Twenty-four-hour ambulatory blood pressure measurement in clinical practice and research: a critical review of a technique in need of implementation

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This review presents evidence that ambulatory blood pressure measurement (ABPM) should be used more widely in clinical practice and hypertension research. The technique, which should be mandatory in trials of antihypertensive drugs, is not being used in all studies of antihypertensive drug efficacy. ABPM is also being under-used in outcome studies. The failure to implement ABPM in primary care and hypertension research is impeding patient management and scientific advancement. ABPM offers so many advantages in assessing the efficacy of blood pressure (BP)-lowering drugs that it should be mandatory in pharmacological trials. Likewise, the technique provides a means of achieving BP control in clinical practice, which is essential if we are to halt the epidemic of the cardiovascular consequences of hypertension. However, if ABPM is to be implemented for these purposes, certain requirements will need to be fulfilled. These include the availability of accurate, patient-friendly and inexpensive devices; standardization of the presentation and plotting of data with summary statistics for day-to-day practice; provision of comprehensive data analysis for research; an interpretative report to facilitate use in busy clinical practice; a trend report to demonstrate efficacy or otherwise of treatment in clinical practice and online transmission of data to provide immediate real-time data analysis. The reasons why ABPM is not being implemented are reviewed, and proposals are made to make the technique more acceptable.

Keywords: ambulatory blood pressure measurement, outcome studies, pharmacological studies, primary care.

Abbreviations: ABPM, ambulatory blood pressure measurement; BP, blood pressure; CBPM, conventional blood pressure measurement; DBP, diastolic blood pressure; SBP, systolic blood pressure

Historical perspective

Conventional measurement

Traditionally, blood pressure (BP) has been assessed, and continues to be measured, with the auscultatory technique introduced into clinical medicine at the end of the nineteenth century. Despite being inaccurate and misleading, this technique has survived largely unchanged for over 100 years. It is salutary to reflect that since Riva-Rocci and Korotkoff introduced the technique, we have landed men on the moon, encircled Mars, invented the automobile and airplane, and, most importantly, revolutionized the technology of science with the microchip. Why, we might ask, has medicine ignored scientific evidence for so long and thereby perpetuated an inaccurate measurement technique in both clinical practice and hypertension research [1]? The same sentiment has been expressed by Floras: ‘As a society, we are willing to contemplate widespread genomic or proteomic subject characterization in pursuit of the concept of ‘individualized medicine’. By contrast, blood pressure measurement is one of the few areas of medical practice where patients in the twenty-first century are assessed almost universally using a methodology developed in the nineteenth century [2]. Quite apart from the inaccuracy of the auscultatory technique, one of its major limitations is that it can only provide a ‘snapshot’ of BP behaviour usually under circumstances that may adversely affect the level of BP.
To overcome these serious methodological shortcomings, techniques for obtaining automated profiles of BP behaviour over 24 h have been developed.

Technological development of ABPM

Ambulatory blood pressure measurement (ABPM) has been available in one form or another for some 30 years, having been developed initially to determine the efficacy of BP-lowering drugs [3, 4]. Although assessing the BP-lowering efficacy of antihypertensive drugs over the 24-h period is a logical scientific premise, the ability to do so has been dependent on technological developments. The first major break with traditional BP measurement was the introduction of a direct intra-arterial technique for the measurement of BP over the 24-h period [5]. The data on antihypertensive drug efficacy provided by studies using this system was particularly valuable because it provided continuous BP measurement throughout the day and night, but use of the technique was limited by safety and ethical considerations [3, 6, 7]. Efforts were focused, therefore, on developing a device that would record ambulant BP noninvasively and in the 1960s the Remler device, which was capable of measuring BP intermittently during the daytime period, provided clinicians with a new technique for evaluating antihypertensive drugs [8]. This device yielded interesting information on drug efficacy but was limited by having to be operated by the patient, which made measurement of nocturnal BP impractical. The next technological advance was the introduction of fully automated devices that could measure BP intermittently at predetermined intervals over the 24-h period [4]. This class of devices, amongst which the SpaceLabs series has been dominant, provided a methodology that was applicable not only for research but also for use in routine clinical practice [9].

Self-measurement of BP

The rising popularity of self-measurement of BP as an alternative methodology for obtaining out-of-office BP has tended to distract attention from the clinical use of ABPM. It is often wrongly assumed that a single ‘casual’ self-measurement of BP can give an assessment of a patient’s BP that approximates to daytime ABPM [1]. However, to obtain a self-measured BP approximating to daytime ABPM, it is necessary to adhere to a comprehensive schedule of self-measurement requiring the patient to perform daily duplicate morning and evening measurements on 7 days, with the first-day measurements being discarded and the remaining measurements over 6 days being averaged [1, 10]. In contrast, to obtain an ABPM profile, multiple measurements (usually every 30 minutes) are obtained over one entire day, with the important added advantage of the nocturnal BP being available for analysis [1].

Advantages of ABPM

The advantages of ABPM, which have been stated in comprehensive reviews [1, 11–13], have influenced recommendations for the technique to be an indispensible investigation in clinical practice [14–16]. These advantages may be briefly summarized as follows: first and foremost, ABPM simply gives more measurements than conventional BP measurement, and real BP is reflected more accurately by repeated measurements. ABPM provides a profile of BP away from the medical environment, thereby allowing identification of individuals with a white-coat response or masked hypertension; many of the former with white-coat hypertension who would have been prescribed BP-lowering drugs on the basis of conventional measurement may not require medication, whereas the latter are in need of efficacious 24-h BP control. By showing BP behaviour in the windows of a 24-h period, such as the white-coat and nocturnal periods, it is possible to assess the efficacy of antihypertensive medication throughout the day and night rather than relying on a casual BP measured with an inaccurate technique under artificial circumstances – the demonstration of the 24-h effect of BP-lowering drugs has implications for both clinical practice and pharmacological research; ABPM can demonstrate a number of patterns of BP behaviour that may be relevant to clinical practice, such as nocturnal hypertension; ABPM is a much stronger predictor of CV morbidity and mortality than conventional measurement, and evidence is growing that nocturnal BP measured by ABPM may be the most sensitive predictor of CV outcome, from which it follows that the measurement of night-time BP should be an important part of clinical practice; [1, 14] importantly, ABPM provides a means for not only improving the diagnosis and management of hypertension, but also for ensuring that effective control of hypertension is implemented at community level; [17] finally, even though ABPM is more expensive than conventional measurement, the technique has been shown to be cost-effective, both in specialist services and in primary care and the financial savings to be made from more rational drug prescribing and the achievement of better BP control with ABPM await evaluation [1, 18].
However, despite all the advances in technology and the abundant evidence in favour of ABPM the statement made by Garret and Kaplan in 1987 that ABPM ‘is an idea whose time has come’ [19] has simply not been realized. A major aim of this review will be to examine the reasons why this is so and to examine ways in which ABPM may be made more acceptable in clinical practice and hypertension research.

