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24-hour blood pressure monitoring: its efficacy and techniques

The value of 24-h blood pressure monitoring to assess the efficacy of antihypertensive drug treatment

› Eoin O'Brien

Efficacy and sustainability of 24-h blood pressure control: focus on olmesartan-driven products

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The value of 24-h blood pressure monitoring to assess the efficacy of antihypertensive drug treatment

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Abstract

Ambulatory blood pressure monitoring (ABPM) in pharmacological trials has evolved over the years. It is now evident that its advantages greatly outweigh the limitations arising from BP measurements taken in the clinic. While early studies of antihypertensive drugs were restricted by the need for direct intra-arterial measurement, the development of indirect ambulatory techniques has resulted in more widespread use of ABPM in pharmacological trials. ABPM has demonstrated the BP-lowering efficacy of drugs and BP control, especially in relation to nocturnal hypertension. This review critically evaluates the regulatory recommendations now in place and makes proposals to facilitate the recommendation of the European Medicines Agency for mandatory ABPM in future pharmacological trials of antihypertensive drugs.

DRUG EFFICACY

Until very recently, the assessment of antihypertensive drug efficacy has been dependent on clinic blood pressure (BP) measurement in one form or another. Belatedly, the use 24-h ambulatory BP monitoring (ABPM) is beginning to replace clinic BP measurement. That scientific reasoning has been so reluctant to accept a methodology that can give, among many advantages, an assessment of duration of drug effect makes it timely to review the development of pharmacological trials if for no other reason than to ensure that ABPM becomes mandatory for all future studies of antihypertensive drug efficacy.

Clinic blood pressure measurement

Traditionally the efficacy of BP-lowering drugs has been assessed with conventional BP measurement using the technique introduced into clinical medicine in 1896. Despite being grossly inaccurate and misleading, this technique has survived largely unchanged for over a century. 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 a grossly 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" [2].

In fairness to researchers involved in pharmacological studies of drug efficacy, the main sources of inaccuracy—systematic error, terminal digit preference, and observer prejudice or bias—were well recognized and two devices were invented to overcome these deficiencies [3]. The first of these, the London School of Hygiene sphygmomanometer, was accepted without validation as the "gold" standard in pharmacological research for many years, until it was shown to be inaccurate and was withdrawn from the market [4]. This was succeeded by the Hawksley, or "zero-muddler," sphygmomanometer, which was accepted uncritically as the instrument of choice for epidemiological and research studies because it reduced observer bias and obscured digit preference; after some 30 years in use, it too was shown to be inaccurate and is no longer used [5].

When we consider that the phenomena of white coat hypertension (WCH), nocturnal dipping, and morning surge cannot be even suspected with conventional BP measurement and that the technique can give no

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indication of the duration of antihypertensive drug effect, it is a matter of some wonderment that researchers can persist in using the technique. It is indeed worrisome that the editors of scientific journals and their peer reviewers can give scientific credence to studies performed with a discredited 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 studies that do not provide ABPM.

Bearing these considerations in mind, it is surprising, therefore, that so many studies continue to rely on clinic BP measurement to assess drug efficacy [6-15]. 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 or its effect on nocturnal phenomena, such as nondipping and morning surge. In monetary terms, the modest cost of ABPM would be more than repaid by the scientific data showing the circadian efficacy of BP lowering.

Advantages of ABPM versus clinic BP measurement

There are several advantages of 24-h ABPM over conventional BP measurements in demonstrating the efficacy of BP-lowering drugs, which are noted in the following sections.

Detection of white coat responders - The white coat effect has little or no effect on average ABPM levels. Though a white coat effect may be evident in the first hour of ABPM (and possibly also in the last hour) when the patient is in the medical environment [16], the average BP measurements during the daytime and nighttime periods are devoid of the white coat effect. This is in contrast to all measurements obtained by clinic BP monitoring, which are affected when this phenomenon is present, and a reduction in BP can be attributed erroneously to drug efficacy rather than to attenuation of the white coat effect [17].

More than 20% of patients with borderline hypertension diagnosed by clinic BP measurement have normal daytime ABPM [18]. If patients with WCH are included in a pharmacological study, as is often the case when patients are recruited by clinic BP measurement, we might expect as many as one-fifth of these patients not to have sustained hypertension and to be, therefore, unsuitable for the study [19]. Moreover, patients with WCH may respond differently to antihypertensive drugs and develop more side effects [20].

ABPM helps prevent inappropriate patients from being recruited for clinical trials to assess BP-lowering drugs by identifying those patients with elevated BP in the medical environment who have otherwise normal pressures over 24 h. Likewise, patients with hypertension with high clinic BPs, who might be excluded from recruitment if the BP level is above the entry cut-off level, can be identified and included in the study.

A number of studies have shown that therapeutic decisions based on ABPM are superior to those based on clinic BP measurement [21-24]. For example, in the Valsartan and Amlodipine for the Treatment of Isolated Systolic Hypertension in the Elderly (Val-Syst) trial comparing the efficacy of valsartan and amlodipine using ABPM, there was no difference between the two drugs in reducing clinic BP and ABPM. However, a further analysis showed that the BP-lowering effects of the drugs differed according to the measurement used at baseline. The treatment-induced reduction in mean clinic systolic BP was considerably greater than the reduction in mean 24-h ABPM (31.9 vs 13.4 mmHg, respectively). This difference can be attributed to a white coat reaction that is present with clinic BP measurement but absent with ABPM. In the patients with WCH, there was no change in 24-h BP or in the BP level between 8 and 9 am at the end of the therapeutic period, whereas there was a large decrease in clinic systolic BP. Had ABPM not been available, this apparently beneficial effect would have been erroneously attributed to treatment [24].

Absence of placebo response - Unlike conventional BP measurement, 24-h ABPM is virtually devoid of a placebo effect. The absence of a placebo response with ABPM was identified nearly 30 years ago [25-28]. The phenomenon has been demonstrated in most patients with hypertension and, as a consequence, placebo control in studies dependent on clinic BP measurements is deemed mandatory [29]. The absence of a placebo response is present with both invasive [25-28] and noninvasive ABPM [29-35], though one study has demonstrated a small placebo response with daytime ABPM [36].

