Cardiac organ damage in systemic hypertension: Impact of gender, etiology, and comorbidities

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Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2024

UNIVERSITY OF BERGEN

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Date of defense: 15.03.2024

Year: 2024

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Print: Skipnes Kommunikasjon / University of Bergen

1. Scientific environment

This research project was a collaborative effort between several institutions, including the Bergen Hypertension and Cardiac Dynamics group and the Centre for Research on Cardiac Disease in Women, Faculty of Medicine, University of Bergen, the Department of Heart Disease, Haukeland University Hospital, the Department of Medicine, Section of Endocrinology, Haukeland University Hospital and Section for Cardiovascular and Renal Research, Oslo University Hospital, Ullevål.

The Bergen Hypertension and Cardiac Dynamics group is led by Professor Eva Gerdts and includes 1 senior researcher, Helga Midtbø, 1 associate professor, Dana Cramaruic, 1 post-doctoral fellow, 6 PhD candidates, 1 research-medical student, 1 researcher, 1 research nurse, and 1 engineer. The group specializes in hypertensive heart disease, cardiometabolic risk factors, and sex/gender differences in cardiac structure and function, utilizing echocardiography as the primary clinical method. They also run the Echocardiography Research Laboratory which has served as core laboratory for large international trials. The Center for Research on Cardiac Disease in Women was established during this PhD-project. In addition to facilitating research on cardiac disease in women, the Center serves as a hub for researchers from various fields who are interested in this topic, providing a platform for collaboration and inspiration.

The Department of Heart Disease at the Haukeland University Hospital is the leading facility for cardiovascular care in Western Norway. The Department provides a wide range of specialized services and treatments including cardiac surgery, catheter-based interventions, and advanced non-invasive cardiac imaging including echocardiography.

Study 1 was based on data from the national IDA study, and the Section for Cardiovascular and Renal Research, Oslo University Hospital, Ullevål coordinated the data collection. The thesis was conducted during a 3-year Doctoral research fellowship funded by the Research Council of Norway. The data collection in Bergen was performed at the Research Unit for Health Surveys, a core facility at the

University of Bergen, and funded by a grant from the Western Norway Regional Health Authorities.

Studies 2 and 3 utilized data collected at the Department of Medicine, Haukeland University Hospital by Marianne Grytaas. The echocardiograms on these study participants were performed at the Department of Heart Disease.

2. Acknowledgments

First, I would like to express my gratitude to all the study participants in the IDA and PA study for their valuable contributions to this research. You are bringing science forward.

I extend my deepest appreciation to my main mentor, Professor Eva Gerdts. You have been an exceptional mentor, and working under your guidance has been a privilege and an absolute pleasure. Despite facing various challenges during my research, your unwavering support and encouragement helped me stay confident and focused. Thank you for generously sharing your vast knowledge and expertise, and for inspiring me with your passion and curiosity for science. Above all, I consistently felt well-supported, despite your busy schedule.

I am equally grateful to my co-mentor Marianne Grytaas for helping me navigate the complex intricacies of endocrine hypertension. Your patience and accessible responses to all my questions, as well as your provision of clear and thorough feedback, have been immensely valuable.

I thank the other senior researchers in the group, Knut Matre, Helga Midtbø, Dana Cramariuc, and Hilde Halland for their inspirational work, discussions, and feedback. Marina Kokorina, I am deeply grateful for your invaluable contribution to my work and for being an inspiring echocardiography teacher in the clinic. Special thanks to Liv Himle for her exceptional organizational skills that helped me stay on top of my work, and to Hilde Jacobsen for providing invaluable assistance with my datasets. I also appreciate your kind and supportive nature.

I will miss the time spent with my wonderful PhD colleagues and good friends. Anja's dedication to organizing cozy coffee breaks was highly appreciated. I am deeply thankful to Rune for introducing the concept of Napoleonskake-Friday, to Lisa for providing honest and valuable feedback, to Ester and Eigir for guiding me when I was new, and to Annabel and Rasmus for the countless hours spent analyzing echocardiography in the dark. I am very happy that Aisteja and Christian joined the

research group, adding an even more wonderful dynamic to the group atmosphere. Marit, working back-to-back with you in our office was great; we managed the perfect balance between work and talk. Lastly, a special thanks to the skilled and bright Johannes for his invaluable technical support.

To my IDA colleagues Lene, Stine, Ola, Eirik, Karl Marius, Camilla, Anne-Cecilie, Morten, Sverre, Aud, Marit, Mimmi, Vibeke, and Ulla – I am deeply grateful for your tireless efforts in making this project a success. A special thanks to Camilla and Stine for keeping me motivated with daily morning conversations during the pandemic.

I am grateful to the dedicated study personnel at the University of Bergen Research Unit for Health Surveys for their exceptional professionalism and quality work, along with being such welcoming and friendly colleagues.

I would also like to thank the Research Council of Norway and the Western Norway Regional Health Authorities for financial support.

Finally, a big thanks to my family. Dear Robert, I am eternally grateful for your consistent dedication in keeping our home organized and tidy. Additionally, your invaluable graphical support and visual input on my work have been greatly appreciated. I also thank my daughters, Live and Vera, for constantly pulling me out of the research bubble. Lastly, I thank my mother Amy, and my father Harald Terje, for their unwavering pride, love, and support.

3. Abstract

Background: Uncontrolled systemic hypertension is a major risk factor for cardiovascular (CV) morbidity and mortality worldwide and may be present in patients both with essential and secondary hypertension. This increased CV risk is largely attributed to the development of cardiac organ damage, which encompasses structural and functional alterations in the heart, such as left ventricular (LV) hypertrophy and left atrial (LA) enlargement. When cardiac organ damage is established, the risk for subsequent clinical CV disease like myocardial infarction, stroke, heart failure, and atrial fibrillation is high. Studies in essential hypertension have demonstrated a higher prevalence of cardiac organ damage in women than in men, and less blood pressure (BP) control and regression of LV hypertrophy by antihypertensive treatment in women. Lower adherence to treatment has been suggested as a potential underlying cause for these gender differences. In primary aldosteronism (PA), which is the most common cause of secondary hypertension, LV hypertrophy is more common than in essential hypertension. However, gender-specific reports on cardiac organ damage in PA are limited.

Objective: This thesis aimed to explore factors influencing the presence and regression of cardiac organ damage in uncontrolled treated hypertension and in PA, with a specific focus on gender differences and comorbidities.

Methods: Study 1 included 523 patients with uncontrolled treated hypertension, confirmed by 24-h BP monitoring, who were prescribed ≥ 2 antihypertensive drugs. The patients were recruited in a national multicenter study. We assessed the association of antihypertensive drug adherence based on serum drug concentrations, with the presence of LV hypertrophy and LA enlargement by echocardiography in women and men. Aldosterone-to-renin ratio (ARR) was measured as a screening for PA. Studies 2 and 3 utilized data from 113 patients with PA, consecutively recruited at the Department of Medicine, Haukeland University Hospital at the time of diagnosis. In Study 2, cardiac organ damage in women and men with PA was compared to matched controls with essential hypertension. Study 3 explored factors

associated with persistent cardiac organ damage in PA after one year of specific treatment, either adrenalectomy or mineralocorticoid receptor antagonist.

Results: Study 1 demonstrated a higher prevalence of LV hypertrophy and LA enlargement in women compared to men with uncontrolled treated essential hypertension. Differences in drug nonadherence did not explain this gender difference. Furthermore, the prevalence of a positive PA screening test was high in both genders. Study 2 showed that PA is associated with a higher prevalence of LV hypertrophy compared to essential hypertension in both women and men. Study 3 demonstrated a higher prevalence of persistent cardiac organ damage in PA patients receiving medical therapy compared to surgical therapy. All three studies highlighted the pivotal role of metabolic comorbidities, such as obesity, impaired glucose metabolism, and renal impairment as important contributors to cardiac organ damage in both genders.

Conclusion: This project demonstrates the substantial impact of gender on cardiac adaptation to chronic hypertension. It further demonstrates that the presence of underlying PA, metabolic comorbidities, and renal impairment contribute to cardiac organ damage in both genders. For the first time, this study demonstrates that nonadherence to antihypertensive drugs does not explain the higher prevalence of cardiac organ damage in women. Thus, the cause of this gender gap remains unresolved.

4. Sammendrag

Bakgrunn: Ukontrollert systemisk hypertensjon fører til økt risiko for kardiovaskulær sykdom og død både ved essensiell og sekundær hypertensjon. Den økte risikoen skyldes i stor grad utvikling av strukturelle og funksjonelle forandringer i hjertet som for eksempel venstre ventrikkel hypertrofi (VVH) og forstørret venstre atrium. Slik organskade på hjertet fører til økt risiko for hjerte-karsykdom som hjerteinfarkt, hjerneslag, hjertesvikt og atrieflimmer. Studier på pasienter med essensiell hypertensjon, har vist at kvinner har høyere forekomst av organskade i hjertet sammenlignet med menn. I tillegg går organskaden i mindre grad tilbake ved god medikamentell blodtrykksbehandling hos kvinner enn hos menn. Studier har pekt på at lavere medikamentetterlevelse hos kvinner kan bidrag til denne kjønnsforskjellen. Primær hyperaldosteronisme (PA) er den vanligste årsaken til sekundær hypertensjon, og ukontrollert hypertensjon sees ofte ved denne tilstanden. PA er assosiert med høyere forekomst av VVH sammenlignet med pasienter med essensiell hypertensjon, på tross av tilsvarende blodtrykksverdier og alder. Imidlertid, er kjønnsspesifikk forskning på pasienter med PA mangelfull.

Mål: Denne avhandlingen hadde som mål å undersøke faktorer som påvirker endeorganskade på hjertet hos pasienter med PA og essensiell hypertensjon, med et spesielt fokus på kjønnsforskjeller og komorbiditet.

Metoder: Studie 1 inkluderte 523 pasienter med ukontrollert hypertensjon, bekreftet med forhøyet 24-timers dagtidsblodtrykk, som brukte minst 2 blodtrykksmedisiner. Vi undersøkte sammenhengen mellom medikamentetterlevelse og forekomst av VVH og forstørret venstra atrium. Etterlevelse av blodtrykksmedisiner ble vurdert ved måling av serum konsentrasjonen av blodtrykksmedisinene, og organskade i hjertet ble vurdert med ekkokardiografi. Som en screeningtest på PA målte vi aldosteron-renin ratio (ARR). Studie 2 og 3 inkluderte 113 pasienter med nydiagnostisert PA. I studie 2 sammenlignet vi forekomst av organskade i hjertet ved PA med matchete pasienter med essensiell hypertensjon. I studie 3 undersøkte vi faktorer assosiert med persisterende organskade i hjertet hos pasienter med PA etter 1 år med spesifikk behandling, enten kirurgi eller medikamentell behandling.

Resultater: Studie 1 viste en høyere forekomst av VVH og forstørret venstre atrium hos kvinner sammenlignet med menn med ukontrollert behandlet hypertensjon. Forskjeller i medikamentetterlevelse kunne ikke forklare denne kjønnsforskjellen. Videre, viste studien at en stor andel av pasientene hadde positiv screening test for PA. Studie 2 viste at PA var assosiert med en høyere forekomst av VVH hos både kvinner og menn sammenlignet med essensiell hypertensjon. Studie 3 viste at pasienter med PA som var medikamentelt behandlet, hadde høyere forekomst av persisterende organskade i hjertet etter 1 år med behandling, sammenlignet med pasientene som ble behandlet med kirurgi. Alle studiene viste at samtidig fedme, forstyrrelser i glukosemetabolismen og nedsatt nyrefunksjon påvirket forekomst av organskade i hjertet hos både kvinner og menn.

Konklusjon: Dette prosjektet viser betydningen av kjønn for organskade i hjertet hos pasienter med kronisk hypertensjon. PA som underliggende årsak, metabolske sykdommer og nedsatt nyrefunksjon bidrar til organskade hos begge kjønn. Studien er den første som viser at dårlig medikamentetterlevelse ikke forklarer hvorfor kvinner har høyere forekomst av organskade på hjertet enn menn. Årsaken til denne kjønnsforskjellen er derfor fortsatt uforklart.

5. List of Publications

1. **Aune A**, Ohldieck A, Halvorsen LV, Brobak KM, Olsen E, Rognstad S, Larstorp ACK, Søraas CL, Rossebø AB, Rösner A, Grytaas MA, Gerdts E. Gender differences in cardiac organ damage in hypertension: Assessing the impact of drug adherence – submitted Journal of Hypertension 2023

2. **Aune A,** Kokorina M, Grytaas MA, Midtbø H, Løvås K, Gerdts E. Preclinical cardiac disease in women and men with primary aldosteronism. Blood Pressure. 2021 Jul 4;30(4):230-6.

3. **Aune A**, Gerdts E, Kokorina M, Kringeland E, Midtbø H, Løvås K, Grytaas MA. Persistent cardiac organ damage in surgically and medically treated primary aldosteronism. Journal of Hypertension. 2022 Jun 1;40(6):1204-11.

6. Contents

7. Abbreviations

ACE	Angiotensin-converting enzyme
ACR	Albumin-creatinine ratio
ARR	Aldosterone-to-renin ratio
BMI	Body mass index
BP	Blood pressure
CI	Confidence Interval
CKD	Chronic kidney disease
CV	Cardiovascular
DM	Diabetes mellitus
E/e’	Filling pressure (Peak early trans mitral blood flow to average mitral annular velocity ratio)
EF	Ejection fraction
eGFR	estimated glomerular filtration rate
GLP1	Glucagon-like peptide 1
GLS	Global longitudinal strain
$HbA1_c$	Hemoglobin $A1_c$
LA	Left atrium
LV	Left ventricle
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
OR	Odds ratio
RCT	Randomized controlled trial
RWT	Relative wall thickness
24-h	24-hour

8. Introduction

8.1 Hypertension

Hypertension, defined as persistently elevated office blood pressure (BP) (≥ 140/90 mmHg), is the leading modifiable risk factor for cardiovascular (CV) disease, morbidity, and mortality worldwide [1]. Hypertension is highly prevalent. In 2019 the age-adjusted prevalence worldwide was 32% among women and 34% among men aged 30-79 years [2]. The prevalence of hypertension has remained constant for the last two decades, but the actual number of persons with hypertension has doubled during this period, as a consequence of longevity and aging. Low-income countries have a higher prevalence of hypertension compared to high-income countries, which also extends to Europe [1].

The life course development of BP differs by gender. Although young women have a lower BP than men, systolic and diastolic BP increases steeper in women from the third decade and onwards [3]. Among individuals under 50 years old, the hypertension prevalence is higher in men, whereas among those over 65 years of age, the prevalence is higher in women [3], reflecting the gender difference in BP development with aging.

8.2 BP measurement

Office BP measurement is the most extensively utilized method in clinical practice and clinical research [1]. It provides substantial evidence of the association between BP and CV risk, as well as the protective effect of antihypertensive treatment [1]. Consequently, the diagnosis of hypertension and the established thresholds for initiating treatment, and treatment goals are based on office BP measurements. According to the European Society of Hypertension Guidelines for the management of arterial hypertension, elevated BP is defined as standardized repeated office BP values ≥ 140/90 mmHg in both genders [1]. The main limitations of office BP

measurement are the inability to provide nighttime measurements, detect “white coat hypertension” and “masked hypertension”, and capture diurnal BP variability [1]. These limitations can be addressed with out-of-office BP measurements, which are increasingly used. Home BP monitoring offers multiple BP readings in the patient’s everyday environment, providing high reproducibility at a low cost, but does not provide nighttime readings [1]. For accurate assessment of BP control, including nighttime measurements, 24-h ambulatory BP monitoring is recommended [1]. Ambulatory hypertension is defined as an average 24-h BP ≥ 130/80 mmHg, corresponding to the threshold of ≥ 140/90 mmHg for office BP measurement [1] (Table 1).

Table 1. The current European definitions of hypertension

Method	Systolic BP (mmHg)		Diastolic BP (mmHg)
Office BP*	≥ 140	or	≥ 90
Ambulatory BP			
Awake mean	≥ 135	or	≥ 85
Asleep mean	≥ 120	or	≥ 70
24-h mean	≥ 130	or	≥ 80
Home BP mean	≥ 135	or	≥ 85

**Standard office BP measurements (attended)*

8.3 Essential and secondary hypertension

Hypertension is categorized as either essential or secondary. Essential hypertension has no underlying cause and is assumed to be present in 80-90% of the hypertension population. Secondary hypertension is caused by a specific underlying condition, with primary aldosteronism (PA) being the most frequent [1,4] (Table 2). Despite its

significance, PA is often overlooked. Both detected and undetected PA contribute significantly to uncontrolled hypertension in both genders [1].

Table 2. Common causes of secondary hypertension [5]

Cause	Prevalence in hypertension
Primary aldosteronism	5-15%
Obstructive sleep apnea	5-10%
Renal parenchymal disease	2-10%
Renovascular disease (Atherosclerotic renovascular disease or fibromuscular dysplasia)	1-10%
Rare endocrine causes	1-3%
Coarctation of the aorta	<1%

8.4 Uncontrolled treated hypertension

Effective hypertension treatment reduces the risk of clinical CV disease and mortality [1]. However, despite the widespread availability, proven efficacy, and good tolerability of antihypertensive drugs, uncontrolled treated hypertension remains a challenge [2,6]. Uncontrolled treated hypertension is defined as elevated BP despite treatment with antihypertensive drugs. A comprehensive pooled analysis of hypertension prevalence revealed that globally, less than half of the treated patients achieved optimal BP control [2].

Inadequate control rates are prevalent in both genders, with studies presenting inconsistent gender-specific prevalence rates – some studies indicate poorer control among women, and others indicate the same as among men [6]. Notably, a Canadian national health survey reported a concerning rise in uncontrolled treated hypertension among older women from 2007 onwards [7]. Similarly, a recent real-world analysis

from Sweden reported worse BP control in women than men among those older than 60 years [8]. The reasons for this gender difference in BP control remain unclear.

In addition to undetected secondary hypertension, the most common causes of uncontrolled treated hypertension in both genders include physician failure to adequately up-titrate treatment (commonly referred to as physician inertia), insufficient use of combination pills, and poor patient adherence to prescribed antihypertensive drugs [1]. Studies have also demonstrated that achieving BP control in patients using nonsteroidal inflammatory drugs and contraceptives containing estrogen presents a greater challenge [1]. Additionally, the achievement of BP control is complicated by the presence of obesity or systemic inflammation, both conditions being more prevalent in women [9,10].

Apparent treatment-resistant hypertension is present in up to 10-20% of patients with hypertension and is defined as elevated office BP despite appropriate lifestyle modifications and treatment with optimal doses of three or more antihypertensive drugs, including a thiazide/thiazide-like diuretic, a renin-angiotensin-aldosterone system blocker, and a calcium channel blocker [1]. True resistant hypertension is rare, affecting approximately 5% of patients with hypertension [1]. The diagnosis must be confirmed by elevated ambulatory 24-h BP and causes of pseudo-resistant hypertension like nonadherence to therapy and secondary hypertension must be excluded [1].

8.5 Drug nonadherence

Nonadherence to antihypertensive drugs is an important contributor to uncontrolled hypertension [1]. However, assessing drug adherence is challenging, and the reported prevalence in studies also tends to vary with geographic region, patient selection, and the applied assessment method [11]. A recent meta-analysis including 27 million patients with hypertension, reported a global prevalence of nonadherence varying between 27-40% [11]. In this meta-analysis, most studies measured drug adherence indirectly, i.e., using methods like physician's interview and pill counts. Yet, a few

studies used direct measurements of drug concentrations in urine or blood [11]. Studies assessing adherence by direct methods reported a lower prevalence of nonadherence than those assessing adherence by indirect methods [11].

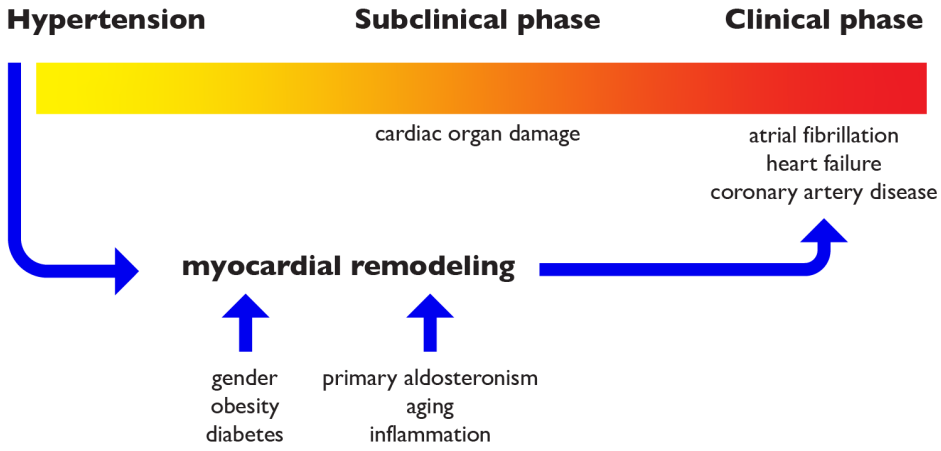
Whether drug nonadherence is more common in women compared to men remains controversial. No difference in adherence was found between genders in a meta-analysis of 82 studies [12]. However, a study of 1348 patients with uncontrolled hypertension that assessed adherence directly by measuring drug concentrations in urine or serum, found a higher prevalence of drug nonadherence in women compared to men [13]. A higher prevalence of nonadherence among women could possibly be related to a higher prevalence of adverse effects from commonly used antihypertensive drugs, including diuretics, beta-blockers, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors in older women compared to men [14]. However, additional data is required to ascertain whether adherence rates vary by gender.

8.6 Cardiac organ damage and risk of clinical CV disease

Uncontrolled hypertension leads to CV organ damage, defined as structural and functional changes in the large and small arteries as well as in the heart, kidney, brain, and eyes [1]. This process is accelerated by the presence of additional CV risk factors or comorbidities [1]. This thesis focused on cardiac organ damage, which serves as a transitional stage between a healthy heart and clinical cardiac disease, like myocardial infarction, heart failure, and atrial fibrillation [1] (Figure 1). The primary motivation for antihypertensive treatment is to prohibit the development of organ damage and thereby reduce the risk of clinical CV disease [1]. Established cardiac organ damage can be reversed by optimal antihypertensive treatment, lowering the CV risk. Common forms of cardiac organ damage include left ventricular (LV) hypertrophy, and left atrial (LA) enlargement, which is independently associated with

an impaired LV myocardial function, all being independent risk factors for clinical CV disease.

Figure 1. Development of cardiac organ damage in hypertension



If LV hypertrophy is detected in a patient with hypertension, current guidelines reclassify the CV risk to high, independent of the BP level [1]. Likewise, LA enlargement is independently associated with clinical CV disease including atrial fibrillation, stroke, and heart failure, independent of co-presence of LV hypertrophy [15–17]. In essential hypertension, both LV hypertrophy and LA enlargement are more prevalent in women than in men [18–21]. Although women generally have a lower absolute CV risk than men, this advantage is offset when LV hypertrophy is present [19,22]. Furthermore, studies have shown that LV hypertrophy is less modifiable in women than in men and that women are more prone to develop LV hypertrophy despite antihypertensive drug treatment [23,24].

Reduced systolic function assessed by LV ejection fraction (EF) is established as a major predictor of clinical CV disease in a variety of populations [25]. However,

LV EF may remain normal despite a considerable reduction in myocardial contractility [26,27]. More advanced echocardiographic measures, like LV midwall shortening and LV global longitudinal strain (GLS), offer earlier detection of LV myocardial dysfunction [27,28]. Although LV midwall shortening, like LV EF is influenced by LV geometry, women with hypertension have higher values for midwall shortening independent of LV geometric pattern [29]. Both reduced LV midwall shortening and LV GLS provide supplementary prognostic value beyond that of the traditional CV risk factors in hypertension [28,30].