Requirements for ABPM

Many of the following requirements have been achieved, and some are aspirational but within the reach of modern technology.

**ABPM devices**

*Device accuracy.* Ambulatory blood pressure measurement devices differ from other automated devices on the market, for example devices for self-measurement of BP, in that virtually all that are available on the market have been subjected to independent validation, mostly according to the European Society of Hypertension (ESH) International Protocol, and most of these are accurate although this often depends on the circumstances of use [20, 21]. The recent availability of the revised ESH protocol online with the capability of real-time analysis of validation data should greatly facilitate the validation process and hopefully lead to more devices being validated in patient subgroups, such as patients with atrial fibrillation, the elderly, children and pregnant women [20]. It is important for physicians and patients using ABPM to ensure that the device being used has been recommended for clinical use by checking the website http://www.dableducational.org, which provides the latest accuracy data on all BP-measuring devices.

*Device design.* In spite of the technological advances of recent years, it has to be noted with regret that there has been little by way of innovation in device design for ABPM; users are still obliged to wear a device on the waist connected via tubing to an inflatable cuff worn on the upper arm. However, the devices have reduced in size, and the disturbance caused by the noise of the inflation pump has decreased greatly over recent years.

**ABPM software**

Whereas the current generation of devices for ABPM – the hardware – is generally acceptable to patients, the same cannot be said for the software accompanying ABPM devices. Put another way, the patient as one category of user may be reasonably served by the ABPM devices on offer, but the physician who has to make sense of the considerable data provided by ABPM is often faced with a bewildering report with reams of paper containing plots, histograms and data analysis that has no relevance for clinical practice. The result is that a busy general practitioner is forced to extract the mean daytime and night-time BP so as to obtain a pertinent working analysis at the cost of much more information that may be gleaned from the 24-h BP cycle [1, 13]. At another level, the researcher is denied a mass of informative information simply because it is not presented in a cogent manner and is not available for online storage and analysis. It has been necessary, therefore, to direct attention to designing software that can, on the one hand, provide the basic information in a user-friendly format for clinical practice, whilst on the other being able to store and retrieve the data required for the sophisticated needs of clinical research. The dabl® ABPM system has been developed to fulfil these requirements [1, 13, 22–24], and its features may be summarized as follows:

*Clinical report.* The report for clinical use has been designed to be comprehensive and concise so that all the data are easily read on one page (Fig. 1):

1. A standardized plot format with BP levels on the vertical axis and time of day on horizontal axis,
with windows of the 24-h period and normal bands clearly demarcated

2 Plot of systolic blood pressure (SBP) and DBP throughout the 24-h period with facility for plotting heart rate and mean BP

3 Summary statistics for SBP, DBP and heart rate in the windows of the 24-h period

4 Interpretative report indicating the normal or abnormal patterns and if the required measurements for a valid recording have been met

5 Medication details

6 Facility for showing error readings if required

**Interpretative report.** The interpretative report has been validated against expert observers. The variance in reporting ABPM data, which is common amongst expert observers, is removed by computerized dabl®-generated interpretative reports, thereby improving the diagnostic decisions based on 24-h ABPM [24]. Apart from consistent analysis of data, the interpretative report has a number of other advantages: it serves as an educational process for users of ABPM who are not familiar with the technique; it can be provided to patients so as to allow for their participation in management, and it removes the need for a physician report with consequent financial saving. A selection of fourteen 24-h patterns of ABPM and the computer-generated reports are available in the supplementary files (see: Figs S1–S13.)

**Circadian patterns of ABPM.** In clinical practice, there is a tendency to concentrate on the mean day and night-time BP levels without giving consideration to the information that can be obtained from studying and interpreting the circadian patterns that can add greatly to the clinical management of hypertension. The common patterns of ABPM (Table 1 and Figs S1–S13) include white-coat hypertension, white-coat effect, systo-diastolic hypertension, isolated systolic hypertension, isolated diastolic hypertension, nocturnal dipping and nondipping, reverse dipping, extreme dipping, siesta dipping, isolated nocturnal hypertension, the morning surge, masked hypertension and ambulatory hypotension [22–68].

**Trend report.** The provision of a trend report allows ABPMs to be compared over time and clearly demonstrates the efficacy or otherwise of treatment strategies. If ABPM is to be used to achieve better BP control, it is essential for prescribing doctors (and patients) to be able to see whether medication is achieving control throughout the day and night-time periods. The dabl® ABPM system provides a trend report showing the daytime and night-time levels of BP in relation to the normal bands for each ABPM so that it can be clearly seen whether medication is achieving BP control.

**Research report.** The dabl® system allows for the storage of data for detailed analysis for research and audit according to evidence-based definitions for time-weighted arithmetic and mean values for measures of blood pressure level and in view of recent evidence that BP variability may give information over and above BP mean levels and that reduction in BP variability may be beneficial [69–71], time-weighted measures of variability such as standard deviations and coefficient of variation and measures of white-coat hypertension, white-coat effect, nocturnal dip and morning surge are also provided. The dabl® system also provides informative indices associated with outcome, which include area under the curve calculations, BP load parameters, trough and peak levels, the smoothness index, cusum-derived statistics, and most recently the ambulatory arterial stiffness index, which has been shown to predict CV mortality in a large cohort of hypertensive individuals, particularly from stroke. This association, which is evident even in normotensive subjects, may permit early categorization of hypertensive patients at risk from CV events, thus indicating those in need of aggressive BP lowering [72].

