High Blood Pressure & Cardiovascular Prevention (2024) 31:157–166
https://doi.org/10.1007/s40292-024-00632-6

ORIGINAL ARTICLE

Gender Differences in Cardiac Organ Damage in Arterial Hypertension: Assessing the Role of Drug Nonadherence

Arleen Aune[1,2] · Annabel Ohldieck[1,2] · Lene V. Halvorsen[3,4,5] · Karl Marius Brobak[6,7] · Eirik Olsen[8] · Stine Rognstad[3,9] · Anne Cecilie K. Larstorp[3,5,10] · Camilla L. Søraas[3,5,11] · Anne B. Rossebø[12] · Assami Rösner[13] · Marianne Aa. Grytaas[14] · Eva Gerdts[1,2]

Received: 14 January 2024 / Accepted: 3 March 2024 / Published online: 26 March 2024

Abstract

Introduction Cardiac organ damage like left ventricular (LV) hypertrophy and left atrial (LA) enlargement is more prevalent in women than men with hypertension, but the mechanisms underlying this gender difference remain unclear.

Methods We tested the association of drug nonadherence with the presence of LV hypertrophy and LA enlargement by echocardiography in 186 women and 337 men with uncontrolled hypertension defined as daytime systolic blood pressure (BP) ≥ 135mmHg despite the prescription of at least two antihypertensive drugs. Drug adherence was assessed by measurements of serum drug concentrations interpreted by an experienced pharmacologist. Aldosterone-renin-ratio (ARR) was measured on actual medication.

Results Women had a higher prevalence of LV hypertrophy (46% vs. 33%) and LA enlargement (79% vs 65%, both $p < 0.05$) than men, while drug nonadherence (8% vs. 9%, $p > 0.514$) did not differ. Women were older and had lower serum renin concentration and higher ARR than men, while 24-h systolic BP (141 ± 9 mmHg vs. 142 ± 9 mmHg), and the prevalences of obesity (43% vs. 50%) did not differ (all $p > 0.10$). In multivariable analyses, female gender was independently associated with a two-fold increased risk of LV hypertrophy (OR 2.01[95% CI 1.30–3.10], $p = 0.002$) and LA enlargement (OR 1.90 [95% CI 1.17–3.10], $p = 0.010$), while no association with drug nonadherence was found. Higher ARR was independently associated with LV hypertrophy in men only (OR 2.12 [95% CI 1.12–4.00] $p = 0.02$).

Conclusions Among patients with uncontrolled hypertension**,** the higher prevalence of LV hypertrophy and LA enlargement in women was not explained by differences in drug nonadherence.

Registration URL: https://www.clinicaltrials.gov; Unique identifier: NCT03209154.

Keywords Uncontrolled hypertension · Cardiac organ damage · Left ventricular hypertrophy · Left atrial enlargement · Gender · Sex · Drug adherence · Obesity · Aldostero-Renin Ratio · Primary aldosteronism

1 Introduction

Globally, hypertension is the most significant modifiable risk factor of cardiovascular (CV) morbidity and mortality in women and ranks second only to tobacco smoking in men [1]. Achieving blood pressure (BP) control is crucial for reducing the risk of cardiac organ damage, reflecting preclinical CV disease, in individuals with hypertension [1]. However, despite the availability of antihypertensive drugs, achieving BP control, particularly of the systolic BP, remains a challenge [2]. Studies indicate that fewer women reach the BP target, yet research on antihypertensive drug treatment effects specifically in women is limited [3, 4].

Recently, drug non-adherence has emerged as a major underlying cause of lack of BP control and is suggested to be particularly common among older women [1, 3, 5–7]. In a recent meta-analysis including 27 million patients with hypertension, the prevalence of nonadherence to antihypertensive medication varied between 27 and 40% among the included studies [8]. Assessing drug adherence is challenging, and while indirect methods like physicians' interviews and pill count are criticized for their inaccuracy and complexity in clinical practice, serum drug concentration measurement is emerging as the preferred method [9].

Extended author information available on the last page of the article

Uncontrolled hypertension frequently leads to cardiac organ damage such as left ventricular (LV) hypertrophy and left atrial (LA) enlargement, which are strongly associated with subsequent clinical CV morbidity and mortality [1, 10]. Previous studies in essential hypertension have demonstrated that women have a higher prevalence of LV hypertrophy and LA enlargement than men when prognostically validated gender-specific threshold values for identification of cardiac organ damage are used [11–13]. Furthermore, women more often than men remain with residual LV hypertrophy despite adequate antihypertensive treatment [11], and are more prone to develop incident LV hypertrophy even during antihypertensive drug treatment [14]. These findings have been independent of concomitant metabolic disorders like obesity and diabetes mellitus, as well as impaired renal function, factors that may all contribute to a higher prevalence of cardiac organ damage [13–15]. However, these previous studies did not take gender differences in drug adherence into account. Granger et al. demonstrated that good drug adherence is associated with improved survival, even when treated with a placebo [16]. This suggests that adherent patients adopt a generally healthier lifestyle, that may potentially influence the prevalence of cardiac organ damage [16]. From this, we hypothesized that differences in drug adherence may contribute to a higher prevalence of cardiac organ damage in women with treated uncontrolled hypertension.

2 Methods

2.1 Study Population

Uncontrolled systolic BP is the most common type of uncontrolled hypertension and was used as basis for inclusion in our study [1]. The present study included 523 patients with confirmed uncontrolled hypertension (daytime systolic BP ≥ 135 mmHg) despite prescription of ≥ 2 antihypertensive drugs that participated in a national multicenter study performed at the four largest university hospitals in Norway in 2017–2022 [17]. To identify suitable participants, the primary study recruited a total of 1156 individuals aged ≥ 18 years with uncontrolled office systolic BP despite being prescribed ≥ 2 antihypertensive drugs and with a stable treatment regimen for at least 4 weeks (42% women). 24-hour (24-h) ambulatory BP recording at the baseline visit revealed that surprisingly many of the recruited patients (45%) had controlled daytime systolic BP (Fig. 1). The remaining 562 patients with uncontrolled daytime systolic BP between ≥ 135 mmHg and <170 mmHg (safety threshold), were invited to the follow-up visit which included echocardiography (Fig. 1). Of those, 548 showed up for echocardiography (Fig. 1). For the present analysis, 21 of these were excluded due to poor image quality precluding analysis, and 5 due to myocardial infarct scarring in the left ventricle (LV) (Fig. 1). Thus, 523 patients with uncontrolled treated hypertension are included in the present pre-specified sub-study (Fig. 1). Most patients (57%) were referred by primary care physicians, 15% were referred by secondary medical centers and 27% were self-referred through newspaper advertisements and public media discussion. A detailed description of the study inclusion and protocol has been previously published [17]. The study was approved by the Regional Ethical Committee (2017/804) and was conducted in accordance with the Helsinki Declaration.