The absence of a placebo effect with noninvasive ABPM allows the opportunity of simplifying the design and conduct of efficacy studies of antihypertensive drugs. For example, in randomized placebo-controlled trials ABPM performed before and repeated at the end of the treatment period may suffice, making the crossover design with its risks of carryover effects and the need for prolonged placebo administration unnecessary [37]. ABPM may also remove the need for a run-in phase to exclude normotensive patients and detect truly hypertensive patients [38]. This significant advantage overcomes the ethical problem of keeping patients with hypertension off treatment for weeks or months [39].

Reduction in patient numbers - It is becoming more difficult to recruit patients for pharmacological trials, especially for studies aimed at determining the efficacy of drugs in mild hypertension. The average BP over 24 h is 3 times more reproducible than are clinic BP values [40-42], and this allows the number of patients needed in parallel and crossover design studies to be reduced without loss of statistical power [42]. The reduction of cohort size for children in pharmacological trials is also substantially greater with ABPM [43,44].

Provision of a 24-h profile - ABPM provides a profile of BP behavior over the 24-h period rather than the snapshot provided by clinic BP. This profile allows assessment of the efficacy of antihypertensive drugs not only over the entire 24-h period but also during windows of the 24-h cycle [45,46]. For example, the 24-h period can be divided into white coat, daytime, siesta, vesperal (evening), nighttime, and matinal windows. A number of patterns may be observed in these windows: the white coat phenomena of WCH and white coat effect, a siesta dip, and dipping, nondipping, reverse dipping, excessive dipping, and morning surge in the nocturnal period. As the mechanisms involved in determining BP at different times may differ, not surprisingly, drugs can vary in their effects in these windows [47]. Measures of the levels for systolic and diastolic BP and heart rate can be analyzed to assess drug effect during each of these periods.

Assessment of blood pressure variability - The most important measures of circadian variation are the nocturnal dip and the morning surge [48]. Nocturnal hypertension (or a nondipping pattern) is the most important finding associated with increased target organ

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involvement and increased cardiovascular (CV) morbidity and mortality. Recently, BP variability has been shown to be an important prognostic marker that is likely to become a target for antihypertensive drug treatment [49,50]. The prognostic impact of BP variability is largely dependent on the variability of BP over time, but the many measures of variability that may be obtained from ABPM make this an interesting alternative, especially for assessing the effect of antihypertensive medication on this parameter [51].

Provision of derived measures - A number of indexes may be derived from ABPM. For example, the 24-h rate–pressure product, which is the product of systolic pressure and heart rate, is a measure of myocardial oxygen consumption [52]. The ambulatory arterial stiffness index (AASI), which is calculated from systolic and diastolic pressure over 24-h, independently predicts stroke and CV fatality risk [53]. Analysis of hourly mean BPs and changes over 24 h allows determination of the efficacy of a drug at half-hourly time points, thereby showing the optimal dosing regimens for a particular drug. Traditional trough-to-peak ratio can be calculated, as well as the more recent ABPM-derived smoothness index [54]. The trough-to-peak ratio, which expresses the pharmacological effect of the drug at the end of dosing (trough) relative to its peak is often used to denote BP efficacy, but this index does not provide data on the degree of BP reduction throughout the whole 24-h period and is characterized by a high degree of variability in individual patients, as it focuses on BP values obtained over very short time intervals. The smoothness index overcomes the limitations of the trough-to-peak ratio by providing an assessment of both the degree of 24-h BP reduction and its distribution pattern throughout the BP-recording period. The more effective and constant the therapeutic effect over the dosing interval (ie, the greater the average BP reduction and the lower the between-hour differences in the BP reduction induced by treatment), the higher the smoothness index value. It can be expected that BP-lowering drugs with high smoothness indexes may be superior in preventing the CV consequences of hypertension [54].

Identification of drug-induced hypotension - ABPM allows ready identification of drug-induced hypotension, particularly in association with a post-prandial fall in BP and during a siesta dip—phenomena that are particularly common in the elderly. Antihypertensive drugs with a prolonged duration of effect, or administered frequently, may cause a profound reduction in nocturnal BP in some patients, which may lead to myocardial ischemia and infarction [55]. Hypotension induced by excessive medication in patients with coronary arterial disease can induce episodes of overt and silent ischemia [56]. Indeed, the adage that "the lower blood pressure the better" is being questioned, and Zanchetti has suggested modifying this to "the earlier the better" [57]. Recent studies have shown that tight control of BP among patients with diabetes and coronary artery disease and in patients with renal disease was not associated with improved CV outcomes compared with usual control [58,59].

Technological development and pharmacological trials

ABPM, which has been available in one form or another for some 30 years, has been advocated for studies of BP-lowering drugs for almost as long, but it has been slow to find acceptance [60,61]. 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 advance was the introduction of a direct intra-arterial technique for the measurement of BP continuously over the 24-h period [62-64]. The data on antihypertensive drug efficacy provided by studies using this system was particularly valuable because it provided continuous BP measurement over the 24-h period, but use of the technique was limited by safety and ethical considerations [63,64]. 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 [65,66]. This device yielded interesting information on drug efficacy but was limited by having to be operated by the patient, which precluded recording of nocturnal BP. The next technological advance was the introduction of fully automated devices that could measure BP intermittently at predetermined intervals over the 24-h period [67]. This class of devices, among which the SpaceLabs series has been dominant, has allowed clinical scientists to assess not only the BP-lowering efficacy of drugs but also their influence on circadian patterns such as nocturnal BP and the morning surge [68]. The latest technological development has been the provision of software systems that can analyze the data from ABPM and provide not only statistical data on mean levels of BP throughout the 24-h period but also indexes of BP and the relationship of drug effect to the time of ingestion and the association of drug level with BP lowering [69].