8.7 Factors associated with cardiac organ damage

Recognizing risk factors of cardiac organ damage in hypertension is essential for both primary and secondary prevention of clinical CV disease. While existing research has identified several risk factors in women and men, these studies are predominantly conducted in populations of essential hypertension.

As outlined above, female gender has been independently associated with a higher prevalence of LV hypertrophy and LA enlargement in essential hypertension [18,19,31]. Although diverse risk factors for cardiac organ damage have been identified in women and men, only a minority of studies have reported results stratified by gender. Importantly, established gender differences in traditional CV risk factors do not explain the overrepresentation of cardiac organ damage in women. Thus, the cause of this gender gap remains unresolved.

Patients with persistently uncontrolled hypertension will eventually develop cardiac organ damage [1]. In particular, the robust association between systolic BP and LV mass index is well-established [32]. Yet, the development of cardiac organ damage is influenced by multiple factors. In patients with hypertension, the presence of additional risk factors often carries the same significance as the BP value itself [24,33]. However, many of these factors are directly or indirectly linked to BP. Hypertension is a major risk factor for chronic kidney disease (CKD) and is the second most common cause of end-stage CKD [1]. The diagnosis of CKD relies on insensitive renal

markers, including estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (ACR), and CKD is often advanced at the time of detection [1]. Consequently, co-presence of cardiac organ damage is frequent in patients with renal organ damage [34]. Obesity and type 2 diabetes mellitus (DM) are overrepresented in hypertension and have a solid impact on LV remodeling [19,31,35]. Several studies have demonstrated that this association is more pronounced in women than in men [19,35,36]. Obesity is also an independent predictor of both LA enlargement and impaired systolic myocardial function [18,37].

In recent years, chronic systemic inflammation has been recognized as an additional significant contributor to LV remodeling [38,39]. In psoriasis patients, a recent study found that circulating biomarkers of T cell-mediated inflammation were associated with higher LV mass index [40]. Systemic inflammation is present in autoimmune diseases, but also in type 2 DM, obesity, and hypertension [41,42]. In experimental studies, high salt intake and angiotensin II both stimulate the immune system and promote organ damage, as well as hypertension [43]. While limited, some studies have explored gender-specific associations between inflammation and cardiac organ damage. Notably, one study demonstrated that higher C-reactive protein was associated with higher LV mass in females only [44]. Women often display a stronger immune response than men, as demonstrated by higher vaccine-specific antibody levels post-vaccination [45]. Additionally, most autoimmune diseases are more prevalent in women compared to men.

Lastly, numerous studies have documented that PA is associated with a higher prevalence of LV hypertrophy than matched patients with essential hypertension [46,47]. Nevertheless, the applicability of this association to both genders has not been explored. Furthermore, studies on PA have predominantly focused on LV hypertrophy, while other forms of cardiac organ damage have been less explored in PA.

8.8 Primary aldosteronism

PA is a disorder characterized by excessive secretion of aldosterone from the adrenal glands and is the most common secondary and potentially curable form of systemic hypertension [48]. The excess aldosterone secretion is independent of stimulation by the renin-angiotensin-aldosterone system and potassium levels, often described as autonomous aldosterone secretion. Excess aldosterone causes hypertension, suppression of renin levels, increased sodium reabsorption, increased potassium secretion, and cardiovascular, metabolic, and renal damage.

Patients with PA have elevated CV risk compared to those with essential hypertension, partly due to a higher prevalence of LV hypertrophy, which is independent of BP values [46]. PA affects the adrenal gland either unilaterally, most often caused by an aldosterone-producing adenoma, or bilaterally, most often caused by bilateral micro- and macronodular hyperplasia. Rare subtypes are familial forms and aldosterone-producing carcinoma [46]. Due to increased potassium secretion caused by aldosterone, hypokalemia may be present, although normokalemia is more common.

PA was initially considered a rare disease. However, with the introduction of aldosterone-to-renin-ratio (ARR) screening and broader screening criteria, the detection rate of PA increased by 5-15 folds [48]. It is now widely accepted that PA is the most common form of secondary hypertension in both genders. Studies have reported a wide variation in PA prevalence, depending on the characteristics of the selected population and the diagnostic methods used [49]. The estimated prevalence of PA is 5-15% in the general hypertension population and around 20% in populations with resistant hypertension [4,5,49–51]. Few studies have reported results stratified by gender. Traditionally, PA is considered to affect the genders equally, however, gender-specific reports are scarce. Recent research has revealed a complex gender pattern of women with unilateral PA tending to be younger than men, whereas women with bilateral PA tend to be older than men [52]. A recent Australian study investigating the prevalence of PA in 247 patients with newly diagnosed hypertension

in the primary care setting, found a similar prevalence in women and men (14 vs. 15%) [53], whereas the results from a similar Chinese study that included 1,020 patients, indicated a higher prevalence in women (6 vs. 3%) [54]. Of note, in both studies, a substantial proportion of women with elevated ARR declined to undergo confirmatory testing. Furthermore, women are often underrepresented in clinical studies in PA [54,55].

In the real-life setting, PA is largely underrecognized, consequently exposing these patients to an increased risk of CV, metabolic, and renal complications [51]. Screening for PA in hypertension is recommended in various cases, including hypertension with hypokalemia, sleep apnea, adrenal mass, and resistant hypertension [4,50]. However, in a recent review including > 200,000 patients, it was revealed that only 3.4% of patients with hypertension with one or more of these risk factors were actually screened for PA [56]. While some experts suggest PA screening for all hypertensive patients, this approach will burden the healthcare system, and further research is needed to conduct a cost-benefit analysis of such an approach [48].

The diagnosis of PA is a 3-step process including screening, confirmatory testing, and subtype differentiation [50]. The recommended screening test is the calculation of ARR, however, the ARR is influenced by many factors. To assure reliability, the current guidelines advise the withdrawal of drugs influencing the ARR two to four weeks prior to blood collection. This primarily applies to antihypertensive drugs that interfere with the renin-angiotensin-aldosterone system and non-steroidal anti-inflammatory drugs [57]. A confirmatory test is then performed to ascertain or dismiss the diagnosis, with the saline infusion test being the most widely used method in Europe. Subtype differentiation is performed by adrenal vein sampling and is the recommended gold standard to distinguish unilateral PA from bilateral PA [50]. Adrenal CT is additionally recommended in all patients, primarily to exclude the presence of an aldosterone-producing carcinoma [50].

Unilateral PA can be cured by adrenalectomy and bilateral PA should be managed by life-long administration of mineralocorticoid receptor antagonist (MRA) [50]. A recent meta-analysis demonstrated a lower long-term mortality rate in unilateral

PA following adrenalectomy than in those medically treated [58]. Hundemer et al. reported similar findings [59]. However, they suggested that this risk difference was driven by medically treated patients with persistent suppressed renin, which is a marker of inadequate mineralocorticoid receptor (MR) blockade. On the other hand, medically treated patients with renin stimulation as a result of adequate MR blockade had a similar CV risk to those with essential hypertension [59]. However, the CV risk is still 2-3-fold increased compared to the normotensive population. Thus, previous studies indicate that medical therapy might be similarly effective as surgery in reducing CV risk when administered adequately to successfully block the MR.

8.9 Regression of cardiac organ damage in primary aldosteronism during specific treatment

Numerous studies have reported regression of LV mass index in response to specific PA treatment [60]. Of note, a larger reduction in LV mass index has been observed in patients with unilateral disease following adrenalectomy, compared to medically treated patients [61]. In these studies, however, inadequate MRA treatment was not considered, and gender-specific results were not reported. Hence, research addressing the extent to which inadequate MR blockade influences the persistence of cardiac organ damage is warranted. Furthermore, identifying additional risk factors that contribute to the persistence of cardiac organ damage and subsequently elevated CV risk in PA is spoken for.

9. Hypothesis and study aims

Hypothesis

We hypothesized that gender influences the development of cardiac organ damage in uncontrolled treated hypertension and in PA independent of other CV risk factors. Furthermore, we hypothesized that persistent cardiac organ damage is common in PA despite treatment.

Specific Aims:

Study 1: To assess whether a higher prevalence of LV hypertrophy and LA enlargement in women is explained by gender differences in drug adherence.

Study 2: To explore the gender-specific associations of PA with LV hypertrophy and LV myocardial function.

Study 3: To explore factors associated with persistent cardiac organ damage in relation to surgical and medical treatment of PA.

10. Materials and methods

10.1 Study design and patient population

10.1.1 Study 1. The IDA cohort

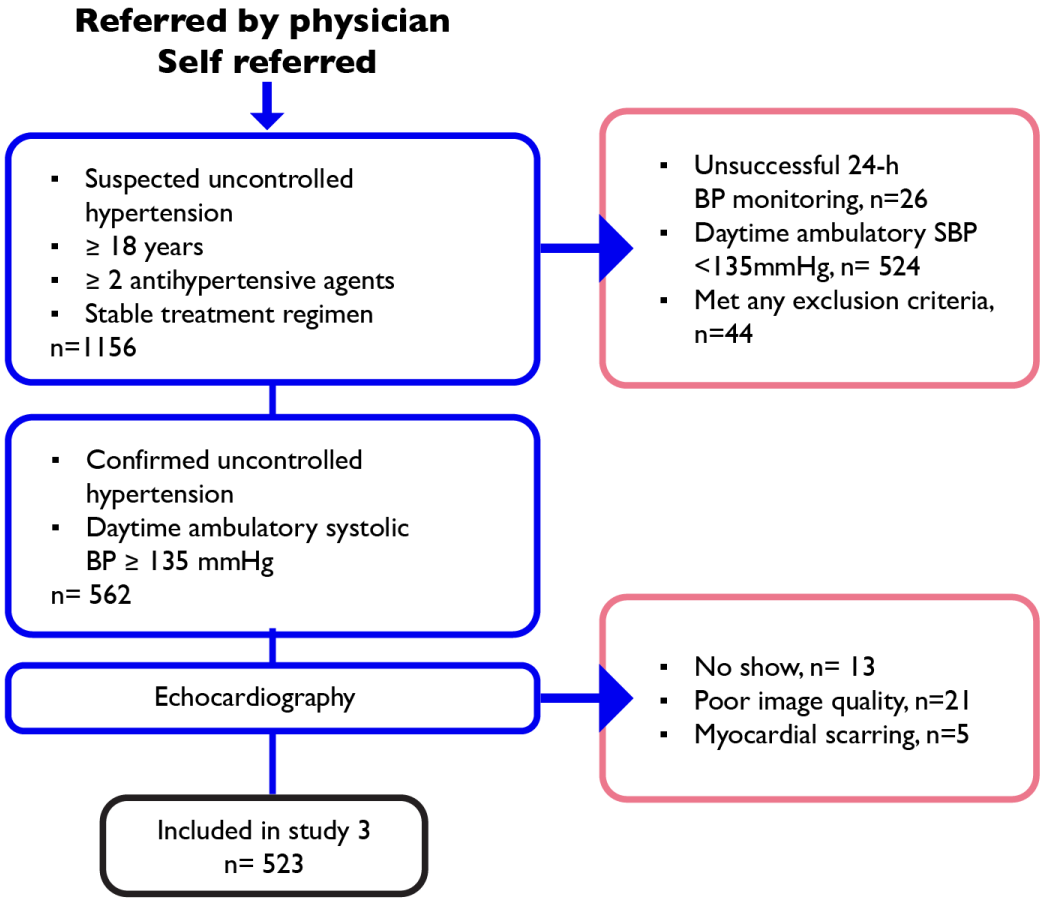
***"I**ndividualize**D** blood pressure treatment: a multidisciplinary **A**pproach to uncontrolled hypertension in order to reduce morbidity and mortality* (the IDA study)", was a prospective, open, multi-center study conducted at the four major university hospitals in Norway. The primary objective of the study was to conduct a randomized controlled trial (RCT) with an intervention to improve drug adherence. To identify patients suited for the RCT, 1156 patients with suspected uncontrolled systemic hypertension were included. The patients were primarily referred from primary physicians (57%) or secondary centers (15%). Patients could also contact the research units directly in response to newspaper advertisements and information on social media platforms (27%). These patients underwent prescreening to ensure eligibility based on the inclusion criteria. The inclusion criteria were age ≥ 18 years, being prescribed ≥2 antihypertensive drugs, and having a stable treatment regimen for four weeks. Patients who met any of the following exclusion criteria at the primary visit were subsequently excluded from participating in further visits: eGFR<30 mL/min/1.73m^2, ACR >300 mg/mmol, poor Norwegian language skills, pregnancy, illegal drug abuse, or psychiatric disorders and impaired cognitive function that could limit the ability to evaluate the efficacy or safety of the protocol. 629 patients (54%) were included at Oslo University Hospital, 218 (19%) at Bergen University Hospital, 149 (13%) at Tromsø University Hospital, ≥and 160 (14%) at Trondheim University Hospital. (Clinical Trials number: NCT03209154).

Study 1

Among the initial 1156 patients recruited in the IDA study, 562 patients had confirmed uncontrolled hypertension (defined as an ambulatory daytime systolic BP ≥ 135 mmHg in this study) despite using at least 2 antihypertensive agents and were eligible for the second visit which included echocardiography. Among these, 548

showed up for the second visit. 21 of these were excluded due to poor image quality and 5 due to regional myocardial infarct scarring in the LV since these were not eligible for the sub-study on cardiac organ damage (Figure 2). Thus, the Study 1 cohort included 523 patients participating in the IDA study with confirmed uncontrolled hypertension.

Figure 2. Flowchart of inclusion and exclusion for Study 1.



BP, blood pressure; 24-h, 24-hour

10.1.2 Studies 2 and 3. PA cohort

Study 2 and 3 utilized data from a cohort of 109 patients with PA. The patients were consecutively recruited from Haukeland University Hospital, Department of Medicine, by my co-mentor, Marianne Grytaas during her doctoral studies. Diagnosis of PA was confirmed in patients with elevated ARR through recumbent saline infusion testing, with a positive test defined as a post-infusion plasma aldosterone level > 140 pmol/L. Adrenal vein sampling was performed at the time of inclusion for subtype differentiation. The inclusion period for the study lasted from 2013 to 2016, with patients undergoing follow-up visits at 3 and 12 months. Transthoracic echocardiography was performed at baseline and at the 12-month visit at the Department of Heart Disease, and all studies were digitally stored in the hospital PACS. The echocardiographic study results were not included in the formal doctoral thesis. (Clinical Trials number NCT02832388).

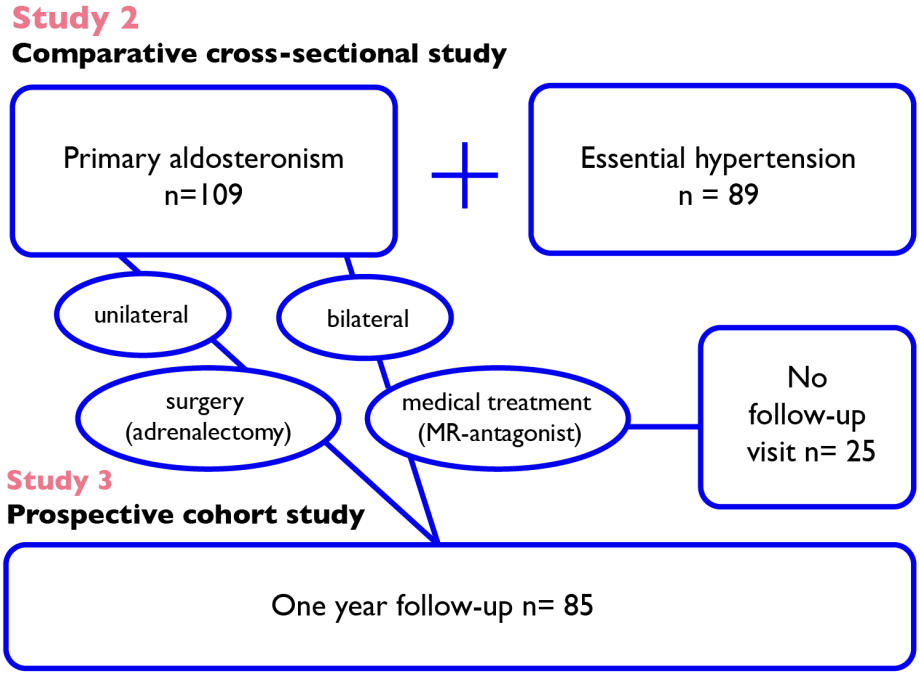
Study 2

Study 2 was a cross-sectional study of 109 patients with PA and 89 matched controls with essential hypertension (Figure 3). The control subjects were identified within the FAT-associated CardioOvasculaR dysfunction (FATCOR) study [62], a study cohort established at the European Society of Hypertension Excellence Centre in Bergen. The control subjects had essential hypertension and were matched for gender, presence of obesity, and age within a five-year range.

Study 3

Study 3 was a prospective follow-up study of 85 PA patients receiving specific PA treatment for 12 months. Among the original population of 113 PA patients, 25 patients resided in other health regions and were followed up in their local hospital (Figure 3). Based on subtype differentiation, patients were grouped into patients receiving surgical therapy (unilateral PA) or medical therapy with MRA (bilateral PA). Of note, one patient with unilateral PA declined surgery and received medical therapy. This study investigated the presence of persistent cardiac organ damage after one year of medical versus surgical treatment for PA.

Figure 3. Flow chart for the PA study cohort



10.2 Echocardiography

10.2.1 Examination and image analysis

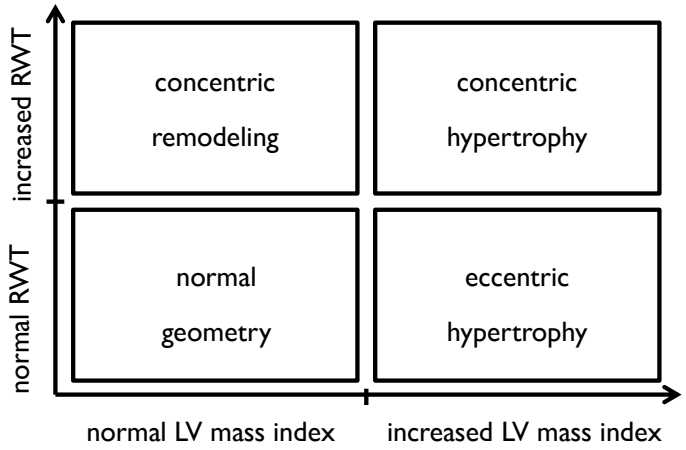
Both populations were examined with two-dimensional transthoracic echocardiography following the same standardized imaging protocol. Image analysis was performed at the Echocardiography Core Laboratory at the University of Bergen, Bergen, Norway, on an offline digital workstation equipped with Image Arena Software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). Examinations were first read by a junior investigator (PA-population by the same technician, IDA-population by the PhD candidate) and subsequently, all proofread by the main mentor, in accordance with the current recommendations for echocardiographic core laboratory procedures [63], following the guidelines for

chamber quantification[25]. During proofreading, the measurements from the first reader were visible for the second reader to adjust on the exact frame where they had been made. For the PA population and controls with essential hypertension, we also assessed LV GLS by speckle tracking echocardiography, using the Automated Function Imaging and apical 2-, 3-, and 4-chamber views of the LV on a dedicated workstation equipped with EchoPac BT202 (GE Vingmed Ultrasound, Horten, Norway). Intra-observer reproducibility of LV mass and midwall shortening was performed in the PA cohort by reanalysis of 24 randomly selected study participants.

10.2.2 LV mass and geometry

LV dimensions and wall thicknesses were measured in a two-dimensional parasternal long-axis view according to the current guidelines [25]. LV mass was calculated using Devereux's validated formula [64] and was indexed for height squared meter$^{2.7}$. LV hypertrophy was identified by prognostic gender-specific cut-off values for LV mass index (>47.0 g/m$^{2.7}$ in women and >50.0 g/m$^{2.7}$ in men) in line with the European guidelines on the management of hypertension [1]. RWT was calculated as 2x posterior wall thickness/LV internal diameter in end-diastole and was considered increased if >0.42 [25]. Concentric remodeling was defined as increased RWT with normal LV mass index, whereas concentric LV hypertrophy was defined as increased RWT with increased LV mass index (Figure 4). Eccentric LV hypertrophy was defined as increased LV mass index and normal RWT [25] (Figure 4).

Figure 4. LV geometric phenotypes



10.2.3 LA enlargement

LA systolic volume index was estimated by the biplane Simpson's method combining four and two-chamber views [25], and indexed for height^2. LA was considered enlarged (referred to as dilated in paper one) if ≥ 16.5ml/m^2 in women and ≥ 18.5ml/m^2 in men[5].

10.2.4 LV function

LV systolic function was assessed as LV ejection fraction by biplane Simpson's method [25], LV midwall shortening by validated equations [30], and LV GLS by speckle tracking echocardiography.

LV Midwall shortening

LV Midwall shortening was estimated from validated equations taking the epicardial migration of the midwall during systole into account [65].LV Midwall shortening was considered low if less than 16% in women and less than 14% in men [66].

LV GLS (studies 2 and 3)

Strain is defined as the change in length of an object within a certain direction relative to its baseline length [5]. LV GLS is the most used strain-based measure of global systolic LV function and expresses the length change of the LV myocardium between end-diastole and end-systole in the longitudinal direction [5]. Peak LV GLS was calculated from 18 individual LV segments based on the 3 apical imaging planes on image loops with frame rate ≥50 frames per second. The endocardial border was tracked automatically and adjusted manually if needed to avoid the inclusion of the pericardium and optimize tracking. End-systole was defined by aortic valve closure using pulse wave Doppler. LV GLS was considered low if more than -18.5% in women and more than -16.9% in men [67].

LV diastolic function

The American Society of Echocardiography and the European Association of Cardiovascular Imaging 2016 guidelines recommend evaluation of LV diastolic function by assessment of mitral inflow, annular velocities, tricuspid regurgitation velocities, and LA volume index [68]. LV diastolic dysfunction is indicated if, in patients with normal LV EF, two or more of the following variables meet the cut-offs: early diastolic mitral annular plane velocity (e'), septal e' < 7cm/second, and lateral e' < 10cm/second, average transmitral filling velocity (E) to the average septal and lateral e' ratio >14, peak tricuspid regurgitation velocity at >2.8m/s or LA maximal volume index >34ml/m^2, without presence of atrial fibrillation or valve disease. Of note, the cut-off for the LA volume index is not gender-specific in these guidelines. Additional echocardiographic measurements can support the diagnosis. An elevated E/e' ratio has a high specificity for increased LV filling pressures [68]. In studies 2 and 3 E/e' ratio was used as an estimate of LV filling pressure. We also consistently used gender-specific cut-off values for enlarged LA indexed for $height^2$, as indicated above and recommended by the European guidelines for management of hypertension [5,69].

10.2.5 Cardiac organ damage definitions

In the papers that this thesis is based upon, the terms preclinical cardiac disease and cardiac organ damage have been used interchangeably, reflecting the reviewers' and editors' preferences in the publication process. In this synopsis, the term cardiac organ damage is preferred. This term encompasses both structural and functional alterations to the heart due to chronic hypertension. In Study 1 the presence of cardiac organ damage was defined as the presence of LV hypertrophy or LA enlargement. In study 2 we focused on LV hypertrophy and myocardial function assessed as LV midwall shortening and LV GLS. In study 3, cardiac organ damage was defined by the presence of any of the following: LV hypertrophy, LA enlargement, low LV midwall shortening, or low LV GLS. Persistent cardiac organ damage was defined as cardiac organ damage present both at baseline and at follow-up.

