Obesity Facts

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Renin-to-Aldosterone Ratio Is Associated with Ambulatory Blood Pressure Levels and Control in Treated Hypertensive Patients with Overweight or Obesity

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Keywords
Renin · Aldosterone · Ambulatory blood pressure · Overweight · Obesity

Abstract

Introduction: Combination therapy, including a renin-angiotensin system inhibitor (RASi) and a thiazide diuretic (TZD) or a calcium channel blocker (CCB), is the first-line approach in hypertension management and modulates circulating markers of the renin-angiotensin-aldosterone system. Excess adiposity may induce renin-aldosterone axis dysregulation and contribute to blood pressure variability and treatment resistance. This study aimed to evaluate the association between the renin-to-aldosterone ratio (RAR) and ambulatory blood pressure monitoring (ABPM) in treated hypertensive patients with central overweight (OW) or obesity (OB). ***Methods:*** In a cross-sectional design, 97 adults with essential hypertension and OW/OB on stable RASi + TZD and/or CCB therapy were matched with 97 normal-weight hypertensive controls. All participants underwent 24-h ABPM and orthostatic direct renin concentration (DRC) and plasma aldosterone concentration (PAC) measurements. RAR was calculated as the ratio between DRC and PAC. For the analyses, values were normalized using natural logarithm (Ln). ***Results:*** LnRAR and LnDRC were inversely associated with 24-h, daytime, and night-time ABP levels in controls, but not in OW/OB patients. However, higher LnRAR and LnDRC values were linked to greater odds of achieving ABP control in both OW/OB and normal-weight for 24h [LnRAR OR 1.74 (1.25-2.42), $p = 0.001$ in OW/OB], daytime, and night-time periods, whereas LnPAC showed no significant associations. Two-way ANOVA confirmed that patients with controlled ABP had higher median LnRAR and LnDRC values than those with uncontrolled ABP, regardless of weight status (p for interaction >0.05). ***Conclusion:*** RAR, primarily driven by higher DRC levels and likely linked to a pharmacologic response to RAS inhibition, shows a mechanism-based association with ABP control in treated hypertension, regardless of the presence of visceral OB.

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Introduction

Combination therapy of angiotensin-converting enzyme inhibitors (ACE-inhibitors, ACEis) or angiotensin II receptor blockers (ARBs), collectively referred to as renin-angiotensin system inhibitors (RASi), together with thiazide or thiazide-like diuretics (TZDs) and/or along with calcium channel blockers (CCBs), is an established and effective pharmacologic approach for the management of essential hypertension [1, 2]. According to current European hypertension guidelines, these drug classes are recommended as preferred first-line agents for both initiation and intensification of antihypertensive therapy [3].

Due to direct interference on the renin-angiotensin-aldosterone system (RAAS) or due to the drug's own mechanism of action, these therapeutic agents affect the circulating levels of RAAS biomarkers, such as direct renin concentration (DRC) and plasma aldosterone concentration (PAC). In stable treatment with RASi ± TZDs, an increase in DRC and a concomitant decrease in PAC are typically observed. Due to their vasodilatory properties, CCBs may also increase DRC; however, PAC tends to remain unchanged or slightly increased [4]. By exploiting these interactions, some authors have recently tested the aldosterone-to-renin ratio, a measure traditionally used to screen for primary aldosteronism, as a potential biomarker for predicting the response to antihypertensive treatment, with inconsistent findings [5, 6]. In our previous paper on essential hypertensive patients treated with ACEis or ARBs, we demonstrate how a higher renin-to-aldosterone ratio (RAR), indicative of effective RAAS inhibition/modulation by treatment, is associated with lower night-time BP and better overall BP control. Therefore, we speculated that the RAR could be a useful biomarker in the management of essential hypertension for assessing both treatment efficacy and adherence in real-life clinical practice [7], following the hypothesis that an adequate pharmacological modulation of the RAAS is associated with an improved BP response to treatment.

On the other hand, the complex interaction between RAAS biomarkers and antihypertensive treatment may be confounded by the concomitant presence of pathological conditions, beyond primary aldosteronism. Excessive visceral adiposity, commonly observed in many patients with essential hypertension, has been shown to dysregulate the RAAS. Visceral adipose tissue secretes not only adipokines but also RAAS components, including angiotensinogen and the peptide angiotensin II, which contribute to the overactivation of its pathway and obesity (OB)-related hypertension. Even within "normal range," this increase in plasma aldosterone concentration constitutes what can be considered an "inappropriate secondary hyperaldosteronism" in overweight (OW)/obese patients, due also to an "escape" from the inhibition of aldosterone secretion during ACEi and ARB therapy [8–10]. This represents just one among the mechanisms by which visceral fat disrupts the balance of the RAAS. Other contributing pathways include increased sympathetic nervous system activity, insulin resistance (IR), and the presence of obstructive sleep apnea, all of which indirectly modulate RAAS function.

Given this complex interplay among RAAS activity, antihypertensive pharmacotherapy, and adiposity, this study aims to explore the clinical role of the RAR, as a biomarker of treatment efficacy, in individuals with essential hypertension and centrally distributed OW or OB, who are treated with combination therapy including a RASi with TZD and/or CCB, the first-line antihypertensive therapy. Specifically, the present study investigates the possible association between RAR and 24-h ambulatory blood pressure monitoring (ABPM) parameters in a hypertensive population with OW/OB compared to a matched population of normal-weight hypertensive patients (control group).