Direct intra-arterial ambulatory blood pressure monitoring - Over 30 years ago, a series of studies using direct intra-arterial ABPM to provide continuous 24-h BP was conducted by Raftery and his group at Northwick Park Hospital in London and Sleight and his colleagues at the John Radcliffe Hospital in Oxford; the studies dramatically demonstrated the value of ABPM in assessing the efficacy of BP-lowering drugs [26,27,70-79]. In the earliest of these studies, atenolol taken once daily in the morning was shown to lower BP during the day but to have little effect on either nighttime BP or the morning rise in BP. The prescient 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-hour cycle [70].

The Oxford group used intra-arterial ABPM to demonstrate the difference in efficacy and 24-h duration of action between 4 beta-blocking drugs—atenolol, metoprolol, pindolol, and slow-release propranolol—in a double-blind randomized study. Whereas all 4 beta-blockers achieved a significant reduction in mean arterial BP 28 h after the last single daily dose was taken, the extent to which each drug lowered BP differed over 24 h (atenolol lowered mean arterial BP for all 24 h, metoprolol for 12, pindolol for 15, and slow-release propranolol for 22 h), and had clinic BP only been measured no difference between these 4 drugs would have emerged. The authors concluded:

1. Metoprolol needed to be taken more frequently, or in its slow-release form, to achieve a significant reduction in BP over 24 h.

2. Pindolol lowered mean arterial BP significantly throughout most waking hours; however, its sympathomimetic properties may have prevented it from lowering BP significantly during sleep.
3. Atenolol and slow-release propranolol were effective when taken once daily [26].

Looking back on these early studies, one might wonder why ABPM did not become mandatory for all studies of antihypertensive drug efficacy. However, direct intra-arterial ABPM was not without risk and the technique posed ethical issues that precluded its use except in a few specialized centers [60,64,80-82].

Noninvasive ambulatory blood pressure monitoring - Around the same time as these studies with direct intra-arterial measurement were being conducted, the present author and associates began using noninvasive ABPM to assess the efficacy of BP-lowering drugs [61,83-87]. In these studies, ABPM was carried out over a 12 to 16 h period because the devices used were not fully automated and could not, therefore, measure nighttime BP. However, with the advent of automated devices capable of measuring BP at predetermined intervals over the 24-h period, ABPM became "an idea whose time has come" [88]. 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 [87,89-93]. In such studies, where a clinic fall in BP was confirmed by ABPM, the latter also demonstrated what conventional BP measurement can never show, namely, the duration of antihypertensive effect over the dosing interval. Second, clinic BP measurement could fail to detect the BP-lowering effect demonstrated by ABPM [83,94,95]. The studies showing this phenomenon used smaller numbers, and for this reason their power to detect differences between treatments with clinic BP measurement was low. However, the greater number of observations available with ABPM, by reducing within-subject variability, compensated to some extent for this deficiency. Finally, reductions in clinic BP could be significant, but ABPM might be either nonconfirmatory [61,72,84,96,97] or show that the clinic BP reduction coincided only with a brief period of BP reduction on ABPM [85]. Thus, in a study of the antihypertensive efficacy of verapamil in the elderly evaluated by ABPM where clinic BP assessments were carried out within 4 h of dosing, a marked effect on clinic BP measurement was observed, but ABPM revealed that control was poor for the remainder of the expected duration of the drug's action [85]. However, in other studies using ABPM [36,61,84,97,98] this loss of BP control was not observed, raising another possibility, namely that the physiological basis of BP elevation in the clinic may be different from that outside the clinic and that the dose of an antihypertensive agent effective in lowering clinic BP may not be effective in reducing ABP. This hypothesis is supported by the observation that nitrendipine reduces BP effectively in the clinic, but this effect is blunted on ABPM during work periods [96], possibly due to increased adrenergic activity associated with work. Similarly comparison of the beta-blocker timolol with methyldopa showed similar significant reductions in clinic BP measurement, but ABPM was significantly reduced with timolol only [97]. Likewise, both the beta-blocker betaxolol and verapamil reduced clinic BP, but only betaxolol significantly reduced ABPM [98]. These studies suggest that beta-blocking drugs have a sustained effect on ABPM not shared by drugs with other modes of action. Of considerable practical importance is the fact that many preparations 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 [97].

In 2004, Mancia and Parati carried out a major meta-analysis to determine the effect of antihypertensive treatment on ABPM compared to clinic BP measurement so as to obtain a differential assessment of the magnitude of the reduction on clinic BP compared with 24-h ABPM values, and the reduction in daytime compared to nighttime BP [39]. Of 984 studies reviewed, 44 studies employing approximately 6000 patients met the strict criteria to ensure comparability. The treatment-induced reduction with antihypertensive treatment was greater on clinic BP measurement than it was on ABPM, probably due to the absence of a white coat reaction and placebo effect and less regression to the mean of averaged pressures with ABPM than with clinic BP. Also the reduction in nighttime BP was smaller on ABPM than it was for daytime BP, possibly reflecting the practice of administering drugs in the morning rather than at night. The authors pointed out that the findings in the Heart Outcomes Prevention Evaluation (HOPE) trial were at variance with other studies in the meta-analysis in that the reduction in BP over 24 h was similar to that for clinic BP and was greater at night than during the day [99]. The former difference can probably be explained by inaccurate clinic BP measurements minimizing the true magnitude of the antihypertensive effect of the BP-lowering drug, ramipril, and the greater nocturnal reduction in BP was probably due to ramipril being administered at bedtime [100,101]. The authors concluded that 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 angiotensin-converting enzyme (ACE) inhibitors are a clear example of the importance of performing ABPM in trials on CV protection [39].

Noninvasive 24-h ABPM is being used increasingly in clinical trials of antihypertensive drugs and, to a lesser extent, in nondrug treatment for hypertension [39,102]. The reduction in BP is almost always less with ABPM than it is with clinic BP measurement [39]. 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 analyze its effects on nighttime BP, the need to enroll fewer patients, and better correlation of the results with clinical outcomes [103]. Also in contrast to their effects on clinic BP measurement, placebos have a negligible effect on ABPM [25-35].

