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Review

Blood Pressure Monitoring in Cardiovascular Disease

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Abstract: While the practice of taking blood pressure readings at the physician's office continues to be valid, home blood pressure monitoring is being increasingly used to enhance diagnostic accuracy and ensure a more personalized follow-up of patients. In the case of white coat hypertension and resistant arterial hypertension, ambulatory blood pressure monitoring is indispensable. Recent studies attach great importance to nocturnal blood pressure patterns, with a reduction in these becoming a treatment goal, a strategy known as chronotherapy. Home blood pressure monitoring is useful for both diagnosis and follow-up of arterial hypertension. Its use, particularly if combined with other patient-support interventions, serves to improve blood pressure control. Telemonitoring is associated with a decrease in blood pressure values and an increase in patient satisfaction. All studies highlight the importance of patients being supported by a multidisciplinary health care team, since blood pressure telemonitoring with a support team is more effective than simple data telemonitoring. Further studies are called for, especially on the illiterate population, with difficulties posed by technological accessibility and transcriptions into different languages. More cost-effectiveness studies and long-term results are needed to ascertain the true benefit of blood pressure telemonitoring.

Keywords: ambulatory blood pressure; cardiovascular medicine; cardiovascular diseases; hypertension; telemedicine; combined modality therapy; telecommunications networks

Abbreviations

AHT: arterial hypertension; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring; OBPM: office blood pressure monitoring; RAH: resistant arterial hypertension; AF: atrial fibrillation; ESH/ESC: European Society of Hypertension/European Society of Cardiology; AHA: American Heart Association; HIT: Health Information Technology; PCMH: Patient-Centered Medical Home

Arterial hypertension (AHT) is a known risk factor for the development of cardiovascular diseases in general, and cerebrovascular accident in particular. Blood pressure (BP) values display a high degree of variability in each individual. Consequently, different methods have been designed for out-of-office measurement of blood pressure, in order to ascertain patients' "real" BP values. The different BP measurement modalities must be performed under standardized conditions with validated devices, to ensure that they can really contribute to correct decision-making in clinical practice, and strengthen the relationship between patients and health professionals [1].

This paper seeks to update existing evidence on BP monitoring and its application in the management of cardiovascular disease. To this end, we conducted a bibliographic search of the Medline database, using the following keywords: ambulatory blood pressure; cardiovascular medicine; cardiovascular diseases; hypertension, telemedicine; combined modality therapy; telecommunications networks. Similarly, we reviewed the Cochrane Library, UpToDate, leading clinical practice guidelines, and the recommendations of international scientific societies.

1. Blood Pressure Monitoring in the Diagnosis of Arterial Hypertension

There are three methods for diagnosis of arterial hypertension (AHT):

- ambulatory blood pressure monitoring (ABPM);
- home blood pressure monitoring (HBPM);
- office blood pressure monitoring (OBPM).

1.1. Ambulatory blood pressure monitoring

Using this technique, BP values are obtained with a device that the patient should ideally be wearing over the course of 24–48 h. This monitor takes measurements every 15–20 minutes during the day and every 30–60 minutes at night. With this method, AHT is defined as mean 24-hour BP > 130/80 mmHg, mean daytime BP > 135/85, and mean nocturnal BP > 120/70 [2,3].

ABPM is considered to be the most accurate method of diagnosis of AHT, and the best predictor of future cardiovascular events. Hence, it should preferably be used to confirm diagnosis of AHT in office measurements of elevated BP. Should ABPM be unfeasible, owing to scant availability or high cost, HBPM would be an acceptable alternative. ABPM can be used in certain circumstances, such as [4–6]:

- suspicion of white coat AHT;
- suspicion of episodic AHT (e.g., pheochromocytoma);
- resistant AHT;
- symptoms of hypotension in patients during hypertensive drug treatment;
- autonomic dysfunction;
- suspicion of masked hypertension.

In addition to the above, other potential indications include:

- determination of nocturnal AHT or "nondipper" status;
- evaluation of large variations in self-measurements of BP;
- evaluation of whether antihypertensive treatment moderates morning blood pressure;
- evaluation of BP in pregnant women with suspicion of pre-eclampsia.

ABPM reveals the BP load that represents the increase in BP during daytime and nighttime hours which exceeds the systolic blood pressure (SBP) and diastolic blood pressure (DBP) values established in the normal range. This load is closely related to the variations resulting from the circadian rhythm described by BP. In most subjects, BP follows a circadian rhythm, with values decreasing during the period of sleep. This corresponds to a fall of 10–20% in nocturnal blood pressure values, a phenomenon that is known as the normal or "dipper" pattern, and is in contrast to the so-called reduced dipper pattern characterized by a 1–10% decline, the nondipper or riser pattern characterized by a zero reduction or, on the contrary, an increase, or the extreme dipper pattern characterized by a fall of >20%. Patients with no such 10–20% reduction in their nocturnal BP have an increased cardiovascular risk, e.g., appearance of left ventricular hypertrophy, cardiac failure or vascular complications, while those who are diabetic display an association between increased albuminuria and increased progression of nephropathy [7–9].

1.2. Home blood pressure monitoring

This technique consists of BP being taken by the patient him/herself with the aid of automatic and semiautomatic devices. Twelve to fourteen readings should be taken over the course of a week, including measurements in the morning and evening. Measurements obtained with this method show a closer correlation with ABPM than with OBPM readings. With this type of measurement, AHT is defined as BP > 135/85 mmHg. As compared to OBPM, HBPM enables multiple BP readings to be

taken on a number of days in the subject's home environment. As compared to ABPM, HBPM allows for day-to-day measurements of BP, and is less expensive, more readily available and more easily repeatable: it should be borne in mind, however, that, unlike ABPM, it does not allow for readings to be taken during the patient's daytime activities or rest period [10–14].