Methods

Study Population and Design

A cross-sectional observational study was conducted involving 97 eligible outpatients evaluated at our European Society of Hypertension (ESH) Excellence Centre for the Diagnosis and Management of Hypertension (IRCCS INRCA, Ancona, Italy) between July 2022 and July 2023. Inclusion criteria (study group): Age >18 years, diagnosis of essential hypertension, valid ABPM on stable antihypertensive treatment (at least 3 months) with a combination regimen including an ACEi or ARB in association with a TZD and/or a CCB, central OW defined as a body mass index (BMI) ≥27 kg/m^2 and a waist circumference (WC) > 102 cm in men and > 88 cm in women, OR-OB defined as a BMI≥ 30 kg/m^2. Control group: a numerically equivalent population of normal-weight essential hypertensive patients was selected, matched for age, sex, smoking status, and renal function. Online supplementary Figure S1 (for all online suppl. material, see https://doi.org/10.1159/000552327) describes the BMI distribution in the two groups. Exclusion

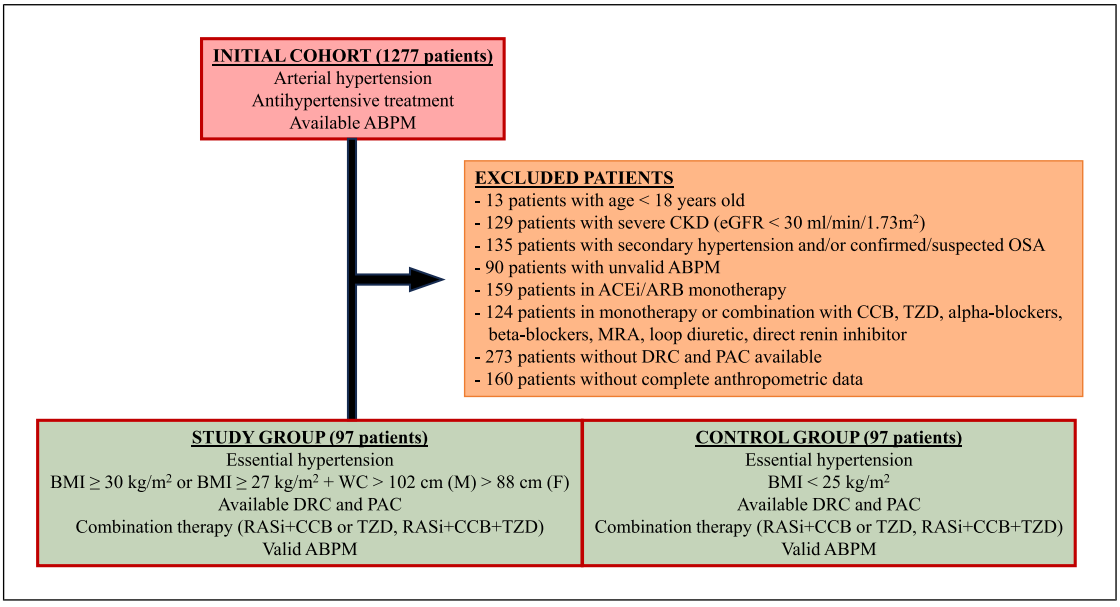

Fig. 1. Flowchart of the study population. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OSA, obstructive sleep apnea; ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blockers; MRA, mineralocorticoid receptor antagonists; DRC, direct renin concentration; PAC, plasma aldosterone concentration; BMI, body mass index; WC, waist circumference; RASi, renin-angiotensin system inhibitor; TZD, thiazide/thiazide-like diuretic.

criteria: severe chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (calculated using the chronic kidney disease-EPI equation), current treatment with mineralocorticoid receptor antagonists or the use of any other antihypertensive medications not specified in the combination regimen, secondary hypertension (ruled out by screening for DRC and PAC regarding primary aldosteronism, and other confounders-like obstructive sleep apnea [OSA] were ruled out if diagnosed, as per standard clinical practice). The flow of study participants is described in Figure 1. All participants provided written informed consent. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its subsequent revisions. Ethical approval was obtained from the INRCA Institutional Ethics Committee (CE INRCA, Ancona, Italy).

Data Collection and Definitions

Comprehensive clinical data collected included demographic characteristics, anthropometric measures (BMI, WC), current cardiovascular comorbidities and pharmacotherapy, laboratory evaluations [sodium, potassium, eGFR, glucose, total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides], and indirect insulin independent bioanthropometric indexes of IR. The low-density lipoprotein-cholesterol was calculated using the Friedewald equation as modified by Martin-Hopkins [11]. Smoking habit was defined as current smoking or previous smoking of at least 100 cigarettes in a lifetime; BMI was calculated as weight in kilograms divided by height in meters squared; WC was measured in the horizontal plane midway between the lowest ribs and the iliac crest; Metabolic Score for IR (METS-IR) and the triglyceride/glucose index were calculated using anthropometric and laboratory parameters [12]. Total treatment intensity score (TIS) was calculated as the sum of the prescribed daily dose to the maximum approved daily dose ratio for each antihypertensive medication [13].

DRC and Plasma Aldosterone Concentration Measurement

DRC (mU/L) and PAC (ng/dL) were measured on blood samples drawn on the morning of the clinical visit. The sample were obtained after at least 2 h in the upright position, and determined by immunochemiluminescent assay (CLIA) on a LIAISON XL® analyzer (DiaSorin, Italy). Analytical performance was assessed in 20-day precision studies. For DRC, within-run coefficients of variation (%CV) ranged from 1.2% to 6.6%, and between-run %CV ranged from 4.1% to 10.0% across

different concentration levels. For PAC, within-run % CV ranged from 1.8% to 4.2%, while between-run %CV ranged from 5.6% to 10.5% across different concentration levels. The patient was advised to maintain a stable diet and not to follow a particularly low-sodium diet in the days before the test, so as not to affect the dosages. RAR was calculated as the ratio between DRC and PAC.

Ambulatory Blood Pressure Measurement and Control

ABPM was performed using the Spacelabs model 90,207 and 90,217 devices with appropriately sized cuffs. Measurements were recorded at 15-min intervals during the day (6:00 a.m.–10:00 p.m.) and every 20 min at night (10:00 p.m.–6:00 a.m.). The higher average office BP value between arms was used for the analyses and to place the ABPM, thus avoiding errors due to interarm BP differences [14]. The device provided mean BP values for 24h, daytime, and night-time periods. The minimum quality criteria for a satisfactory ABPM recording were based on the published recommendations [15]. The night-to-day ratio was expressed as the ratio of mean night-time systolic BP (SBP) to mean daytime SBP percent. The dipper status was defined as a nocturnal SBP reduction ≥ 10% relative to daytime SBP. Controlled hypertension (ABPM criteria) was defined as follows: 24-h SBP <130 mm Hg and 24-h DBP <80 mm Hg, daytime SBP <135 mm Hg and daytime DBP <85 mm Hg, night-time SBP <120 mm Hg, and night-time DBP <70 mm Hg.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median and interquartile range. Skewed variables (RAR, DRC) were normalized using the natural logarithm (Ln) transformation (LnRAR, LnDRC). Categorical variables were expressed as absolute numbers and percentages. Groups were compared using the unpaired *T* test, Mann-Whitney test, and Chi-Square tests. Spearman's test was used to evaluate correlations between RAAS biomarkers and ABPM parameters. Multivariable linear regression analyses were used, with ABP parameters as dependent variables. Multivariable logistic regression analyses were used, with ABP control (binary) as the dependent variable. Adjustment models were model 1 adjusted for age and sex, model 2 adjusted for age, sex, eGFR, and TIS. Two-way analysis of variance (ANOVA) test was used to assess the interaction between weight status and ABP control on RAR and DRC values. Receiver-operating characteristic (ROC) curves were used to evaluate the accuracy (AUC) of RAR and DRC in discriminating ABP control. All statistical analyses, including the matching process, were conducted with MedCalc® version 23.2.8 for Microsoft Windows. A p value <0.05 was considered statistically significant.

