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Cardiovascular and Renal Complications in Patients with Resistant Hypertension

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Abstract With an increased prevalence, resistant hypertension is recognized as an entity with a high cardiovascular morbidity and mortality. In a large cohort of patients with resistant hypertension, the crude incidence rate of total cardiovascular events reached 4.32 per 100 patient-years of follow-up (19.6 %), with a cardiovascular mortality of 8.3 % (incidence rate of 1.72 per 100 patient-years). Cardiovascular event rates are significantly higher in resistant hypertensives compared with non-resistant (18.0 % versus 13.5 %). In the same way, the prevalence of established cardiovascular and renal disease, as the asymptomatic organ damage (represented by left ventricular hypertrophy, carotid wall thickening, arterial stiffness, and microalbuminuria) is higher in these patients. Many studies have demonstrated a strong association between damage to these organs with higher blood pressure levels, the diagnosis of true resistant hypertension, and refractory hypertension. All efforts should be employed in order to control blood pressure and also to regress and/or prevent subclinical cardiovascular and renal damage. The focus should be on prevention of cardiovascular and renal complications, improving the prognosis of resistant hypertension.

Keywords Resistant hypertension · Cardiovascular complications · Renal complications · Prognosis

This article is part of the Topical Collection on *Resistant Hypertension*

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Introduction

Hypertension is a common clinical condition related to higher risk of stroke, heart failure, myocardial infarction, and renal disease [1, 2]. Despite successes in prevention and treatment, hypertension currently remains a major cause of morbidity and mortality [3]. It was estimated that in 2025, there will be approximately 1.5 billion adults with hypertension worldwide [4], which determines a huge importance in health and economics aspects considering that high blood pressure (BP) is one of the leading risk factors for global disease burden [5].

A considerable proportion of general hypertensive patients, estimated between 10 – 20 %, are defined as resistant hypertension (RHT), diagnosed when there is failure to reach office BP control despite using at least three anti-hypertensive medications in adequate dosages, ideally including one diuretic. Patients using at least four anti-hypertensive drugs to control BP also are considered RHT [6•]. These patients have higher prevalence of diabetes, dyslipidemia, physical inactivity, and sleep apnea [6•, 7–9], and develop more target organ damage (TOD) in the heart, brain, kidneys, and blood vessels when compared with patients with controlled hypertension [7, 10–14]. Consequently, they have a higher incidence of major cardiovascular events such as coronary artery disease, stroke, and heart failure [15••, 16, 17]. As was pointed out in a recent review, the relationships between cardiovascular disease and TOD can be bidirectional in RHT [18]. Persistently high BP is implicated in structural and functional changes leading to development of left ventricular hypertrophy, increased aortic stiffness, atherosclerotic plaques, microvascular disease, and renal dysfunction, and turns hypertension gradually more resistant to treatment [18]. It may sound redundant, but that is exactly the meaning: RHT aggravates RHT. The more severe and longer is the sustained hypertension, the worse will be TOD development. Reciprocally, with more established TOD, the worse will be the treatment resistance.

More recently, a new subgroup was defined called refractory hypertension. The term "refractory" was formerly used as a synonym of "resistant", but Acelajado and colleagues used it to define an "extreme phenotype of anti-hypertensive treatment failure" [16]. In two previous studies, the prognosis of refractory hypertension could be evaluated. [17, 19••]. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) [20] is a longitudinal population-based study of 30,000 African-American and white adults aged≥45 years that looked for the causes for the excess stroke mortality in the Southeastern US and among African-Americans. In the analysis of patients from this study [19••], uncontrolled hypertension despite using at least five drugs, was related to higher cardiovascular risk. The other one, the Reduction of Atherothrombosis for Continued Health (REACH) registry [21], evaluated over 67,000 patients (≥45 years) in 44 countries with at least 3 risk factors for atherothrombosis and/or established arterial disease. The main purpose of the study was to evaluate if cardiovascular risk factors present comparable patterns in different countries around the world. In this study, after a follow-up of 4 years, patients with refractory hypertension (using five or more anti-hypertensive drugs) had higher risk of CV mortality compared with those on three or fewer agents [17].

Despite pharmacological interventions, BP control in RHT patients remains challenging, and new interventional procedures, such as renal sympathetic denervation, have been recently been proposed and extensively discussed, although some doubts still remain regarding the sustained effect in decreasing BP and the possibility of reversing sub-clinical damage with prognostic impact on cardiovascular outcomes [22]. Although not fully established, it reopens the discussion whether we should have as aims of treatment (pharmacological or not) the regression of TOD, especially sub-clinical alterations, beyond and despite the BP goal to be achieved [23]. Because of the relevance of this topic, the objective of this review is to update data available related to RHT and TOD with emphasis on cardiovascular and renal complications, including sub-clinical damage and prognostic aspects.