1.3. Office blood pressure monitoring

Notwithstanding the above, OBPM continues to be the method of choice for diagnosis and management of AHT in cases where ABPM is not available [15,16].

A series of guidelines must be followed to ensure that the data are reliable [17,18]:

- Time of measurement: readings should always be taken at the same time, and patients should refrain from all physical exercise, tobacco use and/or caffeine intake in the preceding 30 minutes.
- Type of device: mercury sphygmomanometers are no longer used in many European countries, and have been replaced by semiautomatic or oscillometric sphygmomanometers. The instruments most frequently used for both OBPM and HBPM are semiautomatic devices [15,19].

Some oscillometric and semiautomatic devices are capable of taking a number of office BP readings whilst the patient is alone or resting, without the need for a health professional to intervene. Compared with the conventional measurement method, this may serve to reduce white coat AHT [4].

- Cuff size: use of an appropriate size is essential; if the cuff is too small, blood pressure values will be overestimated [20].
- Patient position: patients should remain seated, with their backs resting against a chair, without having their legs crossed. The patient's arm should be positioned at the height of his/her heart, and he/she should be left sitting in a quiet, relaxed environment for the space of 5 minutes prior to measurement. DBP may rise by around 6 mmHg if the patient's back is not supported, while SBP may rise by 2 to 8 mmHg if the patient's legs are crossed [19,21,22].
- Cuff position: the cuff should be placed over the brachial artery, 3 cm from the antecubital fossa, and the patient should not be wearing any tight-fitting garment that might compress or exert pressure on his/her body [19].
- Measurement technique: Neither the patient nor the observer should talk. Two measurements should be taken at an interval of 1–2 minutes. Should the second measurement differ from the first by 5 mmHg, readings should continue to be taken until a stable figure is obtained. The final result will be the mean of the last two measurements. For diagnosis of AHT, elevated BP values must be obtained on three consecutive visits, separated by one or more weeks [23].

1.4. White coat hypertension

BP is usually higher when measured at the physician's office, a phenomenon that may be attributable to an alert response and anxiety, or to a response influenced by an unusual situation. This

is the so-called "white coat effect", a phenomenon to be distinguished from the term, "**white coat AHT**", defined as an entity in which BP readings at the physician's office are elevated, with numbers indicative of AHT, but then decline when BP is taken at home. White coat AHT is also known as isolated clinic AHT or masked normotension. **Masked AHT** would correspond to patients with normal office BP and elevated home BP. The term **persistent AHT** is used when values are abnormal at both measurement sites [20].

Prevalence of white coat AHT is found in 15% to 30% of the population, and is most frequent in women, elderly persons and non-smokers [24].

White coat AHT is defined as office BP > 140/90 mmHg and out-of-office BP < 140/90. A number of studies have shown that patients with elevated office BP values may undergo a decrease of 15/7 mmHg in SBP and DBP, respectively, when the BP reading is taken at a third visit. There are some cases in which the decrease is not seen until the sixth visit [4,24].

In patients with figures indicative of isolated AHT, the frequency of organ damage, cardiovascular risk factors and appearance of AHT and diabetes is double that of the normotensive population. Yet, there is debate as to whether this causes more long-term cardiovascular complications than does normotension. The risk of cardiovascular damage is less prevalent in isolated office AHT than in persistent AHT [4,20].

The Task Force of the English International Consensus Conference on Blood Pressure Monitoring recommends the use of ABPM for diagnosis of white coat AHT, in any case where the patient presents with office BP ≥ 140/90 mmHg on 3 visits, with 2 home BP readings < 140/90 mmHg, and displays no end-organ damage [23].

The NICE guideline recommends that all persons over the age of 18 years with elevation of blood pressure should undergo ABPM, to rule out white coat AHT and potentially prevent unnecessary antihypertensive treatment [25].

2. Blood Pressure Monitoring in the Follow-up of Patients with Arterial Hypertension

The different methods that can be used for follow-up of BP control in patients who are already diagnosed are the same as those used for their diagnosis [20,25,26], namely:

- OBPM: the goal in patients with treated hypertension is to reduce BP to 140/90 mmHg in those aged under 80 years, and to below 150/90 mmHg in those aged 80 years or over.
- ABPM or HBPM: the goal of control is to achieve BP numbers of less than 135/85 mmHg in persons aged under 80 years, and less than 145/85 mmHg in persons aged 80 years or over.

As part of AHT patient follow-up, after the treatment has been established visits should be made every 2–4 weeks to adjust it until the target BP is attained. Once the control goal has been achieved, patients must be examined every 3–6 months by the nursing staff and annually at the physician's office: exceptions to the rule are patients that present with associated comorbidity, who should be

controlled more frequently. In cases where there are changes in therapy, patients should be examined at 2–3 weeks to test their tolerance and adherence to treatment [21,27].

In patients with isolated systolic hypertension, care must be taken to avoid reducing DBP aggressively (<55 to 60 mmHg), since excessively low values have been associated with increased risk of myocardial infarction and cerebrovascular accident [28–30].

As with ABPM, HBPM readings vary widely over the course of the day, being influenced by factors such as stress, smoking habit, caffeine intake, natural circadian variation, and exercise, with the result that multiple readings are required to determine the average level [34].