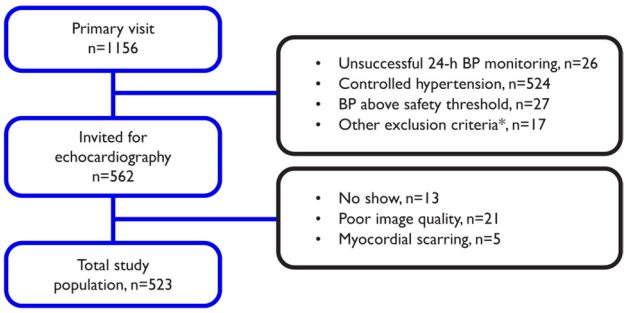

Fig. 1 Flow chart of the process of patient exclusion. *Other exclusion criteria: Estimated glomerular filtration rate < 30 mL/min/1.73 m^2, urine albumin-creatinine ratio > 300 mg/mmol, poor Norwegian language skills, pregnancy, known drug abuse, or psychiatric disorders and impaired cognitive function that could limit the ability to evaluate the efficacy or safety of the protocol. *BP* blood pressure

2.2 Cardiovascular Risk Assessment

Attended office BP was measured in triplets in the seated position after 5 minutes of initial rest, using a validated device, and the office BP was taken as the average of the two last measurements [1]. Ambulatory 24-h BP was measured on the non-dominant arm using a validated device [1]. BP was measured every 20 min during daytime and every 30 minutes during nighttime. If < 70% of the BP measurements were technically successful, the ambulatory BP recording was repeated.

Self-reported medical history data was collected through a structured physician-patient interview. CV disease was defined as history of any of the following events: Myocardial infarction, angina pectoris, percutaneous coronary intervention, coronary bypass grafting, transient ischemic attack, or stroke.

The patient's weight and height were measured. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2. Albumin-creatinine ratio (ACR) was measured in morning spot urine. ACR ≥ 3 mg/mmol was considered elevated

[18]. eGFR was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation [19].

The aldosterone-to-renin ratio (ARR) was calculated using aldosterone and direct renin concentration measurements, without adjusting for interfering antihypertensive medication. ARR > 35 pmol/mIU was considered a positive screening test for primary aldosteronism [20].

2.3 Drug Nonadherence

Serum drug concentrations were measured using ultra-high-performance liquid chromatography coupled with tandem mass spectrometry (UHLPC-MS/MS), and was available for the 23 most commonly prescribed antihypertensive drugs in Norway, as previously described [17, 21, 22]. An experienced pharmacologist interpreted the adherence status based on information about dosage, time since the last intake, and predefined serum reference ranges [17, 21, 22]. To minimize the influence on patient behaviour, no instructions regarding the administration of BP medication were given prior to the study visits, and patients were not informed about the serum drug measurement. Patients were defined as nonadherent if serum drug concentrations measured at the primary visit documented that at least one prescribed antihypertensive agent was undetectable or below the defined serum reference range [22].

2.4 Echocardiography

Transthoracic echocardiography was performed using a standardized imaging protocol at all study centers. Echocardiograms were digitally stored and transferred for analyses at the Echocardiography Core Laboratory at the University of Bergen, Norway, which uses Tomtec Arena Software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany) and dedicated workstations. The images were initially analyzed by a junior investigator (AA) and proofread by a senior investigator (EG) in accordance with the current recommendations for echocardiographic core laboratory procedures [23, 24]. Cardiac organ damage was considered present if left ventricular (LV) hypertrophy and/or enlarged left atrium (LA) volume was found in the individual patient. LV hypertrophy was identified by 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).[1] LV hypertrophy was considered concentric if relative wall thickness (RWT) > 0.42, and eccentric if RWT ≤ 0.42 [1]. LA systolic volume was estimated by the biplane Simpsons's method combining the apical four and two-chamber views [23]. The LA volume was indexed for height squared meter^2 and defined as enlarged if ≥ 16.5ml/m^2 in women and ≥ 18.5 ml/m^2 in men [1]. The presence of mitral valve regurgitation was assessed by colour Doppler echocardiography and severity was graded as mild, moderate, or severe [25].

2.5 Statistical Analysis

Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as absolute numbers and percentages. Differences between women and men were tested by the student's unpaired t-test, Mann-Whitney U test, and Pearson's chi-square test as appropriate.

Covariables of LV hypertrophy and LA enlargement were identified in univariable and multivariable logistic regression analysis. All variables in Table 1 were evaluated in univariable analysis ($p < 0.1$). The enter method was used for the multivariable analysis, including covariables with significant univariable associations and clinical relevance while accounting for collinearity. A variance inflation factor > 1.4 was used to identify collinearity. When multiple variables represented similar aspects, we selected the variable with the strongest univariable association. Age and nonadherence were included in all multivariable models. Interaction analyses between gender and nonadherence in the models for LV hypertrophy/LA enlargement were performed by adding the product gender × drug nonadherence to the multivariable models. Logistic regression results are reported as odds ratio (OR), corresponding 95% confidence interval (CI), and p-value. A 2-sided p-value < 0.05 was considered statistically significant in all analyses.

The study had statistical power 0.80 with an alpha 0.05 to detect a 13% difference in the prevalence of LV hypertrophy between genders.

3 Results

3.1 Clinical Characteristics

Nonadherence to antihypertensive drugs was unexpectedly low in the study with no difference between women and men (8% vs. 9%, $p = 0.51$) (Table 1). The prevalence of obesity was high in both women and men (43% vs. 50%, $p = 0.126$) (Table 1). Women were older and had a longer duration of hypertension than men (Table 1). Women had lower direct renin concentration and higher ARR (Table 1). While women had higher office systolic BP, their 24-h systolic BP was similar to men's, indicating a more pronounced white-coat effect in women (9.8 ± 14.4 mmHg) than in men (4.5 ± 14.4 mmHg, $p < 0.001$). On average, women and men were prescribed the same number of antihypertensive agents, but women were prescribed less calcium channel blockers (Table 1).