10.3 Assessment of CV risk factors

10.3.1 BP

Office BP

Standardized office BP was obtained by trained personnel according to the latest guidelines from the European Society of Cardiology/European Society of Hypertension using validated, regularly calibrated devices with the appropriate cuff size [1]. Seated, attended BP measurement was measured in triplets with one-minute intervals, after an initial rest of five minutes. The average of measurements 2 and 3 was calculated and recorded as the office BP. BP was considered elevated when systolic BP ≥ 140mmHg or diastolic BP ≥ 90mmHg [1] (Table 1).

Ambulatory blood pressure (Study 1)

Ambulatory 24-h BP was measured on the non-dominant arm using a validated, regularly calibrated device with an appropriate cuff size [1]. If a BP difference of

≥10mmHg between the arms was detected by office measurements, the arm with the highest pressure was used. The device was programmed to inflate every 20 minutes during the day and every 30 minutes during the night. Valid ambulatory BP recordings had at least 70% successful readings and no more than two consecutive hours without successful readings. Ambulatory daytime systolic BP was considered elevated if ≥ 135 mmHg [5] (Table 1).

10.3.2 Comorbidities

History of comorbidities was obtained through patient records and structured patient interviews. The presence of type 2 DM was defined by history of type 2 DM in the IDA study, and by either history of type 2 DM, HbA1c > 6.5%/48mmol/mol, or non-fasting serum-glucose ≥ 11.1mmol/L in the PA studies. Atrial fibrillation was considered present if known history of atrial fibrillation or if atrial fibrillation was documented on the electrocardiogram in the individual patient. Renal function was evaluated by eGFR and ACR in a morning spot urine. In study 3, clinical CV disease was considered present in the individual patient with a history of myocardial infarction, angina pectoris, percutaneous coronary intervention, coronary bypass graft, transient ischemic attack, or ischemic stroke. In Study 1, an elevated ARR (>35 pmol/mIU) was considered indicative of PA, although no prior adjustments of antihypertensive treatment were performed [4]. In Study 3, plasma renin was considered low if plasma renin activity was less than 0.5 mg/l per hour or plasma renin concentration was less than 4.4 mIU/L.

Overweight and obesity

Body mass index (BMI) was calculated as body weight in kilograms divided by body height in meters squared. The criterion of the World Health Organization was used to identify obesity (BMI≥ 30kg/m^2).

10.3.3 Assessment of nonadherence to antihypertensive drugs (study 1)

In Study 3 we assessed adherence to antihypertensive drugs by measuring serum drug concentration. The analysis was performed at the Department of Pharmacology at Oslo University Hospital, Ullevål, by using ultra-high-performance liquid chromatography coupled with tandem mass spectrometry (UHPLC-MS/MS). This laboratory provides measurements of serum drug concentration for the 23 most commonly prescribed antihypertensive agents in Norway [70]. The patients were not informed about the serum drug concentration measurement. To minimize the impact on patient adherence, we refrained from providing instructions on whether to take their usual drugs before the study visits. Adherence status was assessed by an experienced pharmacologist, based on information on serum drug concentrations, dosage, patient-reported time since last intake of the drug, and prespecified cut-off values for each drug [70–72] (Table 3).

Table 3. Established serum reference ranges for antihypertensive drugs

TABLE 3. Established serum reference ranges of antihypertensive drugs

	Dose (mg) low-high	I Serum concentrations from literature (nmol/L)	II Calculated concentrations (nmol/L)			III $C_{12\text{-}24h}$ patient samples (nmol/L) Median (range)	Established $C_{12\text{-}24h}$ serum concentration range (nmol/L)
			C_{24h}	C_{12h}	C_{av}		
Doxazosin (depot)	4-8	22-332	5.2-46	8.1-71	8.4-73	n=3 28 (18-80)	**5-80**
Beta-blockers							
Atenolol	50-100	375-3755	76-196	299-768	400-1029	n=1 (228)	**75-750**
Bisoprolol	5-20	31-307	14-84	29-178	32-196	n=5 22 (10-137)	**10-200**
Carvedilol	12.5-50	49-369	2.6-16	7.4-44	8.8-52	n= 3 9 (8-176)	**2.5-50**
Labetalol	200-2400	76-609	n.a.	56-1067	107-2048	-	**50-1000**
Metoprolol (depot)	50-200	30-2244	1.6-9.7	17-105	39-235	n= 34 109 (8-702)	**10-500**
Propranolol	80-320	77-3470	n.a.	52-398	134-1024	n=2 (52-146)	**50-400**
CCBs							
Amlodipine	5-10	7,3-37	9.7-33	12-40	12-41	n=21 26 (9.7 -61.8)	**10-40**
Diltiazem (depot)	240-480	73-965	42-123	128-373	156-455	n=1 (303)	**100-500**
Lercanidipine†	10-20	No data	0.23-1.9	0.57-4.8	0.65-5.5	n=5 0.7 (0.28-1.52)	**0.2-5**
Nifedipine (depot)	20-60	58-433	10-53	28-142	33-165	n=5 104 (31-212)	**20-150**
Verapamil (depot)	120-480	44-1100	20-188	40-376	44-407	n=2 (32-500)	**40-400**
ACEIs							
Enalaprilat	5-40	26-130	8.6-129	18-275	20-302	n=2 (14-21)	**10-300**
Lisinopril	5-80	2,5-173	8.3-170	17-340	18-368	n=2 (10-37.9)	**10-300**
Ramiprilat	2.5-10	2,6-103	4.3-31	7.8-55	8.3-59	n=8 7.5 (4-19)	**4-60**
ARBs							
Candesartan	8-32	182-409	20-122	48-289	54-325	n=22 37.5 (12-166)	**15-200**
Irbesartan	150-300	4434-7701	451-1525	855-2893	915-3094	n=5 357 (107-586)	**300-3000**
Losartanic acid	50-100	(458-1488)	31-80	146-374	211-540	n=5 48 (35-73)	**30-350**
Telmisartan	20-80	25-225	7.5-57	11-81	11-82	-	**8-80**
Valsartan	80-320	1837-13777	263-1523	636-3691	723-4191	n=11 952 (359-1891)	**300-4000**
Thiazide diuretics							
Bendroflumethiazide	1.25-5	119-235	1.5-10	3.8-26	4.3-30	-	**1.5-30**
Hydrochlorothiazide	12.5-50	61-122	15-92	41-262	49-311	n=26 44.5 (19-149)	**15-300**
Potassium-sparing diuretics							
Canrenone	25-100	147-206	17-170	28-285	30-298	n=2 (27-89)	**15-300**
Eplerenone	25-50	No data	3.4-21	55-341	158-980	-	**3.5-350**

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10.4 Statistical analyses

The Statistical Package for Social Sciences (SPSS) software versions 25-26 (IBM, Armonk, New York USA) was used for statistical analysis. Continuous variables are reported as mean±SD or as median with interquartile range as appropriate. Categorical variables are reported as absolute numbers and percentages. Differences between groups were tested by student's unpaired t-test, Mann-Whitney U test, Pearson's chi-square test, or one-way analysis of variance (ANOVA) as appropriate. Within-group changes during follow-up in Study 3 were tested with paired samples t-test, Wilcoxon signed-rank test, or uncorrected McNemar test as appropriate. Univariable and multivariable logistic and linear regression analyses were used to identify covariables independently associated with the presence of cardiac organ damage in Studies 1 and 2, as well as with the presence of persistent cardiac organ damage in Study 3. The covariables included in the multivariable models were either associated with the dependent variable in the univariable analysis ($p < 0.10$) or were of relevant clinical significance based on previous knowledge. A variance inflation factor > 1.4 was used to identify collinearity to ensure statistically sound models. Intra-observer reproducibility of measurements of LV mass and LV midwall shortening was assessed by intraclass correlation coefficients (Studies 2 and 3). In Study 1, statistical power calculations documented 80% power (β) for detecting significant differences in the prevalence of LV hypertrophy between women and men. Study 2 had 80% statistical power to identify differences in prevalence of LV hypertrophy in gender-specific analysis. Study 3 had 80% statistical power to identify 35% differences in prevalence of persistent LV hypertrophy between treatment groups at one-year follow-up. All power calculations had a significance level (α) of 0.05

10.5 Ethics

All study participants signed a written informed consent. The studies were performed according to the declaration of Helsinki and the study protocols were approved by the Regional Committee for Medical and Health Research Ethics (2013/742 and 2017/804)

11. Main results

11.1 Study 1

Gender differences in cardiac organ damage in hypertension: Assessing the impact of drug adherence

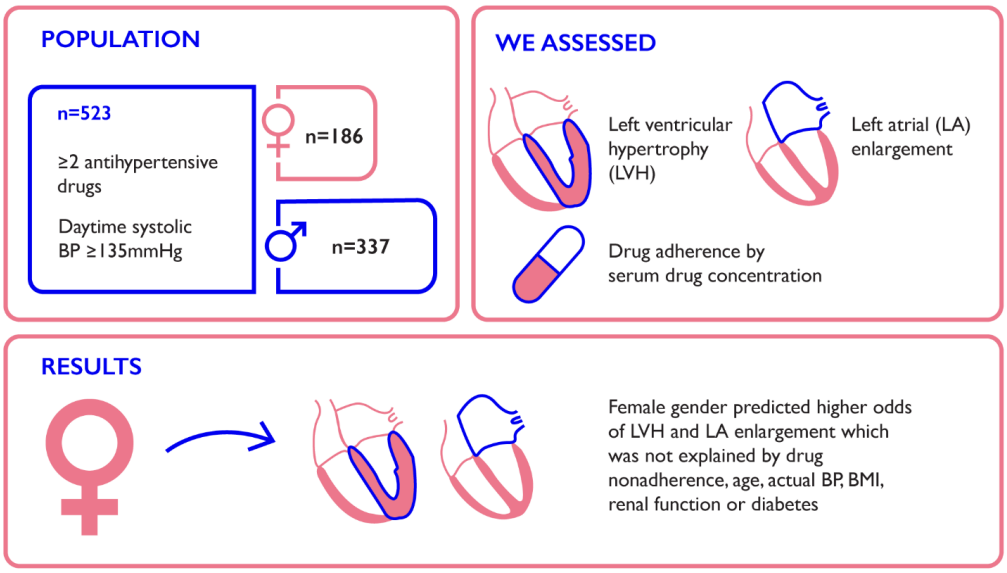


Figure 5. Graphical abstract Study 1.

Study 1 was a cross-sectional study including 523 patients (36% female) with uncontrolled systemic hypertension despite being prescribed ≥ 2 antihypertensive agents. The aim was to explore gender differences in the prevalence of cardiac organ damage and assess the role of drug adherence in explaining these potential differences.

Women were younger (66±11 vs. 62±10 years) and had a longer reported duration of hypertension (18±12 vs. 15±11 years, both $p<0.05$), whereas BMI, eGFR, ARR, prevalence of type 2 DM, hypercholesterolemia, clinical CV disease, and atrial

fibrillation did not differ. Among women with elevated ARR in our study, two women were < 50 years of age (probably premenopausal), and eight received exogenous estrogen. Obesity was highly prevalent in both genders (43% vs. 50%, p=0.126). Ambulatory systolic daytime, nighttime, and 24-h BP did not differ between genders. Drug non-adherence was similarly low in women and men (8% vs. 9%, p=0.501).

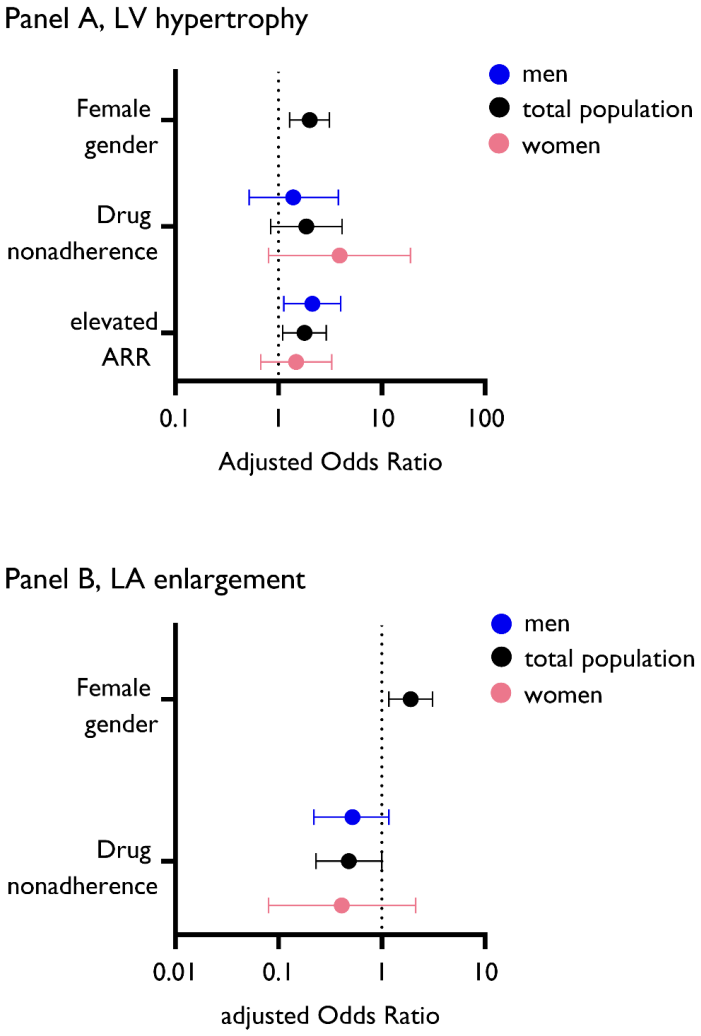
Cardiac organ damage was common in both genders. Women had a higher prevalence of LV hypertrophy (45% vs. 32%, p=0.006), and enlarged LA (79% vs 65%, p<0.001) compared to men.

In multivariable logistic regression analysis drug nonadherence was not associated with the presence of LV hypertrophy or LA enlargement in either gender (Figure 6). Female gender was associated with LV hypertrophy despite adjusting for drug adherence, age, BMI, ACR, systolic 24-h BP, and elevated ARR (OR 2.00 [95% CI 1.28-3.10]) (Figure 6, Panel A). In gender-specific analysis, LV hypertrophy was associated with higher BMI in both genders and with ambulatory 24-h systolic BP, age, and elevated ARR in men. LV hypertrophy and elevated ARR remained uncorrelated in women also when excluding premenopausal women and those on exogenous estrogen.

Female gender was also independently associated with LA enlargement after adjusting for drug adherence, age, BMI, ambulatory 24-h systolic BP, LV hypertrophy, and mitral valve regurgitation (OR 1.90 [95% CI 1.17-3.10]) (Figure 6, Panel B). In gender-specific analysis, both higher BMI and LV hypertrophy were associated with LA enlargement in both genders, with the addition of mitral regurgitation as covariable in women and older age as covariable in men.

Also, low LV midwall shortening was more common in women (12% vs. 5%, p=0.002). However, when adjusting for confounders including age, BMI, eGFR, elevated ARR, hypercholesterolemia and concentric LV hypertrophy, the association with female gender was lost (OR 1.82 [95%CI 0.88-3.77]), and low LV midwall shortening remained associated with only concentric LV hypertrophy (OR5.33 [95% CI 2.60-10.95) and age (OR 1.06 [95% CI 1.01-1.11]).

Figure 6. The Association of female gender, drug nonadherence and ARR with cardiac organ damage in multivariable logistic regression analysis.



The model in Panel A is further adjusted for age, body mass index, 24-h systolic blood pressure, duration of hypertension, elevated albumin-creatinine ratio, type 2 diabetes mellitus, hypercholesterolemia, and cardiovascular disease. The model in Panel B is further adjusted for age, body mass index, 24-h systolic blood pressure, duration of hypertension, elevated albumin-creatinine ratio, LV hypertrophy, and mitral valve regurgitation. ARR, aldosterone-to-renin ratio; LV, left ventricular; LA, left atrial

11.2 Study 2

Preclinical cardiac disease in women and men with primary aldosteronism

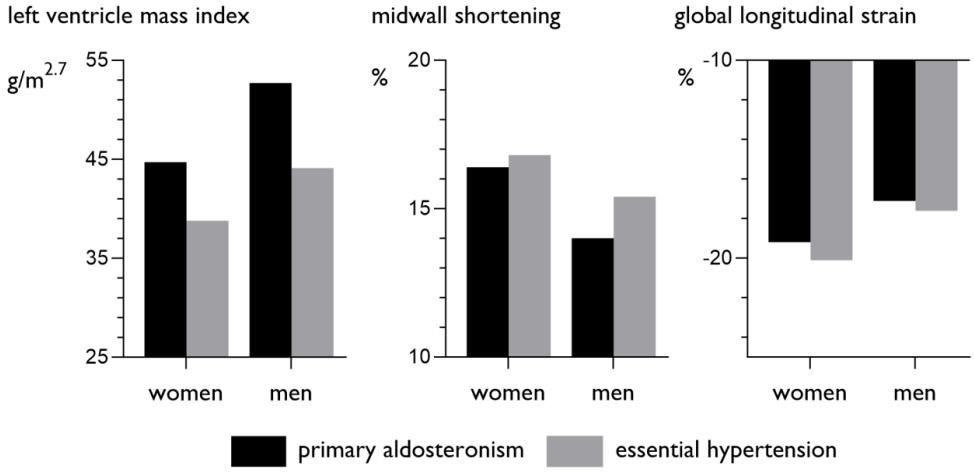
The aim of this study was to investigate gender-specific associations between PA and LV structure and function in a cohort of 109 patients with PA and 89 controls with essential hypertension, of whom 33% were women. Compared to essential hypertension, patients with PA were older (mean age 57±11 vs. 53±9 years), had higher systolic BP (148±19 vs. 141±17 mmHg), lower BMI (29.9±5.3 vs. 31.7 kg/m^2) and lower renal function (85±25 vs. 93±13 ml/min/1.73^2, all p<0.05). Men with PA were older (mean age 60±10 vs. 55±7 years) and had lower renal function (82±24 vs. 95±13 ml/min/1.73^2, both p<0.05) than men with essential hypertension, whereas there were no significant differences in characteristics between women in the two groups.

The prevalence of LV hypertrophy was more common in PA than essential hypertension, both in men (57 vs. 27%) and women (41 vs. 10%, both p<0.005). LV midwall shortening was lower in PA men compared to essential hypertension (14.0 vs. 15.4%, p=0.023), whereas no significant difference was observed in women. LV GLS did not differ between PA and essential hypertension in either gender (Figure 7).

In gender-specific multivariable logistic regression analysis LV hypertrophy was associated with PA when adjusting for systolic BP, age, and obesity in both genders (women: OR 6.88 [95% CI 1.45-32.63], men: OR 3.46, [95% CI 1.49-7.99]). Obesity was strongly associated with LV hypertrophy in both genders (women: OR 5.41 [95% CI 1.24-23.66] men: OR 2.34 [95% CI 1.02-5.37]), whereas systolic BP was associated with LV hypertrophy in the total population only (OR 1.02 [95% CI 1.00-1.05]). Low LV midwall shortening was associated with PA in univariable analysis, but the association was lost when adjusting for confounders in multivariable linear regression analysis. When adjusting for clinical variables low LV midwall shortening was associated with higher systolic BP in the total study population and in women, but this association was lost when further adjusting for LV mass index.

Low LV GLS was not associated with PA in univariable or multivariable analysis. BMI was the main confounder of low LV GLS in both genders.

Figure 7. LV mass index, LV midwall shortening, and LV GLS in women and men with PA compared to women and men with essential hypertension.



11.3 Study 3

Persistent cardiac organ damage in surgically and medically treated primary aldosteronism

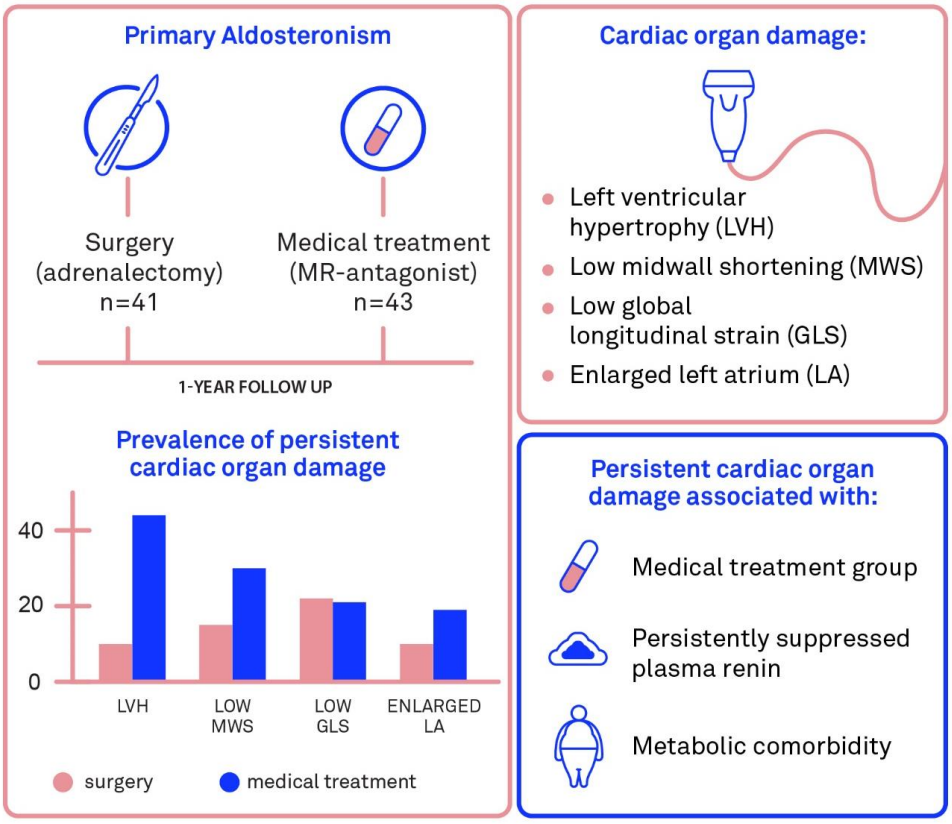


Figure 8. Graphical abstract Study 3

A total of 84 patients (27% women, mean age 56±11 years) with PA were followed for one year after initiation of either surgical (n=41, all unilateral PA) or medical (n=43, 42 bilateral, one unilateral PA) therapy with MRA. The aim of the study was to identify factors that influenced the persistence of cardiac organ damage during specific PA treatment.

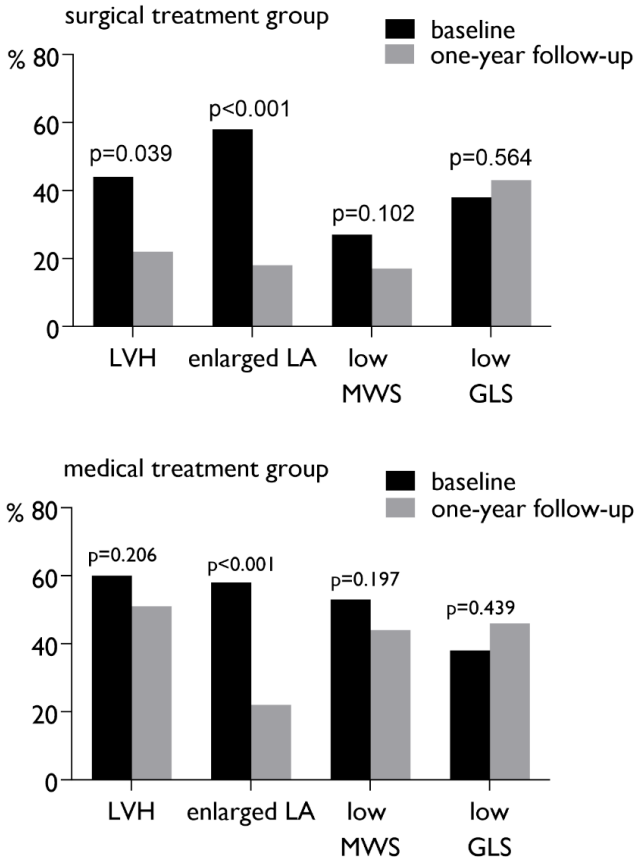
At baseline, patients in the medical treatment group had a higher prevalence of type 2 DM and higher HbA_{1c}, whereas there were no differences in gender, age, duration of hypertension, office BP, BMI, or the number of antihypertensive drugs. LV mass index and prevalence of LV hypertrophy did not differ between the groups. The medical treatment group had a higher prevalence of low LV midwall shortening compared to the surgical group (23 vs. 11%, $p<0.05$), whereas the prevalence of low LV GLS and LA enlargement did not differ. Both LV mass [interclass correlation 0.88 (95% CI 0.71–0.95)] and midwall shortening [interclass correlation 0.91 (95% CI 0.80–0.96) both P < 0.001] demonstrated good intra-observer reproducibility.