Considering these advantages, it is perhaps surprising that noninvasive ABPM has not been used more extensively in evaluating BP-lowering drugs. Nonetheless, the technique is finding growing use in the evaluation of the efficacy of drugs over 24 h [104-118]. In fact, 24-h ABPM has been particularly effective in showing the noninferiority of one drug or drug combination over another. For example, in a multicenter, double-blind, parallel-group, forced-titration study ABPM—but not clinic measurements—showed that the fixed-dose combination of valsartan/hydrochlorothiazide (HCTZ) was a significantly more effective treatment regimen than amlodipine/HCTZ, with similar tolerability. In addition, valsartan/HCTZ was significantly more effective than amlodipine/HCTZ in lowering ABP from 6 am to 6 pm and from 6 pm to 6 am [119]. Many studies have shown that combination therapies with ACE inhibitors and angiotensin receptor blockers (ARBs) with a diuretic provide additive effects and significant reductions in clinic BP measurement and ABPM [120-127]. Comparison of the ARB, olmesartan medoxomil, with the calcium channel blocker (CCB), amlodipine besylate, demonstrated that each drug had similar antihypertensive efficacy in patients with mild-to-moderate hypertension when assessed

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with conventional cuff BP measurement [128]. However, with ABPM a significantly greater number of patients treated with olmesartan achieved individual ambulatory systolic and diastolic BP goals than did those treated with amlodipine [129].

The combination of olmesartan/amlodipine has been shown to be effective in lowering BP in a number of studies using clinic BP measurement [129-135]. These studies demonstrating the efficacy of combination therapy with olmesartan/amlodipine cannot provide information on BP lowering over 24 h outside of a clinic environment during daily activities. This is a serious limitation, especially as olmesartan appears not only to provide highly effective 24-h ABPM control [136-139], but is more effective in doing so than other ARBs (**Figures 1** and **2**) [140]. In an extensive review of over 60 studies to determine if there were differences in BP-lowering efficacy among ARBs, there were too many confounding factors to allow such a comparison [140]. However, a systematic review of 35 studies, in which drug efficacy was assessed according to strictly standardized criteria using ABPM, showed that the ARBs differ significantly not only in their antihypertensive activity but also in the duration of effect [140].

ABPM has also been used in pharmacological studies in children and has been shown to substantially reduce the number of children put at potential risk in blinded antihypertensive drug trials by up to 75%. There is, therefore, a strong rationale for expert bodies and regulatory authorities to consider recommending the primary use of ABPM in pediatric randomized clinical trials submitted for approval purposes [44].

BLOOD PRESSURE CONTROL

One of the major advantages of ABPM in studies of antihypertensive drug efficacy is that the degree of BP control achieved with an antihypertensive drug may be

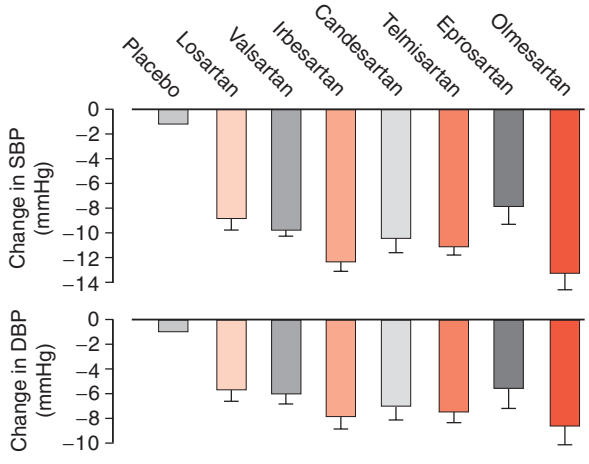

Figure 1. Change in 24-h systolic blood pressure (SBP) and diastolic blood pressure (DBP), as assessed by ambulatory blood pressure monitoring, following treatment with different angiotensin II type 1 receptor blockers or placebo.
(Reproduced with permission from Fabia MJ, Abdilla N, Oltra R, Fernandez C, Redon J. Antihypertensive activity of angiotensin II AT1 receptor antagonists: a systematic review of studies with 24 h ambulatory blood pressure monitoring. *J Hypertens* 2007;25:1327-1336)