Table 1 Clinical characteristics in women and men with uncontrolled treated hypertension

Variable	Female n = 186 n (%) or mean ± SD	Male n = 337 n (%) or mean ± SD	*p*	Adherent n = 478 n (%) or mean ± SD	Nonadherent n = 45 n (%) or mean ± SD	*p*
Female sex, n (%)				172 (36)	14 (31)	0.514
Age (years)	66 ± 11	62 ± 10	< 0.001	64 ± 11	57 ± 12	< 0.001
Duration of hypertension (years)	18 ± 12	15 ± 11	0.006	16 ± 11	13 ± 9	0.037
Body mass index (kg/m^2)	29.7 ± 6.5	30.4 ± 4.6	0.162	30 ± 5	30 ± 5	0.796
Obesity, n (%)	80 (43)	167 (50)	0.143	223 (47)	24 (53)	0.398
Concomitant disease and organ function						
Type 2 diabetes mellitus, n (%)	33 (18)	75 (22)	0.233	102 (21)	6 (14)	0.227
Hypercholesterolemia, n (%)	90 (48)	153 (45)	0.512	225 (47)	18 (40)	0.363
Cardiovascular disease, n (%)	40 (23)	62 (20)	0.388	94 (21)	8 (21)	0.959
Atrial fibrillation, n (%)	20 (11)	43 (13)	0.513	59 (12)	4 (9)	0.526
Creatinine (μmol/L)	68 ± 18	87 ± 21	< 0.001	80 ± 21	76 ± 21	0.145
eGFR (ml/min/1.73 m^2)	81 ± 18	83 ± 17	0.153	81 ± 17	89 ± 18	0.002
ACR (mg/mmol)	4.0 ± 11.7	9.5 ± 36.1	< 0.001	8.0 ± 31.0	3.8 ± 11.4	< 0.001
Elevated ACR (%)	33 (18)	95 (29)	0.008	119 (25)	9 (20)	0.439
HbA_{1c} (mmol/mol)	40.9 ± 9.9	41.1 ± 9.2	0.048	41.1 ± 9.7	39.9 ± 13.0	0.055
Serum aldosterone (pmol/L)	266 ± 188	279 ± 209	0.525	273 ± 201	293 ± 206	0.431
Direct renin concentration (mIU/L)	65 ± 140	87 ± 189	0.020	82 ± 179	44 ± 81	0.569
Aldosterone-to-renin ratio (pmol/mIU)	32 ± 48	31 ± 57	0.040	32 ± 56	25 ± 27	0.235
Elevated aldosterone-to-renin ratio n (%)	50 (28)	76 (23)	0.242	113 (24)	14 (33)	0.225
Blood pressure and heart rate						
Office systolic BP (mmHg)	152 ± 18	148 ± 16	0.008	149 ± 17	145 ± 19	0.015
Office diastolic BP (mmHg)	83 ± 11	85 ± 12	0.010	84 ± 11	95 ± 13	< 0.001
Heart rate at rest (beats/minute)	69 ± 12	68 ± 13	0.383	68 ± 13	61 ± 12	0.078
Pulse pressure (mmHg)	69 ± 17	63 ± 14	< 0.001	65 ± 15	61 ± 14	0.048
24-h systolic BP (mmHg)	141 ± 9	142 ± 9	0.314	141 ± 9	143 ± 10	0.216
Daytime systolic BP (mmHg)	145 ± 8	146 ± 9	0.275	146 ± 8	148 ± 10	0.207
Nighttime systolic BP (mmHg)	129 ± 14	129 ± 14	0.698	129 ± 14	130 ± 15	0.747
24-h diastolic BP (mmHg)	77 ± 10	82 ± 9	< 0.001	79 ± 9	85 ± 9	< 0.001
Daytime diastolic BP (mmHg)	81 ± 9	85 ± 9	< 0.001	83 ± 9	89 ± 10	< 0.001
Nighttime diastolic BP (mmHg)	67 ± 9	72 ± 10	< 0.001	70 ± 10	75 ± 9	< 0.001
Medication overview						
Number of antihypertensive agents, n (%)	2.9±1.0	3.0±1.0	0.099	3.0±1.0	3.3±1.1	0.054
Angiotensin II receptor blocker n, (%)	154 (83)	275 (82)	0.786	75 (16)	5 (11)	0.415
ACE inhibitor, n (%)	23 (12)	57 (17)	0.162	392 (82)	38 (84)	0.683
Calcium channel blocker, n (%)	124 (67)	263 (78)	0.004	349 (73)	38 (84)	0.095
Diuretic, n (%)	119 (65)	219 (65)	0.783	313 (66)	26 (58)	0.301
Betablocker, n (%)	72 (39)	110 (33)	0.170	161 (34)	21 (47)	0.080
Mineralocorticoid receptor antagonist, n (%)	11 (6)	18 (5.4)	0.790	25 (5)	5 (11)	0.088
Other antihypertensive drugs, n (%)	23 (12)	48 (14)	0.540	65 (14)	6 (13)	0.960
Drug adherence						
Nonadherent, n (%)	14 (8)	31 (9)	0.514			
Echocardiography						

Table 1 (continued)