Results

Description of the Study Population

Baseline characteristics of the study population according to weight status are shown in Table 1. The two groups (normal-weight, n = 97; OW/OB, n = 97) were comparable for age, sex distribution, smoking status, eGFR, TIS, and RAAS biomarkers (DRC, PAC, RAR). As expected, the group with OW/OB had significantly higher BMI (33.9 ± 3.9 vs. 25.1 ± 1.3 kg/m^2, $p < 0.001$) and WC (112 ± 10.5 vs. 99.8 ± 10.9 cm, $p < 0.001$). Also, the group with OW/OB showed a dysmetabolic pattern with lower high-density lipoprotein-cholesterol, higher triglycerides, and significantly higher IR indexes (triglyceride/glucose index and METS-IR). ABPM showed that mean 24h and daytime BP values were similar, but the group with OW/OB had a significantly higher night-time DBP [66 (52–72) vs. 54 (52–70) mm Hg, $p = 0.005$] and a lower percentage of dippers (23.7% vs. 38.1%, $p = 0.030$). The prevalence of controlled BP across 24h, daytime, and night-time was similar between groups.

Correlations and Associations with Ambulatory BP Levels

In the normal-weight group, RAR and DRC showed significant inverse correlations with 24h SBP, daytime SBP, night-time SBP, and night-time DBP (e.g., RAR with 24h SBP: $r = -0.34$, $p < 0.001$; DRC with 24-h SBP: $r = -0.36$, $p < 0.001$). In contrast, PAC did not correlate with any of the ABPM parameters. In both normal-weight and participants with OW/OB, no significant correlations were observed between TIS and RAAS biomarkers or ABP parameters. The complete Spearman's correlation analysis is presented in online supplementary Table S1.

Multivariable linear regression confirmed that higher LnRAR and LnDRC were consistently and significantly associated with lower systolic ABP parameters and night-time DBP, even after full adjustment (model 2). However, in the OW/OB group, this inverse linear association was lost. RAR and DRC were not significantly correlated with ambulatory SBP or DBP parameters in adjusted models. Table 2 summarizes the results of the multivariate linear regression analyses of RAR, DRC, and ABP parameters according to weight status.

Table 1. Characteristics of the study population according to weight status

	Normal-weight (n = 97)	OW/obese (n = 97)	p value
Demographics and anthropometrics			
Age, years	53.8±9.1	53.8±9.1	$p = 0.990$
Sex (M, %)	71.1	71.1	$p = 0.990$
BMI, kg/m^2	25.1±1.3	33.9±3.9	$p < 0.001$*
WC, cm	99.8±10.9	112±10.5	$p < 0.001$*
Smokers (%)	29.9	32	$p = 0.750$
Diabetes (%)	6.1	10.3	$p = 0.297$
Laboratory parameters			
Sodium, mmol/L	139.8±3.4	139.1±3.6	$p = 0.140$
Potassium, mmol/L	4.2±0.4	4.1±0.4	$p = 0.700$
eGFR, mL/min/1.73 m^2	87.7±15.9	87.5±15.7	$p = 0.990$
Glucose, mg/dL	98 (88–119)	101 (90–112)	$p = 0.630$
Total cholesterol, mg/dL	201 (171.7-224.2)	205 (178.7-220.5)	$p = 0.660$
HDL-C, mg/dL	53 (44-61)	45 (40-54)	$p = 0.002$*
LDL-C, mg/dL	127.8 (99.3-147.6)	125.1 (109.5-144.1)	$p = 0.460$
Triglycerides, mg/dL	103 (75-154.2)	136 (89-187)	$p = 0.005$*
TyGi	4.67±0.33	4.78±0.30	$p = 0.014$*
METS-IR	39.15±6.02	52.41±8.57	$p < 0.001$*
DRC, mU/L	19.6 (7.7-46.1)	20.5 (9.4-54.5)	$p = 0.640$
Plasma aldosterone concentration (ng/dL)	12.3 (8.4-18.1)	12.7 (7.1-18.2)	$p = 0.660$
Renin-aldosterone-ratio	1.6 (0.6-4.8)	1.8 (0.6-5.4)	$p = 0.510$
Antihypertensive therapy			
RASi + CCB (%)	44.3	38.1	$p = 0.060$
RASi + TZD (%)	23.7	34.0	$p = 0.110$
RASi + CCB + TZD (%)	32.0	27.8	$p = 0.530$
Treatment intensity score	1.5 (1-2)	1.5 (1.2-2)	$p = 0.990$
Ambulatory blood pressure parameters			
24-h SBP (mm Hg)	118 (108.5-130.5)	114 (106-131.2)	$p = 0.230$
24-h diastolic BP (mm Hg)	79 (75.7-84.2)	78 (74.7-83)	$p = 0.290$
Daytime SBP (mm Hg)	121 (107.7-134.2)	112 (103-132)	$p = 0.090$
Daytime diastolic BP (mm Hg)	84 (79-89)	83 (77.9-89)	$p = 0.590$
Night-time SBP (mm Hg)	99 (95-123)	110 (97.7-120)	$p = 0.110$
Night-time diastolic BP (mm Hg)	54 (52-70)	66 (52-72)	$p = 0.005$*
Night-to-day ratio (%)	8.5 (5.6–11.1)	7.7 (5-10)	$p = 0.600$
Dippers (%)	38.1	23.7	$p = 0.030$*
Controlled 24-h BP (%)	52.6	50.6	$p = 0.990$
Controlled daytime BP (%)	60.8	64.9	$p = 0.550$
Controlled night-time BP (%)	63.9	53.6	$p = 0.140$

eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TyGi, triglyceride/glucose index; METS-IR, metabolic score for insulin resistance; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; TZD, thiazide/thiazide-like diuretic; BP, blood pressure. p value is for the difference between the normal-weight group and the OW/obese group. *p value <0.05.