**Central hosting and electronic transfer of data.** If ABPM is to realize its full potential, it is essential that the data generated can be transmitted electronically for central hosting so as to be able to provide real-time data to users of the system. The largest study to date utilizing electronic transfer of ABPM data in primary care comes from Spain, where a nationwide project to promote the use of ABPM in primary care settings has been established, and this has provided a perspective on community hypertension that is very different to that obtained with conventional measurement [1, 17]. An Irish registry using the dabl® system now containing over 130 000 ABPMs in over 80 000 patients drawn from specialized centres, primary care physicians, community health centres and pharmacies linked to a centrally hosted centre from which data can be transmitted online as required [Vellinga A, O’Brien E, Murphy AW, unpublished data]. These registries are allowing for accurate demographic categorization of national BP characteristics so that
intervention strategies to achieve BP control and prevent the CV consequences of hypertension can be initiated.

**ABPM in primary care**

Ambulatory blood pressure measurement has been shown to be feasible, cost-effective and able to provide information that can improve management and blood pressure control [1]. An Irish study in primary care showed that only 12% of patients achieved target BP with conventional measurement compared with more than one-third of patients with ABPM. Furthermore, medication was changed in 38% of patients as a result of ABPM; 32% had a new medication started, and 14% of untreated patients with elevated conventional BP measurement who were candidates for drug treatment were not commenced on medication because ABPM was normal [73]. In the Spanish registry, study conventional BPs were significantly higher than ABPM in patients categorized as being at low-to-moderate added risk, with a greater difference in those categorized as being at high risk in spite of receiving much more antihypertensive treatment. Moreover, high-risk hypertensive patients showed a high prevalence of circadian rhythm abnormalities on ABPM, with a nondipping pattern being common [17, 74]. In both studies, BP control was better when assessed by ABPM than by conventional BP, indicating that the white-coat effect with the latter measurement is leading to an underestimation of BP control in the community. BP control was underestimated in more than one-third of patients and overestimated in some 5% by conventional BP as compared to ABPM. Notably, BP was uncontrolled by both methods of measurement in 43% of patients. High-risk patients showed poorer ABPM control then low-to-moderate risk patients in spite of receiving much more antihypertensive treatment [73, 74]. These studies clearly indicate that more effective control of BP is possible by using ABPM in primary care.

**ABPM in pharmacological research**

Ambulatory blood pressure measurement was first used over 30 years ago in pharmacological studies of the efficacy of BP-lowering drugs [3, 4]. Atenolol taken once daily in the morning was shown to lower BP during the day but to have little effect on either night-time BP or the morning rise in BP. The pre-scient conclusions of this study merit quoting in full because they are as relevant today as when they were written in 1979: The circadian rhythm of blood pressure raises many questions about the timing of antihypertensive drug dosage and the effects of traditional regimens. Single measurements in outpatient clinics are unlikely to yield useful information on the effects of drugs on this basic cycle. If treatment aims at lowering blood pressure to a “normal” level (140/90 mmHg) clearly it is desirable to lower it to that level throughout the 24-h cycle’ [75]. In another early study using intra-arterial ABPM, it was shown that whereas four beta-blockers achieved a significant reduction in mean arterial ABPM, the extent to which each drug did so differed over the 24 h, and importantly the authors highlighted a very basic principle that has too often been forgotten, namely, that had clinic BP only been measured no difference between these four drugs would have emerged [76].

Around the same time as these studies with direct intra-arterial measurement were being conducted, my department began using noninvasive ABPM to assess the efficacy of BP-lowering drugs [3]. From the results of early studies using daytime and 24-h ABPM, a number of patterns emerged. First, ABPM could be in agreement with clinic BP measurements. In studies in which a clinic fall in BP was confirmed by ABPM, the latter also demonstrated what conventional BP measurement can never show, namely the pattern of antihypertensive effect over the dosing interval. Secondly, clinic BP measurement could fail to detect the BP-lowering effect demonstrated by ABPM. Finally, reductions in clinic BP could be significant, but ABPM might be either nonconfirmatory or show that the clinic BP reduction coincided only with a brief period of BP reduction on ABPM [3]. These early studies showed that many drugs would have been declared as quite efficacious BP-lowering agents by conventional BP measurement, whereas ABPM showed a pattern of activity that was far less impressive.

Later studies have shown that treatment-induced BP lowering is greater on office BP measurement than on ABPM, because of the absence of a white-coat reaction, negligible placebo effect and less regression to the mean of averaged pressures, and that the reduction in night-time BP is smaller on ABPM than for daytime BP, possibly reflecting the practice of administering drugs in the morning rather than at night [77]. The potential advantages of ABPM for assessing treatment effects in clinical trials include the ability to evaluate the duration of action of a drug and to analyse its effects on night-time BP, the need to enrol fewer patients, the almost complete absence of a
### Table 1 Summary of ambulatory blood pressure measurement (ABPM) use in clinical practice