Resistant Hypertension and Cardiovascular Complications

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) is a structural remodeling of the heart. The thickening of ventricle walls in response to pressure overload results in an increase of left ventricular mass (evaluated by left ventricular mass indexed to body surface area - LVMI). It is one of the most frequent cardiac complications due to persistent high BP levels. Assessed by echocardiography or electrocardiography, it is considered an asymptomatic TOD and equally a risk factor predictive of worse prognosis [2, 23, 24]. Based on updated criteria, the prevalence of echocardiographic LVH in RHT patients ranges from 55 to 75 % [6•, 8, 25], and may vary depending on the method used to calculate LV mass. The most recent definition of LVH is based on LVMI >115 g/m^2 for men and >95 g/m^2 for women [2, 26], but many studies used older values with LVMI>125 and>110 g/m^2, obviously reducing the estimated prevalence.

Concentric hypertrophy (represented by a left ventricular wall-to-radius ratio of ≥0.42) is the most common type of LVH found in RHT [11, 18]. In previous studies with general hypertensives, concentric hypertrophy was more consistently associated with increased cardiovascular risk [2, 27] and with the degree of BP load [28]. LVH is also related to other TOD and cardiovascular markers of worse prognosis [8, 29]. In a cross-sectional study with 705 RHT patients, 534 with echocardiographic LVH, microalbuminuria, and high C-reactive protein were independently associated with LVH diagnosis [29].

When LVH is assessed by electrocardiography (ECG-LVH), although it has less sensitivity, it keeps its prognostic importance. The presence of ECG-LVH, usually detected by Sokolow-Lyon index (SV1+ RV5 or V6>35 mm) or by the Cornell voltage QRS duration product (>244 mV*ms^{-1}), is an independent predictor of cardiovascular events in RHT patients [30••]. In a large study with RHT patients, using 24-h ambulatory blood pressure monitoring (ABPM), ECG- LVH criteria were fulfilled in 18.5 % of patients with true RHT [31••]. Studies conducted in a Brazilian cohort of RHT patients demonstrated an ECG-LVH prevalence varying between 26 to 29 % [30••, 32]. Although echocardiography has an obvious higher sensitivity to detect LVH than ECG, it was previously observed that some electrocardiographic alterations as QTc interval prolongation (>440 ms) and a Cornell product >240 mV*ms^{-1} were associated with increased risk of LVH measured by echocardiogram. When these two alterations are combined, the risk of a high LVMI increases about nine-fold [32]. Furthermore, these ECG measurements are cheaper and easily available, and it was demonstrated that the regression of these electrocardiographic abnormalities during treatment of RHT patients also can improve cardiovascular outcomes and may constitute additional therapeutic goals in RHT management [30••, 33, 34].

In addition, echocardiography provides information about left ventricular diastolic filling and diastolic function. Diastolic dysfunction is a very important condition closely related to hypertension, explaining about 50 % of heart failure occurrence. Most relevant, these alterations may occur in the absence of systolic dysfunction and even without LVH [2], and are associated with increased risk of cardiovascular events, independent from left ventricular mass and ambulatory BP

[35]. However, there are no studies evaluating the prognosis of diastolic function in RHT.

Studies recently conducted in patients after renal sympathetic denervation have demonstrated that left ventricular mass and diastolic dysfunction can be reverted, independent from BP reduction, which may reveal a new bridge between cause-and-effect in TOD development [22]. Aldosterone levels and the effects of spironolactone were also evaluated in the regression of left ventricular mass, measured by cardiac magnetic resonance, in RHT patients. After 3 months of treatment, the authors demonstrated a higher reduction of left ventricular mass and volume, left atrial volume and wall thickness in high aldosterone patients compared to group with normal aldosterone levels [36].

Similarly, in a case-control study, patients with primary aldosteronism had significantly greater left ventricular measurements including LVMI compared with control group. High salt intake determined by 24-h urinary sodium excretion, was an independent predictor for left ventricular wall thickness and mass among these patients, but not in those with essential hypertension. In this way, aldosterone blockade associated with low salt-intake probably results in target organ protection and lower cardiovascular risk. [37]

These arguments sustain that not only the duration and degree of BP elevation, but other neuro-humoral factors, such as activation of the sympathetic nervous system and renin-angiotensin-aldosterone system, are involved with myocardial hypertrophy pathophysiology [38].

