Guideline

European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring

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Ambulatory blood pressure monitoring (ABPM) is being used increasingly in both clinical practice and hypertension research. Although there are many guidelines that emphasize the indications for ABPM, there is no comprehensive guideline dealing with all aspects of the technique. It was agreed at a consensus meeting on ABPM in Milan in 2011 that the 34 attendees should prepare a comprehensive position paper on the scientific evidence for ABPM.

This position paper considers the historical background, the advantages and limitations of ABPM, the threshold levels for practice, and the cost–effectiveness of the technique. It examines the need for selecting an appropriate device, the accuracy of devices, the additional information and indices that ABPM devices may provide, and the software requirements.

At a practical level, the paper details the requirements for using ABPM in clinical practice, editing considerations, the number of measurements required, and the circumstances, such as obesity and arrhythmias, when particular care needs to be taken when using ABPM.

The clinical indications for ABPM, among which white-coat phenomena, masked hypertension, and nocturnal hypertension appear to be prominent, are outlined in detail along with special considerations that apply in certain clinical circumstances, such as childhood, the elderly and pregnancy, and in cardiovascular illness, examples being stroke and chronic renal disease, and the place of home measurement of blood pressure in relation to ABPM is appraised.

The role of ABPM in research circumstances, such as pharmacological trials and in the prediction of outcome in epidemiological studies is examined and finally the implementation of ABPM in practice is considered in relation to the issue of reimbursement in different countries, the provision of the technique by primary care practices, hospital clinics and pharmacies, and the growing role of registries of ABPM in many countries.

Keywords: ambulatory blood pressure monitoring, clinic blood pressure measurement, clinical indications, guidelines, home blood pressure measurement, recommendations, research application

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1. INTRODUCTION

The Working Group on Blood Pressure Monitoring of the European Society of Hypertension (ESH) published recommendations for blood pressure (BP) measurement in 2003 [1] and a guideline for home BP measurement (HBPM) in 2008 [2]. Ambulatory blood pressure monitoring (ABPM) is a subject of considerable scientific interest with over 10 000 papers listed on PubMed in 2012. In 2001, the United States Center for Medicare and Medicaid Services approved ABPM for reimbursement for the identification of individuals with white-coat hypertension [3]. Since then healthcare providers in many other countries provide reimbursement for ABPM and in 2011, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom recommended that ABPM should be offered as a cost-effective technique to all people suspected of having hypertension [4].

One of the first meetings to examine the potential of ABPM was held in Ghent in 1978 [5]. The ESH Working Group on Blood Pressure Monitoring has held several consensus conferences on ABPM since the first one in Berlin over 20 years ago [6]. The most recent one was held in Milan in 2011 at which the technique was comprehensively reviewed. It was agreed that a writing committee, consisting of Eoin O'Brien, Gianfranco Parati, and George Stergiou, should draft two documents – a comprehensive review of the scientific evidence for ABPM that was presented at the Milan conference taking into consideration also relevant publications up to the end of January 2013 (the present paper) and a second short paper with concise instructions as to how the best information could be obtained from 24-h ABPM in clinical practice. A number of drafts were circulated to all the participants in the Consensus Conference for their comments and suggestions and the final version of the present paper is based on the agreed comments from 34 international experts. Data from randomized controlled trials of sufficient power with ABPM are still small and this limits formal grading of recommendations based on the available evidence. As the number of references cited in this paper is large and in the interest of saving journal space, some references have been listed in the supplementary file, http://links.lww.com/HJH/A283 that accompanies this paper. In the text citations these references are identified by the letter w after the reference number.

2. HISTORICAL PERSPECTIVE

Traditionally, BP in the office or clinic has been assessed with the auscultatory technique, which was introduced into clinical medicine at the beginning of the twentieth century, and which has survived to this day in clinical practice. Although the technique is inherently accurate, it is

dependent on observer attention to detail, which is often lacking, and it provides only a momentary measurement of BP, usually under circumstances that can influence the level of BP being measured. To overcome these serious methodological problems, techniques for obtaining automated profiles of BP over 24 h and measures of BP in the home setting have been developed.

ABPM has been available in one form or another for some 50 years, having been developed initially to study the circadian changes in BP and to determine the influence of BP-lowering drugs on the 24-h profile. The first major break with traditional BP measurement was the introduction of a direct intraarterial technique for the measurement of BP over the 24-h period. The data on antihypertensive drug efficacy provided by studies using this system were particularly valuable because they provided continuous BP measurement throughout the day and night, but use of the technique was limited by safety and ethical considerations. Efforts were focused, therefore, on developing a device that would record ambulatory BP noninvasively and in the 1960s, the Remler device, which was capable of measuring BP intermittently during the daytime period, provided clinicians with a new technique for assessing BP. This device was limited by having to be operated by the patient, which made measurement of BP impossible during sleep. The next technological advance was the introduction of fully automated devices that could measure BP intermittently at predetermined intervals over the 24-h period. This class of devices provided a methodology that was applicable not only for research but also for use in routine clinical practice [7–10,1w].

3. GENERAL CONSIDERATIONS

3.1. Why is ambulatory blood pressure monitoring superior to conventional blood pressure measurement?

Traditionally, office BP measurement has been performed using a sphygmomanometer and stethoscope. Recently, automated office BP measurement has been proposed as an alternative to traditional measurement. Automated office BP is the mean of multiple BP readings recorded with a fully automated device with the patient resting quietly, alone, in the office/clinic [11]. It has several advantages over manual BP, especially in routine clinical practice, by virtually eliminating office-induced increases in BP, improving accuracy, minimizing observer error, and providing a more standardized measurement technique using an automated oscillometric sphygmomanometer [2w]. The mean automated office BP for diagnosing hypertension is similar to the mean awake ambulatory BP and home BP ($\geq$135/85 mmHg). Preliminary data suggest that automated office BP is a better predictor of target organ damage [3w,4w], especially compared with routine manual office BP, which correlates poorly with intermediate end-points, such as left ventricular mass [5w]. Longitudinal clinical outcome studies with automated office BP have not yet been reported.

BP recorded in the patient's home is a significantly better predictor of future cardiovascular risk than is office BP. Standard protocols have been developed for recording home BP [2] and include the mean of duplicate readings taken twice daily for 7 consecutive days with readings from the first day excluded. The cut-point for hypertension using home BP is the same as for the awake ambulatory BP ($\geq$135/85 mmHg). In order to avoid reporting bias [12], a home BP recorder with a memory for storing readings should be used and the patient should take the device to the physician's office to have the mean home BP verified directly from the device's display. More recently, remote transmissions of home BP readings [13] is becoming available allowing BP readings recorded in the home to be automatically sent to a data collection center via a telephone modem or internet link and from there forwarded to the physician's office.

The advantages of ABPM, which have been stated in comprehensive reviews [1,10,14], have influenced recommendations for the technique to be used much more widely in clinical practice [15–18,6w,7w]. These advantages may be briefly summarized as follows (Box 1): first and foremost, ABPM simply gives many more measurements than conventional BP measurement, and usual BP is reflected more accurately by repeated measurements; ABPM provides a profile of BP away from the medical environment, thereby allowing identification of individuals with a white-coat response or masked hypertension; ABPM can demonstrate a number of patterns of BP behavior over 24 h that may be relevant to clinical practice, such as nocturnal hypertension or increased BP variability; by showing BP behavior in different windows of a 24-h period, such as the white-coat and nocturnal periods as well as the BP fluctuations triggered by environmental stimuli, it is possible to assess the efficacy of antihypertensive medication throughout the day and night rather than relying on a casual BP; ABPM is a stronger predictor of cardiovascular morbidity and mortality than conventional measurement, and evidence is growing that nocturnal BP measured by ABPM is an important predictor of cardiovascular outcome, from which it follows that the measurement of night-time BP should be an important part of clinical practice; and ABPM provides a means for not only improving the diagnosis and management of hypertension, but also for ensuring that effective control of hypertension is achieved throughout the entire 24-h period (Box 1).

3.2. Ambulatory blood pressure monitoring thresholds for clinical practice

As with conventional BP measurement, the levels of BP that constitute normality for ABPM have been a subject of much

Box 1 Advantages of ambulatory blood pressure monitoring over clinic blood pressure

- Gives a larger number of readings than office blood pressure measurement
- Provides a profile of blood pressure behavior in the patient's usual daily environment
- Allows identification of white-coat and masked hypertension phenomena
- Demonstrates nocturnal hypertension
- Assesses blood pressure variability over the 24-h period
- Assesses the 24-h efficacy of antihypertensive medication
- Is a stronger predictor of cardiovascular morbidity and mortality than office measurement

debate over the years [19–24,1w,8w–19w]. The issue is more complex than for conventional measurement because normality needs to be defined for both daytime and night-time pressures and outcome data are scarce.

In defining normality for ABPM, it is necessary to move on from diagnostic thresholds, determined in a statistical way in normotensive and/or hypertensive reference populations, to outcome-driven thresholds. The International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO) based on 5682 participants followed for 9.7 years determined ABPM thresholds, which yielded 10-year cardiovascular risk (for cardiovascular, cardiac, and stroke outcomes) corresponding to high BP on office measurement (>140/90 mmHg). Corresponding thresholds for hypertension with ABPM were 131.0/79.4 for 24 h, 138.2/86.4 for daytime, and 119.5/70.8 mmHg for night-time [25].

Whereas outcome-driven thresholds are currently available for adults, the question remains to be resolved whether they are applicable across the whole age range and in all conditions, or whether separate recommendations are necessary for older and very old individuals and for pregnant women. In the case of children and adolescents, a different approach is needed, and therefore, thresholds based on population distribution have been proposed (See Section 6.7).

Head *et al.* [26] examined a different approach to derive age-related and sex-related ABPM equivalents to clinic BP thresholds for diagnosis and treatment of hypertension by accounting for age and sex. They also compared clinic measurements taken by nonmedically qualified health professionals with those taken by doctors to assess whether a 'white-coat' effect might have influenced the findings of previous studies that were based solely on doctor's measurements. This analysis provided a range of daytime ABPM measurements equivalent to recognized clinic BP thresholds, which when predicted from clinic BP values were close to those derived from other outcome analyses.

The threshold values in the recent NICE guidelines [4], the JNC 7 guideline [27], and the ESH/ESC guidelines for 2003, 2007, and 2013 [1,28,29], and the results of outcome studies, such as IDACO [25] and Ohasama [30], have contributed to the definition of consensus values summarized in Box 2. It is recognized that the levels in Box 2 might be regarded as conservative by some and it is acknowledged that further studies are needed to define thresholds more precisely, particularly in high-risk patients.

3.3. Cost-effectiveness of ambulatory blood pressure monitoring

The cost-effectiveness of ABPM has been considered from a number of perspectives. First, ABPM may enable financial savings in drug prescribing. ABPM is superior to other measurement techniques in demonstrating the efficacy of antihypertensive drugs in pharmacological trials [31,32]. Adjustment of antihypertensive therapy according to ABPM rather than office BP has been shown to result in less antihypertensive medication being prescribed without compromising target organ involvement [33]. It has also been shown that, in patients on treatment with BP-lowering drugs, ABPM was a better predictor of cardiovascular outcome than office BP [34]. Reduction in office BP due to amelioration of the white-coat effect, especially in elderly patients, who have greater BP variability, may be attributed wrongly to a BP-lowering effect of antihypertensive medication if ABPM is not used to assess treatment efficacy [35].

Box 2 Thresholds for hypertension diagnosis based on ambulatory blood pressure monitoring

24-h average	≥130/80 mmHg
Awake (daytime) average	≥135/85 mmHg
Asleep (night-time) average	≥120/70 mmHg

Second, by identifying patients with white-coat hypertension, ABPM may improve drug prescribing in a cost-effective manner [36]. The cost of care for hypertension is dominated by the long-term occurrence of cardiovascular complications and the costs for drug treatment, rather than by the short-term cost for visits and investigations [37,20w].

Third, ABPM can identify individuals with normal BP in the office but elevated BP levels in daily life ('masked hypertension'), a condition that has been shown to carry the same adverse prognosis as sustained arterial hypertension both in the clinic and in daily life (see Section 6.3).

Until recently, ABPM is generally cited as being more expensive than other measurement techniques, though it has been shown to be cost-effective, both in specialist services and in primary care [36,21w]. This has been attributed to the fact that only tangible benefits have been considered, such as identifying patients with white-coat hypertension, and the savings that might be made from the more efficient prescribing of BP-lowering drugs. However, cost-effectiveness considerations must be extended to include the financial potential of the technique not only to improve the diagnosis and management of hypertension, but also as a means of ensuring that effective control of hypertension is implemented at community level [9]. ABPM is the most effective technique for identifying white-coat hypertension, which may be present in as many as 20% of people who appear to have hypertension with office BP, and these patients may be spared years of unnecessary and expensive drug treatment, which is often not free from side-effects. They may also avoid being penalized unnecessarily for insurance or employment by having the diagnosis of 'hypertension' misapplied [9].

A number of studies have analyzed the cost–benefit aspects of ABPM. Krakoff [36] has shown that potential savings of 3–14% for cost of care for hypertension and 10–23% reduction in treatment days when ABPM was incorporated into the diagnostic process. On an annual basis, the cost of ABPM would be less than 10% of treatment costs. Other cost–benefit analyses have shown that ABPM is most cost-effective for the diagnosis and management of newly diagnosed hypertension [9,21w].

Recently, NICE undertook detailed cost–benefit analysis for ABPM and showed that the use of ABPM is the most cost-effective method of confirming a diagnosis of hypertension in a population suspected of having high BP based on a conventional BP screening measurement of more than 140/90 mmHg and that the technique would result in substantial savings to the UK National Health Service [4,38]. However,

the validity of the underlying assumptions by NICE has not been universally accepted [39].

Other potential benefits of ABPM that have not been considered by NICE are the savings to be made in having drug treatment targeted to achieve 24-h BP control and the substantial savings to be made by the prevention of stroke and other cardiovascular consequences of hypertension with improved BP control. Nor has NICE considered the potential benefits of identifying the white-coat and masked hypertension phenomena in treated individuals, or of treating nocturnal hypertension, which is a major predictor of outcome.

In a further extensive study of the cost of ABPM, a Markov model-based probabilistic cost-effectiveness analysis concluded that ABPM is the most cost-effective strategy for the diagnosis of hypertension for men and women of all ages, mainly by virtue of its potential to reduce misdiagnosis and to direct better targeted treatment [38].

As the cost of ABPM and hypertension management differ greatly from country to country and is dependent on the method of healthcare delivery, the cost-effectiveness of ABPM may need to be evaluated at a national level. For example, in Japan, it has been estimated that the introduction of ABPM for the management of hypertension has reduced medical costs by about 9.48 trillion yen over 10 years [40] (see Section 8.2).

3.4. Limitations of ambulatory blood pressure monitoring

The technique of ABPM has many advantages over other available techniques, but it has its limitations, which include availability; the provision of intermittent measurements during which the patient is sedentary rather than 'ambulatory'; the possibility of inaccurate readings during activity and the inability to detect artefactual measurements; the technique makes demands on the patient, time is needed to fit the device and it may cause discomfort, particularly during the night, resulting in resistance from some patients to having repeat ABPM [1,10,14]; limited reproducibility when the procedure is not standardized [41]; and cost implications, although the cost of devices is reducing and cost–benefit analyses have shown that short-term costs are justified by long-term savings (see Section 3.3; Box 3).

Box 3 Limitations of ambulatory blood pressure monitoring

Application
- Limited availability
- May cause discomfort, particularly at night
- Reluctance to use by some patients, especially for repeat measurement
- Cost implications (although the cost of devices is reducing and possibly more cost-effective than office measurements)

Function
- Imperfect reproducibility
- Provision of intermittent measurements in sedentary rather than ambulatory conditions
- Possibility of inaccurate readings during activity
- Inability to detect genuine artefactual measurements

4. DEVICES AND SOFTWARE

4.1. Choosing an ambulatory blood pressure monitoring device

4.1.1. Selecting an accurate device

An accurate device is fundamental to all BP measurements; if the device used to measure BP is inaccurate, attention to methodological detail is of little relevance. It is acknowledged that the accuracy of BP-measuring devices should not be based solely on claims from manufacturers, which can at times be somewhat misleading. Instead, independent validation using an established protocol with the results published in peer-reviewed journals should be demanded [42,22w]. However, manufacturers often ignore this recommendation and potential purchasers are generally unaware of this requirement, assuming – not unreasonably – that if a product reaches the market place, it will measure BP accurately. The most popular validation protocol is the European Society of Hypertension International Protocol (ESH-IP) and a recent review showed that from the publication of the first version of the ESH-IP in 2002 until June 2010, 48 studies of device accuracy have been reported using the British Hypertension Society (BHS) protocol, 38 using the AAMI standard, and 104 using the ESH-IP 2010 [23w]. Thus, it seems that the ESH-IP succeeded in expanding by three-fold to four-fold the use of validation procedures worldwide compared with the period before its publication [23w]. A criticism by members of the AAMI Committee that the reduction in the number of patients might compromise the validity of the protocol [24w] has been shown to be statistically unfounded [25w]. The availability of the ESH-IP in an on-line version will further facilitate the validation of ABPM devices [26w].

Since the ESH-IP was first published, there has been an improvement in the performance of the oscillometric devices for BP measurement [23w], but protocol violations and misreporting have been particularly common, suggesting that there is a need for stricter standardization for conducting and reporting a validation study [27w]. The revised version of the ESH-IP protocol applied tighter validation criteria for the pass level [42] and the application of these more stringent criteria is expected to double the validation failure rate allowing more accurate devices to enter the market [23w].

The AAMI protocol requires additional testing for ABPM devices in 85 patients in the supine, seated, and standing positions, and stipulates that three devices should be assessed in ambulatory conditions, all of which would be very difficult and costly to perform [43,28w]. The BHS protocol, which is rarely used now, also requires an in-use (field) assessment of ambulatory monitors [44]. The International Organization for Standardization (ISO) protocol also requires additional clinical validation in 35 patients in standardized conditions of physical activity (after exercise on a bicycle ergometer or treadmill to increase heart rate by 10–20%) [45].