In view of the cost and limited availability of ABPM, increasing attention is being paid to HBPM using lower-cost semiautomatic devices. Such measurements correlate more closely with the values yielded by ABPM (both 24-hour and diurnal) than with those yielded by OBPM [11,35].

Furthermore, HBPM measurements afford a better prognostic predictive value of adverse events (e.g., cerebrovascular accident, end-stage renal disease) than do OBPM measurements [13,35,36].

In addition, self-measurement of BP can improve control of AHT, especially if combined with other patient support interventions [37–40] and a personalized medication education plan [41,42].

In 2013, a meta-analysis of 52 trials which randomly assigned patients to this type of surveillance or to standard OBPM, found significant benefits associated with self-measured BP, with the following results [38]:

- a decrease in BP at 6 months of 3.9 with HBPM versus 2.4 mmHg with OBPM;
- a decrease in BP at 12 months of 8.3 with HBPM (when combined with additional support interventions) versus 4.4 mmHg with OBPM.

Even so, the effectiveness of HBPM in reducing and controlling BP is less clear in patients having a low socioeconomic level, e.g., in an urban study of 900 patients, most of whom were black or Hispanic, self-measurement of BP along with training in its use had no effect on reducing SBP (which decreased by 15 mmHg in comparison with 14 mmHg in the control group) or the proportion of patients who achieved BP goals (39% in both groups) [43].

HBPM is a valuable tool in the daily management of hypertensive patients. It can be said that any individual with elevated BP could perform HBPM, provided that he/she possessed the requisite physical conditions and ability to comprehend the technique. HBPM should always be used under medical supervision, with regular re-assessment by healthcare staff [20,27,32,44].

Insofar as AHT patient follow-up is concerned, HBPM may be useful in the following cases:

- ✓ identification of white coat effects in AHT patients;
- ✓ variability of BP during a specific medical visit or over the course of series of such visits;
- ✓ autonomic, postural, postprandial hypotension after a short nap or rest (*siesta*) or induced by drugs;
- ✓ elevated office BP or suspicion of pre-eclampsia in pregnant women;

- ✓ confirmation of resistant AHT;
- ✓ evaluation of response to treatment;
- ✓ suspicion of non-adherence to antihypertensive treatment.

HBPM would thus be indicated in all patients with treated AHT, provided that there were no contraindications to its use (such as the existence of a physical or mental disability that hindered the performance or comprehension of the technique, lack of motivation, obsessive personality, hypochondria or extreme anxiety about the technique, arrhythmias such as atrial fibrillation, numerous extrasystoles, extreme bradycardia, pronounced tremor, increased arterial stiffness or risk of selfmedication), and in patients who needed rigorous BP control, such as hypertensives with limited access to the healthcare system (for reasons of timetable, geography, etc.), in order to manage the space between visits and to confirm hypertension where ABPM was not tolerated, was rejected by the patient, or was unavailable [45]. Existing evidence suggests the need to obtain a minimum of 12 to 14 readings, taken in the morning and evening, over a period of one week [10–12,44,46].

The appropriate way for patients to measure BP, as suggested by the American Heart Association (AHA) and the European Society of Hypertension and European Society of Cardiology (ESH/ESC) [11,20], is for two readings to be taken (at an interval of one to two minutes), while the patient is seated, in the morning and again at night (i.e., four measurements per day) on a minimum of three, but preferably seven, consecutive days. The measurements of the first day must be discarded.

Once blood pressure values have been stabilized after the introduction of treatment, the frequency of control depends on the stability of BP and any changes in treatment, where required. In stable hypertensive patients with controlled BP, HBPM should be performed for a minimum of one week per trimester, i.e., an average of 12 measurements in the morning and at night, to ascertain whether BP remains controlled.

3. Blood Pressure Monitoring in Children

There is a growing body of evidence to show that BP in children predicts BP in adults [47,48]. AHT in children is defined by reference to percentiles, obtained on the basis of a normal distribution of BP in healthy children [49,50]. The major determinant of BP in children and adolescents is weight. Consequently, the numbers obtained must be adjusted according to patients' height, age and sex [51].

Diagnosis of AHT is made after obtaining BP values higher than the 95th percentile on three separate visits.

The AHA classifies blood pressure at pediatric age into various categories [52]:

- Normal BP—both office/casual (< 90^{th} percentile) and ambulatory BP (mean SBP or DBP < 95^{th} percentile, and SBP or DBP load < 25%) are normal.
- Prehypertension—office/casual BP > 90^{th} percentile but < 95^{th} percentile, and mean ambulatory BP is normal (mean SBP or DBP < 95^{th} percentile), but BP load is elevated (SBP

or DBP load ≥ 25%).

- Ambulatory hypertension (also referred to as sustained hypertension)—both office/casual BP (> 95th percentile) and ambulatory BP are elevated (mean SBP or DBP > 95th percentile, and SBP or DBP load of 25–50%).
- Severe ambulatory hypertension (at risk of end-organ damage)—office/casual BP (> 95th percentile) is elevated and ambulatory BP is elevated with a markedly elevated BP load (mean SBP or DBP > 95th percentile, and SBP or DBP load > 50%).
- White coat hypertension—office/casual BP is elevated (≥ 95th percentile) but out-of-office BP is normal (mean SBP or DBP < 95th percentile, and SBP or DBP BP load < 25%).
- Masked hypertension—office/casual BP is normal (< 90th percentile), but ambulatory BP is elevated (mean SBP or DBP > 95th percentile, and SBP or DBP load of 25–50%).

