ITALIAN SOCIETY OF HYPERTENSION (SIIA) GUIDELINES FOR CONVENTIONAL AND AUTOMATED BLOOD PRESSURE MEASUREMENT IN THE OFFICE, AT HOME AND OVER THE 24 HOURS.

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INTRODUCTION

Accurate blood pressure (BP) measurement is an essential pre-requisite for proper management of hypertension, independently from the technique employed. Different problems, however, may affect different measuring techniques. Although the conventional Riva-Rocci-Korotkoff approach is still the corner stone in the diagnostic and therapeutic management of arterial hypertension, several concerns have been raised over the years on its ability to accurately and reliably reflect the BP load exerted on the cardiovascular system in individual patients (Table 1) [1].

Table 1. Reasons for inadequacy of traditional BP measurement [1].

- Limited accuracy of diastolic BP estimation (not infrequent in obesity, aged subjects, etc.)
- Microscopic fraction of 24h BP values
- Alerting reaction:
  - Overestimation of initial blood pressure
  - Underestimation of effect of treatment
- BP highly variable

This has led to detailed recommendations not only on how to make a better use of this time-honoured approach, but also to the development of new techniques for automated BP measurement. These techniques may overcome the problems generated by the "white-coat effect" and may also allow obtaining profiles of BP values in a given condition rather than relying on isolated measurements under circumstances that may in themselves influence the level of BP recorded. They include techniques for self-measurement of BP (SBPM) in the home or work place, and for ambulatory BP monitoring (ABPM) by automated devices. Use of these different approaches may indeed lead to an improved assessment of the patients' "real" BP levels, provided that the most appropriated method for any given condition is adopted, and the selected approach is implemented with the required methodological care. This paper is the result of cooperation between members of the Working Group on Blood Pressure Monitoring of the Italian Society of Hypertension, and is aimed at providing physicians and researchers with the necessary information for adequate BP measurement in different clinical and experimental conditions, regardless of the technique employed. These recommendations are based both on the recent indications published by the European Society of Hypertension (ESH) Working Group on Blood Pressure Monitoring [2] and on the experience collected by a number of Italian investigators who have been active in investigating these issues over the last 25 years [3].

This paper includes three main sections:

Part 1 deals with a number of general aspects of BP measurement, regardless of which technique is employed;

Part 2 focuses on office BP measurement, namely on conventional auscultatory BP measurement (CBPM) or measurement carried out with automated or semi-automated devices;

Part 3 deals with out-of-office BP measurement with automated or semi-automated devices, by separately considering its application with ABPM and SBPM

PART 1. General Aspects of BP Measurement

1.1 Accuracy of BP measuring devices

The first important step when approaching BP measurement is aimed at ensuring the accuracy and safety of BP measuring devices over time [4]. This includes maintenance of mercury manometers, calibration and maintenance of aneroid devices and identification and selection of accurate automated devices.

Their accuracy need to be tested and proved not based only on claims from manufacturers, but through truly independent validation studies, the results of which were published in peer-reviewed journals [5]. European (EU) states are legally obliged to obtain EU certification on the safety and basic accuracy requirements of BP measuring devices [6-8]. This indicates a kind of "technical" validation only, however, and cannot be extrapolated to infer conclusions on "clinical" validation. Indeed, the European Union recommends an independent clinical evaluation of BP measuring devices according to established international protocols [9-12]. However, at least until now, such a validation is not a compulsory requirement. Validation of BP measuring devices should therefore follow the protocols proposed by internationally acknowledged ad hoc societies. One of them is the Association for the Advancement of Medical Instrumentation (AAMI), which in 1987 published standards for evaluation of automated and aneroid sphygmomanometers, including a protocol for assessing the accuracy of devices [13]. These recommendations were followed in 1990 by the protocol of the British Hypertension Society (BHS) [14]. Standards and recommendations of these protocols were updated in 1993 [9-10]. These two protocols, which have been used to evaluate a consistent number of devices until now [5], are characterized by important differences in their detailed recommendations. However they have as a common objective the standardization of validation procedures, aimed at establishing minimum standards of accuracy and performance, and at facilitating comparisons between devices. A common limitation of both these protocols is their difficult application to routine evaluation of BP measuring devices. In the attempt to overcome this problem, the Working Group on Blood Pressure Monitoring of the ESH has recently published a simplified protocol to facilitate the evaluation process [11]. A list of the BP measuring devices which have been subjected to validation was published and updated over the years [5,15,16]. All these surveys, however, soon become outdated. This is why no listings of validated

devices are made in this monograph. This information may be obtained from websites such as those of ESH [17] or BHS [18] or from the website endorsed by the Italian Society of Hypertension (www.pressionearteriosa.net) [19] or by the European Society of Hypertension Working Group on Blood Pressure Monitoring (www.dableducational.org) [20] both containing more recent information.

Further development in this field is represented by the recent proposal of an integrated validation of automated devices which includes not only the assessment of their accuracy, but also the evaluation of their practical usability and applicability in daily life scenarios [21].

1.2 Practical recommendations to obtain accurate BP measurements

The difficulty of obtaining accurate BP measurements is related not only to the accuracy of the devices selected, but also to the intrinsic characteristics of the BP signal. Indeed, BP is a highly variable haemodynamic parameter which may be influenced by a variety of physical, psychological and environmental factors which affect BP especially during the day-time [4,22-25]. Failure to account for these different influences on BP, may result in erroneous diagnosis and inappropriate management of hypertension [26-29].

Generally accepted recommendations to ensure the best possible conditions for BP measurement include those discussed and summarized in Table 2.

Table 2. conditions for optimal BP measurement

- Full explanation of the procedure and proper patient's education
- Correct attitude of patient and observer
- Correct posture of the patient
- Arm support
- Arm position at heart level
- Proper arm selection
- Selection of cuff and bladder of adequate size

1.2.1 Patients' Relaxation

Before taking a BP measurement, the patient should be allowed to relax over a short period of rest (at least 5 minutes) in a quiet room at a comfortable temperature. Any reason for which such a baseline requirement cannot be fulfilled, should be reported together with the BP reading obtained. Furthermore, patients should be advised not to talk before and during the BP measurement and to avoid crossing their legs (Table 3).

Table 3. Correct patient attitude to BP measurement

- Measure BP in a quiet room
- Patient must be relaxed since at least 5 minute
- Talking must be avoided before and during BP measurement
- Leg crossing must be avoided

1.2.2 Accounting for the emotional impact of BP measurement by the doctor (white coat effect)

BP measurement by the doctor has been known for decades to induce a pressor reaction in the patient. The occurrence of a transient BP increase during sphygmomanometric measurements in the clinic environment was first described in 1897 by Scipione Riva-Rocci ["….the simple application of the instrument (the sphygmomanometer) can cause a temporary rise in BP. It is therefore necessary to take not just one reading, but several in succession, such as 3 in three minutes or 5 in five minutes, until an average constant pressure is obtained…."] [30]. The quantitative importance of this phenomenon, however, was not fully appreciated until the early eighties of the last century, when, with the advent of intra-arterial ABPM techniques, the precise assessment of dynamic changes in BP, occurring under different behavioural conditions became possible. One of the first attempts to quantitatively describe the pressor effect of the doctor's visit was made in 1983 by Mancia et al. by using the Oxford intra-arterial ABPM system [25,31]. They observed that the BP rise associated with this phenomenon i) becomes evident since the very beginning of the physician's visit, often before the time of actual cuff BP measurement, ii) persists for approximately 10-15 minutes (i.e. the duration of the visit) and iii) is accompanied by a parallel rise in heart rate [25,32-36]. This observation was interpreted as the haemodynamic result of a patient's alarm reaction to the physician's visit, a reaction that was later referred to as the "white-coat effect" [34]. The potential clinical importance of this phenomenon

was emphasised by the observation that i) it is of considerable magnitude, the maximal increase in intra-arterial systolic and diastolic BP observed in the first 2-4 minutes of the physician's visit being on average 27/14 mm Hg [25,36], ii) its size is largely different in different subjects [25,36], which makes it hardly predictable in the individual patient, iii) it does not easily fade with time, as it was of comparable magnitude at the time of four consecutive visits (always performed by the same physician) repeated over a 48 hour intra-arterial BP recording period [36].

The invasive techniques applied in the pioneering studies on this issue, however, are not applicable for obvious practical reasons in clinical studies including large groups of patients. Therefore "surrogate" non-invasive solutions for the quantification of this phenomenon, more easily applicable both in epidemiological research and in a clinical setting, have been proposed. The introduction of non-invasive intermittent automated BP monitoring techniques has indeed made it possible to obtain BP values out of the doctor's office, that are not influenced by the stressful conditions associated with clinic BP measurement [35]. This has led to the suggestion that the difference between office and mean day-time ambulatory or home BP values might provide an easier, although indirect, assessment of the "white-coat effect" [34]. As a consequence of this assumption, although with limited experimental support, the condition characterized by a persistently high BP in the office environment and a persistently normal BP outside the physician's office, has been regarded as to reflect the persistence over time of an alerting reaction to the physician's visit, being responsible for the repeated finding of elevated office BP readings vis-à-vis normal day-time or home BP levels. On this background, such condition is commonly referred to as "white-coat hypertension" [37-39].

Notwithstanding its diffusion as the most popular approach to indirectly quantify the "white-coat effect" and the "white-coat hypertension" phenomena [39], no sound evidence has ever been provided in the past, nor it is now available, that the observed difference between office and ambulatory BP values indeed reflects the actual BP rise induced by the physician's visit. On the contrary, data recently obtained through techniques for non-invasive continuous finger BP monitoring [4,36,40] employed during the physician's visit support the opposite conclusion. In fact, the difference between clinic and ambulatory average day-time BP has been shown in two papers by Lantelme et al. [36] and by Parati et al. [37] to carry no or negligible correlation with the magnitude of the true "white-coat effect", as assessed directly by this approach. The same conclusion was reached in a study by Palatini et al. [33]. The results of these studies therefore are far from supporting

use of the difference between clinic and day-time BP as a reliable quantitative index of the "white-coat effect". The reasons for the discrepancy between these direct and surrogate measures of the white-coat effect are likely to be manifold, and at least in part certainly depend on the different types of BP measurements from which they are derived. In case of the direct assessment, BP reactivity to the physician is precisely quantified both in its size and duration, taking as reference the BP levels recorded under the standardized resting conditions preceding the doctor's visit. In case of the surrogate approach based on the clinic-day-time BP difference important methodological problems are to be faced. On one side, clinic BP is quantified from the average of a limited number of readings (usually 1 to 3), with the risk of a poor reproducibility of the values so obtained. On the other side, day-time average BP can hardly be regarded as a reliable "reference" BP level, because it includes the effects on BP by varying degrees of physical activity and by the multiple and different stressful conditions occurring in daily life. The choice of day-time BP as reference level for computing the "white-coat effect" is further undermined by the possibility that (see below) subjects hyper-reactive to the physician's visit might also be hyper-reactive to daily life stress, leading to higher day-time BP levels and thus, at variance from the assumptions underlying the adoption of this surrogate method, to a smaller rather than to a wider clinic-day-time BP difference. Use of the difference between clinic and home BP may be free from the above problems, but has to face other methodological difficulties, such as the number of home BP readings to be considered, the accuracy of the home BP devices employed and the reliability of patients in reporting the measured values. This is why the practical relevance of this surrogate approach also needs to be further investigated [37].

The BP increase triggered by the doctor's visit [4,30-37] may be regarded as a physiological reaction – known as the "alerting" reaction - which commonly occurs in a medical environment. It may be observed in both normotensive and hypertensive individuals [25]. As mentioned above, the white coat effect should not be considered as synonymous for "isolated office or clinic hypertension" or "white-coat hypertension". The latter term rather refers to the combination of normal BP levels outside the medical environment with BP values in the hypertensive range at the time of consultation. [38,39]. The importance of this phenomenon in clinical practice is that decisions on whether to prescribe antihypertensive drugs or not, should not be made on the basis of measurements affected by such an alerting reaction.

1.2.3 Explanation of the procedure and patient's education

The entire procedure of BP measurement should be adequately explained, based on the assumption that adequate information might reduce patient's anxiety and might help avoiding the white-coat reaction. Moreover, health care professionals should invite patients to learn more about problems related to hypertension and BP measurement. Illustrated material on paper or on DVD should be available for motivated patients and information on dedicated websites should be given (Table 4).

Table 4. Patient's education by doctor for achievement of reliable BP measurement

• Fully explain the procedures of BP measurement
• Inform patient on the clinical impact of high blood pressure
• Motivate patient with Illustrated material on paper or on DVD

1.2.4 Recommendations for the observer

BP measurement should not be carried out in a hurry. The observer should not deflate the cuff too rapidly; this might lead to an underestimation of systolic and overestimation of diastolic pressures. To avoid forgetting the measured values, the BP readings should be documented soon after BP has been measured (Table 5).

Table 5. Recommendations for the observer

• The cuff must not be deflated too rapidly (>2-3 mm Hg/sec)
• The BP values must be recorded on paper as soon as they have been measured

1.2.5 Posture of the patient

It has not been established whether BP should be measured in the lying or sitting position. Only small BP differences are usually observed from the lying to the sitting posture, and for practical reasons the sitting position should be preferred. BP on standing should also be measured especially in elderly subjects and in patients on treatment. As for the length of the resting time which should precede the measurement, there is

general agreement that 5 min of rest should precede the lying and sitting positions and 1 min the standing measurement [26-29] (Table 6).

Table 6. Patient's posture

- Measure BP in the sitting position after 5 min of rest
- Measure BP also after 1 min of standing position
- Standing measurement is particularly important in the elderly or in the treated patients

1.2.6 Arm support and position

During BP measurement it is essential for the arm to be supported, especially when the individual is in the standing position. This can be achieved if the subject's arm is held by the observer at the elbow [26-29]. This procedure avoids the isometric exercise which may increase BP and heart rate especially in hypertensive patients [41]. The forearm must also be at the level of the heart: if the arm is below heart levels an overestimation of systolic and diastolic pressures occurs, while raising the arm above heart level leads to underestimation. Paying attention to these aspects is particularly important for the sitting and standing positions, when the arm is likely to be dependent on the individual's side. However, even with a patient in the supine position an error of 5 mm Hg for diastolic pressure may occur if the arm is not supported at heart level [26-29] (Table 7). Patients performing self measurement of BP, particularly when using devices for measuring BP at the wrist (see below), should be instructed about the potential errors related to inappropriate arm position.

Table 7. Arm support and position

- Use an arm support to avoid isometric exercise (especially for standing position)
- Arm must be in the horizontal position during measurement
- Arm must be at the heart level (particularly important for wrist monitors)

1.2.7 Arm selection

Some studies using simultaneous measurement have demonstrated significant differences between arms [26,27], and this difference may be variable over time. Thus BP differences between arms over consecutive measurements may reflect both BP variability and errors of measurement. Therefore, bilateral measurement should be made at the first visit and, if consistent differences greater than 20 mm Hg for systolic or 10 mm Hg for diastolic pressure are detected, the patient should be assessed for excluding arterial disease [42] (Table 8).

Table 8. Arm selection

- Perform a bilateral arm measurement at the first visit
- If between-arm difference is >20 mm Hg for systolic and >10 mm Hg for diastolic, select the arm with the highest BP

1.2.8 The cuff and bladder

The inflatable rubber bladder should be long enough to match the arm circumference and should be contained within an inelastic cloth, the full length of which should extend beyond the end of the inflatable bladder [27]. To secure the cuff round the arm, velcro surfaces are commonly used, which should be discarded when they lose their grip. Miscuffing may lead to inaccurate BP measurements, and use of a cuff with a bladder of inappropriate dimensions for the arm is a serious source of error (Table 9).

Table 9. Mismatching of bladder and arm [27].

Mismatch	Consequence
Bladder too small (undercuffing)	• Overestimation of BP • Range of error 3.2/2.4-12/8 mm Hg (as much as 30 mm Hg in obesity) • More common than overcuffing
Bladder too large (overcuffing)	• Underestimation of BP • Range of error 10-30 mm Hg

Use of too narrow or too short bladders (undercuffing) leads to overestimation of BP, and thus to overdiagnose hypertension, a problem often overlooked by many doctors when measuring BP in obese

subjects. Conversely, use of too wide or too long bladders (overcuffing) may lead to BP underestimation, with the possibility of diagnosing hypertensive individuals as being normotensive [43].

Moreover, manual cuff inflation itself may cause a transient but substantial increase (of up to 40 mm Hg) in systolic BP caused by the muscular exercise related to cuff inflation [44].