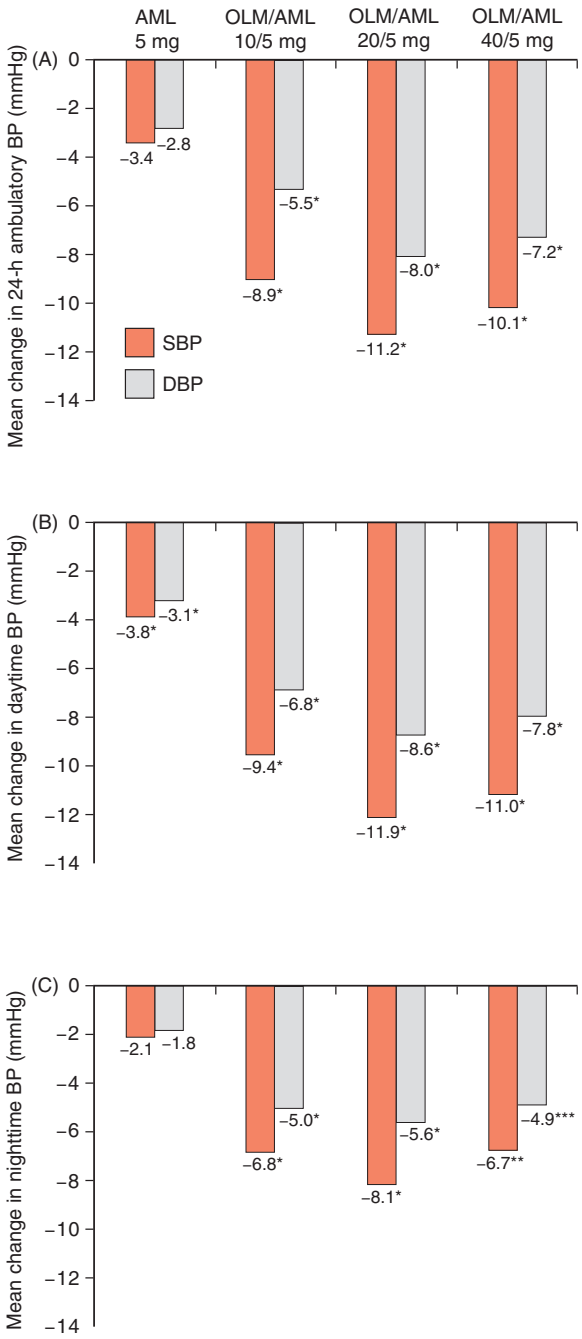

Figure 2. Mean changes in ambulatory blood pressure over (A) 24-h, (B) daytime blood pressure, and (C) nighttime after 8 weeks of double-blind treatment with olmesartan (OLM)/amlodipine (AML) 10/5 mg, 20/5, 40/5 mg, and amlodopine 5 g (from week 8 to week 16).
*$p \leq .0001$ versus AML 5 mg.
**$p < .0002$ versus AML 5 mg.
***p .0005 versus AML 5 mg.
Abbreviations: BP, blood pressure, DBP, diastolic blood pressure; SBP, systolic blood pressure.
(Reproduced with permission from Fabia MJ, Abdilla N, Oltra R, Fernandez C, Redon J. Antihypertensive activity of angiotensin II AT1 receptor antagonists: a systematic review of studies with 24 h ambulatory blood pressure monitoring. *J Hypertens* 2007;25:1327-1336)

determined over the entire 24-h period. This, as has been discussed, is not possible with clinic BP measurement; it is also not possible with self-measurement of BP, which is limited by being unable to provide nocturnal BP.

The increasing use of combinations of different classes of antihypertensive drugs within one tablet—the "flexipill"—is leading to the performance of comparative trials to show the superiority of combination therapy over monotherapy or the superiority of one combination therapy over another [51,141-143]. In these studies, differences in clinic BP are likely to be small, whereas ABPM will allow for subtle differences in efficacy between drug combinations, such as nocturnal BP reduction, restoration of dipping in nondippers, reduction of morning surge, and attenuation of BP variability, to be evaluated.

Nocturnal and matinal blood pressure control

One of the earliest studies to question not only the importance of 24-h BP control but also the mechanism of different classes of drugs on nocturnal BP was by Raftery and colleagues in 1979. Using direct intra-arterial measurement of 24-h BP, they observed that atenolol was effective in lowering daytime BP but had little or no effect on nocturnal BP or on the morning surge in BP. They postulated that "this lack of nocturnal and early morning control cannot be related to falling blood concentrations of the drug since the pattern is similar when the dose is given late at night" [70]. These authors went on to question the mechanism of action of drugs on nocturnal BP: "The mechanism by which beta-blocking drugs lower blood pressure is not clearly understood, but if the early morning rise were due to a sustained alpha-receptor-mediated sympathetic discharge beta-blockers might not be effectual. This hypothesis remains to be tested" [70]. The importance of nocturnal BP control was investigated further by Floras and colleagues who demonstrated with direct intra-arterial measurement that the fall in mean daytime arterial pressure with 4 beta-blockers was similar, but that during sleep atenolol and slow-release propranolol lowered mean arterial pressure, whereas metoprolol and pindolol did not [26]. They went on to admit that "the advantage of lowering blood pressure during sleep is not yet established, although it might be surmised that any lowering of blood pressure, whether by day or by night, might confer additional benefit to a patient with hypertension" [26]. These early studies, which presciently alluded to the potential of ABPM as a sensitive indicator of pharmacodynamics, were limited in their applicability by practical and ethical issues inherent in the technique of direct intra-arterial measurement. The reasoning of the authors of these early studies was subsequently supported by evidence that a nondipping pattern of nocturnal BP is associated with poor outcome [144]. Indeed, we might ask why we have had to wait nearly a quarter of a century to explore the therapeutic potential of nocturnal BP lowering and the differing effects of drugs on ABPM [46,145]? The pharmaceutical industry, researchers, and regulatory agencies are only now beginning to turn attention to this period of the 24-h cycle, which may be a more important target for BP lowering than the daytime period [146].

The efficacy of the various classes of antihypertensive drugs for restoring normal dipping are not well studied. However, diuretics, ACE inhibitors, ARBs, and CCBs appear to be superior to alpha- and beta-blockers [147,148]. Antihypertensive drugs that lower 24-h BP may have different effects on nocturnal BP in dippers and nondippers. For example, in the PeRindopril prOtection aGainst Recurrent Stroke Study (PROGRESS) [149], the ACE inhibitor, perindopril, induced a sustained decrease of 24-h BP in hypertensive patients with lacunar infarction, but the greatest reduction in nighttime BP was seen in nondippers who have a higher incidence of cerebrovascular disease, raising the possibility that better control of nighttime BP may have been achieved in nondippers thereby benefiting outcome [150,151].

In older individuals with systolic hypertension, dihydropyridine CCBs and thiazide diuretics lowered daytime BP to a greater extent than did ACE inhibitors or beta-blocking drugs. Perindopril had the greatest effect on nocturnal BP, whereas atenolol did not lower nocturnal BP [152].

Whatever the explanation for the varying effects of different groups of antihypertensive drugs, which need to be assessed in more detail in prospective studies, that some drugs may accentuate nocturnal dipping, that others may blunt the normal nocturnal fall in BP, and that others have no effect on diurnal rhythmicity, raises important questions in assessing antihypertensive drug effect and in choosing a drug for an individual patient.

Individualized antihypertensive medication targeting abnormal diurnal patterns may offer particularly good protection in high-risk groups, such as patients with a rise in nocturnal BP, extreme dippers, and patients with a morning surge in BP [148,153]. However, drugs may vary in their ability to alter the nuances of nocturnal BP [154]. For example, in one study the comparison of an ARB with a CCB showed that although both drugs significantly reduced 24-h mean BP compared with placebo, treatment effect was greatest with the ARB, especially during the morning period. Importantly, BP measured in the clinic failed to detect differences between the two classes of drug [155].