Clinical monitoring of BP is indicated in children aged under 3 years only where they have presented with complications during the neonatal period, systemic diseases, or family history of AHT. In children aged over 3 years, measurements on each visit to the pediatrician are indicated [19,50,53].

For correct measurement of BP in children, the following must be borne in mind:

- Suitable cuff size
- Correct technique:

(a) prior to BP measurement, no stimulants or food should be taken;

(b) prior to BP measurement, the patient should be left sitting in a quiet, relaxed environment for the space of 5 minutes;

(c) measurement should be preferably made on the right arm in line with standard tables;

(d) electronic devices should be used but if the reading exceeds the 90th percentile, it should be checked using auscultatory techniques;

(e) if coarctation of the aorta is suspected, BP should be obtained in all four extremities;

(f) at least 2 BP readings must be taken at each visit, at an interval of 1 to 2 minutes.

Among adults, BP measurements yielded by ABPM show a closer correlation with cardiovascular complications than do those yielded by OBPM. In children the evidence is more limited. Most of the data pertain to children from European countries, and the degree to which these are applicable to other ethnic populations is thus uncertain. Efforts are therefore needed to establish ABPM rules for all pediatric populations [54].

In the interim, the usual practice is to use the AHA guidelines for ABPM of children. The devices used for taking 24-hour BP readings in children employ the oscillometric method, which calculates mean blood pressure directly using an algorithm. The algorithms must be adapted to the absence of variations in DBP with respect to weight and age in children, in contrast to the appropriate variation in SBP. Devices which rely on the auscultatory method are less used in pediatrics because children find them uncomfortable and there are no pediatric guidelines for such

devices [50].

White coat AHT in children ranges from 13% to 46%, according to the different studies published. The use of ABPM is cost effective in such cases and can generate cost savings before embarking on routine evaluations of children with AHT (blood analysis, electrocardiogram, echography, echocardiography). While some studies report that white coat AHT in children is associated with left ventricular hypertrophy and carotid artery intimal wall thickening, it is not altogether clear that that this would correlate with progression of AHT as in adults [55,56].

Among children, a nondipper pattern in ABPM is most common in secondary AHT and obese subjects. However, there are no long-term data that would support an increased cardiovascular risk in children with zero nocturnal decline in blood pressure. The absence of a nocturnal decrease in BP is more common in children with secondary AHT than in those with primary untreated AHT: hence, ABPM may be useful to differentiate primary from secondary AHT [57]. Its use may provide important information on patients with chronic kidney disease, diabetes, autonomic dysfunction or suspicion of white coat AHT, or for the purpose of assessing response to antihypertensive drugs [58].

In pediatric patients, ABPM would be indicated in the following cases [59]:

- differentiation between ambulatory and white coat hypertension;
- detection of masked hypertension;
- determination of the effectiveness of antihypertensive treatment;
- evaluation of BP in patients with chronic diseases associated with hypertension, such as chronic kidney disease, diabetes mellitus, autonomic dysfunction, obesity, sleep apnea, and genetic syndromes (e.g., neurofibromatosis type 1, Turner syndrome, or Williams syndrome).

4. Blood Pressure Monitoring in Elderly Patients

Despite the paucity of evidence, what does seem clear is that there is an increase in prevalence of white coat AHT [60–62]. ABPM would be useful, not only to unmask this phenomenon [3,20,25,45,60,63,64], but also to prevent overtreatment in hypertensive elderly, something that paradoxically appears to increase cardiovascular risk [65,66]. Lastly, it seems clear that masked hypertension is not more frequent in patients of advanced age [67,68].

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. It has an estimated prevalence of 1–2% in the general population and is a very important risk factor in cerebrovascular accidents. In this connection, some clinical practice guidelines recommend palpation of the radial pulse during routine measurement of BP, by way of opportunistic screening of this arrhythmia in patients aged over 65 years [25].

Palpation of the pulse, albeit inexpensive, is only a moderately accurate method, with a sensitivity of 87% and a specificity of 81%. In this respect, there are new automatic BP monitors that detect alterations in heart rate: these devices have an algorithm to detect variations of over 25% in heart rate during measurement of BP. This type of device can be useful to screen for AF, both chronic

and paroxysmal, since it achieves a sensitivity of 98% (95% CI: 95–1.0) and a specificity of 92% in its validations (95% CI: 88–96). Three successive readings should be taken, and if there is suspicion of AF, an electrocardiogram should be performed to settle the issue. If paroxysmal AF is suspected, a greater number of measurements should be considered, in order to enhance diagnostic accuracy [69].

5. Blood Pressure Monitoring in Resistant Arterial Hypertension

RAH is defined as any case where, despite showing good compliance with treatment and receiving adequate doses of triple antihypertensive therapy including a diuretic, the patient's control figures continue to lie outside the target range, i.e., SBP ≥ 140 and DBP ≥ 90 in the general population, and ≥ 140/85 in patients with diabetes or chronic kidney disease. Patients who require four or more drugs for good control are also included [20,70].

Prevalence ranges from 10% to 30% in the different series [71,72]. ABPM plays a fundamental role in the approach to such patients, in terms of diagnosis, prognosis and treatment, preventing erroneous diagnosis of resistant hypertension as well as unnecessary overtreatment [73,74]. On being presented with a patient with RAH, the first thing to do is to confirm that it is a genuine case of RAH, by ruling out both secondary AHT and possible "pseudo-resistance". Pseudo-resistance is said to exist where the cause of poor control is linked, among other things, to inappropriate measurement of BP, problems of adherence to treatment (both pharmacologic and non-pharmacologic), use of pressor agents, or white coat AHT.