To avoid the consequences of miscuffing a number of approaches have been used over the years. Correction formulae have been suggested to adjust measurement errors, a procedure which has the disadvantage of further complicating the BP measurement. Other investigators have proposed the availability of a range of cuffs, so that the user after measuring the arm circumference can choose the appropriate cuff size. This requirement is usually neglected in clinical practice. However, at least cuffs for small, standard and large arms should be available in every doctor's office. According to the BHS [26] a standard cuff with a bladder measuring 12 x 26 cm for the majority of adult arms, a large cuff with a bladder measuring 12 x 40 cm for obese arms, and a small cuff with a bladder measuring 12 x 18 cm for lean adult arms and children, should be available. At variance with the BHS, the American Heart Association recommends four cuffs [45]: a small adult cuff with a bladder measuring 10 x 24 cm for arm circumference 22–26 cm, an adult cuff with a bladder measuring 13 x 30 cm for arm circumference 27–34 cm, a large adult cuff with a bladder measuring 16 x 38 cm for arm circumference 35–44 cm, and an adult thigh cuff with a bladder measuring 20 x 42 cm for arm circumference 45–52 cm. More recently, cuffs containing bladders of varying dimensions have been made available. One of these models (Tricuff, Pressure Group AB & CoKB, AJ Medical HB, Sweden) allows the user to choose the most suitable bladder for the arm in which pressure is being measured. However, this model did not find widespread use because of cuff stiffness, and because of its cost. An adjustable cuff which may encircle all adult arms has been designed by a British Company [4] but there is no sufficient experience to recommend its use.

1.3 Individual factors affecting BP measurement

BP measurement in certain groups of subjects may face specific problems, due to age, body habitus, or haemodynamic alterations. This is in particular the case of children, the elderly, obese individuals, pregnant women with or without pre-eclampsia, and patients receiving antihypertensive drugs.

1.3.1 Children

Health care professionals should be aware that BP variability is greater in children than in adults. In children, systolic pressure is preferred to diastolic pressure because of greater accuracy and reproducibility. The crucial issue, however, is cuff size. Three cuffs with bladders measuring 4 x 13 cm, 8 x 18 cm and the adult dimensions 12 x 26 cm are required to encompass all arm dimensions. The widest cuff practicable should be used. BP measurement is particularly difficult in children younger than 1 year because Korotkoff sounds are not reliably identified. This problem may be encountered also in children younger than 5 years. In such cases, Doppler ultrasound or oscillometry should be used [46]. Obtaining steady haemodynamic conditions is obviously more difficult in children than adults. An adequate period of rest can hardly be obtained in children. For the above problems, a child's BP should be evaluated with a large enough number of readings taken in separate visits. Body size is the most important determinant of BP in childhood and adolescence, and the US National High Blood Pressure Education Group on Hypertension Control in Children and Adolescents provides reference values related to both age and height [47]. Reference values are available also for the Italian population [48].

1.3.2 Elderly people

Frequent and sharp BP oscillations that can affect the accuracy of measuring techniques can be often observed in elderly individuals. BP variability is more frequent in clinical conditions such as autonomic failure or isolated systolic hypertension. The latter condition is the most common form of hypertension in the elderly and the results of several studies have shown that office systolic BP may average 20 mm Hg more than day-time ambulatory BP in the elderly, with overestimation of true systolic hypertension [49]. Hypotensive episodes interspersed with hypertensive peaks and alteration of the 24h pattern commonly occur in autonomic failure. This condition is difficult to deal with, because antihypertensive treatment may exacerbate periods of hypotension [50]. Antihypertensive therapy should thus be tailored on the basis of the results of ABPM. Mild postural and postprandial hypotension without other clinical signs of autonomic dysfunction is also common in the elderly [50]. As this often coexists with increased supine BP, a thorough assessment of BP in all positions is mandatory in the elderly, and the BP effects of drugs such as alpha-blockers, diuretics and also non-cardiovascular drugs, should be carefully evaluated.

As stated above, the difference between office and ambulatory BP is greater in the old subject, which leads to a high rate of white-coat hypertension in this group (see Part 3). Assessment of BP out of the office is thus often necessary in the elderly. Arterial stiffening may lead to inaccurate BP measurements in the elderly and cause the so-called pseudohypertension. This condition can be detected with direct BP measurement [51]. When pseudohypertension is suspected, referral to a specialist cardiovascular centre should be considered.

1.3.3 Obese people

Obesity is frequent in patients with hypertension and may result in inaccurate BP measurements. The risk of such an inaccuracy is greater when obesity is associated with childhood, young or advanced age, diabetes and pregnancy. In this regard, it is not well known whether the accuracy of measurements differs between the oscillometric and the auscultatory methods in the latter population.

1.3.4 Arrhythmias

The changes in stroke volume which accompany cardiac arrhythmias make it difficult to measure BP in this condition. Automated devices vary greatly in their ability to correctly detect BP in patients with arrhythmias, and devices should be validated independently in patients with arrhythmias [52]. BP measurement is particularly difficult in atrial fibrillation, and in this condition only a rough estimate of BP can be obtained. Several readings should be obtained and averaged to overcome beat-to-beat variability. The oscillometric method depends on a smooth profile of successive pressure waves to determine BP, and thus this technique is not always able to measure BP in patients with atrial fibrillation. The deflation rate should be no faster than 2 mm Hg per heartbeat. The same problem applies to bradyarrhythmias because a too rapid deflation would result in underestimation of systolic and overestimation of diastolic pressure.

1.3.5 Pregnancy

Care should be used when measuring BP in pregnancy, because BP measurement presents some special problems [53] in this setting with important implications for patient management (see also Part 3). One controversial issue is whether the fourth or fifth sound should be used to identify diastolic BP. Today, there is general consensus that disappearance of sounds (fifth phase) should be taken except when sounds persist

to zero, when the muffling of sounds should be used [54,55]. It is however frequently recommended to report on charts the diastolic BP values obtained in correspondence of both the fourth and the fifth Korotkoff sounds.

1.3.6 Patients on treatment

Although long lasting antihypertensive drugs are expected to produce homogeneous BP lowering effect throughout the 24h, changes in the BP effect over time may occur especially with shorter acting compounds. For this reason, in patients receiving treatment with antihypertensive drugs, the timing of measurement may be important to assess the actual BP control, and several measurements may be required especially in patients on multiple therapy.

1.3.7 Exercise BP

There has been debate over whether exercise BP provides more important prognostic information than resting BP. Today, there is evidence that an exaggerated BP response with exercise testing may be predictive of future hypertension [56-58], left ventricular hypertrophy [59], and mortality from myocardial infarction [60]. During incremental exercise, systolic BP increases progressively as a result of increasing cardiac output, whereas diastolic pressure is subject to modest changes. Although normal values of maximum systolic BP according to age [61] have been defined, it is not known whether these values are clinically meaningful. In addition, these limits do not take into account the fact that also resting BP increases with increasing age. An age independent upper limit of 180 mm Hg systolic for exercise BP at 100 W standardized bicycle test has been proposed [62]. The lack of widely accepted normalcy limits and the costs related to standard ergometry make it hard for this procedure to be used in routine clinical practice. Another reason for concern is that reliable diastolic BP values may be difficult to obtain during exercise testing with standard sphygmomanometry. As prognostic data are mainly available for systolic BP during exercise, it would be reasonable to use only systolic values in clinical practice. The type of ergometer and exercise protocol may also influence the results and this calls for standardization of exercise testing at least for the evaluation of the hypertensive patient. Although assessment of exercise BP is not justified in routine clinical practice whenever an exaggerated BP response to exercise is seen in normotensive or hypertensive

individuals, it should not be ignored, and this information should be included in the general assessment of the hypertensive subject.

PART 2. Office BP measurement with conventional auscultatory method or with automated and semi-automated devices

2.1 Problems related to the observer

The results of standard auscultatory sphygmomanometry largely depend on the accurate identification and interpretation of Korotkoff sounds or pulse wave by the operator [63]. Errors in measurement can occur at different points of the observer-device interaction, but the weakest ring of the chain is the observer.

The most common errors related to the observer are [64]: i) systematic failure to perform correct measurements; (ii) digit preference and rounding off most often to zero; (iii) observer bias, based on the preconceived notion of what the pressure should be in the individual subject under scrutiny (Table 10).

The systematic error of the observer is often due to the poor knowledge of the measurement recommendations [65,66], because instructions to health care personnel are often superficial. This problem should not be overlooked in clinical practice and training procedures should include reading of published recommendations and direct training on the measurement technique using a binaural or multiaural stethoscope. The use of video-films that incorporate instructions with examples of how BP should be measured may be of help [26-29]. To this regard, the Italian Society of Hypertension has recently produced a training DVD video for health care professionals and patients [67].

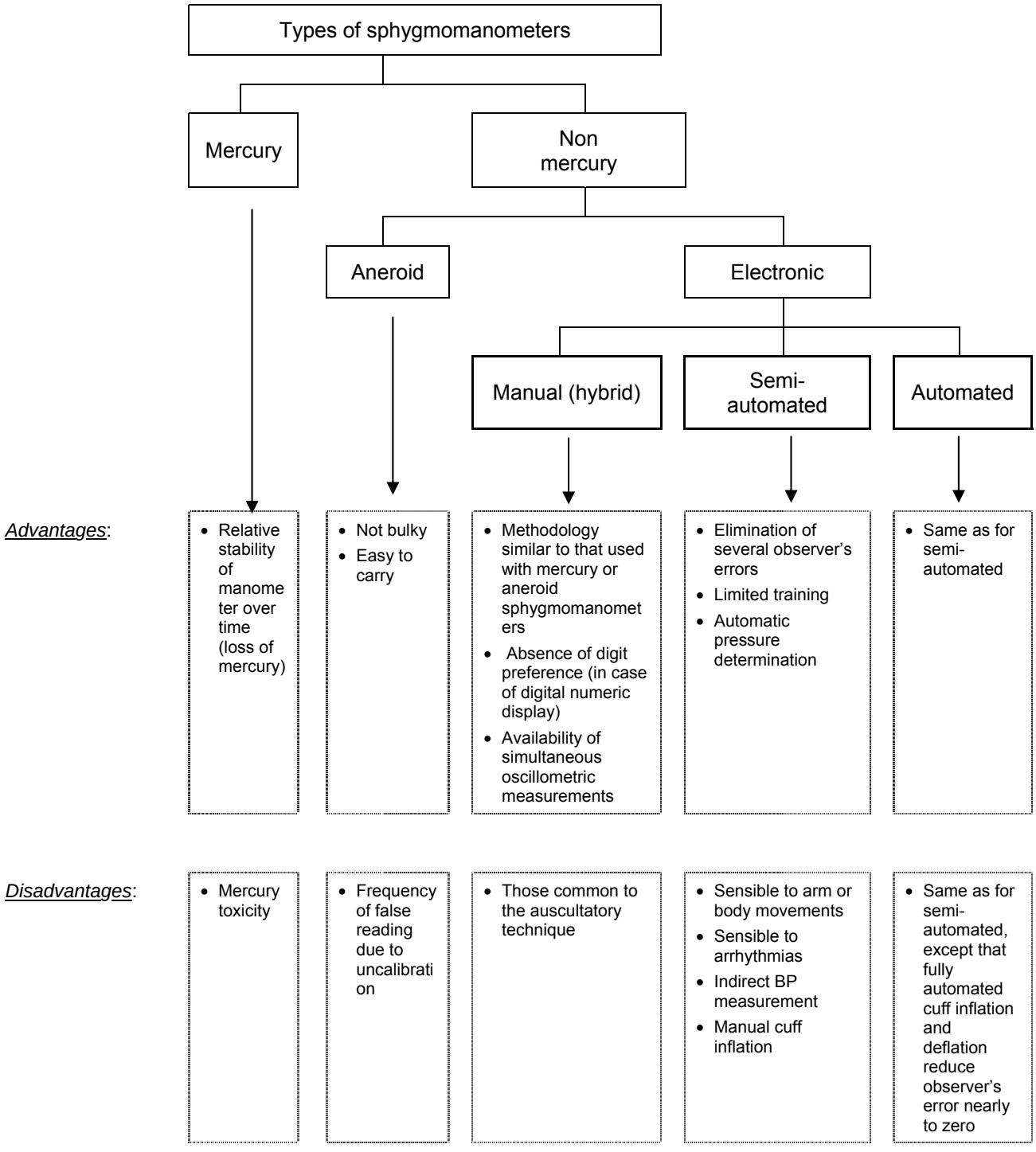
Table 10. Problems related to the observer

- Systematic failure to perform correct measurement
- Rounding off the pressure readings (digit preference)
- Observer prejudice or bias

2.2 Sphygmomanometers

The mercury sphygmomanometer is still the most reliable device, provided its efficiency is checked periodically. The same problem applies to the aneroid manometer, which is not generally as accurate, and necessitates of frequent calibrations. Both devices have an inflation/deflation system connected by rubber tubing to an occluding bladder and measure BP by auscultation with a stethoscope [63]. Figure 1

Figure 1. Types of sphygmomanometers.



The standard devices are operated manually, through a bulb which inflates the bladder and a valve for air release. Air leaks can occur in the tubing system from cracked or deteriorating rubber or from defective control valves. Thus, maintenance of these parts is crucial for the correct device functioning to avoid underestimation of systolic and overestimation of diastolic pressures which may occur in case of leakage. Maintenance and calibration should be performed for all BP measuring devices on a regular basis (every 6-

12 months) (Table 11). As mentioned above, air leak or other problems can occur easily with sphygmomanometers and a maintenance policy should thus be mandatory in all hospitals [68]. Although doctors are aware of these drawbacks they are often reluctant to have their sphygmomanometers checked and serviced. It's an observer's duty to report faulty equipment or lack of appropriate cuffs, and to refuse to use defective or inappropriate equipment

Table 11. Maintenance and calibration of sphygmomanometers

Type of manometers	More frequent causes of inaccuracy	Periodicity of check
1. Mercury sphygmomanometer	• Loss of mercury • Valve and filter obstructed or damaged • Abrasions of the graded scale • Rubber tubes or cuffs damaged	6 months
2. Aneroid manometer	• Valve obstructed • Rubber tubes or cuffs damaged • Damage of mechanical system of levers and springs	6 months

2.2.1 Mercury toxicity

The future of mercury sphygmomanometry for BP measurement is seriously threatened because of concerns about mercury toxicity. In fact the mercury sphygmomanometer is going to disappear from clinical practice in the next few years. In some countries, the use of mercury is no longer permitted in hospitals. This has increased the interest of doctors and manufacturers for mercury-independent devices such as the aneroid sphygmomanometers or the electronic devices, either manual or automated. This will result in a gradual disappearance of mercury from clinical use in the next few years.

2.2.2 Aneroid manometers

Aneroid sphygmomanometers allow BP to be measured through a bellows and lever system, which is subject to progressive decline in performance, leading to an increasing likelihood of false-low readings. However, progress in metal components and manufacturing processes has led to improved performance of these

devices throughout the years. According to recent results obtained in a large variety of aneroid sphygmomanometers used at the University of Michigan, for an accuracy standard of ±3 mm Hg the error rate was 4.4% as compared to the 33-46% of previous studies [69]. This led the authors to conclude that accurate aneroid sphygmomanometers can be used as an alternative to mercury manometers provided calibration is performed on a yearly basis. When aneroid instruments are calibrated against a mercury sphygmomanometer, a mean difference of 3 mm Hg is considered to be acceptable [70]. Many aneroid sphygmomanometers are available on the market, but only a few have passed clinical tests following international protocols.

2.2.3 Alternatives to the mercury sphygmomanometer

2.2.3.1 Non-automated devices

The oscillometric method can be used for office measurement, but only devices independently validated according to standard protocols should be used. Oscillometric devices have the advantage of being able to take multiple measurements. However, the oscillometric method has a number of inherent limitations. One main problem with this technique is that the amplitude of the oscillations depends on several factors other than BP, most importantly the stiffness of the arteries. Recently, devices have been developed that combine some of the features of both electronic and auscultatory devices, and are referred to as "hybrid" sphygmomanometers. They use an electronic pressure gauge, similar to that used in oscillometric devices, as a substitute for the mercury column. BP is taken in the same way as with a mercury or aneroid device, by an observer using a stethoscope and listening for the Korotkoff sounds. The cuff pressure can be displayed as a simulated mercury column, as a digital readout, or as a simulated aneroid display. Hybrid sphygmomanometers have the potential of minimizing terminal digit preference, which is a major source of error with mercury and aneroid devices. They have thus the potential to become a replacement for mercury sphygmomanometry, because they possess some of the best features of both mercury and electronic devices. The Greenlight 300 (Cossar and Son, London, UK) is a device that uses an electronic transducer instead of the mercury column. More recently a similar device has been developed by A&D (UM-101). This type of devices may be more suitable for the physician because he or she is still able to measure BP using the auscultatory technique.

2.2.3.2 Automated or semi-automated devices

Automated or semi-automated oscillometric BP devices are increasingly being used for office BP measurement. Automated devices can eliminate several observer errors and avoid the problem of the observer bias and digit preference. Moreover, a long period of training is not necessary as it is with the standard auscultatory technique and these devices can be easily used also at patients' home. The readings obtained in such condition with the use of automated or semi-automated devices are usually lower than those taken by a physician or nurse because of avoidance of the alarm reaction. Another advantage of automated or semi-automated measurement is the ability to take a series of sequential readings and automatically average them. The main disadvantage is the error inherent in the oscillometric method. This is due to the fact that systolic and diastolic BP values are computed through a proprietary algorithm which is not disclosed to the operators. For such a reason a reliable use of these devices requires to have them validated by internationally accepted protocols (see below). Indeed, several automated or semi-automated devices proved to be inaccurate, although the performance of new devices is increasingly improving. Another problem with oscillometric techniques is that they cannot measure BP reliably in patients with tachyarrhythmias. In some individuals, large discrepancies have been observed between the oscillometric and the auscultatory method and this difference can not be predicted on the basis of subjects' clinical characteristics.

