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Ambulatory Blood Pressure Monitoring in the Diagnosis, Prognosis, and Management of Resistant Hypertension: Still a Matter of our Resistance?

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Abstract Resistant hypertension, commonly described as the failure to achieve goal blood pressure (BP) despite an appropriate regimen of three antihypertensive drugs at the maximal tolerated doses, one of which is diuretic, is increasingly recognized as an important problem of public health. Large population studies with office measurements suggest that the prevalence of resistance hypertension is approximately at 6–12 % of the general hypertensive population and 8–28 % of treated hypertensives. However, these estimations do not take into account factors of pseudo-resistance, most importantly, the white-coat effect that can be effectively ruled out with ambulatory blood pressure monitoring (ABPM). Recent studies have clearly shown that when ABPM is used, at least 30–35 % of patients labeled as "resistant hypertensives" turn out to have well-controlled BP on ambulatory basis, a finding changing entirely the estimates of prevalence of resistance hypertension and actual patient handling. Furthermore, current evidence suggests that ABPM is a much more accurate predictor of cardiovascular events in resistant hypertension compared to office BP and thus can offer a better risk stratification for these high-risk individuals. Finally, ABPM offers the potential of a better evaluation of the effect of pharmacologic and non-pharmacologic therapeutic interventions. This review attempts to summarize recent evidence on the advantages of ABPM in the diagnosis, prognosis, and management of resistant hypertension.

Keywords Ambulatory blood pressure monitoring · Cardiovascular risk · Resistant hypertension · White-coat effect

Introduction

Hypertension is a leading cause of cardiovascular morbidity and mortality accounting for 49 % of ischemic heart disease, 69 % of cerebrovascular disease, and 7.1 million deaths per year worldwide [1–3]. The independent and continuous relationship of hypertension with incident cardiovascular events along with its prevalence at 25–30 % of the adult population, render high blood pressure (BP) the most important modifiable cardiovascular risk factor [4–6] and therefore a major issue of public health. Although awareness and treatment of hypertension have improved over the years, the rates of control in the general hypertensive population remain unacceptably low, i.e., below 20–30 % in many Western countries, with few exceptions in countries that implemented targeted public health programs aiming at improving hypertension care [7–9]. Of note, an important proportion of the hypertensive population cannot achieve adequate BP control even when treated with three or more antihypertensive medications. These individuals currently fall within the diagnosis of "resistant hypertension" [4, 10, 11], an entity recently reported to have a prevalence between 6–12 % of the hypertensive population and 8–28 % among treated hypertensive patients [12••, 13].

A cluster of lifestyle parameters, biologic factors, and other associated conditions have been identified to contribute to

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resistant hypertension including volume overload, secondary causes of hypertension, several pharmacologic agents, and other pathologic entities such as obesity, diabetes, and older age [14]. In addition, a significant amount of patients appear to have resistant hypertension, whereas they are truly well-controlled. These patients have apparent resistant hypertension or "pseudo-resistance" [13, 15], a phenomenon that can be generated by various conditions, such as improper BP measurement, heavy calcification of the arteries in the elderly, poor patient adherence, physician inertia, and, most importantly, the white-coat effect [16]. Effectively ruling out pseudo-resistance and identifying patients with true resistant hypertension is a matter of great importance in order to avoid over-treatment and the relevant complications in patients with pseudo-resistance and focus further diagnostic and therapeutic efforts in individuals who truly need them.

Similarly to white-coat hypertension in the general hypertensive population, a significant amount of patients initially diagnosed as resistant hypertensives in office, turn out to have well-controlled BP after proper evaluation with ambulatory blood pressure monitoring (ABPM). Several well-conducted observational studies with ABPM have demonstrated that the white-coat phenomenon can misclassify as many as 30 % of the patients labeled to have resistant hypertension with office measurements [17••, 18, 19]. Such observations clearly suggest that the prevalence of resistant hypertension arising from studies with office measurements is overestimated whereas ABPM can offer a more realistic estimation of the magnitude of the problem. The utility of ABPM in patients with resistant hypertension extends beyond the proper diagnosis of the white-coat effect and true resistant hypertension. Recent evidence clearly suggests that ABPM can predict more accurately than office BP the cardiovascular events in patients with resistant hypertension and thus constitute an important tool for risk stratification [20, 21••], after which decisions regarding the intensity of appropriate treatment can be applied. Lastly, ABPM can also be a valuable tool for effective follow-up of patients with resistant hypertension, including assessment of the success of therapeutic interventions and adjustment of the therapeutic schemes [22•, 23].

This article will discuss the advantages of ABPM use in patients with resistant hypertension deriving from studies relevant to the diagnosis, prognosis, and treatment of such individuals.