The prevalence of white coat AHT among patients with RAH is high, with approximately one in four patients presenting with it. 24-hour ABPM is an appropriate initial step before investigating or treating patients with seemingly resistant hypertension [71,75]. Rios et al., [76] examined ABPM-based control of 3042 patients who complied with RAH criteria, with the following results: 522 (17.2%) had true isolated office hypertension (elevated office BP with good diurnal and nocturnal ABPM control); 260 (8.6%) had false office isolated hypertension (elevated office BP with good diurnal control but elevated SBP or DBP in the nocturnal period as measured by ABPM); and74.3% were true resistant hypertensives. Without the performance of ABPM, it would not have been possible to identify such patients.

To sum up, ABPM measurements enable patients with RAH to be classified into four subgroups, i.e., true RAH, white coat AHT, controlled AHT, and masked AHT. This classification is important because it determines a different therapeutic and follow-up approach. Some studies have shown that ABPM parameters can provide a better stratification of cardiovascular risk than can office BP. High ambulatory BP values are a predictor of cardiovascular morbidity and mortality in patients with RAH, whereas office BP has no prognostic value [77,78]. The risk is also higher for patients with a nondipper pattern. On evaluating the decline in nocturnal SBP with ABPM, Hermida et al., [79] have shown it to be a predictor of better cardiovascular prognosis, with every 5-mmHg reduction in nocturnal SBP being associated with a 15% reduction in future events.

Treatment of RAH is complex. It usually includes the triple combination of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, a long-acting dihydropyridine calcium-channel blocker (usually amlodipine) and a long-acting thiazide diuretic (preferably chlorthalidone or indapamide). If the triple therapy at the maximum recommended and tolerated dosage fails to achieve control of BP, the recommendation is to add a fourth drug, normally a mineralocorticoid receptor antagonist, and, if necessary, to continue adding drugs sequentially. In selected cases where the drugs have failed, consideration may be given to experimental invasive treatment with techniques such as radiofrequency ablation of renal sympathetic nerves (renal denervation) or electric stimulation of the carotid sinus baroreceptors [80,81].

ABPM is a tool of great use in the treatment of patients with RAH. On the one hand, it enables the effectiveness of such monitoring to be tested, and on the other, it helps decide on the best time of day for taking the drug. If ABPM values are available for treatment adjustment purposes, therapy can be adjusted to the nocturnal pattern of blood pressure control, thereby making it possible to check, not only whether BP has been normalized, but also whether nocturnal BP has been reduced. By basing the treatment regimen on chronotherapy, good control can thus be optimized [79,82,83].

In a percentage of RAH patients, estimated at around 3%, control cannot be achieved, despite maximum doses of 5 or more drugs, including chlorthalidone and a mineralocorticoid-receptor antagonist [84]. Some authors suggest that in these patients with refractory hypertension, it is adrenergic hyperactivity and not hypervolemia that is the cause of the problem [85]. Before concluding that a patient presents with resistant refractory hypertension, ABPM should be performed to confirm this. Decision-making in these complex patients should not be governed by isolated office or out-of-office determinations but rather by ABPM. Chronotherapy based on ABPM values makes for a more rational treatment regimen.

In conclusion, ABPM should, if possible, be performed on all patients with RAH. However, it is essential in any case where there are differences between home- and office-based controls and in patients with RAH without organ damage. ABPM provides data of prognostic value and is of undeniable use in the treatment and follow-up of patients with RAH.

6. Ambulatory Blood Pressure Monitoring in Patients at High Cardiovascular Risk, i.e., Those Suffering from Diabetes Mellitus, Cardiovascular Disease, Kidney Disease or Cerebrovascular Accident

Research has highlighted the role of nocturnal BP as an independent and highly important determinant of cardiovascular risk in patients with high cardiovascular risk, including those with established cardiovascular disease. In the latter, nocturnal BP tends to be elevated, with an increase in the prevalence of nondipper patients, who experience almost three times the number of cardiovascular events than do dipper patients. Consequently, ABPM has demonstrated its relevance in these patients for diagnosis, follow-up and choice of optimal treatment, owing to the

chronotherapeutic effect. A number of studies consider it important for office BP measurements to be supplemented with HBPM and ABPM-based measurements for diagnosis of arterial hypertension in patients with high cardiovascular risk. At present, there are insufficient data to recommend the routine use of such measurements, yet there are ongoing studies aimed at definitively establishing the importance of their use [86,87].

Stress has been laid on the importance of ABPM and HBPM in the follow-up of diabetic patients, since these are better than office BP in terms of correlation with clinical repercussions and long-term disease course, and prediction of progression to diabetic nephropathy. ABPM and HBPM are useful instruments for establishing treatment and individual cardiovascular risk because diabetic patients tend to have elevated nocturnal BP values and a high prevalence of nondipper hypertension pattern. Proposed changes to the guidelines for the use of ABPM in diabetic patients seek to extend its use in routine practice and as an instrument of routine diagnosis, in order to reduce underdiagnosis of "masked AHT", elevation of nocturnal BP, white coat AHT, and isolated AHT. Moreover, once the treatment has been established, both HBPM and ABPM are important for patient follow-up, in order to provide an objective measure of the efficacy of the antihypertensive treatment and to prevent nocturnal hypotension [88–91].