Variable	Female n = 186 n (%) or mean ± SD	Male n = 337 n (%) or mean ± SD	*p*	Adherent n = 478 n (%) or mean ± SD	Nonadherent n = 45 n (%) or mean ± SD	*p*
IVSd (cm)	1.21 ± 0.23	1.28 ± 0.21	< 0.001	1.25 ± 0.22	1.28 ± 0.21	0.466
LVIDd (cm)	4.59 ± 0.47	5.07 ± 0.55	< 0.001	4.90 ± 0.57	4.88 ± 0.58	0.771
LVPWd (cm)	0.93 ± 0.17	0.99 ± 0.16	< 0.001	0.97 ± 0.17	0.96 ± 0.13	0.708
LV mass index (g/m$^{2.7}$)	46.6 ± 13.4	46.9 ± 12.4	0.781	46.8 ± 12.9	46.5 ± 11.8	0.861
Relative wall thickness	0.41 ± 0.92	0.39 ± 0.08	0.062	0.40 ± 0.08	0.40 ± 0.07	0.941
LV hypertrophy n (%)	85 (46)	110 (33)	0.004	176 (37)	19 (43)	0.410
LA volume index (ml/m^2)	22.2 ± 6.6	22.4 ± 8.6	0.460	22.5 ± 8.0	20.5 ± 7.6	0.070
Enlarged LA n (%)	141 (79)	215 (65)	< 0.001	331 (71)	25 (56)	0.028
Ejection fraction (%)	61 ± 5	59 ± 5	< 0.001	59.5 ± 5.0	59.5 ± 4.0	0.980
Mitral valve regurgitation, n (%)	89 (48)	126 (38)	0.023	42 (198)	38 (17)	0.619
Mild	122 (46)	83 (37)	0.042	189 (41)	16 (36)	0.595
Moderate	6 (3)	4 (1)	0.105	9 (2)	1 (2)	0.877
Severe	0	0	NA	0	0	NA

eGFR estimated glomerular filtration rate, *ACR* albumin-creatinine ratio, *BP* blood pressure, *ACE* angiotensin-converting enzyme, *IVSd* interventricular septum diastole, *LVIDd* left ventricle inner diameter diastole, *LVPWd* left ventricle posterior wall diastole, *LV* left ventricle, *LA* left atrium

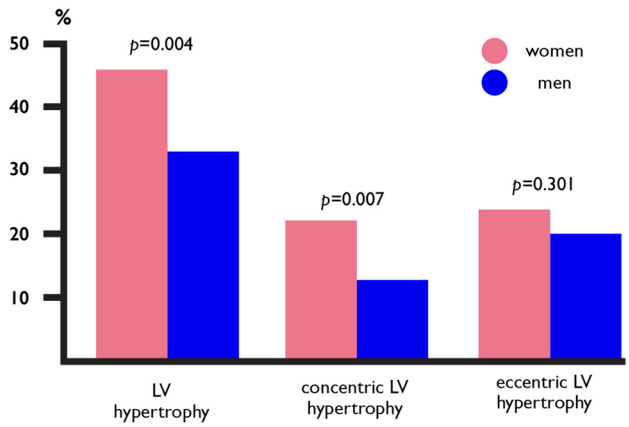

Fig. 2 Prevalence of concentric and eccentric LV hypertrophy in women and men with uncontrolled treated hypertension. *LV* left ventricular

Compared to adherent patients, nonadherent patients were younger and had a shorter duration of hypertension (both p < 0.05) (Table 1). Furthermore, they had higher 24-h diastolic BP and a higher eGFR (both p < 0.05), while 24-h systolic BP, BMI, and prevalences of comorbidities were similar in the drug-adherent and nonadherent groups (Table 1).

3.2 Prevalence of Cardiac Organ Damage

LV hypertrophy was common in both genders, with a higher prevalence in women than men (46% vs. 33%, p = 0.004) (Table 1). Women had more concentric LV hypertrophy than men, whereas the prevalence of eccentric LV hypertrophy was comparable (Fig. 2). The majority of patients had LA enlargement with a higher prevalence in women (70% vs. 65%, p < 0.001) (Table 1). Furthermore, women had a higher prevalence of mitral valve regurgitation than men (Table 1). The prevalence of LV hypertrophy did not differ between adherent and non-adherent patients (Table 1).

3.3 Factors Associated with LV Hypertrophy

Drug nonadherence was not associated with LV hypertrophy in either gender (Table 2, Panel A). In the total study cohort, female gender was associated with a two-fold increased risk of LV hypertrophy (OR 2.01 [95% CI 1.30–3.10], p = 0.002) independent of significant associations with higher age, 24-h systolic BP, higher BMI and elevated ACR (Table 2, Panel A; Fig. 3). Interaction analysis showed no interaction between gender and drug nonadherence with the presence of LV hypertrophy. In gender-specific analyses, LV hypertrophy was only associated with higher BMI in women and with higher BMI, age, and 24-h systolic BP in men (Table 2, Panel A). Secondary models based on significant covariables identified separately in women and men yielded consistent results (Table S1). When adding elevated ARR to the primary model, elevated ARR was associated with presence of LV hypertrophy in men (OR 2.12 [95% CI 1.12–4.00], p = 0.02) but not in women (OR 1.48 [95% CI 0.67–3.28], p = 0.338) (Table S2).

Table 2 Covariables of LV hypertrophy (Panel A) and LA enlargement (Panel B) in women and men, uni- and multivariable logistic regression analysis.