Association with Ambulatory BP Control

Logistic regression analysis demonstrated that higher values of LnRAR and LnDRC were independently associated with increased odds of ABP control across all periods (24h, daytime, night-time) in both normal-weight and in the group with OW/OB, after full adjustment (Table 3). In patients with OW/OB, LnRAR OR for 24-h BP control was 1.74 (95% CI 1.25–2.42, $p = 0.001$) and LnDRC OR for 24-h BP control was 1.72 (95% CI 1.19–2.50, $p = 0.003$). The two-way ANOVA showed that patients with controlled ABP had higher median RAR and DRC values than those with uncontrolled, regardless of the weight status. All p values for the interaction between ABP control status and weight status were > 0.05 (Fig. 2).

Table 2. Linear regression of renin-aldosterone ratio, DRC and ambulatory blood pressure parameters according to weight status

Group	Model	Outcome	LnRAR β (95% CI)	LnDRC β (95% CI)
Normal-weight	Unadjusted	24-h SBP	−3.76 (−5.68 to −1.84)§	−4.23 (−6.20 to −2.25)§
		24-h DBP	0.37 (−0.73 to 1.46)	0.33 (−0.80 to 1.47)
		Daytime SBP	−3.16 (−5.30 to −1.03)§	−3.95 (−6.12 to −1.76)§
		Daytime DBP	0.92 (−0.27 to 2.10)	0.69 (−0.54 to 1.94)
		Night-time SBP	−4.21 (−6.46 to −1.96)§	−4.71 (−7.03 to −2.38)§
		Night-time DBP	−2.36 (−3.97 to −0.76)§	−2.93 (−4.58 to −1.29)§
		Night-to-day ratio	0.59 (−0,28 to 1,47)	0.29 (−0.63 to 1.21)
	Model 1*	24-h SBP	−3.76 (−5.70 to −1.81)§	−4.26 (−6.29 to −2.24)§
		24-h DBP	0.22 (−0.86 to 1.30)	0.99 (−1.03 to 1.23)
		Daytime SBP	−3.16 (−5.33 to −0.99)§	−3.98 (−6.22 to −1.75)§
		Daytime DBP	0.81 (−0.38 to 2.00)	0.53 (−0.72 to 1.79)
		Night-time SBP	−4.26 (−6.54 to −1.98)§	−4.83 (−7.21 to −2.46)§
		Night-time DBP	−2.43 (−4.06 to −0.80)§	−3.09 (−4.76 to −1.41)§
		Night-to-day ratio	0.65 (−0,22 to 1,53)	0.38 (−0.55 to 1.31)
	Model 2**	24-h SBP	−3.58 (−5.55 to −1.61)§	−4.12 (−6.19 to −2.06)§
		24-h DBP	0.12 (−0.97 to 1.22)	−0.02 (−1.16 to 1.15)
		Daytime SBP	−2.97 (−5.17 to −0.77)§	−3.82 (−6.11 to −1.53)§
		Daytime DBP	0.70 (−0.48 to 1.89)	0.46 (−0.79 to 1.73)
		Night-time SBP	−4.11 (−6.41 to −1.82)§	−4.83 (−7.23 to −2.43)§
		Night-time DBP	−2.29 (−3.94 to −0.64)§	−3.00 (−4.71 to −1.29)§
		Night-to-day ratio	0,67 (−0.19 to 1.54)	0.48 (−0.44 to 1.41)
OW				
Obese	Unadjusted	24-h SBP	−2.35 (−4.55 to −0.15)§	−2.48 (−5.08 to 0.12)
		24-h DBP	0.91 (−0.30 to 2.12)	0.67 (−0.76 to 2.11)
		Daytime SBP	−1.46 (−3.88 to 0.96)	−1.19 (−4.06 to 1.68)
		Daytime DBP	0.66 (−0.59 to 1.91)	0.47 (−1.01 to 1.95)
		Night-time SBP	−2.57 (−5.10 to −0.04)§	−2.54 (−5.55 to 0.46)
		Night-time DBP	−1.09 (−2.80 to 0.63)	−1.23 (−3.26 to 0.79)
		Night-to-day ratio	0,38 (−0.49 to 1.25)	0.51 (−0.52 to 1.55)
	Model 1*	24-h SBP	−2.21 (−4.46 to 0.03)	−2.30 (−4.97 to 0.37)
		24-h DBP	0.85 (−0.37 to 2.07)	0.59 (−0.86 to 2.04)
		Daytime SBP	−1.52 (−4.00 to 0.97)	−1.25 (−4.21 to 1.70)
		Daytime DBP	0.46 (−0.79 to 1.70)	0.20 (−1.27 to 1.68)
		Night-time SBP	−2.40 (−4.99 to 0.18)	−2.32 (−5.40 to 0.75)
		Night-time DBP	−1.13 (−2.89 to 0.63)	−1.28 (−3.37 to 0.79)
		Night-to-day ratio	0.22 (−0.65 to 1.10)	0.32 (−0.72 to 1.36)
	Model 2**	24-h SBP	−2.07 (−4.34 to 0.19)	−2.17 (−4.86 to 0.51)
		24-h DBP	0.90 (−0.33 to 2.14)	0.61 (−0.85 to 2.09)
		Daytime SBP	−1.39 (−3.90 to 1.12)	−1.12 (−4.10 to 1.85)
		Daytime DBP	0.50 (−0.76 to 1.76)	0.23 (−1.26 to 1.72)
		Night-time SBP	−2.27 (−4.88 to 0.34)	−2.25 (−5.35 to 0.84)
		Night-time DBP	−0.95 (−2.70 to 0.80)	−1.15 (−3.22 to 0.91)
		Night-to-day ratio	0.23 (−0.60 to 1.07)	0.38 (−0.59 to 1.37)

SBP, systolic BP; DBP, diastolic BP; β, regression coefficient; CI, confidence interval; eGFR, estimated glomerular filtration rate; TIS, treatment intensity score. §p value <0.05. *Model 1: Adjusted for Age and Sex. **Model 2: Adjusted for Age, Sex, eGFR, and TIS.