The prevalence of suppressed plasma renin was reduced in both groups after treatment, however, 23% of patients in the medical treatment group still had suppressed plasma renin at one-year follow-up. LV end-diastolic diameter was reduced, and RWT increased in both groups, whereas the wall thicknesses did not change. Accordingly, LV mass index decreased in both groups (surgical group: 47.4±11.2 vs. 42.3±11.3 $g/m^{2.7}$, medical group: 52.0±13.6 vs. 48.3 ± 12.3$g/m^{2.7}$), but the prevalence of LV hypertrophy decreased significantly only in the surgical treatment group (Figure 9). Low LV GLS and LV midwall shortening remained common in both groups during follow-up, whereas the prevalence of LA enlargement was substantially decreased in both groups (figure 9).

The prevalence of persistent LV hypertrophy at follow-up was higher in the medical treatment group (44% vs. 10%, $p<0.001$), whereas the prevalence of persistently low LV midwall shortening, LV GLS, and LA enlargement did not differ. In stepwise multivariable logistic regression analysis, the medical treatment group was associated with persistent LV hypertrophy independent of significant associations with BMI, DM, and pulse pressure at follow-up (OR 4.73 [95% CI 1.20-18.68]). When analyzing the treatment groups separately, persistent LV hypertrophy was associated with baseline post-saline infusion testing aldosterone concentration [OR 1.08 (95% CI 1.01–1.14), $p = 0.020$], independent of confounders in the medical treatment group only. Persistently low LV GLS was only associated with higher HbA_{1c} (OR 2.37 [95% CI 1.12-5.07]). Persistently low LV midwall shortening was associated with persistently low plasma renin independent of a significant association

with eGFR (OR 6.11 [95% CI 1.39-26.7]). Persistently enlarged LA was associated with higher BMI (OR 1.18 [95% CI 1.02-1.37]) and lower eGFR (OR 0.96 [95% CI 0.93-0.99]).

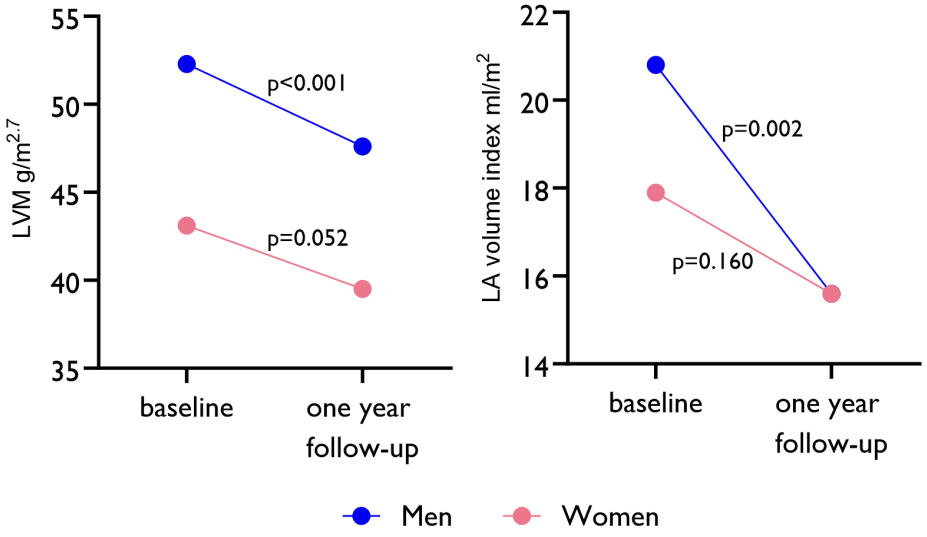
Figure 9. Prevalence of cardiac organ damage at baseline and one-year follow-up in the surgical versus the medical treatment group



LVH, left ventricular hypertrophy; LA, left atrium; MWS, midwall shortening; GLS, global longitudinal strain

In a sub-analysis, we stratified change in LVM index and LA volume index by gender. In men, both variables were reduced during follow-up (LVM index: 52.3 vs. 47.6 g/m$^{2.7}$, LA volume index: 20.8 vs. 15.6 ml/m^2, both p<0.001), whereas in women the change was less pronounced and not statistically significant (LVM index: 43.1 vs. 39.5 g/m$^{2.7}$, LA volume index: 17.9 vs. 15.6 ml/m^2, both p>0.05) (Figure 10).

Figure 10. The average change in LVM index (panel A) and LA volume index (panel B) in women and men before and after surgical and medical PA treatment



LVM, left ventricle mass index; LA, left atrial volume

12. Discussion

This thesis demonstrates that cardiac organ damage is more common in women than men in treated presumed hypertension, while the opposite was found in secondary hypertension caused by PA. The findings of the project expand current knowledge on cardiac organ damage in systemic hypertension. First, Study 1 demonstrated that antihypertensive drug nonadherence did not explain the higher prevalence of LV hypertrophy and LA enlargement in women with uncontrolled treated hypertension. Further, elevated ARR on actual medication was associated with the presence of LV hypertrophy in men. In Study 2, PA was independently associated with the presence of LV hypertrophy both in women and men. Finally, in Study 3, persistent cardiac organ damage in PA remained common one year after initiation of specific treatment, especially in the medical treatment group and in patients with concomitant metabolic disorders.

12.1 Gender-specific prevalence of cardiac organ damage

In Study 1, the higher prevalence of LV hypertrophy and LA enlargement in women compared to men with uncontrolled treated hypertension extends prior research by our group in essential hypertension. In the Losartan Intervention For Endpunct reduction (LIFE) study, similar results were found in older subjects with hypertension and electrocardiographic signs of LV hypertrophy [73]. In the Campania Salute Network project, similar results were found in middle-aged subjects with treated hypertension [19]. Despite the growing interest in gender differences in CV medicine, the precise mechanisms underlying these gender differences remain unclear [35]. Understanding these mechanisms is essential for tailored therapeutic approaches for both genders. Furthermore, our studies extend information on cardiac organ damage prevalence and its association with metabolic comorbidity in both women and men with PA.

12.1.1 Gender-specific prevalence of LV hypertrophy

In the IDA study, among patients with uncontrolled treated hypertension, the prevalence of LV hypertrophy was 45% in women and 32% in men. This is considerably higher than what has been reported in the general population. For instance, the Framingham Heart Study, in a diverse population (age 17-90 years, 55% women, 28% with hypertension), the overall prevalence of LV hypertrophy was 19% in women and 16% in men [74]. Of note, the prevalence increased significantly with increasing age, especially among women. In the age group of 70-90 years, 49% of women and 33% of men were affected (cut-offs for LV mass indexed to height were 120g/m in women and 150 g/m in men) [74]. The prevalence of LV hypertrophy in the IDA study corresponds closely with the gender-specific prevalence reported in the Campania Salute Network project which used the same gender-specific cut-off values for diagnosis of LV hypertrophy. In this prospective observational cohort study of individuals with treated hypertension in the Campania region in Southern Italy, LV hypertrophy was observed in 43% of women and 32% of men [19]. Of note, office systolic BP was on average uncontrolled in both women and men with LV hypertrophy in that study (149 mmHg in both genders), but ambulatory BP measurements were not reported [19].

In populations with resistant hypertension, the prevalence of LV hypertrophy has been higher. In a study of middle-aged individuals (mean age 48 years, 41% female) with resistant hypertension, a 50% prevalence of LV hypertrophy was reported [75]. In this study, resistant hypertension was defined as mean daytime BP ≥ 135/85 mmHg while on 3 antihypertensive drugs at optimal doses, including a diuretic. Another study, which included older patients with a higher proportion of females (mean age 62 years, 69% female), reported an even higher prevalence of 72% [76]. In this study, resistant hypertension was defined as either office BP ≥140/90 mmHg when using 3 antihypertensive drugs in full dosages, or using ≥4 drugs regardless of clinic BP levels, ideally including a diuretic. However, neither of these studies reported gender-specific prevalences of LV hypertrophy.

Within the PA cohort in Study 2, it should be noted that significantly more men than women had LV hypertrophy (57 vs. 41%). This contrasts with the common observation in essential hypertension, where women typically have a higher prevalence of LV hypertrophy [1,19]. Furthermore, studies in essential hypertension have demonstrated that age and higher BMI are both closely linked to LV hypertrophy, particularly among women [1,31]. Therefore, the relatively lower prevalence of LV hypertrophy in women in Study 2, might be explained by women being substantially younger (52 vs. 60 years) and leaner (BMI 28.2 vs. 30.6 kg/m^2) compared to men. Of note, male gender was not associated with LV hypertrophy when adjusting for confounders, including age and BMI.

The overall LV hypertrophy prevalence of 52% in PA patients in Study 2 was high. Comparative studies employing the same guideline-recommended definitions of LV hypertrophy in PA are limited. Muiesan et al. reported a similar LV hypertrophy prevalence at 50% in a cohort of 125 newly diagnosed PA patients, with a mean age of 50 years and 43% women [77]. Salvetti et al. recently reported a slightly lower LV hypertrophy prevalence of 39% in a cohort of 99 patients newly diagnosed with PA [78].

12.1.2 Eccentric versus concentric LV hypertrophy

Among patients with LV hypertrophy in the IDA study, the eccentric phenotype was more frequent than the concentric phenotype and was similarly prevalent across genders. In contrast, concentric LV hypertrophy was more prevalent among women than men, aligning with previous research in essential hypertension [73]. Concentric LV hypertrophy has also been associated with increased total peripheral resistance [79,80]. Among patients with LV hypertrophy, participating in the LIFE study, the presence of DM was associated with a higher prevalence of persistent LV hypertrophy after 5 years of antihypertensive treatment [81]. In a population-based cross-sectional study in rural China, patients with combined hypertension and DM had a significantly higher prevalence of concentric LV hypertrophy compared to groups with normal BP and hypertension without DM, and this risk was more pronounced in women [82].

Compared to the eccentric phenotype, concentric LV hypertrophy poses a higher risk of clinical CV disease [23].

Similarly, in the PA cohort of Study 2, eccentric LV hypertrophy was the predominant phenotype in both genders. In a cohort of 125 newly diagnosed PA patients, Muiesan et al. reported a more balanced distribution, with 31 patients having eccentric and 26 having concentric LV hypertrophy [77]. However, patients in this study had a lower BMI compared to our cohort. Eccentric LV hypertrophy is commonly observed in obese individuals and is associated with volume overload [79,83]. A recent study of 94 severely obese patients undergoing bariatric surgery (average age 45 years, 57% having hypertension), observed a substantially higher preoperative prevalence of eccentric than concentric LV hypertrophy (32 vs. 3%) [84]. Following a substantial decrease in BMI one year after surgery, the prevalence of eccentric LV hypertrophy decreased to 16%, whereas the prevalence of concentric LV hypertrophy remained unchanged. Thus, the overrepresentation of eccentric LV hypertrophy in both the PA and IDA cohorts in our studies may be attributed to the high prevalence of obesity. In addition, autonomous aldosterone secretion is characterized by increased water and sodium re-absorption, which may promote volume overload in PA. Of note, in some obese patients, particularly those with concurrent hypertension and impaired glucose metabolism, a concentric phenotype is more prevalent and less modifiable by weight loss [83].

12.1.3 Gender-specific prevalence of LA enlargement

LA enlargement is a common and often overlooked manifestation of cardiac organ damage. Indeed, when using the guideline-recommended gender-specific cut-off values for LA volume index, previous studies have suggested that LA enlargement is the most common form of cardiac organ damage in essential hypertension, with a higher prevalence in women than men[19,21].

In the population-based Tromø-study, Løchen et al. recently demonstrated that long-term elevated BP increased the risk of incident atrial fibrillation in both genders,

but the association was stronger in women [85]. In the Campania Salute Network, estimated LA volume increased the risk of composite CV events (stroke, myocardial infarction, sudden cardiac death, heart failure, transient ischemic stroke, de novo angina, carotid stenting, or atrial fibrillation) during a median follow up of 49 months in 5844 adults with hypertension [16]. The estimated LA volume was obtained from the LA diameter by a validated non-linear equation and indexed to height^2 [16]. Furthermore, a retrospective analysis of 796 women with incident atrial fibrillation from the Women's Health Study, demonstrated that 41% had enlarged LA, defined as an anteroposterior LA diameter > 40mm [86].

As reported, the majority of patients in both the PA and the IDA cohorts had LA enlargement, and in the IDA cohort, LA enlargement was more prevalent in women. LA enlargement was associated with LV hypertrophy, however, it was also prevalent among patients without LV hypertrophy. Similar results were reported by Airal et al. in 484 patients newly diagnosed with essential hypertension, who were of a similar age but had a lower prevalence of obesity and DM compared to the IDA cohort [21].

12.1.4 Gender-specific prevalence of impaired Systolic myocardial function

In accordance with previous studies in essential hypertension, women had better systolic LV myocardial function in patients with uncontrolled treated hypertension, and in patients with PA, assessed as LV EF, LV midwall shortening, and LV GLS (Study 2) [29,73]. The LIFE study demonstrated that this gender-specific association was independent of age, BMI, DM, and heart rate [29].

In a retrospective analysis of the population-based Strong Heart Survey, Bella et al. examined LV systolic function in a subgroup of 144 women and 106 men with normal body weight, fasting glucose levels, glucose tolerance, and normotension, and established gender-specific normal ranges (95% CI) for measures of LV systolic function [66]. The lower limit of normal range for midwall shortening was 2% greater in women than in men (16% vs. 14%) [66].

When applying these gender-specific cut-off values for low LV midwall shortening in Study 1, women had a higher prevalence of low LV midwall shortening compared to men. However, this was explained by higher age and more concentric LV hypertrophy in women. Similarly, in unadjusted analysis, a study by Cramariuc et al. in patients with asymptomatic, mild-moderate aortic stenosis, a higher prevalence of low LV midwall shortening was found in women compared to men [87], whereas the LIFE study reported a similar prevalence of low LV midwall shortening between genders, in patients with essential hypertension and electrocardiographic LV hypertrophy [73]. Both studies used the same gender-specific cut of values for low midwall shortening [66]. In 294 patients participating in the LIFE study, de Simone et al. demonstrated that patients with a lower baseline LV midwall shortening had a higher CV risk compared to those with normal baseline LV midwall shortening, and that low LV midwall shortening added prognostic value beyond that of LV hypertrophy alone [30]. Of note, gender-specific cut-offs were not used in this study.

Study 3 demonstrated that low LV GLS and LV midwall shortening were both common in PA, albeit at a lower prevalence than LV hypertrophy and LA enlargement. In a retrospective study of 288 patients with hypertension, Saito et al. found that low GLS was associated with a higher incidence of heart failure, myocardial infarction and stroke, during a 4-year follow-up, independent of associations with concentric LV hypertrophy and age [88]. As cut-off for low GLS the study used >-16% in both genders [88]. Notably, studies reporting the prevalence of low LV GLS using gender-specific cut-off values are scarce, both in essential hypertension and PA.

12.2 Impact of delayed hypertension diagnosis and age on cardiac organ damage

Lønnebakken et al. demonstrated that a longer duration of hypertension is associated with less regression of LV hypertrophy during antihypertensive treatment [33]. Hence, delayed diagnosis and treatment initiation as well as an extended hypertension

duration in women, could potentially account for the observed gender differences in cardiac organ damage prevalence [89]. However, hypertension duration was adjusted for in the IDA study. Yet, assessing the duration of hypertension is inherently challenging due to hypertension being asymptomatic in most subjects, and the absence of systematic hypertension screening in adults in the Norwegian primary healthcare. Thus, in most subjects, the true duration of hypertension is unknown. Consequently, age is often used as an indicator for hypertension duration in research. Nevertheless, this approach is imprecise when pooling data from both genders, given the gender difference in age-associated BP development [3].

Recent research indicates that the association between systolic BP and clinical CV disease is evident at lower BP levels in women compared to men [90]. This finding suggests that also cardiac organ damage may develop at a lower BP level in women than men. Furthermore, a recent study from the Global Cardiovascular Risk Consortium, that pooled individual-level data from 1,518,028 participants in 112 cohort studies in eight geographic regions, demonstrated a stronger association between a 20 mmHg increase in systolic BP and the incidence of clinical CV disease in women under 60 years of age, compared to men [91]. Taken together, these findings suggest a potential need for lower BP thresholds in women compared to men, which is advocated for by some experts, as a tool to combat delayed diagnosis and treatment in women [89].

In the SPRINT trial, randomizing 9,361 adults with systolic BP > 130 mmHg and at least one additional CV risk factor (36% women) to intensive BP treatment (systolic BP < 120 mmHg) versus standard BP treatment (systolic BP < 140 mmHg), intensive BP treatment reduced major CV events significantly [92]. However, in gender-specific analyses, this advantage of intensive BP treatment was not demonstrated in women, likely due to their underrepresentation in the study cohort [92]. Of note, two retrospective sub-studies in the SPRINT trial, which specifically investigated whether clinical CV outcomes differed between genders in response to intensified BP treatment, reached contrasting conclusions [93,94].

12.3 Impact of BP on cardiac organ damage

Hypertension is the primary risk factor for cardiac organ damage [1]. In 1988 it was demonstrated in the Framingham Heart Study that systolic BP was independently associated with LV hypertrophy in both genders [74]. Notably, the increased risk constituted by BP was larger in men than in women [74]. In our studies, systolic BP was comparable in women and men across both cohorts and was independently associated with cardiac organ damage. However, in gender-specific analysis in the IDA study, the association was only significant among men. The weaker association between systolic BP and cardiac organ damage in women, compared to men, may be attributed to the absence of gender-specific hypertension thresholds, as discussed earlier. Moreover, a higher prevalence of metabolic and inflammatory co-morbidities in women, along with gender differences in arterial stiffening with aging and in pressure wave reflection in the proximal aorta, may have contributed further [35,95].

In Study 3, a stronger association with persistent LV hypertrophy was observed for higher pulse pressure compared to systolic BP. High pulse pressure is associated with more advanced arterial stiffness [20], and this finding may reflect advanced arterial stiffness in response to long-standing hypertension among PA patients. Additionally, the vascular effects of aldosterone, including hypertrophic remodeling, fibrosis, inflammation, and endothelial dysfunction, could have further contributed to the development of arterial stiffness [96].

In the PA cohort, the prevalence, and persistence of LA enlargement, low LV midwall shortening, and low LV GLS were not associated with any BP variables. However, all patients within this cohort had long-standing hypertension, which may have already impacted the CV organs adversely, thus diminishing the relative significance of the actual BP value [97].

12.4 Impact of obesity on cardiac organ damage

A strikingly high prevalence of obesity was observed in our studies, approaching 50% in both the PA and IDA cohorts. This is much higher than the prevalence reported by the General Obesity Federation in the general European population, which was 28% among women and 26% among men in 2020 [98]. This higher obesity prevalence in women compared to men was not observed in our PA cohort, in which a tendency towards a lower prevalence of obesity among women was observed. Since women were younger than men in this study, this is potentially explained by men reaching peak obesity prevalence at a younger age than women, as reported by the Global Burden of Disease Obesity Collaborators [99].

It is well known that obese individuals have a substantially increased risk of developing hypertension [1]. In the population-based Tromsø Study, it was further demonstrated that an increase in BMI among obese women led to a greater increase in systolic BP compared to men [100]. Additionally, it is more challenging to achieve BP control in obese individuals [1]. For example, Reisin et al. demonstrated that overweight and obese patients required a higher number of antihypertensive drugs to attain BP control, compared to normal-weight patients [101]. This study included 33,252 patients with hypertension and at least one additional CV risk factor, of whom 14,014 were obese. This finding might explain the high obesity prevalence in the IDA cohort of patients with uncontrolled treated hypertension. Furthermore, Ohno et al. suggested that obesity may contribute to the development of bilateral PA, which could explain the heightened prevalence in the PA population [102].

Obesity, deemed a global epidemic by the World Health Organization, poses a significant and escalating health challenge. It is well demonstrated that obesity is a major contributor to CV morbidity and mortality [99,103,104]. By 2035, the obesity prevalence in Europe is estimated to increase to 39% among men and 35% among women, and the prevalence is estimated to become even higher in North, Central, and South America [98].

In our studies obesity and BMI were strongly associated with cardiac organ damage in both genders, which was consistent in both the IDA and PA cohorts. While the increased CV mortality in obesity historically was attributed to the accumulation of CV risk factors, there is growing evidence to suggest the involvement of direct mechanisms as well.

The association between obesity and cardiac organ damage is well documented, including LV remodeling and hypertrophy, LA enlargement, and LV systolic and diastolic dysfunction [104]. Obesity is characterized by volume overload and increased cardiac workload due to increased energy demands [105]. These hemodynamic changes lead to cardiomyocyte hypertrophy. Additionally, obesity triggers non-hemodynamic myocardial changes, including interstitial fat infiltration, triglyceride accumulation in contractile elements, and cardiac fibrosis via inflammatory pathway activation [105]. Weight loss primarily improves LV geometry through hemodynamic mechanisms, while non-hemodynamic changes appear more chronic and less modifiable [105].

In the IDA study, BMI was independently associated with LV hypertrophy and LA enlargement in both genders. In line with this finding, Mancusi et al. reported from the Campania Salute Network project that obesity was associated with a substantially increased prevalence of LV hypertrophy independent of confounders [31]. Furthermore, Gerdts et al. demonstrated an independent association of obesity with LA enlargement when adjusting for LV hypertrophy [18]. Several studies indicate that the link between obesity and LV hypertrophy is more pronounced in women than men [35,36]. This aligns with our finding in the IDA study: BMI was the only factor associated with LV hypertrophy in the adjusted analysis in women, whereas in men, BMI, age, and ambulatory systolic BP were all significant confounders.

Also in the PA population, a robust, independent association between obesity and LV hypertrophy was evident in both genders. Accordingly, a recent study demonstrated that PA patients with obesity had a higher prevalence of LV hypertrophy compared to those without obesity [106]. The same study demonstrated a higher prevalence of persistent hypertension after adrenalectomy in obese patients [106].

Study 3 extends this knowledge by demonstrating that higher BMI was strongly associated with both persistent LV hypertrophy and persistently low LV GLS after one year of specific PA treatment. This persistence of cardiac organ damage despite a substantially decreased BP, may in part be explained by chronic non-hemodynamic myocardial damages caused by obesity [105].

12.5 Impact of DM on cardiac organ damage

Studies in essential hypertension have suggested that type 2 DM has a stronger influence on LV hypertrophy in women than men [19,35]. This observation is supported by findings from the IDA study, where type 2 DM was exclusively associated with LV hypertrophy in women and not in men. However, this association was lost when adjusting for BMI.

Several studies in PA have reported a higher prevalence of metabolic syndrome and insulin resistance when compared to essential hypertension [4]. Various mechanisms including aldosterone excess, but also concomitant glucocorticoid excess have been suggested as potential contributors [4,107]. However, in our PA cohort, the prevalence of type 2 DM and HbA_{1c} levels were similar to those in the essential hypertension cohort. Notably, given the well-established association between obesity and type 2 DM [103], the high prevalence of obesity might have influenced the type 2 DM prevalence, in both the PA and the essential hypertension cohorts in our study.