The superiority of one ARB over another in reducing morning BP may be due to the duration of action of different drugs—ARBs with a longer half-life being superior to those that do not achieve full 24-h effect [156-161]. For example, a study comparing the ARB telmisartan, which has a long half-life, with valsartan, which has an intermediate half-life, showed that the former drug lowered both systolic and diastolic BP to a greater extent than did the latter during the last 6 h of the dosing interval. In addition, on a day in which a dose was missed, there was a notable trend for greater BP reduction during the latter part of the dosing interval on telmisartan versus valsartan [158].

The inability of clinic BP to give any indication of antihypertensive drug effect on the nocturnal phenomena, such as the morning surge, is illustrated in two prospective, observational studies in treated patients with hypertension [162,163]. Again, many patients who appeared to have well-controlled BP on routine clinic measurement had uncontrolled BP during the early morning hours.

As much of the morning surge may be mediated by involvement of the renin-angiotensin system, it would seem logical to assess drugs that target angiotensin II [164]. Another mechanism worthy of manipulation to enhance nocturnal pharmacological therapy is dietary potassium supplementation and sodium restriction to restore normal dipping [165]. The consistent lowering of nocturnal BP by the renin inhibitor aliskiren in combination with a thiazide diuretic, an ACE inhibitor, or an ARB is another potential therapeutic strategy for reducing nocturnal hypertension [166].

There are many studies showing that an elevated nocturnal BP or a diminished nocturnal fall in BP is associated with poor CV outcome both in populations [167-170] and in patients with hypertension [21,48, 171-173]. Isolated nocturnal hypertension, which may be present in 7% of patients with hypertension, can be diagnosed only with ABPM, and its presence in patients in antihypertensive drug trials could have an important influence on the 24-h efficacy of BP-lowering drugs.

Recent analyses of the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) confirmed what had been previously shown in the Dublin Outcome Study, namely, that one SD elevation of the nighttime systolic and diastolic BP increased CV risk by approximately 20%, whereas daytime BP did not independently predict mortality outcomes, and was only associated with CV, coronary, and stroke events (**Figure 3**) [48,174]. As was once said so truly of hypertension—the only way of diagnosing the condition is by measuring the BP—is true of nocturnal hypertension as well: that is, the only means of diagnosing the condition and characterizing its magnitude is by performing 24-h ABPM. Whatever the difficulties may be in implementing ABPM in clinical practice so as to be able to diagnose nocturnal BP, there can be no scientific justification for performing clinical trials without being able to detect the effect of antihypertensive medication on nocturnal BP [175,176].

Chronotherapy: the timing of dosing

Traditionally, BP-lowering drugs with a once-daily regimen of administration are taken in the morning. It is perhaps surprising how little attention has been paid to the possibility of achieving a more beneficial effect on CV outcome by reducing nocturnal BP either by nighttime dosing or by designing drugs aimed specifically to reduce nocturnal BP. ABPM permits prescribing doctors to identify the best timing of drug administration to achieve BP control not only over the 24-h period but also to target windows of the 24-h profile in which BP elevation is present [177]. This chronotherapeutic approach is justified not only by evidence showing the superiority of ABPM in predicting CV outcomes in both treated and untreated patients with hypertension [23,48,170], but also by data showing that inadequate control of BP may be particularly detrimental during nighttime and morning hours [176,178,179].

The importance of 24-h BP coverage has been well illustrated in the HOPE study [99]. In the main study, the group receiving ramipril had approximately 35% fewer CV events, despite an insignificant reduction in BP of 3/2 mmHg; the outcome benefit was attributed to ACE inhibition, which was recommended in all high-risk patients regardless of baseline BP. However, it became evident from a later analysis of the ABPM substudy that ramipril was actually taken in the evening with clinic BP measured some 10 to 14 h later the following day [55]. The reported insignificant change in BP in the main study gave no indication of a "whopping" 17/8 mmHg reduction in BP during the nighttime period, which translated into a 10/4 mmHg average reduction in BP over the entire 24-h period [180].

There is evidence that evening administration of drugs may achieve better nocturnal and morning BP control than may customary dosing in the morning [181-187]. There is also evidence that evening dosing may not only reduce nocturnal BP more than when drugs are administered in the morning, but that patients with a nondipping nocturnal pattern may revert to normal dipping [186,188,189].

Evidence to date clearly suggests that pharmacological research should be directed toward designing drugs with the primary purpose of modifying nocturnal manifestations of hypertension. However, it should also be possible to modify nocturnal BP using the drugs or drug combinations presently available with 24-h BP coverage. Hermida and colleagues examined the hypothesis that nondipping in patients with hypertension might be due, at least in part, to the absence of 24-h therapeutic coverage in patients treated with single morning doses. They showed that in patients taking bedtime medication, ABPM control was double that of patients taking morning medication. Moreover, in patients with true resistant hypertension, bedtime medication resulted in a significant