Discrimination Ability for Ambulatory BP Control

ROC analyses showed that both RAR and DRC demonstrated moderate discriminatory ability for ABP control in both groups and in the different time periods, as AUC values ranged from 0.637 to 0.746 (Fig. 3, bottom). Direct pairwise comparisons between the two groups (normal-weight vs. OW/OB) revealed no statistically significant differences in AUC values of RAR

Table 3. Logistic regression analysis of RAR and DRC for controlled ambulatory blood pressure according to weight status

Group	Model	Outcome (controlled ABP)	LnRAR	LnDRC
			OR (95% CI), *p* value	OR (95% CI), *p* value
Normal-weight	Unadjusted	24-h BP	1.61 (1.18–2.19), $p = 0.002$	1.59 (1.15–2.19), $p = 0.002$
		Daytime BP	1.41 (1.05–1.89), $p = 0.024$	1.54 (1.12–2.12), $p = 0.008$
		Night-time BP	1.67 (1.22–2.29), $p = 0.001$	1.86 (1.31–2.66), $p = 0.006$
	Model 1*	24-h BP	1.62 (1–19–2.22), $p = 0.002$	1.60 (1.15–2.22), $p = 0.002$
		Daytime BP	1.40 (1.04–1.89), $p = 0.027$	1.51 (1.09–2.10), $p = 0.013$
		Night-time BP	1.68 (1.22–2.30), $p = 0.001$	1.89 (1.32–2.71), $p = 0.005$
	Model 2**	24-h BP	1.62 (1.18–2.23), $p = 0.002$	1.58 (1.13–2.20), $p = 0.003$
		Daytime BP	1.39 (1.03–1.88), $p = 0.031$	1.50 (1.07–2.09), $p = 0.013$
		Night-time BP	1.66 (1.20–2.28), $p = 0.018$	1.86 (1.29–2.68), $p = 0.007$
OW				
Obese	Unadjusted	24-h BP	1.79 (1.29–2.48), $p = 0.001$	1.79 (1.24–2.58), $p = 0.001$
		Daytime BP	1.83 (1.30–2.59), $p = 0.001$	2.17 (1.43–3.31), $p = 0.003$
		Night-time BP	1.57 (1.15–2.14), $p = 0.004$	1.64 (1.14–2.36), $p = 0.002$
	Model 1*	24-h BP	1.75 (1.26–2.43), $p = 0.001$	1.73 (1.19–2.50), $p = 0.003$
		Daytime BP	1.88 (1.31–2.69), $p = 0.001$	2.23 (1.44–3.44), $p = 0.003$
		Night-time BP	1.57 (1.14–2.16), $p = 0.004$	1.64 (1.13–2.37), $p = 0.002$
	Model 2**	24-h BP	1.74 (1.25–2.42), $p = 0.001$	1.72 (1.19–2.50), $p = 0.003$
		Daytime BP	1.90 (1.31–2.76), $p = 0.001$	2.21 (1.41–3.44), $p = 0.001$
		Night-time BP	1.56 (1.14–2.15), $p = 0.005$	1.64 (1.13–2.37), $p = 0.002$

*Model 1: adjusted for age and sex; **Model 2: adjusted for age, sex, eGFR, and TIS. OW/OB, overweight/obesity; RAR, renin-aldosterone ratio; DRC, direct renin concentration; OR, odds ratio; CI confidence interval; BP, blood pressure; eGFR, estimated glomerular filtration rate; TIS, treatment intensity score.

and DRC across the 24h, daytime, or night-time periods (Fig. 3; Table 4). Furthermore, a sensitivity analysis according to the combinations of drug classes on the overall population was performed. Both DRC and RAR, regardless of the time period, showed a significantly higher discriminative performance in the group of patients treated with a triple combination of RASi+CCB+TZD compared to the group receiving RASi+CCB. On the contrary, no difference emerged comparing double combination therapy (RASi+CCB vs. RASi+TZD) and between RASi+TZD and the triple combination (online suppl. Fig. S2 and Table S2).

Discussion

In this study, conducted on a cohort of adults with essential hypertension receiving stable combination therapy that included a RASi, a TZD, and/or a CCB, both DRC and the RAR showed significant inverse correlations with several ABP parameters, particularly night-time BP, whereas PAC alone was not associated with any of the ABP measures. A significant and independent inverse linear association was observed between the RAR and DRC and ABP parameters in the normal-weight group, which was lost in patients with visceral OW or OB. However, when the outcome was shifted to ABP control, the independent associations of both RAR and DRC remained significant in both groups.

In treated patients with essential hypertension, greater RAAS modulation – primarily through elevated renin levels – appeared to be associated with better BP control. However, this association should be interpreted cautiously, as it likely reflects pharmacologic effects (renin elevation and aldosterone suppression due to RASi and/or diuretic therapy) rather than a direct marker of treatment response.

Prior studies have proposed phenotyping hypertension based on underlying pathophysiological mechanisms, including baseline renin concentrations as a surrogate for volume overload versus increased vascular resistance [16, 17]. Stratifying hypertensive patients by