It has recently been suggested that the validation of automated BP-measuring devices should be complemented by an overall quality check. The PA.NET International

Quality Certification Protocol denotes additional criteria of quality for BP-measuring devices that fulfilled basic validation criteria, published in full in peer-reviewed medical journals. On the basis of this evaluation, a quality certification is released to the manufacturer and published on www.pressionearteriosa.net and www.dableducational.org [46].

The majority of devices for ABPM use oscillometry to measure BP, but some devices also measure BP by microphonic detection of the Korotkoff sounds and such devices need to have both measurement methods validated according to accepted validation protocols [29w].

4.1.2. Validation requirements for ambulatory blood pressure monitoring devices in special populations

Separate validation is required in specific populations, such as children and adolescents, pregnant women and the elderly, and in certain diseases, such as obesity and arrhythmias [30w]. Patients with arrhythmias, children, the elderly, and pregnant women present special challenges for validation of oscillometric ABPM devices. However, although ABPM devices are used frequently in these patient populations, specific validation studies have often not been performed; this limitation applies also to other methods of BP measurement, such as home and office measurements. The validation status of ABPM devices in different populations can be checked on dedicated websites (e.g. www.pressionearteriosa.net or www.dableducational.org). Although specific validation studies of ABPM devices in these special populations are desirable in the future, devices that have been validated in the general hypertensive population can be used so that high-risk patients are not denied the benefit of ABPM.

Children

Four ABPM devices have been validated in children and adolescents [31w–34w]. A number of factors that include consent, adherence to the validation protocol, which phase to choose for defining DBP, size of cuff, and level and range of BP make validation studies in children much more difficult than in adults [47,35w].

Pregnancy

A number of ABPM devices have been validated in normotensive and hypertensive women in pregnancy and preeclampsia and although more devices are being recommended for use in clinical practice, there are several devices that are not accurate in pregnancy [48,49,36w–41w]. In pregnancy, auscultation of DBP has been controversial leading to differences of opinion between muffling and disappearance of sounds as the criterion for DBP [49]. There is now general agreement that disappearance of sounds is the best measure of DBP [50].

The elderly

Validation data in elderly patients are available only for the SpaceLabs 90207 [42w]. It is important to define clearly the age group in which the device is being assessed. Individuals over the age of 65 years will also have a higher prevalence of diseases and conditions that can affect arterial stiffness, and therefore, influence the outcome of validation studies. The elderly have an increased prevalence of arrhythmias including atrial fibrillation, bradycardia, and ventricular tachyarrhythmias and are more likely to have inter-arm differences in pressures due to upper arm arterial disease, which would make them unsuitable for validation studies [51].

Patients with arrhythmias

There are no formal validation studies using established protocols for ABPM devices in this special population. In patients with arrhythmias, it is difficult to standardize the heart rates during validation. Good recordings can be obtained with ABPM in most patients, although there is a tendency for electronic devices to overestimate DBP in patients with atrial fibrillation [52].

Obese patients

No validation studies of ABPM monitors have been performed in the obese population. Obesity has an adverse impact on vascular stiffness, influencing thereby the accuracy of the oscillometric technique and these patients have large arms, which may complicate recruitment for validation studies, particularly when a specified range of cuffs has to be assessed [53].

Patients with renal disease

Only one ABPM device has been validated for patients with renal disease [43w]. Validating devices in patients with end-stage renal disease (ESRD) and chronic kidney disease (CKD) presents a number of problems [43w,44w] that include finding an available upper extremity, the effect of arterial stiffness on the oscillometric methodology, especially for DBP [54], and the demanding schedule of dialysis that makes recruitment of patients difficult.

4.1.3. Additional features for ambulatory blood pressure monitors

All ABPM monitors measure BP and pulse rate and most provide measurements not only for SBP and DBP but also for mean BP and pulse pressure. Over the past decade, ABPM devices have been developed to measure or calculate, intermittently or continuously, other parameters, such as the ECG, pulse wave velocity, and central BP. Furthermore, accessories such as position sensors and accelerometers for physical activity analysis have been incorporated to provide a more precise pathophysiological profile. Major limitations of these innovative devices are their relatively high price and the need to validate the associated functions according to adequate protocols and to provide evidence for their clinical usefulness. Until these requirements are fulfilled, the use of such ABPM devices should be restricted to research laboratories and specialized centers.

Ambulatory blood pressure monitoring and home blood pressure

Devices, which can be used either for 24-h ABPM or in a 7-day mode to collect multiday BP data, are being developed and one has been validated [45w,46w].

Ambulatory blood pressure monitoring and ECG

Devices have been developed allowing 24-h ABPM with continuous 24-h ECG in a single procedure. Besides the usual well established indications for each of these procedures, the interaction between these two signals provides complementary interrelated information in one procedure. The use of the real heart rate to determine the deflation rate can provide more precise BP measurement, and additional extra BP measurements can be triggered by abnormal ECG activities such as arrhythmias and ST segment abnormalities. Limitations are the relatively high cost of monitors and software, the complexity compared to the simple ABPM procedure, and the difficulties in performing validation studies for the combined functions [47w,48w]. These disadvantages are offset, to some extent, by being able to perform the two procedures simultaneously in older patients in whom arterial hypertension and paroxysmal atrial fibrillation often coexist. Another development has been the use of spectral analysis of heart rate to provide a means for improving screening for obstructive sleep apnea (OSA) [49w,50w].

Ambulatory blood pressure monitoring and arterial function

Devices are being developed that measure arterial stiffness so as to provide interesting information on 24-h ABPM and on arterial function [51w–55w].

Ambulatory blood pressure monitoring and position sensing

Position sensors have been developed to determine whether the patient is standing or lying during ABPM recording, and this facility allows an estimation of the sleep period [55,56w].

Ambulatory blood pressure monitoring and activity sensing

Activity sensors and accelerometers have been developed for monitoring patient activity during ABPM so as to provide an indirect measure of activity and rest, with the former being an estimate of the awake period and the latter of sleep. Some of these sensors are incorporated in the device, whereas others are complementary accessories placed either at wrist, thigh, or chest level [57w].

Ambulatory blood pressure monitoring and central blood pressure

Several 24-h oscillometric ABPM monitors use specific algorithms and software for pulse wave analysis by recording 24-h ABPM data as well as calculating central BP [56, 51w–53w,58w–61w]. Further studies are needed, however, to demonstrate the validity and clinical usefulness of these devices, which at present should not be used for making clinical decisions.

4.2. Software for ambulatory blood pressure monitoring data analysis

Recommendations on procedures for ABPM use tend to concentrate on the accuracy of the device's hardware, with little attention being paid to software presentation and analysis of ABPM data. As a consequence, the practising physician, who has to interpret the considerable amount of data provided by ABPM, is often faced with a bewildering report with reams of paper containing plots, histograms, and data analysis that have little relevance for clinical practice. It is important for ABPM software programs to be suitable for the intended use of the device. For example, in a busy general practice, perhaps only basic data giving average 24-h, daytime and night-time values and a visual plot are all that will be required, whereas for research purposes statistical detail on the windows of the 24-h profile and other indices may be required [10]. A recent study has stressed that whereas monitors for ABPM are subject to extensive validation protocols, there is no international guideline on the software processing of the collected raw data to prevent error being introduced by the software permutations. An example of software-induced error was demonstrated for the SpaceLabs Report Management System 92506, which showed errors in 92% of reports amounting to a numerical difference between printout and on-screen hourly averages ranging from −37 to 18 mmHg for SBP and from −16 to 10 mmHg for DBP [62w]. An additional problem can arise from the calculation of 24-h average BP values that are not weighted for the different number of hourly measurements during daytime and nighttime; weighted hourly BP values have been shown to be more reliable than calculations based on the average of all individual readings [57].

The use of ABPM in clinical practice can be facilitated by standardizing the graphic presentation of ABPM data, much as is the case for ECG recordings, so that the presentation of data is independent of the type of ABPM monitor used and the user is not required to become familiar with a variety of programs. Standardization also facilitates the interchange of ABPM recordings between databases, such as a hospital and primary care practice. Moreover, if ABPM software programs provide a printed report of the standardized ABPM data with a validated interpretative report [58] (signed by the physician in charge of the service, whenever legally required), doctors and nurses unfamiliar with the technique are assisted in learning the variety of patterns generated by ABPM, and because an individualized physician report is not a requirement in most cases, the cost of ABPM is reduced [1,10] (Box 4).

4.2.1. Software requirements

The following facilities are recommended for ABPM software in clinical practice [1,9,10].

Clinical report

The following information should be available in a one-page report:

1. Standardized plot format with each BP measurement on the vertical axis and time of day on horizontal axis, with different windows of the 24-h period identified and normal bands clearly demarcated. The sleep time interval used to calculate asleep BP should be indicated (shaded) and preferably based on the individuals' sleep time report (diary cards). In the plot, the

Box 4 Software requirements

Clinical report
- Ambulatory blood pressure measurement analysis and report should be standardized independent of the monitor type
- Standardized plot of all the blood pressure measurements with daytime and night-time windows and normal blood pressure bands demarcated
- Average SBP, DBP, and heart rate to be displayed
- Nocturnal blood pressure decline (%) for SBP and DBP
- Summary statistics for time-weighted average SBP and DBP and heart rate for the 24-h period, daytime and night-time, with standard deviations and number of valid blood pressure readings
- Facility for showing error readings, if required

Optional requirements
- Automated software generated interpretative report indicating the normal or abnormal patterns and whether the requirements for a valid recording are fulfilled
- Facility to plot heart rate and mean blood pressure
- Trend report for comparing repeated ambulatory blood pressure measurement recordings
- Ability to centrally host data

Research report
- Data storage and raw data export capability for research analysis and audit
- Parameters include variability measures (such as 24-h SD, 24-h weighted SD, average real variability, coefficient of variation), area under the curve calculations, blood pressure load parameters, rate–pressure product, trough and peak levels, smoothness index (the last two parameters requiring ABPM data before and during treatment to be available), cusum-derived statistics, and ambulatory arterial stiffness index.

upper value of the Y-axis should not be fixed, but adjustable to the highest BP value recorded, in order to maximize the graphic presentation of BP variations over the 24-h period. A plot of SBP and DBP throughout the 24-h period with a facility for plotting heart rate and mean BP so as to provide evidence of circadian behavior should be provided.

2. Summary statistics for time-weighted SBP and DBP and heart rate in the windows of the 24-h period and separately for the awake and asleep subperiods, with the respective standard deviations and the number of valid BP readings included in the analysis and a facility for indicating the time of going to bed and awakening.
3. Medication details.
4. Facility for showing error readings, if required.

Interpretative report

To remove the variance associated with the ABPM interpretation by human observers and to simplify the evaluation of results in routine clinical practice for those unfamiliar with the technique, there should be an automated software-generated interpretative report indicating normal or abnormal BP patterns and whether there are sufficient measurements for the recording to be valid [10]. The interpretative report should be validated by testing the computer-generated report against reports from experts [58,59].

Trend report

The provision of a trend report allows ABPMs to be compared over time to demonstrate the response to changes in management. If ABPM is to be used to achieve better BP control, it is important for prescribing doctors (and patients) to be able to see whether medication is achieving control throughout the entire 24-h period.

Research report

The system should be capable of storing data for detailed analysis for research and audit according to evidence-based definitions for time-weighted arithmetic and mean values for measures of BP level. In view of evidence that short-term BP variability may give information over and above mean BP levels and that reduction in 24-h BP variability may be beneficial [63w], time-weighted and other measures of short-term BP variability are helpful for on-going research in this area. Informative indices associated with outcome, such as area under the curve calculations, BP load parameters, trough and peak levels, the smoothness index (the last two parameters requiring ABPM data before and during treatment to be available), cusum-derived statistics, and most recently the ambulatory arterial stiffness index (AASI), should also be provided [60,61]. The system should be capable of storing and exporting raw data for research purposes and additional analyses [60,61,63w].

4.2.2. Indices derived from ambulatory blood pressure monitoring recordings

Average BP values (over 24 h, daytime, and night-time) are undoubtedly the most important parameters obtained from ABPM recordings, based on outcome data. However, a large number of additional indices with promising clinical evidence may be derived from ABPM recordings, and some of them are occasionally included in the reports generated by ABPM systems.

Blood pressure load

This index is defined as the percentage of readings in a given period (24-h, day, or night), which exceed a predefined threshold value, typically set at the proposed normalcy level for average BP values of that period. The aim of BP load is to quantify the number of readings with elevated BP and mathematically it depends on both average BP levels and distribution of BP readings [62]. Although in theory clinically appealing, and thus commonly incorporated in the ABPM software, this index has a number of limitations. Firstly, there is no evidence that the thresholds defined for average BP values have any prognostic meaning when applied to single BP measurements. Secondly, when comparing recordings with similar average BP levels, differences in BP load can be largely explained by differences in

BP variability, making this index largely redundant. Thirdly, BP load does not contain the prognostically important information on how much the threshold level has been exceeded. To overcome the latter limitation, it has been proposed to modify the classic BP load definition by calculating the total area under the time–pressure curve when BP exceeds the threshold [63]. Finally, although some studies support the usefulness of BP load in predicting organ damage [64,64w], it has never been convincingly demonstrated that it provides any additional and clinically relevant information, independently of what is obtained by focusing on average BP values. The use of BP load in children has also been examined, but it has not been found helpful in diagnosis [65w].

Rate–pressure product

This index, which is defined as heart rate multiplied by SBP, is used as an index of myocardial work during exercise and it has prognostic relevance [66w]. The availability of both heart rate and BP data in ABPM makes it possible to obtain the index readily, especially if ABPM is accompanied by actigraphy [65]. Although potentially promising, the clinical application of this index requires further research.

'Vascular' indices

Several ABPM-based indices have been proposed to provide information on vascular wall properties. Their rationale is based on the observation that the stiffness of the arterial wall increases when it is being stretched; in patients with impaired arterial wall elasticity, SBP increases more steeply than DBP, whereas in a patient with elastic arteries, SBP and DBP increase in parallel. The AASI, which is calculated as 1 – slope of regression of DBP on SBP, is readily obtainable from ABPM [60,66].

AASI appears to have a direct relationship to carotid–femoral pulse wave velocity (a validated index of large arteries' stiffness) and an independent relationship with cardiovascular outcomes [60,61,67w–70w], However, the ability of AASI to reflect arterial stiffness has been challenged because of its dependence on nocturnal BP fall and the fact that it implies the use of asymmetric regression, possibly affecting the precision of slope estimation [67–69,71w,72w]. Modifications to AASI have been proposed, but further data are awaited as to their ability to surpass AASI in predicting outcome [73w,74w].

The Q–Kd interval, which measures the time interval between the onset of the QRS on the electrocardiogram (Q) and the last Korotkoff sound (K) corresponding to the diastolic pressure (d), has also been shown to have prognostic value [70].

Indices for indicating the pattern of treatment-induced changes in 24-h blood pressure lowering

Two principal indices are available for assessing the smoothness and consistency of antihypertensive treatment effect over 24 h with ABPM. The trough-to-peak ratio is the ratio between BP reduction achieved by treatment at the end of dosing interval (trough, which for drugs administered once daily means 24 h after the last dose intake) and peak BP reduction, usually achieved a few hours after dose intake [71,72]. The trough-to-peak ratio is characterized by a high degree of variability in individual patients and is, therefore, not suitable for application to clinical practice [73]. The smoothness index is calculated as the ratio between the average of hourly BP reductions over 24 h and the standard deviation (SD) of such an average value, thus integrating information on the size of BP reduction by treatment and on its homogeneity throughout the 24-h period [71,73]. The smoothness index is highest for potent drugs or drug combinations, which also provide the most homogeneous BP reduction. It is more reproducible than the trough/peak ratio [71,73] and predicts treatment-induced changes in indices of organ damage, including left ventricular mass and carotid arterial wall thickness [75w]. A recent meta-analysis has provided information on clinical determinants of the smoothness index, such as age, ethnicity, sex, and smoking [74]. The relevance of these indices in predicting the impact of treatment on outcome and the reference values remain to be assessed.

5. PROCEDURE

5.1. Training requirements

The technique of ABPM is a specialized one, and should be approached with the care reserved for any such procedure. An understanding of the principles of traditional BP measurement, cuff fitting, monitor function, and analysis and interpretation of ABPM data is required. In practice, a nurse with an interest and experience in hypertension can master the use of ABPM devices after a relatively brief training. However, the interpretation of ABPM profiles requires experience in the technique, which is best provided by the doctor in charge of an ABPM service [1,9].

5.2. Fitting an ambulatory blood pressure monitor

Time needs to be given to fitting the monitor and preparing the patient for the monitoring period if good results are to be obtained [1,9]. The key to successful ABPM is educating the patient on the process of monitoring and the instructions should be explained and printed on a diary card. In clinical practice, measurements are preferably performed on a routine working day. Although ABPM is best not performed while patients are admitted to hospital because hospitalization leads to underestimation of BP and overdiagnosis of nondippers [10], there are occasions, such as the evaluation of severely resistant hypertension and assessment of patients following a stroke, when ABPM in hospital may be indicated.

The frequency of measurement during the 24-h period is generally not more than every 15 min (which could interfere with normal activity), nor less than every 30 min (which could give an inadequate number of measurements). More frequent measurements at night may disturb sleep and sleep disturbance has been shown to reduce the prognostic value of ABPM [75]. To improve reproducibility, repetition of ABPM should be performed on like days, for example, on routine working or recreational days. A diary card can be used to record symptoms and events that may influence ABPM measurements.

5.3. Explanation to patient

The first step is adequate explanation of the procedure in an attempt to allay anxiety, especially in nervous patients. Patients having ABPM for the first time should be told that there is minor discomfort caused by inflation of the cuff. It is important to emphasize to the patient to follow his/her usual daily activities but, as much as possible, to remain still with the arm relaxed and not extended or contracted at heart level during each BP measurement [1,9]. It can be helpful to have patients record periods of stress, the time of meals, the time of a siesta, the time of going to bed and rising, the quality of sleep, and the time and type of drug ingestion.