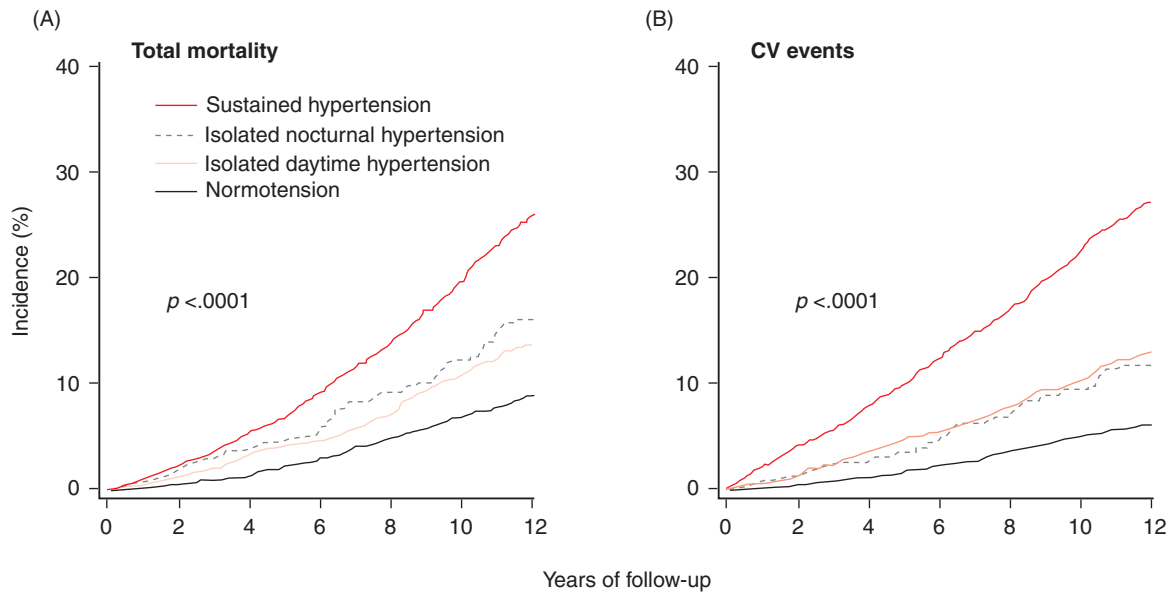

Figure 3. Cumulative incidence of total mortality (A) and all cardiovascular (CV) events (B) by ambulatory blood pressure status. *p* values are for the differences among the 4 categories by log rank test.
(Reproduced with permission from Fan HQ, Li Y, Thijs L, et al; on behalf of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from10 populations. *J Hypertens* 2010;28(10):2036-2045)

reduction in the 24-h mean of systolic and diastolic BP, and this reduction was much more prominent at nighttime [190]. Bedtime dosing with an ACE inhibitor in patients with a nondipping pattern of hypertension improves efficacy during the nocturnal period [191]. However, in 42,947 treated patients in the Spanish Society of Hypertension Ambulatory Blood Pressure Monitoring Registry, nondipping was associated with the use of a higher number of antihypertensive drugs but not with the time of day at which antihypertensive drugs were administered [192].

Antihypertensive medication directed at nighttime BP may not necessarily alter nocturnal hypertension patterns for the better. For example, a nondipping or dipping pattern could be transformed into an extreme dipping pattern with injudicious therapy. The objective should be to reduce BP at the same time as preserving the physiological circadian dipper pattern. This is particularly important in stroke survivors, in whom ABPM is mandatory because it determines the appropriate dose of antihypertensive drug and the optimum time of administration to avoid inducing nondipper, riser, and extreme dipper circadian profiles with treatment [193].

Given the extensive evidence for the increased prevalence of CV events in the early morning hours, antihypertensive drugs that provide BP control during the early morning surge should provide greater protection against target organ damage and enhance patient prognosis. This period has been dubbed the "blind spot" in current clinical practice [194]. Pharmacological research into ways of altering the morning surge is limited [195]. However, reduction of the morning surge in BP may be beneficial in preventing target organ involvement in hypertension [196].

Chronotherapy in hypertension for alpha-adrenoceptor antagonists, beta-adrenoceptor antagonists, diuretics, ACE inhibitors, ARBs, and CCBs has been reviewed recently by Smolensky and his colleagues [197]. There were clinically significant treatment–time differences in the beneficial and/or adverse effects in these 6 different classes of BP-lowering drugs. Generally, CCBs were more effective at bedtime than at morning dosing, and, in the case of dihydropyridine derivatives, bedtime dosing significantly reduced the risk of peripheral edema. ARBs and ACE inhibitors given at bedtime, as opposed to awakening, not only improved overall BP control but also tended to convert nondippers to dippers, as well as reducing urinary albumin excretion. While the therapeutic and prognostic implications of these findings require further evaluation, they provide cogent evidence in favor of assessing the effects of antihypertensive therapy on sleeping BP.

Parati and Bilo pointed out that the benefits of nocturnal dosing should be apparent only with relatively short-acting drugs and would not be expected with drugs that have a long and sustained action with trough-to-peak ratio close to 100% [177]. However, there are other pharmacokinetic factors that influence the plasma levels of antihypertensive drugs, such as the influence of circadian rhythms on gastric pH and emptying, gastrointestinal motility, biliary function and circulation, glomerular filtration, liver enzyme activity, and blood flow to the duodenum, kidney, and other organs [181].

Finally, it would be remiss to leave the subject of chronotherapy without stating that there is no evidence that evening administration of antihypertensive drugs will have a beneficial effect on CV outcome; in so doing the need for such studies is emphasized.

BENEFIT OF TREATMENT ON OUTCOME

It is beyond the scope of this review to examine in detail the growing number of studies in which ABPM has been used as a marker of CV morbidity and mortality. However, it is relevant to consider briefly how ABPM has been used 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. This has been due to the results of a number of studies showing that ABPM parameters may be more accurate predictors of CV risk [21,23,48,198-203]. These studies suggest that, in order to improve the CV risk profile of patients with hypertension, optimal antihypertensive therapy should provide sustained BP reduction and smooth BP control over the full 24-h period. ABPM is not only superior to conventional BP in predicting morbidity and mortality, but also that BP in certain periods of the 24-h profile, such as in the nocturnal and matinal windows, may be especially sensitive predictors of outcome, which makes it important to study the response to drug treatment during these periods in outcome studies [21,48, 204-207]. Quite apart from the fact that BP elevation in certain windows of the 24-h cycle may predict outcome, there is additionally a tendency for CV events to occur more often in the early morning period [208,209].

A number of major outcome studies have undertaken ancillary trials using ABPM to further examine the results of the main study [99,210-213]. Because ABPM is a more demanding technique than clinic BP, ancillary studies using ABPM have smaller numbers than the main study, and this can result in the ancillary study population being unrepresentative of the main study population. Moreover, ancillary studies often lack a baseline ABPM, making it impossible to determine the transition from no treatment at baseline to the effect of full-dose medications [214].