Definition of Resistant Hypertension

Resistant hypertension has been formerly defined in the seventh report of the US Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) as the failure to achieve goal BP<140/90 mmHg (or 130/80 mmHg in patients with diabetes mellitus or chronic kidney disease) in patients with hypertension despite an appropriate regimen of three antihypertensive drugs at the maximal tolerated doses, one of which is diuretic [10]. A subsequent position statement of the American Heart Association (AHA) considered patients whose BP is controlled by ≥4 antihypertensive medications to be also resistant to treatment (controlled resistant hypertension) [11]. More recently, it has been suggested that a time frame of at least 3 months of effective treatment should be included in the definition of resistant hypertension [24, 25]. Although resistant hypertension by definition is considered not controlled, it should not be used identically with the term "uncontrolled hypertension" which refers to all hypertensive patients without adequate BP control under treatment [12••].

The Role of ABPM in Diagnosis of Resistant Hypertension

Prevalence of Resistant Hypertension Based on Office BP Readings

Until a few years ago, the exact prevalence of resistant hypertension was not properly defined; however, recently, large population-based studies have provided direct epidemiologic data according to which the prevalence of resistant hypertension with office BP readings is estimated between 6–12 % in the hypertensive population and 8–28 % in all drug-treated hypertensive patients (Table 1) [12••, 13, 17••, 26–29].

An early retrospective, cross-sectional study using electronic medical records aimed to assess the prevalence of resistant hypertension in an ambulatory care setting. McAdam-Marx et al. [26] evaluated 29,474 adult hypertensive patients with regular follow-up visits between 2002 and 2005. Among them, 2670 patients met the criteria for resistant hypertension, defined as office BP≥140/90 mmHg in patients treated with ≥3 antihypertensive drugs including a thiazide diuretic. The patients with resistant hypertension represented 9.1 % of the entire study sample and 12.4 % of the drug-treated hypertensive population.

In another study, Persell et al. [27] aimed to estimate the prevalence of resistant hypertension using data from the National Health and Nutrition Examination Survey (NHANES) between the years 2003 and 2008. The investigators defined resistant hypertension as BP≥140/90 mmHg in patients receiving ≥3 antihypertensive drugs in the past month or patients taking ≥4 antihypertensive drugs irrespective of BP levels (86 % of the participants were receiving a diuretic). The study demonstrated that 8.9 % (SE 0.6 %) of the adult hypertensive US population and 12.8 % (SE 0.9 %) of all drug-treated hypertensives met the criteria for resistant hypertension. Excluding patients receiving ≥4 antihypertensive drugs, the prevalence of resistant hypertension changed to

Table 1 Studies reporting the prevalence of resistant hypertension with office and ABPM measurements

Study, year (Ref.)	Definition of resistant hypertension with office BP criteria	Number of subjects	Type of subjects	Prevalence of resistant hypertension (office BP)	Definition of resistant hypertension with ABPM criteria	Prevalence of true resistant hypertension (%)	Prevalence of white-coat-resistant hypertension (%)
Studies with office BP							
McAdam-Marx et al. [26]	BP≥140/90 mmHg in patients treated with ≥3 antihypertensive drugs including a thiazide diuretic	29,474	Hyp.	9.1 % in the hypertensive population 12.4 % in the drug-treated hypertensive population	–	–	–
Persell et al. [27]	BP≥140/90 mmHg in patients treated with ≥3 antihypertensive drugs in the past month or treated with ≥4 antihypertensive drugs irrespective of BP levels	5230	Hyp.	8.9 % in the adult hypertensive US population 12.8 % in the drug-treated hypertensive population	–	–	–
Egan et al. [28]	BP≥140/90 mmHg in patients treated with ≥3 antihypertensive drugs or BP≤140/90 mmHg in patients treated with ≥4 antihypertensive drugs	13,375	Hyp.	In the drug-treated hypertensive population: 15.9 % (1988–1994) 21.2 % (1999–2004) 28.0 % (2005–2008) In the total hypertensive population (when resistant hypertension defined as BP≤140/90 mmHg in patients treated with ≥4 antihypertensive drugs): 5.5 % (1988–2004) 8.5 % (1999–2004) 11.8 % (2005–2008)	–	–	–
Sim et al. [29]	BP≥140 and/or 90 mmHg in patients treated with ≥3 antihypertensive drugs or treated with ≥4 antihypertensive drugs irrespective of BP control	470,386	Hyp.	12.8 % in the hypertensive population 15.3 % in the drug-treated hypertensive population Excluding patients controlled on ≥4 medications: 9.4 % in the hypertensive population 7.9 % in the drug-treated hypertensive population	–	–	–
Studies with ambulatory BP							
Mezzetti et al. [30]	BP>140/90 mmHg in at least three visits with 1 week apart in patients treated with ≥3 antihypertensive drugs	27	Res. Hyp.	–	Upper limits (mean+2 SD) of a clinically normotensive population of the study's geographical area. True resistant hypertension (office BP>140/90 mmHg and 24-h BP≥135/85 mmHg and daytime ambulatory BP≥139/90 mmHg), white-coat-resistant hypertension (office BP>140/90 mmHg and 24-h BP<135/85 mmHg and daytime ambulatory BP<139/90 mmHg)	26 % (office BP>140/90 mmHg and 24-h BP≥135/85 mmHg and daytime ambulatory BP≥139/90 mmHg) 48 % (daytime ambulatory BP≥135/85 mmHg)	74 % (office BP>140/90 mmHg and 24-h BP<135/85 mmHg and daytime ambulatory BP<139/90 mmHg) 52 % (daytime ambulatory BP<135/85 mmHg)
Hernandez-del-Rey et al. [31]	Average of three measurements of SBP≥160 mmHg and/or DBP≥95 mmHg in patients treated with ≥3	60	Res. Hyp.	–	True resistant hypertension (mean daytime ambulatory BP>135/85 mmHg), white-coat-resistant hypertension	68 %	32 %