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<thead>
<tr>
<th>Windows of the 24-h profile</th>
<th>Patterns of ABPM</th>
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<tr>
<td><strong>White-coat window</strong></td>
<td><strong>White-coat hypertension</strong></td>
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<tr>
<td>This window extends from the beginning of ABPM recording and lasts for 1 h [22, 25] during which blood pressure (BP) may be influenced by the alerting circumstances of the medical environment, for example in the presence of a doctor or nurse. ABPM is the method of choice for diagnosing white-coat hypertension, which is readily diagnosed in this window [11, 26, 27]. ABPM is recommended by national and international guidelines in Europe and the United States to exclude the condition [11, 12]; the European Society of Hypertension recommends that patients in whom a diagnosis of hypertension is being contemplated based on an elevated office BP should have ABPM to exclude white-coat hypertension [12].</td>
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<td><strong>Daytime window</strong></td>
<td><strong>Systo-diastolic hypertension</strong></td>
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<td>The daytime window follows the white-coat window and is the period when the subject is away from the medical environment and engaged in usual activities [30]. For almost all subjects with hypertension, BPs during this window are lower than office or clinic BP [27, 32]. However, BPs during this period are subject to stress, activity, arm movement, and the effect of exercise and other activities, such as driving, all of which may have an influence on the mean level of BP recorded [33]. These effects are largely absent from BP measured during the nocturnal period [14, 34]. The patterns in the daytime window can be evident on office BP but this can give no indication of the duration of the pattern or the response to drug treatment. The patterns present in the daytime window may be carried into the night-time window.</td>
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<td><strong>White-coat hypertension</strong></td>
<td>This is present when the office BP is higher than daytime ABPM, which is nonetheless increased above normal; it is present in most hypertensive patients [12] [Supplementary fig– Fig. S1]</td>
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<td><strong>Systo-diastolic hypertension</strong></td>
<td>Systolic and diastolic hypertension is the commonest day time pattern [12, 35]. Mean daytime BP is superior to clinic BP in predicting outcome, but inferior to nocturnal BP [14, 36]. The severity of hypertension is also indicated (Fig. S2)</td>
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<td><strong>Isolated systolic hypertension</strong></td>
<td>The severity of isolated systolic hypertension may be over estimated with office BP because of the white-coat effect; for example, office systolic BP in the elderly may average 20 mmHg more than daytime ABPM [37]. ABPM shows the duration of isolated systolic hypertension and predicts outcome more accurately than office BP [38] (Fig. S3)</td>
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<td><strong>Masked hypertension</strong></td>
<td>Masked hypertension is present when office BP is normal but daytime BP &gt;135/85 mmHg. Prevalence in adults is at least 10%, which is estimated to be as many as 10 million people in the United States. Adults with masked hypertension have increased target organ involvement and increased cardiovascular morbidity [12, 31, 39] (Fig. S4)</td>
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<td><strong>Ambulatory hypotension</strong></td>
<td>This is common in the elderly with autonomic or baroreceptor failure and ABPM may show postprandial and postural hypotension. Drug-induced hypotension and hypotension in young patients with symptoms may also be diagnosed with ABPM, [11, 31] (Fig. S5)</td>
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<td><strong>Siesta dipping</strong></td>
<td>This is common in some Mediterranean societies, but many elderly patients take a siesta and failing to account for the siesta dip may distort the day/night ratio of ABPM [40, 41.] The magnitude of the siesta dip may have prognostic implications [42] (Fig. S6)</td>
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<td><strong>Isolated diastolic hypertension</strong></td>
<td>This can also be present on clinic BP but is more readily studied with ABPM. Prevalence is estimated to be 3.6% [28]. If systolic BP is normal, high diastolic BP is probably not associated with an adverse prognosis [43] (Fig. S7)</td>
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</table>
A morning surge is defined as a rise in BP > 55 mmHg from the lowest night-time reading. Cardiovascular events, such as myocardial infarction, ischaemia and stroke, are more frequent in the morning hours soon after waking than at other times of day. Circadian variations in biochemical and physiological parameters help to explain the link between acute cardiovascular events and the early morning BP surge [65, 66]. In older hypertensive subjects with a morning surge the risk of stroke is increased almost threefold [67]. Greater carotid intima-media thickness and circulating inflammatory markers coexist in hypertensive patients with a morning surge possibly contributing to the increased cardiovascular risk in these patients [25, 68] (Fig. S13).

Nocturnal hypertension or a diminished nocturnal fall in BP is associated with poor cardiovascular outcome both in populations and in hypertensive patients [1, 14, 26, 48, 61–63]. Blunted night-time dipping is associated with angiographic coronary artery stenosis in men, [55] lower cognitive performance, [56] left ventricular hypertrophy, [57] and renal target organ involvement [58]. For each 10-mmHg increase in mean night-time SBP, the mortality risk increases by 21% [14, 59] (Fig. S9).

Reverse dipping
Present when BP rises above daytime pressures rather than falling during the night. These patients (also referred to as risers, or extreme nondippers) have the worst CV prognosis, both for stroke and cardiac events [47] (Fig. S10).

Extreme dipping
Present when there is a marked nocturnal fall in BP. Patients with atherosclerotic disease are at risk of nonfatal ischaemic stroke and silent myocardial ischaemia if excessive BP reduction is induced by injudicious BP-lowering treatment [47, 60]. Extreme dipping is closely associated with an excessive morning surge in BP [48] (Fig. S11).

Isolated nocturnal hypertension
Isolated nocturnal hypertension, which may be present in 7% of hypertensive subjects, can only be diagnosed with ABPM. One standard deviation elevation of night-time BP increases cardiovascular risk by approximately 20%. Nocturnal hypertension in patients in antihypertensive drug trials could have an important influence on the 24-h efficacy of BP-lowering drugs [59] (Fig. S12).

The majority of people have a dipping nocturnal pattern, which can be defined in different ways [11–14] (Fig. S8).

### Table 1
(Continued)

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<th>Windows of the 24-h profile</th>
<th>Patterns of ABPM</th>
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<tr>
<td><strong>Vesperal and nocturnal windows</strong></td>
<td><strong>Dipping</strong></td>
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<td>Depending on whether BP falls, rises or remains static in these windows determines the dipping status of patients. In the normal individual, there is a decline in BP in the vespertal window from daytime levels of BP that reaches a plateau during the night-time period. This period (9.01 PM to 0.59 AM on the basis of ABPM commencing at 9 AM) is not included in the estimation of day and night mean pressures because this period represents a time during which bed rest is inconsistent and, therefore, cannot be categorized reliably [44]. In hypertensive patients (or some normotensive patients with CV disease), the decline in BP during the vespertal window may be absent (nondipping) so that BPs do not reach basal levels [35, 45–47]. BP may rise in the vespertal window to reach levels that are higher than daytime levels (reverse dipping) [48]. Alternatively, there may be a marked fall in BP during the vespertal window to give the phenomenon of extreme dipping [49]. Therefore, what happens to BP in the vespertal window predicates the BP level in the nocturnal window.</td>
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<td>The nocturnal window follows the vespertal window and is the period between 1.00 and 6.00 AM [26]. BPs in this window are most likely to coincide with sleep (or if not with actual sleep, with the greatest cessation of activity) and are likely, therefore, to represent a steady state. There is compelling evidence that nocturnal BP is superior to casual pressure in predicting outcome [14, 34, 46, 50, 51]. There are a number of methodological limitations to recording BP at night [34, 44, 52]. But despite doubts about reproducibility of the night-to-day ratio, night-time BP is more standardized and consequently more reproducible than daytime BP (sleep being a more stable state than activity) and this feature gives nocturnal BP its predictive value [53, 54].</td>
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<tr>
<td><strong>Matinal window</strong></td>
<td><strong>Dipping</strong></td>
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<td>The matinal window extends from the end of the nocturnal window to the commencement of daytime activities following rising. This period (6.01–8.59 AM) is not included in the estimation of day and night mean pressures because it represents a time during which bed rest is inconsistent and, therefore, cannot be categorized reliably [44]. However, the magnitude of the rise in BP in the matinal window may yield valuable prognostic information. In normal subjects, a modest rise in BP occurs in the matinal window preceding awakening from sleep to merely restore the previous daytime level of BP [64]. However, this pre-awakening rise in BP in hypertensive patients may exceed the daytime average to give the pre-awakening or morning surge [1].</td>
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<tr>
<td>A morning surge is defined as a rise in BP &gt; 55 mmHg from the lowest night-time reading. Cardiovascular events, such as myocardial infarction, ischaemia and stroke, are more frequent in the morning hours soon after waking than at other times of day. Circadian variations in biochemical and physiological parameters help to explain the link between acute cardiovascular events and the early morning BP surge [65, 66]. In older hypertensive subjects with a morning surge the risk of stroke is increased almost threefold [67]. Greater carotid intima-media thickness and circulating inflammatory markers coexist in hypertensive patients with a morning surge possibly contributing to the increased cardiovascular risk in these patients [25, 68] (Fig. S13).</td>
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placebo response and better correlation of the results with clinical outcomes [3, 77].

