in the overall management of patients with PA. The potential of disease-specific treatment has been highlighted with evidence suggesting that high doses of an MRA and adrenalectomy reverse mortality. Concerns have been raised that medically treated patients receive insufficient MRA doses. Factors such as age at diagnosis and established CVD comorbidity have been explored and were associated with a further increase in mortality risk, which was not seen in young patients and patients without comorbidities: this highlights the consequences of delayed diagnosis. Impaired bone health has emerged as a complication of PA, although the underlying mechanism is poorly understood. To place findings in context, the following topics summarize available evidence and provide insights that might serve as a basis for further research.

## 5.2 TRENDS IN INCIDENCE OF PRIMARY ALDOSTERONISM AND PRIORITIES

Study I, a population-based study from Sweden, found that the incidence of PA has increased from a median (IQR) of 2 (1–2) patients per million people between 1987 and 1996 to 6 (4–9) patients between 1997 and 2006 and 17 (12–24) patients between 2007 and 2016. At the end of the study (December 31, 2016) the prevalence of PA was 231 patients per million (0.022%). Greater access to AVS has significantly affected the proportion of patients being assessed and diagnosed with unilateral disease, as seen by the number of adrenalectomies, which became more frequent. Hence, trends also suggest that the number of individuals with unilateral disease requiring surgical intervention will increase. Prevalence estimates were substantially lower than the range of rates reported from cross-sectional studies from Sweden.[60-62] The magnitude of undiagnosed PA ranged from 3500 to 20 000 people.

The incidence of PA appears to be increasing in the general population. This is likely due to increased awareness about the risk of CVD complications and less due to the broadening of the definition of PA. We compared patient characteristics diagnosed in different time periods to understand factors driving these trends and their implications. Guidelines focus on screening high-risk individuals for PA but the definitions and criteria used to verify PA vary widely.[58,67,141] Although diagnostic methods were not the same during the studied period, the bulk of these patients were diagnosed using conservative cut-offs and most had hypokalemia at presentation (80%).[56] This contrasts with previous studies which suggest that 37% of patients with confirmed PA present with hypokalemia.[23,34] A study from Korea, in which clinical criteria and comprehensive screening were used to identify patients with PA, reinforced previous observations with only 40% of patients presenting with hypokalemia among patients diagnosed most recently (2016–2021).[28] A study from 2016 found that screening recommendations for PA were not uniformly adopted by general practitioners in Germany and Italy.[172] We conclude that more efforts are needed to improve the diagnosis of patients with less severe phenotypes.

Despite these incremental increases in case identification, effective health planning is required to address the higher overall healthcare needs of a growing population. It is increasingly appreciated that PA represents a spectrum of clinical disease severity.[27] As the question of cost-effectiveness arises, we should keep in mind that the most significant cost to the healthcare system is that of untreated PA.[173] However, looking across the continuum of PA,

diagnosing edge cases with marginal PA has to be carefully weighed. As the prevalence of PA continues to evolve,[34] our primary focus should be to identify individuals where evidence suggests that targeted treatment can prevent complications rather than diagnosing as many individuals as possible.

The accurate and timely diagnosis of PA is crucial as it lays the groundwork for effective treatment and positive patient outcomes. Optimizing the management strategy for PA involves comprehensive screening of groups with a high probability of PA.[63] Efforts to simplify screening and standardize protocols for evaluating treatment options will be crucial in improving patient outcomes. Simplified diagnostic algorithms should emphasize that patients with a severe phenotype do not need confirmatory testing, which is often disregarded.[63] Our study prompted a critical reflection on current screening guidelines for PA in Sweden and internationally, emphasizing the need for a more efficient screening process.[174,175]

## 5.3 WHY SHOULD YOUNG PATIENTS UNDERGO ADRENAL VEIN SAMPLING?

In Study II, laterality determined by AVS in young patients was compared with that determined by imaging studies, both used as standard care at Sahlgrenska University Hospital. Discordant findings were reported in nine of 45 (20%) patients <40 years of age. Despite the small number in the study group, this work complements previous studies in this field and supports using AVS to diagnose unilateral disease in young patients with PA accurately.