Table 1 (continued)

Study, year (Ref.)	Definition of resistant hypertension with office BP criteria	Number of subjects	Type of subjects	Prevalence of resistant hypertension (office BP)	Definition of resistant hypertension with ABPM criteria	Prevalence of true resistant hypertension (%)	Prevalence of white-coat-resistant hypertension (%)
	antihypertensive drugs over at least 2 months				(mean daytime ambulatory BP≤135/85 mmHg)		
Veglio et al. [32]	BP>140/90 mmHg for at least 3 months in patients treated with ≥3 antihypertensive drugs in near maximal doses	49	Res. Hyp.	–	True resistant hypertension (daytime ambulatory BP≥135/85 mmHg), white-coat-resistant hypertension (daytime ambulatory BP<135/85 mmHg)	61 %	39 %
Brown et al. [18]	BP≥140/90 in patients treated with ≥3 antihypertensive drugs	118	Res. Hyp.	–	True resistant hypertension (daytime ambulatory BP≥135/85 mmHg), white-coat-resistant hypertension (daytime ambulatory BP<135/85 mmHg or daytime ambulatory BP<135/85 mmHg and 24-h BP<125/80 mmHg)	72 % (daytime ambulatory BP≥135/85 mmHg) 81 % (daytime ambulatory BP≥135/85 mmHg and 24-h BP≥125/80 mmHg)	28 % (daytime ambulatory BP<135/85 mmHg) 19 % (daytime ambulatory BP<135/85 mmHg and 24-h BP<125/80 mmHg)
Muxfeldt et al. [33]	BP≥140/90 mmHg in patients treated with ≥3 antihypertensive drugs	286	Res. Hyp.	–	True resistant hypertension (24-h BP≥135/85 mmHg), white-coat-resistant hypertension (24-h BP<135/85 mmHg)	56.3 %	43.7 %
Muxfeldt et al. [34]	BP≥140/90 mmHg in patients treated with ≥3 antihypertensive drugs	497	Res. Hyp.	–	True resistant hypertension (24-h BP≥135/85 mmHg), white-coat-resistant hypertension (24-h BP<135/85 mmHg)	63 %	37 %
De la Sierra et al. [17••]	BP≥140 and/or 90 mmHg in patients treated with ≥3 antihypertensive drugs, including a diuretic	8295	Res. Hyp.	14.8 % in treated hypertensive population 12.0 % in patients with BP≥140/90 mmHg excluding patients with normal BP but treated with ≥4 antihypertensive drugs	True resistant hypertension (24-h BP≥130 and/or 80 mmHg), white-coat-resistant hypertension (24-h BP<130 and/or 80 mmHg)	62.5 %	37.5 %
Brambilla et al. [19]	BP>140/90 mmHg despite the use of the maximum tolerated dose of ≥3 antihypertensive drugs including a diuretic or patients taking ≥4 antihypertensive drugs independently of BP values	423	Res. Hyp.	14.8 % in treated hypertensive population 12.0 % in patients with BP≥140/90 mmHg excluding patients with normal BP but treated with ≥4 antihypertensive drugs	True resistant hypertension (24-h BP≥130/80 mmHg), white-coat-resistant hypertension (24-h BP<130/80 mmHg)	60 %	23.2 %

ABPM ambulatory blood pressure monitoring, *BP* blood pressure, *DBP* diastolic blood pressure, *Hyp* hypertension, *Res. Hyp* resistant hypertension, *SBP* systolic blood pressure

6.4 % of all hypertensives and 9.2 % of all treated hypertensive individuals.

In a similar study, Egan et al. [28] evaluated 13,375 hypertensive adults of the NHANES database, subdivided into three timely defined data sets from 1988 to 2008. The investigators of the study defined apparent treatment-resistant hypertension as uncontrolled BP (BP≥140/90 mmHg) despite the use of ≥3 antihypertensive medications. The results showed an increased prevalence of apparent treatment-resistant hypertension from 15.9 % in 1988–1994 to 28.0 % in 2005–2008 among the treated hypertensive population. Moreover, when the AHA statement for resistant hypertension was included in the analysis (office BP≤140/90 mmHg in patients taking ≥4 antihypertensive drugs), the overall prevalence of resistant hypertension reached an 11.8 % of the total US hypertensive population between 2005 and 2008 representing an increase from 5.5 % in 1988–1994 to 8.5 % in 1999–2004.