When we consider that the phenomena of white-coat hypertension, nocturnal dipping and the morning surge, cannot be even suspected with conventional BP measurement and that the technique can give no indication of the duration of antihypertensive drug effect, it is remarkable that researchers can persist in using the technique, and it is indeed worrying that the editors of scientific journals and their peer reviewers can give scientific credence to studies performed with an inaccurate and limited technique. We must question also why the bodies that regulate the approval of antihypertensive drugs have not made BP measurement over 24 h mandatory for studies of drug efficacy and why the pharmaceutical industry funds such studies. Although 24-h ABPM is being used increasingly in clinical trials, it is surprising, nonetheless, that many studies continue to rely on clinic BP measurement to assess drug efficacy [3, 78–87]. Whereas these studies may be well conducted and may indeed show that the BP-lowering effect at one point in the 24-h profile is superior or inferior to another drug (or combination of drugs), they cannot provide information on the duration of BP-lowering efficacy of the drug being evaluated nor its effect on nocturnal phenomena, such as nondipping and the morning surge. The inevitable question raised by these studies is simply how much more effective they might have been had they been able to provide information on duration of drug effect and the BP-lowering effect in individual windows of the 24-h profile. In monetary terms, the modest cost of ABPM would have been more than repaid by the scientific data showing the circadian efficacy of BP lowering. In contrast, studies using both ABPM and conventional BP measurement clearly show the added value of ABPM in detecting pharmacological effects that would not have been evident from conventional measurement alone [88–98] (Table 2). Of interest in the context of this review is the fact that in two of these studies ABPM failed in almost a quarter of patients, which emphasizes the need to resolve the practical issues that result in such an unacceptable level of failure [92, 95].

**Regulatory recommendations for pharmacological studies**

The US Food and Drug Administration (FDA) guidelines that are still in draft form state that 'The effect of the drug over the duration of the dosing interval has generally been evaluated in recent years with ABPM studies (which can incorporate dose-response elements and an active control), but studies that measure blood pressure at approximate peak and at trough (predosing) blood levels can also be used’ [99]. The current European Medicines Agency (EMA) guidelines recommend that: ‘As ambulatory blood pressure monitoring (ABPM) provides a better insight to blood pressure changes during everyday activities, ABPM is strongly recommended for the evaluation of new antihypertensive agents, although there are insufficient data to accept ABPM as the sole basis for efficacy in an approval process’ [100]. The guideline then goes on to stipulate the requirements for ABPM but unfortunately these fail to give attention to the practical realities that are necessary if the technique is to be successfully implemented in pharmacological studies. For example, the requirement for the number of readings is imprecise: ‘Time intervals should be short enough to get meaningful and reliable results at day and during night-time’ [100]. Finally, the EMA requirements should be specific and stipulate detailed recommendations for performing ABPM in clinical trials, such as the frequency of measurements, the time of commencement and termination of ABPM, the relationship of measurements to drug ingestion, the ABPM levels in the 24-h windows, the minimum number of measurements in each window, the provision of time-weighted means, the number of consecutive measurements that can be missed, and the method of demarcating day and night-time periods [3]. The dabîl® ABPM system has been modified to provide real-time analysis of ABPM in an ambulatory substudy within phase III multicentre clinical trials providing features that include separate viewing and editing facilities for investigators, monitors and supervisors, full multi-centre support allowing investigators to access data relating to their specific centre, with monitors and supervisors having access to data from all centres, provision of audit and progress reports to assist monitors to check data, validation of all ABPMs and comprehensive export of ABPM raw data and statistics.

**ABPM to demonstrate outcome**

Ambulatory blood pressure measurement has been used as a marker of cardiovascular morbidity and mortality in a number of major studies to provide data on the effect of antihypertensive drug medication on outcome that cannot be provided by conventional BP measuring techniques [101–105]. This has been because of the evidence from a number of studies showing not only that ABPM parameters may be more
accurate predictors of cardiovascular risk but that optimal antihypertensive therapy should provide BP control over the full 24-h period and that control of BP may be particularly relevant in certain periods of the 24-h profile, such as in the nocturnal and matinal windows [14, 46, 62, 106–111]. However, as with

Table 2 Clinical trials of antihypertensive drug efficacy in 2010 using ambulatory blood pressure measurement and conventional blood pressure measurement (CBPM)