5.4. Identification of daytime and night-time periods and editing ambulatory blood pressure monitoring data

One simple and popular method for identifying daytime and night-time subperiods is to assess the time of awakening and sleeping from diary card entries. Another method is to use a fixed-narrow time interval approach in which, for example, the retiring (2101 to 0059 h) and rising (0601 to 0859 h) periods (which are subject to considerable variation) are eliminated, with the daytime period being from 0900 to 2100 h and night-time from 0100 to 0600 h; in this way, the variations in the time spent in bed that may exist between the young and the old and in different cultures are to some extent eliminated from the analysis [1,76w]. This method has the disadvantage of eliminating information on the white-coat window, on the early phase of night sleep when dipping can be most evident, and on the early morning surge of BP, which may be associated with cardiovascular events. However, these windows can be analyzed separately for research or if considered important in practice. In countries where a daytime siesta is popular, a record of sleeping times both during day and night is important and ABPM software should be able to adjust for this; otherwise, there may be underestimation of the nocturnal BP dip and overdiagnosis of nondippers [77w].

Many statistical techniques exist for editing ABPM records, and no one method is ideal [1,76w]. The detection of artefactual readings and the handling of outlier values (which may or may not be erroneous) have indeed been the subject of debate [76w]. There are a number of ways of separately analyzing BPs recorded during the day and night [76,78w]. Several automatic procedures have been proposed to reject outlying measurements based on a univariate, multivariate, or temporal approach. More complex procedures requiring the intervention of the observer have been proposed, but they are time consuming and not suitable for clinical practice [77]. It has been shown that rejection of outliers may alter the results of ABPM in individual patients, sometimes significantly affecting average SBP levels [77,78,79w]. Editing procedures can reduce mean systolic ABPM by 4 mmHg in comparison with unedited recordings, thereby decreasing the likelihood of diagnosing sustained hypertension. In one study, the prevalence of sustained hypertension was decreased by 6–10% when several editing methods were applied to raw 24-h data [79w]. To make the results of different laboratories comparable, common editing criteria for ABPM should be used. The problem is to establish which of the methods proposed in the literature provides the most reliable data. While awaiting more objective criteria to identify a universally acceptable editing procedure, we recommend that editing is not necessary for calculating average 24-h, daytime, and night-time values and that only physiologically impossible readings should be deleted from recordings. However, when there are excessive artefacts in a tracing, a repeat recording rather than editing should be performed. Some editing might be required when focusing on analysis of BP variability, for the quantification of which the presence of artefacts may introduce appreciable errors. If editing is considered necessary, a method proposed by Casadei *et al.* [80w] and modified by Winnicki *et al.* [78] provides comparable performance to other proposed editing procedures.

There are no firm data on which to base recommendations for a satisfactory ABPM recording, but the recommendation for having at least 70% of expected measurements provides a basic working recommendation for clinical practice. This figure will be influenced by the period demarcated as daytime (awake) or night-time (asleep) periods, and by the number of measurements selected (usually 30-min but often 15 or 20-min intervals). In the previous ESH guideline on measurement, it was recommended that there should be a minimum of 14 measurements during the day and seven measurements at night [1]. Having considered what evidence is available and the practical issues of performing repeat ABPM in practice, it seems reasonable to increase the minimum of daytime measurements to 20 while retaining a minimum seven measurements at night based on measurements being performed every 30 min and with fixed time periods being used to define day (0900 to 2100 h) and night (0100 to 0600 h) [1] (Box 5).

5.5. The arm for measurement

ABPM is best measured in the nondominant arm so as to interfere as little as possible with daily activity, unless there

Box 5 Evaluation of ambulatory blood pressure monitoring data

Definition of daytime and night-time

- Daytime and night-time intervals are best defined using sleeping times reported by individual users' diary cards (awake and asleep periods)
- Fixed narrow time intervals can be applied by discarding transition periods between daytime and night-time (e.g. daytime defined as 0900–2100 h and night-time 0100–0600 h)

Editing requirements

- Editing is not necessary for calculating average 24-h, daytime, and night-time values
- The ambulatory blood pressure monitoring should be repeated, if the following criteria are not met
  - 24-h recording with at least 70% of expected measurements
  - 20 valid awake (0900 to 2100 h)
  - 7 valid asleep (0100 to 0600 h)
  - Blood pressure measurements at 30-min intervals
  - For research purposes at least two valid daytime and one valid night-time measurement per hour

has been documented evidence of a difference in BP between arms in which case the arm known to have the higher BP values should be chosen [1]. It is common practice for BP to be measured by a conventional technique at the same time as an ABPM monitor is being fitted and to determine whether there is a discrepancy between the techniques. However, BP variability is such that any such comparison has little validity and, to determine a significant difference, it is necessary to perform simultaneous measurement according to a definitive protocol, and this is not feasible in practice [42]. Because of these limitations, the practice of performing a comparative measurement is not recommended.

5.6. Selecting the appropriate cuff and bladder

There is unequivocal evidence that either too narrow or too short a bladder (undercuffing) will cause overestimation of BP, so-called 'cuff hypertension', and there is growing evidence that too wide or too long a bladder (overcuffing) may cause underestimation of BP. Undercuffing has the effect in clinical practice of overdiagnosing hypertension and overcuffing leads to hypertensive patients being diagnosed as normotensive. Either eventuality has serious implications for the epidemiology of hypertension and for clinical practice [79]. It is important, therefore, to select a cuff containing an inflatable bladder of correct length and width for the arm in which ABPM is to be measured. All ABPM devices should provide cuffs containing bladders for small, medium, and large-sized arms as recommended in international guidelines [1,80,81]. However, in many obese individuals, the large bladder sizes cannot be used because the arm length is too short to accommodate the bladder [81w]. Another problem is that the cylindrical shape of the commonly used cuffs does not always wrap snugly around conical-shaped arms in obese and very muscular arms [82,82w,83w]. Recently, novel oscillometric home monitors with cuff technology that allows a single fixed-size cuff to be used on a wide range of arm circumferences have been developed [84w–87w].

Another issue that needs consideration is the possibility that the discomfort caused by inflation of a large cuff in obese patients might cause elevation of BP. This issue becomes more important during ABPM because of repeated measurement, especially during night-time sleep. Oscillometric devices for home use that measure BP during cuff inflation may induce less discomfort because the measurement is completed before maximal inflation [84w,88w]. However, to date, no study has specifically addressed this issue.

Forearm BP measurement may have to be considered when extreme obesity makes upper arm BP measurement impossible. BP measurements tend to be higher with forearm compared with upper arm measurement, but methodological differences in these studies make it difficult to provide recommendations for all populations [83,89w–94w]. Despite the questionable accuracy of forearm BP measurement, it may be the only acceptable option for ABPM in individuals with very large upper arms, provided the patient is instructed to keep the forearm at heart level during measurement [94w].

No wrist devices have been validated for ABPM, whereas technology for continuous beat-to-beat monitoring of ambulatory BP in the finger has been developed using the volume-clamp method first described by Penaz [95w]. A number of studies that compared this technology with intraarterial or noninvasive BP measurement showed underestimation of BP, particularly diastolic, yet it remains a practical alternative to intraarterial measurement for the evaluation of beat-to-beat BP changes and variability in research studies [84,96w–98w].

5.7. Conditions in which ambulatory blood pressure monitoring may be difficult to perform

Obese patients

Obesity is a well established major risk factor for hypertension with higher prevalence in specific population groups, such as patients with diabetes mellitus [99w] or OSA [100w]. Despite the increasing prevalence of obesity worldwide [101w] and the close link between obesity and hypertension, scarce data are available on the application of ABPM in obese and extremely obese individuals. ABPM is often required in these individuals and technical difficulties should not exclude them from such a valuable technology [79]. The problem of miscuffing in obese pregnant women may result in diagnostic discrepancies [85].

Patients with atrial fibrillation

BP measurement in patients with atrial fibrillation is less precise as this type of arrhythmia is accompanied by increased beat-to-beat BP variability due to variations in ventricular filling time, stroke volume, and contractility. International guidelines [1,81] recognize the relatively poor precision of a single BP measurement and recommend repeated readings in order to improve the accuracy of estimates. Theoretically, ABPM should fulfill this stipulation as it provides a relatively high number of readings in a short period of time. Unfortunately, published evidence regarding the role of ABPM in patients with arrhythmias and, specifically in patients with atrial fibrillation, is scarce.

Patients with atrial fibrillation have been usually excluded from trials using ABPM, as well as from validation protocols of ABPM devices. Four studies have addressed the possible value of ABPM in patients with atrial fibrillation [48w,102w–104w]. The evidence from these studies suggests that ABPM may be useful in these patients, provided its limitations are taken into account. The proportion of readings with errors, the variability of BP, and the repeatability coefficients do not appear to be different from those in patients in sinus rhythm. DBP measured using an ABPM monitor in patients with atrial fibrillation appears to be relatively higher than that obtained with the traditional office measurement or by the same ABPM procedure when the patient achieves sinus rhythm. This finding is supported by a review and meta-analysis of studies that validated electronic devices in patients with sustained atrial fibrillation, which showed consistent overestimation of DBP [52]. In spite of this, and although larger trials in patients on atrial fibrillation are recommended, there is no reason to exclude

such patients from ABPM procedures. Some novel oscillometric devices have an embedded algorithm for automated detection of atrial fibrillation during routine BP measurement, which appears to have high diagnostic accuracy [105w–107w]. However, to date this function has not been tested in ABPM devices (Box 6).

6. CLINICAL INDICATIONS FOR AMBULATORY BLOOD PRESSURE MONITORING

6.1. Role of ambulatory blood pressure monitoring in the diagnosis of hypertension

In reaching a consensus on the clinical indications for ABPM, we have relied on the recommendations of international guidelines published from 2000 to 2013 [1,21,27,28,62,86–94]. All these guidelines were in agreement that ABPM is indicated for the exclusion or confirmation of suspected white-coat hypertension; all but one were in agreement that ABPM is indicated for the confirmation of a diagnosis of hypotension and to identify patients with resistant hypertension; 80% recommended ABPM to assess drug efficacy over the 24-h period and for the assessment of the nocturnal dipping status and more than half recommended ABPM to identify masked hypertension. The most recent NICE guideline published in 2011, stated unequivocally that ABPM should be offered to anyone suspected of having hypertension by virtue of having had an elevated conventional BP measurement [4]. Given the strong recommendations supporting the greater use of ABPM in clinical practice, it is now incumbent on each country to provide ABPM services to patients who will benefit from improved management of hypertension as outlined below (Box 7).

Box 6 Requirements for obtaining a satisfactory ambulatory blood pressure measurement

Basic requirements
- Patients must be capable of understanding and coping with the device
- Ambulatory blood pressure measurement should be performed preferably on a routine working day
- Repeat ambulatory blood pressure measurements should be on like days, for example, on routine working or recreational days
- 10–15 min needed to program and fit the device, depending on first or follow-up recording
- Patient should be relaxed in quiet room

Fitting the monitor
- Ensure that there is sufficient battery power
- Enter patient details into monitor
- Initialize monitor
- Select frequency of measurement – usually 15–30 min for day and night
- Inactivate measurement LCD display.
- Apply cuff to nondominant arm
- Choose appropriate cuff with bladder length to encircle 80–100% of arm circumference
- Center of bladder should be over the brachial artery
- Place cuff on bare arm with tubing passing upward around patient's neck to be connected to the monitor on the waist
- Perform trial measurement to check working and to familiarize patient with the monitor and bleeping sounds

Advice to the patient
- Procedure should be explained and instructions printed on a diary card
- Patients should be told to follow their usual daily activities but to remain still during measurement with the arm relaxed at heart level
- Instruct patient to place monitor on the bed or beneath the pillow at night
- Warn patient not to take a shower or bath
- Advise patient not to drive but if this is necessary to stop driving if possible during measurement
- Mark the brachial artery so that if the cuff becomes loose, the patient can refit it
- Give patient oral and written instructions and a diary card to record the time of drug intake, the time of rising and going to bed, and any symptoms
- Instruct patient how to switch off the monitor in case of malfunctioning, such as repeated inflation
- If appropriate, instruct patient on how to remove and inactivate monitor after 25 h

Removing the monitor
- Usually removed by operator, but patients can be instructed to remove monitor and send it to the operator's center
- Download the data from the monitor
- 24-h minimum: 70% of expected number of readings and at least 20 valid daytime and seven night-time blood pressure measurements
- If minimum requirement not met, measurement should be repeated, though suboptimal data can be helpful

6.2. White-coat phenomena

6.2.1. White-coat hypertension (isolated clinic hypertension)

In clinical practice, the main indication for performing ABPM is to determine accurately an individual's BP status. The main advantages of ABPM over other forms of BP measurement are to identify untreated patients who have high BP readings in the office but normal readings during usual daily activities outside of this setting, and to identify varying 24-h BP profiles. Pickering *et al.* [95,108w] introduced the term 'white-coat hypertension' to describe this condition, which is now commonly defined as a BP reading at least 140 mmHg systolic and/or at least 90 mmHg diastolic in the clinic/office and a mean awake ambulatory SBP/DBP less than 135 and less than 85 mmHg [28]. A comparison

Box 7 Clinical indications for ambulatory blood pressure monitoring

- Identifying white-coat hypertension phenomena
  - White-coat hypertension in untreated patients
  - White-coat effect in treated or untreated patients
  - False-resistant hypertension in treated patients
- Identifying masked hypertension phenomena
  - Masked hypertension in untreated patients
  - Masked uncontrolled hypertension in treated patients
- Identifying abnormal 24-h blood pressure patterns
  - Daytime hypertension
    - Siesta dipping/postprandial hypotension
  - Nocturnal hypertension
    - Dipping status
    - Morning hypertension and morning blood pressure surge
    - Obstructive sleep apnea
    - Increased blood pressure variability
- Assessment of treatment
    - Increased on-treatment blood pressure variability
    - Assessing 24-h blood pressure control
    - Identifying true-resistant hypertension
- Assessing hypertension in the elderly
- Assessing hypertension in children and adolescents
- Assessing hypertension in pregnancy
- Assessing hypertension in high-risk patients
- Identifying ambulatory hypotension
- Identifying blood pressure patterns in Parkinson's disease
- Endocrine hypertension

between the ambulatory BP and office BP obtained in routine clinical practice by the physician ordering the ABPM gives the best measure of the degree of white-coat hypertension which is present [11]. The first few ambulatory BP readings taken in the ABPM unit are often higher than subsequent readings because of transient anxiety experienced by some patients in this setting [109w]. This increase in BP is usually not as great as that seen in the office of the referring physician [96]. Readings obtained during the first hour of the ABPM recording have sometimes been excluded from the calculation of the mean awake ambulatory BP as they may reflect the patient's white-coat effect and not their BP during usual daily activities.

In recent years, there has been increased interest in BP readings obtained using ABPM during sleep. Nocturnal BP is now recognized to be superior to daytime BP in predicting cardiovascular risk [16,97]. The traditional definition of white-coat hypertension is based on an elevated office BP with a normal BP during the awake period on ABPM in untreated patients [1,110w], but because of the contribution of asleep BP as a predictor of outcome, it seems illogical to exclude this period from consideration and it is proposed that an alternative definition of white-coat hypertension might encompass patients with office readings at least 140/90 mmHg and a mean 24-h BP less than 130/80 mmHg.

White-coat hypertension is virtually eliminated if office readings are obtained through use of automated BP measurement in the office waiting room [96]. In circumstances in which ABPM is not available, home BP readings performed according to standardized protocols have also been used to diagnose white-coat hypertension [28].

Findings in a number of clinical outcome studies in different populations have clarified the clinical significance of white-coat hypertension. Almost invariably, individuals with elevated office BP who have normal average readings on ABPM were at much lower risk of experiencing cardiovascular events than patients whose clinic and ambulatory BP were both elevated [97–102,111w]. Nonetheless, in some clinical outcome studies [98–102,111w,112w], patients with this condition may have a slightly increased, nonsignificant cardiovascular risk compared with normotensive controls. In almost every instance in which this increase has been noted, the ambulatory BP of the white-coat hypertensive patients was higher than in the normotensive individuals, even though mean ambulatory BP values for both groups were in the normotensive range. This difference in ambulatory BP could account for the slightly higher cardiovascular risk in the white-coat hypertension group.

There are other reasons why white-coat hypertension may not be a completely benign condition. The risk of developing sustained hypertension in subsequent years may be increased in patients with white-coat hypertension [100,102,112w]. Furthermore, some studies have associated white-coat hypertension with an increased prevalence of target organ damage [113w–115w]. Once again, the mean ambulatory BP in the control groups in these studies has generally been lower compared with the white-coat hypertensive patients. Although a meta-analysis performed by the IDACO group did not find any increase in cardiovascular events in patients with white-coat hypertension, there was a significant increase in risk in specific subgroups, including men and patients with diabetes [111w]. This meta-analysis also clearly showed that any increased risk of experiencing a future cardiovascular event because of white-coat hypertension was quite small and substantially lower than the risk seen with either persistent hypertension or masked hypertension.

Nonetheless, some patients initially identified as having white-coat hypertension will go on to develop sustained hypertension in future years. Whether the percentage doing so exceeds the expected number of normotensive individuals with comparable 24-h ambulatory BP values but normal office BP remains uncertain. The potential risks of white-coat hypertension may also be confounded by antihypertensive drug therapy prescribed because of the high office BP readings. So far, it has not been possible to account for this factor in the analysis of cardiovascular risk in patients with white-coat hypertension who are receiving medical care over many years in the community.

Several hypertension guidelines [27,28] recommend ABPM when white-coat hypertension is suspected. The basis for selecting patients with possible white-coat hypertension is somewhat imprecise as there are no characteristics that have a high specificity for diagnosing this condition. Findings in several studies [95,116w–118w] have suggested that the prevalence of white-coat hypertension in untreated patients with uncomplicated hypertension increases in the presence of the following: office SBP 140–159 mmHg or DBP 90–99 mmHg; female sex; increasing age; nonsmokers; hypertension of recent onset; limited number of BP measurements in the office; and normal left ventricular mass. Nonetheless, the clinical characteristics associated with white-coat hypertension are not sufficiently strong to estimate accurately the probability of an individual patient having this condition. Perhaps, the best reason to suspect white-coat hypertension is when patients with high office BP report normal BP readings taken at home or in the community. Indeed, a high out-of-office reading is the primary indication for reimbursement of ABPM by government insurance plans in some countries such as the United States.