The largest study to assess the prevalence of resistant hypertension included a diverse and representative population of the Kaiser Permanente Southern California health system [29] and used an electronic medical record-based approach according to which 470,386 hypertensive patients between 2006 and 2007 were identified. Using a definition of resistant hypertension as BP≥140 and/or 90 mmHg despite triple antihypertensive regimen or medication with ≥4 antihypertensive drugs irrespective of BP control, the investigators identified 60,237 individuals as having resistant hypertension (12.8 % of the hypertensive population and 15.3 % of all treated patients). When patients controlled on ≥4 medications were excluded, the prevalence of uncontrolled resistant hypertension fell to 9.4 % in the hypertensive population and 7.9 % in all drug-treated individuals.

Prevalence of Resistant Hypertension Based on ABPM Readings

While the above-mentioned studies have provided direct estimates of the prevalence of resistant hypertension, all were unable to exclude patients with pseudo-resistant hypertension. Pseudo-resistance refers to apparent lack of appropriate BP control in a patient who is prescribed ≥3 medications and is caused by several factors, such as improper BP measurement, heavy arterial calcification in the elderly, patient non-adherence, physician inertia and, most importantly, the white-coat effect [14]. The white-coat effect, defined as the elevation of clinic BP resulting in higher BP values in office compared to ambulatory or home readings [35], is a major confounder when evaluating patients with resistant hypertension and its impact on the occurrence of resistant hypertension (white-coat-resistant hypertension) is significant, according to several studies.

The first studies to provide data regarding the impact of the white-coat effect on the prevalence of resistant hypertension were small. Mezzetti et al. [30] performed ABPM in 27 patients with resistant hypertension (office BP>140/90 mmHg in at least three visits 1 week apart despite a triple antihypertensive regimen). The investigators did not use previously reported cutoff ABPM values but those representing the upper limits (mean+2 SD) of a clinically normotensive population of the study's geographical area. They noted that 26 % of patients had true resistant hypertension (office BP>140/90 mmHg, 24-h BP≥135/85 mmHg, and daytime ambulatory BP≥139/90 mmHg) whereas 74 % had white-coat-resistant hypertension (office BP>140/90 mmHg, 24-h BP<135/85 mmHg, and daytime ambulatory BP<139/90 mmHg). When patients were evaluated according to different ABPM cutoff values as those suggested by Pickering et al. (135/85 mmHg for daytime ambulatory BP) [36], another six patients with white-coat-resistant hypertension were reclassified as true resistant hypertensives.

Hernandez-del Ray et al. [31] studied 60 patients with resistant hypertension [an average of three measurements of systolic blood pressure (SBP) ≥160 mmHg and/or diastolic blood pressure (DBP) ≥95 mmHg in patients treated with a triple-drug regimen, over at least 2 months] in a further attempt to quantify the white-coat phenomenon using ABPM. The investigators observed that 68 % of the subjects had true resistant hypertension (daytime ambulatory BP>135/85 mmHg) whereas 32 % had white-coat-resistant hypertension (daytime ambulatory BP≤135/85 mmHg).

In another study, Veglio et al. [32] performed ABPM in 49 patients with resistant hypertension (office BP>140/90 mmHg for at least 3 months despite triple drug therapy in near maximal doses, including a diuretic). According to the cutoff values suggested by Pickering (135/85 mmHg for daytime ambulatory BP), the investigators identified 61 % of the study patients with true resistant hypertension (daytime ambulatory BP≥135/85 mmHg) and 39 % with white-coat-resistant hypertension (daytime ambulatory BP<135/85 mmHg).

Consequently, Brown et al. [18] in a retrospective study evaluated the extent of white-coat effect in 118 patients with resistant hypertension defined according to the JNC 6 report and observed that those with white-coat-resistant hypertension were 28 % according to the ABPM criteria of JNC 6 (daytime BP<135/85 mmHg) and 19 % using a combination of the JNC 6 and the World Health Organization–International Society of Hypertension (WHO-ISH) (24-h BP<125/80 mmHg) criteria.

In a larger cross-sectional study, Muxfeldt et al. [33] enrolled 286 resistant hypertensive patients (office BP≥140/90 mmHg despite the use of ≥3 antihypertensive drugs including a diuretic). After ABPM assessment, 56.3 % of the patients were classified as having true resistant hypertension (24-h BP≥135/85 mmHg) whereas 43.7 % as having white-coat-resistant hypertension (24-h BP<135/85 mmHg). In a

subsequent analysis of a larger sample of 497 patients with resistant hypertension, the same group [34] reported a prevalence of true resistant hypertension of 63 % as compared to 37 % of white-coat-resistant hypertension.

More recently, in another large cohort of 423 resistant hypertensive patients (office BP≥140/90 mmHg despite triple antihypertensive regimen in maximum tolerated doses including a diuretic, or ≥4 antihypertensive drugs independently of office BP values), Brambilla et al. [19] observed that 60 % of the population had true resistant hypertension (24-h BP≥130/80 mmHg) whereas the remaining pseudo-resistance (non-compliance, white-coat hypertension). Among them, 58.3 % (23.1 % of the total sample) had white-coat-resistant hypertension (24-h BP< 130/80 mmHg).