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<tr>
<th>Study</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Valsartan/hydrochlorothiazide and amlodipine/hydrochlorothiazide in stage 2 hypertension by ethnicity: the EVALUATE study [88]</td>
<td>CBPM failed to show a difference in treatment response related to ethnicity that was evident with ambulatory blood pressure measurement (ABPM)</td>
</tr>
<tr>
<td>Amlodipine and angiotensin-converting enzyme inhibitor combination versus amlodipine monotherapy in hypertension: a meta-analysis of randomized controlled trials [89]</td>
<td>ABPM showed superior reduction in blood pressure (BP) for combination treatment over the full 24-h period but not during the trough period</td>
</tr>
<tr>
<td>Efficacy of amlodipine and olmesartan medoxomil in patients with hypertension: the AZOR Trial Evaluating Blood Pressure Reductions and Control (AZTEC) study [90]</td>
<td>Study confirmed CBPM reduction but in addition showed reduction throughout 24-h period</td>
</tr>
<tr>
<td>Divergent results using clinic and ambulatory blood pressures. Report of a darusentan–resistant hypertension trial [91]</td>
<td>ABPM showed reduction in systolic blood pressure (SBP) over 24h that was not evident with CBPM</td>
</tr>
<tr>
<td>Effects of telmisartan and amlodipine in combination on ambulatory blood pressure in stages 1–2 hypertension [92]</td>
<td>ABPM showed superiority of combination therapy over monotherapy throughout 24-h period. Of note, 25% of ABPMs failed</td>
</tr>
<tr>
<td>Efficacy and tolerability of olmesartan/amldipine combination therapy in patients with mild-to-severe hypertension: focus on 24-h blood pressure control [93]</td>
<td>ABPM showed that olmesartan/amldipine combination is associated with effective and smooth 24-h BP control, particularly during the final hours of dosing, in patients with moderate-to-severe hypertension</td>
</tr>
<tr>
<td>Is very low dose hydrochlorothiazide combined with candesartan effective in uncontrolled hypertensive patients? [94]</td>
<td>ABPM showed reductions in BP in windows of 24-h period</td>
</tr>
<tr>
<td>Antihypertensive efficacy and safety of olmesartan medoxomil and ramipril in elderly patients with mild-to-moderate essential hypertension: the ESPORT study [95]</td>
<td>CBPM control obtained with olmesartan was confirmed with 24 h ABPM but in addition the antihypertensive effect of olmesartan was shown to be smoother and more long lasting than that of ramipril, this ensuring better control of BP variability and 24-h control in the hours farthest from the last drug intake. Of note is the fact that 23% of ABPMs failed</td>
</tr>
<tr>
<td>Blood pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomized, double-blind, placebo-controlled, active comparator study [96]</td>
<td>Differences of effect of LCZ696 on SBP especially at night were shown that were not evident with CBPM, and this important finding suggests that the drug might be particularly useful in treating isolated systolic hypertension especially at night</td>
</tr>
<tr>
<td>The efficacy and safety of irbesartan in primary hypertension even if a dose is missed: results from the NO PROBLEM Study [97]</td>
<td>Systolic, diastolic and mean ABPM values before and on the day of a missed dose did not differ significantly</td>
</tr>
</tbody>
</table>
### Table 3  
**Ambulatory blood pressure measurement (ABPM) in studies to determine outcome based on cardiovascular endpoints**