Nonfunctional adenomas are uncommon in young patients.[96,176] This has led to doubts on whether AVS is truly indicated in the age group <40 years with visual evidence of unilateral disease. When guidelines were released in 2016, the Task Force deemed there was not enough evidence to recommend AVS for younger patients with a solitary adenoma. However, the reliability of conventional imaging in this context has not been evaluated using large patient samples.[91,177] One of the factors that makes this presumption questionable is the heterogeneity of histopathological features in unilateral PA. In patients with unilateral disease, small regions with strong aldosterone synthase activity, known as aldosterone-producing cell clusters, may be the source of aldosterone secretion.[105] Patients with apparent normal adrenal glands benefit from AVS investigations. As reported by Riester et al.,[178] seven out of 28 young patients with apparently normal adrenal glands lateralized on AVS. Guidelines were

published in 2016 and some new studies have been published since then. The surgical outcome of 69 patients <40 years of age with severe PA and unilateral adenoma on imaging were presented in the study of Umakoshi et al.[179] Concordance between CT/MRI and AVS was found in 79% (31/39) of patients between 35 and 40 years of age and 90% (27/30) of patients <35 years of age. Thus, recommendations to omit AVS in patients with a solitary adenoma and age <35 years are not well supported by more recent data.

Inaccurate assessments have important implications for patients with PA. Different readings have important consequences for patient care and may negatively influence long-term outcome. The potential for a minor measurement error to result in a missed opportunity for curative surgery is an example of variability in reading, while a nonfunctional adenoma puts a patient at unnecessary risk for surgery. Despite improvements in imaging techniques, difficulties remain in differentiating small nodules from hyperplasia, as shown by discrepancies in interpretation among radiologists.

A diagnostic test to assess laterality in PA should be accurate to offer patients the option of cure and have high specificity to avoid unnecessary adrenalectomy. As discussed as follows, early diagnosis can be particularly advantageous for younger patients in terms of CVD outcome by addressing the reversible cause of hypertension. Indeed, patient age is one of the most important prognostic factors in those treated by adrenalectomy.[180] There is considerable international interest in this study, which has been proposed as a basis for further revisions of the current guidelines.[181]

## 5.4 CAN SPECIFIC TREATMENT WITH A MINERALOCORTICOID RECEPTOR ANTAGONIST OR ADRENALECTOMY PREVENT MORTALITY IN PRIMARY ALDOSTERONISM?

Study III used large nationwide administrative health records and databases to identify all Swedes age >18 years with PA from 2019 to 2019 and study mortality outcomes. A total of 2419 patients diagnosed from 1997 to 2019 were identified in the NPR, of whom 686 received adrenalectomy. The study showed people with PA have a higher risk of all-cause mortality (HR 1.23, 95% CI 1.10–1.38) and CVD mortality (1.57, 1.30–1.89) compared to age- and

sex-matched controls without PA from the general population. Subgroup analysis provided valuable insights into the impact of different treatments on patient outcomes. Patients treated by adrenalectomy and patients treated with high-dose MRAs had similar mortality risk to age- and sex-matched controls. On the contrary, targeted treatment for PA did not reverse excess mortality in patients >56 years of age at the time of diagnosis, those with CVD comorbidity, and those treated with low doses of MRAs. As detailed in the Results section, mortality was increased in patients diagnosed in earlier time periods and in most recent patients, and remained significantly increased up to 10 years after diagnosis.

In a prospective cohort study of 300 patients with PA from Germany, there was no significant difference in survival between patients with PA and hypertensive controls or normotensive controls.[148] A meta-analysis of six observational studies quells concerns about long-term mortality in PA.[151] An increased crude 3-year mortality in 3039 patients with PA was reported compared to patients with essential hypertension (HR 2.0, 95% CI 1.3–2.9); however, no differences were observed at 5, 7, 5, and 10 years.[151] Interestingly, the largest cohort included in the meta-analysis encompassed 2448 patients and had a mean follow-up duration of 4.3 years,[150] whereas one of the studies recorded no events in either arm after 7.5 years of follow-up.[182] Long-term mortality and CVD outcomes may be affected by factors unrelated to healthcare services, such as socioeconomic factors, treatment adherence, and retention in care, which were not addressed in previous studies.

The large sample size of our cohort and the accumulated evidence of earlier studies enable us to conclude that long-term mortality is increased in PA. Moreover, our study provides valuable information to help identify high-risk patients for optimal clinical management. Understanding how mortality varies by MRA dose, age at presentation, and comorbid conditions may help to tailor treatment and prevent complications in patients with PA effectively.