Elevated ABPM values in the first 24 hours after a cerebrovascular accident are associated with an increase in the incidence of formation of acute edema, while variations in the first week increase the risk of a new cerebrovascular accident in the following three months. Studies have shown ABPM's important role in establishing the antihypertensive treatment, its greater sensitivity as compared with office BP, and its use as a follow-up tool in these patients. This is due to the fact that there is an observed loss of control of circadian rhythm of BP in the first 24 hours after a cerebrovascular accident, which in most instances is maintained across time, so that there is an increase in elevated nocturnal blood pressure among such cases [92–94].

Elevated blood pressure values in ABPM are the best instrument for prediction of left ventricular hypertrophy in the long term and progression of renal dysfunction, inasmuch as ABPM is a significant long-term predictor when compared to other ways of measuring blood pressure. In end-stage renal disease, the data suggest higher mortality in patients undergoing hemodialysis, in whom higher ABPM values are obtained. Furthermore, the data support the fact that HBPM is indispensable for management of hypertension in patients with chronic kidney disease, whether or not they are receiving dialysis, since hypertension displays a strong predictive value in the outcomes of end-stage renal disease, thereby establishing itself as an independent risk factor of end-stage renal disease. Despite the evidence, however, there are still very few study results available [95–98].

Even so, notwithstanding all the results obtained, there are relatively few data on BP as measured by ABPM in patients with high cardiovascular risk, and those data that do exist come from small-scale studies. There is nothing definitively established as regards the role of ABPM, how it is to be performed, its duration, the need for repetition, the time period in which it should be performed, and diagnostic thresholds in patients with high cardiovascular risk. Currently, the normality reference

values are similar for all population groups. Some societies and studies, such as that by Hermida et al., have set lower blood pressure values for patients with high cardiovascular risk, based on studies which evaluate the appearance of cardiovascular events. Accordingly, the following objective ABPM values have been set for patients with high cardiovascular risk, including those with diabetes, chronic kidney disease and previous cardiovascular episodes: active waking BP < 120/75 mmHg and mean resting BP of 105/60 mmHg. As yet, however, there is no consensus on accepting these numbers as objective values for patients with high cardiovascular risk [86].

7. Pharmacologic Applications of Blood Pressure Monitoring: Chronotherapy

Studies of 24-hour BP records indicate that the mean nocturnal and diurnal readings are as important as the reading taken at the time of day when BP surges, and BP load (construed as the percentage of BP that exceeds a specific pre-established level, accepted by most clinical guidelines), and that these values are fundamental for calculating a given patient's cardiovascular risk. In most patients, BP, like other clinical variables, has a circadian rhythm. Hence, in the majority of patients —both normotensive and hypertensive—this circadian pattern is characterized by a sharp surge in BP in the early hours of the morning, coinciding with awakening, which is then maintained throughout the day until the evening, when it begins to fall and reaches its lowest level during sleep. Clinical studies indicate that such repetitive measurements of BP are superior to measurement of clinic BP in predicting the appearance of cardiovascular complications [99].

Different studies have shown increased cardiovascular risk in patients who do not present with a decline in nocturnal BP [9,99].

In the majority of individuals, this decline ranges from 10% to 20%. Patients in whom BP does not fall by this percentage are known as "nondipper", a term coined by O'Brien [100].

24-hour BP monitoring can detect surges in BP in the early hours of the morning, which can contribute to the rise in incidence of sudden death, myocardial infarction and cerebrovascular accident [101–103]. Theoretically, such surges cannot occur with drugs that cover the 24 hours of the day (long-acting agents). Some drugs, including atenolol and enalapril, can lose a great part of their effect in the early hours of the morning and may therefore have to be taken twice per day [104,105]. Furthermore, in patients with nocturnal or nondipper hypertension, ABPM can help determine the best time of administration of antihypertensive agents. In one study, valsartan taken at bedtime succeeded in re-establishing the nocturnal reduction in BP [106].

Chronotherapy can be defined as the scheduled administration of medication aimed at adapting it to the body's circadian rhythm. The impact of chronotherapy involving the taking at least one medication at bedtime could be of clinical importance, based on the growing number of ABPM-based studies which show that the decline in nocturnal BP is associated with better cardiovascular outcomes than is either the diurnal or 24-hour mean [107–111].

The MAPEC (Monitorización Ambulatoria de la BP y Eventos Cardiovasculares/Ambulatory

monitoring of BP and cardiovascular events), a prospective single-centre study which investigated 3344 normotensive and hypertensive subjects [112,113], together with its substudies corresponding to diabetic [114] and kidney patients [115], showed that nocturnal administration of at least one antihypertensive drug across a mean follow-up of 5.6 years led to an approximately 70% reduction in risk in respect of the principal variable, namely, total mortality and cardiovascular events. This principal outcome was linked to reduction in nocturnal BP, reduction in nondipper cases, and enhanced general control of ambulatory BP. The authors reported that, after a follow-up of 5.6 years, the baseline parameters of ambulatory BP monitoring, including mean diurnal SBP, nocturnal SBP and reduction in SBP during sleep, showed a better correlation with the appearance of cardiovascular events (n = 331) than did clinic BP. They found that there was a 13% decrease in cardiovascular risk for every 5-mmHg drop in BP during sleep ($p < 0.001$), and that this reduction in risk was independent of the changes in other aspects of the circadian BP pattern. The reduction in BP levels during sleep and the difference in BP between periods of diurnal activity and nocturnal rest were the most powerful predictors of future cardiovascular events.