Variable	All, n = 523		Women, n = 186		Men, n = 337	
	Univariable OR (95% CI)	Multivariable OR (95% CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Panel A. LV hypertrophy						
Female sex	1.66 (1.15–2.41)*	2.01 (1.30–3.10)*	n.a.	n.a.	n.a.	n.a.
Nonadherence	1.33 (0.71–12.49)	1.96 (0.91–4.22)	1.72 (0.57–5.18)	3.66 (0.84–16.04)	1.21 (0.56–2.66)	1.48 (0.58–3.81)
Age (years)	1.02 (1.00–1.04)*	1.04 (1.01–1.06)*	1.00 (0.97–1.03)	1.02 (0.98–1.06)	1.03 (1.00–1.06)*	1.05 (1.02–1.08)*
Body mass index (kg/m^2)	1.13 (1.09–1.17)*	1.15 (1.10–1.20)*	1.13 (1.07–1.20)*	1.16 (1.09–1.25)*	1.13 (1.08–1.19)*	1.13 (1.06–1.20)*
24-h systolic BP (mmHg)	1.05 (1.03–1.07*	1.03 (1.01–1.06)*	1.05 (1.01–1.08)*	1.03 (0.99–1.07)	1.06 (1.03–1.09)*	1.04 (1.01–1.08)*
Duration of hypertension (years)	1.02 (1.02–1.03)*	1.00 (0.98–1.02)	1.03 (1.00–1.06)*	1.03 (0.99–1.06)	1.00 (0.98–1.03)	0.98 (0.96–1.01)
Elevated ACR	1.91 (1.27–2.87)*	1.70 (1.03–2.82)*	2.38 (1.09–5.19)*	1.83 (0.70–4.77)	2.01 (1.22–3.92)*	1.71 (0.92–3.15)
Type 2 diabetes mellitus	1.44 (0.94–2.22)*	1.02 (0.61–1.73)	2.17 (1.01–4.69)*	1.25 (0.47–3.29)	1.25 (0.73–2.14)	0.95 (0.50–1.82)
Hypercholesterolemia	1.44 (0.94–2.22)*	1.22 (0.80–1.87)	1.08 (0.60–1.92)	1.11 (0.55–2.25)	1.71 (1.08–2.71*	1.30 (0.76–2.23)
Cardiovascular disease	1.64 (1.05–2.55)*	1.41 (0.85–2.33)	1.21 (0.60–2.46)	1.07 (0.44–2.59)	1.94 (1.10–3.43)*	1.52 (0.80–2.89)
Panel B. LA enlargement						
Female sex	2.07 (1.35–3.17)*	1.90 (1.17–3.10)*	n.a.	n.a.	n.a.	n.a.
Drug nonadherence	0.50 (0.27–0.94)*	0.48 (0.23–1.00)*	0.44 (0.14–1.39)	0.41 (0.08–2.13)	0.55(0.26–1.15)	0.52 (0.22–1.17)
Age (years)	1.04 (1.02–1.06)*	1.03 (1.01–1.06)*	1.01 (0.98–1.04)	1.02 (0.97–1.07)	1.05(1.02–1.07)*	1.04 (1.01–1.07)*
Body mass index (kg/m^2)	1.09 (1.05–1.13)*	1.10 (1.04–1.15)*	1.13 (1.05–1.22)*	1.12 (1.02–1.23)*	1.09(1.03–1.15)*	1.08 (1.01–1.15)*
24-h systolic BP (mmHg)	1.05 (1.02–1.07)*	1.03 (1.00–1.06)*	1.07 (1.02–1.13)*	1.06 (1.00–1.12)	1.04(1.01–1.07)*	1.02 (0.99–1.05)
Duration of hypertension (years)	1.02 (1.00–1.04)*	1.00 (0.98–1.02)	1.02 (0.98–1.05)	0.98 (0.94–1.03)	1.02(0.10–1.04)	1.00 (0.98–1.03)
Elevated ACR	1.60 (1.99–2.55)	1.20 (0.70–2.04)	1.19 (0.45–3.14)	0.75 (0.22–2.60)	1.97(1.15–3.38)*	1.34 (0.74–2.42)
LV hypertrophy	4.77 (2.92–7.79)*	3.09 (1.84–5.27)*	12.88(3.78–43.88)*	6.92 (2.07–23.13)*	3.28(1.13–3.66)*	2.37 (1.30–4.32)*
Mitral valve regurgitation	2.19 (1.46–3.29)*	2.22 (1.41–3.50)*	4.36 (1.86–10.20)*	5.48 (2.07–14.51)*	1.61(1.00–2.60)	1.62 (0.96–2.73)

BP blood pressure, *ACR* albumin-creatinine ratio, *LV* left ventricular, *OR* odds ratio, *CI* confidence interval *n.a.* not applicable

*p<0.05

3.4 Factors Associated with LA Enlargement

Drug nonadherence was not associated with higher prevalence of LA enlargement in either gender (Table 2, Panel B). Female gender was associated with an increased prevalence of LA enlargement (OR 1.90 [95% CI 1.17–3.10], p = 0.010) after adjusting for confounding factors (Table 2, Panel B; Fig. 3). Interaction analysis showed no interaction between gender and drug nonadherence with the presence of LA enlargement. In gender-specific analyses, LA enlargement was associated with higher BMI and LV hypertrophy in both genders, with mitral valve regurgitation in women, and with older age in men (Table 2, Panel B). Secondary models based on significant covariables identified separately in women and men yielded consistent results (Table S3). Adding elevated ARR to the primary models did not alter the results, and elevated ARR was not associated with LA enlargement in any group.

4 Discussion

Previous clinical studies in essential hypertension have repeatedly reported a higher prevalence of LV hypertrophy and LA enlargement in women compared to men when using gender-specific criteria [12, 13, 26]. Our study adds to these by demonstrating that the higher prevalence of LV hypertrophy and LA enlargement in women was not explained by differences in drug adherence among patients with uncontrolled hypertension despite being prescribed at least 2 antihypertensive drugs.

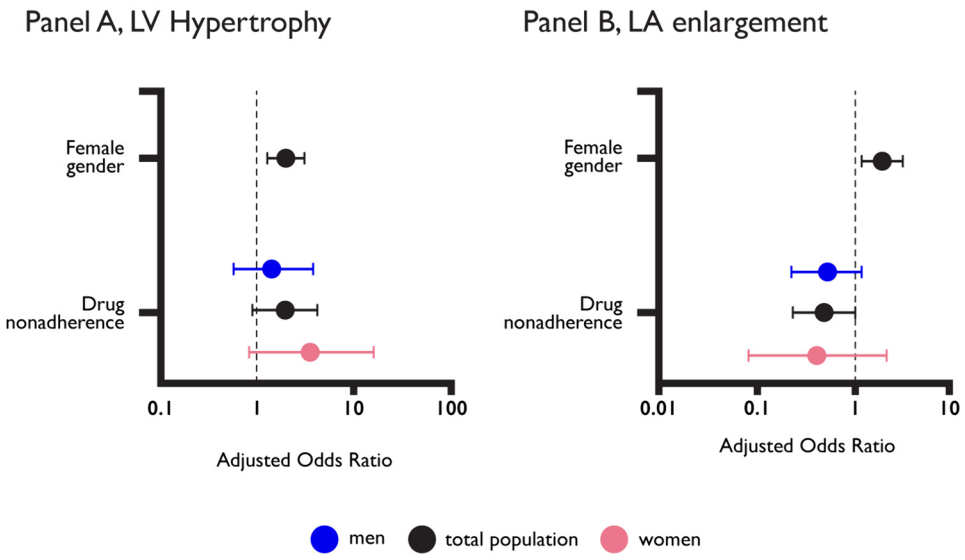

Fig. 3 Association of female gender and drug nonadherence with cardiac organ damage in multivariable logistic regression analysis. The model in Panel A is further adjusted for age, body mass index, 24-h systolic blood pressure, duration of hypertension, elevated albumin-creatinine ratio, type 2 diabetes 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. *LV* left ventricular