2.3 Training of observers

As the number and type of BP measurement devices increase, more people are measuring BP more frequently either in the medical or the non-medical setting. The training given to patients or family members should be as comprehensive and similar to that recommended for health care professionals especially if the auscultatory technique is being used. In fact, the accuracy of the readings can be optimal only if the observer is appropriately trained about how BP should be measured.

2.4 Position of manometer

With use of mercury manometers, measurement errors can occur unless the eye is kept close to the level of the meniscus (parallaxis errors). The mercury column should be kept in vertical position and at eye level and should be no further than 1 m away. This can be best achieved with the use of standmounted models. In case

aneroid devices are used, the aneroid scale must be front-viewed, with the eye on a line perpendicular to the centre of the face of the gauge.

2.5 Application of the cuff

A cuff of the appropriate size should be chosen according to the patient's arm circumference (see above). The cuff should be wrapped around the arm, with the lower edge 2–3 cm above the point of brachial artery pulsation [26,63]. The rubber tubes are usually placed inferiorly, but to keep the antecubital fossa easily accessible for the stethoscope it is now recommended that they should be placed superiorly, whenever the cuff shape allows it.

2.6 Palpatory measurement

The palpatory measurement allows the observer to identify the approximate level of systolic pressure. The cuff should be rapidly inflated to about 30 mm Hg above the point at which the pulse disappears from the brachial artery and then slowly deflated. The radial pulse can be used whenever the brachial one is not easily detectable. The pressure at which the pulse reappears roughly corresponds to systolic BP. The palpatory estimation is important for detecting the so-called "auscultatory gap", which occurs when phase I sounds disappear as pressure is progressively reduced in the bladder, and reappears at a lower level. If not recognized through pulse palpation, this will cause an underestimation of systolic pressure. The palpatory technique is useful mainly in subjects in whom auscultatory phenomena may be difficult to detect correctly, such as pregnant women, patients in shock or during exercise testing.

2.7 Measurement procedure

The stethoscope should be placed over the brachial artery. The bell of the stethoscope should preferentially be used but the diaphragm covers a larger area and is easier to be used. The stethoscope should be placed gently without exerting excessive pressure, which might distort the artery and produce sounds below diastolic pressure. Attention should be paid not to touch the clothing, cuff or rubber tubes with the stethoscope, to avoid friction sounds. The cuff should then be inflated rapidly to about 30 mm Hg above the previously palpated systolic pressure and deflated at a rate of 2–3 mm Hg/sec (Table 12).

Table 12. Auscultatory measurement procedure

• Palpatory measurement of systolic BP prior to commence auscultatory measurement
• Stethoscope placed over the brachial artery (use preferentially the bell)
• Cuff must be inflated 30 mm Hg above the systolic BP
• Cuff must be deflated at a rate of 2–3 mm Hg/ beat or sec
• Korotkoff phase I (appearance of sounds) must be selected for systolic BP determination
• Korotkoff phase V (disappearance of sounds) must be selected for diastolic BP determination
• After disappearance of V tone, cuff must be deflated rapidly
• Immediate recording on paper of the pressure readings

2.7.1 Auscultatory phenomena

During the cuff deflation, the sounds first described by Korotkoff and later elaborated by Ettinger can be heard [71] . After sound disappearance, the cuff should be deflated rapidly and completely to prevent venous congestion of the arm before the measurement is repeated. (Table 13)

Table 13. Korotkoff Sounds

Phase I	The first appearance of faint, repetitive, clear tapping sounds which gradually increase in intensity for at least two consecutive beats is the systolic BP
Phase II	A brief period may follow during which the sounds soften and acquire a swishing quality
Auscultatory gap	In some patients sounds may disappear altogether for a short time
Phase III	The return of sharper sounds, which become crisper to regain, or even exceed, the intensity of phase I sounds. The clinical significance, if any, to phases II and III has not been established
Phase IV	The distinct abrupt muffling of sounds, which become soft and blowing in quality
Phase V	The point at which all sounds finally disappear completely is the diastolic pressure

2.7.2 Identification of diastolic BP

A controversial point is represented by the correct way of measuring diastolic BP – the so-called “diastolic dilemma”. Phase IV (muffling of sounds) may be very close to phase V (disappearance of sounds), but usually the difference is of a few mm Hg (less than 5 mm Hg) and rarely greater than 5 mm Hg. However, in some subjects such as children, pregnant women, or anaemic or elderly patients sounds may still be heard when cuff pressure is deflated to zero. In this event, muffling of sounds (phase IV) should be recorded for

diastolic pressure. For most subjects, there is now a general consensus that disappearance of sounds (phase V) should be taken as diastolic pressure.

2.7.3 Number of measurements

As mentioned above, BP is subject to high variability with a tendency to decline when measured repeatedly. For this reason it is recommended that several readings are taken especially when large differences occur between consecutive measurements. A number of visits should be made over a number of weeks or months before any diagnostic or therapeutic decision is made (72). At each visit, at least two measurements at 1 min intervals should be taken.

2.8 Recording BP

The following points should be recorded with the BP measurement: i) position of the body, i.e. lying, sitting or standing; ii) the arm in which the measurement has been made, i.e. right or left (BP in both arms on first visit); iii) arm circumference and inflatable bladder size; iv) phases IV and V for diastolic BP for discrepancies larger than 5 mm Hg; iv) auscultatory gap if present; v) state of anxiety if present; vii) time of drug(s) ingestion.

PART 3. Out-of-office BP measurement with automated or semi-automated devices

Automated or semi-automated BP measurements can be adopted in different conditions, including SBPM at home, ABPM over the 24h (automated devices, only) and repeated BP assessment in the doctor's office. The last application is more and more frequently considered by physicians due both to the increasing awareness of the interference introduced by the "white-coat effect" phenomenon in the clinical management of hypertensive patients, and to the availability of devices that offer the possibility of repeated automated BP measurements in the clinic or office waiting room, yielding their average values right before consultation (e.g. BP-Tru, Omron 907, Microlife WatchBP Office) actual ability of this approach to improve hypertension diagnosis and management is still matter of research, however, and use of automated or semi-automated devices for repeated BP measurement is presently suggested only for out-of-office BP monitoring [73,74].

When considering automated (or semi-automated) BP measurements, a number of issues need to be dealt with appropriately. These issues will be separately addressed in the following paragraphs.

3.1 Device Choice and Validation

Automated BP measuring devices are at present most commonly based on the oscillometric technique and on the use of stable electronic transducers. This implies that these devices quite accurately measure mean BP, corresponding to the point of maximal oscillation of cuff air pressure during cuff deflation, and then calculate systolic and diastolic BP values. The latter procedure is carried out through proprietary algorithms, different for different devices, and usually not made available by manufacturers. For this reason, the accuracy of the systolic and diastolic BP readings yielded by any of these systems has to be checked against conventional measurements performed in highly standardized conditions, according to one of the available protocols endorsed by American and/or European Hypertension Societies [9-12]. The need for such a validation comes from the fact that accuracy is a mandatory requirement for all BP measurements [9] and from the general agreement that accuracy of any given BP measuring device should not be only based on claims from manufacturers, but should rather be supported by data from validation studies provided by independent investigators and published in peer-reviewed journals [10]. This issue has been dealt with in Part 1 of these guidelines. Common aim of these protocols was the standardization of validation procedures, to

facilitate comparison of one device with another, and the definition of a minimum standard of accuracy to be achieved by all "validated" devices. The accuracy of available automated BP measuring devices has been assessed in a number of studies the results of which have been published in a few summary papers [5,75-77]. Given however the speed at which these surveys become outdated, no listings of validated devices are provided in the present recommendations, a choice in line with the last European recommendations on BP monitoring [2]. Such information needs to be continuously updated, and can be obtained from websites such as those of the ESH [17] or BHS [18], or from a website endorsed by the Italian Society of Hypertension [19] or finally from website endorsed by the European Society Working Group on BP Monitoring [20]. In the EU the safety and basic accuracy requirements of BP measuring devices are governed by specific rules [6-8]. Adoption of such a general quality control, however, is not enough to guarantee the accuracy of a BP measuring device when used in clinical practice. Such an accuracy should be verified by ad hoc validation studies according to the protocols mentioned above. Recent discussion is now focussing on an additional issue in this field, i.e. the need to couple the validation of device accuracy with the assessment of the technical, functional and commercial features of any given BP measuring device, in order to provide an overall quality evaluation of the device. In this perspective, relevant parameters to be collected include: information on operativity, display dimensions, battery life, duration of measurement, memory availability, quality/price ratio, marketing distribution, warranty coverage, service facilities with qualified technical assistance, etc. Such an evaluation protocol has recently been developed by an independent association and endorsed by the Italian Society of Hypertension [21].

3.1.1 Wrist or arm cuff devices

As documented in the history of medicine, several attempts to assess BP in humans focused on the wrist, including the "sphygmometers" manufactured by Hérisson, Vierordt, Marey and Dudgeon in the XIX Century [78-81]. The first quantitative assessment of radial BP that had a clinical application was made possible by the "sphygmometers" and "sphygmomanometers" introduced by von Bash [82] and by Potain [83] which opened the way to the sphygmomanometer described only a few years later by Scipione Riva-Rocci [84,85]. In spite of its very simple application, however, this approach was abandoned only a few years later, mainly because of the high variability in the wrist BP values obtained. Over the last few decades,

technological progress has led physicians to reconsider the possibility of measuring BP at the wrist level, thanks to the introduction of electronic and more or less complex computer-operated devices. These devices, usually smaller and cheaper than those previously available, sometimes only slightly bigger than a sports watch, are based on oscillometric automated wrist BP readings [86]. In the very last few years, electronic devices which measure BP from the wrist have become a very popular approach to SBPM at home, with their sale comprising approximately 50% of all electronic devices for SBPM sold annually in Germany [87]. In fact, wrist devices have gained as much as 30% of the market share for all automated BP measuring devices worldwide [88]. Interestingly, more than 90% of patients performing SBPM seem to prefer wrist rather than arm devices [89], the popularity of the former (in particular among elderly subjects) probably depending on their small size and light weight and by the fact that their use is found quite easy and convenient, as the cuff can be more easily wrapped around the wrist than around the arm, and because they allow BP measurements to be obtained without undressing. Moreover, some patients also prefer wrist devices because they experience much less discomfort when a cuff is automatically inflated around the wrist rather than around the upper arm. These devices have the potential advantage of being more suitable than arm devices in obese subjects with extremely large or with cone-shape upper arms, although, to the best of our knowledge, the accuracy of wrist devices in obese patients has been only occasionally tested according to international protocols (19,20).

As in the case of finger devices, one of the major disadvantages of wrist devices is that the wrist must be held at heart level during each BP measurement. If this is not done, substantial systematic errors may occur due to the influence of the arm–heart hydrostatic pressure difference [90]. Another problem is the possible error introduced by flexion or extension of the wrist during measurement, which may lead to different degrees of compression of radial and ulnar arteries by the inflated cuff. Therefore, because of these drawbacks and due to the limited data provided from properly conducted validation studies (the majority of which have yielded negative results), most authorities still recommend that devices measuring BP at the arm level should be preferred to wrist devices [91].

These indications are in agreement with the latest Guidelines for Hypertension management issued by the ESH and European Society of Cardiology and by the American Joint National Committee [2,72,92]. In spite of these discouraging recommendations, however, whether wrist SBPM devices should or should not be used

in the clinical management of hypertensive patients at home is still a matter of debate in the scientific community, due to the complex intertwining of the advantages and disadvantages that characterize their use. This calls for further investigation in this field before a final conclusion can be reached.

3.2 Technical requirements or problems, data handling, statistical analysis

3.2.1 Technical problems

3.2.1.1 Absolute contraindications to automated BP monitoring

Ambulatory and home BP recordings can be performed in most patients. However some specific conditions or physical characteristics of the patient may prevent reliable recordings to be obtained, especially in case of ambulatory monitoring [2,3,93,94]. This because of the inherent limitations of the indirect oscillometric or microphonic technique used to measure BP. Major problems may be found in the following conditions:

i) Atrial fibrillation or frequent ectopic beats or other arrhythmias preventing a regular series of heart beats to be recorded;
ii) Subjects undertaking heavy physical activity or frequently using the monitored arm during the recording (labourers, athletes, drivers, etc.);
iii) Poor patient's compliance: particularly relevant for home BP monitoring which requires direct patient's involvement in BP measurement.

In these conditions it is almost impossible to obtain a good quality BP recording, and most of the measurements fail due to hardware problems, or, if successful are of questionable accuracy.

3.2.1.2 Relative contraindications to automated BP monitoring

In some other conditions a special attention has to be paid in interpreting the results obtained, due to a high chance of inaccurate BP measurements. These conditions are:

i) Severe arm muscular hypertrophy or obese subjects with large arms (mid upper arm circumference >32 cm). In this case appropriate large adult cuffs must be used;

ii) Lean subjects with an arm circumference <26 cm. In this case appropriate small cuffs must be used;

iii) Severe arm function impairment (hemiplegics or paraplegics);

iv) Significant difference in mean sphygmomanometric BP simultaneously taken from both arms (≥10 mm Hg for systolic or ≥5 mm Hg for diastolic BP).

In case of use of cuff size other than the standard adult one, interpretation of results should be done carefully, because limited evidence from trials is available on the accuracy and the clinical value of the BP values so obtained. When a significant BP difference is found between arms, this indicates the existence of an arterial disease. If BP has to be monitored in any case, it should be recorded from the arm with the higher BP levels [2,3,93]

3.2.1.3 Possible source of artefactual readings

Occurrence of artefactual readings in automatic BP recordings is not an unusual finding [95]. This is particularly true in the case of ambulatory BP recordings where the dynamic conditions of measurement may increase the risk of errors. Knowledge of the possible source of artefactual readings is important for their prevention.

Studies simultaneously comparing non-invasive and intra-arterial recordings, have clearly shown that the between-method discrepancy is much greater during ambulation than at rest, indicating that when the patient is moving freely in uncontrolled conditions, measurements errors occur more easily [96,97]. Failed or erroneous readings may also occur for:

i) Incorrect cuff positioning, particularly frequent in case of home BP measurements, since cuff is placed by the patient and not by the doctor;

ii) Use of a cuff too small or too large;

iii) Cuff displacement during the ambulatory monitoring period, a condition which is not rare in obese subjects and that can be prevented by firmly fitting the cuff and checking its position at the end of the recording [98].

Attention should also be paid in checking whether the device cuff is set to be used on the right or on the left arm.

Inaccurate readings may also be generated when arm position is consistently above or below the heart level, as it may happen during night sleep when subjects are lying with the cuffed arm above the heart [2]. In this case BP may be 10 mm Hg lower than the true BP.

3.2.2 Data handling and statistical analysis

3.2.2.1 Data editing

Whether outlying readings should be rejected and not considered for data analysis has been matter of controversy for years [2,3,95]. Some studies have shown that data editing process mainly affects the calculation of the average levels of systolic BP and the standard deviations of both systolic and diastolic BP [97-100]. The effect on individual mean values might be large (up to ±3 mm Hg in the various studies) and even greater for standard deviation, which can be reduced by editing up to 40% of the value obtained from analysis of raw data.

However, some automatic editing should be applied at least to ambulatory BP recordings, because of the higher risk of artefacts as compared to home BP recordings. Whenever data editing has to be applied, a blind automatic procedure by a computer should be recommended. In order to make results of different laboratories comparable, common editing criteria should be used throughout the world. At the end of this automatic editing procedure the operator (doctor or nurse) should always check both the removed and accepted readings on the basis of the patient's diary.

Since in some cases artefactual readings may lie within the patient's usual BP range, devices providing oscillometric or Korotkoff sounds tracings, together with the measured BP values, should be preferable, because they allow an objective assessment of data quality [97].

Different editing procedures have been adopted by various authors, but none could be demonstrated being superior to the others [99-101]. Methods rejecting outliers can be roughly classified in three groups.

A] Univariate methods, which reject readings falling outside a given range. The simplest of these methods is based on selection of arbitrary thresholds allowing automatic removal of artefacts [2,96-98]. This method is the most recommended one, because rather conservative and not time consuming for the doctor, and thus ideal to be used in the clinical practice (Table 14 and Figure 2)

Table 14. Range of valid data according to the most common univariate editing criteria.

- Systolic BP between 50 and 300 mm Hg
- Diastolic BP between 40 and 150 mm Hg
- Pulse pressure between 10 and 150 mm Hg
- Systolic BP > diastolic BP
- Heart rate between 40 and 150 bpm

B] Multivariate methods allow simultaneous examination and comparison of multiple parameters from the same reading [102]. This can be done by using pre-defined algorithms or by correlating systolic and diastolic BP values for each reading and visually inspecting the residuals [103].

C] Temporal methods are based on analysis of series of sequential data. The slope of systolic and diastolic BP curves versus time may be used, or moving averages may be calculated, then rejecting data outside the 5th and 95th percentile of data distribution, or autocorrelation analysis may be employed [104-106].

After the automatic and visual editing procedure, a summary with the number of valid and not valid readings, the percentage of data removed over the whole 24h, the day and night-time subperiods, the number of readings per hour and the number of missing hours should be provided.