Coronary Artery Disease

The prevalence of atherosclerotic coronary artery disease (CAD) varies in different series of RHT patients from 10 % [31••] to 37 % [8, 19••] and it seems to be directly associated with high BP [19••]. In a previous RHT cohort study [15••] in which 556 patients were evaluated after a median follow-up of 4.8 years, the crude incidence rate of total cardiovascular events was 4.32 per 100 patient-years of follow-up, with a total of 44 CAD events (23 acute myocardial infarction, 16 myocardial revascularization, and five sudden deaths). Evaluating the prognostic value of ABPM parameters, the presence of non-dipping pattern duplicated the risk of CAD events [39].

Regarding heart complications in RHT, many analyses have been recently published confirming the poor prognosis, mainly related to cardiac mortality. Three studies [17, 19••, 40] published in the last year have evaluated the higher cardiovascular risk in RHT patients compared with control or non-resistant patients. All studies analyzed data from large hypertensive populations (from the REACH study, the REGARDS study, and the International Verapamil SR-Trandolapril Study [INVEST]) using the traditional definition of RHT, and all of them have equally demonstrated a higher risk of adverse outcomes (including cardiovascular mortality, myocardial infarction, and stroke). INVEST is a randomized, open label, blinded endpoint study that enrolled 22,576 patients (≥50 years) with hypertension and coronary artery diseases at 862 centers in 14 countries [41]. The study compared cardiovascular outcomes in patients treated with a therapeutic scheme including a calcium antagonist or not. In a post hoc analysis, it was demonstrated that patients with RHT (6,490 from a total of 17,190 patients) had a 47 % higher risk of cardiovascular mortality and 61 % higher risk for nonfatal stroke than patients with controlled BP. Moreover, nonfatal stroke was the only adverse outcome that differed in RHT patients compared to uncontrolled hypertensives [40]. In another study performed specifically in patients with coronary heart disease, 11.1 % of 10,001 individuals were considered as having "apparent treatment-resistant hypertension". This group had a 69 % increased risk of coronary heart disease mortality and a 53 % higher risk of any cardiovascular event in comparison to the non-resistant subgroup [42].

Cerebral and Vascular Disease

The brain is the most notable of the target organs related to high BP; arterial hypertension is directly involved in the pathogenesis of stroke and dementia [43]. It was previously demonstrated that the risk of stroke increases continuously above BP levels of approximately 115/75 mmHg.

In RHT patients, these figures seem to be much higher. In a recent prospective evaluation, after a follow-up of 4 years, the risk of non-fatal stroke in the RHT group was 26 % higher than in the non-resistant group [17]. In the same study, it was demonstrated a higher risk associated with the numbers of anti-hypertensive drugs in use (higher in the group on at least five drugs) [17]. Another prospective study [15••] with more than 500 RHT patients showed that higher 24-h systolic and diastolic BP increased the risk of stroke in 42 % and 62 %, respectively, and the baseline diagnosis of true RHT triples this risk. Similarly, Calhoun and colleagues [19••] compared refractory hypertension (at least five drugs) with resistant hypertension (traditional definition, at least three drugs) and non-resistant hypertensive patients. The median Framingham 10-year coronary disease and stroke risk score for all patients with refractory hypertension was, respectively, 50 % and 28 % higher than the risk score for individuals with classic resistant hypertension and more than two-fold the risk score of all participants treated for hypertension. After adjustment for age, race, sex, and geographic region of residence in North America, the median 10-year predicted stroke risk was 8.1 % (95 % CI: 5.9–10.3) higher among those with refractory hypertension than in all treated hypertensive individuals [19••].

Otherwise, there were some subclinical markers of cerebrovascular disease, such as increased common carotid artery

Table 1 Studies performed in patients with resistant hypertension investigating the prevalence and/or incidence of major cardiovascular complications