A recent national Canadian survey reported a concerning rise in uncontrolled treated hypertension in women [3]. Poor drug adherence was suggested as a potential cause, based on other reports demonstrating a higher prevalence of drug nonadherence in older women compared to men [2, 6]. Furthermore, gender differences in barriers to antihypertensive drug adherence have been reported in older individuals [5]. The low prevalence of drug nonadherence in our study was unexpected. A 20% prevalence of nonadherence was reported in a previous Norwegian study in apparent treatment-resistant hypertension, identified from daytime systolic BP, as also used in the present study [27]. However, nonadherence was indirectly assessed in the previous study [27]. A recent meta-analysis of hypertension studies reported a global prevalence of 27–40% [8]. Of note, lower prevalence was found in Western countries and when adherence was based on serum drug concentrations [8].

One possible explanation of the gender differences in cardiac organ damage in hypertension is the stronger impact of obesity and diabetes on LV remodeling in women compared to men [13, 28–30]. In a longitudinal study of 4290 patients with hypertension without LV hypertrophy at baseline, Izzo et al. demonstrated that both obese and lean women had a substantially higher incidence of LV hypertrophy during follow-up than obese men [14]. In the present study, obesity was equally prevalent and strongly associated with LV hypertrophy in both genders independent of confounders, and in fact the only significant covariable in adjusted analysis in women. Furthermore, presence of type 2 diabetes mellitus was correlated with LV hypertrophy exclusively in women. However, this correlation became nonsignificant when adjusting for BMI, in line with previous reports [31, 32]. Also, renal dysfunction is a recognized confounder of LV hypertrophy [33, 34]. Elevated ACR was more prevalent in men in our study and associated with LV hypertrophy independent of gender, in line with previous reports [34].

LA enlargement was the most common type of cardiac organ damage in both genders and was associated with higher BP and BMI. While higher 24-h systolic BP was associated with a higher prevalence of LA enlargement, drug nonadherence was not. In fact, drug nonadherence was associated with a lower prevalence of LA enlargement in the total population, possibly attributed to their younger age, shorter duration of hypertension, and lower renal function [12]. Interestingly, partly different confounders of LA enlargement were identified in women and men. As expected, more women had mitral regurgitation [12, 35], which was linked with LA enlargement. This adds to results from the Losartan Intervention for End-point Reduction in Hypertension study, which found mitral valve regurgitation a predictor of LA enlargement independent of gender [12]. However, that study did not report gender-specific results [12]. Furthermore, LA size was assessed by LA anterior-posterior diameter. Taken together, a stronger link between LA enlargement and mitral valve regurgitation in women than in men with hypertension is suggested [36].

Primary aldosteronism (PA) is a common and often overlooked cause of secondary hypertension [37]. In our study, standardized diagnostic testing for PA was not performed, but 28% of women and 23% of men had elevated screening ARR on actual medication, suggestive of underlying PA. PA has been linked to higher prevalence of LV hypertrophy in both genders [33]. Furthermore, emerging evidence suggests that even milder, renin-independent autonomous aldosterone secretion, below current diagnostic criteria for PA, may be associated with cardiac organ damage [38]. In the present study, elevated ARR

was independently associated with LV hypertrophy only in men. The lack of association between elevated ARR and LV hypertrophy in women may reflect the known higher incidence of falsely elevated ARRs in women, especially when direct renin concentration measurement is used, as in the current study [39].

5 Study Limitations

Some study limitations should be noted. First, the cross-sectional study design prohibits the documentation of cause-effect relationships. Second, drug adherence was assessed at a single time point, and thus relates to short term adherence. Third, the Hawthorne effect may have resulted in an underestimation of nonadherence since some patients may have improved their drug adherence temporarily prior to the consultation [9]. Furthermore, selection bias may have occurred due to the voluntary nature of study participation, potentially favouring the recruitment of drug-adherent patients. The study also had an underrepresentation of women. Finally, measurements of aldosterone and renin were not standardized and may have been affected by actual medication. However, there is a growing consensus among PA experts that discontinuing antihypertensive drugs before the initial PA screening is not necessary [40, 41]. In our study, most patients were using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, which may have led to a falsely low ARR, possibly resulting in an underestimation of the true prevalence of elevated ARR [39, 40].

6 Conclusion

This study provides novel evidence that the higher prevalence of LV hypertrophy and LA enlargement in women compared to men with uncontrolled treated hypertension was not explained by gender differences in drug nonadherence, assessed by serum drug concentrations. BMI was the only significant covariable of LV hypertrophy in women in adjusted analysis, underscoring the importance of weight control in the prevention of LV hypertrophy in women. Elevated ARR was common, pointing to the value of routine screening for PA in patients with uncontrolled systolic BP despite treatment with two or more antihypertensive drugs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40292-024-00632-6.

Declarations

Disclosures The authors report no disclosures.

Conflicts of interests The Authors have no conflict of interest.

Funding Grants from the Research Council of Norway (Grant number 273563), the South East Norwegian Regional Health Authorities (Grant number 2017014), and the Western Norway Regional Health Authorities (Grant number F-12150).

Data Availability The data may be made available by the authors upon reasonable request.