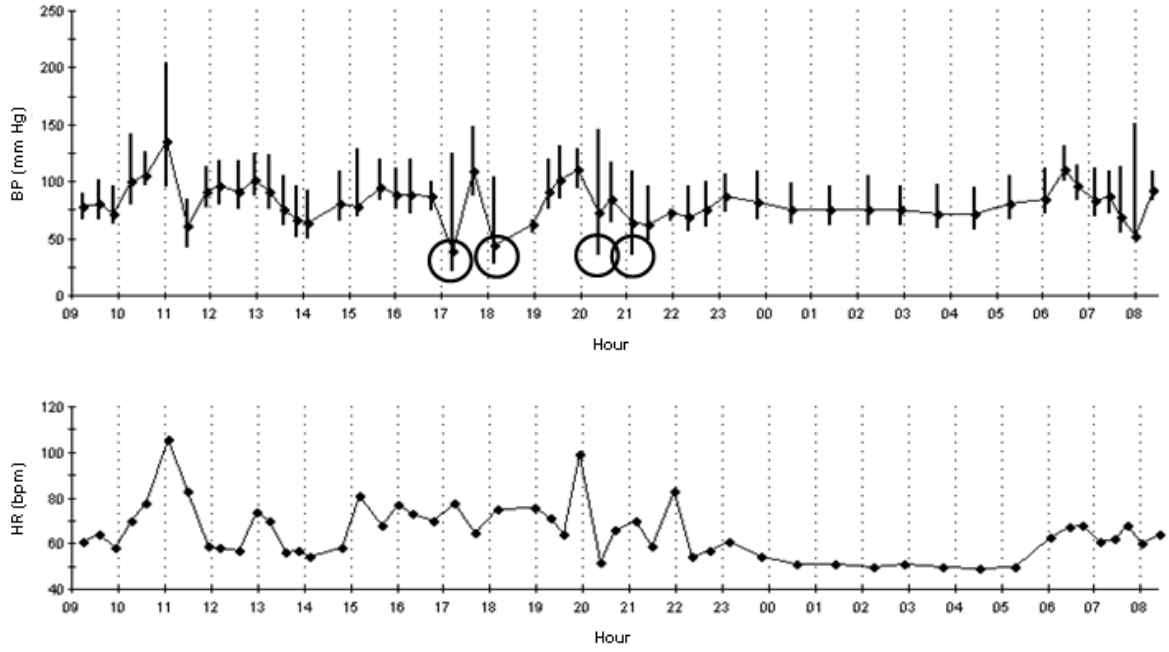


Figure 2. Example of a 24h ambulatory BP recording in which very low diastolic BP values (<40 mm Hg) were automatically identified and rejected from the analysis by the program used to this purpose [107].

3.2.2.2 Minimal requirements for statistical analysis

In case of ABPM, a recording should be regarded as suitable for statistical analysis if the following criteria are satisfied [2]:

i) At least 24h of valid BP recording;

ii) At least 2 valid measurements per hour during the day;

iii) At least 1 valid measurement per hour during the night;

iv) At least 70% of the readings expected on the basis of preset frequency of measurements.

In case of home BP monitoring it is mandatory that at least 1 week of monitoring is available, with at least 2 morning and two evening measurements for each day of monitoring, and a minimum of 12 measurements over the week [108-111].

3.2.2.3 Analysis of ambulatory BP recordings

Many statistical analyses are available for describing the multiple aspects of ambulatory BP recordings. However, the basic summary of a 24h recording should at least include the parameters reported in Table 15, separately for systolic and diastolic BP, and heart rate.

Table 15. Basic parameters for ABPM analysis.

• List of each single reading with hour and minute of occurrence
• A graphical display of single readings with BP or heart rate value referred to the vertical axis and time on the horizontal axis
• Maximal and minimal value occurring over the whole recording, and time of occurrence
• Average 24h value
• Average day-time and night-time value (selection of day-time and night-time periods should be based on the diary or when this information is lacking a fixed time interval should be employed, i.e. 7-23 for day-time and 23-7 for night-time in case of wide –fixed intervals)
• Absolute and relative (%) day-night difference [112]
• Listing and linear graph of hourly averages (optional)

Presentation of data should be independent of the type of monitor employed and manufacturers of ABPM devices should ensure standardization of analysis software.

Analysis of ambulatory BP recordings may provide numerous additional data which can be useful particularly for research purposes [112-122].

Besides averages, the median values and area under the curves may help in assessing the consistency of data. The importance of pulse pressure has been outlined in recent papers, so that analysis of this parameter may also be carried out for special purposes [114,115].

Some papers have also demonstrated the prognostic and clinical importance of the morning surge, though there is no definite agreement on how this parameter is calculated [116,117]. Usually the morning surge is obtained by calculating the difference between the BP values measured in the few minutes or hours following rising from bed in the morning and the last moments or hours before rising. An alternative approach focuses on the difference between the lowest BP value at night and the highest BP values observed in the morning after awakening [117].

Recently it has been proposed to analyze the first and last hours of the recording, during which the patient is in the hospital for fitting and removing the monitor, respectively. Indeed, it has been shown that elevation of BP in these periods, as compared to the rest of the day-time period, may be useful for diagnosis of white-coat hypertension [118]. An additional parameter recently described is the Ambulatory Arterial Stiffness Index (AASI). This parameter has been proposed to provide an indirect measure of arterial stiffness through the evaluation of the relationship between diastolic and systolic BP changes over the 24hours (119), and has been reported to carry relevant prognostic information. More recently, some caution has been suggested in its interpretation, as it seems to closely depend on the amplitude of nocturnal BP fall independently from the degree of arterial stiffness (120)

Non-invasive BP monitors also allow evaluation of BP and heart rate variabilities, though the value of such estimates is limited due to the discontinuous nature of BP measurements and to the fact that no reference values for these indices are yet available [23,121,122]. The parameters listed in Table 16 can be calculated.

Table 16. Analysis of BP variability from ABPM recordings.

- Frequency histograms, expressed as number or percentage of values at 10 mm Hg intervals
- Standard deviation of the 24h, day-time and night-time mean values [23,122]
- Weighted 24h Standard deviation [123]
- Variation coefficient of 24h, day-time and night-time values [23]
- Range of values over the 24h, day-time and night-time expressed as the maximal value minus the minimal value
- Day-night ratio of mean values
- Absolute and relative (%) day-night difference of standard deviations
- Cumulative sums of differences between mean 24h values and each individual measurement (cusums) [124]
- BP loads for day-time and night-time BP, i.e. percentage of BP values above normal reference value for the daytime (≥135-130/85 mm Hg) and night-time (≥ 120/70 mm Hg) periods [113]
- BP peaks, i.e. percentage of values above a given threshold

The 24h BP profile can also be analyzed by means of curve fitting techniques to obtain an easier description of circadian BP fluctuations. Different non-parametric methods can be employed. The advantage of these methods is that they do not make any assumption on the shape of the distribution of BP values. Therefore they can be employed either when the distribution is non-normal or when data are nominal or ordinal [125]. Caution should be exercised, however, in using these techniques because they can lead to excessive smoothing of BP profiles, due to the low and uneven sampling rate allowed by the presently available discontinuous BP monitors. Possible curve fitting methods are reported in Table 17.

Table 17. Curve fitting methods for analysis of ABPM.

- Linear interpolation (hourly averages)
- Cubic spline models (spline interpolation): it is based on a third-degree (cubic) polynomial fitting the BP curve through different knots which are arbitrarily chosen. It may lead to overmodeling of the BP profile [126]
- Cosinor analysis: it assumes that the 24h BP profile can be reduced to a single sym-metrical sine wave and does not take into account that BP profiles are multiphasic and asymmetrical [125,126].
- Fourier analysis (with 3 or 4 harmonics): this approach has to face the problems due to the occurrence of unevenly spaced measurements (different frequency of measures, artefacts) and to the low frequency of sampling allowed by the commonly available monitors [127,128]
- Square wave fitting: it models a 24h BP profile by a square wave and might be useful to identify day-time and night-time periods [129]
- Double logistic model (130).

3.2.2.4 Assessment of the effect of antihypertensive therapy

Assessment of the effect of a given antihypertensive drug may be useful for clinical purposes or for the evaluation of a new drug in a pharmacological trial [131]. When ABPM is used in these circumstances, care should be taken to standardize subjects' activities as well as the starting time of the recording.

BP recordings performed before and during treatment in a given subject can be compared in different ways: i) by computing the changes induced by treatment in the average 24h, day and night mean values; ii) by plotting the hourly BP changes from the time of the drug assumption (any time hourly BP values are considered, it should be taken into account that their reproducibility is lower than that of 24 hour mean values); iii) by calculating the peak and trough changes and the trough-to-peak ratio [132,133]; iv) by calculating the smoothness index [134,135].

As shown by Omboni et al. [132,133] the peak BP change induced by treatment should be computed by averaging the BP values of two adjacent hours selected between the 2nd and 8th hour from the time of the drug intake (where the maximal BP fall induced by treatment occurs) and by subtracting this average value from the average value obtained over the corresponding pretreatment period. The BP change at trough should correspond to the period between the 22nd and the 24th hour from the time of the drug intake (in case of drugs administered once a day). The trough-to-peak ratio should express the percentage of the peak effect of the drug which persists in the hours farthest from drug assumption. Such a quantification represents an arithmetic index of the duration of the antihypertensive effect of a drug and of the occurrence of a balance BP reduction over the 24h (Figure 3, panel A) [132,133].

Calculation of trough-to-peak ratio from ambulatory recordings has the main limitation of making use of a small portion of the 24h BP monitoring, thus inadequately reflecting the distribution of the antihypertensive effect over the 24h [133,137]. As reported by Rizzoni et al. [134] and Parati et al. [135], this limitation is overcome by the smoothness index obtained by dividing the average of the 24 hourly reductions in pressure induced by treatment by its standard deviations (Figure 3, panel B) [132,136].

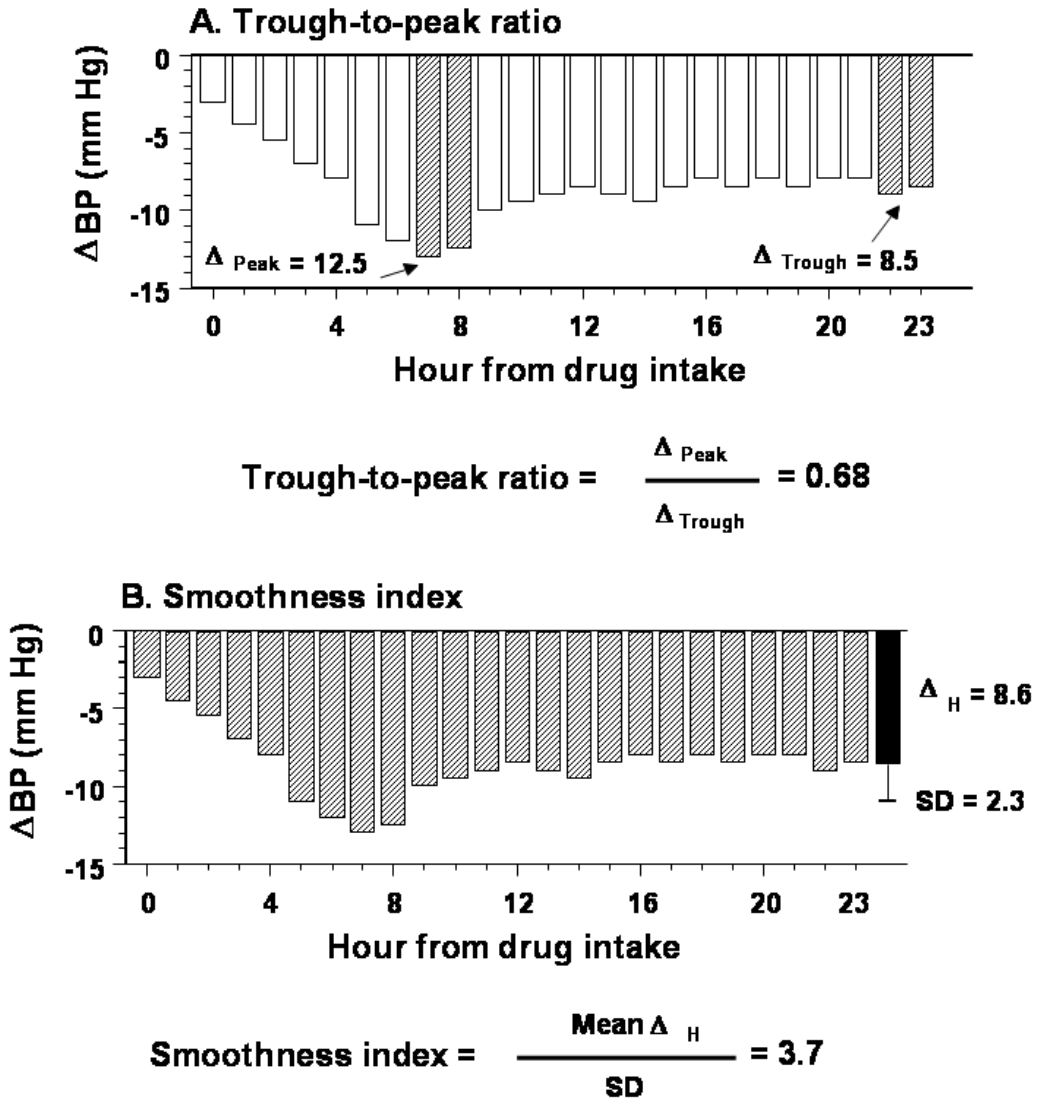


Figure 3. Example of calculation of the trough-to-peak ratio (panel A) and the smoothness index (panel B) [132-136].

3.2.2.5 Analysis of home BP recordings

The use of memory equipped automatic home BP monitors is now widely recommended. This reduces the observer bias and allows fully automatic analysis by software, as done with ambulatory recordings.

A basic summary of home BP recordings should include information listed in Table 18 [2,94,108,109].

Table 18. Basic SBPM summary.

• List of each single readings with date, hour and minute of occurrence
• A graphical display of single readings with BP and HR value referred to the vertical axis and date and time on the horizontal axis
• Maximal and minimal value occurring over the whole recording period, and time (date, hour and minute) of occurrence
• Average value of systolic and diastolic BP, and heart rate for the whole recording period
• Percentage of BP values above normal reference value, i.e. ≥135 mm Hg for systolic and ≥85 for diastolic BP
• Listing and linear graph of day-by-day averages

International guidelines suggest to exclude from the analysis data obtained from the first day of monitoring, because they are higher than subsequent values due to the learning phase of the patient [2,94,108,109]. It is also true that these values may be clinically useful to diagnose white-coat hypertension, as done for ambulatory BP recordings [138]. Additional analyses may be represented by:

i) Calculation of whole period standard deviation for BP and heart rate;

ii) Day-by-day difference between morning and evening BP and heart rate values or morning-to-evening ratio. This parameter may be useful to assess daily changes in BP and heart rate, as done for day-night changes with ambulatory monitoring;

iii) Calculation of the ratio between the morning change in home BP (trough effect measured 24h after drug intake) to the evening increase in home BP (plateau effect measured 12h after drug intake). Calculation of this parameter, which requires days of monitoring without treatment followed by days of monitoring under treatment, is similar to the trough-to-peak ratio and may be used for assessment of duration of antihypertensive drug treatment [139,140].

3.3 Indications and standards for proper use

3.3.1 ABPM

Indication and standard for proper use of ABPM are based on ESH recommendations for conventional, ambulatory and home BP measurement [2].

The conditions in which ABPM may be particularly useful are listed in Table 19 [141].

Table 19. Conditions in which ABPM may be useful [141].

- Patients with borderline hypertension
- Patients with suspected white-coat or masked hypertension
- Patients with nocturnal hypertension
- Patients with large short-term or long-term BP variability
- Elderly individuals
- Diabetic patients
- Pregnancy
- Episodic hypertension or (symptomatic) hypotension
- Research purposes
- Evaluation of new antihypertensive drugs in subjects with
  - *High office BP and low total CV risk*
  - *Marked discrepancy between BP values measured in the office and at home*
  - *Resistance to drug treatment*
  - *Suspected sleep apnoea*

It should be recalled, however, that in a number of conditions, also when defining the risk profile of the hypertensive patient, proper use of repeated office BP readings may offer information of comparable value as that obtained from ABPM. This does not detract from the clinical value of ABPM, which offers unique information on BP profiles, but supports the possibility that in several instances correct performance of accurate office BP readings may fit the clinical needs when managing routine hypertensive patients [141].

3.3.1.1 Fitting the monitor to the patient

The cuff of the monitor (standard adult size, width 13 cm, length 32 cm,) must be wrapped around the mid portion of the non-dominant upper arm. For large arms (circumference >32 cm) large cuffs (15 x 30-35 cm) should be used. If the dominant arm is not eligible (severe arm muscular hypertrophy, severe arm function impairment, hemiplegics or paraplegics, etc.) the dominant arm should be chosen. Before shifting arm, whenever possible the cuff bladder should be properly repositioned within the cuff layers in order to exert

optimal compression in correspondence of the brachial artery. When this is not possible, different cuffs should be used for right and left arms. For monitors based on the auscultatory technique special care should be taken in order to place the microphone appropriately over the brachial artery, above the antecubital fossa. If the microphone is not enclosed in the cuff, it should be taped on the skin in the proper position. If the microphone is enclosed in the cuff and cannot be taken out, the cuff itself should be fixed in the proper position by means of adhesive straps. Proper positioning of the arm cuff is important also in case of oscillometric measurements. In this case the bladder should be centred over the brachial artery and the cuff might be fixed to the skin by adhesive tape whenever the cuff undergoes easy displacements.