Although the above-mentioned characteristics increase the probability that a patient has white-coat hypertension, it has to be emphasized that no one group seems to be exempt from white-coat hypertension; it may affect the young, the elderly, normotensive individuals, and pregnant women. The consequences of failing to identify the condition are considerable. Young (and indeed the not so young) people may be penalized for insurance and pension policies, and for employment. Life-long treatment may be prescribed unnecessarily, and if antihypertensive medication is given to people whose 24-h pressures are normal, they may be made unwell by the adverse effects of medication. In the elderly, in whom white-coat hypertension is common, the inappropriate use of drugs may have serious debilitating consequences. It is recommended that people with white-coat hypertension should have the diagnosis confirmed in 3–6 months and be followed at yearly intervals with ABPM, or home BP monitoring, so as to detect whether and when sustained hypertension occurs [1,21].

Children with white-coat hypertension tend to have a higher left ventricular mass index than confirmed normotensive individuals [117w,119w], but there are no long-term follow-up studies of children with white-coat hypertension.

Due to the limited association of white-coat hypertension with the alerting reaction to the presence of a physician, it has been suggested that the alternative term 'isolated office hypertension' is more appropriate because the combination of elevated BP in the office and normal ambulatory BP levels may depend also on factors other than the alerting reaction to the doctor's visit [103,120w]. The same considerations apply to white-coat hypertension identified through home BP monitoring [121w].

With the prevalence of white-coat hypertension in the community being as high as 20–25% [88], it is extremely important to make an accurate diagnosis of this condition. This goal can best be achieved by performing 24-h ABPM and/or home BP monitoring in all patients with uncomplicated, stage 1 and 2 essential hypertension before prescribing antihypertensive drug therapy. ABPM is cost-effective [38] in that it reduces healthcare expenditures by decreasing drug costs, physician visits, and adverse effects due to inappropriate treatment. Finally, after the initial diagnosis of white-coat hypertension has been made, patients should have their BP status monitored more carefully, preferably with home BP or automated office BP. If a trend toward higher BP readings is noted, then ABPM should be repeated in order to detect the development of sustained hypertension [21].

6.2.2. White-coat effect

'White-coat effect' is defined as the rise in BP that occurs in the medical environment regardless of the daytime ABPM level or the use of antihypertensive drugs. In general, 'white-coat effect' is present when the office BP is higher than the awake ambulatory BP. White-coat hypertension exists if the office BP is high and the awake ambulatory BP is normal in a patient not yet receiving antihypertensive medication. Thus, white-coat hypertension could be seen as a subset of white-coat effect, although it has been demonstrated that office BP values higher than ambulatory BP may occur independently of a white-coat effect [103].

Patients with an office BP at least 20 mmHg systolic and/or 10 mmHg diastolic higher than the awake ambulatory BP have been designated as having a 'clinically important ' white-coat effect [4,122w]. This term was introduced to distinguish these patients from those who have only a small difference between office and ambulatory BP, a difference too small to warrant changes in drug therapy. Treated patients with office BP at least 140/90 mmHg and awake ambulatory BP less than 135/85 mmHg could be designated as having 'pseudo-resistant hypertension due to white-coat effect' [104], as they have apparent hypertension based upon office readings, but are actually normotensive. White-coat effect is a recognized cause of 'false-resistant' hypertension [105] and may be present in anyone treated for hypertension, regardless of the number of drugs being taken [104]. Other patients may have only mild hypertension based on ABPM and yet appear to have severe hypertension due to a white-coat effect on office BP [103,121w,123w].

It is important to detect those patients with white-coat effect in order to avoid prescribing unnecessary antihypertensive drug therapy, which could lead to serious adverse effects. White-coat effect is more likely to occur in individuals with the same characteristics as those associated with white-coat hypertension (see above). White-coat effect may be somewhat diminished if office BP is recorded with strict adherence to guidelines for proper BP measurement [11].

The white-coat effect may not be necessarily the same as the increase in BP, which has been reported when a physician enters the room to see the patient, sometimes called an 'alerting reaction' [106]. The presence of a physician (or any other health professional) does increase BP, but it is only one component of the white-coat effect. Even if the patient is alone and records BP by activating an automated sphygmomanometer, there may still be some alerting effect present [124w], although this has not been found when systematically checking the effect of self-BP measurements on intraarterial BP simultaneously recorded [125w]. Thus, factors related to the patient, such as anxiety, the presence of a doctor or nurse, and the medical environment may each contribute to higher office BP readings, with nurses usually having a smaller BP effect than doctors [126w].

In some patients, the pressor response to the clinic environment can be directly observed in the ABPM tracing, with BP values characteristically higher in the initial (and possibly also final) portion of the recording (when the patient attends the clinic for device placement and removal) and may be influenced by the alerting circumstances of the office/clinic environment, compared with the remaining period [109w].

Patients who have exhibited a white-coat effect may need to be followed with other types of BP readings such as automated office BP, home BP, and repeat ABPM, especially if a trend to higher BP readings is noted.

6.3. Masked phenomena

6.3.1. Masked hypertension

The usual definition of masked hypertension is that it is present in patients who have a normal office BP 140/90 mmHg or less with elevated daytime BP on ABPM or home BP at least 135/85 mmHg [107,108]. However, as with the definition of white-coat hypertension, it is inappropriate to exclude nocturnal BP and the definition should be extended to include also 24-h BP values at least 130/80 mmHg. Concerning the question as to whether or not the definition of masked hypertension should be applied also to individuals on BP-lowering medication and not only to untreated individuals, it is clearly inappropriate to apply the term to individuals on treatment because by definition hypertension has been diagnosed and cannot be 'masked'. Therefore, when treated individuals have a normal office BP but persistently elevated ambulatory or home BP, the term 'masked uncontrolled hypertension' is more appropriate (see next paragraph).

The problem for clinical practice is how to identify and manage these patients, which may affect 10% of the general population [108]. The phenomenon might be suspected in individuals who have had an elevated clinic BP at some

time, in young individuals with normal or high-normal office BP and left ventricular hypertrophy, in individuals with a family history of hypertension in both parents, patients with multiple risk factors for cardiovascular disease, and perhaps diabetic patients. It appears to be more prevalent in patients of male sex, in younger age groups (including children and adolescents), in those with higher awake heart rate, or high cholesterol levels, and in obese patients and those who smoke and ingest alcohol [127w]. Exercise-induced hypertension also increases the likelihood of masked hypertension [128w,129w]. The BP increase at night triggered by OSA has been noted to contribute to masked hypertension, in particular when the latter condition is defined by considering 24-h or night-time ABPM values.

Adults with masked hypertension have increased risk of target organ damage and cardiovascular morbidity [1,99,101,108]. In adolescents, masked hypertension has been shown to be present in nearly 40% of individuals and these were more than twice as likely to have a parental history of hypertension, and to have a higher ambulatory pulse rate, BMI, and greater prevalence of left ventricular hypertrophy than normotensive individuals [109,134w].

Although no definitive data are available, masked hypertension has been estimated to occur in approximately 10–30% of individuals, with the variability in these figures depending on the diagnostic criteria used to identify this condition and on the characteristics of the population examined [108,109].

A study of the agreement between ABPM and home BP in the diagnosis of masked hypertension has shown that more patients with masked hypertension are detected by ABPM (14%) than by home BP (11%) [110]. The masked hypertension pattern has been shown to persist in approximately 50% of children, with 10% of them progressing from masked hypertension to sustained hypertension during a median follow-up period of 37 months [109,134w]. In a small group of adults with masked hypertension, 71% of individuals continued to manifest the phenomenon at repeat ABPM, whereas 80% of those with masked hypertension on repeat ABPM had masked hypertension or sustained hypertension on the first ABPM [135w]. A study evaluating masked hypertension over three ABPMs within 6 months showed a declining prevalence of the phenomenon with repeated ABPMs [136w].

6.3.2. Masked uncontrolled hypertension

As mentioned above, it is not appropriate to apply the term masked hypertension to patients receiving antihypertensive treatment because if a patient is receiving BP-lowering drugs, hypertension can no longer be defined as 'masked'. What could be 'masked', however, is poor control of BP with medication during the day or night-time periods in spite of normal office BPs. This phenomenon, which is best denoted by the term 'masked uncontrolled hypertension', is deserving of separate consideration because patients need to be identified so that they can be offered effective therapeutic BP control throughout the 24-h period to prevent the cardiovascular consequences of uncontrolled hypertension [71,111] (Box 8).

Box 8 Definition of white-coat and masked hypertension phenomena*

White-coat hypertension
- Untreated patients with elevated office blood pressure ≥140/90 mmHg ** and
- 24-h ambulatory blood pressure measurement <130/80 mmHg and
- Awake ambulatory blood pressure measurement <135/85 mmHg and
- Sleep measurement <120/70 mmHg or
- Home blood pressure <135/85 mmHg

Masked hypertension
- Untreated patients with office blood pressure <140/90 mmHg and
- 24-h ambulatory blood pressure measurement ≥130/80 mmHg and/or
- Awake ambulatory blood pressure measurement ≥135/85 mmHg and/or
- Sleep measurement ≥120/70 mmHg or
- Home blood pressure ≥135/85 mmHg

Masked uncontrolled hypertension
- Treated patients with office blood pressure <140/90 mmHg and
- 24-h ambulatory blood pressure measurement ≥130/80 mmHg and/or
- Awake ambulatory blood pressure measurement ≥135/85 mmHg and/or
- Sleep measurement ≥120/70 mmHg or
- Home blood pressure ≥135/85 mmHg

*Diagnoses require confirmation by repeating ambulatory blood pressure monitoring or home blood pressure monitoring within 3–6 months, depending on the individual's total cardiovascular risk.
**Ambulatory blood pressure values obtained in the clinic during the first or last hour of a 24-h recording may also partly reflect the white-coat effect.

6.4. Abnormal 24-h blood pressure patterns

Abnormal BP patterns include a number of conditions characterized by different behavior of BP during the daytime and/or the night-time. One such condition is an increase in short-term BP variability within the 24 h, which can only be assessed with 24-h ABPM. More details on this BP phenotype and on its clinical relevance are provided in Section 6.5.1.

6.4.1. Daytime hypertension

The daytime window of ABPM is the period when the patient is away from the medical environment and engaged in usual activities [10]. For almost all patients with hypertension, BPs during this window are lower than office or clinic BP [26,112]. However, BPs during this period are subject to effects of work and environmental stress, activity, body and arm movement, and the effect of exercise and other activities, such as driving, all of which may have an influence on the average level of BP recorded as well as on BP variability [137w]. These effects are largely absent in BP measured during the nocturnal period [16,138w]. Systolic and diastolic hypertension is the commonest daytime pattern in patients aged less than 60 years [1,113]. Average daytime BP is superior to clinic BP in predicting outcome, but inferior to nocturnal BP in some populations and conditions [16]. For example, white-coat hypertension tends to be more common in women, isolated systolic hypertension and nocturnal hypertension tend to occur more frequently in the elderly, and isolated diastolic hypertension is found more frequently in younger individuals [113].

6.4.2. Siesta dipping and postprandial hypotension

The classical siesta is common in some Mediterranean societies, but many patients, particularly the elderly, take a rest after lunch and this may be accompanied by sleep; the combination of a postprandial fall in BP together with

lowering of BP with sleep may induce a significant reduction in BP, and failing to account for this may distort the night/day ratio of ABPM and may lead to overdiagnosis of nondippers [77w,139w]. The magnitude of the postprandial dip and its effect on prognosis remains to be investigated [114]. Software programs for ABPM should be capable of allowing for an afternoon dip in the calculation and interpretation of awake and asleep average ABPM values and in the assessment of the nocturnal dip.

6.4.3. Nocturnal hypertension

ABPM is the ultimate noninvasive BP-measuring technique that permits measurement of BP during sleep [10]. Preliminary data suggest that specially modified home BP monitors may also be useful for this purpose [140w,141w]. The definition of the so-called 'dipping status' of a patient is traditionally based on the behavior of BP on going from wakefulness to sleep, depending on whether BP falls, rises, or remains constant. In physiologic conditions, there is a decline in BP when shifting from wakefulness to sleep. This BP fall is usually quantified by defining the daytime and the night-time periods based on the patient's diary or through use of wide-fixed or preferably narrow-fixed time intervals. In the former case, the entire 24-h time is arbitrarily subdivided into awake and asleep subperiods, by including all recording hours. In the latter case, transition times between day and night and between night and day are not included in the estimation of day and night average pressures, because of differences in the times when patients go to bed or wake up, leading to inconsistencies in bed rest time among individuals, which prevent it from being categorized reliably [115].

In some patients, the nocturnal decline in BP may be absent (nondipping) so that BP does not reach what could be defined as 'basal' levels during sleep [113,116,117,142w]. In some instances, BP may even rise during sleeping hours to reach levels that are higher than daytime levels (reverse dipping or rising) [118]. Alternatively, there may be a marked fall in BP during the night window to give the phenomenon of extreme dipping [119,143w–145w]. The magnitude of the rise in BP in the morning around the awakening time may also yield valuable prognostic information, and is commonly referred to as the 'morning surge' [112,118–120].

There is compelling evidence that nocturnal BP is superior to casual pressure in predicting outcome [16,116,121]. This has led investigators to suggest that the most important parameter for predicting outcome is the level of night-time BP, rather than any measure of day-night BP difference [138w,146w]. Given also the limited reproducibility of daytime BP levels, due to interference by individual daytime activities, cardiovascular risk stratification might be more accurate if based on night-time BP levels. This possibility should be addressed by interventional trials specifically targeting nocturnal BP. Isolated nocturnal hypertension, which may be present in 7% of hypertensive patients, can only be diagnosed with ABPM. Nocturnal hypertension in patients participating in antihypertensive drug trials could have an important influence on the 24-h efficacy of BP-lowering drugs [122]. An increase in night-time BP may indicate the occurrence of pathologic conditions, such as OSA [123] and nocturnal hypotension has been implicated in the progression of glaucoma [124,147w,148w].

6.4.4. Dipping, nondipping, extreme dipping, and rising

Although the degree of night-time dipping (defined as the difference between daytime and night-time BP) has a normal distribution in a population setting [10,29,112,109w]. It is generally agreed that a nocturnal BP fall more than 10% of daytime values, which corresponds to a night/day ratio of more than 0.9 is acceptable as an arbitrary cutoff to define patients as 'dippers' [112]. However, night/day ratio, which is poorly reproducible, is only a different mathematical expression of the same information on the relationship between day and night BP as dipping size, and these two quantities are interchangeable. Moreover, the definition of dipping as a nocturnal BP fall less than 10% (or a day/night ratio >0.9) is confusing, because 0–10% dipping is included in nondipping, whereas there is obvious dipping. A more clear definition of the BP behavior between day and night could include the following four categories, based on the night/day ratio: rising or absence of dipping (ratio $\geq$1.0); mild dipping (0.9 <ratio $\leq$1.0); dipping (0.8 <ratio $\leq$0.9); and extreme dipping (ratio $\leq$ 0.8) [120] (Fig. 1).

There are a number of methodological limitations to recording BP at night. In spite of these, night-time BP is more standardized and consequently potentially more reproducible than daytime BP (sleep being a more stable state than activity), a feature which gives nocturnal BP its predictive value [10,16,138w,149w,150w]. Nocturnal BP has the best overall reproducibility [10,125,145w], although this has not been shown to be the case in all studies [151w]. The majority of people have a dipping nocturnal pattern [10,14,152w,153w].

A diminished nocturnal fall in BP is associated with poor cardiovascular outcome both in population studies and in hypertensive patients [1,10,14,16,112,121,122,126–130, 109w,111w,146w,154w–156w]. Blunted night-time dipping is associated with angiographic coronary artery stenosis in men [155w], lower cognitive performance [146w], left

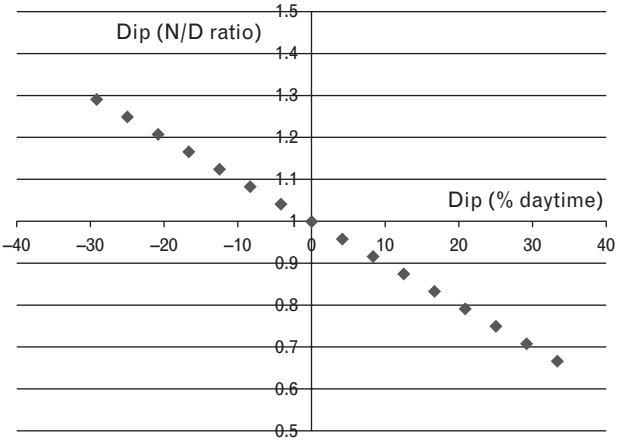

FIGURE 1 Mathematical correspondence between night/day (N/D) ratio and dipping rate expressed as percentage of daytime values (%Dip). Night/day ratio is just a different mathematical expression of the same information on the relationship between day and night blood pressure (BP) as the one provided by dipping size (%), and these two quantities are interchangeable as shown in the figure.

ventricular hypertrophy [128,156w], and renal damage [122,129]. This association parallels the finding that for each 10-mmHg increase in mean night-time SBP, the mortality risk increases by 21% [15,122]. A recent meta-analysis suggests that both the quantity and quality of sleep may also predict cardiovascular outcome, thereby raising the question as to how sleep may influence nocturnal BP [130].

A nocturnal 'rising' pattern occurs when BP rises above daytime pressures rather than falling during the night, thus resulting in a night/day BP ratio more than 1. These patients have the worst cardiovascular prognosis, both for stroke and cardiac events [117].

Finally, a marked nocturnal fall in BP, arbitrarily defined as a night-time BP reduction more than 20% of daytime values, is defined as 'extreme dipping'. The evidence for an association of extreme dipping pattern with a poor outcome is not strong, but patients with atherosclerotic disease may be at risk of nonfatal ischemic stroke and silent myocardial ischemia if excessive nocturnal BP reduction is induced by injudicious BP-lowering treatment [31,117]. Extreme dipping is closely associated with an excessive morning surge in BP, which may make the interpretation of the latter phenomenon more complex [118]. Reduced dipping at night and, even more so, a rising pattern may be regarded as a marker of the occurrence of pathologic conditions at night, such as OSA [123].