References

1. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, Muiesan ML, Tsioufis K, Agabiti-Rosei E, Algharably EAE, Azizi M, Benetos A, Borghi C, Hitij JB, Cifkova R, Coca A, Cornelissen V, Cruickshank K, Cunha PG, Danser AHJ, Pinho RM de, Delles C, Dominiczak AF, Dorobantu M, Doumas M, Fernández-Alfonso MS, Halimi JM, Járai Z, Jelaković B, Jordan J, Kuznetsova T, Laurent S, Lovic D, Lurbe E, Mahfoud F, Manolis A, Miglinas M, Narkiewicz K, Niiranen T, Palatini P, Parati G, Pathak A, Persu A, Polonia J, Redon J, Sarafidis P, Schmieder R, Spronck B, Stabouli S, Stergiou G, Taddei S, Thomopoulos C, Tomaszewski M, Borne PV de, Wanner C, Weber T, Williams B, Zhang ZY, Kjeldsen SE, Members: AF. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). J Hypertens. 2023;10–1097.
2. Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Marešová V, White CMJ, Petrák O, Gulsin GS, Patel V, Rosa J, Cole R, Zelinka T, Holaj R, Kinnell A, Smith PR, Thompson JR, Squire I, Widimský J, Samani NJ, Williams B, Tomaszewski M. Risk factors for nonadherence to antihypertensive treatment. Hypertension. 2017;69(6):1113–20.
3. Leung AA, Williams JVA, McAlister FA, Campbell NRC, Padwal RS, Committee HCR and E, Tran K, Tsuyuki R, McAlister FA, Campbell NRC, Khan N, Padwal R, Quan H, Leung AA. Worsening hypertension awareness, treatment, and control rates in canadian women between 2007 and 2017. Can J Cardiol. 2020;36(5):732–9.
4. Lodi E, Carollo A, Martinotti V, Modena MG. Hypertension and pharmacological therapy in women. High Blood Press Cardiovasc Prev. 2018;25(2):147–50.
5. Holt E, Joyce C, Dornelles A, Morisky D, Webber LS, Muntner P, Krousel-Wood M. Sex differences in barriers to

antihypertensive medication adherence: findings from the cohort study of medication adherence among older adults. J Am Geriatr Soc. 2013;61(4):558–64.
6. Lawson AJ, Hameed MA, Brown R, Cappuccio FP, George S, Hinton T, Kapil V, Lenart J, Lobo MD, Martin U, Menon M, Nightingale A, Rylance PB, Webb DJ, Dasgupta I. Nonadherence to antihypertensive medications is related to pill burden in apparent treatment-resistant hypertensive individuals. J Hypertens. 2020;38(6):1165–73.
7. Osude N, Durazo-Arvizu R, Markossian T, Liu K, Michos ED, Rakotz M, Wozniak G, Egan B, Kramer H. Age and sex disparities in hypertension control: the multi-ethnic study of atherosclerosis (MESA). Am J Prev Cardiol. 2021;8: 100230.
8. Lee EKP, Poon P, Yip BHK, Bo Y, Zhu M, Yu C, Ngai ACH, Wong MCS, Wong SYS. Global burden, regional differences, trends, and health consequences of medication nonadherence for hypertension during 2010 to 2020: a meta-analysis involving 27 million patients. J Am Heart Assoc. 2022;11(17): e026582.
9. Burnier M. Drug adherence in hypertension. Pharmacol Res. 2017;125(Pt B):142–9.
10. Gerdts E, Wachtell K, Omvik P, Otterstad JE, Oikarinen L, Boman K, Dahlöf B, Devereux RB. Left atrial size and risk of major cardiovascular events during antihypertensive treatment. Hypertension. 2007;49(2):311–6.
11. Gerdts E, Okin PM, de Simone G, Cramariuc D, Wachtell K, Boman K, Devereux RB. Gender differences in left ventricular structure and function during antihypertensive treatment. Hypertension. 2008;51(4):1109–14.
12. Gerdts E, Oikarinen L, Palmieri V, Otterstad JE, Wachtell K, Boman K, Dahlöf B, Devereux RB, Study LIFER in H (LIFE). Correlates of left atrial size in hypertensive patients with left ventricular hypertrophy. Hypertension. 2002;39(3):739–43.
13. Gerdts E, Izzo R, Mancusi C, Losi MA, Manzi MV, Canciello G, Luca ND, Trimarco B, de Simone G. Left ventricular hypertrophy offsets the sex difference in cardiovascular risk (the Campania Salute Network). Int J Cardiol. 2018;258:257–61.
14. Izzo R, Losi MA, Stabile E, Lönnebakken MT, Canciello G, Esposito G, Barbato E, Luca ND, Trimarco B, de Simone G. Development of left ventricular hypertrophy in treated hypertensive outpatients. Hypertension. 2017;69(1):136–42.
15. Muiesan ML, Paini A, Aggiusti C, Bertacchini F, Rosei CA, Salvetti M. Hypertension and organ damage in women. High Blood Press Cardiovasc Prev. 2018;25(3):245–52.
16. Granger BB, Swedberg K, Ekman I, Granger CB, Olofsson B, McMurray JJ, Yusuf S, Michelson EL, Pfeffer MA, investigators for the C. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet. 2005;366(9502):2005–11.
17. Bergland OU, Halvorsen LV, Søraas CL, Hjørnholm U, Kjær VN, Rognstad S, Brobak KM, Aune A, Olsen E, Fauchald YM, Heimark S, Thorstensen CW, Liestøl K, Solbu MD, Gerdts E, Mo R, Rostrup M, Kjeldsen SE, Høieggen A, Opdal MS, Larstorp ACK, Elmula FEMF. Detection of nonadherence to antihypertensive treatment by measurements of serum drug concentrations. Hypertension. 2021;78(3):617–28.
18. Levey AS, Jong PE de, Coresh J, Nahas ME, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17–28.
19. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Lente FV, Greene T, Coresh J, Collaboration) CE (Chronic KDE. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009;150(9):604.
20. Mulatero P, Monticone S, Deinum J, Amar L, Prejbisz A, Zennaro MC, Beuschlein F, Rossi GP, Nishikawa T, Morganti A, Seccia TM, Lin YH, Fallo F, Widimsky J. Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. J Hypertens. 2020;38(10):1919–28.
21. Thorstensen CW, Clasen PE, Rognstad S, Haldsrud R, Føreid S, Helstrøm T, Bergland OU, Halvorsen LV, Aune A, Olsen E, Brobak KM, Høieggen A, Gustavsen I, Larstorp ACK, Søraas CL, Opdal MS. Development of UHPLC-MS/MS methods to quantify 25 antihypertensive drugs in serum in a cohort of patients treated for hypertension. J Pharmaceut Biomed. 2022;219: 114908.
22. Rognstad S, Søraas CL, Bergland OU, Høieggen A, Strømmen M, Helland A, Opdal MS. Establishing serum reference ranges for antihypertensive drugs. Ther Drug Monit. 2021;43(1):116–25.
23. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233–71.
24. Galderisi M, Nistri S, Mondillo S, Losi MA, Innelli P, Mele D, Muraru D, D'Andrea A, Ballo P, Sgalambro A, Esposito R, Marti G, Santoro A, Agricola E, Badano LP, Marchioli R, Filardi PP, Mercuro G, Marino PN. Methodological approach for the assessment of ultrasound reproducibility of cardiac structure and function: a proposal of the study group of Echocardiography of the Italian Society of Cardiology (Ultra Cardia SIC) Part I. Cardiovasc Ultrasoun. 2011;9(1):26.
25. Jones EC, Devereux RB, Roman MJ, Liu JE, Fishman D, Lee ET, Welty TK, Fabsitz RR, Howard BV. Prevalence and correlates of mitral regurgitation in a population-based sample (the Strong Heart Study)**The views expressed in this study are those of the authors and do not necessarily reflect those of the Indian Health Service. Am J Cardiol. 2001;87(3):298–304.
26. Gerdts E, Cramariuc D, de Simone G, Wachtell K, Dahlöf B, Devereux RB. Impact of left ventricular geometry on prognosis in hypertensive patients with left ventricular hypertrophy (the LIFE study). Eur J Echocardiogr. 2008;9(6):809–15.
27. Elmula FEMF, Hoffmann P, Larstorp AC, Fossum E, Brekke M, Kjeldsen SE, Gjønnæss E, Hjørnholm U, Kjær VN, Rostrup M, Os I, Stenehjem A, Høieggen A. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. Hypertension. 2014;63(5):991–9.
28. Gerdts E, Regitz-Zagrosek V. Sex differences in cardiometabolic disorders. Nat Med. 2019;25(11):1657–66.
29. Mancusi C, Gerdts E, Losi MA, D'Amato A, Manzi MV, Canciello G, Trimarco V, Luca ND, de Simone G, Izzo R. Differential effect of obesity on prevalence of cardiac and carotid target organ damage in hypertension (the Campania Salute Network). Int J Cardiol. 2017;244:260–4.
30. Lønnebakken MT, Izzo R, Mancusi C, Gerdts E, Losi MA, Canciello G, Giugliano G, Luca ND, Trimarco B, Simone G de. Left ventricular hypertrophy regression during antihypertensive treatment in an outpatient clinic (the campania salute network). J Am Heart Assoc. 2017;6(3).
31. Hammond IW, Devereux RB, Alderman MH, Laragh JH. Relation of blood pressure and body build to left ventricular mass in normotensive and hypertensive employed adults. J Am Coll Cardiol. 1988;12(4):996–1004.
32. Hendriks T, Said MA, Janssen LMA, Ende MY van der, Veldhuisen DJ van, Verweij N, Harst P van der. Effect of systolic blood pressure on left ventricular structure and function. Hypertension. 74(4):826–32.