3.3.1.2 Frequency of measurements

Blood pressure should be measured at 15 minutes intervals to guarantee reliable information on hourly average BP values even in case of occasional artefactual readings. If BP variability has also to be assessed, the interval between measurements should not be longer than 10 minutes [121]. On the contrary, if subject's activities are standardized, a different frequency of readings should be chosen for day- and night-time. In this case the between-measurement interval might be 15 minutes during the day and 20 minutes during the night. In case of poor patient's compliance, the between-measurement interval at night could be as long as 30 minutes.

3.3.1.3 Starting time

When ABPM has to be repeated in the same subject, the time of beginning of the recording should be standardized (± 1h difference), to allow information on 24h BP profiles to be compared. Such a standardization is mandatory in case of multicentre trials, the preferable starting time being in the morning between 8:30 and 10:00, approximately 30 min before drug intake. The recommended duration of the recording is 25 hours to ensure a complete 24 hour BP profile to be obtained [142]. During the recording the visualization of BP values on the liquid crystal display should be disabled.

3.3.1.4 Accuracy of BP values in any given subject

In each subject before starting the recording BP values provided by the device should be tested by a trained operator (using a stethoscope) against a mercury column connected to the cuff of the monitor by a Y tube. Two measurements should be taken sequentially at 2 min intervals in the sitting position, followed by other two measurements in the upright position, after 2 min standing. If a difference greater than ±10 mm Hg and ±5

mm Hg (for systolic and diastolic BP respectively) between simultaneous automatic and observer's readings is found, the cuff and/or the microphone should be repositioned and then a new test should be performed. If the discrepancy between auscultatory and automatic readings still persists, this means that ambulatory BP recording cannot be accurately performed in that subject. Whenever possible, however, a different device should be employed. The comparison between auscultatory and automatic measurements should be performed also at the end of the recording, in order to exclude errors due to displacement of the cuff during the monitoring period. The accuracy of the non-invasive BP transducer should be periodically checked against a mercury column. The investigator should report to the manufacturer the occurrence of any significant discrepancy between the value given by the transducer and those read on the mercury column. Proper functioning of the microphone should also be frequently verified.

3.3.1.5 Instructions to the patient

The patient should be instructed about the procedures to follow during each automatic BP measurement and in particular he or she should be asked to keep the arm still and to remain motionless at the time of automatic cuff inflations. The patient has to be informed about the general features of the device and should be motivated and actively involved in order to obtain a reliable recording. The patient is not allowed to take a shower during the recording. He or she should also be advised to avoid unusual activities and to take special care of the monitor, to prevent any accidental damage. To this purpose the patient should wear the monitor bound around his/her waist by a belt not only during the day, but also during the night.

The patient is requested to keep a diary of his/her main activities [143,144]. In such a diary the patient will report at least the following data:

i) Time of sleep;

ii) Time of awakening;

iii) Time of getting up from bed;

iv) Other bed times (e.g. siesta);

v) Time of main meals (indicating whether a given meal is light or heavy);

vi) Time and features of behavioural and occupational activities;

vii) Occurrence of symptoms (in these instances the patients should be advised to take additional measurements);

viii) Time of therapy (drug intake).

Suggestion for the proper use of ABPM are summarized in Table 20.

Table 20. Proper use of an ambulatory BP monitor [2].

- 15–30 min needed for fitting and setup
- Relax patient in a quiet room
- Enter patient's details into monitor
- Measure BP in both arms
  - If SBP difference ≤20 mm Hg and/or DBP difference ≤10 mm Hg, use non-dominant arm
  - If SBP difference >20 mm Hg and/or DBP difference >10 mm Hg, use arm with greater pressure
- Select appropriate cuff
- Select frequency of measurement (usually every 15-20 min during day and every 30 min at night, ideally 15 min over the 24 hours)
- Inactivate liquid crystal display
- Give patient written instructions and a diary card
- Instruct patient how to remove and inactivate monitor after 24 h

3.3.2 SBPM

The recommendations for SBPM are similar to those for BP measurement in general [2,94], but there are some points which should be highlighted:

i) SBPM should be performed under medical supervision;

ii) There should be a 5 min period of rest before measurement;

iii) The cuff of the measuring device must be kept at the level of the heart on the arm with the highest BP;

iv) For commencement phase, treatment phase and follow-up phase, SBPM should be performed for at least 7 workdays with duplicate morning and evening measurements, and the first day should be discarded; a minimum of 12 measurements and even more measurements up to 24-25 are desirable for an accurate diagnosis;

v) SBPM should be carried out in the week preceding the visit to the physician's office;

vi) In the between visits intervals, duplicate BP measurements taken once per week appear to be appropriate for long-term SBPM in controlled hypertensives;

vii) SBPM measurements may be performed more frequently if the trend in the measurements is not homogeneous, and a high variability between measurements is present;

viii) Patients' diaries may be unreliable, and memory equipped devices are preferred.

3.3.2.1 Use in primary care

SBPM should be considered by primary care physicians just as a tool to gather more detailed information on BP control and on patient's compliance to therapy. Thus, SBPM should not be performed by patients on their own initiative out of medical control, which also implies the risk of using unreliable devices bought on the free market.

3.3.2.2 Frequency and timing of SBPM

There are no precise indications on the frequency of SBPM. Clearly, the measurement frequency may vary according to the variability of BP or the information that is being sought [145]. Morning and evening values may differ to a larger extent in treated than in untreated individuals, especially in subjects taking complex therapies [146]. Although no precise criteria are available on optimal timing and frequency of measurements, the recommendations of the German Hypertension League [145] and of the ESH [2], recently updated (Parati G et al., J Hypertension 2008) may be followed.

In untreated patients, there should be an initial measurement period with two readings taken in the morning and in the evening at predefined times (6.00-9.00 and 18.00-21.00), over the week preceding the visit to the physician's office. The average of the 7-day values is desirable for an accurate diagnosis. As habituation to measurement may occur also for SBPM, first-day readings should be excluded from the final analysis [147].

Once treatment is initiated, SBPM should be used exactly as in the pre-treatment phase and the readings should preferably be taken at trough, i.e. before drug intake in case of once daily administration [145].

Once good BP control is achieved (follow-up phase), duplicate HBP measurements taken once per week, and for 7 workdays in the last days before each visit to the physician's office, are indicated. If large oscillations of BP are recorded, or hypertension is still poorly controlled, more measurements are needed. The minimum number of measurements performed in each period should be 12, but a desiderable number is 24-25 [145].

3.3.2.3 Factors affecting SBPM reliability

Several factors may affect SBPM reliability. Self-reported BP readings are often unreliable as demonstrated by studies which compared the BP values reported by patients in their logbooks with those stored in the device memory [148]. Several patients tend to underreport their BP readings or to eliminate measurements that are considered outside the usual trend. Memory-equipped devices have the potential to reduce observer prejudice. However, these devices are more expensive, and need to be connected with a printer or a personal computer.

Most SBPM devices are still purchased without doctor's advice and patients are not trained for their proper use. It should also be pointed out that many doctors are unaware of the accuracy and reliability of the equipment being used by their patients, and that they themselves ignore the state of the market for automated devices [149]. Doctors are expected to train their patients on the use of SBPM equipment, on the BP measuring procedure, on possible BP variations in response to psychological stimuli, on need for maintenance of the equipment, and also more generally on the features of arterial hypertension and on its management. Printed information should be made available for those patients who are anxious to know more about hypertension and self measurement [26,28,29,150].

BP varies with the seasons, being higher in winter and lower in summer, and these variations should be considered in the interpretation of SBPM measurements in individual patients [151].

Few patients are unable to perform SBPM, but it may be unsuitable for patients with physical problems, or mental disabilities, if there is no familiar support helping them with the measurements. SBPM is most suited to hypertensive patients who wish to contribute to their own management.

3.4 Normalcy limits

As the relationship between BP and cardiovascular risk is continuous, every partition value between normal and abnormal BP is arbitrary. However, for practical reasons operational thresholds must be adopted to decide on whether antihypertensive treatment should be started.

3.4.1 ABPM

Different methodological approaches have been used for the determination of threshold values, which led to inconsistent results (see point 3.5.2) [152-155]. The only general agreement is that the thresholds currently applicable for conventional sphygmomanometry cannot be extrapolated to automated measurements. The normalcy limit for ABPM shown in Table 21 is derived from statistical considerations in a large population database comprising some 5,422 normotensive and untreated hypertensive individuals [153,155]. Limits compatible with high day-time and 24h systolic BP are 5 mmHg higher, as suggested by the recent 2007 ESH/ESC Guidelines.

Table 21. Diagnostic thresholds for ABPM in adults [2,72].

Thresholds compatible with normal ambulatory blood pressure	
24-hour	<125/80 mm Hg
Awake or day-time	<130/85 mm Hg
Asleep or night-time	<120/70 mm Hg
Thresholds compatible with high ambulatory blood pressure	
24-hour	≥130/80 mm Hg
Awake or day-time	≥135/85 mm Hg
Asleep or night-time	≥120/70 mm Hg

3.4.2 SBPM

The 135/85 mm Hg threshold recently proposed by the Working Group of the ESH and by the 2007 ESH/ESC Guidelines for hypertension under SBPM is the same as that for mean day-time ABPM (Table 22) [72,156-158]. Whether this recommendation is correct will be verified in future studies, such as the ongoing HOMED-BP (Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure) study [159], which aims to determine the goal BP levels in patients monitoring their BP values using automated devices.

Table 22. Diagnostic thresholds for SBPM [2,72].

- Data from longitudinal studies limited
- Reference values are derived principally from statistical evaluation of databases
- ≥135/85 mm Hg may be considered as compatible with hypertension
- <130/85 mm Hg may be considered as normal values
- <120/80 mm Hg may be considered as optimal values
- SBPM needs to be further evaluated in prospective outcome studies

Support for the normal and abnormal demarcation values is based on firm evidence from a number of studies. Evidence is not yet available to make recommendations for the intermediate pressure ranges between "normal" and "abnormal", or for recommendations regarding the achievement of lower BP targets in high risk patients, as made for office BP readings. It must however be emphasized that the suggested values are only a guide to "normality" and that lower "optimal" values may be more appropriate in patients whose total risk-factor profile is high, and in whom there is concomitant disease, such as diabetes mellitus [2].

3.5 Application in population studies

3.5.1 Advantages of ABPM

Table 23 lists main advantages and limitations of ABPM. A body of evidence indicates that ABPM is a better predictor of outcome than CBPM [2]. However, despite considerable supportive data, the role of ABPM is often restricted to certain clinical situations such as suspected white-coat hypertension or resistant hypertension. For reasons of cost and the complexity of the technique, ABPM has been rarely employed in population studies. However, the few populations studied with ABPM have provided important data on many controversial issues. The main reason for assessing ambulatory BP across a general population or a sample of selected individuals is to provide an answer to the following main questions: can we identify normal limits for ambulatory BP? Does ambulatory BP have a greater prognostic value for cardiovascular events than conventional BP? Can ambulatory BP be profitably used for evaluating the effect of antihypertensive therapy in treated subjects?

Table 23. Advantages and limitations of ABPM [160] .

Advantages	Limitations
• No observer bias and digit preference	• Possible inaccuracy of automated BP readings, particularly in true ambulatory conditions
• Large number of BP values available over 24h in daily life	• Interference with patient's daily activities
• No alerting reaction to BP automated measurements (no white-coat hypertension)	• Quality of sleep affected to a greater or lesser degree
• Higher reproducibility of 24h average BP	• Limited reproducibility of hourly BP values
• No placebo effect	• Reference "normal" ambulatory BP values still under debate
• Allows assessment of 24h, day-time, night-time and hourly BP	• Need for more evidence on prognostic value of different ABPM parameters
• Allows assessment of BP variability (although limited with discontinuous BP monitoring)	• High costs
• Allows assessment of day-night BP changes ("dippers", "non dippers", "extreme dippers"), better if performed over repeated recordings	
• 24h Average BP more closely related to target-organ damage of hypertension	
• Superior prognostic value of 24h, day-time or night-time average BP	
• Allows assessment of effectiveness and time distribution of BP control by treatment over 24h, also through mathematical indices (trough:peak ratio and Smoothness Index)	

3.5.2 Conventional versus ambulatory BP in cross-sectional analyses

There is general agreement that ambulatory BP is lower than conventional BP and that the between-method difference increases for increasing values of conventional BP [152,153]. Ambulatory BP is distributed over a narrower range than conventional BP, and the distribution is less skewed [152,153]. The correlation coefficients between conventional and ambulatory BP may vary according to the conventional BP range of the population studied and are reported not to be higher than 0.7. [153,154]. This indicates that conventional BP can only partially predict BP recorded during daily life. These findings imply that the limits of normality for ambulatory BP should be lower than those established long ago for conventional BP. However, how to identify the normal ambulatory BP limits has been a matter for dispute for long and the problem is still unresolved. This is proved by the different ambulatory BP normal limits reported in the official document of different Scientific Societies [72,92]. Initially, mean +2 standard deviations day-time or 24h ambulatory BP

measured in normotensive populations was taken as the upper normalcy limit for ambulatory BP [155,158]. However, this procedure was subject to a selection bias because subjects were defined as normotensive on the basis of conventional BP and the limits of normality were identified with a statistical method rather than from the relationship between ambulatory BP and cardiovascular risk. Another method uses correspondence criteria, which derives ambulatory BP levels corresponding to a casual BP of 140/90 mm Hg or 160/95 mm Hg [153,161,162]. Such values were obtained in the Ohasama study [156], the PAMELA study [153], the Belgian population study [157] and others. The relationship between conventional and ambulatory BP has not, however, been well enough characterized to obtain sufficiently accurate corresponding values (the correlation coefficient of the relationship between conventional and ambulatory BP being approximately 0.5). Also the method based on the regression line of ambulatory BP on conventional BP presents some limitations and is not suitable for clinical practice. Different regressions should be drawn for men versus women, for elderly versus younger individuals, for normotensive vs. hypertensive subjects etc. On the basis of the experience collected from studies carried out in several populations, which demonstrated that day-time systolic BP is on average 10-15 mm Hg lower than systolic conventional BP, and that day-time diastolic BP is on average 10-15 mm Hg lower than diastolic conventional BP, the European Working Group on BP measurement of the ESH has established that the upper normal limit of ABPM is an average day-time ABPM of less than 130-135 mm Hg systolic and 85 mm Hg diastolic [2,72]. However, lower levels are advocated for high-risk groups, such as diabetic patients (<130/80 mm Hg). Moreover, day-time ambulatory BP values ≥140/90 mm Hg are defined as "probably abnormal". This position overcomes the problem of defining a "normal" ambulatory BP, as the above intervals can be considered as operational thresholds for clinical practice rather than true limits of normality. The 130-135/85 mm Hg threshold level for day-time ambulatory BP is close to that identified in a Japanese general population studied with ABPM [163]. In 1,542 subjects 40 years of age or older, Okubo et al. [163] found a J relationship between ambulatory BP and mortality. These authors identified the following reference values as the optimal BP ranges that predict the best prognosis: 120 to 133 mm Hg for systolic BP and 65 to 78 mm Hg for diastolic BP. 24h ambulatory BP values >134/79 mm Hg and <119/64 mm Hg were related to increased risks for cardiovascular and noncardiovascular mortality, respectively. Using a similar approach, Kikuya et al recently worked out an outcome driven reference frame for ABPM drawn from 5562 subjects enrolled in four population studies [164].

3.5.3 Circadian BP variation

A higher BP level during the day and a lower one at night is usually observed both in subjects with normotension and in those with essential hypertension. Elderly individuals have been reported to have an attenuation of the night-time BP fall [153,165]. Under several pathophysiological conditions, however, circadian BP variation is diminished, even in patients with essential hypertension, sometimes being inverted to show a nocturnal elevation of BP [166]. Subjects who show normal nocturnal dipping (night-time BP fall >10% of day-time level) are called dippers, whereas those with diminished nocturnal dipping or a nocturnal elevation of BP (inverted dippers) are classified as non-dippers. Kario et al. [167] have used the term "extreme dipper" for subjects with a nocturnal dip of 20% or more of diurnal BP [167]. The magnitude of the nocturnal BP fall increases with the increase in diurnal BP level. Calculation of the upper normal limits for night-time ambulatory BP has met with the same problems encountered for 24h or day-time BP. According to the Working Group of the ESH, a normal night-time ambulatory BP should be lower than 120/70 mm Hg [2,72]. Several studies have shown that blunted BP fall at night predicts a higher rate of cardiovascular events in future life [167-170]. In the general population of the Ohasama study, the incidence of stroke in dippers receiving antihypertensive treatment was significantly lower than that seen in treated non-dippers [169] as well as in treated extreme dippers [171]. In elderly women, the severity of periventricular hyperintensity increased with an increase in amplitude of the nocturnal decline [170]. The trend in cardiovascular mortality was, however, different. A significantly higher relative hazard was observed in non-dippers and inverted dippers [172]. These results indicate that exaggerated nocturnal dipping in elderly individuals may cause cerebrovascular lesions and that non-dipping mediates cardiovascular mortality.