With regard to prognosis, it has been suggested that risers have the worst prognosis, whereas the prognosis is not necessarily different between dippers and mild dippers, and between dippers and extreme dippers [120].

Investigation of nocturnal BP behavior using ABPM may provide information on the presence of salt sensitivity, a condition associated with increased sympathetic activity and an increased cardiovascular risk [131,132,157w–159w].

There are, thus, many patterns of nocturnal BP behavior, and although these may be associated with an adverse prognosis, there has been relatively little study into the benefits of therapeutic modification of nocturnal patterns. However, there is overall agreement that the reduction of nocturnal hypertension should be an objective so as to achieve BP control over the entire 24-h period.

6.4.5. Morning hypertension and morning blood pressure surge

In the presence of a nocturnal BP reduction, a morning increase in BP, at awakening and even more so when resuming daytime activities, has to be regarded as a physiologic phenomenon. However, some studies have suggested that a more pronounced morning BP surge quantified by ABPM may carry negative prognostic implications [119,133,134,160w–166w], but this has not been confirmed in other investigations [135,136]. Circadian variations in other biochemical and physiological parameters besides BP (such as heart rate, plasma cortisol, plasma catecholamines, platelet aggregability, etc.) help to explain as triggering factors the increased occurrence of acute cardiovascular events in early morning hours [137,167w].

Given the methodological problems in determining the morning surge that include its association with the degree of night-time BP fall, different methods for its quantification, poor reproducibility, and the variety of definitions used in different studies, its relevance to clinical practice is limited.

A measure of the morning surge based on a mathematical estimate of the rate and amplitude of the rise, which has been shown to be higher in hypertensive patients and in patients with white-coat hypertension, is modifiable by some BP-lowering drugs, suggesting that the measure may be theoretically useful to highlight those individuals at greatest risk of cardiovascular events and for determining an important effect of antihypertensive therapy [134,166w] (Box 9).

6.4.6. Obstructive sleep apnea

OSA is one of a number of sleep-related breathing disorders that include habitual snoring, central sleep apnea, and OSA syndrome (OSA accompanied by daytime symptoms, and sleep hypoventilation syndrome) [138,168w]. It has been known since polysomnographic recordings were first described that alternating obstructive apnea and hyperventilation episodes during sleep are accompanied by acute changes in nocturnal cardiovascular parameters, which include wide oscillations in BP and heart rate [139].

In addition to increasing the risk for car accidents, worsening the quality of life, mood and cognitive performance, OSA is an additional and independent risk factor for cardiovascular diseases [140]. There is increasing evidence that OSA and hypertension, as well as the need of their combined treatment, should be considered in patients with refractory hypertension and a nondipping BP profile [27,28,123,141–143,169w–185w]. Although this association may be partly mediated by coexisting risk factors, such as obesity, there is evidence supporting an independent role of OSA in the pathogenesis of both night-time and daytime hypertension, even if this issue is still matter of debate [143,174w,175w].

Box 9 Patterns of disrupted diurnal blood pressure variation identified by ambulatory blood pressure monitoring

Dipping:	Nocturnal blood pressure fall >10% of daytime values or Night/day blood pressure ratio <0.9 and >0.8 – normal diurnal blood pressure pattern
Reduced dipping:*	Nocturnal blood pressure fall from 1 to 10% of daytime values or Night/day blood pressure ratio <1 and >0.9 – reduced diurnal blood pressure pattern
Nondipping and rising:	No reduction or increase in nocturnal blood pressure or Night/day ratio ≥1 – associated with poor cardiovascular risk
Extreme dipping:	Marked nocturnal blood pressure fall >20% of daytime values or Night/day ratio <0.8 – debatable cardiovascular risk
Nocturnal hypertension:	Increased absolute level of night-time blood pressure Associated with increased cardiovascular risk – may indicate obstructive sleep apnea
Morning surge:	Excessive blood pressure elevation rising in morning Definitions, thresholds, and prognostic impact debatable

*The classic definition of nondipping (nocturnal blood pressure fall <10% or night/day ratio >0.9) may be criticized because 'reduced dipping' is in effect a form of 'nondipping'.

The prevalence of hypertension ranges from 35 to 80% in OSA patients, and appears to be influenced by the severity of OSA. Patients with respiratory disease tend to be hypertensive, and up to 40% of hypertensive patients are diagnosed with OSA [144], with the figure being as high as 85% in patients with resistant hypertension.

Patients with OSA may have increased activity of the sympathetic nervous system, blunted baroreflex sensitivity, and an increase in plasma aldosterone levels [123,138–140,145,146,168w,186w,187w]. OSA is commonly associated with obesity and the metabolic syndrome or diabetes [188w]. There are several reasons why ABPM is useful in this population: many patients have multiple risk factors and, therefore, require a particularly accurate diagnosis of hypertension and evaluation of BP control; the prevalence of drug-resistant hypertension is high often requiring complex treatment regimens to achieve adequate 24-h BP control; and the prevalence of a nocturnal nondipper or riser profile is common and it may be possible to achieve reduction of BP and normalization of circadian profile with effective continuous positive airway pressure (CPAP) treatment [123]. A flow chart related to use of ABPM in the diagnostic evaluation of patients with suspicion of OSA is shown in Fig. 2 [147].

6.5. Assessment of treatment

6.5.1. Blood pressure variability and treatment

ABPM should be performed in patients in whom BP tends to be unstable and highly variable with office or clinic BP measurement or with home BP monitoring. Patients with increased BP variability are more likely to have white-coat or masked hypertension and they are at higher cardiovascular risk. Unstable BP may also be an indication that antihypertensive treatment is being ineffective and ABPM will demonstrate both the efficacy of treatment and the smoothness of BP reduction [72].

BP is a highly dynamic parameter characterized by continuous fluctuations [72]. The dynamic behavior of BP values over the 24-h period was first demonstrated with intraarterial BP monitoring in ambulant patients [72,192w–194w], and noninvasive 24-h ABPM provides a robust assessment of short-term BP variability, provided the interval between measurements is not longer than 15 min [71,148,149,1w,195w,196w].

Although ABPM provides a relatively large number of BP readings over the 24-h period, it does not allow continuous beat-by-beat monitoring of BP, and thus it does not allow assessment of the more sophisticated parameters of BP variability, such as spectral indices or baroreflex sensitivity analysis [72,150,197w].

Although short-term BP variability within 24 h can be readily assessed with ABPM, long-term BP variability, which may be prognostically relevant, requires repeated BP measurements over several days, weeks, or months and, thus, is only feasible based on data from home BP monitoring or, less easily, through analysis of visit-to-visit BP variability by clinic BP measurements or repeated ABPM [151,197w].

Evidence from longitudinal and cross-sectional observational studies has indicated that short-term BP variability

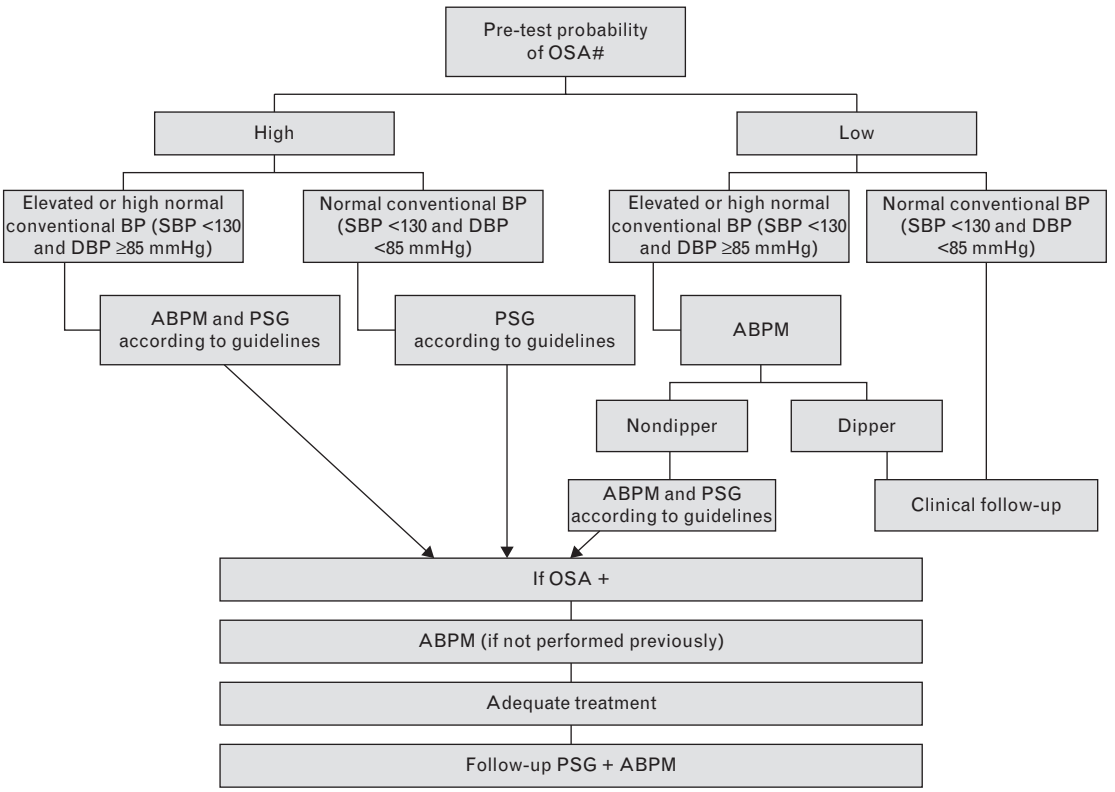

FIGURE 2 Proposed algorithm for the diagnostic management of patients with hypertension associated with obstructive sleep apnea (OSA). ABPM, ambulatory blood pressure monitoring; BP, blood pressure; PSG, polysomnography; #: According to clinical evaluation and questionnaires, for example, Epworth and Berlin questionnaires. With permission from Ref. [147].

within the 24-h period may contribute to cardiovascular risk [133,135,149–154,192w,195w–207w]. Evidence that correction of deranged BP variability has a positive impact on prognosis is only present in experimental animals [208w] and there are no consistent data as yet on the benefits deriving from reduced short-term BP variability in humans.

ABPM has been used to assess the effects of therapeutic strategies on reducing nocturnal BP, and there is some evidence suggesting that administration of antihypertensive drugs in the evening rather than in the morning may restore normal nocturnal dipping, and that cardiovascular risk may be reduced, but these results need to be confirmed by further trials [155,209w–211w]. Treatment effects on short-term BP variability may also be assessed by calculating various ABPM indices to quantify the persistence and homogeneity of a BP-lowering effect (see Section 4.2.3.4.) [71,73,74,75w]. Visit-to-visit office BP variability and ambulatory BP variability, which predict cardiovascular outcomes, may also provide a means to assess drug treatment efficacy [151,156,154w,197w,206w,212w].

In conclusion, based on the available evidence, short-term BP variability might be considered for risk stratification in population and cohort studies. However, it does not yet represent a parameter for routine use in clinical practice because of the current lack of generally accepted thresholds separating normal from pathologic BP variability levels, and because controlled intervention studies are still needed to establish whether a treatment-induced reduction in short-term BP variability will be accompanied by a reduction in cardiovascular events and mortality.

6.5.2. Assessing efficacy of blood pressure control

ABPM may be useful in the management of hypertension with drug therapy [1,213w,214w]. In a well controlled study, adjustment of antihypertensive treatment based on either ABPM or clinic BP measurement resulted in less intensive drug treatment in patients managed with ABPM despite comparable BP control in both groups. Furthermore, left ventricular mass was not increased in patients managed with ABPM, even though they received less antihypertensive medication [33]. ABPM also provides a better assessment of the response to treatment than does clinic BP; the efficacy of treatment without the white-coat effect can be ascertained, excessive drug effect and the occurrence of symptoms can be determined, the duration of BP control over the 24-h period and the consequences of missed doses on BP can be demonstrated [215w].

The inability of clinic BP to assess antihypertensive drug effect on the nocturnal BP dip or on the morning surge was illustrated in two prospective observational studies in treated hypertensive patients, who appeared to have well controlled BP on routine clinic measurements, but had uncontrolled hypertension during the early morning hours [157,158].

The antihypertensive effect of drug therapy can also be quantified by applying specific mathematical indices, such as the trough-to-peak ratio and the smoothness index to ABPM data [71,216w,217w]. These indices have different characteristics and different indications. The smoothness index combines information on BP lowering size and on homogeneity of BP reduction over the 24-h time; it is highly reproducible and is associated with rate of organ damage progression in individual patients. Trough-to-peak ratio, which only quantifies the distribution of antihypertensive drug effect over 24 h is best when averaged for groups of patients, and is characterized by a very low reproducibility in individual patients. Therefore, its use is mostly confined to pharmacologic research.

ABPM can also demonstrate the excessive effects of BP-lowering treatment, in particular at the time of symptoms during the 24-h period and especially at the time of peak effect of the drug, which can be related to episodes of hypotension [10,14].

6.5.3. Resistant hypertension

Hypertensive patients whose clinic BP remains persistently high despite taking three or more antihypertensive drugs at maximum dose including a diuretic are defined as having resistant hypertension and may account for 10% of hypertensive patients referred to specialized clinics [105,218w–220w]. Despite extensive diagnostic work-up, in many cases it is not possible to find a potentially correctable cause for the elevated BP, even though compliance to medication seems to be adequate [28,221w]. Patients whose hypertension is uncontrolled are more likely to have target organ damage and a higher long-term cardiovascular risk than are patients whose BP is controlled. For a better risk stratification, BP measurement outside the clinical environment is recommended in order to exclude the existence of a persistent white-coat effect, which might erroneously suggest the occurrence of resistant hypertension when in fact BP is controlled in daily life [2,27,28,159].

In a large Spanish registry, about one-third of 8295 patients with resistant hypertension based on office BP measurements had normal ABPMs, suggesting the presence of a white-coat effect or 'false' resistance [159], which has also been termed 'pseudo-resistant hypertension' [104,105]. Rather than create another category, it is best to regard patients with this phenomenon as exhibiting a white-coat effect and that ABPM has simply demonstrated that they do not have resistant hypertension. The reverse phenomenon may also be detected with ABPM, whereby patients on maximal drug therapy have low office but elevated ambulatory BP [222w].

The recommendation to use out-of-office BP measurements in resistant hypertension is based on the evidence that ABPM gives better prognostic information than office measurement [160–163]. One study showed that in patients with resistant hypertension, with or without a previous cardiovascular event, ABPM was an independent marker of risk for new cardiovascular events, suggesting that ABPM was useful in stratifying the risk in patients with resistant hypertension [163]. Two studies [161,162] have confirmed these results and reinforced the superiority of ABPM over office BP for stratifying risk. Also home BP monitoring may be useful in identifying patients with 'true-resistant' and 'false-resistant' hypertension, although this approach at present cannot provide information on night-time BP [162].

6.6. Hypertension in the elderly

The elderly can show striking variability of BP with periods of hypotension interspersed with hypertension on ABPM

[164]. This pattern, which is often indicative of autonomic failure, is important to identify so that treatment can be tailored to take account of such fluctuations in BP [204w]. There are four major age-related changes in the ABPM profile in the elderly: white-coat hypertension is more common than in younger adults; there is a predominant increase in 24-h SBP with a mild decrease in 24-h DBP after 60–70 years of age, and as a result, an increase in 24-h pulse pressure and the prevalence of 24-h isolated systolic hypertension; there is exaggerated ambulatory BP variability and morning BP surge; and disrupted diurnal BP variation (nondipping) and postural and postprandial hypotension are more common in the elderly [88,165,166].

Outcome studies in the elderly have shown 24-h SBP to be more closely associated with both fatal and nonfatal cardiovascular events and/or total mortality than office BP [126,167,168,223w–227w], and 24-h ambulatory pulse pressure has also been associated with cardiovascular disease [169,228w], with associations being closer for stroke than coronary artery disease [170].

The physiological nocturnal BP fall gradually diminishes with increasing age. Nondippers and risers with higher nocturnal than daytime BP are more frequently found in the elderly and these BP patterns are more closely associated with target organ damage, cardiovascular events, and mortality [169–171,228w]. In addition, nondipping and nocturnal hypertension in the elderly are associated with cognitive dysfunction and impaired physical activity [172]. In elderly diabetic hypertensive patients, the absence of the usual decline in nocturnal heart rate is associated with an increase in total and cardiovascular mortality [229w] and a synergistic effect of BP and heart rate nondipping on cardiovascular events has been reported in elderly hypertensive patients [173]. The quality of sleep in elderly patients can be affected by concomitant conditions, such as prostatic hypertrophy, sleep apnea, and sleep fragmentation [230w], and in such cases, nocturnal BP loses some of its prognostic significance [75].

Whether extreme dipping with marked nocturnal BP fall is associated with increased cardiovascular risk is uncertain with some studies showing increased risk [173,174,231w] and others failing to show an association [88,175]. The risk of extreme dipping in the elderly may be partially explained by its association with a steeper morning surge in BP, which frequently accompanies an excessive nocturnal fall in BP [134]. The disrupted circadian BP variation in the elderly is also associated with orthostatic BP dysregulation [232w], and reverse dipping is associated with orthostatic hypotension [176].

BP variability significantly increases with age, predominantly due to baroreflex failure and increased arterial stiffness and may advance target organ damage and trigger cardiovascular events in the elderly patients [177].

An increase in the physiological morning BP surge is determined by advancing age and higher 24-h BP level. The exaggerated morning BP surge can only be identified by ABPM and is associated with increased risk of subclinical target organ damage, cardiovascular events, and cardiovascular and total mortality, independently of age and average 24-h BP [164,233w]. However, a recent study did not show an excess risk of cardiovascular morbidity and mortality in hypertensive patients with exaggerated morning BP surge, emphasizing on the contrary the increased risk associated with nondipping or rising BP pattern at night [136].

Daytime sleep (siesta) may modify the diurnal variation of BP as well as of the cardiovascular risk in the elderly [233w]. Two-peak diurnal BP variation (morning and evening) in stroke onset was observed in elderly patients who had a siesta, which occurred in parallel with a two-peak diurnal variation in BP, heart rate, and physical activity, suggesting that an abrupt change in physical activity is not only a major determinant of the diurnal variation of BP, but might also be an important triggering factor for a stroke event [178].