Nevertheless, results from our Study 3 highlight the impact of impaired glucose metabolism on cardiac organ damage. This is the first study to demonstrate a significant association between type 2 DM and persistent LV hypertrophy in PA, as well as between higher HbA_{1c} and persistently low LV myocardial systolic function assessed by LV GLS.

12.6 Impact of renal function on cardiac organ damage

LV hypertrophy is highly prevalent in CKD, even at early stages [108]. In the IDA study, elevated ACR was independently associated with LV hypertrophy in the total population. Similarly, the LIFE study reported a comparable link between higher LV mass and ACR, independent of age, systolic BP, DM, and race [34]. However, increased ACR was found in only 34% of the LIFE participants with LV hypertrophy, pointing out that elevated ACR cannot be used as a substitute for diagnosing LV hypertrophy by echocardiography. Still, these findings underscore a strong link between CKD and LV hypertrophy independent of blood pressure [109]. This may, in part, reflect distinct manifestations of long-standing hypertension which burdens the whole CV system including all end-organs [5].

In a recent meta-analysis, Monticone et al. demonstrated that patients with PA are more susceptible to kidney damage than individuals with essential hypertension, independent of BP levels [110]. This is likely attributed to chronic glomerular hyperfiltration, a characteristic of untreated PA that contributes to kidney function deterioration [110,111]. In Study 2, PA patients had a lower eGFR compared to essential hypertension patients, despite the assumed presence of glomerular hyperfiltration [110]. At one year follow-up both surgically and medically treated patients had a substantial decrease in eGFR. An acute fall in eGFR upon initiation of PA-specific treatment is a well-documented phenomenon and reflects the reversal of volume overload and glomerular hyperfiltration [112]. Indeed, a recent study demonstrated that medically treated patients with a small initial fall in eGFR had a significantly steeper long-term decline in eGFR, compared to those with a larger initial decrease [112]. The LIFE study demonstrated an independent association between ACR and LV midwall shortening in essential hypertension [34]. This thesis adds to that by demonstrating that in Study 2 in PA, eGFR was independently associated with lower LV midwall shortening in men, and with persistently low LV midwall shortening and LA enlargement in the total cohort in Study 3.

Gender differences in renal function are well demonstrated. CKD is more prevalent in women than men [113,114]. However, in this thesis, eGFR was similar between genders in both the PA and the IDA cohorts. In the PA cohort, this might be explained by women being younger than men. In the IDA cohort patients with severely impaired renal function were excluded (eGFR<30 mL/min/1.73m^2 or urine ACR >300 mg/mmol). Despite a higher prevalence of CKD in women, several studies have observed that ACR is higher in men than women and that men are more often receive kidney replacement therapy [115,116]. Accordingly, men had higher ACR than women in the IDA study. Furthermore, studies have shown that obesity is stronger associated with CKD in women than in men with hypertension [113]. In patients with PA, recent research revealed that women treated with MRA had a more pronounced temporal decline in eGFR during treatment compared to men [117].

12.7 Nonadherence to antihypertensive drugs and prevalent organ damage

Uncontrolled hypertension is the hallmark of cardiac organ damage [1]. Recent research has reported a rise in uncontrolled treated hypertension particularly among elderly women [7,8]. Nonadherence to antihypertensive drugs is a major contributor to uncontrolled hypertension and is increasingly recognized as a new CV risk factor [118,119]. Granger et al. demonstrated that good drug adherence leads to enhanced survival outcomes, even when receiving a placebo [120]. This suggests that those who adhere to their medication also are more likely to have a healthier overall lifestyle [120]. Gender differences in adherence to antihypertensive drugs have been suggested as a potential explanation for the higher prevalence of cardiac organ damage in women [7]. However, our Study 1 found no association between drug nonadherence and the higher prevalence of LV hypertrophy and LA enlargement in women. Consequently, this study contributes new information about the gender differences in cardiac organ damage by demonstrating that drug nonadherence did not explain these differences in the IDA study.

In the IDA study, adherent and nonadherent patients showed no significant differences in factors associated with cardiac organ damage, including gender, systolic BP, BMI, and prevalence of elevated ARR. When compared to the prevalence of nonadherence reported in many previous studies in hypertension, the IDA study had a lower prevalence [1,11]. Notably, the prevalence of nonadherence varies by patient selection, with the highest rates reported in resistant hypertension [1]. Furthermore, nonadherence is less prevalent in Western countries and when assessed objectively by concentration measurement in urine or serum [11]. A nonadherence prevalence similar to ours was found in a French observational study of 174 patients with treated essential hypertension (mean age 67 years, average use of 2.6 antihypertensive drugs). These patients were referred to the hypertension department of the Pompidou University Hospital in Paris, primarily for advice on antihypertensive treatment. Adherence was assessed by urine drug concentration [121]. An English study conducted at the Leicester BP Centre, which also used urine drug concentration, reported a nonadherence prevalence of 25%. This study included 209 patients with uncontrolled hypertension, including 126 new referrals, 66 undergoing follow-up, and 17 undergoing evaluation for renal denervation [122]. Of note, the patients in this study had a significantly higher 24-h systolic BP compared to patients in the IDA study, and the highest nonadherence prevalence was observed among those referred for renal denervation [122].

12.8 Cardiac organ damage in PA

12.8.1 PA prevalence and underrecognition

Although PA is the most common cause of secondary hypertension and specific, effective, targeted treatment is available, the diagnosis is largely underrecognized [51,123]. A recent Australian study reported an elevated ARR prevalence of 35%, and a confirmed PA prevalence of 14% among patients newly diagnosed with hypertension, screened in primary care before the initiation of antihypertensive drugs [53]. In the IDA study, we found a high prevalence of elevated ARR: 28% among women and 23%

among men. However, the majority of patients were on renin-angiotensin-aldosterone system inhibitors at the time of screening, and the actual prevalence of elevated ARR is likely even higher [123]. Although current standard for diagnosis still recommends discontinuation of potentially interfering antihypertensive drugs, like ACE inhibitors, angiotensin II blockers, and diuretics, there is growing consensus that may be unnecessary before the initial PA screening [123,124].

The Endocrine Society recommends PA screening in hypertension patients at high risk for PA, including those with hypokalemia, obstructive sleep apnea, adrenal incidentaloma, suspicious family history, or moderate/severe/resistant hypertension [50]. Unfortunately, several studies indicate that the majority of patients at high risk for PA are never screened [56,125,126], missing the opportunity for targeted CV risk-reduction therapy. In the IDA study, the high prevalence of elevated ARR in patients with uncontrolled treated hypertension, suggests poor awareness among many Norwegian primary care physicians about PA as the most common cause of secondary hypertension.

The term “overt PA” is frequently used to describe PA diagnosed in accordance with the current guidelines [123], as we did in Studies 2 and 3. However, compelling recent evidence suggests that milder forms of PA, which are not detected by current PA criteria, are quite common [123,127]. Patients with these milder forms of PA also referred to as “mild autonomous aldosterone secretion”, have an increased risk of developing hypertension and increased risk of CV complications compared to essential hypertension, although to a lesser extent than those with overt PA [127].

In a study of 663 patients with mild hypertension or normotension, where the presence of overt PA was ruled out, Hundemer et al. evaluated the ability to increase plasma renin after 5 days of sodium restriction. The inability to increase plasma renin was considered a sensitive indicator of renin suppression. The study demonstrated that the patients with the most suppressed renin activity particularly had greater autonomous aldosterone secretion (higher ARR, higher urine aldosterone excretion rate, higher systolic BP, and lower renal plasma flow), which was associated with vascular dysfunction [128]. This study contributes to the growing recognition that

autonomous aldosterone secretion exists at a continuum of disease with prognostic implications, that extend below the current diagnostic criteria for PA [123,127,129].

Interestingly, the PATHWAY-2 study demonstrated that in patients with true resistant hypertension (overt PA was excluded), adding spironolactone (MRA) to treatment with 3 antihypertensive drugs, was more effective at reducing BP compared to doxazosin (α-antagonist) and bisoprolol (β-antagonist) [130]. Importantly, the greatest BP-lowering effect of spironolactone was seen in patients with the most suppressed renin [130]. This finding suggests that a substantial proportion of patients previously diagnosed with resistant hypertension may, in reality, have mild autonomous aldosterone secretion that falls below the current PA diagnostic criteria [127].

The ARR, as a screening test for PA, has low sensitivity in detecting milder PA forms, partly due to significant daily variation in aldosterone levels [127,129,131]. Importantly, even with a positive screening test, mild autonomous aldosterone secretion may not reach the threshold for the confirmatory test [127]. Experts advocate for a revised and simplified diagnostic approach to improve earlier detection of PA [124,127,131].

12.8.2 The role of aldosterone excess

The well-documented independent association between PA and LV hypertrophy suggests that aldosterone excess contributes to LV hypertrophy [46,77,78]. It has been demonstrated that aldosterone directly induces cardiac myocyte hypertrophy [132]. Furthermore, studies have indicated that aldosterone also induces changes in the extracellular matrix, leading to cardiac interstitial collagen deposition and subsequently myocardial fibrosis [133,134]. Accordingly, a recent study found a higher prevalence of myocardial fibrosis in 27 newly diagnosed PA patients, compared to 54 patients with essential hypertension matched for BP, age and gender [135]. Myocardial fibrosis was assessed by gadolinium-enhancement using cardiac magnetic resonance imaging.

Results from the IDA study extend existing knowledge by demonstrating that elevated ARR was associated with a two-fold increased risk of LV hypertrophy in men with uncontrolled treated hypertension. This may indicate that a wider specter of autonomous aldosterone secretion leads to LV hypertrophy. However, as a confirmatory PA test was not performed, it is not known whether these male patients with elevated ARR indeed had overt PA, fulfilling current diagnostic criteria, or milder forms of autonomous aldosterone secretion. To our knowledge, no study has investigated the association between milder forms of autonomous aldosterone secretion and cardiac organ damage.

The association between ARR and LV hypertrophy in the IDA study was not found in women. The community-based Framingham Offspring Study of 3,326 individuals (53% women, mean age 59 years, with representation across all age groups), demonstrated lower renin and higher ARR in women compared to men. In line with this, studies have shown that ARR is physiologically elevated in premenopausal women in the luteal phase of the menstrual cycle, and in postmenopausal women receiving exogenous estrogen when direct renin concentration is used [136]. Excluding premenopausal women and women receiving exogenous estrogen from the analysis, did not change the results.

In a recent retrospective cross-sectional study, including 442 patients with clinically indicated ARR, Solanki et al. aimed to investigate the need for age- and sex-specific thresholds for ARR. The study found a significantly higher ARR in postmenopausal women not receiving exogenous estrogen, compared to age-matched men [137]. This finding persisted even after excluding patients taking ACE inhibitors, angiotensin II receptor blockers, and diuretics [137]. Given that these women had a similar degree of hypertension compared to age-matched men, the authors interpreted the higher ARR as likely pathologic rather than solely physiologic. However, confirmatory PA testing was not conducted systematically in this study, leaving the true prevalence of autonomous aldosterone secretion unknown.

Study 2 extends existing knowledge by demonstrating that PA was associated with LV hypertrophy in both women and men, independent of confounders.

However, PA was not associated with lower LV myocardial function. While PA and lower LV midwall shortening were associated in univariable analyses in men, this association was lost when adjusting for LV hypertrophy. Similarly, Muiesan et al. reported lower LV midwall shortening in PA compared to essential hypertension in unadjusted analysis but did not stratify for gender [77]. A recent meta-analysis, which included our study along with 4 other small PA studies, reported a lower LV GLS in PA compared to essential hypertension [138]. In contrast, our study found similar LV GLS values in PA and essential hypertension. This discrepancy may be attributed to a higher BMI in the essential hypertension group compared to the PA group in our study, since impaired LV GLS is common in obesity [37], as also demonstrated in both genders in our study.

12.8.3 Regression of cardiac organ damage during specific PA treatment

Study 3 demonstrated that many patients remained with persistent cardiac organ damage at follow-up, despite a large reduction in LV hypertrophy.

Persistent LV hypertrophy was more common in the medical treatment group independent of significant associations with obesity and type 2 DM. This finding contrasts the results of a recent meta-analysis, which indicated a similar reduction in LV mass with both treatments [60]. However, it aligns with the findings of two studies that reported a significant reduction in LV mass in surgically treated patients only [61,139].

A recent publication has drawn attention to the challenge of inadequate MRA treatment in medically treated PA [59]. Furthermore, Köhler et al. demonstrated that medically treated PA patients with suppressed plasma renin concentration after one year of treatment, had less regression of LV hypertrophy compared to those with unsuppressed renin [140]. However, in their study, LV mass was calculated using the equation for measurements performed by Penn convention, which overestimates LV mass by 20% when measurements done by the current American Society of Echocardiography convention are applied, as specified in their paper [64]. Our Study 3

expands this knowledge by demonstrating that persistently low plasma renin at the one-year follow-up was also associated with persistently lower LV myocardial function as assessed by LV midwall shortening.

Furthermore, we found that higher pretreatment post-saline infusion testing aldosterone levels were associated with persistent LV hypertrophy only in the medically treated patients, probably reflecting that the severity of autonomous aldosterone secretion impacts LV remodeling in patients with bilateral PA. Similarly, Catena et al. reported that pretreatment aldosterone was associated with a change in LV mass, independent of change in BP, in a cohort of 54 PA patients (24 surgically treated and 30 medically treated) [47].

Furthermore, specific PA treatment led to a significant reduction in the prevalence of LA enlargement in both groups. Three studies that evaluated LA anterior-posterior diameter, found no change in either group after specific treatment [61,139,141]. On the other hand, one study found a reduction in LA diameter in the surgical group only [142]. However, it is widely recognized that the LA volume index, employing guideline-recommended gender-specific cut-off values, as used in our study, better reflects actual LA size, especially in women and obese individuals [21,69].

Study 3 demonstrated that LV GLS did not improve in any groups during treatment. Notably, a study by Chen et al., published shortly after the publication of Study 3, found an improved LV GLS six months after surgery but not with medical treatment [143]. Of note, this study had a small sample size, consisting of 39 surgically treated and 28 medically treated PA patients. Furthermore, the surgically treated patients in their study had substantially lower BMI compared to our patient cohort, which could potentially account for the differing results.

As outlined above, studies indicated that myocardial fibrosis is more prevalent in PA compared to essential hypertension [135]. Notably, lower LV GLS has been linked to myocardial fibrosis, assessed by late gadolinium-enhanced cardiac magnetic resonance imaging [144]. The persistently low LV GLS in both treatment groups in our study, may, therefore reflect the presence of cardiac fibrosis, which is known to be less responsive to treatment than cardiomyocyte hypertrophy, especially when

uncontrolled metabolic comorbidities are present [135]. Studies in essential hypertension have demonstrated improved LV midwall shortening in parallel with the regression of LV hypertrophy during antihypertensive treatment [145,146]. In contrast, LV midwall shortening did not improve in either group in our study, which aligns with findings reported by Catena et al.[47].

Up to now, no study has assessed gender-specific regression of cardiac organ damage after PA treatment. Unfortunately, due to the limited representation of women in Study 3, gender differences could not be fully explored in our study. However, in secondary gender-specific analyses, we observed a trend towards greater regression of both LV hypertrophy and LA enlargement in men compared to women, without adjusting for confounders. Evidence suggests that PA is associated with a higher prevalence of obesity and type 2 DM [102,147]. Recent studies indicate that this association is more pronounced in women with bilateral PA, potentially suggesting that cardiac organ damage may be less modifiable in women with PA compared to men [147,148]. However, further research with a balanced gender distribution in larger PA studies is needed to confirm these findings.

12.9 Methodological considerations – strengths and limitations

12.9.1 Terminology: Sex or gender?

Sex and gender are intricately linked, yet they present distinct concepts. “Sex” refers to the biological characteristics, including reproductive organs, sex chromosomes, and hormonal profiles, categorized as female or male[149]. On the other hand, “gender” encompasses the social and cultural roles and behaviors associated with being women and men[149]. In cardiac organ damage in hypertension, considering both sex- and gender-related differences is relevant, but it may not always be clear which term fits best. In our studies, patients were categorized as women or men based on the gender recorded in the Norwegian Population Register. Initially, we used the term “sex” to refer to females/women and males/men (Studies 2 and 3). However, as we progressed with Study 1 (which was completed last), we recognized that “gender” was a more suitable term within this context [149]. In this thesis, we strive for consistent terminology: using “sex” to denote biological differences between females and males, and “gender” to denote differences that also depend on the interaction of the individual with the environment [149].

12.9.2 Study design

Study 1 employed a cross-sectional design. Cross-sectional studies enable the identification of associations between dependent and independent variables, yet their primary role is hypothesis generation, and they do not document causation. One advantage of a cross-sectional design is the ability to encompass substantial sample sizes with cost-effectiveness and temporal efficiency.

Study 2 employed a comparative cross-sectional design, with a cohort of patients with PA and a control group with essential hypertension, matched for gender, obesity, and age within a 5-year range. This study design enables a comparison between the

exposed and non-exposed cohorts and the identification of variables associated with exposure versus non-exposure. However, the cross-sectional design, by its nature, does not allow the determination of causality. Furthermore, the potential for selection bias is present, as participants in the groups may differ beyond the matching variables. However, in our study, relevant variables were adjusted for in the multivariable regression analysis.

Study 3 employed a prospective cohort design, which is considered the most robust among observational study designs. These studies, characterized by their longitudinal approach, have the capability to establish causation or to provide strong evidence for causal relationships. Since participants are enrolled before the development of the outcome (in our study, persistent cardiac organ damage) in prospective cohort studies, the potential for selection bias is limited. However, prospective cohort studies are more time-consuming compared to cross-sectional studies. Furthermore, loss to follow-up commonly occurs, reducing the sample size and potentially introducing bias if those lost to follow-up systematically differ from those who remain. Notably, in our study, the patients lost to follow-up resided in other health regions, a factor that is unlikely to introduce bias.

12.9.3 Sample size

Despite a good power to detect differences in the prevalence of LV hypertrophy, type 2 errors might be present regarding other analyses in Studies 1 and 2, due to the small sample sizes. This especially accounts for women who were underrepresented in both studies.

12.9.4 Selection bias

Underrepresentation of women

The underrepresentation of women in clinical trials is a common problem in hypertension research, as well as in medical research in general. Regrettably, women were also underrepresented in both study populations constituting this thesis. The PA cohort was consecutively included at the time of diagnosis during a predefined inclusion period. There is no evidence to suggest that women have a lower prevalence of PA than men [57]. This raises the possibility that physicians may be less aware of the condition in women, that women with suspected PA are less likely to be referred to secondary care, or that women are less eager than men to accept participation in research projects.

Selection bias in the IDA study

In the IDA study, participants were required to attend scheduled outpatient visits, which included planning, traveling, and comprehensive examinations including a 24-h BP measurement. It is likely that the need for voluntary participation in such visits introduced a selection bias, particularly among patients who were nonadherent to their antihypertensive drugs, as they might be less interested in participating. This could contribute to the low prevalence of non-adherence in our study. Furthermore, since women were underrepresented in the study, there is a possibility that women were more likely to decline participation.

12.9.5 Precision and accuracy

Precision can be enhanced by increasing the sample size and by improving the study design and the accuracy of the methods.

Reliable echocardiographic exams

The reproducibility of echocardiographic analysis can vary depending on factors such as type of measurement, operator expertise, image quality, and the specific

echocardiographic tool used. Use of echocardiographic core laboratory analysis is therefore recommended in particular in multicenter studies, but also for clinical studies with serial analysis performed by different operators [63]. Further, it is important that image analysis is performed by personnel blinded to the clinical data, including treatment allocation or gender. As described (paragraph 10.2.1), echocardiographic analysis was performed using the same validated system in our experienced echocardiography core laboratory, demonstrating good intra-observer reproducibility in many previously reported studies. Inter-observer reproducibility for LV GLS was recently evaluated in a separate cohort, analysed in our core laboratory by the same senior reader, and demonstrated excellent reproducibility [150]. Together, this has ensured robustness and reliability of our results.

Evaluation of nonadherence

Nonadherence to antihypertensive drugs was assessed by serum drug concentration measurements, which is recognized as the most accurate method with good reproducibility[108]. While this approach may be the most reliable among available methods of detecting nonadherence, it does not account for the daily variability and might be affected by the Hawthorne effect [1]. The Hawthorne effect refers to the potentially increased patient adherence to antihypertensive drugs prior to the study visit, driven by the awareness of participating in a BP study [1,108]. Furthermore, there is a chance that some patients with suboptimal adherence who sporadically took their drugs in the days leading up to the study visit could have been misclassified as adherent due to the strict definition of nonadherence. This strict definition was, however, necessary because most patients took their medications at a time corresponding to peak concentration levels (Cmax), where concentrations fluctuate significantly. To avoid misclassifying patients as nonadherent, we used the lower limit of the expected trough value as the cut-off.

Office BP measurement versus out-of-office measurements

In the recently released 2023 European Society of Hypertension Guidelines [1], it is highlighted that out-of-office BP measurements have a stronger association with

organ damage in hypertension compared to office BP measurements. The inclusion of additional ambulatory BP monitoring in Studies 1 and 2 would have strengthened the studies and possibly the relationship between BP and cardiac organ damage.

12.9.6 Other limitations

It is well documented that chronic low-grade inflammation is commonly present in hypertension, obesity, diabetes, and PA [41,42]. Recent studies also suggest a link between inflammation and LV remodeling [38,39]. Unfortunately, our studies did not assess the association between inflammation, cardiac organ damage, and related gender differences, as inflammatory markers that have recently been associated with clinical CV disease, like C-reactive protein, serum amyloid A, interleukins, and fibrinogen were not included in the present project.

Concomitant cortisol co-secretion in PA is common, is associated with increased metabolic risk, and may impact cardiac remodeling [107,142]. Unfortunately, assessment of cortisol co-secretion was not performed in our PA cohort, and possible confounding effects of cortisol co-secretion could therefore not be evaluated.

12.10 Ethical considerations

During the final stages of our preparations before starting the IDA study outpatient visits in Bergen, the Covid-19 pandemic struck. Initially, the inclusion process was put on hold. However, as we gained more knowledge about the virus and Norway's restrictions eased in June 2020, we made the decision to resume data collection. This choice was made after careful consideration, consulting the health officer at the University of Bergen weighing the risks against the benefits of participation for the patients, most of whom had an increased risk of severe disease if they contracted the virus. The University of Bergen Research Unit for Health Surveys core facility is modern and dedicated to outpatient research only and located outside the hospital campus. It has a separate parking lot, and most patients arrived in their own car to

avoid exposure to virus through human contact during public transportation. The study personnel exhibited extra caution and wore face masks and gloves. Consequently, we considered participation in the study safe, with only a minor rise in the risk of contamination. On the other hand, patients benefited from participating through a comprehensive cardiac examination, including 24-h BP, ECG, and echocardiography at a time when general practitioners were extremely busy. At end of study, the patients and their doctors received advice on individual antihypertensive medication, and we referred patients to secondary care specialists when necessary. However, conducting clinical research during a pandemic was highly time-consuming and challenging, and the pandemic may have influenced the patient's decision to participate. Potentially, participants who were dependent on public transportation and afraid of using this may have declined participation despite an interest in contributing to research. Furthermore, many patients avoided in-person consultations with their general practitioner during the pandemic, and digital consultations precluded the opportunity for BP measurement and referral to the IDA study.

13. Conclusions

We hypothesized that gender influences the development of cardiac organ damage in uncontrolled treated hypertension and in PA independent of other CV risk factors. Furthermore, we hypothesized that persistent cardiac organ damage is common in PA despite treatment.