33. Aune A, Kokorina M, Grytaas MA, Midtbø H, Løvås K, Gerdts E. Preclinical cardiac disease in women and men with primary aldosteronism. Blood Press. 2021;30(4):1–7.
34. Wachtell K, Palmieri V, Olsen MH, Bella JN, Aalto T, Dahlöf B, Gerdts E, Wright JT, Papademetriou V, Mogensen CE, Borch-Johnsen K, Ibsen H, Devereux RB. Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: the LIFE study. Am Heart J. 2002;143(2):319–26.
35. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999;83(6):897–902.
36. Moonen A, Ng MKC, Playford D, Strange G, Scalia GM, Celermajer DS. Atrial functional mitral regurgitation: prevalence, characteristics and outcomes from the National Echo Database of Australia. Open Hear. 2023;10(1): e002180.
37. Brown JM, Siddiqui M, Calhoun DA, Carey RM, Hopkins PN, Williams GH, Vaidya A. The unrecognized prevalence of primary aldosteronism: a cross-sectional study. Ann Intern Med. 2020;173(1):10–20.
38. Vaidya A, Carey RM. Evolution of the primary aldosteronism syndrome: updating the approach. J Clin Endocrinol Metabolism. 2020;105(12):3771–83.
39. Stowasser M, Ahmed A, Pimenta E, Taylor P, Gordon R. Factors AFFECTING THE ALDOSTERONE/RENIN RATIO. Horm Metab Res. 2011;44(03):170–6.
40. Vaidya A, Hundemer GL, Nanba K, Parksook WW, Brown JM. Primary aldosteronism: state-of-the-art review. Am J Hypertens. 2022;35(12):967–88.
41. Mulatero P, Bertello C, Veglio F, Monticone S. Approach to the patient on antihypertensive therapy: screen for primary aldosteronism. J Clin Endocrinol Metab. 2022;107(11):3175–81.

Authors and Affiliations

Arleen Aune[1,2] · Annabel Ohldieck[1,2] · Lene V. Halvorsen[3,4,5] · Karl Marius Brobak[6,7] · Eirik Olsen[8] · Stine Rognstad[3,9] · Anne Cecilie K. Larstorp[3,5,10] · Camilla L. Søraas[3,5,11] · Anne B. Rossebø[12] · Assami Rösner[13] · Marianne Aa. Grytaas[14] · Eva Gerdts[1,2]

✉ Arleen Aune
arleen.aune@uib.no

[1] Department of Clinical Sciences, University of Bergen, P.P. box 7804, 5020 Bergen, Norway

[2] Department of Heart Disease, Haukeland University Hospital, Bergen, Norway

[3] Section for Cardiovascular and Renal Research, Oslo University Hospital Ullevål, Oslo, Norway

[4] Department of Nephrology, Oslo University Hospital Ullevål, Oslo, Norway

[5] Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[6] Section of Nephrology, The Arctic University of Norway, Tromsø, Norway

[7] Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway

[8] Department of Emergency Medicine, St. Olavs University Hospital, Trondheim, Norway

[9] Department of Pharmacology, Oslo University Hospital Ullevål, Oslo, Norway

[10] Department of Medical Biochemistry, Oslo University Hospital Ullevål, Oslo, Norway

[11] Section for Environmental and Occupational Medicine, Oslo University Hospital Ullevål, Oslo, Norway

[12] Department of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway

[13] Department of Clinical Medicine, UIT, The Arctic University, Tromsø, Norway

[14] Department of Medicine, Haukeland University Hospital, Bergen, Norway