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension [62]</td>
<td>In older patients with isolated systolic hypertension, ambulatory systolic blood pressure (BP), especially when measured at night or when exceeding 142, 145, or 132 mmHg, respectively, on 24-h, daytime, and night-time measurement was a significant predictor of cardiovascular complications over and above conventional systolic BP</td>
</tr>
<tr>
<td>Comparative effects of ramipril on ambulatory and office blood pressures: a HOPE substudy [113]</td>
<td>Night ABPM, 1 year after randomization, was significantly lowered during treatment with ramipril 10 mg once daily at bedtime compared with placebo. OBP and mean day ABPM showed a modest and insignificant fall, which was of the same order as the significant but modest BP fall observed in the overall HOPE study population. Based on these findings it is likely that more of the benefits of ramipril in HOPE may be related to BP reduction (especially during night-time) than what was explained by the effects on OBP seen in both the main study and this study. The effects on cardiovascular morbidity and mortality seen with ramipril in the HOPE study may relate to effects on BP patterns over the 24-h period</td>
</tr>
<tr>
<td>Twenty-four hour ambulatory blood pressure in the Hypertension Optimal Treatment (HOT) study [104]</td>
<td>At baseline 24 h average blood pressures were significantly and markedly lower than OBP. Office, 24 h, day and night blood pressures were all significantly reduced by treatment. There was a marked reduction in night- as compared to daytime values. Treatment reduced not only office but also ABPM throughout the 24 h. The reduction was less marked for ambulatory than for office BP</td>
</tr>
<tr>
<td>Follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study [114]</td>
<td>In the PAMELA population, risk of death increased more with a given increase in home or ambulatory than in office BP. Systolic BP was almost invariably superior to diastolic BP, and night BP was superior to day BP. BP values within 24 h were prognostically different; night BP showed a steeper relationship with the risk of death than day BP, and more importantly, the goodness of fit to the risk model was greater for night than for day BP values. This further supports the recommendation to extend ABPM to a 24-h time interval</td>
</tr>
<tr>
<td>Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study [14]</td>
<td>ABPM is a stronger predictor of cardiovascular mortality than conventional BP measurement (CBPM), and that night-time is superior to daytime ABPM in predicting cardiovascular mortality in a Western hypertensive population who were not using antihypertensive medication at the time of BP measurement. These results have two important clinical messages: ABPM is superior to clinic measurement in predicting cardiovascular mortality, and night-time BP is the most potent predictor of outcome. In our study, for each 10-mmHg increase in mean night-time systolic BP, the mortality risk increased by 21%</td>
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Table 3 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusion</th>
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<tr>
<td>Ambulatory blood pressure monitoring after 1 year on valsartan or amlodipine-based treatment: a VALUE substudy [105]</td>
<td>Mean CBPM was 140.0/80.8 mmHg on valsartan and 139.6/80.3 mmHg on amlodipine (NS) HR was significantly higher throughout a major part of the 24-h period in the latter group. VAL had a more pronounced effect on ABP in the first 7 h postdose but during the period 20–24 h after dosing, SBP levels were significantly lower in the amlodipine group (difference – 2.7 mmHg). Night-time ABP had a superior predictive power compared with daytime ABP, and SBP was more closely related than diastolic BP to endpoints</td>
</tr>
<tr>
<td>Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study [115]</td>
<td>The night-time BP predicted mortality and nonfatal outcomes, irrespective of treatment status. The daytime blood pressure independently predicted the composite of all fatal and nonfatal cardiovascular events, especially in untreated participants. These findings therefore support recording ABPM during the whole day. The proposed thresholds for the 24-h blood pressure, 14 rather than the dipping pattern, should inform clinical decisions</td>
</tr>
<tr>
<td>African American Study of Kidney Disease and Hypertension Trial [116]</td>
<td>ClinicBP provides an incomplete and potentially misleading assessment of the severity of hypertension in African Americans with hypertensive kidney disease, in large part because of increased night-time BP. A remarkably high prevalence of nondipping or reverse dipping, elevated night-time BP and masked hypertension was documented. Higher night-time BP and masked hypertension were associated with increased severity of hypertension-related target organ damage. The use of ABPM reveals a very high prevalence of masked hypertension, which, in turn, may be associated with hypertension-related target organ damage</td>
</tr>
<tr>
<td>Study</td>
<td>Conclusion</td>
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<tr>
<td>Ambulatory blood pressure monitoring predicts cardiovascular events</td>
<td>Examination of the average 24-h BP changes in each treatment group showed that patients in the amlodipine–perindopril arm had a lower night-time systolic BP when compared with those in the atenolol–thiazide arm, but during the day, systolic BP was higher in the former group. In the ASCOT ABP substudy, a 1SD increase in night-time or 24-h systolic BP increased the possibility of a cardiovascular event after adjustment for systolic CBP by 26 and 29%, respectively. The findings of the ASCOT ABP substudy have clear clinical relevance. Despite the abundance of evidence for the superiority of ABPM over clinic BP as a predictor of outcome, current guidelines generally recommend ABPM only in selected circumstances. The importance of night-time BP control supports the use of ABPM in the follow-up of treated patients. Only ABPM allows adjustment of therapy to control night-time BP, which may be crucial in determining outcome.</td>
</tr>
<tr>
<td>Prognostic value of isolated nocturnal hypertension on ambulatory</td>
<td>Isolated nocturnal hypertension predicts cardiovascular outcome in patients who are normotensive on office or on ambulatory daytime BP measurement. One SD elevation of the night-time SBP and DBP increased cardiovascular risk by approximately 20%. INH can only be diagnosed by automated measurement of BP during sleep. ABPM is the best technique to obtain the night-time measurements in an identical way as those during daytime. This study adds to the growing evidence that ABPM should be applied more widely in clinical practice and highlights the importance of having BP monitored during the whole day, rather than during a limited time window.</td>
</tr>
<tr>
<td>measurement in 8711 individuals from 10 populations [59]</td>
<td></td>
</tr>
<tr>
<td>Prognostic value of the morning blood pressure surge in 5645</td>
<td>An exaggerated morning surge, exceeding the 90th percentile of the population, is an independent risk factor for mortality and cardiovascular and cardiac events, especially in smokers. Conversely, a sleep-through or preawakening morning surge in SBP &lt;20 mmHg is probably not associated with an increased risk of death or cardiovascular events.</td>
</tr>
<tr>
<td>subjects from 8 populations [117]</td>
<td></td>
</tr>
<tr>
<td>Perspectives: Morning surge in blood pressure and cardiovascular</td>
<td>Review of all papers to date. Based on evidence gathered in the last several years, morning BP surge is one of the treatable ambulatory BP variabilities and is a potential risk for cardiovascular disease independent of the average of 24-h BP.</td>
</tr>
<tr>
<td>risk: evidence and perspectives [118]</td>
<td></td>
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</tbody>
</table>
pharmacological trials, the use of ABPM has been tentative and complimentary to conventional BP, rather than being the methodology of choice. As a consequence, ancillary studies using ABPM have often enrolled small numbers that are unrepresentative of the main study population or they lack a baseline ABPM, making it impossible to determine the transition from no treatment at baseline to the effect of full-dose medications and thereby limiting greatly the conclusions of the ancillary studies [112]. The major outcome studies that had ABPM ancillary studies are listed in Table 3 [14, 59, 62, 103–105, 113–118]. These studies provide a wealth of information on the analysis which is beyond the scope of this review but, whatever the strengths and shortcomings of these studies may be, one message emerges clearly and that is the superiority of nocturnal blood pressure, whether it be the nondipping or morning surge pattern or both, in predicting outcome. Indeed, considering the large cost of outcome studies, it is difficult to understand why ABPM with real-time analysis is not employed as the primary method of measurement so as to allow assessment of the true value of BP lowering across the windows of the 24-h profile in preventing cardiovascular outcome. If an example was needed to emphasize this point, we need look no further than the Heart Outcomes Prevention Evaluation (HOPE study) study. In the main study, treatment with the angiotensin-converting enzyme (ACE) inhibitor ramipril induced an insignificant reduction in BP of 3/2 mmHg, and based on these findings, the beneficial outcome on CV morbidity and mortality (approximately 35% fewer CV deaths) was attributed to ACE inhibition, which was recommended in all high-risk patients regardless of baseline BP [101]. However, when the ABPM substudy was analysed some considerable time later [113], it became evident that ramipril rather than inducing an ‘insignificant reduction’ had effected a ‘whopping’ 17/8 mmHg reduction in BP during the night-time period, which translated into a 10/4 mmHg average reduction in BP over the entire 24-h period [119]. The limitation of relying on conventional measurement is further emphasized in the HOPE study by the fact that the methodology of clinic BP measurement was poor and ramipril had been ingested in the evening with clinic BP measured some 10–14 h later the following day. The conflicting data provided by the main HOPE study and by the HOPE-ABP monitoring substudy on the role of BP reduction in explaining the reduced event rates associated with treatment by ACE inhibitors are a clear example of the importance of performing ABP monitoring in trials on cardiovascular protection [77].

Generally, ancillary ABPM studies in major outcome studies have shown that the ABPM predicts outcome better than conventional BP, that the night-time BP is more predictive than the daytime, and that clinic BP measurement is invariably higher than ABPM because of a white-coat reaction with the former measurement, which is absent with ABPM. Indeed, whereas a white-coat effect is common in hypertensive patients, ABPM may show that patients recruited for outcome studies based on clinic BP have ambulatory normotension, i.e. white-coat hypertension. This eventuality cannot be avoided even if a high office BP is made a requirement for recruitment, but most importantly, as has been pointed out by Mancia and his colleagues, because patients exhibiting this phenomenon may have a better prognosis than patients with both clinic and ambulatory hypertension, their inclusion in outcome studies may affect the number of morbid and fatal events and thereby confound the power calculations on which the study size is calculated [104].