In the largest study on the field, de la Sierra et al. [17••] used the AHA definition of resistant hypertension (office BP ≥140 and/or 90 mmHg with ≥3 antihypertensive drugs, including a diuretic) and identified 8295 patients with resistant hypertension among a group of over 68,000 treated hypertensive individuals included in the Spanish ABPM registry. Based on office measurements, the prevalence of resistant hypertension was 14.8 % among treated hypertensives and 12.0 % when only patients with BP≥140/90 mmHg were included (i.e., excluding patients with normal BP but treated with ≥4 antihypertensive drugs). After evaluation of ABPM data, however, the prevalence of resistant hypertension changed dramatically, as the authors identified that 37.5 % of the originally identified resistant patients had white-coat-resistant hypertension (24-h BP<130/80 mmHg) whereas 62.5 % had true resistant hypertension (24-h BP≥130/80 mmHg).

Based on the above (Table 1), it can be easily deducted that ABPM should be mandatory in the diagnosis of resistant hypertension, as at least one third, and in some studies almost half, of patients labeled with the diagnosis of resistant hypertension based on appropriate office readings, turn out to have controlled BP with the use of ABPM. The significance of this finding is not related only to the technical issue of correct prevalence of resistant hypertension in the general hypertensive population (i.e., shifting from 12 % to 6–9 %) but, most importantly, to appropriate hypertension management strategies. By dividing these two groups of patients, a more targeted therapeutic approach could be implemented by avoiding costly extra investigations towards secondary hypertension and unnecessary overtreatment with undesirable side effects of already controlled patients. Interestingly, Brown et al. [18] calculated more than a decade ago that if 24-h ABPM was performed before conducting further investigations in apparent resistant hypertensives, the overall savings per year per 100 resistant hypertensive patients would be approximately between US$22.000 and US$42.500.

The Role of ABPM in Prognosis of Resistant Hypertension

The superiority of ABPM over office BP in resistant hypertension goes beyond ruling out white-coat effect and distinguishing between true resistant and apparent resistant hypertensive patients. Several studies have demonstrated that ABPM can predict more accurately cardiovascular outcomes in these individuals thus enabling doctors to better stratify their cardiovascular risk and subsequently modify the relative therapeutic interventions (Table 2) [20, 21••, 37–39, 43].

Indirect data supporting the role of ABPM as a stratification tool in resistant hypertension has been provided by the cross-sectional Spanish ABPM Registry. After a median follow-up of 4 years, de la Sierra et al. [40] observed that in 2115 hypertensive patients of high or very high cardiovascular risk (among which 30 % met the criteria for resistant hypertension), nocturnal SBP was the best predictor of cardiovascular events [hazard ratio (HR) for each SD increase=1.45; 95 % confidence interval (CI)=1.29–1.59; $p<0.001$] adjusting for baseline cardiovascular risk and office BP.

In an attempt to provide more direct data, Redon et al. [37] enrolled in a prospective study 86 resistant hypertensive patients (office DBP>100 mmHg for three visits at 1-month intervals, under treatment with ≥3 antihypertensive drugs including a diuretic) and performed a single baseline 24-h ABPM. After a median follow-up of 49 months, patients in the highest tertile (mean daytime DBP>97 mmHg) according to ABPM when compared to the patients in the lowest tertile (mean daytime DBP<88 mmHg), had a much higher incidence of cardiovascular events (13.6 vs 2.2 per 100 patient-years) and a significant progression of target organ damage (TOD) [risk ratio (RR)=3.70; 95 % CI=2.82–4.58; $p<0.03$ vs RR=2.11; 95 % CI=1.36–2.86; p=not significant (NS)]. Moreover, higher ambulatory DBP was an independent risk factor for future cardiovascular events (RR=6.20; 95 % CI= 1.38–28.1; $p<0.02$). The prognostic significance of ambulatory BP as an independent risk factor remained even after exclusion of patients with previous cardiovascular events (RR=8.76; 95 % CI=1.07–71.8; $p=0.05$). In contrast to ambulatory BP, office BP was not an independent risk factor for cardiovascular events.

The second important study in the field extended our knowledge by studying the cardiovascular risk also in patients with apparent resistant hypertension and normal ambulatory BP. Pierdomenico et al. [38] enrolled 276 resistant hypertensive patients (office BP≥140 and/or 90 mmHg despite triple therapy, in at least two visits) and performed ABPM according to which 146 patients had white-coat-resistant hypertension (daytime ambulatory BP<135/85 mmHg) and 130 suffered from true resistant hypertension (daytime ambulatory BP≥135/85 mmHg). After a median follow-up of 5 years, true resistant compared with white-coat-resistant hypertension patients

Table 2 Studies reporting the role of ABPM in prognosis of resistant hypertension