Postural and postprandial hypotension, which are more common in the elderly [153,233w], and which can be exaggerated by antihypertensive drugs, such as diuretics or alpha-blockers, and also by noncardiovascular drugs, such as neuroleptics and antidepressants, are best diagnosed with ABPM.

6.7. Hypertension in children and adolescents

There is increasing interest in pediatric hypertension because of evidence for increased prevalence of hypertension among children and adolescents [109,179]. In 2009, the ESH published guidelines for hypertension management in children and adolescents [109], which are consistent with the 2004 US Task Force Guidelines on pediatric hypertension [179]. Moreover, a scientific statement on ABPM in children and adolescents has been published by the American Heart Association [180].

According to both European and American recommendations, ABPM is now increasingly recognized as being indispensable for the diagnosis and management of hypertension in children and adolescents [109,179,180]. In children, ABPM is particularly useful for the detection of white-coat and also masked hypertension [109,179,180], which may be more common than white-coat hypertension. Masked hypertension appears to be a forerunner of sustained hypertension and has been associated with left ventricular hypertrophy [109,180,134w]. Moreover, in children and adolescents with type-1 diabetes, ABPM is a valuable tool for the evaluation of nocturnal hypertension, which appears to be associated with the development of microalbuminuria [181].

The clinical use of ABPM depends on the use of normal BP ranges as reference values. In adults, the most meaningful reference values for both office BP and ABPM have been based on long-term prospective studies relating BP to cardiovascular morbidity and mortality rates. In children, it is very difficult, if not impossible, to validate diagnostic reference values based on morbidity and mortality because of the very low incidence of clinical events in this age group. Therefore, reference values for normal and high office and ambulatory BP have been developed from the distribution of BP readings in thousands of children, grouped by age, sex, and height [182,183,234w]. In future, it may be possible to refine these values by relating signs of target organ involvement, such as left ventricular mass, to the ambulatory BP.

BP measurement in children presents a number of difficulties and variability of BP is greater than in adults with the result that any single reading is less likely to represent the

TABLE 1. Tables of percentiles for ambulatory blood pressure (systolic/diastolic) values for clinical use in children and adolescents

	Boys				Girls			
	Day		Night		Day		Night	
Height (cm)	90th	95th	90th	95th	90th	95th	90th	95th
120	122/80	125/82	103/61	106/63	118/80	120/82	103/63	106/65
125	122/80	125/82	105/61	108/63	119/80	121/82	104/63	107/66
130	122/80	126/82	106/62	110/64	120/80	122/82	106/63	108/66
135	123/80	126/82	108/63	111/65	120/80	123/82	107/63	109/66
140	123/80	126/82	109/63	113/65	121/80	124/82	108/63	110/66
145	124/79	127/81	111/64	114/66	123/80	125/82	109/63	112/66
150	125/79	128/81	112/64	116/66	124/80	126/80	110/63	113/66
155	127/79	130/81	113/64	117/66	125/80	128/82	111/63	114/66
160	129/79	133/81	114/64	118/66	126/80	129/82	111/63	114/66
165	132/80	135/82	116/64	119/66	127/80	130/82	112/63	114/66
170	134/80	138/82	117/64	121/66	128/80	131/82	112/67	115/71
175	136/81	140/83	119/64	122/66	129/81	131/82	113/63	115/66
180	138/81	142/83	120/64	124/66	–	–	–	–
185	140/81	144/84	122/66	125/66	–	–	–	–

Data from [109,180,182,183].

true BP. Cuff dimensions are most important and the appropriate cuff size should be used according to arm length (4×8, 6×12, 9×18, 10×24 cm, to cover 80–100% of the individual's arm circumference) and width (40% of the arm circumference) [109,179]. Oscillometric devices may have different levels of measurement accuracy in children compared with the adults and, therefore, require separate validation. Few devices designed for ABPM have been successfully validated in children. The use of ABPM in clinical trials may be even more important in children than in adults because of the limitations of office BP in detecting hypertension in the small number of children having this condition (Table 1).

6.8. Hypertension in pregnancy

The role of ABPM for the diagnosis of hypertension in pregnancy and the prediction of maternal and fetal complications has generated considerable interest in recent years [235w]. ABPM is particularly useful in pregnancy for detecting white-coat and nocturnal hypertension. White-coat hypertension, which may occur in as many as a third of pregnant women, has a more favorable outcome than sustained hypertension diagnosed by ABPM. White-coat hypertension has been shown to persist in 50% of women with good pregnancy outcomes, whereas 40% developed benign gestational hypertension and had good pregnancy outcomes, with only 8% developing proteinuric preeclampsia, compared with 22% among 158 women with hypertension confirmed by ABPM [184]. Nocturnal hypertension occurs in about 60% of pregnancies and is higher in women with preeclampsia than in those with gestational hypertension [184]. Nocturnal hypertension is associated with higher risk of maternal and fetal complications [184–186,236w–238w].

Although ABPM is regarded as superior to clinic BP, its predictive accuracy remains low and the most predictive component of BP remains uncertain [187]. Ambulatory pulse pressure [239w] and daytime DBP have been shown to be predictive of birth weight [186].

Because of the hemodynamic changes occurring in pregnancy, BP-measuring devices need to be separately validated in pregnancy [240w].

Several guidance documents for the management of hypertension in pregnancy have provided suggestions on the use of ABPM and have acknowledged its usefulness in detecting white-coat hypertension and predicting women at risk of developing hypertension later in pregnancy [188,189,241w,242w]. Thresholds for ABPM according to gestational age have been provided for clinical use (Table 2) [190].

6.9. Hypertension in high-risk patients

ABPM is particularly helpful in hypertensive patients who for various considerations are regarded as being at high risk of cardiovascular disease. White-coat hypertension, masked hypertension, nocturnal nondipping and nocturnal

TABLE 2. Ambulatory blood pressure monitoring values according to gestational age (blood pressure range with upper normal value in parentheses[a])

	24-h ambulatory BP				Sleep ambulatory BP			
Gestational age (week)	9–17	18–22	26–30	31–40	9–17	8–22	26–30	31–40
SBP (mmHg)	101–118 (121)	96–127 (126)	97–133 (128)	103–136 (131)	93–109 (110)	88–120 (114)	87–125 (117)	85–131 (123)
DBP (mmHg)	60–71 (73)	56–78 (76)	56–84 (78)	57–85 (82)	50–64 (64)	46–68 (66)	46–76 (68)	47–77 (72)

BP, blood pressure. Modified from [189].
[a]Upper normal value defined as mean + 2 SD.

hypertension, and increased BP variability are more frequent and pronounced in these patients than in low-risk patients with high BP. These phenomena are best detected with ABPM, which is merited on the grounds that identification of these BP characteristics may improve the management of patients already exposed at a high risk of cardiovascular events.

6.9.1. Diabetes

ABPM is particularly useful in diabetic patients for characterizing the nocturnal profile, because a nondipping or hypertensive nocturnal BP pattern is more common in diabetic patients and is a strong predictor of future cardiovascular events. Nondipping may reflect autonomic dysfunction, but other pathophysiological mechanisms, such as OSA, are commonly encountered in obese patients with type 2 diabetes [15,171,191]. The nondipping pattern found in diabetic patients may be associated with short duration of sleep [243w].

Some studies have shown that the reproducibility of BP values in diabetic patients is better with ABPM than with office BP; in particular, the reproducibility of nondipping is higher in diabetic patients than in the general population [244w]. The prevalence of white-coat hypertension may also be lower in this population, especially in patients with diabetic nephropathy [245w]. On the other hand, masked hypertension may be present in one out of two patients with type 2 diabetes [246w], further increasing the risk of brain and kidney [247w] and possibly also cardiac damage [248w,249w].

An increase in SBP during the night may antedate the development of microalbuminuria in young patients with type 1 diabetes, and the magnitude of the nocturnal dip in BP predicts the development of microalbuminuria [181,250w]. Although carefully taken clinic BP can identify many patients with diabetes in need of treatment, ABPM can identify a significant number of patients with 'masked hypertension' either during the day or the night-time [15,191].

Apart from day–night BP changes, ABPM is able to provide information on other features of BP variability that may be of interest in diabetic patients and have clinical relevance. An increase in overall BP variability, commonly expressed as a standard deviation of average 24-h, day or night BP values, may be a marker of deranged autonomic control in patients with diabetic autonomic neuropathy [251w], and may be an independent predictor of cardiovascular complications. Postprandial hypotension, which is often associated with autonomic neuropathy, may be present in diabetic patients [252w]. Morning hypertension, which is an adverse marker in nondiabetic patients, is common in diabetic patients and in one study, it was shown to predict the rate of progression of diabetic nephropathy [159w].

ABPM provides a number of other relevant parameters, over and above average SBP and DBP values, which can be useful in diabetic patients. These include a rough estimate of heart rate variability, which when decreased may indicate diabetic neuropathy; pulse pressure which, when increased, may be a surrogate marker of arterial wall stiffening; and the AASI, which predicts cardiovascular events and organ damage [253w].

An important application of ABPM in hypertension is related to its ability to evaluate the changes in BP induced by antihypertensive therapy with greater accuracy and in a much more detailed fashion than is the case for office BP [31]. Because adequate BP control is especially important in diabetic patients, it becomes essential to verify the appropriateness of antihypertensive treatment with ABPM. ABPM identifies patients with masked uncontrolled hypertension, (see Section 6.3.2), or patients with true-resistant hypertension. ABPM also allows for assessment of the efficacy of treatment on particularly important periods of the circadian cycle, such as the night-time and morning. Studies using ABPM in diabetic patients treated for hypertension have shown that restoring nocturnal BP fall in diabetic nondippers may be a difficult task with conventional antihypertensive therapy [254w] and that oral drugs used in type 2 diabetes, in particular thiazolidinediones, may have a beneficial effect on 24-h BP level and may also improve the day–night profile in diabetic [255w–258w] or prediabetic patients [259w,260w]. By the same token, hypoglycemic drugs may have adverse off-target effects on BP that can be identified with ABPM [192,193].

The use of ABPM in diabetic patients to determine the association between BP variability and the prevalence of microvascular and macrovascular complications merits further study [261w–263w]. ABPM devices use oscillometry almost exclusively to measure BP, but altered vessel wall properties in diabetic patients may differ from those in nondiabetic patients. Therefore, validation of devices for ABPM should be performed separately in diabetic patients [264w]. An important, and still unresolved issue, is the definition of ABPM cut-off points for hypertension diagnosis and therapeutic targets in diabetic patients. Such thresholds are fairly well defined for patients at low-to-intermediate risk based on the results of outcome studies, whereas no similar definitions are available in diabetes [194].

6.9.2. Stroke

ABPM can be useful both in monitoring the acute effects of ischemic and hemorrhagic stroke and in predicting outcome in stroke survivors. A frequent finding in stroke patients is the loss of nocturnal BP dipping, which may lead to worse target organ damage and facilitate recurrent stroke. Moreover, BP recorded during sleep or in the early morning is more predictive of first or recurring stroke events than daytime SBP, especially in the elderly [195]. Conventional BP recordings may, therefore, be inadequate to precisely identify these changes in BP over 24 h. There are limited data on circadian rhythm in acute stroke patients [265w,266w]. Both hypertensive and normotensive patients have been shown to have similar percentages of abnormal circadian rhythm of SBP and more nondipping and reverse dipping patterns when assessed with repeat ABPM [195]. However, there seem to be differences in the ABPM profile in acute stroke subtypes of different etiology, which might have implications in the optimal management of poststroke hypertension [266w]. In the West Birmingham Stroke Project, patients with ischemic stroke showed a loss of the diurnal BP rhythm, whereas a trend toward reverse dipping was seen in patients with intracerebral hemorrhage [267w].

Alterations in the 24-h profile on ABPM were associated with a worse prognosis, including a higher rate of stroke, in the Spanish Cardiorisk Study [268w]. Moreover, a close association has been reported between stroke and increased 24-h BP variability. An increase in short-term BP variability and in morning BP surge may increase the risk for stroke and cardiovascular events [153,203w]. In summary, both hypertensive and normotensive survivors of stroke develop a chronic disruption of circadian rhythm of BP, which can vary with the stroke type. Modest preservation of nocturnal BP dipping and the physiological circadian pattern of BP may induce a protective effect on cerebral circulation in patients with ischemic stroke. Also, modulation of short-term BP variability may be beneficial in stroke patients, but the value of tentative lowering of BP to maintain the physiological dipping phenomena after acute stroke has yet to be addressed in large randomized controlled trials [269w].

6.9.3. Coronary heart disease

Only a few studies have addressed the usefulness of ABPM in patients with coronary heart disease. In most cases, a significant relationship was found between coronary heart disease prevalence and either nondipping or increased ambulatory pulse pressure [155w,270w]. ABPM can also be useful in predicting prognosis in patients with coronary heart disease [196].

6.9.4. Chronic kidney disease

Hypertension is highly prevalent in CKD, further increasing the already high cardiovascular risk associated with this condition. Early identification of hypertension and achievement of tight BP control is essential for prevention of cardiovascular disease in patients with CKD.

BP control in CKD presents some unique challenges. Patients often show marked alterations, disappearance, or even inversion of the circadian BP pattern. Loss of the normal nocturnal decline in BP is present in about 50% of patients with CKD and in up to 80% in ESRD [271w]. Office BP is misleading even when standardized and this is reflected by the high prevalence of white-coat hypertension (28–30%) and masked hypertension (26–34%) [27]. In ESRD, the marked reductions in intravascular volume immediately after hemodialysis and its progressive increase throughout the period between dialysis can cause marked fluctuations in BP [272w], which may be further influenced by the presence of cardiac dysfunction, increased large artery stiffness, endothelial dysfunction, inadequate volume control, dialysate composition, and administration of erythropoiesis-stimulating agents. BP control in ESRD may be further complicated because of altered pharmacokinetics of antihypertensive drugs, such as impaired elimination of drug.

The few prospective studies in CKD comparing the prognostic role of ABPM versus clinic BP have shown superiority of ABPM in predicting left ventricular hypertrophy [197], cardiovascular events [198,199,273w], all-cause mortality, and progression to ESRD [200,274w]. A recent analysis of a prospective CKD cohort found a superior and independent prognostic value of ABPM (especially night-time SBP) for the primary end-points of mortality from renal disease and fatal and nonfatal cardiovascular events, when compared with office BP [199]. Of note, neither office BP readings nor office BP targets predicted any of the cardiovascular outcomes, raising concerns about the adequacy of office BP targets for CKD recommended by current guidelines.

In ESRD, predialysis and postdialysis office BP is poorly correlated with ABPM, while ABPM between dialysis is prognostically superior to predialysis or postdialysis office BP in predicting development of organ damage and mortality [201]. In a recent prospective cohort of hemodialysis patients, predialysis or postdialysis office BP performed over 2 weeks failed to predict the main outcome of the study, whereas ABPM between dialysis was a significant predictor of mortality [202]. Aside from causing hypertension, volume excess induces alterations in day-to-night BP profiles, which are of prognostic relevance. Elevated nocturnal SBP is an independent predictor of cardiovascular mortality [274w] and a nondipping pattern of BP has shown to be a potent predictor of cardiovascular events and cardiovascular mortality in ESRD [203]. Volume excess may also manifest with certain patterns on ABPM, which might also be prognostically relevant in ESRD [275w].

Longitudinal studies in CKD have demonstrated elevated night-time BP to be a better predictor of fatal and nonfatal cardiovascular events, ESRD, and mortality than daytime or 24-h BP [199,200,204,273w]. The presence of a nondipping pattern of BP has been associated with development of microalbuminuria [181], increase in proteinuria [211w,276w], diminished renal function [205,271w,277w,278w], faster progression of CKD, poor renal prognosis [206,279w–281w], and development and progression of left ventricular hypertrophy [204, 156w,282w].

In conclusion, it is clear that without the use of ABPM, a large proportion of patients with CKD will have unmeasured BP-related risk. Future studies are still needed, however, including data from current on-going registries on ABPM in CKD, to ascertain important questions such as what are optimal ambulatory targets to provide maximum cardiovascular protection in CKD and to determine the amount of BP lowering that will reduce cardiovascular morbidity and mortality.

6.10. Ambulatory hypotension

ABPM can be particularly useful in identifying hypotension in patients with symptoms suggestive of low BP. Hypotension is particularly likely to occur in the elderly in whom postprandial and postural hypotension are common, often because of autonomic or baroreceptor failure. ABPM may also identify hypotension, especially in young slim women and in hypertensive patients with symptoms of dizziness or light-headedness. The diagnosis of symptomatic drug-induced hypotension is important, especially in patients who may have a compromised arterial circulation, such as those with coronary and cerebrovascular disease and fragile elderly patients [1,14,130w,283w]. It should be acknowledged, however, that the accuracy in identifying sudden and short

hypotensive episodes is limited with ABPM, due to the intermittency of BP measurements.

6.11. Hypertension in Parkinson's disease

Parkinson's disease is characterized by important changes in BP regulation, with an increase in 24-h BP variability, often leading to symptomatic orthostatic hypotension, which may affect about 20% of patients [207,284w]. This is attributed to primary autonomic failure with involvement of the peripheral nervous system and to dopamine-mimetic drugs, which are often prescribed [284w]. The characteristic pattern on 24-h ABPM is the reversal of circadian rhythm with daytime and postprandial hypotension and nocturnal hypertension [285w,286w]. Supine hypertension coupled with orthostatic hypotension is observed in up to 50% of patients with Parkinson's disease and autonomic failure, and appears to be driven by residual sympathetic activity and changes in sensitivity of vascular adrenergic receptors; it might be induced or worsened by antihypertensive drugs [208,287w]. Twenty-four-hour ABPM is, thus, a valuable tool for the evaluation of hypotensive episodes during daytime as well as of nocturnal hypertension in these patients.