Study (year) [ref]	Patients (n)	Study design	Population	Duration of follow-up (months)	Objective	Main results
Left Ventricular Hypertrophy						
Cuspidi et al (2001) [11]	105	Cross-sectional	RHT (n=54) vs. non-RHT patients (n=51)	-	Prevalence of cardiac and extracardiac TOD in RHT vs. non-RHT patients	Prevalence of LVH 40 % (RHT) vs. 12 % (non-RHT) Prevalence of carotid IM thickening 36 % (RHT) vs. 14 % (non-RHT)
Salles et al (2007) [29]	705	Cross sectional	RHT patients	-	Relationship of LVH and C-reactive protein and microalbuminuria	Prevalence of LVH: 75.7 % MA (OR: 1.97; 95 % CI: 1.04 – 3.73) and high CRP (1.76; 1.06 – 2.93) were independently associated with LVH
de la Sierra et al (2011) [31••]	8,295	Cross-sectional	RHT patients	-	Clinical differences between true and white-coat RHT patients evaluated by ABPM	Prevalence of ECG-LVH was 18.5 % in true RHT and 14.4 % in white-coat RHT Prevalence of CAD was 9.8 % and stroke was 6.3 % with no significant difference between true and white-coat RHT patients
Salles et al (2010) [30••]	552	Prospective	RHT patients	56	Evaluation of baseline and serial changes in ECG-LVH diagnosis as predictors of cardiovascular morbidity and mortality	Cornell voltage (OR: 1.27; 95 % CI: 1.06 – 1.52) and product (1.30; 1.10 – 1.53) are associated with fatal and non-fatal cardiovascular events. Prevention/regression of Cornell product: 40 % lower risk of CV events.
Salles et al (2009) [33]	538	Prospective	RHT patients	57	Prognostic value of ventricular repolarization prolongation in RHT	Prolonged ventricular repolarization (QTc interval) was associated with CV mortality (OR: 1.45; 95 %CI: 1.07 – 1.97) QTc interval≥460 ms implied a 1.7-fold (1.1 – 2.6) higher risk of fatal and non-fatal CV events.
Salles et al (2010) [34]	532	Prospective	RHT patients	57	Evaluation of baseline and serial changes in strain pattern as predictors of cardiovascular morbidity and mortality	Persistence/development of strain pattern was a predictor of fatal and non-fatal CV events (OR: 1.97; 95 % CI: 1.19 – 3.25) and of stroke occurrence (3.09, 1.40–6.81).
Gaddam et al (2010) [36]	108	Prospective interventional	RHT patients with vs. without hyperaldosteronism	6	Hyperaldosteronims contributes to cardiac volume overload.	Left/right ventricular end-diastolic volumes were greater in patients with high vs. normal aldosterone status. Spironolactone decreases systolic BP and LV mass in both group, but decreases ventricular/atrial volume only in high aldosterone group.
Pimenta et al (2011) [37]	42	Case-control	Patients with vs. without primary aldosteronism		Investigate the relationship between aldosterone, dietary salt, and left ventricular dimensions	Primary aldosteronism presented higher left ventricular mass index and also end systolic and diastolic volumes. Urinary sodium (24-h) was correlated with left ventricular mass only in patients with primary aldosteronism.
Coronary Artery Diseases						
	907	Cross-sectional	RHT patients	-		Prevalence of CAD was 37 %

Table 1 (continued)

Study (year) [ref]	Patients (n)	Study design	Population	Duration of follow-up (months)	Objective	Main results
Muxfeldt et al (2008) [8]					Relationship of ABPM parameters and target organ damage	Enlarged pulse pressure (>63 mmHg) is associated with a high prevalence of CAD (48.4 % vs. 31.6 %) Prevalence of stroke was 18 %. Enlarged pulse pressure (22.3 % vs. 15.2 %) and non-dipping pattern (19.9 % vs. 14.5 %) are associated with a high prevalence of stroke.
Calhoun et al (2014) [19••]	14,809	Cross-sectional	REGARDS Refractory hypertension (n=78) vs. RHT patients (n=2,144) and treated hypertensives (n=12,577)	-	Determine prevalence of refractory hypertension and associated CV risk factors and comorbidities	Prevalence of LVH was higher in refractory hypertension (23.1 %) than RHT patients (18.3 %), and all treated hypertensives (13.1 %) Prevalence of CAD in refractory hypertension (43.6 %), RHT patients (34.9 %), and all treated hypertensives (22.9 %) Prevalence of stroke in refractory hypertension (20.5 %), RHT patients (13.1), and all treated hypertensives (9.2 %)
Smith et al (2014) [40]	17,190	Prospective	INVEST RHT patients (n=6,490) vs. controlled hypertensives (n=7,615) vs. uncontrolled hypertensives (n=3,085)	48	Determine prevalence, predictors, and impact on outcomes of RHT patients with CAD	Prevalence of RHT was 38 % RHT patients had higher risk of primary outcome (all-cause mortality, non-fatal MI, non-fatal stroke) (OR: 1.27; 95 % CI: 1.13 – 1.43), CV mortality (1.47; 1.21 – 1.78), and non-fatal stroke (1.61; 1.17 – 2.22) than controlled hypertensives. No difference for non-fatal MI (0.98; 0.72 – 1.34) was found
Bangalore et al (2014) [42]	10,001	Prospective	RHT patients (n=1,112) vs. treated hypertensives (n=9,889) with CAD	57	Prevalence, predictors, and outcomes in RHT patients with CAD	RHT prevalence was 11.1 % RHT patients had a 69 % increased risk of fatal CAD (95 % CI: 1.22 – 2.34) and 73 % in nonfatal myocardial infarction (1.39 – 2.16) than patients without RHT
Muxfeldt et al (2009) [39]	556	Prospective	RHT patients	57	Prognostic impact of nocturnal BP profile in RHT	Non-dipping pattern is a prognostic marker for fatal and non-fatal CV events (OR: 1.74; 95 % CI: 1.12 – 2.71) and for CAD (2.05; 1.00 – 4.20)
Stroke						
Kumbhani et al (2013) [17]	53,530	Prospective	REACH study	48	Prevalence of CV outcomes in patients with subclinical or established atherothrombotic disease	CV death/ myocardial infarction/ stroke were higher in RHT patients (18.9 % vs. 14.2 %; OR: 1.11; 95 % CI: 1.02 – 1.20). Non-fatal strokes. 6.9 vs. 5.3 %; OR: 1.26; 95 % CI: 1.10 – 1.45). No difference in non-fatal myocardial infarction (4.6 vs. 3.7 %)