Study, year (Ref.)	Type of subjects (resistant hypertension)	Number of subjects	Type of study	Prognostic role of office BP	ABPM-derived parameters and association with CV risk	CV risk in true resistant hypertension	CV risk in white-coat-resistant hypertension
Redon et al. [37]	Defined as office DBP>100 mmHg for three visits at 1-month intervals, in patients treated with ≥3 antihypertensive drugs including a diuretic	86	Prospective cohort	Not an independent risk factor	CV event rate (mean daytime DBP>97 mmHg): 13.6/100 patient-years CV event rate (mean daytime DBP<88 mmHg): 2.2/100 patient-years CV events (higher ambulatory DBP): RR=6.20; 95 % CI=1.38–28.1; $p<0.02$	–	–
Pierdomenico et al. [38]	Defined as office BP≥140 and/or 90 mmHg in patients treated with ≥3 antihypertensive drugs, in at least two visits	276	Prospective cohort	CV events per 10 mmHg increase in SBP: RR=1.16; 95 % CI=1.0–1.36; $p<0.05$	CV events per 10 mmHg increase in daytime SBP: RR=1.34; 95 % CI=1.14–1.56; $p=0.0001$	CV event rate: 4.1/100 patient-years CV events: RR=2.40; 95 % CI=1.01–5.80; $p<0.05$	CV event rate: 1.2/100 patient-years
Salles et al. [39]	Defined as office BP≥140 and/or 90 mmHg in patients treated with ≥3 antihypertensive drugs in full dosages, including a diuretic and considered at least moderately adherent according to a standard questionnaire	556	Prospective cohort	CV events: SBP; HR=1.08; 95 % CI=0.90–1.29; p=NS DBP; HR=1.03; 95 % CI=0.85–1.26; p=NS All-cause mortality: SBP; HR=0.99; 95 % CI=0.78–1.25; p=NS DBP; HR=0.94; 95 % CI=0.73–1.21; p=NS	CV events for 1 SD increases in ambulatory nighttime BP: SBP; HR=1.38; 95 % CI=1.13–1.68; $p<0.001$ DBP; HR=1.36; 95 % CI=1.10–1.69; $p<0.001$	CV events: HR=2.11; 95 % CI=1.34–3.34; $p<0.001$ All-cause mortality: HR=2.00; 95 % CI=1.12–3.55; $p<0.05$	–
Muxfeldt et al. [40]	Defined as office BP≥140 and/or 90 mmHg in patients treated with ≥3 antihypertensive drugs in full dosages, including a diuretic and considered at least moderately adherent according to a standard questionnaire	556	Prospective cohort	–	CV events (non-dipping pattern of BP): HR=1.74; 95 % CI=1.12–2.71; $p<0.05$ CV mortality (non-dipping pattern of BP): HR=2.31; 95 % CI=1.09–4.92; $p<0.05$	CV events, all-cause mortality, CV mortality: HR=2.07; 95 % CI=1.22–3.50; $p=0.007$	CV events, all-cause mortality, CV mortality: HR=1.06; 95 % CI=0.43–2.61; $p=0.90$
Magnanini et al. [41]	Defined as office BP≥140/90 mmHg in patients treated with ≥3 antihypertensive drugs including a diuretic	328	Prospective cohort	CV events per 10 mmHg increase in SBP: RR=1.04; 95 % CI=0.96–1.13; $p=0.26$ CV events per 5 mmHg increase in DBP: RR=0.97; 95 % CI=0.90–1.04; $p=0.38$	–	CV event rate: 5.8/100 women-years, $p=0.06$ CV events (daytime ambulatory BP): RR=1.67; 95 % CI=1.00–2.78; $p<0.05$	CV event rate: 3.7/100 women-years, $p=0.06$
De la Sierra et al. [42]	High or very high added CV risk (presence of one or more of the following: three or more additional CV risk factors; type 2 diabetes; documented target organ damage; and previous documented CV or renal disease) – 30 % meeting the criteria for resistant hypertension	634	Retrospective cohort	–	CV events (nighttime SBP): HR=1.45; 95 % CI=1.29–1.59; $p<0.001$	–	–

ABPM ambulatory blood pressure monitoring, *BP* blood pressure, *CI* confidence interval, *CV* cardiovascular, *DBP* diastolic blood pressure, *HR* hazard ratio, *RR* risk ratio, *SBP* systolic blood pressure

presented a much higher cardiovascular event rate (4.1 vs 1.2 events per 100 patient-years) and a twofold increased risk of a fatal or non-fatal cardiovascular event (RR=2.40; 95 % CI=1.01–5.80; $p<0.05$) after adjustment for traditional cardiovascular risk factors. In contrast, a 10-mmHg increase of office SBP compared with daytime ambulatory SBP was associated with an adjusted risk ratio for cardiovascular event of 1.16 (RR=1.16; 95 % CI=1.0–1.36; $p<0.05$ vs RR=1.34; 95 % CI=1.14–1.56; $p=0.0001$). When the investigators included both office and daytime SBP in the same analysis, office BP did not reach any statistical significance.