Conclusion

Conventional clinic BP measurement is influenced by many factors, which limit the applicability of this technique for research into drug efficacy, but, more importantly, clinic BP measurement cannot provide a comprehensive assessment of duration of effect or of the effect of antihypertensive drugs on nocturnal BP. Home measurement of BP, although useful in assessing BP control in clinical practice, is not as informative as ABPM and cannot provide nocturnal pressures. The benefits of ABPM in the assessment of the efficacy of drug treatment are now so well established that its use should be mandatory in all pharmacological trials of antihypertensive drug efficacy. It is not within the scope of this review to provide the details as to how each and every type of clinical trial might incorporate ABPM but rather to illustrate the feasibility of utilizing ABPM in clinical trials of antihypertensive medication. This review has shown the advantages of ABPM in studies of antihypertensive drug efficacy when the following basic facilities are available: (i) the capability of assimilating a number of parameters over the 24-h period and also within the windows of the 24-h period so as to provide a comprehensive analysis of clinic and ABPM parameters; (ii) provision of real-time data to alert the investigator to the validity or otherwise of the ABPM recordings; (iii) organization of ABPM data so as to permit ongoing analysis; (iv) flexibility of the system so that it can be adapted to provide for the complexity of pharmacological studies of differing design.
Conflict of interest

I have contributed financially to the development of the dabl® ABPM software program for ambulatory blood pressure measurement and I am a member of the Board of dabl Limited, Dublin, Ireland. (http://www.dabl.ie)

Acknowledgements

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Review: ABPM in practice and research

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. White coat effect. The ABPM shows mild daytime systolic hypertension (150 mmHg), borderline daytime diastolic hypertension (87 mmHg), borderline night-time systolic hypertension (123 mmHg) and normal night-time diastolic blood pressure (DBP; 68 mmHg) with a white-coat effect (187 mmHg/104 mmHg). Normal dipping pattern.

Figure S2. Systo-diastolic hypertension. The ABPM shows severe 24-h systolic and diastolic hypertension (209 mmHg/135 mmHg daytime, 205 mmHg/130 mmHg night-time). Non-dipping pattern.

Figure S3. Isolated systolic hypertension. The ABPM shows severe daytime isolated systolic hypertension (176 mmHg/68 mmHg), severe night-time systolic hypertension (169 mmHg) and borderline night-time masked diastolic hypertension (70 mmHg). Non-dipping pattern.

Figure S4. Masked hypertension. Normal clinic BP. The ABPM shows mild 24-h isolated systolic hypertension (143 mmHg/69 mmHg daytime, 128 mmHg/64 mmHg night-time) with a white-coat effect (161 mmHg/80 mmHg). SBP dipping pattern.

Figure S5. Ambulatory hypotension. ABPM shows low daytime systolic and DBP (100 mmHg/59 mmHg) and moderate night-time systolic and diastolic hypertension (146 mmHg/89 mmHg) with a white-coat effect (181 mmHg/102 mmHg). Reverse dipping pattern.

Figure S6. Siesta dipping. The ABPM shows mild daytime systolic and diastolic hypertension (152 mmHg/94 mmHg), optimal night-time systolic blood pressure (111 mmHg) and normal night-time DBP (66 mmHg) with a white-coat effect (158 mmHg/90 mmHg). Measurements taken during the siesta are not included in these averages. Extreme dipping pattern.
**Figure S7.** Isolated diastolic hypertension. The ABPM shows mild 24-h isolated diastolic hypertension (134 mmHg/93 mmHg daytime, 118 mmHg/76 mmHg night-time) with a white-coat effect (157 mmHg/102 mmHg). Normal dipping pattern.

**Figure S8.** Nocturnal dipping. The ABPM shows severe 24-h systolic hypertension (181 mmHg daytime, 153 mmHg night-time) and moderate 24-h diastolic hypertension (107 mmHg daytime, 96 mmHg night-time). Normal dipping pattern.

**Figure S9.** Nocturnal non-dipping. The ABPM shows moderate daytime systolic hypertension (164 mmHg), severe daytime diastolic hypertension (112 mmHg) and severe night-time systolic and diastolic hypertension (157 mmHg/101 mmHg) with a white-coat effect (181 mmHg/134 mmHg). DBP dipping pattern only.

**Figure S10.** Reverse dipping. The ABPM shows normal daytime blood pressure (123 mmHg/71 mmHg), moderate night-time systolic hypertension (141 mmHg) and mild night-time diastolic hypertension (85 mmHg) with a white-coat effect (148 mmHg/91 mmHg). Reverse dipping pattern.

**Figure S11.** Extreme dipping. The ABPM shows mild daytime isolated systolic hypertension (146 mmHg/77 mmHg) and normal night-time blood pressure (114 mmHg/51 mmHg) with a white-coat effect (212 mmHg/109 mmHg). Extreme dipping pattern.

**Figure S12.** Isolated nocturnal hypertension. The ABPM shows mild daytime isolated systolic hypertension (142 mmHg/83 mmHg), severe night-time systolic hypertension (168 mmHg) and moderate night-time diastolic hypertension (91 mmHg) with a white-coat effect (159 mmHg/93 mmHg). Reverse dipping pattern and morning surge.

**Figure S13.** Morning surge. The ABPM shows severe daytime systolic hypertension (183 mmHg), moderate daytime diastolic hypertension (109 mmHg) and moderate night-time systolic and diastolic hypertension (142 mmHg/94 mmHg). Normal dipping pattern.

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**Supplementary Illustrations - Hyperlinks**

**Hyperlink 1. White coat effect.** The ABPM shows mild daytime systolic hypertension (150 mmHg), borderline daytime diastolic hypertension (87 mmHg), borderline night-time systolic hypertension (123 mmHg) and normal night-time diastolic blood pressure (68 mmHg) with a white-coat effect (187 mmHg/104 mmHg). Normal Dipping pattern.

**Hyperlink 2. Systo-diastolic hypertension.** The ABPM shows severe 24-hour systolic and diastolic hypertension (209 mmHg/135 mmHg daytime, 205 mmHg/130 mmHg night-time). Non-dipping pattern.

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![Graph](image1.png)

**Hyperlink 10. Reverse dipping.** The ABPM shows normal daytime blood pressure (123 mmHg/71 mmHg), moderate night-time systolic hypertension (141 mmHg) and mild night-time diastolic hypertension (85 mmHg) with a white-coat effect (148 mmHg / 91 mmHg). Reverse dipping pattern.

![Graph](image2.png)

**Hyperlink 11. Extreme dipping.** The ABPM shows mild daytime isolated systolic hypertension (146 mmHg/77 mmHg) and normal night-time blood pressure (114 mmHg/51 mmHg) with a white-coat effect (212 mmHg/109 mmHg). Extreme dipping pattern.

![Graph](image3.png)
**Hyperlink 12. Isolated nocturnal hypertension.** The ABPM shows mild daytime isolated systolic hypertension (142 mmHg/83 mmHg), severe night-time systolic hypertension (168 mmHg) and moderate night-time diastolic hypertension (91 mmHg) with a white-coat effect (159 mmHg/93 mmHg). Reverse dipping pattern.

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