Table 1 (continued)

Study (year) [ref]	Patients (n)	Study design	Population	Duration of follow-up (months)	Objective	Main results
Salles GF (2008) [15••]	556	Prospective	RHT patients	58	Prognostic value of office ambulatory BP in RHT patients	Daytime systolic and diastolic BP increase risk of fatal and non-fatal CV events in 26 % (1.04 – 1.53) and 31 % (1.05 – 1.63), while nighttime systolic and diastolic BP increased the risk in 38 % (1.13 – 1.68) and 35 % (1.10 – 1.69) Office BP has no prognostic value. True RHT at baseline triplicate the risk of stroke (OR: 3.20; 95 % CI; 1.41 – 7.25)

RHT – resistant hypertension; TOD – target organ damage; LVH – left ventricular hypertrophy; IM – intima-media; CRP – C-reactive protein; MA – microalbuminuria; ABPM – ambulatory blood pressure monitoring; ECG-LVH – left ventricular hypertrophy diagnosed by electrocardiogram; CAD – coronary artery diseases; CV – cardiovascular; BP – blood pressure; LV – left ventricular

intima-media thickness (IMT ≥0.9 mm), with or without carotid plaques, presence of white matter lesions on brain magnetic resonance imaging (MRI), or increased central aortic stiffness (measured by carotid-femoral pulse wave velocity [PWV] >10 m/s), which may help to identify individuals at higher risk for stroke [2].

During the last decade, it had already been demonstrated that RHT patients had increased carotid IMT and higher prevalence of carotid plaques than non-resistant hypertensive individuals [11]. The European Lacidipine Study on Atherosclerosis (ELSA) [44], although not specifically in RHT, confirmed the relationships between increased carotid IMT and adverse cardiovascular outcomes. Curiously, the relation between any IMT measurement and stroke did not attain statistical significance in this study, probably because of the small number of incident strokes during follow-up (only 25 strokes).

More recently, a cross-sectional study with 42 RHT patients showed that cerebral microangiopathy, diagnosed by white matter lesions on MRI, in 19 patients was related to lower heart rate and higher nighttime systolic BP. Compared to 23 RHT patients without cerebral lesions, patients with cerebral microangiopathy had similar carotid IMT, but higher aortic stiffness [45].

Aortic Stiffness

Carotid-femoral PWV is the best indicator of increased aortic stiffness and its association with worse cardiovascular prognosis in several clinical conditions is consistently demonstrated, including in hypertensive patients, and particularly for stroke occurrence. [46]. In a large cross-sectional study [47] including 600 patients with RHT, we had previously reported that 168 patients (28 %) exhibited increased aortic stiffness; and that diabetes, microalbuminuria, low level of HDL-cholesterol, widened 24-h pulse pressure, and a blunted nocturnal BP fall were the covariates independently associated with increased aortic stiffness.