Study 1

The aim of Study 1 was to assess whether a higher prevalence of LV hypertrophy and LA enlargement in women is explained by gender differences in drug adherence.

Conclusion: Drug nonadherence was not associated with a higher prevalence of LV hypertrophy or LA enlargement in either gender. Women had a two-fold higher risk of LV hypertrophy and LA enlargement independent of confounders, but drug nonadherence did not contribute to this gender difference. Elevated ARR was common and associated with the presence of LV hypertrophy.

Study 2

The aim of Study 2 was to explore the gender-specific associations of PA with LV hypertrophy and LV systolic myocardial function.

Conclusion: PA was associated with a higher prevalence of LV hypertrophy in both women and men compared to patients with essential hypertension matched for gender, obesity, and age within a 5-year range. PA was not associated with lower LV myocardial function, assessed as LV midwall shortening or LV GLS, in either gender.

Study 3

The aim of Study 3 was to explore factors associated with persistent cardiac organ damage after one year of surgical or medical treatment in patients with PA.

Conclusion: Persistent cardiac organ damage was prevalent one year after established specific PA treatment, despite a significant reduction in LV hypertrophy

in surgically treated patients, and a significantly reduced prevalence of LA enlargement in both groups. Persistent cardiac organ damage was further associated with metabolic co-morbidities, lower renal function, and inadequate MR blockade.

Overall conclusion:

This project demonstrated that female gender was associated with a higher prevalence of cardiac organ damage in uncontrolled treated hypertension, that was not explained by nonadherence. Furthermore, we demonstrated that in PA, persistent cardiac organ damage was common despite specific treatment, particularly in the medical treatment group. Lastly, underlying PA, obesity, glucose metabolism disorders, and impaired renal function contributed further to cardiac organ damage in both cohorts.

14. Clinical implications and future perspectives

This thesis demonstrates that a higher prevalence of cardiac organ damage in women with uncontrolled treated hypertension was not attributed to gender differences in drug nonadherence in the national IDA study. Future research bridging the knowledge gap of gender differences in cardiac organ damage is warranted for more effective preventive strategies for both genders.

Secondly, we demonstrated that elevated ARR, indicative of PA, was prevalent in women and men with uncontrolled treated hypertension. Importantly, an elevated ARR was associated with a higher prevalence of LV hypertrophy in men. Adding to this, we demonstrated that having overt PA was associated with a higher prevalence of LV hypertrophy in both women and men compared to matched patients with essential hypertension. Given this finding, it was surprising that elevated ARR was not associated with LV hypertrophy in women in the IDA study, but only in men. Previous studies suggest that ARR may be physiologically higher in women compared to men, especially in premenopausal women. This could potentially result in a weaker association between elevated ARR and PA in women, thereby explaining why elevated ARR was not associated with LV hypertrophy in women. To gain clarity and determine whether sex-specific cut-off values are needed, prospective studies with a control group should be performed.

Nevertheless, the high prevalence of elevated ARR in the IDA study and its association with LV hypertrophy, underscore the need to increase awareness about PA and lower the screening threshold for primary care physicians managing hypertension. Heightened awareness can lead to earlier PA diagnosis and improved CV outcome, by preventing and reversing cardiac organ damage. The recommendation to adjust antihypertensive drugs prior to PA screening can present challenges and discourage PA screening. However recent expert guidance suggests that such medication adjustments are unnecessary for the initial PA screening, simplifying the process.

Furthermore, despite specific treatment, our research demonstrated that persistent cardiac organ damage remains common in PA, particularly in the medical treatment group. Our results further suggest that the higher prevalence of persistent cardiac organ damage in the medical treatment group was partly attributed to inadequate MR blockade. This may indicate undertreatment due to physician inertia or poor patient adherence, and highlights the urgency for updated guidelines for monitoring medical treatment in PA.

The current steroidal MRA used for PA treatment increase potassium level and have hormonal side effects due to its non-specificity for the MR. Spironolactone, the most used MRA in Norway, has a high affinity for androgen and progesterone receptors, potentially causing gynecomastia and erectile dysfunction in men and mastodynia in women [131]. These side effects may affect patient adherence, although adherence to MRA in our PA studies was not assessed. Replacing spironolactone with novel, nonsteroidal specific MRA, free from hormone-mediated side effects, could revolutionize PA treatment. These drugs are safe, have lower hyperkalemia rates than spironolactone[151], and are approved for clinical treatment. For instance, finerenone has proven to slow CKD progression in patients with both CKD and diabetes [151], and was recently approved for clinical use in Norway. However, randomized clinical trials in PA have not yet been conducted. Additionally, a recent phase 2 trial of the novel aldosterone synthase inhibitor baxdrostat, effectively reduced BP in patients with resistant hypertension (defined as office BP ≥ 130/80 mmHg using at least 3 antihypertensive drugs including a diuretic) [152]. Given that MRA do not inhibit MR-independent effects of aldosterone [153], aldosterone synthase inhibition holds potential advantages over MR blockade in PA.

Finally, metabolic comorbidities, including obesity and type 2 DM were identified as confounders of cardiac organ damage and its persistence. Obesity, in particular, was highly prevalent in both cohorts and showed a strong association with cardiac organ damage. This underscores the imperative of emphasizing attention to all CV risk factors in patients with hypertension, including weight management alongside BP control. However, achieving substantial nonpharmacological weight loss is a formidable challenge for many patients. Glucagon-like peptide-1 (GLP1)

receptor antagonists have recently demonstrated effectiveness in reducing weight and BP in overweight and obese patients [1]. Hypothetically, the use of GLP1 for weight control may contribute to prevention and reverse cardiac organ damage in the future. Bariatric surgery, including various procedures like bypass surgery, leads to significant weight loss but also presents a range of complications [1]. A recent study in a Norwegian cohort with an average BMI of 41.8 kg/m^2 showed a substantial reduction in BP, regression of LV hypertrophy, and improved LV GLS one-year post-surgery [84].

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Blood Pressure

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iblo20

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To cite this article: Arleen Aune, Marina Kokorina, Marianne Aa. Grytaas, Helga Midtbø, Kristian Løvås & Eva Gerdts (2021) Preclinical cardiac disease in women and men with primary aldosteronism, Blood Pressure, 30:4, 230-236, DOI: 10.1080/08037051.2021.1904775

To link to this article: https://doi.org/10.1080/08037051.2021.1904775

BLOOD PRESSURE
2021, VOL. 30, NO. 4, 230–236
https://doi.org/10.1080/08037051.2021.1904775

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ORIGINAL ARTICLE

Preclinical cardiac disease in women and men with primary aldosteronism

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ABSTRACT

Purpose: We tested the sex-specific associations between primary aldosteronism (PA), left ventricular (LV) hypertrophy and LV systolic myocardial function.

Material and methods: Conventional and speckle tracking echocardiography was performed in 109 patients with PA and 89 controls with essential hypertension (EH). LV hypertrophy was identified if LV mass index exceeded 47.0 g/m$^{2.7}$ in women and 50.0 g/m$^{2.7}$ in men. LV systolic myocardial function was assessed by global longitudinal strain (GLS) and midwall shortening.

Results: PA patients had higher prevalence of LV hypertrophy (52 vs. 21%, $p < 0.001$) than EH patients in both sexes, while GLS did not differ by sex or hypertension aetiology. In multivariable analyses, presence of LV hypertrophy was associated with PA and obesity in both sexes, while lower systolic myocardial function, whether measured by GLS or midwall shortening, was not associated with PA, but primarily with higher body mass index and LV mass index, respectively, in both sexes (all $p < 0.05$).

Conclusion: Having PA was associated with higher prevalence of LV hypertrophy both in women and men, compared to EH. PA was not associated with LV systolic myocardial function in either sex.

ARTICLE HISTORY
Received 25 November 2020
Revised 26 February 2021
Accepted 12 March 2021

KEYWORDS
Primary aldosteronism; hypertension; sex; left ventricular hypertrophy; global longitudinal strain; midwall shortening

Introduction

Uncontrolled hypertension induces preclinical cardiac disease like left ventricle (LV) hypertrophy or LV systolic dysfunction, which are precursors for clinical cardiovascular disease [1,2]. The severity of preclinical cardiac disease is influenced by blood pressure load and the presence of other cardiometabolic risk factors, in particular sex, obesity and diabetes mellitus [3]. Primary aldosteronism (PA) is the most common cause of secondary hypertension and is often found in patients with uncontrolled hypertension [2]. PA causes a variety of cardiovascular, renal, metabolic and bone complications relatively independent of blood pressure (BP) [4]. PA is associated with metabolic syndrome [5], and it has recently been suggested that obesity-related factors contribute to the pathogenesis of idiopathic hyperaldosteronism [6]. It is well known that LV hypertrophy is more common in PA than in essential hypertension (EH) [7,8]. This has been related to aldosterone induced myocyte hypertrophy and cardiac interstitial collagen deposition and fibrosis [8,9]. Despite more prevalent LV hypertrophy, several studies have demonstrated comparable LV ejection fraction in PA and EH [8,10], but few studies in PA have assessed LV myocardial function by speckle tracking echocardiography.

Sex differences in LV hypertrophy and LV myocardial function are well described in EH, but scarcely reported in PA. Previous studies in EH have demonstrated that women are more prone to develop LV hypertrophy than men [11,12], and that regression of LV hypertrophy during antihypertensive treatment is attenuated in women, when obesity is co-present [13]. Several studies have reported that women with LV hypertrophy retain higher systolic function than their male counterparts [11,14,15]. Whether these sex-specific characteristics also apply for patients with PA remains to be explored. The present study aimed at exploring the sex-specific associations of PA with LV hypertrophy and LV myocardial function.

Materials and methods

Study population

We recruited consecutively 109 patients diagnosed with PA at Haukeland University hospital between

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2013 and 2016. In patients with elevated aldosterone-to-renin ratio, PA was confirmed by recumbent saline infusion testing, with a positive test defined as post-infusion plasma aldosterone level > 140 pmol/L [16]. Adrenal vein sampling, under continuous cosyntropin infusion, was performed for subtype differentiation at time of study inclusion. Unilateral disease was found in 47%, with no difference between sexes. Interfering medication was withdrawn for 2–4 weeks before diagnostic assessments. Controls were identified among patients with EH that participated in the FAT-associated CardiOvasculaR dysfunction (FATCOR study), another study cohort established at the European Society of Hypertension Excellence Centre in Bergen [17]. EH and PA patients were matched for sex, presence of obesity and age within a five-year range. The study was conducted in accordance with the Declaration of Helsinki and approved by the Regional Ethics Committee. All participants signed written informed consent before inclusion.

Cardiovascular risk assessment

Attended clinic BP was measured in triplets in the seated position after at least 5 min rest, using a calibrated aneroid sphygmomanometer, in accordance with current guidelines [2]. Clinic BP was taken as the average of the two last measurements. Obesity was identified as body mass index (BMI) $\geq$30.0 kg/m^2. Diabetes mellitus was considered present if history of diabetes mellitus or haemoglobin (Hb) A1c >6.5% was found. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation [18]. Hypokalaemia was considered present in the individual patients if serum potassium <3.5 mmol/L, or the patient was taking potassium supplementation.

Echocardiography

All patients underwent conventional and two-dimensional speckle tracking echocardiography following a standardised imaging protocol using a GE Vivid E9 scanner (GE Vingmed Ultrasound, Horten, Norway). In the PA group, echocardiography was performed as soon as a conclusive diagnosis was reached. Images were analysed in the Echocardiography Core Laboratory at the University of Bergen, Bergen, Norway, on workstations equipped with Image Arena Software version 4.2 (TomTec Imaging systems GmbH, Unterschleissheim, Germany) for conventional measurements. All images were read by a junior investigator and proofread by a single expert reader following current guidelines for chamber quantification [19]. LV hypertrophy was identified by validated prognostic sex-specific cut-off values for LV mass index (>47.0 g/m$^{2.7}$ in women and >50.0 g/m$^{2.7}$ in men), as recommended in the current guidelines on management of arterial hypertension [2]. Relative wall thickness was calculated from posterior wall thickness/LV internal radius ratio and considered increased if >0.42 (19]. LV geometry was defined from relative wall thickness and LV mass index in combination. Concentric remodelling was defined as increased relative wall thickness with normal LV mass index, while concentric LV hypertrophy was defined as increased relative wall thickness and increased LV mass index. Eccentric LV hypertrophy was defined as increased LV mass index with normal relative wall thickness [19]. LV ejection fraction was calculated using biplane method and discs summation (modified Simpson's rule) [19]. Midwall shortening was calculated by validated equations [20]. LV filling pressure was estimated from the ratio of early transmitral filling velocity(*E*) to the average of septal and lateral early diastolic mitral annular plane velocity (*e*') ratio (*E*/*e*' ratio) [21].

Workstations equipped with EchoPac software version BT202 (GE Vingmed Ultrasound, Horten, Norway) were used for two-dimensional speckle tracking echocardiography. The average value of peak systolic global longitudinal strain (GLS) was calculated from 17 individual LV segments based on three apical imaging planes using automatic function imaging. The endocardial border was tracked automatically and adjusted manually when considered suboptimal by visual assessment. Segments with inadequate tracking were excluded. End-systole was defined by aortic valve closure using pulse wave Doppler. In 13 patients average GLS could not be calculated, because two or more segments were not adequately tracked in the same view.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 26 software (IBM, Armonk, NY). Data is reported as mean and standard deviation for continuous variables and as percentages for categorical variables. The study compared PA and EH groups and was further divided into four subgroups: PA women, PA men, EH women and EH men. Groups are compared with un-paired t-tests and chi square tests, and with

one-way analysis of variance (ANOVA) with Scheffe's *post-hoc* test for continuous variables and general linear model with Sidak's post hoc test for categorical variables as appropriate. Uni- and multivariable logistic regression analyses were used to assess the association of PA with presence of LV hypertrophy in the total study population and separately in women and men. All variables with a significant univariable association were included in the multivariable models. Results from logistic regression analyses are reported as odds ratio with corresponding 95% confidence intervals and p values. Uni- and multivariable linear regression analyses were used to assess the association of PA with LV systolic myocardial function measured by GLS and midwall shortening in the total study population and separately in women and men. In the primary multivariable models for GLS and midwall shortening, we adjusted for clinical variables with significant univariable associations. In secondary models, echocardiographic variables with significant univariable associations were added as covariables. Collinearity tools were used to document sound statistics. Results from linear regression analyses are reported as standardised β-coefficients and p values. Statistical significance was defined as $p < 0.05$ in all analysis. The study had statistical power to identify differences in prevalence of LV hypertrophy in sex-specific analysis ($\beta = 80\%$ and $\alpha < 0.05$).

Results

Clinical characteristics

In the total study population PA patients were older, had higher systolic BP, lower BMI and lower renal function compared to EH patients (Table 1). PA men were older and had lower renal function than EH men, while PA women and EH women had similar baseline characteristics (Table 1). Seventy-four percent of PA patients had hypokalaemia, with no difference between sexes ($p = 0.680$).

Echocardiographic characteristics

PA patients had higher prevalence of abnormal LV geometry than EH patients (Figure 1). LV hypertrophy was more common in PA than EH patients both in women (41 vs. 10%) and men (57 vs. 27%, both $p < 0.05$). In the total population women had lower prevalence of LV hypertrophy than men (26 vs 44%, $p = 0.012$). In PA patients with LV hypertrophy, eccentric LV hypertrophy was the domination type in both sexes (71% in women and 60% in men). LV systolic myocardial function assessed by GLS was similar in PA and EH patients in the total study population, but GLS was lower in men than in women in both groups (Table 2). Midwall shortening was significantly lower in PA men than EH men (14.0 vs. 15.4%, $p = 0.023$), but did not differ in women (Table 2).

Factors associated with LV hypertrophy in women and men

In univariable analysis, LV hypertrophy was associated with PA, male sex, age, obesity, higher systolic BP and lower eGFR in the total study population, while no association with HbA1c was found (Table 3). With exception of male sex and eGFR, these factors remained associated with presence of LV hypertrophy in multivariable analysis (Table 3). In sex-specific analyses, PA was associated with LV hypertrophy in both sexes independent of a significant association with obesity (Table 3).

Table 1. Characteristics of women and men with PA compared to EH.

	All ($n = 198$)			Women ($n = 65$, 33%)			Men ($n = 133$, 67%)		
Variable	PA ($n = 109$)	EH ($n = 89$)	P Value	PA ($n = 34$)	EH ($n = 31$)	p Value	PA ($n = 75$)	EH ($n = 58$)	p Value
Age (years)	57 ± 11	53 ± 9	0.010	52 ± 12	51 ± 10	0.985	60 ± 10*	55 ± 7	0.048
BMI (kg/m^2)	29.9 ± 5.3	31.7 ± 3.7	0.008	28.2 ± 5.8	31.1 ± 3.7	0.099	30.6 ± 4.9	32.0 ± 3.7	0.423
Obesity (%)	47	56	0.189	38	39	0.999	51	66	0.342
Current smoking (%)	19	13	0.242	23	15	0.993	17	11	0.918
Diabetes mellitus (%)	18	14	0.439	6	7	0.999	23	17	0.937
HbA1c (%)	5.6 ± 0.8	5.8 ± 0.7	0.083	5.4 ± 0.7	5.7 ± 0.4	0.588	5.7 ± 0.8	5.9 ± 0.8	0.628
Antihypertensive drugs (n)	2.6 ± 1.2	0.7 ± 1.0	<0.001	2.0 ± 1.0	0.4 ± 0.8	<0.001	2.8 ± 1.3*	0.9 ± 1.1	<0.001
Serum sodium (mmol/L)	141 ± 2	141 ± 2	0.448	141 ± 2	141 ± 2	0.977	142 ± 2	141 ± 2	0.706
Serum potassium (mmol/L)	3.6 ± 0.4	4.4 ± 0.3	<0.001	3.6 ± 0.4	4.4 ± 0.3	<0.001	3.6 ± 0.4	4.5 ± 0.3	<0.001
Hypokalaemia (%)	74	0	–	68	0	–	77	0	–
Serum creatinine (umol/L)	91 ± 58	74 ± 13	0.006	76 ± 67	67 ± 11	0.860	98 ± 53	77 ± 12	0.071
eGFR (ml/min/1.73m^2)	85 ± 25	93 ± 13	0.004	92 ± 24	91 ± 13	0.999	82 ± 24	95 ± 13	0.005
Clinic SBP (mmHg)	148 ± 19	141 ± 17	0.005	147 ± 16	139 ± 20	0.400	149 ± 19	142 ± 15	0.195
Clinic DBP (mmHg)	87 ± 12	87 ± 9	0.781	89 ± 12	86 ± 10	0.782	87 ± 12	87 ± 10	0.990

PA: primary aldosteronism; EH: essential hypertension; BMI: body mass index; HbA1c: haemoglobin A1c; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure.
*$p < 0.05$ vs. PA women; †$p < 0.05$ vs. EH women.

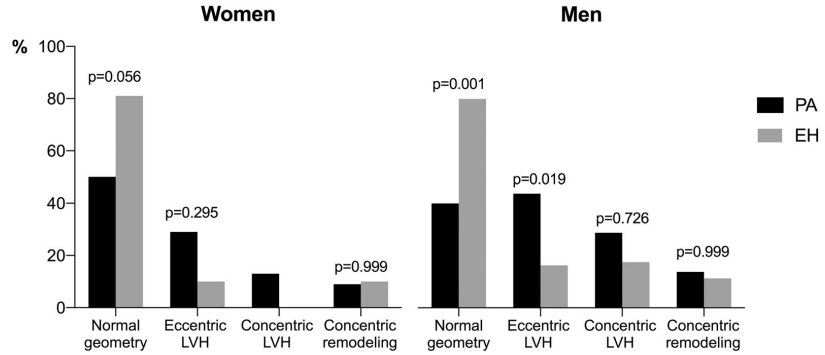

Figure 1. LV geometric patterns in women and men with PA compared to EH.

Table 2. Echocardiographic findings in women and men with PA compared to EH.

	All ($n = 198$)			Women ($n = 65$)			Men ($n = 133$)		
Variable	PA ($n = 109$)	EH ($n = 89$)	p Value	PA ($n = 34$)	EH ($n = 31$)	p Value	PA ($n = 75$)	EH ($n = 58$)	p Value
LVIDd (cm)	5.0 ± 0.6	5.0 ± 0.5	0.816	4.9 ± 0.6	4.8 ± 0.4	0.980	5.1 ± 0.6	5.1 ± 0.4	0.999
IVSd (cm)	1.3 ± 0.3	1.2 ± 0.3	0.001	1.2 ± 0.3	1.1 ± 0.2	0.557	1.4 ± 0.3*	1.3 ± 0.3†	0.035
PWTd (cm)	1.0 ± 0.2	0.9 ± 0.2	<0.001	0.9 ± 0.1	0.8 ± 0.1	0.299	1.0 ± 0.2*	0.9 ± 0.2	0.005
LV mass index (g/m$^{2.7}$)	50.2 ± 12.8	42.2 ± 10.6	<0.001	44.7 ± 11.4	38.8 ± 6.0	0.236	52.7 ± 12.6*	44.1 ± 12.2	0.001
Relative wall thickness	0.40 ± 0.09	0.36 ± 0.08	0.001	0.37 ± 0.08	0.34 ± 0.06	0.556	0.41 ± 0.10	0.36 ± 0.09	0.029
Normal LV geometry (%)	38	70	<0.001	50	81	0.056	32	64	0.001
LVH (%)	52	21	<0.001	41	10	0.037	57	27	0.002
LV ejection fraction (%)	62 ± 6	62 ± 5	0.712	65 ± 5	63 ± 4	0.485	61 ± 6*	62 ± 5	0.968
GLS average	−17.8 ± 3.4	−18.5 ± 3.5	0.175	−19.2 ± 3.1	−20.1 ± 3.3	0.820	−17.1 ± 3.3*	−17.6 ± 3.4†	0.870
Midwall shortening (%)	14.8 ± 2.7	15.9 ± 2.7	0.004	16.4 ± 2.6	16.8 ± 2.7	0.932	14.0 ± 2.3*	15.4 ± 2.6	0.023
E/*e*'	10.1 ± 2.9	8.3 ± 3.3	<0.001	9.9 ± 3.4	8.0 ± 3.2	0.108	10.2 ± 2.7	8.5 ± 3.4	0.028
LA volume index (ml/m^2)	19.6 ± 6.7	19.4 ± 5.6	0.872	17.6 ± 4.6	18.9 ± 6.0	0.879	20.5 ± 7.3	19.8 ± 5.4	0.928

LVIDd: left ventricular internal diameter at end-diastole; IVSd: interventricular septum thickness at end-diastole; PWTd: posterior wall thickness at end-diastole; LVH: left ventricle hypertrophy; *E*/*e*': peak early transmitral filling velocity to the average of septal and lateral early diastolic mitral annular plane velocity; GLS: global longitudinal strain; LA: left atrium.
*$p < 0.05$ vs. PA women; †$p < 0.05$ vs. EH women.

Table 3. The association of PA with LVH in the total study population, and in women and men separately.