3.5.4 BP variability

ABPM provides 50-100 measurements during the course of a day which enables a wider scope of parameters to be derived from the data set. Among these, short term variability has attracted the interest of many investigators, but whether this parameter per se has any prognostic significance in the general population is still a matter for debate. In fact, the prognostic significance of BP variability has scarcely been studied in the general population, whereas the poor prognosis of subjects with reduced heart rate variability has, however,

been widely recognized in several types of cardiovascular disease [173]. In a few cross-sectional analyses and longitudinal analyses in cohort studies, BP variability was found to be a predictor of target organ damage and cardiovascular events [122,174,175]. BP variability was studied in the general population of the Ohasama Study, in which BP and heart rate readings were obtained at 30 min intervals [173]. The subjects were then followed for up to 10 years, and therefore the Authors could examine the prognostic significance of BP variability, heart rate variability and combinations of these variables. The variability of BP and heart rate was estimated as the standard deviation of the day-time or night-time average. There was a significant linear relationship between day-time systolic ambulatory BP variability and the risk of cardiovascular mortality. In addition, cardiovascular mortality increased linearly with the decrease in day-time and the night-time heart rate variability suggesting that BP variability and heart rate variability are associated with cardiovascular mortality independently of each other. Subjects whose day-time systolic ambulatory BP variability was more than 15.8 mm Hg and whose day-time heart rate variability was less than 7.2 bpm had an extremely high relative hazard for cardiovascular mortality. Furthermore, the combination of high BP variability and low heart rate variability increased cardiovascular mortality risk synergistically. A significant correlation between an enhanced BP variability and presence of target organ damage was found also in the population of the PAMELA study, when focusing on the so-called residual BP variability after removal of the main oscillatory components [176].

3.5.5 ABPM for the detection of masked hypertension

One of the main goals of ABPM is to identify subjects with white-coat hypertension (high conventional BP and low ambulatory BP) in order to determine the appropriate management on the ground that subjects with white-coat hypertension are at low risk so that antihypertensive treatment could be deferred [177]. Much less is known on the opposite condition, masked hypertension also referred to as isolated ambulatory hypertension [178-180]. This definition applies to patients in whom conventional BP is low but ambulatory BP is elevated, a condition which remains hidden until ABPM is performed. Several population studies have compared conventional and ambulatory BPs [152,153]. Some have shown day-time pressures to be a little higher than conventional BPs, whereas others have found the reverse. Two recent reports showed that masked hypertension diagnosed either with ABPM [181] or self BP measurement [182] was a significant

predictor of cardiovascular morbidity in elderly individuals. The problem for clinical practice is how to identify these patients, as ABPM will never be performed in subjects who appear to be normotensive at conventional BP assessment. In fact, the available information on masked hypertension comes from studies performed in large samples which included also subjects with normal conventional BP. According to a recent document of the Working Group of the ESH, the phenomenon should be suspected in individuals who have had an increased conventional BP at some time which would justify ABPM assessment in these subjects [2]. However, the prevalence of masked hypertension in subjects with transiently elevated BP and its clinical significance in youth or adulthood is still unknown. Recently, one such analysis was performed within the frame of the HARVEST, a multicentre Study in young subjects with stage 1 hypertension at low cardiovascular risk [183]. This study showed that in 28% of these subjects conventional BP declined to below normal levels during a 3 month observation period. However, roughly 50% of these subjects exhibited high ambulatory BP at 24h monitoring. During a 6-year long follow-up the number of subjects who developed sustained hypertension on multiple conventional BP readings was much higher among the subjects with masked hypertension (35%) than in those with normal conventional and ambulatory BP at baseline (19%), and in an adjusted proportional hazard model, masked hypertension status was associated with a 2.2 increase in the risk of reaching the end point in comparison with the normotensive subjects. These results indicate that among subjects screened for stage 1 hypertension, individuals with masked hypertension after 3 months of observation have increased risk of developing sustained hypertension in later life compared to subjects in whom both clinic and ambulatory BPs are normal. The results obtained in the PAMELA Study are in line with those from the HARVEST. Sega et al. in 3,200 subjects from a general population found that 9% could be defined as masked hypertensives [184]. The left ventricular mass index was higher in the masked hypertensives (91.2 g/m^2) than in the true normotensives (79.4 g/m^2) and similar to the true hypertensives (94.2 g/m^2). Whether masked hypertensives are really at increased risk of cardiovascular morbidity remains to be determined in future prospective studies in large samples.

A major issue concerns the prevalence and the determinants of masked hypertension. According to the PAMELA study ambulatory BP shows much less increase with age than conventional BP [157]. In a Danish study, 86% of men 42 years of age had day-time pressures higher than conventional BP, whereas this was true of only 51% at the age of 72 years [154]. The white-coat effect (the difference between the clinic and

ambulatory pressure) is hence more marked in older people, and because masked hypertension is equivalent to a negative white-coat effect, it is reasonable to assume that masked hypertension would be less prevalent with increasing age. According to Selenta et al. [185], 23% of subjects in a sample of normal volunteers had masked hypertension, defined as a day-time BP >135/85 mm Hg [185]. As stated above, the prevalence was much lower in the PAMELA study, but in that study the limit of normality for ambulatory BP was lower (125/79 mm Hg for 24h ambulatory BP). Pickering et al. [179] found that 13.5% of the subjects in the Cornell Worksite study had masked hypertension, defined as a day-time ambulatory diastolic pressure >85 mm Hg and a clinic pressure <85 mm Hg [186]. In the Ohasama study [187], Imai et al. reported that 10.2% of subjects with normal screening conventional BP had ambulatory pressures that were in the "borderline hypertensive" range (>133/78 mm Hg for 24h average) and another 3.2% in the definitely hypertensive range (24h BP >144/85 mm Hg). Finally, among the stage 1 hypertensives of the HARVEST study, 14% had masked hypertension after 3 months of observations [183]. Overall, the above data show that although the percentage of subjects with masked hypertension is relatively low (10-15%), this number applies to the whole adult population. One main goal of ABPM in population studies in the future will be the identification of subjects with masked hypertension to better define their cardiovascular risk.

3.5.6 BP control in the hypertensive population

Much emphasis has been given in recent years to poor conventional BP control in treated hypertensive subjects all over the world. Only a small percentage of the hypertensive population has conventional BP values <140/90 mm Hg, ranging from 2.4% in Zaire to 27.4% in the United States [72,92]. These figures refer to surveys where BP was measured by random zero or ordinary mercury sphygmomanometers. These disappointing data could partially reflect the inability of BP measured in the office to actually reflect the usual patient's BP and ABPM could provide more objective data on the actual BP control in treated hypertensive subjects. Results of population studies with ABPM, however, have confirmed the results obtained with conventional BP measurement. In fact, assessment of BP control with the use of ABPM provided similar results to those observed for conventional BP measurement. In a survey [188] in which BP was recorded by ambulatory monitors, Mancia et al. showed that both among young individuals and older subjects only a few had good ambulatory BP control. In a recent study, Pannarale et al. [189] found adequate

ambulatory BP control in 47% of patients in primary care and 42.4% of patients in secondary care. Female sex was associated with a higher risk of inadequate BP control of about 50%. Furthermore, patients identified by ABPM as adequately controlled were not the same patients who were considered responders or non-responders to treatment by their physicians on the basis of conventional BP. These findings confirm previous observations on patients with false treatment-resistant hypertension [190] and identify quite a few false responders to treatment. The two above studies indicate that poor conventional BP control in populations is not due to the alerting reaction produced by conventional BP measurement by the doctor but rather reflects poor BP control in daily life. ABPM appears as a valuable tool to ascertain actual BP control in the hypertensive population.

3.5.7 Ambulatory and Home heart rate

The prognostic significance of resting heart rate has recently been confirmed in several large-scale cohort studies [191]. As mentioned above, heart rate is automatically available from ABPM and could be used together with BP to build up the cardiovascular risk profile of an individual. However, the prognostic value of 24h heart rate for cardiovascular mortality has been investigated only in a few studies. Of relevance are the results obtained in the elderly subjects with systolic hypertension from the Syst-Eur study, in which average 24h heart rate emerged as a significant predictor of subsequent mortality [192]. However, the significant relationship between high ambulatory heart rate and mortality disappeared after the data were adjusted for clinic heart rate. The prognostic significance of heart rate obtained from home BP monitoring was investigated in the frame of the Ohasama study [193]. Simultaneous measurements of BP and heart rate at home were obtained in 1,500 subjects over 40 years of age for 21 days. The risk of cardiovascular mortality increased linearly with increase in heart rate even after adjusting for BP level, and, surprisingly, the risk related to fast heart rate was even greater than that related to high BP. In spite of the evidence stemming from studies performed with either clinic or ambulatory heart rate, the clinical role of heart rate is still overlooked by clinicians. It is difficult to understand why doctors do not take into account this valuable clinical variable and it is advisable that in future population studies with ABPM also the prognostic information of 24h heart rate is used.

3.5.8 Advantages and limitations of ABPM in population studies

If ambulatory BP measurement becomes the gold standard because of its high predictive power and reliability, it could also be used for population screening. The exclusion of false-negative and false-positive cases by means of ABPM could result in higher cost-effectiveness for screening and treatment of hypertension. Obviously, ABPM can not be used as a diagnostic tool for screening the general population but it could be used in specific subsets at higher risks to identify the portion of subjects with high ambulatory BP. One clear example is the detection of masked hypertension in subjects with transiently elevated conventional BP level [179]. As stated above, the results of a number of longitudinal studies suggest that ambulatory BP is a more sensitive predictor of cardiovascular outcome than conventional measurement. However, this assumption does not take into account the issue of the number of conventional BP readings which have been used for the comparison with ambulatory BP in those studies. General populations can hardly be assessed with repeated conventional BP measurements as normotensive subjects do not come spontaneously to the doctor. Most hypertensive subjects require antihypertensive treatment within a short period of time and they cannot be followed for long in baseline conditions. As a result, in all available population studies in which the predictive value for cardiovascular events of conventional BP versus ambulatory BP was explored, conventional BP was calculated as the mean of a maximum of six readings collected over a short period of time. The results of an analysis performed in a large sample of young stage 1 hypertensive subjects enrolled in the HARVEST study stress the importance of collecting many conventional BP readings for a better definition of the individual risk [183]. When baseline ambulatory BP was compared with the mean of six conventional BP readings taken during two baseline visits, the prediction of development of sustained hypertension during the following 5 years was greater for ambulatory than conventional BP, in agreement with most studies. However, if the mean of 18 conventional BP readings obtained during the first 6 months of observation was used, the prediction was greater for conventional BP. Ambulatory BP still was a significant predictor of outcome but its role appeared marginal in comparison with that of conventional BP. This indicates that the average of several clinical measurements obtained during different days may provide more precise prognostic information than a larger number of readings obtained during only one day. Obviously, one such attitude is possible only in subjects at low cardiovascular risk and mildly elevated BP levels in whom antihypertensive treatment can be deferred. This finding brings

up the issue of the high cost related to the use of ABPM in population studies. Furthermore, limited compliance of the recruited subjects may raise some doubts about the representativeness of a given study sample for the population as a whole [194]. Sources of variability for the experimental conditions can be the different environmental situations in which ABPM is performed. Results from the HARVEST study showed that not only mean 24h ambulatory BP but also the day-night BP rhythm may vary according to the season in which the ABPM is performed [195]. Cold temperature seems to increase particularly day-time BP with little or no effect on night-time pressure. To overcome this problem, ABPMs in population studies should be distributed all over the year and be equally frequent during cold and hot seasons. This also hinders the possibility of extrapolating data obtained in one Country to worldwide. Other potential sources of errors may be the different rate of subsets within a given population. Smoking, alcohol and coffee use, oestro-progesterone use in women, sedentary habits, etc. have a strong impact on the 24h BP rhythm and level thereby limiting the possibility of generalizing the results obtained in a single sample [196,197]. Finally, the inappropriate application of the ABPM device or poor patient's compliance with the instructions about how the apparatus should be used can lead to faulty recordings. Since the beginning of ABPM, it appeared that some subjects had a large proportion of outlying readings which were unlikely to be accurate. Artefactual readings are often difficult to recognize because they can be included within the patient's usual BP range. As mentioned above, an important source of failed recordings is displacement of the cuff or microphone during the monitoring period [198]. This problem can arise especially in obese subjects. A deterioration in the performance of ABPM devices has been reported in subjects with larger arms in spite of correct cuff use [199], this occurring with either the auscultatory or the oscillometric method. One should therefore be aware that the performance of an ABPM device tends to decrease in obese persons, who should thus be carefully checked using standard sphygmomanometry before they are considered eligible for ABPM. These issues are often overlooked by health-care providers when using ABPM devices, leading to failed 24h recordings.

3.6 Clinical indications and use

3.6.1 Clinical indications for ABPM

ABPM allows a large number of BP measurements to be performed over a period of time, usually the 24h period. These measurements can be plotted to give a profile of BP behaviour. The average 24h value for

ABPM is commonly used to govern decisions, however the clinical use of ABPM has enabled a more clear identification of a number of phenomena in hypertension in respect with other methods of BP measurement [200]. Conditions in which ABPM is indicated are listed in Table 24.

Table 24. Clinical indications to ABPM [2].

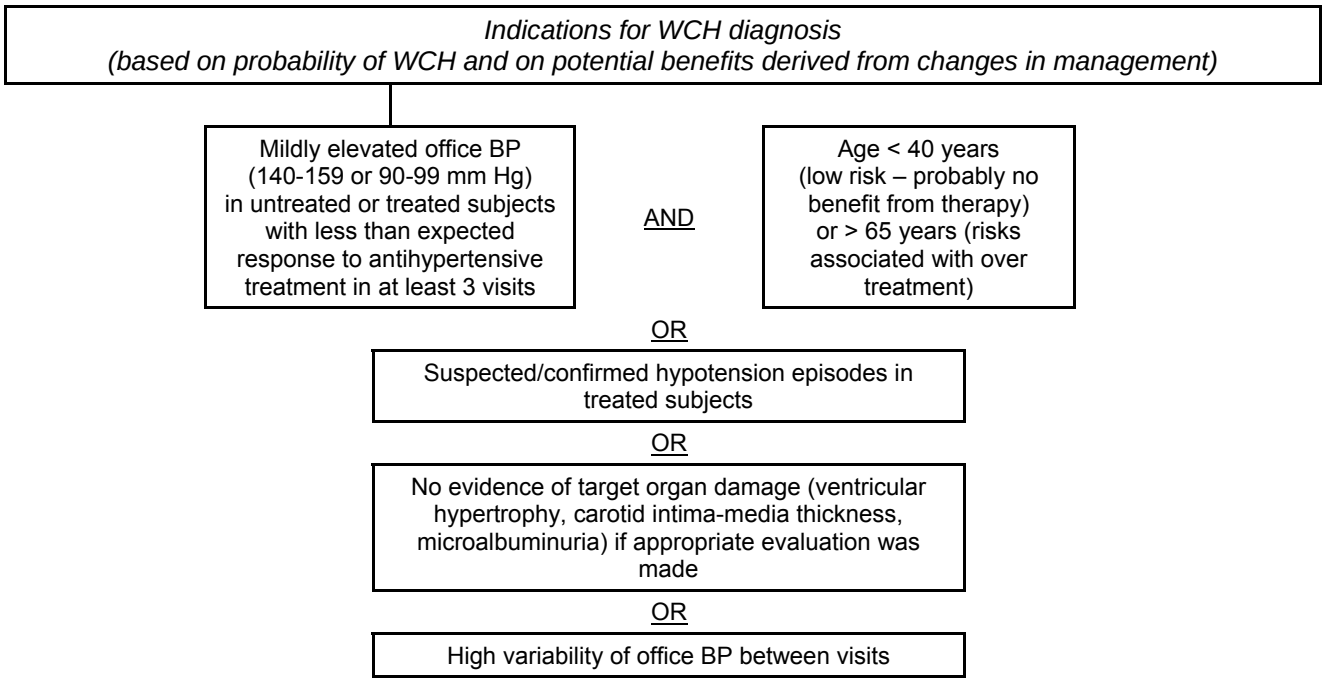
• Suspected white-coat hypertension
• Suspected masked hypertension
• Suspected nocturnal hypertension
• Resistant hypertension
• Elderly patient
• As a guide to antihypertensive drug treatment
• Diabetes
• Hypertension during pregnancy
• Evaluation of hypotension or autonomic failure

3.6.1.1 Patients with suspected white-coat hypertension

White-coat hypertension is a condition characterized by elevated BP in a clinic environment and by normal out of clinic BP levels. This implies that office or clinic readings may lead to errors in diagnosing hypertension and in assessing the effects of antihypertensive treatment. Because the difference between clinic and ambulatory or home BP bears a limited association with the BP rise induced by an alerting reaction during consultation (see point 1.2.2), it has been suggested that the alternative term "isolated office or clinic hypertension" should be used [201]. The most common definition of white-coat or isolated office hypertension is the finding of an office or clinic BP equal or greater than 140/90 mm Hg on at least three occasions, with normal ABPM measurements throughout the 24h period [118]. The prevalence of white-coat hypertension depends on the cut off values of office and ambulatory BP used for its definition, and may range from 10 to 15% of patients in whom ABPM has been prescribed, with a prevalence in the general population probably around 10% [39,184]. The clinical importance of white-coat hypertension remains a debated issue. Available data, including some event-based cohort studies [202-204], suggest that individuals