Nocturnal AHT is highly predominant in patients with chronic kidney disease [35,116]. There are studies on hypertensive patients with kidney disease which show that, if at least one antihypertensive is administered at bedtime, patients present with better control of BP and a clearer reduction in cardiovascular risk than if medications are ingested on awakening [117].

Several trials also go to confirm that the intake of at least one antihypertensive medication at bedtime, as compared to the administration of all medication in the morning coinciding with patient's awakening, is associated with enhanced BP control, a significant decrease in the prevalence of nondipper patterns, and a reduction in urinary protein excretion [118,119].

Chronotherapy of AHT ensures individualized treatment of the hypertensive patient in line with the circadian profile of his/her BP, thus being a good guideline for achieving optimal 24-hour control, and affords greater cardiovascular protection to nondipper patients. However, several evaluations in ophthalmology have found that nocturnal arterial hypotension precipitated ocular vascular disorders such as ischemic optic neuropathy. Some authors have suggested that additional studies of nighttime dosing need to be conducted [118]. In conclusion, studies show that, in comparison with hypertensive patients to whom all medication is administered in the morning on awakening, those to whom one or more antihypertensive drugs are administered at night display improved 24-hour control of BP and a decrease in cardiovascular complications.

8. Blood Pressure Monitoring: What do the Leading Clinical and Scientific Society Guidelines Say?

In their recommendations, different guidelines include ABPM in the management of the hypertensive patient [3,25,45,86]. These guidelines recommend ABPM in the following situations:

- for diagnostic confirmation in patients with elevated clinic blood pressure, if ABPM is

available;

- where there is a large difference between clinic BP and that obtained in HBPM;
- suspicion of white coat AHT;
- discordance between BP values or time of progression of AHT and absence of end-organ damage;
- resistant AHT which does not respond to conventional pharmacologic treatment;
- masked AHT (patient with normal clinic and elevated ambulatory BP);
- patients with signs or symptoms of hypotension during antihypertensive treatment;
- in evaluation of AHT in elderly patients, children and adolescents, pregnancy, patients with high cardiovascular risk, AHT of suspected endocrine origin, and patients with Parkinson's disease.

A validated device is required. The following web page contains a permanent update of all recommended blood pressure measurement devices that meet international standards: www.dableducational.org.

Other pointers contained in clinical practice guidelines include the following:

1. ABPM must be performed with instruments validated in accordance with the international standards of the AAMI (Association for the Advancement of Medical Instrumentation), British Hypertension Society or European Society of Hypertension;
2. mean 24-hour BP values as measured by ABPM, which define a person as hypertensive are SBP ≥ 130 mmHg and DBP ≥ 80 mmHg;
3. mean diurnal BP values as measured by ABPM, which define a person as hypertensive are SBP ≥ 135 mmHg and DBP ≥85 mmHg;
4. mean nocturnal BP values as measured by ABPM, which define a person as hypertensive are SBP ≥ 120 mmHg and DBP ≥ 70 mmHg;
5. dipper pattern is defined as a fall in nocturnal blood pressure of 10–20%;
6. reduced dipper pattern is defined as a fall of 1–10%;
7. nondipper or riser pattern is defined as any case that fails to register a reduction or increase in nocturnal BP;
8. extreme dipper pattern is defined as a nocturnal reduction of over 20%;
9. if there is suspicion of white coat hypertension, ABPM must be performed;
10. in the event of HBPM being used in a case of suspected white coat AHT, values of 145/95 mmHg or over must be deemed to confirm diagnosis of AHT, whereas lower values require the performance of ABPM;
11. patients with isolated clinic AHT must be controlled by OBPM and ABPM, to identify possible progression to maintained AHT;
12. BP values as measured by ABPM correlate with cardiovascular morbidity and mortality in both the general and hypertensive population [120];

13. mean 24-hour SBP values ≥ 135 and DBP values ≥ 80 as measured by ABPM are associated with increased mortality [120].

In line with O'Brien's methodology, the methodologic aspects for performance of ABPM are outlined below [22]: the 2013 ESH/ESC Guidelines for Management of Arterial Hypertension [20] indicate that patients must wear a portable blood pressure monitor on the non-dominant arm for 24–25 hours. When the patient is fitted with the portable blood pressure monitor, the difference between initial BP and that obtained by the operator should not be > 5 mmHg. In the event of this difference being greater, the cuff must be removed and refitted. The patient should not engage in strenuous exercise. In the case of his/her usual daily activities, when the cuff inflates, the patient must cease the activity, keep the arm still and the cuff at the height of the heart, and stop talking. In clinical practice, measurements are normally taken at intervals of 15 to 20 minutes during the day and every 30 minutes during the night. A minimum of 70% of the diurnal and nocturnal pressures must be satisfactory, otherwise monitoring must be repeated.

Interpretation of ABPM:

Special attention must be paid to:

- mean BP values: the values to be borne in mind are 24-hour means of the active waking and rest periods, according to the values indicate above [33,45].

Basing themselves on cardiovascular events, some authors suggest lower values for high-risk patients [86];

- nocturnal pattern: some authors suggest that nocturnal BP is a better predictor of end-organ damage and cardiovascular events, hence the importance of administering one or more medications before going to bed [3,86];
- blood pressure variability: this may serve to assess a patient's cardiovascular risk and adjust his/her medication. One study suggests that the morning surge in BP classically associated with the appearance of cardiovascular events does not increase the risk of cardiovascular events [121].