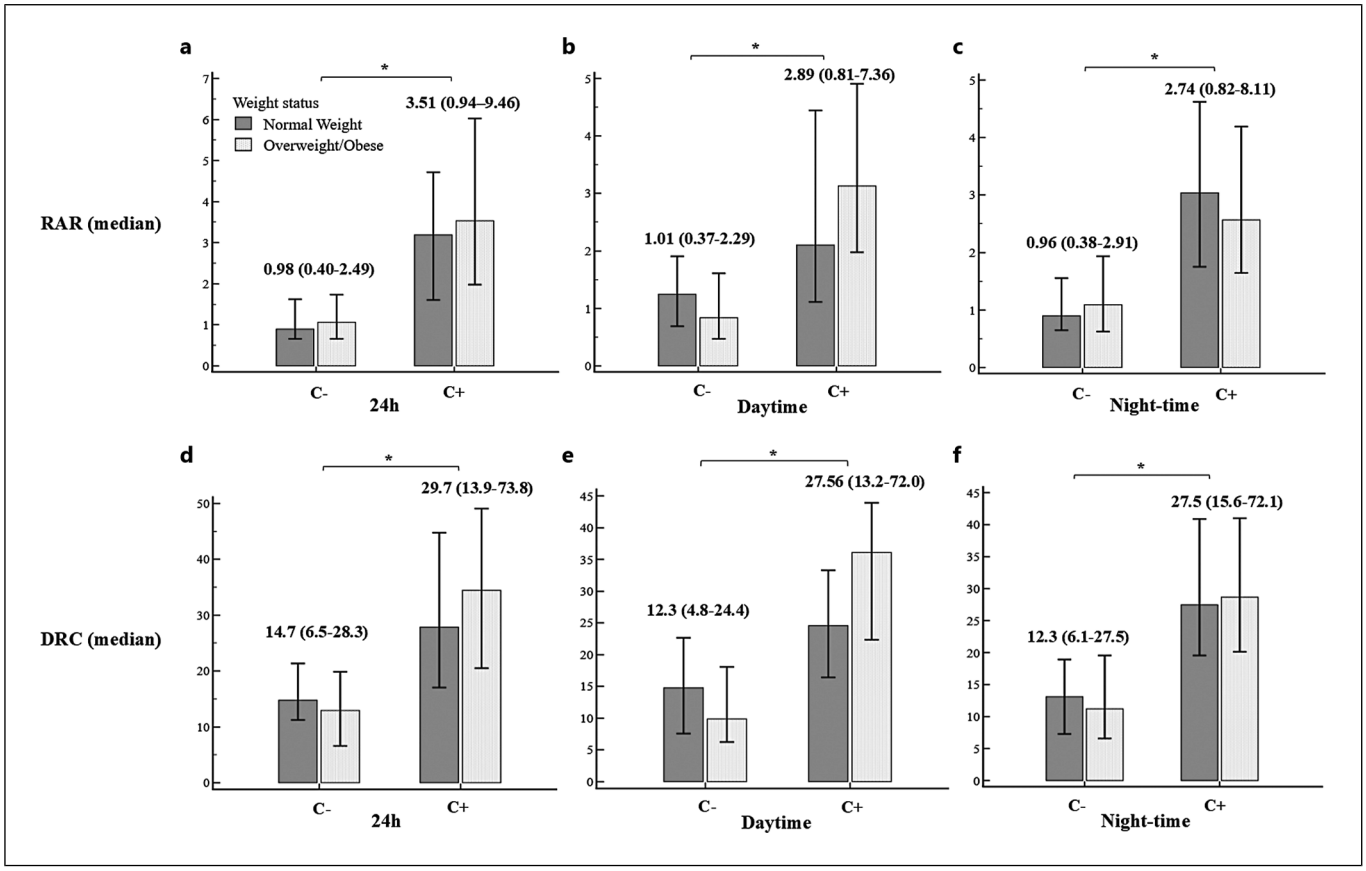

Fig. 2. Median RAR and DRC between controlled and uncontrolled ABP according to weight status. The figure shows the median (interquartile range) values of RAR (panels **a–c**) and DRC (panels **d–f**) in the controlled and uncontrolled BP groups in each ABPM period. Median RAR and DRC of the controlled groups are significantly higher compared to the uncontrolled group, regardless of the ABPM periods (*p values <0.001; Mann-Whitney test). p value for interaction between ABP control and weight status (two-way ANOVA) for RAR: 24-h BP control*weight status = 0.590; daytime BP control*weight status = 0.266; night-time BP control*weight status = 0.894; p value for interaction between ABP control and weight status (two-way ANOVA) for DRC: 24-h BP control*weight status = 0.979; daytime BP control*weight status = 0.501; night-time BP control*weight status = 0.407. RAR, renin-aldosterone ratio; DRC, direct renin concentration; C, control; BP, blood pressure.

renin levels represents a shift from treating hypertension as a single entity toward developing mechanistically informed treatment algorithms. Our findings expand on this paradigm, demonstrating that RAR, which has not been used before in this context, could be a valuable tool for assessing BP behavior in patients with OW/OB treated with RASi-based regimens. This aligns with our previous real-life work, which demonstrated that higher RAR values were associated with improved nocturnal BP profiles in RASi-treated patients [7]. Following the valuable commentary that provided insights into the limitations of interpreting results from this earlier work [18], we attempted to address potential confounding by conducting a DRC and PAC assessment, selecting a more restricted population in terms of comorbidities, focusing on OW/OB and pharmacological therapies, while maintaining the clinical context relevance.

From a mechanistic standpoint, these findings are particularly relevant. Thiazide diuretics (TZDs) reduce blood volume and enhance antihypertensive efficacy but stimulate compensatory RAAS activation due to sodium and water excretion [19]. In this context, a high RAR may reflect sufficient aldosterone suppression by the associated RASi despite a reactive increase in renin, signaling an effective pharmacologic response. Conversely, a low RAR could indicate suboptimal aldosterone suppression, incomplete RAAS blockade, low adherence to therapy, or underlying primary aldosteronism – factors that may contribute to persistent hypertension, particularly at night-time.