### 5.4.1 APPROPRIATE DOSE OF MINERALOCORTICOID RECEPTOR ANTAGONIST IS CRITICAL

Nationwide data opens awareness that patients treated with an MRA (2006–2019) may not have been treated to target. In Study III, we specifically looked at a subpopulation of patients with PA with available information on drug prescription since 2006 and found that the average dispensed dose of MRA

was low, which may be an important reason for limited treatment success. Patients receiving a high-dose MRA had a similar mortality risk to a matched population without PA. Although these results may not fully account for factors such as perception of care, renal function, and drug metabolism, the results do suggest that undertreatment is an important contributing factor to the excess mortality.

Hundemer et al. were among the first to draw an explicit connection between MRA dose, treatment effects, and mortality.[121] In a cohort study of 602 medically treated patients with PA, no significant increase in mortality risk was found for patients with unsuppressed renin who received higher MRA doses; however, mortality for those with low renin was higher compared to hypertensive controls (HR 1.34, 95% CI 1.06–1.71).[121] There is also evidence from two prospective studies that improvements in BP, albuminuria, and left ventricular systolic dysfunction are more pronounced in patients with unsuppressed renin.[183,184] Consequently, renin concentration may become a valuable tool for monitoring the efficacy of MRA treatment.[147]

These observations are important for informing clinical practice. Clinicians should be aware of the increased mortality in PA, especially in MRA-treated patients who are the largest patient group. Patients with bilateral disease can derive ancillary benefits if MRA doses are optimized. Patients with PA require higher doses of MRA than those used in primary hypertension. Independent practice will continue to be a challenge for unfamiliar clinicians. We argue that consistent long-term management is crucial to prevent complications and resource allocation is justified to secure continuity, coordination, and quality of care.

## 5.4.2 IMPORTANCE OF TIMELY MANAGEMENT

In Study III, the time of diagnosis is considered the starting point of disease onset. Consequently, the impact of delayed diagnosis of PA on mortality cannot be assessed. Nevertheless, excess mortality in Study III was limited to patients diagnosed with PA after 56 years of age. These results indicate that age at diagnosis is an important determinant of treatment outcome. This finding is likely because of the low prevalence of comorbidities in young patients with PA and the timely diagnosis and management. It has been stated that young individuals with normal renal and vascular systems can effectively manage increased plasma volume without a significant increase in BP.[27] In a retrospective cohort from Japan[185] and a multicenter study from Europe,[101] younger patients were more likely to benefit from surgical treatment. Two

recently published meta-analyses confirmed that younger patients have not only better clinical outcomes but also better renal outcomes after targeted treatment for PA.[145,186] Another meta-analysis suggests that older age is associated with less intensive lowering of BP after surgery.[180] Confounding factors can make the association between age and treatment outcomes appear stronger than it is. In a study of 450 patients with PA from Spain, similar benefits were observed in older patients as in young patients at 3-year follow-up.[187] The authors concluded that the duration of hypertension may affect more outcomes than age itself.

### 5.4.3 COMORBID CONDITIONS AND OUTCOMES IN PATIENTS WITH PRIMARY ALDOSTERONISM

Established CVD at the time of diagnosis is a major determinant of mortality outcomes in patients with primary aldosteronism. Prolonged aldosterone excess results in a wide array of CVD, metabolic, and renal comorbidities that might not be reversible with treatment.[180,185] Although no justification is possible when using registry data, Study III confirms that established CVD comorbidities are associated with a further increase in all-cause mortality (HR 1.53, 95% CI 1.26–1.85) following PA diagnosis compared to the general population. Multimorbid patients can be challenging to manage and more studies in the relevant population are needed to assess optimal management and whether CVD prevention strategies apply to them. In these patients, whether adrenalectomy confers a mortality advantage remains uncertain. In a meta-analysis, Chen et al.[145] found less favorable outcomes after adrenalectomy in older patients; however, a subsequent meta-analysis of 15 541 patients showed that the relative risk of major adverse cardiovascular events) was lower with increasing age in patients treated with adrenalectomy, as shown in the meta-regression analysis.[144] Future guidelines should consider the complexities of effectively treating patients with comorbidities.