Recently, Muiesan and colleagues [18], in a review of their own data, evaluated the prevalence of simultaneous TOD in RHT, including the subclinical alterations discussed before. They analyzed 317 hypertensive individuals selected from a larger general population sample living in northern Italy and who were participating in an epidemiological study which investigated the association between cardiovascular risk factors and TOD (the Vobarno Study). RHT patients represented 9.5 % of the total sample or 17.3 % considering only those with treated hypertension (n=173). Carotid IMT, aortic PWV, left ventricular mass, and renal function parameters were significantly more abnormal in RHT patients than in controlled hypertensive individuals. There was a high prevalence of carotid plaques observed in the entire population; nevertheless, it was significantly greater in the group of RHT

Table 2 Studies performed in patients with resistant hypertension investigating the prevalence and/or incidence of renal complications

Study (year) [ref]	Patients (n)	Study design	Population	Duration of follow-up (months)	Objective	Main results
de la Sierra et al (2012) [7]	27,897	Cross-sectional	RHT (n=14,461) vs. controlled BP patients (n=13,436)	-	Clinical differences, TOD and ABPM pattern of RHT patients and patients with controlled BP	Positive MA (>30 mg/g) was higher in RHT pats (27.7 % vs. 15.4 %) MA values were 10.0 (3.4 – 34.6) in RHT patients and 5.3 (2.2 – 16.0) in controlled BP Reduced eGFR (<60 ml/min) was more prevalent in RHT group (24.9 % vs. 15.9 %)
Cuspidi et al (2001) [11]	105	Cross-sectional	RHT (n=54) vs. non RHT patients (n=51)	-	Prevalence of cardiac and extracardiac TOD in RHT vs. non-RHT patients	Prevalence of positive MA in the two groups was similar (17 % vs. 12 %) MA values were higher in RHT group (22 [32] vs. 11 [13])
Daugherty et al (2012) [14]	24,499	Prospective	RHT (n=3,960) vs. non-RHT patients (n=19,952)	44	Determine the incidence and prognosis of RHT	Albuminuria was more prevalent in RHT group (0.7 % vs. 0.4 %) and also chronic kidney disease (5.2 % vs. 4.0 %)
Calhoun et al (2014) [19••]	14,809	Cross-sectional	REGARDS Refractory hypertension (n=78) vs. RHT patients (n=2,144) and treated hypertensives (n=12,577)	-	Determine prevalence of refractory hypertension and associated CV risk factors and comorbidities	Prevalence of positive MA was higher in refractory hypertension (54.5 %) than RHT patients (32.8 %) and all treated hypertensives (20.2 %) Prevalence of reduced eGFR (<60 ml/min) was higher in refractory hypertension (35.1 %), RHT patients (27.3 %), and all treated hypertensives (17.1 %)
Muxfeldt et al (2005) [50]	497	Cross-sectional	RHT patients	-	Identify clinical variables associated with true RHT	MAU was higher in true RHT (64.1 [75.0] mg/24 h) than in white-coat RHT (33.1 [55.1] mg/24 h).
Oliveras et al (2011) [51]	356	Cross-sectional	RHT patients	-	Relationship with MA and ABPM parameters.	Prevalence of positive MA was 46.6 % Prevalence of impaired renal function (eGFR<60 ml/min was 26.8 % Nighttime systolic BP was associated with positive MA (OR: 1.014; 95 % CI: 1.001 – 1.026)
Muxfeldt et al (2008) [8]	907	Cross sectional	RHT patients	-	Relationship of ABPM parameters and target organ damage	Prevalence of positive MA was 27.2 % Positive MA was associated with enlarged 24-h pulse pressure (OR: 1.75; 95 % CI: 1.16 – 2.66) and non-dipping pattern (1.61; 1.12 – 2.32).
Salles et al (2011) [49••]	531	Prospective	RHT patients	57	Evaluate baseline and serial changes in MA in RHT as predictors of CV events	Positive MA increased risk of fatal and non-fatal CV events in 95 % (1.25 – 3.06) and tripled the risk of CV mortality (1.54 – 5.54) Regression of MA was associated with a 27 % lower risk of CV events, while development of MA increased the risk in 65 %
Oliveras et al (2013) [52••]	133	Prospective	RHT patients	73	MA and renal function as predictors or CV diseases	Baseline MA was not a CV prognostic marker MA elevation (66 vs. 17 mg/g) was associated with CV events. Changes in eGFR were not associated with CV outcomes.