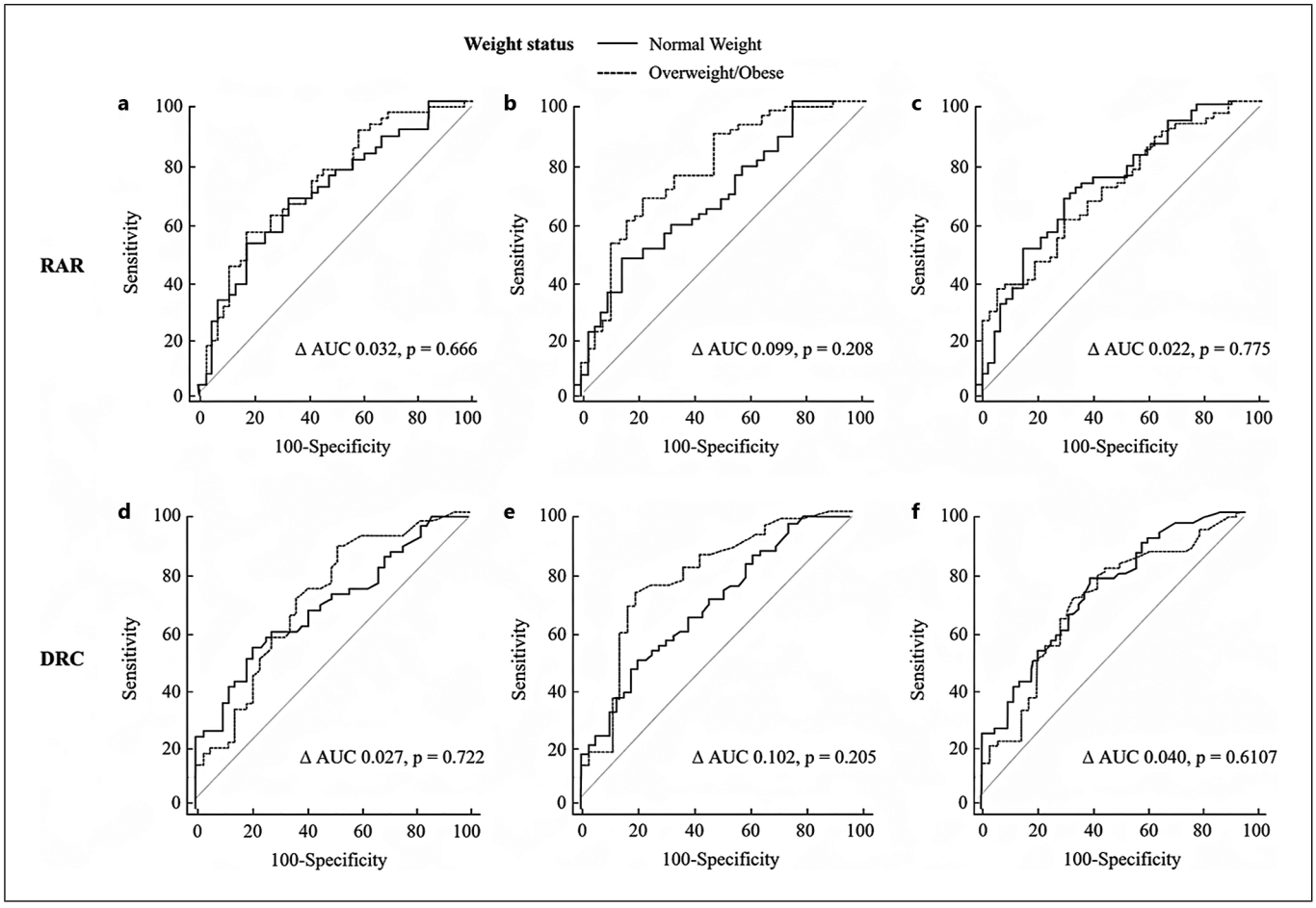

Fig. 3. ROC curves of RAR and DRC for ABP control between patients with normal weight and those with OW/OB. The figure shows the ROCs of RAR and DRC in both weight status and the *p* values of their AUC deltas for each ABPM period (panels **a**, **d**: 24-h BP control. **b**, **e**: daytime BP control. **c**, **f**: night-time BP control). RAR, renin-aldosterone ratio; DRC, direct renin concentration; AUC, area under the curve; CI, confidence interval; BP, blood pressure.

Notably, the accuracy of RAR and DRC on ABP control is greater in patients receiving triple combination therapy, including a diuretic, in whom greater RAAS modulation would be expected. Although it is the DRC that guides the associations found, the RAR dosage might serve the dual clinical purpose of excluding primary aldosteronism and evaluating hormonal and clinical response to treatment.

The observed loss of the inverse linear association between RAR/DRC and BP levels in the OW/OB group, while maintaining the association with BP control, suggests that altered RAAS responsiveness in OB blunts the antihypertensive effects of RAAS blockade. This concept is applicable in the clinical setting of patients with central OB or OW, in which a baseline dysregulation of the RAAS involving a pathological increase in aldosterone production has been extensively described [20].

Multiple factors contribute to this altered responsiveness. In individuals with OW or OB and hypertension, BMI correlated with PAC independently of age, sex, and sodium intake, confirming a pathophysiological link between excessive adiposity and aldosterone secretion [21]. Human adipocytes produce aldosterone through both angiotensin II (AngII)-dependent and independent mechanisms [9, 22, 23]. Metabolically unhealthy OW/OB patients showed higher RAAS activity markers (PAC, AngII, and DRC) compared to metabolically healthy OW/OB patients [24]. Adipose tissue also produces angiotensinogen, further promoting AngII and aldosterone production. The RAAS components dysregulation is

Table 4. Areas under the curve of renin-aldosterone ratio and DRC for ABP control according to weight status

RAR	Group	AUC	95% CI	*p* value
24-h BP control	Normal-weight	0.693	0.591 – 0.783	$p = 0.003$
	OW/OB	0.725	0.625 – 0.811	$p < 0.001$
Daytime BP control	Normal-weight	0.637	0.534 – 0.733	$p = 0.016$
	OW/OB	0.737	0.637 – 0.821	$p < 0.001$
Night-time BP control	Normal-weight	0.696	0.594 – 0.785	$p < 0.001$
	OW/OB	0.674	0.571 – 0.766	$p = 0.002$
Direct renin concentration	**Group**	**AUC**	**95% CI**	***p* value**
24-h BP control	Normal-weight	0.660	0.557 – 0.753	$p = 0.004$
	OW/OB	0.688	0.585 – 0.778	$p = 0.006$
Daytime BP control	Normal-weight	0.645	0.541 – 0.739	$p = 0.012$
	OW/OB	0.746	0.648 – 0.829	$p < 0.001$
Night-time BP control	Normal-weight	0.711	0.610 – 0.798	$p = 0.001$
	OW/OB	0.671	0.568 – 0.763	$p = 0.004$

AUC, area under the curve; CI, confidence interval; BP, blood pressure.

exacerbated in the context of IR and hyperinsulinemia, typical of OW/OB patients with metabolic syndrome, which overactivates both circulating and local RAS [25]. OB is also associated with increased sympathetic nervous system activity, which stimulates the RAAS [26]. Defective natriuretic peptide activity [27] and the presence of OSA further contribute to RAAS overactivation in this population [28, 29]. All these local and systemic mechanisms contribute to maintaining an inappropriately high RAAS [30].

These complex mechanisms in the OW/OB patient population may influence the relationship between BP response to antihypertensive therapy and RAAS hormonal response, leading to the observed differences in BP levels compared to normal-weight controls. Our findings pave the way for future mechanistic studies in humans, with the ultimate goal of greater personalization of antihypertensive therapy.