More recently, Salles et al. [20] studied 556 patients with resistant hypertension (office BP≥140 and/or 90 mmHg, using ≥3 antihypertensive drugs in full dosages, including a diuretic) for a median follow-up of 4.8 years. ABPM provided significant prognostic information for the occurrence of fatal and non-fatal cardiovascular events independently of office BP and traditional cardiovascular risk factors. More specifically, increases of 1 SD in the ambulatory nighttime SBP (22 mmHg) and nighttime DBP (14 mmHg) were associated with a 38 % (HR=1.38; 95 % CI=1.13–1.68; $p<0.001$) and 36 % (HR=1.36; 95 % CI=1.10–1.69; $p<0.001$) higher risk of suffering a future cardiovascular event. Daytime BP was also significantly associated with cardiovascular events (daytime SBP; HR=1.26; 95 % CI=1.04–1.53; $p<0.05$, daytime DBP; HR=1.31; 95 % CI=1.05–1.63; $p<0.05$). In addition, the ABPM diagnosis of true resistant hypertension (mean daytime SBP≥135 mmHg or DBP≥85 mmHg) was significantly accompanied by a twofold risk for fatal and non-fatal cardiovascular events (HR=2.11; 95 % CI=1.34–3.34; $p<0.001$) and was the only independent prognostic factor for all-cause mortality (HR=2.00; 95 % CI=1.12–3.55; $p<0.05$). Interestingly, the investigators observed that office BP was not associated with the occurrence of cardiovascular events (office SBP; HR=1.08; 95 % CI=0.90–1.29; p=NS, office DBP; HR=1.03; 95 % CI=0.85–1.26; p=NS) and did not demonstrate any prognostic significance for all-cause mortality (office SBP; HR=0.99; 95 % CI=0.78–1.25; p=NS, office DBP; HR=0.94; 95 % CI=0.73–1.21; p=NS). A subsequent analysis in the above population [21••], examined for the first time the predictive role of nocturnal dipping patterns in resistant hypertensive patients. The ABPM-derived non-dipping pattern of BP was associated with a 74 % higher risk of suffering a fatal or non-fatal cardiovascular event (HR=1.74; 95 % CI=1.12–2.71; $p<0.05$) and a 2.3-fold higher risk of cardiovascular mortality (HR=2.31; 95 % CI=1.09–4.92; $p<0.05$) above and beyond office BP, ambulatory BP, and traditional cardiovascular risk factors. The above effect was more pronounced in patients with true resistant hypertension (HR=2.07; 95 % CI=1.22–3.50; $p=0.007$) compared to patients with white-coat-resistant hypertension (HR=1.06; 95 % CI=0.43–2.61; $p=0.90$).

Magnanini et al. [39] studied 328 women with resistant hypertension (office BP≥140/90 mmHg in spite of ≥3 antihypertensive drugs, including diuretics). After a mean follow-up of 3.9 years, the investigators demonstrated that patients with true resistant hypertension (daytime ambulatory BP≥135/85 mmHg) as compared to those with white-coat-resistant hypertension (daytime ambulatory BP<135/85 mmHg), had a higher cardiovascular event rate (5.8 vs 3.7 per 100 women-years, $p=0.06$) and their daytime ambulatory BP was a significant and independent risk predictor of cardiovascular events (RR=1.67; 95 % CI=1.00–2.78; $p<0.05$). In contrast, office BP did not demonstrate any significant association with cardiovascular events (office SBP; RR=1.04; 95 % CI=0.96–1.13; $p=0.26$, office DBP; RR=0.97; 95 % CI=0.90–1.04; $p=0.38$).

Taken together, the above evidence suggests that ABPM can predict more accurately fatal and non-fatal cardiovascular outcomes in patients with resistant hypertension. In addition, ABPM-derived information, such as that on patterns of the dipping status display significantly different associations with cardiovascular mortality and could reinforce the role of ABPM as a more powerful prognostic tool in resistant hypertensive patients. Moreover, the increased cardiovascular risk observed in true resistant compared to white-coat-resistant hypertensives, is another important element derived from ABPM that further adds to the prognostic importance of ABPM.

The Role of ABPM in Treatment of Resistant Hypertension

Beyond its role in the diagnosis and prognosis of patients with resistant hypertension, ABPM can also constitute a valuable tool in the adjustment of the therapeutic scheme, the assessment of any therapeutic interventions, and the follow-up of these patients. First, proper diagnosis of true resistant hypertension by ABPM reinforces the treatment plan towards better identification of TOD and intensification of antihypertensive treatment. This is because patients with true resistant hypertension have a higher prevalence of TOD, such as left ventricular hypertrophy, carotid intima-media thickening, microalbuminuria, and retinal lesions [40-45], followed by an increased risk of cardiovascular events. On the contrary, patients with white-coat-resistant hypertension belong to a lower risk group that could evade costly and unnecessary investigations as well as multi-drug schemes.