Variable	Total population		Women		Men	
	Univariable OR (95% CI)	Multivariable OR (95% CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Primary aldosteronism	4.14(2.18–7.86)†	4.09(1.96–8.54)†	6.53(1.65–25.8)*	6.88(1.45–32.63)*	3.58(1.69–7.58)*	3.46(1.49–7.99)*
Male sex	2.28(1.19–4.37)†	1.62(0.72–3.64)	n.i.m.	n.i.m.	n.i.m.	n.i.m.
Age	1.06(1.03–1.10) †	1.06(1.01–1.11)*	1.06(1.00–1.12)*	1.07(0.99–1.14)	1.06(1.02–1.11)*	1.05(0.99–1.12)
BMI (kg/m^2)	1.08(1.01–1.15)*	n.i.m.	1.08(0.97–1.21)	n.i.m.	1.06(0.98–1.15)	n.i.m.
Obesity	1.90(1.05–3.41)*	3.13(1.50–6.53)*	3.14(1.00–9.85)*	5.41(1.24–23.66)*	1.36(0.68–2.74)	2.34(1.02–5.37)*
Clinic SBP (mmHg)	1.03(1.01–1.05)*	1.02(1.00–1.05)*	1.03(1.00–1.07)	1.03(0.99–1.07)	1.03(1.01–1.05)*	1.02(1.00–1.04)
eGFR (ml/min/1.73m^2)	0.99(0.97–1.00)*	1.01(0.99–1.03)	0.99(0.96–1.02)	n.i.m.	0.99(0.97–1.00)*	1.01(0.98–1.03)
HbA_{1c} (%)	1.10(0.73–1.64)	n.i.m.	0.92(0.34–2.54)	n.i.m.	1.04(0.66–1.64)	n.i.m.

CI: confidence interval; BMI: body mass index; SBP: systolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: Haemoglobin A1c; n.i.m.: not in model.
*$p < 0.05$; †$p < 0.01$.

Factors associated with LV myocardial function in women and men

In univariable analysis, lower midwall shortening was associated with PA, male sex, higher age, systolic BP, *E*/*e*' ratio and LV mass index and with lower eGFR and LV ejection fraction in the total study population (all $p < 0.05$). In the primary multivariable model, including clinical covariables, lower midwall shortening remained associated with male sex ($\beta = 0.29$) and higher systolic BP ($\beta = 0.15$, both $p < 0.05$), while the association with PA became statistically not significant. In sex-specific analysis, including clinical covariables, lower midwall shortening was associated with higher systolic BP in women ($\beta = 0.26$, $p < 0.05$), whereas no covariables in the model were significantly associated with midwall shortening in men. In a second multivariable model we

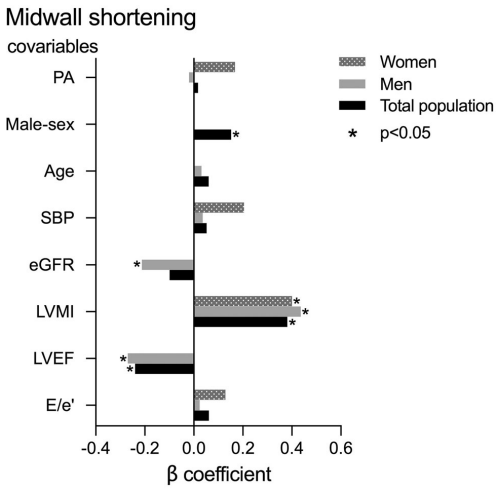

Figure 2. The association of PA with lower midwall shortening in the total study population, and in women and men separately.

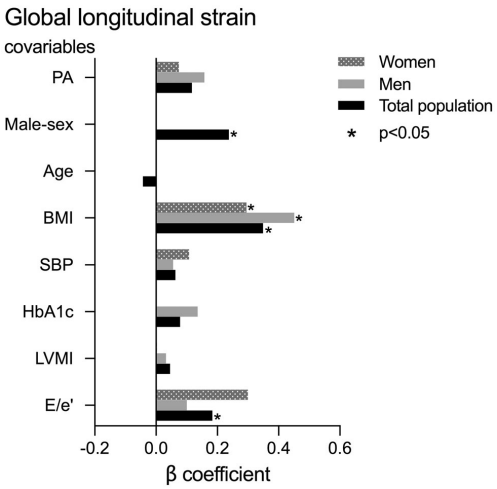

Figure 3. The association of PA with lower GLS in the total study population, and in women and men separately.

adjusted also for LV mass index, *E*/*e*' ratio and LV ejection fraction. In this second model, no significant association of PA with midwall shortening was found. However, lower midwall shortening was associated with male sex, higher LV mass index and lower LV ejection fraction in the total study population, with higher LV mass index and lower LV ejection fraction and eGFR in men, and with higher LV mass index in women. (all $p < 0.05$; Figure 2).

PA was not associated with GLS neither in univariable nor in multivariable analysis. In univariable analysis, lower GLS was associated with male sex, higher age, BMI, systolic BP, HbA_{1c}, LV mass index and *E*/*e*' ratio in the total study population (all $p < 0.05$). In the primary model adjusting for clinical variables, only male sex ($\beta = 0.23$) and higher BMI ($\beta = 0.38$, both $p < 0.05$) remained associated with GLS. In sex-specific analysis adjusting for clinical variables, higher BMI ($\beta = 0.47$, $p < 0.001$) was the only significant covariable for GLS in men, while no covariables were significantly associated with lower midwall shortening in women. In a second multivariable model additionally adjusting for LV mass index and *E*/*e*' ratio, lower GLS was associated with male sex, higher BMI and *E*/*e*' ratio in the total study population, while higher BMI was the main covariable of lower GLS in sex-specific analyses (all $p < 0.05$; Figure 3).

Discussion

This study adds to previous knowledge by demonstrating that PA, as compared to EH, is associated with higher prevalence of LV hypertrophy both in women and men. However, PA was not associated with lower LV systolic myocardial function whether measured by GLS or midwall shortening in either sex.

In line with previous reports, prevalence of LV hypertrophy was higher in PA than EH [7,22,23]. However, the predominate type of LV hypertrophy varied in previous studies comparing LV geometry in PA and EH [10]. Salvetti et al. recently reported higher prevalence of concentric LV hypertrophy in PA [22], whereas Yang et al. reporting sex-specific results, found a higher prevalence of eccentric LV hypertrophy in PA women, but not in men [24]. In our cohort, eccentric LV hypertrophy was the dominating type in PA in both sexes. The independent association of PA with presence of LV hypertrophy in sex-specific multivariable analysis in our study, supports that aldosterone excess contributed to LV hypertrophy both in women and men [25]. However, independent of hypertension aetiology, obesity was strongly associated with LV hypertrophy in both sexes, in line with previous reports in EH [26,27]. Previous reports in larger EH studies have demonstrated that LV hypertrophy is more common in women [11,12]. This was not found in the present smaller cohort, possibly related to women being younger and less obese than women in previous studies. Furthermore, there is evidence that oestrogen inhibits synthesis of aldosterone in women [28]. Oestrogen has been found to attenuate cardiac hypertrophy and fibrosis in studies both in humans and mice [3]. Thus, we can speculate that a protective effect of oestrogen may

contribute to the observed lower prevalence of LV hypertrophy in women in our cohort. However, serum oestrogen was not measured in the present study.

Previous reports comparing LV systolic myocardial function by midwall shortening in PA and EH have yielded diverging results, some reporting lower midwall shortening in PA compared to EH [7,29], whereas others found no difference [8,30]. However, none of these studies reported sex-specific results. Thus, the present study adds to previous knowledge by demonstrating that although midwall shortening was lower in PA men than in EH men, midwall shortening did not differ between PA and EH women, and PA was not associated with lower midwall shortening in the multivariable models. PA women had lower LV mass index than PA men, which may explain why midwall shortening was less deteriorated in PA women [20]. However, independent of hypertension aetiology, higher systolic BP was associated with lower midwall shortening, in line with previous publications [14,27].

GLS is a measure of LV longitudinal myocardial function which has been associated with presence and extent of myocardial fibrosis assessed by gadolinium enhanced cardiac magnetic resonance imaging [31]. Few PA studies have reported LV systolic myocardial function by GLS. Two smaller studies demonstrated lower GLS in PA than EH [23,32]. In contrast, we found comparable GLS in PA and EH, both in women and men, in the present study. The association between obesity and lower GLS is well demonstrated, particularly when hypertension co-exists [27,33], as also demonstrated in the present study for both sexes. However, EH controls had higher BMI than PA, which may have reduced GLS particularly in the EH group. Our finding of comparable GLS in PA and EH groups may also be explained by a low prevalence of myocardial fibrosis in the PA patients in our cohort, as demonstrated in a sub study of 32 PA patients who underwent cardiac magnetic resonance imaging with late gadolinium enhancement or T1 mapping, and who did not have increased myocardial fibrosis compared to healthy subjects [34]. In line with previous reports in EH, midwall shortening and GLS were both higher in women than in men with PA, and male sex was independently associated with lower midwall shortening and GLS in multivariable analysis in the total population [14,15].

Study limitations

There are several limitations to this study. First, the EH and PA patients were not matched for BP values, and duration of hypertension was not known. Furthermore, the clinic BP in the PA group may have been influenced by the routine change of BP medications during the diagnostic work up, and therefore not reflect the individual BP burden preceding the diagnostic work up. The underrepresentation of women in our study cohort is another important limitation, and type 2 error may be present, since power calculation was solely based upon prevalence of LV hypertrophy.

Disclosure statement

The authors declare no conflict of interest.

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III

Original Article

OPEN

Persistent cardiac organ damage in surgically and medically treated primary aldosteronism

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Objective: We compared persistent cardiac organ damage in patients treated surgically or medically for primary aldosteronism.

Methods: Eighty-four patients (age 57 ± 11 years, 27% women) with primary aldosteronism underwent echocardiography at time of diagnosis and after one year of treatment (49% adrenalectomy, 51% medical treatment). Persistent cardiac organ damage was defined as presence of left ventricle (LV) hypertrophy, low LV midwall shortening, global longitudinal strain and/or enlarged left atrium both at baseline and at follow-up.

Results: At one year, a significant regression of LV hypertrophy was observed in surgically (44 vs. 22%, $P = 0.039$), but not in medically treated patients (60 vs. 51%, $P = 0.206$). The prevalence of enlarged left atrium was reduced in both groups (both $P < 0.001$), whereas systolic myocardial function remained unchanged. In multivariable logistic regression analysis, medical treatment [odds ratio (OR) 4.88 (95% confidence interval (CI) 1.26–18.88)] was a strong predictor of persistent LV hypertrophy independent of higher BMI [OR 1.20 (95% CI 1.04–1.38)] and presence of diabetes [OR 6.48 (95% CI 1.20–34.83), all $P < 0.05$]. Persistently low midwall shortening was associated with suppressed plasma renin after one year [OR 6.11 (95% CI 1.39–26.7)] and lower renal function [OR 0.96 (95% CI 0.94–0.99), both $P < 0.05$]. The strongest predictor of persistently low global longitudinal strain was higher HbA_{1c} [OR 2.37 (95% CI 1.12–5.02), $P = 0.024$].

Conclusion: Persistent cardiac organ damage was more common in the medical treatment group and associated with incomplete aldosterone blockade, impaired renal function and presence of metabolic comorbidities.

Graphical abstract: http://links.lww.com/HJH/B925.

Keywords: cardiac organ damage, global longitudinal strain, hypertension, left ventricle hypertrophy, midwall shortening, obesity, primary aldosteronism

Abbreviations: ARR, aldosterone–renin ratio; DDD, defined daily dose; *E*/*e*′, peak early transmitral filling velocity to the average of septal and lateral early diastolic annular plane velocity; GLS, global longitudinal strain; MRA, mineralocorticoid receptor antagonist; PASO, primary aldosteronism surgical outcome; SIT, saline infusion testing

INTRODUCTION

Primary aldosteronism is the most common cause of secondary hypertension [1], and is associated with increased cardiovascular risk independent of the effect of blood pressure (BP) [2]. Unilateral forms of primary aldosteronism are effectively treated with surgical adrenalectomy, whereas medical treatment including mineralocorticoid receptor antagonist (MRA) is recommended in bilateral forms and in patients with unilateral forms unsuited for surgery [3].

Cardiac organ damage is well documented as a precursor of clinical cardiovascular events in essential hypertension [4–7]. In primary aldosteronism, this has in particular been demonstrated for left ventricular (LV) hypertrophy, which is highly prevalent [8–10]. However, although most studies on primary aldosteronism have focused exclusively on LV hypertrophy, some studies have shown that also left atrial enlargement, a risk factor for atrial fibrillation and stroke, and LV myocardial dysfunction, a precursor of heart failure, are common types of cardiac organ damage in primary aldosteronism [8–10]. An essential goal of specific treatment in primary aldosteronism is to prevent cardiovascular complications, and thus regression of cardiac organ damage is crucial [11].

However, it is still debated whether surgery and medical treatment are equally effective in reducing cardiac organ damage. Rossi *et al.* [12] found a significant decrease in LV mass index in surgically treated, but not in medically treated patients, with no difference in the changes observed at one-year and long-term follow-up. In contrast, a meta-analysis including a total of 335 patients found both treatments equally effective in reducing LV mass index [13]. Further-more, during long-term follow-up, a higher incidence of atrial fibrillation in medically than in surgically treated patients with

Journal of Hypertension 2022, 40:1204–1211

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Received 18 November 2021 **Revised** 3 February 2022 **Accepted** 23 February 2022

DOI:10.1097/HJH.0000000000003135

primary aldosteronism was reported [14]. In the present study, we explored factors associated with persistent cardiac organ damage of different types in relation to surgical and medical treatment of primary aldosteronism.

MATERIALS AND METHODS

Study population

We recruited 109 consecutive patients diagnosed with primary aldosteronism at the endocrinology outpatient clinic at Haukeland University Hospital between 2013 and 2016 [10]. Twenty-five patients underwent follow-up visits at hospitals outside our health region, leaving a total of 84 patients in this prospective follow-up study.

Primary aldosteronism was confirmed by recumbent saline infusion testing (SIT), and subtype differentiation was done by cosyntropin-stimulated adrenal vein sampling in all patients, as previously described, and in accordance with current guidelines [3,10]. Interfering antihypertensive medication was withdrawn and replaced by noninterfering medication (primarily doxazosin and/or verapamil) 2–4 weeks prior to diagnostic work up at baseline. Almost one-third of the patients, equally distributed between treatment groups, had been treated with MRA prior to study inclusion, with a median treatment duration of 7 months. Patients with hypokalemia received oral potassium supplementation. Out of 42 patients diagnosed with unilateral primary aldosteronism, 41 underwent adrenalectomy, whereas one patient refused surgery and was offered medical treatment. The remaining 42 patients were diagnosed with bilateral primary aldosteronism. In the surgical treatment group 66% had adenoma and 34% had hyperplasia confirmed by biopsy. All participants provided written informed consent, and the study was approved by the Regional Ethics Committee (REK 2013-742).

Cardiovascular risk assessment

Attended clinic BP was measured in triplicates in the seated position after at least 5 min of rest, using a calibrated aneroid sphygmomanometer, in accordance with current guidelines [15]. Clinic BP was taken as the average of the two last measurements. Antihypertensive treatment is reported as number of antihypertensive drugs and as defined dailydose (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication in adults. Obesity was defined as BMI at least 30.0 kg/m^2. Diabetes mellitus was considered present if a history of diabetes mellitus or hemoglobin A_{1c} (HbA_{1c}) more than 6.5% was found at baseline. Atrial fibrillation was considered present if a history of atrial fibrillation or atrial fibrillation documented on the baseline electrocardiogram was found in the individual patient. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation. Hypokalemia was defined as serum potassium less than 3.5 mmol/l or use of potassium supplementation drugs in the individual patients. In February 2016 the renin-essay in our local laboratory was changed from plasma renin activity (Gammacoat; DiaSorin, Saluggia, Italy) to direct plasma renin concentration (LIAISON Direct Renin; DiaSorin), and therefore plasma renin activity was measured in 80% of patients at baseline and in 50% of patients at one-year follow-up, whereas the remaining patients had direct plasma renin concentration measured.

Follow-up

All participants were followed up with a clinical visit one year after surgery or initiation of MRA. Complete, partial or absence of biochemical and clinical curation of primary aldosteronism one year after adrenalectomy was defined according to the primary aldosteronism surgical outcome (PASO)-criteria, based on BP, use of antihypertensive drugs, plasma potassium, aldosterone-renin ratio (ARR) and post-surgery SIT if ARR was persistently elevated [15]. Plasma renin was considered persistently low after treatment if plasma renin activity was less than 0.5 μg/l per h or plasma renin concentration less than 4.4 mIE/l at the one-year visit.

Echocardiography

Conventional and two-dimensional speckle tracking echocardiography were performed following a standardized imaging protocol using a GE Vivid E9 scanner (GE Vingmed Ultrasound, Horten, Norway). Images were postprocessed in the Echocardiography Core laboratory at the University of Bergen, Norway, on workstations equipped with Image Arena Software version 4.2 (TomTec Imaging Systems GmbH, Unterschleißheim, Germany) for conventional measurements and EchoPac software version BT202 (GE Vingmed Ultrasound) for two-dimensional speckle tracking echocardiography as previously reported [10]. Images were analyzed by the same investigator and proofread by a single expert reader following current guidelines for chamber quantification [16]. LV hypertrophy was identified by validated prognostic sex-specific cutoff values for LV mass index (>47.0 g/m$^{2.7}$ in women and >50.0 g/m$^{2.7}$ in men) [15]. Relative wall thickness (RWT) was calculated as 2× posterior wall thickness/LV internal diameter at end diastole [16]. Concentric remodeling, concentric LV hypertrophy and eccentric LV hypertrophy was defined from RWT and LV mass index in combination [16]. Circumferential LV systolic myocardial function was assessed bymidwall shortening, calculated by validated equations, and considered low if less than 16% in women and less than 14% in men [17]. Longitudinal LV systolic myocardial function was assessed by peak systolic global longitudinal strain (GLS) and was calculated from 17 individual LV segments based on apical imaging planes with frame rate more than 50 fps using Automatic Function Imaging. The endocardial border was tracked automatically by the program and adjusted manually when needed. End-systole was defined by aortic valve closure using pulsed wave Doppler. In eight patients average GLS could not be calculated due to low image quality. GLS was considered low if more than −18.5% in women and more than −16.9% in men [18]. LV filling pressure was estimated from the ratio of early (E) transmitral filling velocity to the average of septal and lateral early diastolic mitral annular plane velocity (e') ratio (E/e' ratio) [19]. Left atrial systolic volume was measured with the biplane Simpson's method using apical four and two chambers view [16], indexed for height^2 and considered enlarged if at least 16.5 ml/m^2 in women and at least 18.5 ml/m^2 in men [15].

Cardiac organ damage was defined by presence of LV hypertrophy, low midwall shortening, low GLS and/or enlarged left atrium, and was defined as persistent when present both at baseline and at one-year follow-up.

Statistical analysis

The study cohort was grouped by treatment, that is, surgical vs. medical treatment of primary aldosteronism. Continuous variables are expressed as mean ± SD when normally distributed and as median with interquartile range for nonnormally distributed data. Categorical variables are expressed as absolute numbers and percentages. Differences between groups were tested by student's unpaired *t* tests for normally distributed continuous variables and Mann–Whitney *U* test for those nonnormally distributed, whereas Pearson's chi-square was used for categorical variables. Within group changes during follow-up were tested with paired samples *t* tests for normally distributed continuous variables and with Wilcoxon signed-rank tests for those nonnormally distributed, whereas uncorrected McNemar tests were used for categorical variables. Univariable and multivariable logistic regression analyses were used to identify factors independently associated with persistent LV hypertrophy, persistently low LV midwall shortening, persistently low LV GLS and persistently enlarged left atrium after treatment. Variables with univariable associations (*P* less than 0.10) and variables with known clinical significance (age, sex, BMI, SBP at baseline and at follow-up, persistently suppressed plasma renin) were included in multivariable stepwise forward regression analyses, and variables that remained significant were included in the final models. In the primary multivariable models (Model 1), we included baseline variables only, whereas follow-up variables were added in secondary models (Model 2). Results from logistic regression analyses are reported as odds ratio (OR) with corresponding 95% confidence intervals (CIs) and *P* values. Reproducibility of measurements of LV mass and midwall shortening was assessed by intraclass correlation coefficients. Statistical significance was defined as Pless than 0.05 unless otherwise is indicated. The study had 80% statistical power to identify 35% differences in prevalence of persistent LV hypertrophy between treatment groups at one-year follow-up with a less than 0.05.

RESULTS

Baseline characteristics

The total study population consisted of 84 patients with primary aldosteronism, 27% women, mean age 56 ± 11 years. The prevalence of diabetes and mean HbA_{1c} was higher in the surgical treatment group ($n = 41$) than in the medical treatment group ($n = 43$), whereas there was no significant difference in duration of hypertension, SBP or DBP, DDD of BP-medication, BMI, renal function or prevalence of atrial fibrillation at baseline (Table 1). The surgical treatment group had higher plasma aldosterone levels and higher prevalence of hypokalemia than the medical treatment group (Table 1).

The prevalence of LV hypertrophy did not differ significantly between groups at baseline, and the majority of patients had enlarged left atrium in both groups (Table 2). The medical treatment group had lower LV midwall shortening, whereas LV GLS did not differ (Table 2).

Changes in clinical characteristics during follow-up

A marked decrease in BP occurred in both groups during follow-up (Table 1). The DDD of BP treatment was significantly reduced in the surgical treatment group at follow-up, but not in the medical treatment group (Table 1). In the surgical treatment group, complete biochemical success was achieved in 85%, and clinical success in 27% of patients using the PASO criteria (Fig. 1). At the one-year follow-up persistently suppressed plasma renin was present in 23% of patients in the medical treatment group, compared with in 5% in the surgery treatment group ($P = 0.016$).

Changes in cardiac organ damage during follow-up

LV mass index decreased in both groups, but a significant reduction in prevalence of LV hypertrophy was only seen after surgery (Table 2, Fig. 2). A reduction in LV inner diameter and an increase in RWT were observed in both groups (Table 2). LV myocardial dysfunction remained common in both groups at one-year follow-up (Table 2). In contrast, the prevalence of enlarged left atrium was reduced by two-thirds at follow-up in both groups (Table 2). E/e' decreased in the two groups (Table 2).

The prevalence of any persistent cardiac organ damage was higher in medically treated patients at one-year follow-up (Fig. 3). In particular, persistent LV hypertrophy was more prevalent in medically treated patients, whereas the prevalences of persistently low LV midwall shortening, persistently low LV GLS and persistent enlarged left atrium did not differ significantly between treatment groups.

The intraobserver reproducibility for LV mass [interclass correlation 0.88 (95% CI 0.71–0.95)] and midwall shortening [interclass correlation 0.91 (95% CI 0.80–0.96) both $P < 0.001$] was good.

Factors associated with persistent cardiac organ damage at one-year follow-up

Left ventricle hypertrophy

In univariable logistic regression analysis, persistent LV hypertrophy was associated with medical treatment of primary aldosteronism, older age, longer duration of hypertension, concomitant diabetes mellitus, higher SBP pre and posttreatment, higher DDD of BP treatment and higher BMI at baseline, and with higher pulse pressure, lower eGFR and low plasma renin at the final visit (all $P < 0.10$) (Table S1, http://links.lww.com/HJH/B921). In stepwise multivariable logistic regression analysis including the baseline covariables, persistent LV hypertrophy was associated with medical treatment of primary aldosteronism independent of significant associations with higher age and BMI and presence of diabetes mellitus (Model 1, Table 3). When significant variables at follow-up were added to the model, also higher pulse pressure was identified as an independent covariate of persistent LV hypertrophy (Model 2, Table 3). Additional adjustment for plasma aldosterone concentration at baseline did not change the results. When analyzing the treatment groups separately, persistent LV hypertrophy was associated with baseline post-SIT aldosterone

TABLE 1. Clinical characteristics at baseline and at one-year follow-up in 84 patients treated surgically or medically for primary aldosteronism.