Overall, our results are consistent with previous studies, which demonstrate that plasma renin activity (PRA) predicts the BP-lowering response to both atenolol and hydrochlorothiazide [31], and that diuretics are more effective in low-renin patients while RASi yield better responses in high-renin individuals [32]. However, the antihypertensive response to RASi or TZD may vary with age and ethnicity [33–35], which must be considered in applying RAR-guided approaches across diverse patient populations. The availability of DRC and PAC measurements in patients with central OW or OB and suboptimal BP control offers an effective strategy for screening primary aldosteronism, which has a higher reported prevalence in individuals with OW/OB [36–38].

Current international guidelines recommend DRC and PAC measurements primarily for screening primary aldosteronism, not for treatment monitoring, as examined in our study [3, 39, 40]. Recently, a rise in renin has been proposed as a clinical biomarker also to guide drug therapy in primary aldosteronism, as it reflects the efficacy of mineralocorticoid receptor blockade. In these patients, an elevated cardiometabolic risk persists despite adequate BP control and normalization of serum potassium, and renin levels may indicate the actual effective suppression of the system [41]. Clinically, our findings could suggest an additional advantage in the integration of DRC, PAC, and their ratios (aldosterone-to-renin ratio and RAR) into the routine practice of uncontrolled hypertensive patients with OW/OB on combination therapy. In these patients, RAR may help identify biochemically responsive patients yet remain uncontrolled, guiding additional therapeutic decisions based on RAAS biomarkers, such as RASi intensification, adding an mineralocorticoid receptor antagonist, or further screening for secondary hypertension. Given the low cost and accessibility of renin and aldosterone assays, this strategy is feasible for implementation in real-world settings.

Poor BP control is common in central OW/OB, underdiagnosed, undertreated and therefore a primary driver of adverse clinical outcomes [42]. Conventional home and office BP measurements to test BP control are frequently susceptible to methodological and patient-related factors (such as body position, the white-coat effect, etc.); therefore, ABPM is the gold standard for BP control assessment during

whole day [43, 44]. However, the systematic implementation of ABPM in the real-life setting is often hindered by concerns regarding cost, time, and the requirement for specialized referral for more accurate readings [45]. Notably, in a significant proportion of patients with uncontrolled BP, particularly those with central OB, a form of primary aldosteronism may be present, even if subtle or masked by concomitant therapies [46]. Therefore, screening via PAC and DRC is recommended [39]. Also, given the known modulations of the RAAS induced by RAS inhibitors and the other main antihypertensive drug classes [4], our study evaluated the potential of RAAS biomarkers in identifying patients with a hormonal profile compatible with poorly controlled BP, validated against ABPM findings. In this clinical setting, there is an evident need for plasma biomarkers with a strong mechanistic implication (both pathological and pharmacological) and capable of simultaneously screening for secondary causes of poor BP control and streamlining and refining the appropriate use of ABPM. Taken together, these findings highlight the relevance of RAAS modulation in managing hypertension in patients with visceral adiposity. Although an independent association between RAR values and ABP control clearly emerged in OW/OB, the moderate accuracy of the ROC curves did not allow us to identify precise useful thresholds for clinical practice that would offer a valuable tool for optimizing antihypertensive management in real-world settings. Future prospective studies are warranted to validate these results and explore whether RAAS biomarkers might guide treatment strategies, improving long-term cardiovascular outcomes in this population.

Study Strengths and Limitations

The systematic use of ABPM provides a comprehensive and accurate assessment of BP control. The study comprehensively evaluated the relationship between ABP values and RAAS biomarkers as well as the discrimination utility of PAC and DRC concentrations for ABP control in the specific context of outpatients with central distribution of adiposity and OB. The study includes a precise PRA and PAC that were measured in the same laboratory throughout the study, using a method with sufficient sensitivity. We performed a series of rigorous statistical analyses adjusted for multiple relevant confounders and compared the results with a matched control group of lean individuals, reinforcing the internal validity of the findings further. The higher prevalence of men in our real-life sample reflects the distribution of OW/OB in Italy [47]. Although the sample size did not allow us to perform sex-specific sensitivity analyses, the associations found appear to be independent of sex, as shown by the adjusted models. For the sake of clarity and clinical relevance, we focused on reporting the most interpretatively significant results within the main text. To ensure full transparency and completeness, the results of all additional supportive tests have been provided in the online supplementary material. This approach allowed us to highlight the biomarkers' practical application while maintaining a robust underlying statistical framework.

This study also has several limitations to be addressed. Its observational design limits causal inference, and residual confounding from potentially unmeasured variables cannot be excluded. For example, we were unable to obtain data of known regulators of RAAS, such as dietary sodium and volume depletion. Also, the cross-sectional nature of the data precludes assessment of long-term cardiovascular outcomes available. Finally, although our findings were internally consistent, external validation in an independent cohort would be necessary to confirm their generalizability and strengthen the robustness of our conclusions. Our data do not currently allow us to suggest the systematic use of RAR in everyday clinical practice in treated hypertensives to guide their drug therapy. Further well-designed prospective randomized trials with wider sample sizes comparing RAR-guided management to usual care, both for newly diagnosed and especially for treated but uncontrolled patients, are needed.

Conclusion

RAR is independently and inversely associated with 24h, daytime, and night-time BP control in patients with OW/OB and essential hypertension taking a stable combination antihypertensive RASi-based therapy. This association is likely an expression of the modulation of DRC to antihypertensive therapy. These findings cautiously suggest a potential role of RAR as a mechanism-based index reflecting pharmacodynamic antihypertensive effects and therefore eventually useful to evaluate treatment effectiveness and responsiveness in this population. Future prospective studies are warranted to validate these results and explore whether RAAS biomarkers might guide treatment strategies, improving long-term cardiovascular outcomes.

Statement of Ethics

This observational study was approved by the local institutional Ethics Committee (Comitato Etico IRCCS INRCA, Ancona, Italy; Approval Code: SC/14/443; Approval Date: 24 July 2014). Clinical investigations have been conducted in accordance

with the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments. All patients enrolled in the study gave their written informed consent to participate.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.L. and F.S. contributed to data curation, investigation, methodology, statistical analysis, and writing of the original draft. R.S., F.S., and F.G. contributed to conceptualization, resources, supervision, validation, and project administration. A.G., C.M., S.M., and C.T. contributed to data acquisition and curation. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity, and accuracy.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author (M.L.) upon request.

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