6.12. Endocrine hypertension

Some 70% of patients with endocrine forms of secondary hypertension present with alterations in 24-h ABPM, in particular a blunted nocturnal BP dipping pattern or even a rise in nocturnal BP, with the average reduction in night-time BP in these patients being only a third to a half of that seen in normal individuals [288w]. This is not surprising considering that the production of several hormones, directly or indirectly influencing BP, are themselves subject to circadian rhythms. Circadian BP variation is influenced by the hypothalamo-pituitary-adrenal axis [209]. In patients with Cushing's syndrome, a higher prevalence of nondipping or reverse dipping has been reported compared with patients with essential hypertension or primary aldosteronism [209]. The same is true for patients receiving exogenous glucocorticoid administration for certain autoimmune disorders in whom BP tends to be lower in the afternoon and then begins to rise throughout the night, attaining a peak level in the morning [289w]. Alterations in circadian BP variation in patients with Cushing's syndrome are primarily due to glucocorticoid excess itself rather than to other factors, such as concomitant mineralocorticoid excess. Studies in primary hyperaldosteronism have failed to show a significant association between an altered circadian BP profile and aldosterone levels or aldosterone-to-renin ratio [290w]. Interestingly, a deficiency of cortisol in Addison's disease has also been associated with a loss of circadian BP rhythmicity [210], suggesting the existence of an important relationship between circadian rhythms of cortisol and of BP. Furthermore, normalization of day-to-night BP changes has been observed in these patients following replacement therapy [210].

A higher prevalence of a nondipping profile has been reported in patients with either hypothyroidism [211] or hyperthyroidism [291w,292w] with the risk of nondipping being directly correlated with the severity of thyroid dysfunction [211,291w,292w].

Adrenomedullary hyperactivity and the associated sympathetic activation may not only induce elevations in BP levels but also significantly interfere with circadian rhythm of BP and short-term BP variability. In a study on type 1 diabetic patients, increasing levels of plasma epinephrine and norepinephrine were directly correlated with mean nocturnal BP levels and inversely correlated with night-time BP dipping [293w]. Consistent with these findings, in patients with pheochromocytoma, arterial hypertension is very often accompanied by a blunted or inverted dipping pattern [294w], the degree of impairment being directly related to catecholamine excretion [295w]. Moreover, the excess of catecholamines in patients with pheochromocytoma has been associated with increased BP variability and a 'riser' nocturnal BP profile [296w]. Surgical treatment of pheochromocytoma has been shown to be accompanied by significant reductions in both daytime and especially night-time BP, [297w], with restoration of BP dipping [212], and significant reductions in BP variability [296w].

Overall, it has to be said that no ABPM pattern has been shown to be specific for any of endocrine forms of secondary hypertension. However, the presence of a nondipping pattern, especially in patients with resistant hypertension, should raise a clinical suspicion of secondary hypertension [213,298w], and prompt investigation for secondary hypertension, including endocrine causes.

6.13. Follow-up

6.13.1. When to repeat ambulatory blood pressure monitoring

The decision as to when to repeat ABPM is largely one of clinical judgment, which may be influenced by factors such as excessive BP variability, an office BP that appears to be unrepresentative, an inappropriate response to treatment, an adverse risk factor profile, and the need for tight control of BP throughout 24 h, including the night, such as in hypertensive patients with diabetes mellitus, renal disease, or severe cardiovascular disease [1].

The most common reasons for repeating ABPM are to clarify borderline results with the initial ABPM, to confirm the diagnosis of masked or white-coat hypertension, to assess an apparent poor response to antihypertensive therapy, or to assess the response to modified treatment.

Whenever feasible, home BP monitoring should be recommended for treated hypertensive patients in order to obtain out of office BP data over a long-term follow-up. However, ABPM remains the only method that assesses asleep BP. Repeat ABPM may be indicated if there is persistent discrepancy between office and home BP values. The provision of a trend report showing the degree of BP control achieved between successive ABPM recordings is helpful in deciding when to repeat ABPM [10].

ABPM should be offered to patients suspected of having hypertension whenever possible to obtain a quantification of day and night BP aimed at confirming the diagnosis and the need for long-term intervention [2,4,10].

It is advisable to confirm the diagnosis of white-coat hypertension by repeating out-of-office BP monitoring (if possible ABPM within 3–6 months, depending on the total cardiovascular risk of the individual), because a substantial

number of patients with white-coat hypertension may develop sustained hypertension [1,102,299w–302w]. In patients with confirmed white-coat hypertension and a normal risk factor profile, it is, as a general rule, usually unnecessary to repeat ABPM more frequently than annually, or every 2 years if the pattern appears to be established and consistent, as indeed is often the case [1]. If, on the contrary, a patient with confirmed white-coat hypertension has a high-risk profile, ABPM every 6 months may be indicated so as to detect the transition from the white-coat hypertension state to sustained hypertension and the need for antihypertensive medication. Alternatively, HBPM may be combined with ABPM to reduce the frequency of ABPM. The diagnosis of masked hypertension also requires confirmation within a few weeks or months, dependent on the total cardiovascular risk, and the assessment of BP control in these patients also requires ABPM, which can be combined with home BP monitoring.

The frequency of repeat ABPM to evaluate the efficacy of antihypertensive medication will be dependent on the severity of hypertension and the response to treatment. In patients with severe hypertension and evidence of target organ damage, BP reduction is urgent and in the initial stages of treatment, ABPM may be required frequently as different drug combinations are introduced and dosage levels are altered. In patients with mild hypertension and no evidence of target organ involvement, ABPM has to be repeated less frequently according to the device availability, the individual patient's needs and preference, and the physician's discretion [1].

In an evaluation of the most appropriate time interval to repeat ABPM to ensure sustained BP control in patients with white-coat-resistant hypertension, it was considered necessary to perform a confirmatory ABPM after 3 months of the first white-coat-resistant hypertension diagnosis, and to repeat the procedure at 6-month intervals, except in patients with daytime SBP of 115 mmHg or less in whom ABPM should be repeated annually [214]. HBPMs should be encouraged in all patients with treated hypertension as an approach complementary to ABPM [2].

6.13.2. Ambulatory blood pressure monitoring versus home blood pressure

ABPM and home BP are both useful in the management of patients with hypertension. However, ABPM is capable of providing unique information on an individual's BP status beyond what can be obtained using home BP. Examples include an assessment of BP during sleep (mean night-time ambulatory BP is the best predictor of future cardiovascular events in relation to BP status), readings that are not subject to reporting bias, and BP data obtained during usual daily activities.

HBPM has been recommended as an initial screening procedure to evaluate the out-of-office BP with ABPM being performed when the diagnosis of hypertension is still uncertain [303w]. However, ABPM and home BP provide different and complementary clinical information on an individual's BP status [2,112,19w,304w,305w]. There is some evidence that HBPM and ABPM may provide different predictive target organ information [304w].

ABPM should be performed whenever possible in all patients with suspected hypertension in whom it is necessary to confirm the diagnosis of sustained hypertension (i.e. to exclude white-coat hypertension), to assess the severity of hypertension throughout the 24-h period, to detect nocturnal hypertension, to detect patterns of BP behavior such as isolated systolic hypertension, nondipping and autonomic failure, and to be able to analyze the 24-h data for indices of BP fluctuations, such as AASI, and measures of BP variability [4,10,165,214]. ABPM is particularly appropriate for the initial evaluation, because it provides information within 24 h and without need of training, skills, and commitment, as required for home BP.

In parallel with ABPM, and particularly when ABPM is not readily available, out-of-office assessment of BP may complement office visits by obtaining a HBPM session with duplicate morning and evening measurements for 7 days and calculating the average after discarding the first day; this provides a measurement that approximates to average daytime ABPM [2,38,215]. HBPM also has a role in monitoring BP control in treated patients over extended periods of time between office visits, especially in patients with good BP control on ABPM, and there is the added advantage that HBPM can improve long-term adherence to medication and thereby hypertension control rates [216,217]. Finally, whereas ABPM remains the leading technique in the pharmacological assessment of antihypertensive drugs, HBPM has a potentially valuable role in outcome trials carried out in large populations in which the effects of BP lowering are being assessed over many months or years [112,168,218,219,306w–313w]. A comparison of the different BP measurement methods is shown in Table 3.

7. AMBULATORY BLOOD PRESSURE MONITORING IN RESEARCH

7.1. Ambulatory blood pressure monitoring in pharmacological research

ABPM was first used over 30 years ago in pharmacological studies on the efficacy of BP-lowering drugs [7,31,220,314w]. From the results of early studies using daytime and 24-h ABPM to assess the efficacy of BP- lowering drugs [31], a number of patterns emerged. First, ABPM could be in agreement with clinic BP measurements. Second, clinic BP measurement could fail to detect the BP-lowering effect demonstrated by ABPM. Finally, reductions in clinic BP could be significant, but ABPM might be either nonconfirmatory or show that the clinic BP reduction coincided only with a brief period of BP reduction on ABPM [31]. These early studies showed that many drugs would have been declared as quite efficacious (including 24-h duration of action) with conventional BP measurement, whereas ABPM showed a pattern of activity that was far less impressive.

Later studies have shown that treatment-induced BP lowering is greater with office BP measurement than with ABPM. ABPM does not provoke a white-coat reaction, exhibits negligible placebo effects and less regression to

TABLE 3. Qualities of and information provided by blood pressure measurement techniques*

Qualities of measurement	OBPM	HBPM	ABPM
GENERAL FEATURES			
Cost	Inexpensive	More expensive than OBPM but cheaper than ABPM depending on complexity of devices and provision of telemetry	More expensive than OBPM or HBPM, but cost-effective
Medical requirements	Conventional technique in clinical environment under medical supervision	Should be used under medical supervision, but device often purchased and used without medical supervision	Must be interpreted under medical supervision
Need for training	Doctors and nurses should be trained and tested for competence	Minimal medical training required but patients should receive medical instruction	Training required, but software can facilitate process
Duration of procedure	Brief depending on number of measurements recorded	To equate with daytime ABPM, home BP should be measured x 2 morning and evening for 7 days with first day discarded and other readings averaged.	Usually 24-h BP measurements at 15–30-min intervals during day and night with minimal requirements 70% successful readings and 20 daytime and 7 night-time measurements
Validated accuracy; For accuracy of all devices, see: www.dableducational.org; www.bhsoc.org; www.pressionearteriosa.net	Automated devices replacing mercury sphygmomanometers	Many devices on the market have not been independently validated for accuracy	Most ABPM devices on the market have been successfully validated independently for accuracy
IDENTIFICATION OF BLOOD PRESSURE PATTERNS			
Systo-diastolic hypertension	Commonest diagnosis	Better assessment of severity	Allows assessment of severity over 24 h
Isolated systolic hypertension	SBP $\geq$140 & DBP $<$90 mmHg	SBP $\geq$135 & DBP $<$85 mmHg	24-h ABPM: SBP $>$130 and DBP $<$80 mmHg
Isolated diastolic hypertension	SBP $<$140 & DBP $\geq$90 mmHg	SBP $<$135 & DBP $\geq$85 mmHg	24-h ABPM: SBP $<$130 & DBP $>$80 mmHg
ABPM patterns	Cannot be diagnosed with OBPM	Cannot be diagnosed with standard HBPM	Patterns apparent on ABPM
PREDICTION OF OUTCOME			
Target organ damage, cardiovascular morbidity and mortality	Has been the measure of outcome in the past	Superior to OBPM	Superior to OBPM and stronger evidence than with HBPM; nocturnal hypertension may be sensitive predictor
Provision of indices (See Section 4.2.2)	Not applicable	Not applicable	Can be computed from ABPM recordings
MEASURES OF VARIABILITY	Visit-to-visit BP variability	Day-to-day BP variability	24-h BP variability and visit-to-visit BP variability
GUIDE TO DRUG PRESCRIBING			
Efficacy of treatment over time	Poor guide because of white-coat response and limited BPs	Moderate guide to daytime efficacy that can be readily repeated	Allows assessment of efficacy over 24-h period
Nocturnal BP control	Not applicable	Preliminary data only with specifically developed home monitors	Allows assessment of nocturnal lowering of BP
Reduction of morning surge	Not applicable	Not applicable, but morning BP can be assessed	Allows assessment of treatment effect on morning surge
Detection of excessive BP lowering	Limited because of infrequency of measurement	Better than OBPM	Allows detection of hypotensive episodes throughout the 24-h period
To improve compliance to treatment	May have a minor influence	Major documented advantage of HBPM	Provision of ABPM record to patient may be helpful
To evaluate drug-resistant hypertension	Poor guide because of white-coat response and limited BPs	Provides better assessment than OBPM, but limited evidence	Removes white-coat effect and shows whether BP elevation is persistent
IDENTIFICATION OF HYPOTENSIVE PATTERNS			
Postural hypotension	Difficult to diagnose	Fall in standing HBPM	Time, duration, and relationship to hypotension can be documented
Postprandial hypotension	Difficult to diagnose	Fall in HBPM after meals	Fall in ABPM after meals
Drug-induced hypotension	Difficult to diagnose	Can be detected if HBPM after drug ingestion	Time, duration, and relationship to drug intake can be documented
Idiopathic hypotension	Difficult to diagnose	Can be detected if HBPM related to hypotension	Best diagnosed with ABPM
Autonomic failure	Difficult to diagnose	Not detectable	Daytime hypotension and nocturnal hypertension

Many of the above features of ABPM become of even greater relevance in high-risk patients, such as diabetic patients and in the elderly, who may have complex patterns of 24-h BP and nocturnal hypertension. ABPM, ambulatory blood pressure monitoring; BP, blood pressure; HBPM, home or self-blood pressure measurement; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; OBPM, office blood pressure measurement.
*Modified from [9].

the mean of averaged BP values, and the reduction in night-time BP is smaller on ABPM than for daytime BP [221]. The advantages of ABPM for assessing treatment effects in clinical trials include the exclusion of patients with white-coat hypertension who show little response to antihypertensive drugs, the ability to evaluate the duration of action of a drug and to analyze its effects on night-time BP as well as on BP variability, the almost complete absence of a placebo response, the increase in the power of studies with fewer patients to assess antihypertensive drug efficacy, and the reduction of the sample size required and better correlation of the results with clinical outcomes [31,221].

Studies using both ABPM and conventional BP measurement clearly show the added value of ABPM in detecting pharmacological effects that would not have been evident from conventional BP measurement alone [222,315w–335w]. It is also of interest to note that the use of ABPM in pharmacological trials is not always successful. For example, ABPM recordings can fail to meet the *a priori* criteria for a successful recording in as many as a quarter of patients enrolled for studies [222,332w]. This unacceptable level of rejected measurements can be prevented by having real-time on-line transmission of ABPM recordings so that failed ABPM measurements are notified to the investigators allowing for unsatisfactory ABPM recordings to be repeated.

We do not yet know whether treatment strategies based on BP assessment by ABPM are significantly better than office BP in reducing the rate of cardiovascular events. Notwithstanding this limitation, the above-mentioned advantages of ABPM strongly support the inclusion of ABPM in all future pharmacological trials of antihypertensive drug therapy [31].

7.2. Regulatory recommendations for pharmacological studies

The US Food and Drug Administration (FDA) guidelines acknowledge that ABPM adds valuable information on the duration of antihypertensive drug dosing interval and on dose–response elements [223]. The current European Medicines Agency (EMA) guidelines 'strongly recommend' ABPM for the evaluation of new antihypertensive agents, but adds that 'there are insufficient data to accept ABPM as the sole basis for efficacy in an approval process' [224]. The guideline then goes on to stipulate the requirements for ABPM, but unfortunately these fail to give attention to the practical realities that are necessary if the technique is to be successfully implemented in pharmacological studies [31].

ABPM in clinical research has been facilitated by commercially available systems, which can provide real-time analysis of ABPM in multicenter clinical trials based on ABPM providing features that include separate viewing and editing facilities for investigators, monitors, and supervisors, full multicenter support allowing investigators to access data relating to their specific center, with monitors and supervisors having access to data from all centers, provision of audit and progress reports to assist monitors to check data, validation of all ABPMs, and comprehensive export of ABPM raw data and statistics [31].

A recent interesting aspect of the pharmacological assessment of drugs has been a growing demand for information by the regulatory authorities, especially the FDA, on the effect of noncardiovascular drugs on 24-h BP. Previously, the cardiovascular effects of such drugs has tended to focus on ECG changes such as prolongation of the QT interval, but in the future, noncardiovascular drugs will also be scrutinized for their potential to lower or raise BP [32,192,193,336w] (Box 10).

Box 10 Ambulatory blood pressure monitoring in pharmacological trials

- Ambulatory blood pressure monitoring is clearly superior to any other blood pressure measurement method and indispensable for the investigation of the efficacy, duration of action, and homogeneity of the effect of antihypertensive drugs
- Ambulatory blood pressure measurement is valuable in clinical trials, because it identifies patients with white-coat hypertension, is not affected by placebo, and is more reproducible than office measurements, thereby increasing the study power and reducing the required study sample
- The implementation of ambulatory blood pressure monitoring in outcome trials has been largely limited to nonrandomized subgroups and with incomplete baseline and repeat evaluation.
- Future outcome trials should apply ambulatory blood pressure monitoring in all participants before randomization and at various times during treatment

7.3. Ambulatory blood pressure monitoring in outcome studies

Observational studies have shown that ABPM monitoring predicts the incidence of cardiovascular morbid or fatal events [16,126,218,225,226]. Evidence also exists that the relationship with cardiovascular risk is steeper for 24-h mean BP than for clinic BP [16,126,218] and that use of the two methods together may increase the ability of BP to predict outcome [112].