	Surgery, $n = 41$			Medical treatment, $n = 43$		
	Baseline	One Year	*P* value	Baseline	One Year	*P* value
Female, *n* (%)	13 (32)			10 (23)		
Age (years)	54 ± 11			58 ± 10		
Duration of hypertension (years)	11.8 ± 8.0			15.2 ± 10.3		
Diabetes mellitus, *n* (%)	2 (5)	3 (7)	1.000	9 (21)*	9 (21)	1.000
Atrial fibrillation, *n* (%)	5 (12)	5 (12)	1.000	4 (9)	4 (9)	1.000
BMI (kg/m^2)	29.2 ± 4.3	28.1 ± 3.7	0.013	30.6 ± 6.3	31.1 ± 6.9**	0.518
Obesity, *n* (%)	15 (39)	12 (32)	0.375	22 (55)	21 (52)	1.000
SBP (mmHg)	145 ± 16	128 ± 14	<0.001	151 ± 20	132 ± 18	<0.001
DBP (mmHg)	87 ± 10	81 ± 9	0.009	89 ± 12	81 ± 12	<0.001
Pulse pressure (mmHg)	58 ± 11	47 ± 13	<0.001	62 ± 18	51 ± 15	<0.001
Controlled hypertension, *n* (%)	20 (51)	31 (79)	0.016	19 (45)	34 (81)	<0.001
Antihypertensive drugs, *n*	2.9 ± 1.1	1.5 ± 1.3	<0.001	3.3 ± 1.6	3.4 ± 1.6**	0.472
Antihypertensive drugs (DDD)	3.4 ± 1.8	1.5 ± 1.6	<0.001	4.0 ± 2.7	4.2 ± 2.0**	0.780
ACEi or ARBs (%)	26 (63)	14 (34)	0.004	32 (74)	26 (60)**	0.109
Calcium channel blocker (%)	37 (90)	17 (41)	<0.001	36 (84)	31 (72)**	0.063
Diuretic (%)	11 (27)	4 (15)	0.059	22 (51)*	10 (23)	<0.001
Mineralocorticoid receptor antagonist (%)	13 (32)	3 (7)	<0.001	12 (28)	43 (100)**	<0.001
Beta blocker (%)	13 (32)	10 (24)	0.250	13 (30)	11 (26)	0.774
Alpha blocker (%)	8 (20)	5 (12)	0.250	10 (23)	10 (23)	1.000
Other antihypertensiva (%)	6 (15)	6 (15)	1.000	12 (30)	9 (21)	0.453
PAC (pmol/l)	782 (502–1177)	213 (141–294)	<0.001	467 (349–725)*	638 (476–1190)**	<0.001
Post-SIT PAC (pmol/l)	373 (289–566)	115 (70–160)	<0.001	251 (194–349)*	–	–
Plasma renin activity (μg/l per h)	0.3 (0.1–0.4)	1.5 (0.7–2.5)	<0.001	0.3 (0.1–0.7)	0.7 (0.2–5.9)	0.004
Aldosterone-to-renin ratio (pmol/μg per h)	2410 (1343–8640)	119 (75–251)	<0.001	2333 (585–4725)	1423 (220–6750)**	0.030
Plasma renin concentration (mIU/l)	6 (2–10)	13 (10–41)	<0.001	7 (3–14)	49 (17–101)**	0.012
Aldosterone-to-renin ratio (pmol/mIU)	81 (55–515)	16 (7–31)	0.012	77 (32–124)	12 (6–67)	0.012
Suppressed plasma renin, *n* (%)	27 (72)	2 (5)	<0.001	25 (60)	10 (23)**	<0.001
Creatinine (mmol/l)	74.5 (62.2–88.0)	90.0 (76.0–126.5)	<0.001	81.5 (69.0–91.0)	89.0 (75.0–109.0)	<0.001
eGFR (ml/min per 1.73 m^2)	95.8 (81.2–104.7)	76.5 (53.7–97.1)	<0.001	88.0 (75.9–101.2)	79.2 (63.2–88.8)	<0.001
Potassium (mmol/l)	3.5 ± 0.4	4.4 ± 0.4	<0.001	3.6 ± 0.4	4.2 ± 0.5	<0.001
Hypokalemia[a], *n* (%)	38 (93)	0 (0)	NA	22 (51)*	7 (16)**	<0.001
HbA_{1c} (%)	5.2 (4.9–5.5)	5.4 (5.1–5.4)	0.002	5.5 (5.3–6.0)*	5.7 (5.4–6.0)**	0.068

Data are presented as mean (±SD), median (interquartile range) or number (%). Differences between groups were tested by unpaired *t* test (normally distributed variables), Mann-Whitney *U* test (nonnormally distributed variables) and Pearsons's chi-square for categorical variables. Within group changes were tested with unpaired *t* tests (normally distributed variables), Wilcoxon signed-rank test (nonnormally distributed) and uncorrected McNemar for categorical variables. ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; BP, blood pressure; DDD, defined daily dose; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; PAC, plasma aldosterone concentration; post-SIT, post saline infusion testing.

[a]Hypokalemia was defined as serum potassium less than 3.5 mmol/l or use of potassium supplementation in the individual patients.

*$P < 0.05$ vs. surgical treatment group at baseline.

**$P < 0.05$ vs. surgical treatment group at one-year follow-up.

TABLE 2. Echocardiographic characteristics at baseline and at one-year follow-up in 84 patients, treated surgically or medically for primary aldosteronism.

	Surgery, $n = 41$			Medical treatment, $n = 43$		
	Baseline	One Year	*P* value	Baseline	One Year	*P* value
LVEDd (cm)	5.04 ± 0.49	4.67 ± 0.45	<0.001	4.99 ± 0.59	4.78 ± 0.56	0.006
IVSd (cm)	1.29 ± 0.32	1.26 ± 0.29	0.520	1.39 ± 0.29	1.34 ± 0.24	0.325
LVPWd (cm)	0.96 ± 0.21	0.97 ± 0.21	0.580	1.00 ± 0.16	1.04 ± 0.17	0.268
LV mass index (g/m$^{2.7}$)	47.4 ± 11.2	42.3 ± 11.3	0.001	52.0 ± 13.6	48.3 ± 12.3*	0.049
Relative wall thickness	0.38 ± 0.10	0.42 ± 0.10	0.031	0.40 ± 0.06	0.44 ± 0.10	0.021
LV hypertrophy, *n* (%)	18 (44)	9 (22)	0.039	26 (60)	22 (51)*	0.206
LV ejection fraction (%)	64 ± 5	65 ± 5	0.450	62 ± 6**	65 ± 4	0.002
GLS (%)	−18.3 ± 3.6	−17.2 ± 7.3	0.414	−17.4 ± 3.1	−16.9 ± 3.1	0.215
Low GLS, *n* (%)	14 (38)	16 (43)	0.564	15 (38)	18 (46)	0.439
Midwall shortening (%)	15.5 ± 2.8	15.1 ± 2.4	0.347	14.2 ± 2.0**	14.5 ± 2.8	0.495
Low midwall shortening, *n* (%)	11 (28)	15 (37)	0.285	23 (53)**	21 (49)	0.637
LV fillingpressure (*E*/*e*')	9.9 ± 3.1	8.8 ± 3.1	<0.001	10.3 ± 2.7	9.3 ± 2.6	0.005
Left atrial volume index (ml/m^2)	19.9 ± 7.7	14.7 ± 4.5	<0.001	20.1 ± 6.0	16.5 ± 8.0	<0.001
Enlarged left atrium (%)	24 (59)	17 (21)	<0.001	24 (56)	8 (18)	<0.001

Data are presented as mean (±SD), median (interquartile range) or number (%). Differences between groups were tested by unpaired *t* test (normally distributed variables), Mann-Whitney *U* test (nonnormally distributed variables) and Pearsons's chi-square for categorical variables. Within group changes were tested with unpaired *t* tests (normally distributed variables), Wilcoxon signed-rank test (nonnormally distributed) and uncorrected McNemar for categorical variables. *E*/*e*', peak early transmitral filling velocity to the average of septal and lateral early diastolic annular plane velocity; EDd, end diastolic diameter; GLS, global longitudinal strain; IVSd, interventricular septal diameter; LV, left ventricle; PWd, posterior wall diameter.

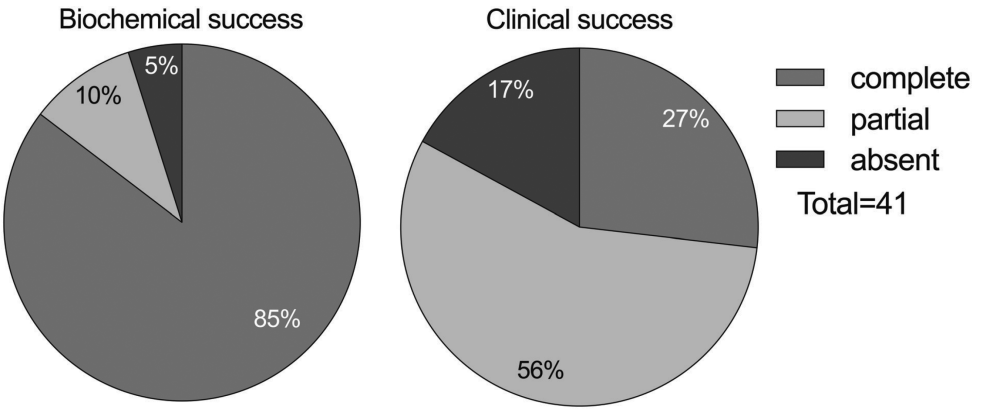

FIGURE 1 Rates of clinical and biochemical success in surgically treated patients according to the primary aldosteronism surgical outcome-criteria.

concentration [OR 1.08 (95% CI 1.01–1.14), $P = 0.020$], independent of significant associations with age, BMI and presence of diabetes mellitus in the medical treatment group. DDD of antihypertensive treatment at baseline [OR 2.10 (95% CI 1.08–4.09), $P = 0.029$] was the strongest predictor of persistent LV hypertrophy in the surgical treatment group.

Circumferential left ventricle systolic myocardial function

In univariable logistic regression analysis, persistently low LV midwall shortening was associated with medical treatment of primary aldosteronism, older age, longer duration of hypertension and lower eGFR at baseline and with suppressed plasma renin and persistent LV hypertrophy at follow-up (all $P < 0.10$) (Table S1, http://links.lww.com/HJH/B921). When including the baseline covariables in a stepwise multivariable logistic regression analysis, persistently low LV midwall shortening was associated with lower eGFR and medical treatment group (Model 1, Table 3). In a secondary model adding the follow-up variables, lower eGFR at baseline and suppressed plasma renin at the one-year visit were significant covariates of persistently low LV midwall shortening (Model 2, Table 3).

Longitudinal left ventricle systolic myocardial function

In univariable logistic regression analysis, persistently low LV GLS was associated with higher HbA_{1c}, obesity and persistent LV hypertrophy (all $P < 0.10$) (Table S1, http://links.lww.com/HJH/B921). In stepwise multivariable logistic regression analysis, only HbA_{1c} remained a significant

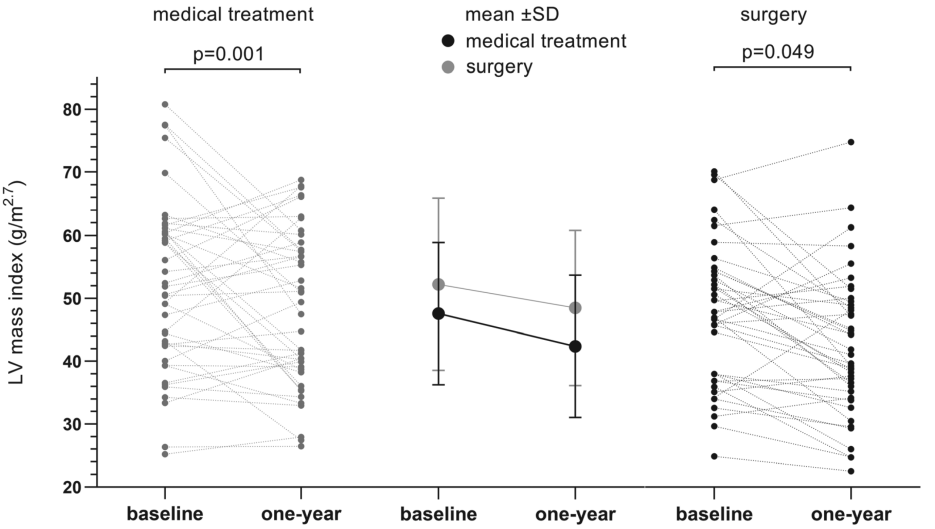

FIGURE 2 Left ventricle mass index ($g/m^{2.7}$) in surgically and medically treated patients with primary aldosteronism at baseline and at one-year follow-up. Each dot represents a patient, line and whiskers indicate mean and SD.

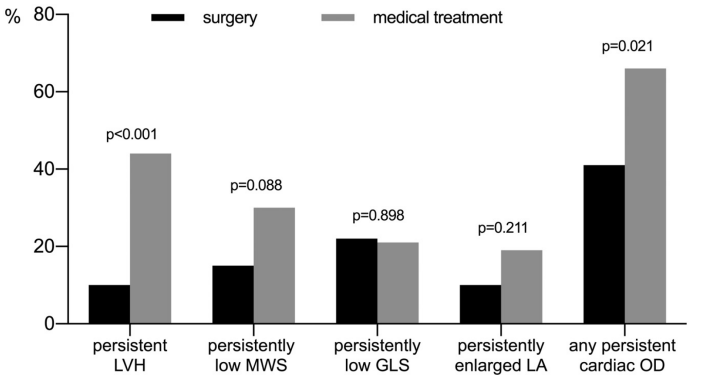

FIGURE 3 Prevalences of different types of persistent cardiac organ damage in surgically and medically treated patients with primary aldosteronism at one-year follow-up. GLS, global longitudinal strain; LA, left atrium; LVH, Left ventricular hypertrophy; MWS, midwall shortening; OD, organ damage.

TABLE 3. Factors associated with cardiac organ damage in 84 patients treated surgically or medically for primary aldosteronism

	Model 1			Model 2		
Outcome variable	**Variable**	**OR (95% CI)**	***P* value**	**Variable**	**OR (95% CI)**	***P* value**
Persistent LV hypertrophy	Medical treatment group	4.88 (1.26–18.88)	0.022	Medical treatment group	4.73 (1.20–18.68)	0.027
	Age (years)	1.09 (1.02–1.17)	0.013	BMI (kg/m^2)	1.18 (1.02–1.38)	0.027
	BMI (kg/m^2)	1.20 (1.04–1.38)	0.012	Diabetes mellitus	9.44 (1.57–56.7)	0.014
	Diabetes mellitus	6.48 (1.20–34.83)	0.030	Pulse pressure at follow-up	1.08 (1.02–1.13)	0.005
Persistently low midwall shortening	Medical treatment group	3.20 (0.94–11.04)	0.066	Persistently low plasma renin	6.11 (1.39–26.7)	0.016
	eGFR (ml/min per 1.73 m^2)	0.96 (0.94–0.99)	0.003	eGFR (ml/min per 1.73 m^2)	0.96 (0.94–0.99)	0.004
Persistent low GLS	HbA_{1c} (%)	2.37 (1.12–5.02)	0.024	HbA1c (%)	2.37 (1.12–5.02)	0.024
Persistently enlarged left atrium	BMI	1.18 (1.02–1.37)	0.013	BMI (kg/m^2)	1.18 (1.02–1.37)	0.031
	eGFR (ml/min per 1.73 m^2)	0.96 (0.93–0.99)	0.027	eGFR (ml/min per 1.73 m^2)	0.96 (0.93–0.99)	0.017
	Atrial fibrillation	6.01 (0.95–37.91)	0.081	Atrial fibrillation	6.01 (0.95–37.91)	0.056

Multivariable stepwise logistic regression analyses. CI, confidence interval; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; HbA_{1c}, hemoglobin A_{1c}; LV, left ventricle; OR, odds ratio.

covariable (Model 1, Table 3). Adding SBP and suppressed plasma renin at one-year follow-up did not change the results (Model 2, Table 3).

Left atrium enlargement

In univariable logistic regression analyses, persistently enlarged left atrium was associated with known atrial fibrillation, lower eGFR and obesity at baseline and higher pulse pressure and E/e' at one-year follow-up (all $P < 0.10$) (Table S1, http://links.lww.com/HJH/B921). In the stepwise multivariable logistic regression analysis, lower eGFR and higher BMI remained significant covariables (Model 1, Table 3). Adding SBP, pulse pressure, suppressed plasma renin and E/e' at one-year follow-up did not change the results (Model 2, Table 3).

DISCUSSION

The current study expands current knowledge of persistent cardiac organ damage in relation to surgical and medical treatment of primary aldosteronism. Despite a large reduction of LV hypertrophy, particularly in surgically treated patients, many patients with primary aldosteronism remained with persistent cardiac organ damage at one-year follow-up in both treatment groups, and consequently with a high residual risk of developing cardiovascular events. The main drivers of persistent cardiac organ damage were metabolic comorbidities and suboptimal MRA treatment.

We found that persistent LV hypertrophy was more common in medically than surgically treated patients. This finding contrasts the results from a recent meta-analysis indicating similar reduction of LV mass with both treatments [13], but confirms observations in two small studies finding significant reduced LV mass index in surgically treated patients only [12,20]. Of note, the higher prevalence of persistent LV hypertrophy in the medical treatment group was independent of significant associations with obesity and diabetes mellitus, both factors associated with higher prevalence and less reversibility of LV hypertrophy in essential hypertension [21]. Several studies advocate that BP reduction is the main confounder of LV mass index reduction in primary aldosteronism [22,23]. In the present study, higher SBP both at baseline and follow-up was significantly associated with persistent LV hypertrophy in univariable analyses. However, these associations became

nonsignificant in the adjusted models. Of note higher arterial stiffness, as reflected by posttreatment pulse pressure, was also independently associated with persistent LV hypertrophy. Catena et *al.* [22] demonstrated an association between changes in LV mass index and pretreatment plasma aldosterone concentration in both surgically and medically treated patients. In contrast, the present study demonstrated an independent association between higher post-SIT-aldosterone concentration and persistent LV hypertrophy only in the medical treatment group. Taken together, the multifactorial pathophysiology of persistent LV hypertrophy in primary aldosteronism is clearly demonstrated.

To our knowledge this is the first study investigating changes in longitudinal LV systolic myocardial function assessed by GLS after specific primary aldosteronism treatment. Of note, GLS remained unchanged independent of treatment group during one-year follow-up in the present study, despite reduction in LV mass. Lower LV GLS has been associated with presence of myocardial fibrosis by gadolinium enhanced cardiac magnetic resonance imaging [24]. The persistently low LV GLS in both treatment groups may therefore reflect presence of cardiac fibrosis, which is more extensive in primary aldosteronism than in essential hypertension, and less modifiable by treatment than cardiomyocyte hypertrophy [25]. However, the strongest predictor of persistently low GLS in our study was higher HbA_{1c}, reflecting the importance of disturbed glucose metabolism for LV myocardial function, in line with previous reports in essential hypertension [26].

Also circumferential LV systolic myocardial function assessed by midwall shortening did not improve during follow-up in either group, in line with results from Catena et *al.* [22]. In contrast, previous studies in essential hypertension have demonstrated that LV hypertrophy regression is accompanied by improved circumferential LV systolic myocardial function, in particular during the first treatment year, although additional smaller improvements may be observed up to three years after initiation of treatment [27,28]. However, one-year regression of LV hypertrophy in the present study resulted from reduced LV inner diameter without change in LV wall thickness. This might explain the lack of improved midwall shortening. A similar LV geometric adaptation to specific treatment of primary aldosteronism has previously been described by Rossi *et al.* [12].

Enlarged left atrium is a common type of hypertensive organ damage, particularly prevalent in women and in obese individuals [29], which predisposes to atrial fibrillation and heart failure. Previous studies on change in left atrial size during primary aldosteronism treatment have yielded diverging results [12,20,30,31]. Two studies found reduction in left atrial anterior-posterior diameter in surgically treated, but not in medically treated patient [12,30], whereas others found no change in either group [20,31]. However, it is well demonstrated that left atrial volume index, as used in the present study, is superior to left atrial anterior-posterior diameter in reflecting actual left atrial size [32]. Thus, the present results add to previous publications by demonstrating a marked reduction in the prevalence of left atrial enlargement in both medically and surgically treated patients with primary aldosteronism, indicating improved LV diastolic function.

Hundemer *et al.* [33] recently related the excess risk of cardiovascular events in medically treated primary aldosteronism to low plasma renin activity after treatment. In the present study, 23% of medically treated patients had suppressed plasma renin at one-year follow-up, indicating insufficient mineralocorticoid receptor blockade due to suboptimal titration of MRA treatment in these patients. This might reflect adverse effects of MRA treatment, physician inertia or poor patient drug adherence, all major problems in management of hypertension [34]. Persistently low plasma renin was also associated with persistent LV hypertrophy, and was an independent confounder of persistently low LV midwall function, adding to a recent publication by Köhler et *al.* [35].

Some limitations of our study should be highlighted. First, the impact of BP on persistent cardiac organ damage may have been underestimated since ambulatory BP was not included in the study. However, 80% of participants had optimally controlled BP at the follow-up visit. On the contrary, drug adherence was not assessed, which would have been of particular value in the medical treatment group. Second, the full effect of primary aldosteronism treatment on regression of cardiac organ damage may not have been achieved after one-year only [27,28]. Third, differences in antihypertensive treatment prior to study inclusion may have influenced cardiac structure and function at baseline, particularly in patients treated with MRA prior to study inclusion. However, MRA treatment did not differ significantly between the treatment groups at baseline. Fourth, the prevalence of obesity was high in the study cohort and generalizing results to other populations may not be appropriate. Concomitant glucocorticoid excess has been associated with presence of metabolic risk factors and with decrease of LV mass index during follow-up after adrenalectomy [30,36]. However, this was not assessed in our cohort. Furthermore, it must be acknowledged that unilateral and bilateral primary aldosteronism are different conditions with different pathogenesis, that may influence prognosis and bias treatment outcome [37]. Finally, the study sample size was calculated based upon persistent LV hypertrophy. The study cohort was small, and type 2 errors cannot be ruled out for other measures of persistent cardiac organ damage. The small study sample also precluded sex-specific analyses.

In conclusion, the present study on primary aldosteronism demonstrates that many patients remain with persistent LV hypertrophy and other types of cardiac organ damage after one year, also among those surgically treated. Thus, many patients with primary aldosteronism remain with a high cardiovascular risk despite treatment. Although persistent LV hypertrophy was less prevalent after surgical treatment, persistent LV systolic myocardial dysfunction was common in both treatment groups. Presence of metabolic comorbidities like obesity, diabetes mellitus and impaired glucose metabolism were identified as major confounders of persistent cardiac organ damage. This points to the importance of a general risk factor management to optimally reduce cardiac organ damage and associated cardiovascular events in primary aldosteronism. As demonstrated, persistent cardiac organ damage was more common in medically treated patients with low plasma

renin at follow-up, indicating that MRA dosing was suboptimal. These findings emphasize the importance of biochemical assessment during follow-up and the need for more detailed recommendations on optimal MRA dosages and their indicators in primary aldosteronism.

ACKNOWLEDGEMENTS

Grant no. 273563 from the Research Council of Norway.

Conflicts of interest

The authors declare no conflicts of interest.

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Errata for
Cardiac organ damage in systemic hypertension: Impact of gender, etiology, and comorbidities

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Thesis for the degree philosophiae doctor (PhD)

at the University of Bergen

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(date and sign. of candidate) (date and sign. of faculty)

Errata

Page 21 Misspellings in Figure 1: “myocordial” corrected to “myocardial” and “fibrilation” corrected to “fibrillation”

Page 36: Incorrect use of periods and capital letters: “every 20. Minutes and every 30. Minutes” is corrected to “every 20 minutes and every 30 minutes”

Page 93: Incomplete references:

Reference 138, “2021” is corrected to “2022” and “96:81-89” is added

Reference 140, “185.5:663-672” is added

Reference 147, “dgad 520” is added

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 9788230853504 (print)
9788230865019 (PDF)