Table 2 (continued)

Study (year) [ref]	Patients (n)	Study design	Population	Duration of follow-up (months)	Objective	Main results
Tanner et al (2013) [54]	9,974	Prospective	REGARDS study RHT patients (n=2,147) vs. non-RHT (n=7,827)	76	Incidence of end-stage renal diseases in RHT patients	110 ESRD cases in RHT (OR: 8.86; 95 % CI: 7.35 – 10.68) vs. 42 ESRD cases (0.88; 0.65 – 1.19) in non-RHT patients
Salles et al (2011) [55••]	531	Prospective	RHT patients	57	Evaluate prognostic value of GRF and GRF associated with MA in RHT patients	Decreased eGFR increase the risk of fatal and non-fatal CV events (OR: 4.27; 95 % CI: 1.79 – 10.20) and CV mortality (4.95; 1.39 – 17.54) Reduced eGFR and presence of MA increased the risk of all CV events (3.0; 1.7 – 5.3), all-cause death (2.9; 1.5 – 5.5) and CV mortality (4.6; 2.2 – 10.0)

RHT – resistant hypertension; TOD – target organ damage; ABPM – ambulatory blood pressure monitoring; MA – microalbuminuria; BP – blood pressure ; eGFR – estimated glomerular filtration rate; ESRD - end-stage renal diseases; CV – cardiovascular

patients (97 % vs. 83 %, p=0.04). Increased aortic stiffness was found in 71 % of RHT group and 44 % of controls.

Nevertheless, none of the sub-clinical cerebrovascular TOD had yet their prognostic importance examined in patients with RHT, which is clearly needed to recommend their routine use in the clinical management of resistant hypertensives.

The principal findings of cardiovascular complications in RHT patients are summarized in Table 1.

Resistant Hypertension and Renal Complications

Reduced glomerular filtration rate (GFR) (30 – 60 mL/min/1.73 m^2) and microalbuminuria (MA) (30 – 300 mg/24 h) are considered asymptomatic organ damage used for cardiovascular risk stratification in general hypertensive subjects [2] and also in RHT patients [6•, 7, 8]. Its screening should be considered a routine procedure in the diagnostic approach of these patients [48], as it is known that MA is a reversible condition [2,49••,50] and can reduce cardiovascular risk.

Microalbuminuria

It is well-known that MA is more prevalent in patients with RHT [7, 10, 11, 14] than non-resistant hypertensives, and this prevalence is strongly associated with higher BP, such as in true uncontrolled RHT [49••, 50] and refractory RHT [19••]. Moreover, there is a high association between MA and other ABPM parameters related to a high cardiovascular risk such as increased nighttime systolic BP [51], enlarged pulse pressure, and non-dipper pattern [8]. A cross-sectional study in a large cohort of RHT patients showed that MA was independently associated with LVH occurrence [34] and with increased arterial stiffness [47].

Prospective studies also confirmed the prognostic importance of microalbuminuria in RHT patients [49••, 52••]. We evaluated prospectively 531 patients with a median follow-up of 4.9 years [49••], and found that baseline MA nearly doubled the risk of any fatal and non-fatal cardiovascular event occurrence and tripled the risk for cardiovascular mortality. Moreover, it was shown that the risk begins with albuminuria values lower than the classic MA cut-off (30 mg/24 h). This study also evaluated prognostic influence of changes in albuminuria during the follow-up, independent of ambulatory BP or serum creatinine changes. Patients who regressed MA, had a 27 % decrease in cardiovascular risk, while those who developed MA presented a 65 % greater CV risk. Recently, Oliveras and colleagues [52••] evaluated 133 RHT patients during a median follow-up of 73 months and observed that baseline MA was not a prognostic marker of fatal and non-fatal cardiovascular events, but persistence or new-appearance of MA predicts cardiovascular diseases. In this way, MA