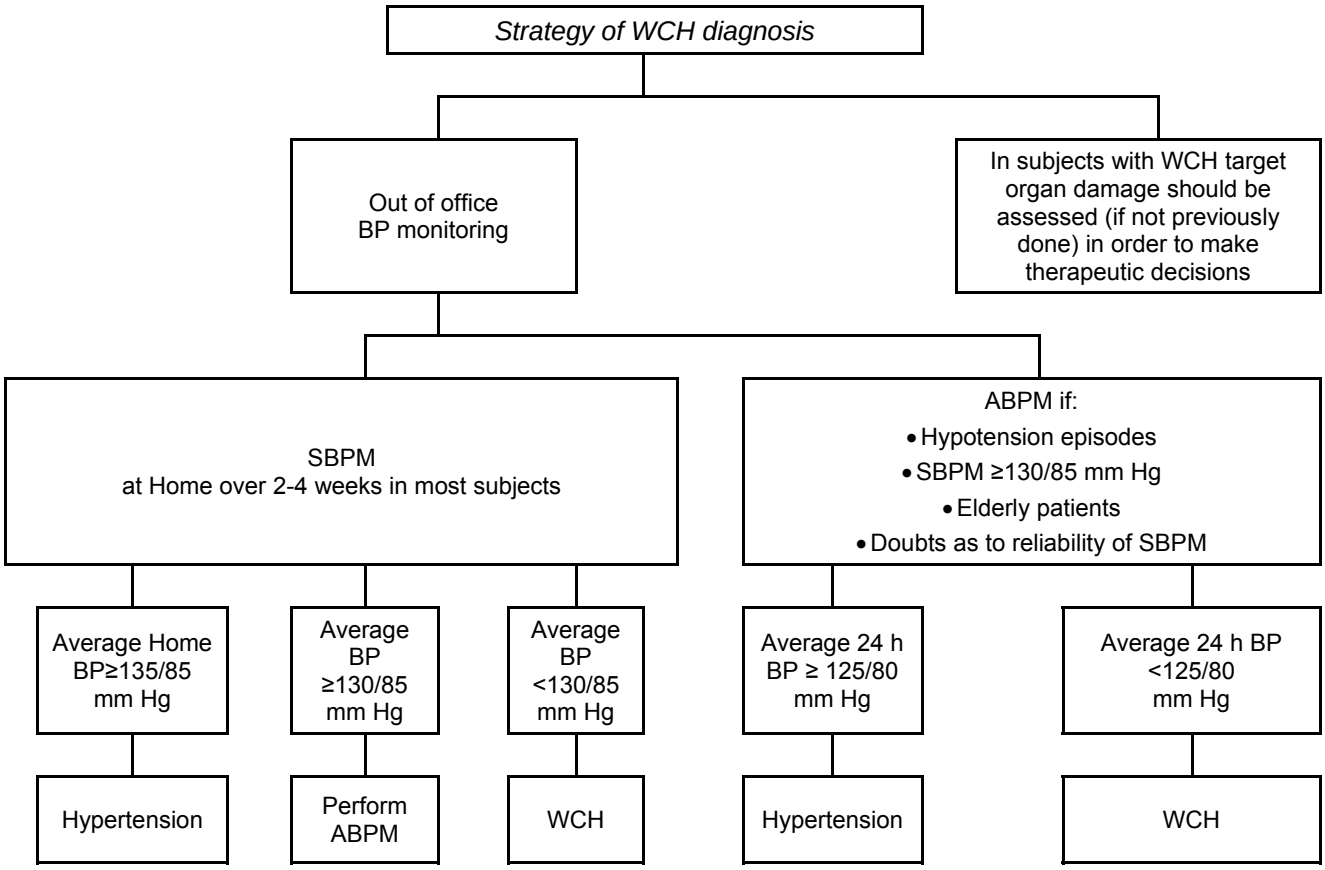
with increased BP on CBPM, who have normal average day-time pressures on ABPM, have a risk of major cardiovascular events comparable to that of clinically normotensive individuals and less than that of individuals with increased day-time pressures. Only did a few studies suggest that patients with white-coat hypertension may be at increased risk, albeit a smaller risk than patients with sustained hypertension [118,184,205]. However, a recent report in a large sample followed for a long period of time has shown that subjects with white-coat hypertension have a risk of stroke comparable to that of subjects with sustained hypertension, casting some doubt on the innocence of this condition. In any case, if patients with white-coat hypertension are at risk, the risk is smaller than that for patients with sustained hypertension. Several hypertension guidelines [72,92,206-208] indicate that suspected white-coat hypertension is an indication for ABPM, but they do not provide any clear suggestion on how to suspect white-coat hypertension. An analysis of data from a number of studies [39,209-211] indicate that, in untreated or treated persons with essential hypertension, the probability of white-coat hypertension increases in those with mild increase in office BP (office systolic BP 140–159 mm Hg or diastolic BP 90-99 mm Hg), aged <40 or >65 years (Table 25). Because of the above controversy on its clinical relevance, unnecessary drug treatment may be avoided or suspended, and subjects affected by this condition should be included in a longitudinal follow-up. People with white-coat hypertension should have the diagnosis confirmed in 3–6 months and be followed at yearly intervals with ABPM in order to detect if and when sustained hypertension occurs [212].

Table 25. Management of white coat hypertension (WCH)



WHC must be reasonably excluded in the following cases:

- In subjects with multiple cardiovascular risk and with high cardiovascular risk (≥10% within 10 years)
- Target organ damage
- Associated conditions (diabetes, congestive heart failure, coronary heart disease, history of stroke/transient ischemic attack) unless a possibility of excessive treatment exists



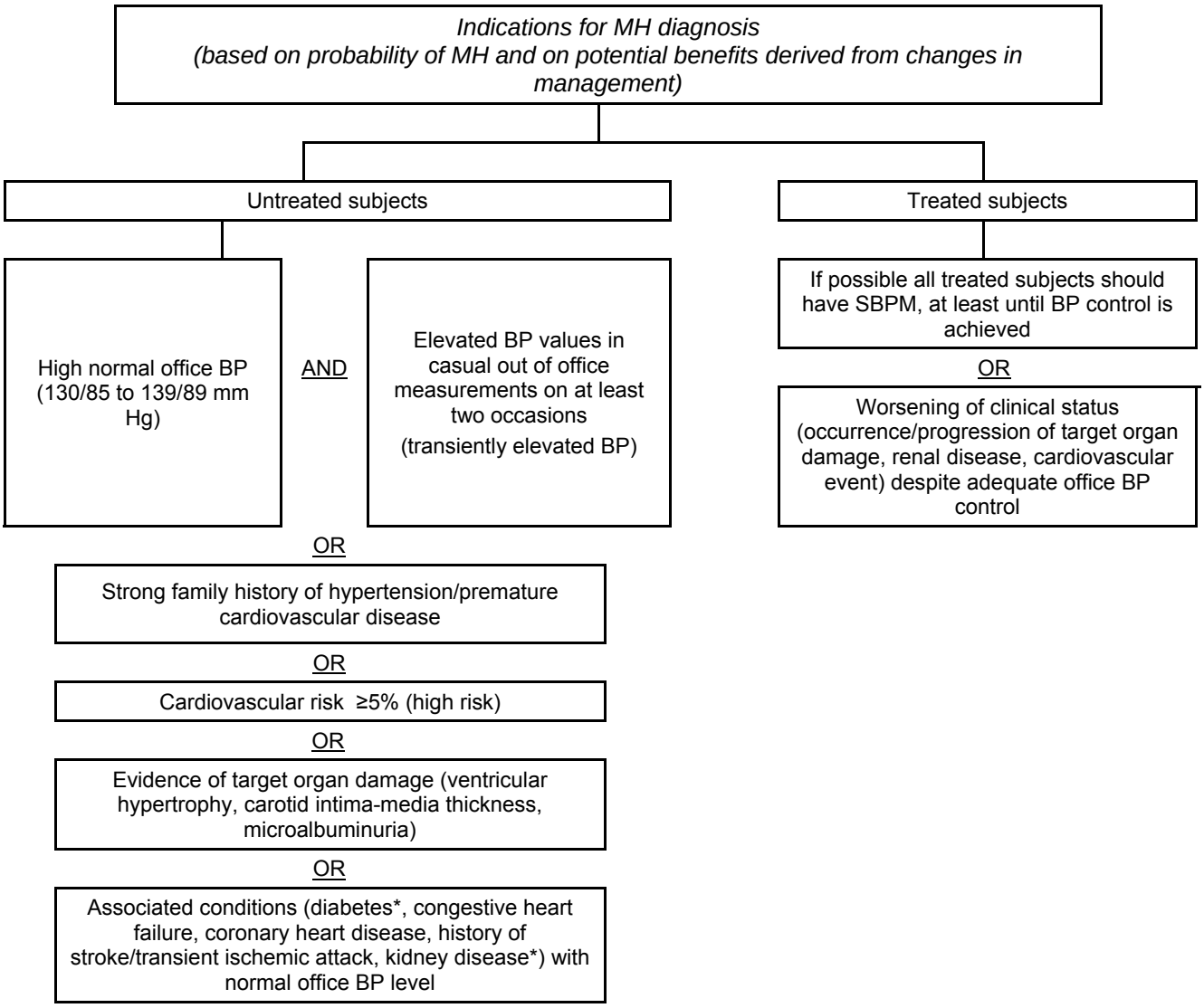
3.6.1.2 White-coat effect

White-coat hypertension should not be taken as a synonymous for "white-coat effect". The latter term describes the acute increase in BP that occurs in the medical environment during consultation, which can be detected by continuous BP monitoring during the doctor's visit regardless of ABP levels. It may occur both in normotensive and in hypertensive subjects. The white-coat effect may contribute to white-coat hypertension, however, there seems to be no predictive association between the two phenomena [213]. The term "white-coat effect" has also been used by some authors [214,215] to identify individuals with an unusually large difference between office and ambulatory readings, regardless of the actual level of either. A clinically significant white-coat effect has been defined as a conventional BP exceeding mean day-time ABPM by at least 20 mm Hg systolic or 10 mm Hg diastolic, or both [214]. This finding may be present in as many as 73% of treated hypertensive individuals [215].

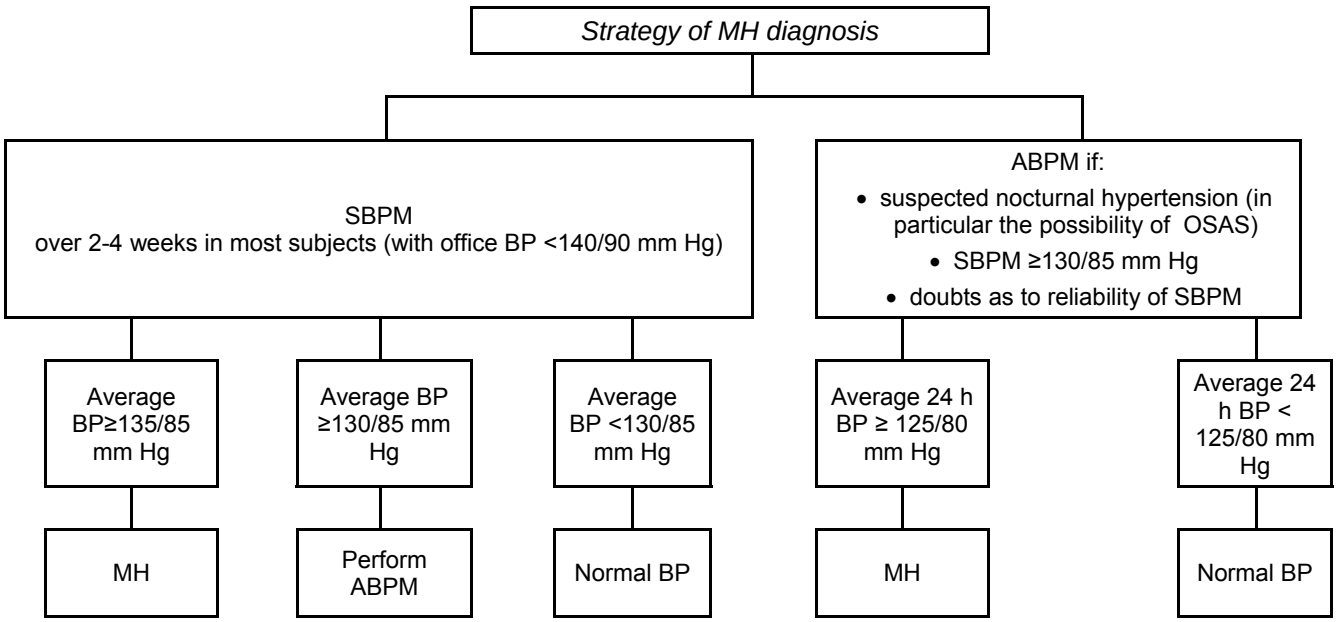
3.6.1.3 Masked hypertension

Subjects in whom conventional BP is normal but ambulatory BP is increased are identified as having "masked hypertension"[178,179]. This phenomenon was previously termed "reverse white-coat hypertension" or "white-coat normotension". Based on the assumption that ABPM gives a better classification of risk than CBPM, these people should thus be regarded as being at higher risk. A practical problem is how to identify and manage this problem, which may occur in a large number of subjects, amounting to as many as 10 million people in the USA [216]. The phenomenon might be suspected in young subjects with normal or normal-high conventional BP who have early left ventricular hypertrophy, in individuals with a family history of hypertension in both parents, in patients with multiple risk factors for cardiovascular disease, and in diabetic patients (Table 26).

Table 26. Management of masked hypertension in clinical practice (MH)



** in diabetic patients and those with kidney disease appropriate office BP cutoff (130/80 mm Hg) should be considered*



3.6.1.4 Resistant hypertension

In patients with resistant hypertension defined as a conventional BP consistently greater than 140/ 90 mmHg in spite of treatment with three antihypertensive drugs, ABPM may indicate that the apparent lack of response may be ascribed, in fact, to the white-coat phenomenon. A worse prognosis is present in patients with refractory hypertension, therefore ABPM may help in stratifying the cardiovascular risk in these patients [216].

3.6.1.5 Elderly patients in whom treatment is being considered

Systolic BP measured conventionally in the elderly is often much higher than ambulatory blood pressure. In subjects with isolated systolic hypertension clinic BP is about 20 mmHg higher than daytime ABPM [217], as demonstrated in a ABPM sub-study of the Systolic Hypertension in Europe Trial. Therefore, an overestimation of isolated systolic hypertension may frequently occur in the elderly, with consequent over treatment of the condition. In the same study it was demonstrated that

systolic ABPM is a significant predictor of cardiovascular risk over and above conventional systolic BP [210]. A second potential advantage of ABPM in the elderly is the detection of hypotensive episodes resulting from baroreceptor or autonomic dysfunction, which may be important in a population particularly prone to the adverse effects of blood pressure-lowering drugs [50].

3.6.1.6 Suspected nocturnal hypertension

Only ABPM allows a non-invasive measurement of BP during sleep. There is no general agreement about the clinical relevance of nocturnal hypertension, but recent evidence has shown that a non-dipping nocturnal pattern is a risk factor for cardiovascular mortality [218-224]. It has also been shown that absence of nocturnal ‘dipping’ of BP is associated with more pronounced target-organ involvement, and suggests the presence of secondary hypertension [209]. As the reproducibility of nocturnal BP is poor, the presence of a non-dipping (or extreme dipping) status should be confirmed by a second recording.

3.6.1.7 Pregnancy

Also in pregnancy, the main advantage of the use of ABPM is the identification of white-coat hypertension, a condition occurring in nearly 30% of pregnancies [225]. Its detection may be particularly relevant in order to avoid unnecessary or excessive administration of antihypertensive drugs. Normal values for ABPM in the pregnant women are usually lower than in non-pregnant women, mean daytime SBP ranging from 115 to 119 mmHg and mean daytime DBP from 69 to 74 mmHg throughout gestational time [226]. The corresponding ranges for mean night-time SBP and DBP are 99-106 and 54-58 mmHg, respectively [226].

In addition, ABPM is better correlated with proteinuria than conventional BP [227] and may better predict hypertensive complications [228].The presence of hypertension according to ABPM is associated with lower birth weight [229]. Since women with white-coat hypertension tend to have more caesarean sections than normotensive women, ABPM may help in reducing caesarean delivery [225]. It should be considered, however, that the changes in arterial wall compliance during pregnancy make oscillometric measurements, based on algorithms developed for non pregnant subjects, potentially less reliable than auscultatory readings. Preliminary data obtained by a study of the Italian Society of Hypertension Working Group on BP Monitoring show that throughout pregnancy ambulatory oscillometric diastolic BP values are consistency lower than the corresponding DBP values determined through microphonic detection of Korotkoff sounds over the 24 hours [Parati et al, unpublished data.] The auscultatory method in turn, has to face the changes in Korotkoff sounds due to the hyperdynamic state typical of pregnancy. Several authors indeed recommend that diastolic ascultatory BP should be identified in correspondence of both the IV and the V Korotkoff sounds. The latest guidelines recommend use of V Korotkoff sound, keeping also the value corresponding to the IV sound in the clinical records [72].