9. Telemonitoring of Blood Pressure

AHT is the most common chronic problem seen at primary care visits, affecting around 30% of the population. It has been conclusively shown that AHT treatment prevents cardiovascular complications, that the treatment is well tolerated, and that inexpensive medication is currently available. Even so, the necessary degree of control of AHT is received by only half of all patients [20].

According to the most recent meta-analyses [122,123], the most effective method for improving blood pressure control of hypertensive patients lies in organizational changes in clinical practice and the empowerment of non-medical professionals (fundamentally nurses and pharmacists) able to make changes in the medication. The use of health information technology can help to bring about

the necessary change in the chronic cardiovascular disease healthcare model. As J.S. Floras has observed [123], "Blood pressure measurement is one of the few areas of medical practice where patients in the 21st century are assessed almost universally using a methodology developed in the 19th century".

The patient-centered medical home (PCMH) is a healthcare model that seeks to establish an association between patients, their families and the healthcare team, outside the clinic. The PCMH [124] has established operating principles which come within a vision of healthcare focused on the patient at home and the use of new technologies [125]. Home-based telemonitoring is a form of telemedicine where the patient performs the BP determinations at home and transmits them to his/her healthcare team via a self-kept log or remotely via the telephone or e-health-related technology. It is estimated that half of all AHT patients in the USA make use of HBPM. Most of the studies which use blood pressure telemonitoring include an educational component, reminder systems [127], environmental modifications, and/or changes in medication (see a recent review of the topic by Leah et al.) [126].

One of the most recent studies to be undertaken was the HyperLink Cluster Randomized Trial [127]. In this clinical trial, Margolis et al., used BP telemonitoring, with the participation of community pharmacists who could adjust the treatment in poorly controlled hypertensive patients. On conclusion of the 12-month study period, the researchers reported achieving a total of 71.2% (95% CI: 62.0–78.9) of well-controlled patients in the intervention group versus 52.8% (95% CI: 45.4–60.2) in the control group, with a mean decrease of 9.7 (95% CI: 6.0–13.4) mmHg in SBP and 5.1 (95% CI: 2.8–7.4) mmHg in DBP. The intervention group intensified the treatment to a greater extent, improved adherence to both drugs and salt restriction, and reported greater patient satisfaction. The benefit persisted at 6 months post-intervention. The cost was US$1350 per patient per year, an amount which could be reduced, according to the authors, by selecting those patients who would benefit most from the intervention.

In a subsequent analysis of the same clinical trial [128], the authors examined which part of the intervention had been the most effective, and concluded that intensification of treatment and greater use of HBPM (weekly measures) were the factors that accounted for 43% of the benefit. Self-reported compliance with adherence and salt intake had a small effect. Changes in lifestyle (exercise, weight, alcohol) had no significant benefits. In the Electronic Communications and Home Blood Pressure Monitoring Trial (e-BP) [129], a twofold improvement in BP control was achieved at a relatively low cost in patients in the intervention group vis-à-vis those in ordinary care, by incorporating a pharmacist who intensified BP management strategies through secure web messaging [130]. In the Collaboration Among Pharmacist and Physicians to Improve Blood Pressure Now trial, the cost to increase the rate of hypertension control by one percentage point was US $22.55 [133].

In real application of these telemonitoring programs in clinical practice, the following determinants are found [131,132]:

Facilitators in the form of better perception of care, patient satisfaction and empowerment, and freeing up of patient-physician consultation time;

Barriers in the form of difficulty of integrating pharmacists in the usual healthcare team, absence of information on computing and software resources, and resistance to the application of protocols.

The Hypertension Intervention Nurse Telemedicine Study (HINTS) [133] reported a 13% improvement in the control of blood pressure at 12 months of study, with improvements in lifestyle and changes in medication by trained nurses. The intervention proved most effective in patients with the worst baseline BP numbers.

The inclusion of community pharmacists in the AHT patient's healthcare team can provide [134,135]:

.education in hypertension and healthy lifestyles;

.counseling on medications and treatment regimens;

.drug safety monitoring;

.BP monitoring based on validated, calibrated devices;

.BP measurement procedure according to current guidelines;

.availability of out-of-office BP monitoring facilities (home and ambulatory);

.high accessibility of pharmacy.

BP telemonitoring at pharmacies may be of use in general-population hypertension screening, though there is less evidence than in the control of established AHT [136]. A pilot study has been conducted on patients with pre-hypertension using smartphone applications [137]. BP telemonitoring has also shown benefits in specific populations, such as older adults with kidney disease and ethnic minorities [138,139].

In conditions other than AHT, BP telemonitoring may also be of use. Hence, there are studies on problems such as diabetes mellitus, where, apart from BP, telemonitoring normally includes metabolic parameters such as glycemia, glycated hemoglobin or cholesterol, sent to the healthcare team by means of mobile health technologies or computerized systems [140,141]. Similarly, there are studies with benefits for overall cardiovascular risk, conducted by dieticians using e-mail [142]. The use of telemedicine in the management of chronic heart failure has likewise shown its utility by adding biomarkers, such as natriuretic peptide and intracavitary monitors, to BP control [143]. In patients with kidney transplants too, there are studies which report achieving a reduction in costs by optimizing pre- and post-transplant BP control with the aid of a telehealth system connected to the multidisciplinary healthcare team [144].

Telematic transmission of clinical data requires a secure confidential environment. It is therefore essential that all clinical parameters communicated, medical alarm/alert rules, and intervention algorithms are clearly defined to ensure the quality of the telemedical application [145].

Conflict of Interest

All authors declare no conflicts of interest in this paper.

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