Another advantage of ABPM in the therapeutic management of patients with resistant hypertension is the detailed assessment of the effects of pharmacologic and non-pharmacologic interventions. An example of the role of

ABPM in the former was a study by Hermida et al. [46] who evaluated the impact on the circadian BP profile by modifying the time of administration and not of prescribed drugs in 700 patients with resistant hypertension divided into two groups, those taking all medications in a single morning dose and those taking at least one BP-lowering drug at bedtime. After 48-h ABPM assessment, it was observed that the amount of patients with controlled ambulatory BP was double among those taking at least one drug at bed time (p=0.008). Moreover, the same group of patients presented a much lower prevalence of non-dipping pattern contrary to patients receiving all medications in the morning (56.9 vs 81.9 %; p<0.001). In a prospective, randomized trial [22•], the same investigators assigned 250 patients with true resistant hypertension under triple antihypertensive regime at daytime in two groups. The first group changed one drug out of the triple regime but kept receiving all the medications at daytime whereas in the second group the same approach was followed with the exception of taking the new drug at bedtime. After 12 weeks of treatment, the investigators observed that the second group experienced a statistically significant ambulatory BP reduction (9.4/6.0 mmHg; p<0.001) with a greater reduction in nocturnal mean BP in relation to the first group. Moreover, a normal dipping profile was observed more frequently in the second group (p<0.001). In another study of 27 resistant hypertensive patients, Almirall et al. [47] demonstrated that shifting all non-diuretic antihypertensive drugs from morning to evening resulted in statistically significant lower ambulatory BP at night (p=0.005 for SBP, p=0.04 for DBP) and enhanced nocturnal BP decline.

The results of recent clinical trials evaluating the efficacy of invasive device-based therapies are also good examples of the usefulness of ABPM in assessing non-pharmacologic interventions in the treatment of resistant hypertension. In a phase I renal denervation study, Krum et al. [48] observed that 6 months after the intervention, office SBP fell by 27 mmHg whereas 24-h SBP by only 11 mmHg. In the Simplicity HTN-2 trial [23], sympathetic renal denervation resulted in a much lower fall of 24-h BP (30–40 %) compared to office BP measurements. In the European DEBut-HT trial (Devise Based Therapy in Hypertension Extension Trial), Scheffers et al. [49•] demonstrated that carotid baroreceptor activation with the Rheos device resulted in lower 24-h SBP/DBP (6.0/4.0 mmHg) reduction as compared with the reduction of office SBP/DBP (21/12 mmHg) at 3 months of follow-up. The disproportionately lower reduction of ambulatory compared to office BP demonstrated by the above-mentioned studies, underline the importance of ABPM when evaluating invasive therapies in the therapeutic management of resistant hypertension.

Another advantage of ABPM in the therapeutic field is that it can assist in the follow-up of patients with resistant hypertension. In an attempt to evaluate the most appropriate time interval to repeat ABPM and ensure the persistence of BP control in patients with white-coat-resistant hypertension, Muxfeldt et al. [50] performed a prospective study in 198 patients with a diagnosis of white-coat-resistant hypertension on baseline ABPM. The investigators repeated ABPM in 3 months and then twice in intervals of 6 months. At the end of the study, one third of the patients with initial diagnosis of white-coat-resistant hypertension retained their status. In contrast, more than half of the patients became true resistant hypertensives after the 15-month period. With their observations, the authors proposed a concise time-specific algorithm to follow up the status of white-coat-resistant hypertension patients. On the other hand, in patients with true resistant hypertension, the authors suggested that ABPM should be repeated whenever a therapeutic scheme adjustment is performed, to ensure proper BP control.

From the existing data, it can be deducted that ABPM can guide therapeutic management of patients with resistant hypertension. More specifically, ABPM diagnosis of true resistant hypertension can lead to proper intensification of treatment due to high cardiovascular risk and unfavorable prognosis. In addition, ABPM gives the opportunity to follow pharmacologic treatments targeting the circadian BP profile, assess the therapeutic effect of non-pharmacologic interventions, and also follow the longitudinal success of BP control of patients with resistant hypertension.

Conclusion

A wealth of clinical data demonstrates the superiority of ABPM over office BP in the diagnosis, prognosis, and therapeutic management of patients with resistant hypertension. In the diagnostic field, the importance of ABPM derives mainly from the detection of white-coat effect, affecting at least 30–35 % of the resistant hypertensive population and representing a major confounder in the initial evaluation of every such patient. The proper detection of white-coat effect among resistant hypertension patients can significantly change the existing prevalence data and have major clinical implications. In the prognostic field, ABPM is clearly a more accurate and independent predictor of cardiovascular morbidity and mortality compared to office BP in resistant hypertension, and thus, a better tool for cardiovascular stratification and relative therapeutic decisions. In addition, some ABPM parameters such as nocturnal BP decline are of significant value in predicting cardiovascular risk. In the therapeutic field, ABPM can guide proper intensification of treatment and pharmacological choices relevant to the circadian BP profile, evaluate the true effect of novel non-pharmacologic interventions and offer accurate follow-up of patient control. Interestingly, despite all convincing evidence, ABPM still has not been implemented in the formal definition of resistant hypertension

according to international guidelines. Is this still a matter of our resistance?

Compliance with Ethics Guidelines

Conflict of Interest Drs. Lazaridis, Sarafidis, and Ruilope declare that they have no conflicts 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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