## 5.5 IS ADRENALECTOMY MORE EFFECTIVE THAN A MINERALOCORTICOID RECEPTOR ANTAGONIST?

The choice of treatment should be based on individual assessments and the patient's values and preferences. Optimal management needs to consider predictors of response such as the patient age and health status at the time of diagnosis, and treatment side effects. A major theme of recent literature on PA

is whether adrenalectomy should be preserved for patients with a high probability of complete clinical cure.[21] Determining factors for biochemical cure are preoperative use of only two or fewer antihypertensive drugs,[188]short duration of hypertension,[101] higher post-SIT aldosterone levels,[189] young age,[101] female sex,[189] and no sign of left ventricular hypertrophy.[190] It has also been shown that patients with KCNJ5 mutations, the most common mutations found in aldosterone-producing adenomas, are more likely to be cured after adrenalectomy.[191] All these factors should be weighed when counseling patients, even though individual response to treatment cannot be predicted. Enabling patients to understand uncertainties about achieving a complete cure is crucial before considering different treatment options. The main problem is that patients with predictors of sustained hypertension after adrenalectomy are also at high risk for complications and mortality.

### 5.5.1 SHOULD ADRENALECTOMY BE PRESERVED FOR PATIENTS WITH PREDICTORS OF COMPLETE CURE?

So far, data comparing patients treated with MRA to patients treated with adrenalectomy has come primarily from observational studies. According to pooled data from four studies, adrenalectomy ($n$=178) and MRA use ($n$=177) showed similar reductions in left ventricular mass after up to 4 years of follow-up.[119] In a meta-analysis published in 2024 which included studies from 2008 to 2022 with a total of 15 541 patients (16 studies),[144] adrenalectomy was associated with lower mortality (HR 0.34, 95% CI 0.22–0.54) and lower risk for major adverse cardiovascular events (0.55, 0.36–0.84) compared to MRA treatment. Furthermore, patients treated with surgery were less likely to be admitted for heart failure (0.48, 0.34–0.70) or developing chronic kidney disease (0.62, 0.39–0.98).[144] Altogether, these results suggest that an MRA might not be as efficacious as unilateral adrenalectomy. A weakness in this evidence is that MRA dose-response effects and other confounders are not taken into account.[116] In line with previous studies, we observed that patients who have undergone adrenalectomy had a better prognosis.[144,145,192] The significance of our study lies in its contribution to understanding that clinical heterogeneity among patients may explain a wide variation in treatment outcomes. Study III indicates that patient age and comorbidities impact treatment strategies. Patients treated by adrenalectomy are younger than patients treated with an MRA, whereas patients with multiple chronic diseases are over-represented in the MRA group. All these factors may have influenced treatment outcomes. Most importantly, the study highlights that a prospective,

randomized study is needed to determine whether MRAs and adrenalectomy are equally efficacious in patients with unilateral disease.

## 5.6 RISK OF FRACTURE IN PRIMARY ALDOSTERONISM

In Study IV, we found that patients with PA >56 years of age had a higher risk of hip fractures compared to controls of the same age and sex regardless of previous fractures, diabetes, pre-existing heart disease, and social factors. Hip fracture risk was increased in patients treated with an MRA but not in patients who had undergone adrenalectomy compared to age- and sex-matched controls from the general population. The results are supported by a previous study that found a higher prevalence of osteoporotic fractures in patients with PA.[153]

The reasons for increased fracture risk in patients with PA are not fully understood. The risk may be attributable to a direct effect of aldosterone on bone metabolism. The MR is expressed in osteoblasts and osteocytes, but its functionality is unclear.[193] Another potential mechanism may involve disruption of parathyroid hormone secretion, which is common in patients with primary aldosteronism.[194] In line with these observations, patients in our cohort were often diagnosed with primary hyperparathyroidism. However, it is unlikely that aldosterone excess has long-lasting effects on bone because of continuous bone formation. Indeed, earlier studies have shown that parathyroid hormone levels and urinary calcium excretion return to normal after successful treatment.[138,153,195,196] Although it has been difficult to disentangle the reasons for the observed sex differences, our findings suggest that women with PA are more vulnerable to fracture. The prevalence of hip fractures was higher in women than men, a pattern that is also observed in individuals without PA.[197] For this reason, the sex differences observed in our estimates could be due to a lack of statistical power. Another reason could be that a substantial proportion of women with PA (65%) may be considered insufficiently treated due to their low prescribed MRA doses.