ABPM has also been performed in subsets of patients in morbidity/mortality trials of antihypertensive drug therapy. In most instances, the number of patients having ABPM has been relatively small [151,337w–342w]. Furthermore, in some studies, ABPM comparisons have considered nonrandomized subgroups, with often clinical and demographic characteristics different from those of the main study. Finally, ABPM has usually been performed only once or twice during treatment, sometimes without any baseline recording. These limitations do not provide the answer to an important question: does inclusion of patients into clinical outcome studies of antihypertensive drug therapy on the basis of ABPM, and their subsequent management using ABPM, provide a better method for assessing hypertension treatment strategies than conventional BP measurement? Use of ABPM in trials has, nevertheless, provided useful data for the following reasons [227]. One, the 24-h mean BP reductions induced by treatment are usually less than the concomitant clinic BP reduction, the ratio between the former and the latter change ranging between 0.6 and 0.7 [221] and even less in the very elderly [228]. Two, there is a significant but by no means close relationship between clinic and 24-h mean BP changes induced by treatment – correlation coefficients of the order of 0.2–0.4 – which means that in a given individual, daily life BP reductions with treatment can hardly be predicted by the clinic BP reductions [229,230,337w,339w]. However, in a single-center study, a substantially higher correlation was

observed between changes in clinic and 24-h BP [231]. Three, in some trials, average clinic BP changes with treatment were reflected by the concomitant 24-h BP changes, but this was not the case in other trials. For example, in the European Lacidipine Study on Atherosclerosis (ELSA) study, treatment with atenolol or lacidipine was associated with similar changes in clinic BP, but atenolol-based treatment induced a greater 24-h BP reduction than lacidipine [229]. Furthermore, in the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril caused a small reduction in clinic BP and a greater one (especially during the night) in ABPM [338w]. Finally, in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), ramipril and telmisartan showed a similar effect on clinic but not on ABPM, which was more effectively lowered by the latter drug with a particularly pronounced reduction when the combination of the two drugs was used [341w]. Likewise in the Simplicity trials to determine the efficacy of renal denervation, the failure to utilize the data from ABPM has left the results of the technique open to serious question [343w].

In conclusion, in order to minimize the above-mentioned limitations, future trials should make use of ABPM in all patients and the design should provide ABPM data both before randomization and at various times during treatment. This will allow more reliable information to be obtained on the debated question whether and to what extent the cardiovascular protection associated with antihypertensive treatment depends on specific BP-independent properties of the drug employed. The presence or absence of cardiovascular protection is presently attributed to a drug if the incidence of cardiovascular events is greater or less in the presence or absence of a reduction in clinic BP. In such a context, it should be acknowledged that establishing the BP changes by clinic BP only is not sufficient.

8. IMPLEMENTATION OF AMBULATORY BLOOD PRESSURE MONITORING IN CLINICAL PRACTICE

8.1. General principles

Despite the large diversity in the structure of healthcare systems across different countries, the vast majority of hypertensive patients are being managed in primary care. Thus, in practice, primary care doctors may establish their own ABPM service, or alternatively they may refer their patients to an external ABPM service, as they routinely do for multiple other medical tests. Models to develop such services might include specialist clinics, healthcare providers in the private sector, pharmacy-based services, and other solutions.

8.2. Financial considerations

The ready provision of ABPM in primary care will be dependent on reimbursement to physicians or other healthcare providers by the national healthcare systems or by private insurance. ABPM is currently reimbursed in several countries, including Switzerland (€90 per ABPM), Italy (€50–70), The Netherlands (€60 for general practitioners only), Germany (€7–8), Greece (€40), United States ($60–120 by Medicare only for white-coat hypertension and $75–225 by private insurances for several indications), Canada by some private insurers (CDN $50–75); in Ontario, the provincial government is currently giving consideration to fund ABPM, probably in the $50–75 range), and China [RBM 150–200 (€20–28), 80–90% reimbursed]. However, in other countries [e.g. Ireland, Belgium, Spain (regional differences exist), Australia], ABPM is not currently reimbursed [344w,345w].

8.3. Specialist clinics

The ESH has accredited 'Centres of Excellence' in hypertension across Europe (http://www.eshonline.org) [232] and promotes a structure connecting these centers with affiliated Blood Pressure and Vascular Protection Clinics [233]. The availability of ABPM is regarded as an essential requirement for both the ESH Centers and Clinics [232,233]. More recently, the American Society of Hypertension launched a similar initiative that involves formal recognition of 'Hypertension Centers' that have demonstrated expertise in the management of complex hypertension (http://www.ash-us.org) [234]. These initiatives can ensure the application of ABPM in many patients with complex hypertension and might also accommodate referrals for ABPM through models of continuing care such as 'shared care' with primary care physicians or 'intermediate care' with specialist nurse teams, or other models [233].

8.4. Primary care

Primary care doctors and practices may establish their own ABPM services, which may be supported by specialist nurses or medical assistants. The progressive decline in the cost of ambulatory monitors in recent years together with reimbursement schemes as mentioned above, is expected to facilitate the spread of the technique in primary care, which will be necessary to meet the increasing demand for routine application of ABPM in practice.

Several studies have investigated the usefulness of ABPM implementation in primary care [9,168,235]. One of these studies showed that BP measurements made by doctors were much higher than those using ABPM [235]. Another study showed that office BP incorrectly labeled nearly a third of patients with a white-coat effect as having poor BP control and that these patients were likely to be recalled for unnecessary follow-up and intervention [346w]. An Irish study in primary care showed that only 12% of patients achieved target BP with office BP compared with more than one-third of patients with ABPM. Furthermore, 38% of patients had a change in their medication as a result of ABPM, 32% had a new medication started, and 14% of untreated patients with elevated office BP, who were candidates for drug treatment, were not started on medication because ABPM was normal [236].

The largest study to date on ABPM in primary care comes from Spain, where a nationwide project to promote the use of ABPM in primary care settings has been established [195,237]. In this large cohort of some 20 000 patients, clinic BPs were higher than ABPM in patients categorized as being at low-to-moderate added risk, with a greater

difference (23/23 mmHg) in those categorized as being at high risk despite receiving much more antihypertensive treatment. Moreover, a nondipping nocturnal BP pattern was common in high-risk hypertensive patients. These data support the wider use of ABPM to gain more accurate risk stratification of patients in the community and to be able to obtain a more accurate estimate of the control of BP in the community [347w]. As in the Irish study, BP control was better when assessed by ABPM than by office BP, indicating that the white-coat effect with office BP is leading to an underestimation of BP control in the community [195,236,237]. BP control was underestimated in more than one-third of patients and overestimated in some 5% by office BP as compared with ABPM. Notably, BP was uncontrolled by both methods of measurement in 43% of patients. High-risk patients showed worse ambulatory BP control than low-to-moderate risk patients in spite of receiving much more antihypertensive treatment [195,237]. Finally, in the Italian MARTE study, assessment of BP control by office measurement was poor and showed that apparent control of BP with office measurement did not reflect 24-h BP control in daily life [18].

8.5. Pharmacies

Whereas primary care practices and hypertension centers will be the main providers of ABPM (provided adequate reimbursement is made available), the valuable role of pharmacies in achieving improved control of hypertension has been recognized for many years [238,239,348w–354w]. Indeed, it has been shown that when pharmacists become engaged in the management of hypertension, BP control improves [239,350w–353w].

When considering pharmacies as providers of ABPM, it is essential that ABPM assessment and reporting is provided in collaboration with primary care physicians and/or specialists. Recently, ABPM has been introduced to pharmacists in a few European countries, and the pharmacy-based service is proving popular with patients and is being increasingly adopted, as shown in a recent Irish report [355w].

For the implementation of ABPM within the pharmacy, automated interpretation of the results by the monitor software according to current guidelines is essential for the initial evaluation of the recording, in order to advise immediate medical consultation whenever required. Thus, if ABPM in a pharmacy is normal, the patient is instructed to bring the report to his/her general practitioner at their next attendance, but, if the ABPM is reported as abnormal, instruction is given to make an appointment as soon as possible [355w]. The advantages of ABPM in pharmacies include greater availability of ABPM to the public; rapid access to a conveniently located pharmacy; short or absent waiting lists; provision of an interpretative report to the patient who is informed as to the degree of BP control; close collaboration between the pharmacist and the patient's general practitioner; provision of a trend report to patients having a repeat ABPM so as to indicate the response to BP-lowering medication; availability of data in a central database to provide demographic information on national BP trends; and patient awareness as to their BP control and encouragement to adhere to medication and management [355w]. Moreover, the pharmacy ABPM service is less costly than that provided by doctors.

8.6. Healthcare providers

Healthcare providers in the private sector that have contracts with the healthcare system or with insurance companies are increasingly providing ABPM services as is the case with multiple other medical tests, such as ultrasound tests, computer tomography, 24-h ECG, and blood tests.

8.7. Ambulatory blood pressure monitoring registries and databases

In recent years, several countries have established registries to assess the impact of ABPM on hypertension management and related outcomes. Disease or condition registries are defined as databases with details of patients having the same diagnosis, such as hypertension [240]. It is important to recognize that a disease registry is not a database containing information on patient cohorts with a particular disease, though such databases may ultimately form the basis for establishing a disease registry. Rather the purpose of a disease registry is to organize a system that uses observational study methods to collect uniform data in order to define the prevalence and to study outcome related to specific strategies that may include scientific research, and epidemiological and health economic methods of analysis. Patients are observed and followed as they present for care, and the data collected generally reflect current practice. Such registries, by classifying patients according to disease, allow patients the opportunity to participate in a research study appropriate to their illness [240]. Governments are beginning to recognize that disease registries may lead to improvements in health outcomes and to lower costs. Through the use of such registries, healthcare providers can compare, identify, and adopt best practices for patients [241]. For example, the Swedish Government is committed to increasing its annual financial support for disease registries from $10 to $45 million by 2013 [362w].

ABPM registries are more commonly based on patients with documented hypertension or on patients referred to doctors for possible hypertension who would benefit from ABPM. Some of the current registries represent a mix of hypertensive and normotensive individuals and are more properly labeled as population studies. Many of the existing ABPM registries serve as valuable databases and could be structured to fulfill the requirements to become disease registries. The following ABPM registries are in existence.

8.7.1. Spanish registry

This registry was established in 2004 with the initial aim of making ABPM readily available in primary care and to create an ABPM education program. The registry involves 1700 doctors and obtained about 150 000 ABPM recordings. Data are transmitted via the Internet from a specialist center to primary care physicians alerting them to the degree of BP control. The results, which have been published in several papers [195,237,268w], have influenced the use of ABPM in primary care and improved the management of hypertension in Spain.

8.7.2. Italian registry

The Telemapa@net Project, started in 2008, is aimed at encouraging the use of ABPM in primary care. The main purpose is to assess the degree of 24-h BP and cardiovascular risk factor control of treated or untreated hypertensive patients and to encourage adherence to national guidelines. Data from patients with uncontrolled treated or untreated arterial hypertension or with indications for ABPM are sent through a GPRS wireless interface to a web-based telemedicine platform, where after automatic analysis a report is sent via E-mail to the primary care physician. Preliminary data from 7000 patients show that BP control differs between office BP and ABPM and ABPM provides a means for doctors to improve the management of hypertension by identifying uncontrolled patients.

8.7.3. Irish registry

A national on-line system with central hosting of ABPM data and the provision of standardized ABPM has been in operation in Ireland for some years. The provision of a trend report has facilitated the identification of poorly controlled hypertensive patients. The registry has been extended to pharmacists so as to make ABPM more accessible to the public and the data from pharmacies are stored centrally. Preliminary analysis shows a high prevalence of white-coat hypertension and nondipping hypertension [236].

8.7.4. Japanese registry

Four population-based studies have been conducted in Japan, among which the most important is the prospective cohort study of some 2000 residents in Ohasama who have been followed with ABPM and assessment of other cardiovascular risk factors [242,132w]. In addition, several ABPM databases have been established in Japan, which include the Jichi Medical School ABPM Study in older Japanese hypertensive patients, the cross-sectional study in Yamanashi University, and the cross-sectional study in Nagoya University.

8.7.5. Australian registry

In 2008, the Australian Database for ABPM was initiated to address the need for ABPM equivalents for target BP for management of hypertension in low-risk and high-risk patients. The database is the result of the cooperative effort of individuals and the financial and logistic support from the High Blood Pressure Research Council of Australia and the National Heart Foundation of Australia, which has enabled this contribution to the appropriate use and interpretation of ABPM and effective management of hypertension [26]. Data are available from over 8000 patients [363w].

8.7.6. International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome database

In 2005, an international consortium of investigators started constructing the IDACO [154,243,364w,365w] based on prospective population-based studies reporting fatal as well as nonfatal outcomes. The database currently includes 12 854 participants recruited in 12 countries from three continents. Articles published so far have demonstrated that although the absolute cardiovascular risk is lower in women than it is in men, the relationship between the risk of a cardiovascular event and the ambulatory BP is stronger in women than men. These observations highlight missed opportunities for cardiovascular prevention in women. In population-based cohorts, both diabetes mellitus and the ambulatory BP contributed equally to the risk of cardiovascular complications without evidence for a synergistic effect.

8.7.7. ARTEMIS registry

The ARTEMIS (international Ambulatory blood pressure Registry: TEleMonitoring of hypertension and cardiovascular rISk project) is endorsed by the ESH and is the first international registry of ABPM aimed at assessing the actual degree of BP and cardiovascular risk control of hypertensive patients followed by doctors in many countries (www.artemisnet.org) [244]. Objectives are the creation of a worldwide network of centers performing ABPM recordings; the collection of a large registry of patients from different countries, of various continents, in whom basic clinical information is available as well as at least one ABPM fulfilling predefined criteria; the design and initiation of a series of research studies focusing on ABPM and based on this collected dataset; the promotion of the application of ABPM in clinical practice and the dissemination of knowledge on its correct use and interpretation; and finally the active collaboration with international scientific societies in their activities related to ABPM, in particular in the preparation of recommendations for ABPM use in clinical and research settings.

The registry was launched in 2010, with a two-step approach. A first phase has collected data from approximately 10 000 patients from 38 countries in five continents (Europe, America, Asia, Oceania, and Africa). Preliminary results provide interesting comparative information on hypertension phenotypes in treated and untreated patients attending hypertension clinics worldwide. In particular, white-coat hypertension was more common in untreated patients, whereas masked uncontrolled hypertension was more common in treated patients. In addition, significantly higher prevalence of sustained hypertension was observed in clinics in Europe and South America than in Asia and Oceania. A second phase using a dedicated web-based multilingual telemedicine system will allow collection of data from patients having consecutive ABPMs.

8.7.8. Ambulatory blood pressure international database

Initiated by Thomas Pickering, the ABP-International database was constructed by systematically merging eight prospective studies from three European, three Japanese, one North American, and one Australian centers. Currently, studies are eligible for inclusion if they involve a random population sample or patients referred to hospital for hypertension, if baseline information on ABPM and cardiovascular risk factors are available, and if the follow-up includes fatal and nonfatal cardiovascular events. ABP-International includes data from 11 235 patients followed for about 6 years, who have experienced about 700 major cardiovascular events. Analysis of this data, which has

focused on the short-term and long-term incidence of stroke in white-coat hypertension and the clinical importance of night-time heart rate for predicting cardiovascular events have been published [166,366w].

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Conflicts of interest

E. O'Brien, G. Parati and G.S. Stergiou, as members of the writing committee, were in receipt of travel support from the Hellenic Society of Hypertension, University College Dublin, University of Milano-Bicocca & Istituto Auxologico Italiano, Milan for meetings in Athens, Milan and Dublin. The following companies provided unrestricted educational grants for the ABPM Consensus Meeting in Milan: Abbott, A & D, IEM, Microlife, Meditech, and Suntech Medical.

E. O'Brien is medical director and a board member of dabl, Ltd. Dublin, Ireland and has been in receipt of past honoraria for lectures with Menarini Ireland and Servier.

D. Clement, A. de la Sierra, P. de Leeuw, E. Dolan, R. Fagard, J. Graves, Y. Imai, E. Lurbe, J.-M. Mallion, M. Myers, G. Ogedegbe, P. Palatini, J. Redon and J.A. Staessen have no conflicts of interest to declare.

The following conflicts of interest have been declared:

R. Asmar: consultancy to Servier – Fukuda; past payment for lectures Bayer, Boehringer and Novartis.

L. Beilin: Board member Medical Research Foundation Royal Perth Hospital; competitive national research grants, NHMRC; stock/stock options, CSL Cochlear.

G. Bilo: current grant for BP measuring device validation study, SENSE A/S.

G.A. Head: accommodation support ESH; current consultancy ResMed; past consultancy Telemetry Research; current grant NHMRC; past lecture payments Novartis Japan; traveling expenses Baker Institute.

K. Kario: current consultancies Omron Healthcare, Daiichi Sankyo, Teijin Pharma.

G. Mancia: current consultancy Siron BV; past lecture payments Bayer, Daicichi Sankyo, Menarini, Recordati, Servier and Takeda; current lecture payments Novartis. Boehringer Ingeleheim.

T. Mengden: past board membership Actelion; consultancy Custo med Germany; current lecture payment Servier, Berlin Chemie; past lecture payments Daichi Sankyo, Takeda; payment for manuscript preparation Takeda.

T. Ohkubo: current lecture payments Astellas, Astra Zeneca, Daiichi-Sankyo, Dainippon-Sumitomo, Merck Sharpe and Dohme, Novartis, Pfizer, Takeda, Tanabe-Mitsubishi, and Omron Health Care.

S. Omboni: current consultancy with Biotechmed Ltd.

L.L. Ruilope: consulting honoraria Astra-Zeneca, Bayer, Novartis, Menarini, Pfizer, Daiichi-Sankyo, Takeda, BMS, Relypsa; consultancy Astra-Zeneca, BMS, Bayer, Novartis, and Relypsa.

A. Shennan: current board membership Hologic, Alere and GSK; current consultancy GSK and Alere; current lecture payments Hologic, Alere, GSK and Ferring; past payment development of educational presentations for BBC.

G. vanMontfrans: past lecture payment Merck Sharp Dohme and Daichii Sankyo; past royalty for book chapter Bohn Stafleu.

P. Verdecchia: current board membership Stroder, Boehringer-Ingelheim; current lecture payments Boehringer-Ingelheim, Malesci, Daiichi-Sankyo, Bayer.

B. Waeber: current board membership Boehringer-Ingelheim, Malesci, Daiichi-Sankyo, Bayer.

J. Wang: current grant A & D; past honorarium Omron; past travel support A & D, Omron; current lecture payments MSD, Novartis, Pfizer, Servier, Takeda.

A. Zanchetti: current lecture payments Menarini, Recordati, CVRx.

Y. Zhang: past consultancy Dachi-Sankyo, Takeda, Novatis, Pfizer, Sanofi; current lecture payments Sanofi, Astra-Zeneca, Novatis, Merck, Takeda.

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