3.6.1.8 Diabetes

In type 1 diabetic patients the lack of a nocturnal decline of BP may predict the onset of cardiovascular complications [230], since it suggests the presence of autonomic dysfunction.

The development of microalbuminuria in young patients with type 1 diabetes is frequently preceded by an increase in systolic ABPM during the night. Therefore ABPM may be useful in patients with type 1 diabetes

and absence of microalbuminuria in order to guide therapeutic strategies to a more effective prevention of the progression of renal disease.

3.6.1.9 Ambulatory hypotension

As previously mentioned when dealing with the clinical use of ABPM in identifying transient reductions of BP in the elderly, ABPM may be a valuable approach for the diagnosis of hypotensive episodes [45]. Also in treated hypertensive patients, ABPM may be useful to demonstrate drug-induced decreases in BP that may be particularly harmful in patients with coronary or cerebrovascular disease [231].

3.6.2 Clinical indications for SBPM

Identifying the applications of SBPM represents a "work in progress", since scientific data are gathered in parallel with the progressively wider use of the technique. Although the use of SBPM should be encouraged in any patient with borderline or high blood pressure, more stringent indications for the clinical use of SBPM are shown in Table 27 (2).

Table 27. Clinical indications to SBPM.

- Suspected white-coat or isolated clinic hypertension
- Suspected masked hypertension
- The elderly
- Pregnancy
- Diabetes
- Resistant hypertension
- Improvement of patient's compliance to treatment

3.6.2.1 White-coat hypertension

SBPM has been proposed as a useful alternative to ABPM also in the identification of subjects affected by white-coat hypertension [232]. However the finding of a normal home BP may not necessarily mean normal BP values in ambulatory conditions. In spite of this, in a number of studies SBPM and ABPM have offered a

similar assessment of both the magnitude and the prevalence of the white-coat effect, although there was disagreement in the classification of a substantial number of subjects. Moreover, the CBPM–SBPM difference is often smaller than the difference between CBPM and average day-time ABPM [38,184,233,234]. Notwithstanding these problems, given the lower cost of SBPM and its easier application, this approach may be appropriate for the long-term follow-up of patients with white-coat hypertension.

3.5.2.2 The elderly

The cognitive and physical problems that may affect elderly patients, may represent a limitation to the generalized application of SBPM in aged individuals. In this regard, fully automated devices have been shown to be more precise and easier to use than semi-automatic and manually operated equipment in this age group.

3.6.2.3 Pregnancy

In pregnant women, SBPM may helpful for identifying subjects with white-coat hypertension and in the regular assessment of the effect of antihypertensive treatment. The use of data storage and electronic transmission of data through telemedicine tools may be particularly useful for patients living far from a maternity clinic. However, limited evidence is available on the normal values for SBPM in pregnancy and, in general, on the reliability and accuracy of oscillometric BP measuring devices in pregnant women.

3.6.2.4 Diabetes

Given the need of obtaining a tight control of BP aimed at reducing cardiovascular and microvascular complications in diabetic patients, SBPM may play an important role by improving patients' compliance to treatment and by providing regular information on persisting achievement of target BP levels in these patients. However, again there are as yet no clinical data to support the use of SBPM in diabetic patients.

3.6.2.5 Resistant hypertension

SBPM at home may help in identifying patients with apparently uncontrolled conventional BP but with controlled out-of-office BP, although ABPM remains the preferred technique to this aim. In the evaluation of patients with suspected resistant hypertension, in the presence of normal values of SBPM, ABPM may be indicated to confirm the degree of BP control

3.6.2.6 Improving compliance to treatment

An important advantage of SBPM at home is related to its ability to involve hypertensive patients in the management of their condition, by providing them with a daily feed-back, alerting them about a poor BP control and thereby improving adherence to treatment [235,236].

3.6.2.7 Predicting outcome

In theory, SBPM may be superior to CBPM in predicting cardiovascular outcome in hypertension [230]. However at present data are more limited as compared with ABPM, and the results of currently ongoing large trials must be awaited. Available evidence provided by cross-sectional studies indicated that the degree of left ventricular hypertrophy, when evaluated with both electrocardiography and echocardiography is more strongly correlated to SBPM values than to CBPM [237-239].

3.7. Evaluation of Treatment

3.7.1 ABPM

There is increasing evidence on the potential of 24h ABPM in guiding the use of antihypertensive medications [240-242]. In particular ABPM allows to i) overcome the negative influence of the white-coat effect, often observed when evaluation of treatment efficacy is based on CBPM, ii) to unmask an excessive drug effect in concomitance with the occurrence of symptoms, and iii) to assess the duration and smoothness of the drug effect over the 24h [243].

The 24h distribution of the BP effect of antihypertensive drugs can be quantified by applying specific mathematical indices to the analysis of ABPM recordings, such as the trough-to-peak ratio and the smoothness index [132,134-136,244]. In particular, the smoothness index, introduced by Rizzoni et al. [134] proved to have many advantages over the older trough-to-peak ratio, since it significantly correlated with changes in markers of target organ damage, such as left ventricular mass index [135] and carotid artery intima-media thickness [136]. In addition, the smoothness index is more reproducible than the trough-to-peak ratio, it is devoid of the placebo effect and it does correlate with BP variability [135]. For all these reasons, the smoothness index is now regarded as a useful tool for evaluating the balance and distribution of BP control by antihypertensive drugs.

Finally, BP values obtained with ABPM are more reproducible than those obtained with CBPM [244,245]. This may allow a reduction of the number of patients that should be enrolled in intervention trials, comparing the antihypertensive effects of different drugs, since the number of patients needed to evaluate a biological effect is deeply influenced by the reproducibility of the measure.

3.7.2 SBPM

SBPM plays a key role in the assessment of long-term response to antihypertensive drug treatment outside the doctor's office. Avoidance of the white-coat effect and assessment of BP levels and variability under daily-life conditions and for several days is the main advantage of using SBPM in treated hypertensive patients [246,247]. To this regard, SBPM may be useful both in clinical practice and pharmacological trials. SBPM may allow to assess the duration of action of an antihypertensive drug over several days or weeks, evaluating different periods of the day [247,248].

3.8 Telemonitoring of BP

The rapid development of data-transmission techniques has led to implementation of BP telemonitoring systems. These systems, the clinical value of which is still in the investigation phase, offer a number of potential advantages (Table 28), such as i) automatic storage, transmission and reporting of measured BP values (either by Internet or through a telephone line); ii) feedback to and quick update of doctor on patient's health status; iii) Centralized analysis, detailed reports and active support to medical decision; iv) active patient's involvement in his/her disease management and increase in patient's compliance to treatment; v) a possible reduction in the number of clinic visits (elimination of unnecessary visits when the BP is well controlled, and remote support to changes in therapy); vi) reduced costs of patient's management.

Table 28. Advantages and drawbacks of Home BP + Telemonitoring

Advantages	***Drawbacks***
• No alarm reaction to BP measurement	• Use of inaccurate, non-validated devices
• Several and highly reproducible measurements over time	• SBPM not completely accepted by doctors or patients
• Teletransmission of readings (feedback to and quick update of doctor on patient's health status)	• System setup at home and data transfer difficult (need of training of and assistance to patients)
• Centralized analysis, detailed reports and active support to medical decision	• Patients poorly motivated
• Active patient's involvement in his/her disease management and increase in patient's compliance to treatment	• Possible measurement errors and low compliance to SBPM measurement in particular subjects (e.g. elderly subjects, patients with disabilities or multiple concomitant diseases, subjects with an active daily life)
• Reduced visits and costs of management	• High costs of service

Preliminary evidence shows that, by avoiding some of the disadvantages of the current use of home BP monitoring, in particular by optimizing SBPM data reporting and interpretation, these systems may represent a powerful tool to increase the rate of hypertension control. This is likely to occur by contributing to more active medication adjustments by the physician as well as to better patients' compliance [249]. Albeit limited in number, the literature suggests that home BP telemonitoring is effective in particular among those patients needing strict BP control.

Two recent Italian studies, the Telebpcare study [250], an open label, randomized, controlled, study and the Morepress-College Study [251-253], an observational study, have contributed to strengthen the evidence of the clinical validity of home BP telemonitoring, with particular reference to its use in the General Practice. In the TeleBPCare study BP telemonitoring was compared with the usual methods of CBPM, to verify the theoretical advantages of the telemedicine approach in terms of better patient's BP control, with possible reductions in health-care costs. Figure 4 shows the characteristics of such a system based on telephone data transmission to a Telemedicine centre evaluating individual patients' recordings and reporting to their general practitioners (Tensiocare®, Tensiomed®, Hungary). In this study 12 General Practitioners enrolled 298 hypertensive patients and followed them up for 6 months, basing disease management on BP

telemonitoring or on conventional measurements taken in their office. In this study the rate of patients under adequate BP control (day-time average BP<130/80 mm Hg), was significantly higher in the group randomized to home BP telemonitoring (62 vs. 50%, $p<0.05$). In this group a trend for cost saving, reduction in medical visits and in the use of antihypertensive medications, and better quality of life was also observed

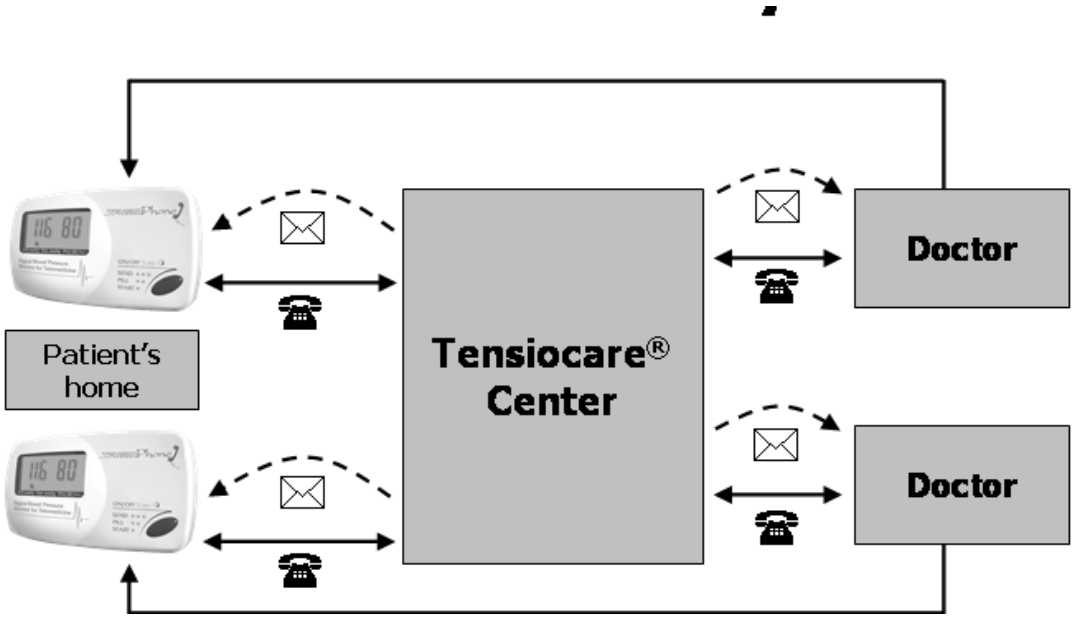


Figure 4. The Tensiocare system used in the Telebpcare Study [243].

The Morepress-College Study assessed the validity of a web-based home BP telemonitoring system (Morepress®, Biotechmed, Italy) [251]. This system was based on self BP monitoring at home and on data transmission to a website by a personal computer or by a GPRS wireless interface (BluMed). The system was characterized by automatic data analysis and reporting to the doctor by e-mail and by simultaneous determination of patients's cardiovascular risk level by the Heart Score [251].

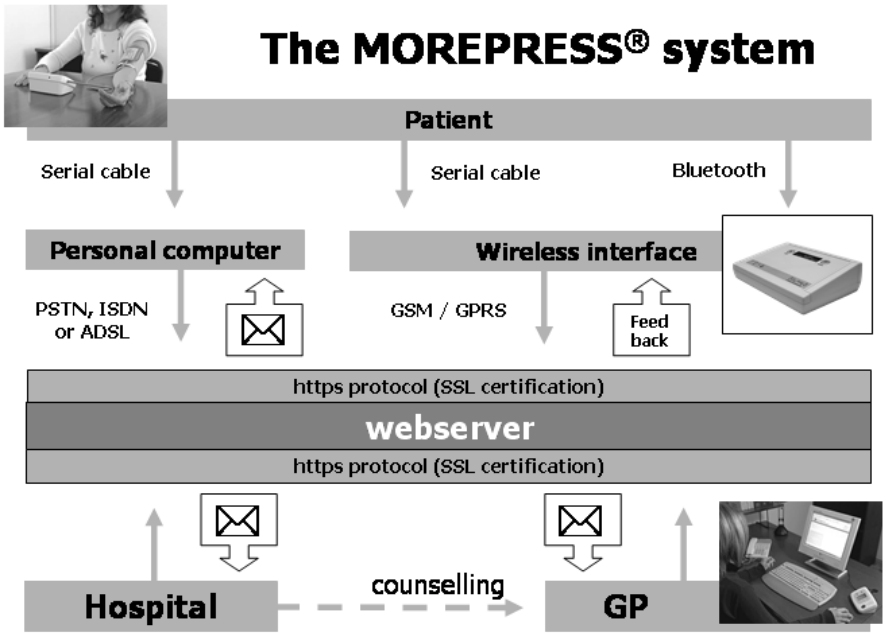


Figure 5. The MOREPRESS® system used in the College Study [244].

In the Morepress-College Study 259 General Practitioners recruited 789 treated and untreated hypertensive individuals, who were monitored for 20,088 days [252]. The system helped in identifying patients with isolated clinic hypertension or masked hypertension which amounted to 35% of the total sample. The study demonstrated the usefulness of web-based telemonitoring system not only for evaluating BP control of hypertensive individuals, but also their cardiovascular risk, which was higher for patients having home and office BP above normal limits or with hypertension only in the clinic. A telephone survey to doctors revealed that 95% of them judged home BP telemonitoirng useful to improve the management of hypertensive individuals [253].

Further studies, particularly in selected high risk populations are needed, to demonstrate the validity of home BP telemonitoring, whose applicability in the general practice is presently still limited by its high cost and by technological problems with data transmission.

3.9 SBPM: instructions to users or patients

In this paragraph a summary of instructions to be given to the patient for a correct SBPM at home is provided. These simple instructions can be used by doctors to prepare leaflets to be forwarded to their patients. Major details on the procedures for SBPM are available from the new ESH Guidelines on Home Blood Pressure Monitoring [254].

General Recommendations

- SBPM should be performed under medical supervision
- SBPM is a complement to BP measurement in the doctor's office
- Avoid overuse of the method and self modification of treatment on the basis of self-home measurements
- Only reliable devices must be used

Conditions of measurement

- 5 minutes of rest prior to BP self-measurement
- 30 min without smoking, alcohol, caffeine, tea, heavy meal or exercise
- Seated, back supported, arm resting on the table at heart level
- Proper cuff bladder placement
- Immobile, not talking during BP self-measurement
- Repeated readings 1-2 minutes apart
- Results recorded on paper unless device with memory
- Measurements in stressful conditions can be misleading and should be avoided

Type of manometer

- Mercury sphygmomanometers: banned
- Aneroid sphygmomanometers: need calibration and training, not recommended
- Wrist or finger devices: not recommended
- Semi-automated or automated electronic devices for upper arm: preferred
- Use clinically validated and accurate devices (check on www.pressionearteriosa.net website)
- Cuff: bladder to encircle 80-100% of arm circumference

	Arm circumference at midpoint (cm)
Small cuff	22-26
Standard cuff	27-34
Large cuff	35–44
Thigh cuff	45–52

How often to measure

- Initial assessment and assessment of treatment, before each clinic/office visit: at least 3 and preferably up to 7 days
- Twice-a-day measurements: duplicate readings in the morning (before drug intake if treated) and evening (preferably before dinner)
- First day of each monitoring session to be discarded
- Long-term follow-up: once-a-week if BP is stable + 1 week before doctor's visit

What is normal

Average of a series of measurements (at least 12, better 24-25 readings, taken on 7 days)

- ≥135/85 mm Hg may be considered as compatible with hypertension
- <130/85 mm Hg may be considered as normal values
- <120/80 mm Hg may be considered as optimal values

Interpretation

- Interpretation of "average BP of several days"
- Measurements on "single occasions" might be quite high or low: little value - may not be representative of "usual" BP
- Elevation of self-monitored BP is not in itself an indication for treatment: the physician will advise on when and which treatment is indicated
- Normal BP in the doctor's office does not imply normal BP at home (masked hypertension): special attention and interpretation by the physician

Who should self-measure BP?

- Patients with isolated clinic hypertension (BP normal at home and high in the doctor's office)
- Patients with masked hypertension (BP high at home and normal in the doctor's office)
- Hypertensive patients not adequately responding to drug treatment
- Hypertensive patients not regularly taking antihypertensive drugs (low compliance to treatment)
- Elderly
- Pregnant women
- Diabetics

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