Compared to age- and sex-matched controls without PA, patients who have undergone adrenalectomy were not at increased fracture risk, while patients treated with an MRA had a higher risk of hip fracture. These results are not fully explained by suboptimal MRA treatment. HRs for patients treated with low doses of MRA were comparable to HRs of patients treated with high doses, even though statistical significance was only reached in the subgroup treated

with low doses. Treatment-specific differences may be associated with MRA mechanisms of action. MRAs works by inhibiting overactivated MRs and aldosterone levels remain elevated after treatment initiation. This is important to consider because aldosterone may act through other pathways that are not mediated through the MR.[198] Further research is needed to determine whether nongenomic aldosterone effects contribute to bone impairment.

# 6 CONCLUSION

1. The incidence of PA is increasing. Notable progress has been made in diagnostic strategies but PA is still under-recognized. Efforts should be made to raise awareness of PA while simultaneously increasing resources to optimize treatment management.
2. CT/MRI scans are unable to accurately differentiate unilateral from bilateral forms of PA. Consequently, conventional imaging is insufficient to guide optimal treatment. The most reliable means to assess PA laterality is AVS regardless of age at presentation and imaging findings.
3. One of the key findings of this thesis is that patients with PA have increased mortality risk compared to controls from the general population, which is mainly due to CVD. Age >56 years, established comorbidities at the time of diagnosis, and MRA undertreatment are significant determinants of mortality, emphasizing the need for continued monitoring of this population.
4. Hip fracture risk was elevated in patients with PA but further research is needed on the impact of aldosterone excess on bone health.

Optimized screening strategies, timely diagnosis, accurate subtype distinction, and consistent long-term management of patients with PA are the keys to improving healthcare delivery for people with PA.

# 7 FUTURE PERSPECTIVES

Further research is needed in clinical research areas within PA along with new medications, advancements in functional imaging, and translation of genetic research into clinical practice.

PA is a progressive disease that starts much earlier than current diagnostic criteria can capture. New diagnostic tools are needed to detect individuals with PA as early as possible and provide adequate treatment to improve long-term outcomes.

The Swedish healthcare system is facing a growing population with PA, which immediately raises the issue of individualized management for PA.[199] Since access to lateralizing procedures is limited and costly, a "trade-off" perspective is worth exploring.[63] Besides efforts to develop scalable noninvasive lateralizing methods, there is an increased focus on predictors that may help clinically to recognize patients with bilateral disease, which in turn could avoid unnecessary invasive investigations.[77,177,200] Prognostic models based on patient characteristics and disease severity that predict likely treatment responses would be a clinically important advance.

Input from patients who are directly affected is also important. A randomized clinical trial (adrenalectomy *vs* eplerenone) is currently underway addressing patient-related outcomes such as quality of life and cost-effectiveness.

It is of great importance to study complications in PA and how to prevent them. Merging data from the NPR with other official registries provided advanced opportunities to study long-term outcomes in PA but some clinically important variables could not be assessed. An initiative has recently been undertaken by our research group to create a disease-specific register where important clinical data may be entered. As a first step, it can be used to study factors that have not been sufficiently studied such as BP levels, hyperlipidemia, and metabolic profile. A further goal is to study the diagnostic process and optimal treatment choices for patients with advanced age and comorbidity. Lastly, there is a major need for objective markers to evaluate treatment efficacy in patients treated with an MRA and determining optimal MRA dose for each patient.

Genetic profiles open perspectives for earlier identification, noninvasive subtype distinction, and personalized medicine in the future.[17,18,20,21,191] Whether mutation carriers with certain characteristics require different

diagnostic procedures is unclear.[20,191] Further studies are needed to clarify how steroid metabolomic profiles in conjunction with radiological and clinical information could be used to guide clinical decisions in PA.[199,201]

New therapeutic choices may become available. Clinical trials of aldosterone synthase inhibitors have shown promising results.[202,203] Other novel approaches such as ablation of adrenal tumors are under investigation.[204] Testing their efficacy in preventing PA complications would be an interesting research area.

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