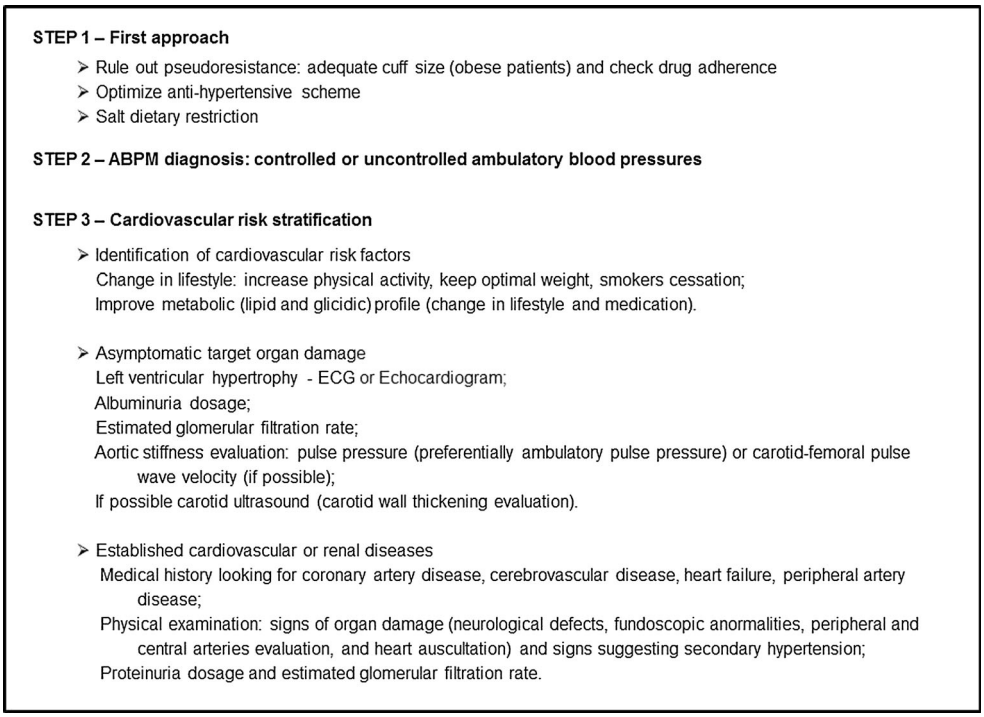

Fig. 1 Diagnostic approach of patients with resistant hypertension

prevention and reduction may be a therapeutic target in RHT patients [49••, 52••].

Moreover, cardiovascular and renal effects of aldosterone excess seem to be dependent on high dietary salt intake. Pimenta et al [53] evaluated prospectively 84 RHT patients according their aldosterone status, sodium and protein excretion, and observed a positive correlation between protein and sodium excretion in patients with high 24-h urinary aldosterone, but not in patients with normal aldosterone status. These findings suggested that the combination of high dietary salt and aldosterone excess should increase urinary protein excretion.

Chronic Kidney Disease

The presence of chronic kidney disease (CKD), defined as an estimated GFR <60 mL/min/1.73 m^2, is considered the strongest predictor of RHT [6•, 14, 17]. This is one of the well-established characteristics of patients with RHT [7, 14, 54], is associated with the severity of RHT [19••, 36], and also with other ABPM parameters known to be associated with worse prognosis, such as an adverse dipping pattern [8, 51]. Oliveras et al. [51] had shown a strong association between albuminuria and renal function impairment in RHT patients.

Recently, the REGARDS study [54], comparing 2,147 RHT patients and 7,827 patients without treatment-resistance during a follow-up of 6.4 years, showed that RHT presented an increased risk (6.32; 95 % CI: 4.30 – 9.30) for end-stage renal disease.

Our group evaluated [55••] prospectively 531 RHT patients (median follow-up 4.9 years) and showed that a GFR<60 mL/min per 1.73 m^2, either estimated by the Cockroft-Gault equation or by the MDRD formula, presented a incidence rate of fatal and non-fatal cardiovascular events significantly higher than patients with GFR>60 mL/min per 1.73 m^2 (6.13 vs. 3.54 and 5.88 vs. 3.05, respectively). A low GFR estimated by the MDRD formula was an important prognostic marker for cardiovascular events in the three stages of decreasing GFR compared with a GFR>90 mL/min per 1.73 m^2. Moreover, the combination of a reduced estimated GFR (<60 mL/min per 1.73 m^2) and MA (>30 mg/24 h) tripled the risk of total cardiovascular events and all-cause mortality and quadrupled the risk of cardiovascular mortality. These results pointed to the importance of a different approach for RHT patients with CKD [56], focusing on persistent volume overload, more intensive renin-angiotensin-aldosterone system blockade, and nocturnal BP control. The principal findings of renal complications in RHT patients are summarized in Table 2.

In conclusion, resistant hypertension is an increasingly clinical condition that carries a high morbidity and mortality compared with patients with controlled hypertension. All efforts should be focused on achieving a better BP control, with a comprehensive diagnostic and treatment approach [48], including strategies to increase drug adherence, change in lifestyle, investigation of secondary causes of hypertension, and appropriate anti-hypertensive drug combination with emphasis on the use of diuretics (ideally chlorthalidone) and a

mineralocorticoid receptor antagonist. Furthermore, BP control should be based on out-of-office blood pressure measurements, preferably by ABPM, during the whole follow-up. Moreover, the investigation of asymptomatic and established TOD is extremely necessary in this group of patients (Fig. 1). Such an approach may lead to cardiovascular and renal TOD regression and improved prognosis.

Compliance with Ethics Guidelines

Conflict of Interest Elizabeth S. Muxfeldt, Fabio de Souza, Victor S. Margallo, and Gil F. Salles declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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