Generally, these ancillary studies have shown that 24-h ABPM predicts outcome better than conventional BP and that the nighttime BP is more predictive than daytime BP. Clinic BP measurement is invariably higher than ABPM due to a white coat reaction with the former measurement, which is absent with ABPM. Indeed, whereas a white coat effect is common in patients with hypertension, ABPM may show that patients recruited for outcome studies based on clinic BP may in fact have ambulatory normotension, that is, WCH. This condition cannot be avoided even if a high clinic BP is made a requirement for recruitment. 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 [212]. Other factors for consideration in outcome studies are:

1. The greater reduction in clinic BP may be due in part to a placebo effect, which is largely absent with ABPM.
2. ABPM reductions in BP will demonstrate a J-curve phenomenon should this be induced by treatment.
3. Heart rate changes on ABPM can give a measure of therapeutic effect with drugs, such as beta-blockers or dihydropyridine calcium antagonists, which might be expected to modulate heart rate and influence outcome.
4. Clinic BP shows only a weak relationship with 24-h average BPs, confirming the limited ability of clinic BP to reflect BPs in daily life [212].

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CURRENT REGULATORY RECOMMENDATIONS IN CLINICAL TRIALS

From the foregoing review, it is abundantly evident that the scientific argument for using ABPM in all studies assessing the efficacy or long-term protective benefits of BP-lowering drugs is irrefutable and there can no longer be a case for performing such studies using clinic BP as the measure by which efficacy is judged. This being so, the next step in this review is to examine the recommendations of the regulatory bodies on the use of ABPM in trials of antihypertensive drugs.

Recommendation of the US Food and Drug Administration

The US Food and Drug Administration (FDA) guidelines, which are still in draft form, state: "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 (pre-dosing) blood levels can also be used" [215,216]. The document also suggests that ABPM is "perhaps" not subject to bias. The primary purpose of the guideline is to obtain values for the trough-to-peak ratio regardless of how BP is measured.

Recommendation of the European Medicines Agency

The current European Medicines Agency (EMA) guideline unequivocally recommends ABPM in clinical trials: "As ambulatory blood pressure monitoring (ABPM) provides a better insight to blood pressure changes during everyday activities and is better standardised than casual readings, ABPM is required for the evaluation of new antihypertensive agents" [217]. The EMA draft revision guideline drawn up by the Committee for Medicinal Products for Human Use (CHMP), "Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension," is however, somewhat ambivalent in its general recommendations on BP measurement. First, clinic BP is put forward as the standard: "Measurements with a calibrated mercury sphygmomanometer are the standard. If not available, another device may be used which is calibrated carefully in proportion to a mercury sphygmomanometer." This statement is followed by the requirements for conventional measurement of BP and, as these stipulations preface the preceding recommendation for ABPM, it could be interpreted that conventional measurement is still permissible for the evaluation of the efficacy of BP-lowering drugs. However, presumably this recommendation applies only to the requirements for clinic BP measurement, which will, of course, continue to be used in pharmacological trials. It should not, therefore, diminish the positive recommendation for ABPM, which is a major step forward in that the term *required* must now be taken to mean that ABPM at last is *mandatory* in all studies for the evaluation of antihypertensive drugs [218]. The guideline then goes on to stipulate the requirements for ABPM.

Proposed modification to the recommendation of the European Medicines Agency

The European guideline (like that of the US guideline) tends toward the view that the value of ABPM can be derived from simple analysis of day- and nighttime BP and that the technique provides a convenient method for determining peak efficacy with trough efficacy being assumed to be the value just before administration of the following day's dose. In doing so, it disregards the potential for ABPM to easily collect data that can provide valuable information on antihypertensive drug effect in different windows of the 24-h profile.

The EMA recommendations could be greatly improved. First, the requirement for readings every 15 min during the daytime can be difficult to obtain and, more importantly, the frequency of recording interferes with normal activity. If there is need for a repeat measurement, the interval is effectively reduced to 12 min. Second, the requirement for two or one evaluable measurements during every hour of the day and night, respectively, does not make it clear if "every hour" refers to hours denoted by the hour part of the time or whether the gap between two measurements cannot be greater than 60 min. The distinction is important because if it refers to a gap, then a single missed reading at night followed by a repeat reading would result in a gap of about 63 min and the failure of the ABPM. Hourly mean pressures based on weights of readings covering the standard hours are preferred. 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 nighttime periods.

With regard to the accuracy of devices for ABPM, the EMA recommendations stipulate that ABPM devices must fulfill international validation procedures, such as the protocols of the Association for the Advancement of Medical Instrumentation (AAMI) or British Hypertension Society (BHS), whereas the International Protocol of the European Society of Hypertension (ESH; which has just been revised [219,220]) is now the protocol that is most used for the independent validation of devices (**Figure 4**) [221]. Only those ABPM devices that have been validated and recommended for clinical use should be acceptable for studies of antihypertensive drug efficacy (see http://www.dableducational.org).

The EMA recommendation that ABPM devices providing BP measurement by both auscultation and oscillometry are preferred is obsolete and should be removed. The dabl Educational Trust Website lists 4 such devices, 3 of which are discontinued and therefore obsolete. The remaining listed device—the Nissei DS-250—was validated in 2003 and, as the validation data were inadequate, the device is rated as being of questionable accuracy and therefore it is not recommended for clinical use [222].

The EMA stipulation for performing ABPM on like days should not confine repeat ABPMs to the same day of the week but rather emphasize that ABPM recordings should be performed on days when there is a similar activity profile—either recreational or working days, which should not be interchanged [223]. The recommendation that the same recorder be used for repeat ABPM measurements is impractical. The recommendation should rather stipulate that the same type of device be used throughout the study. Finally, the EMA recommendations should include a computerized methodology to facilitate the performance of clinical trials and to permit standardized collection of data so as to be able to readily compare the results of different trials.

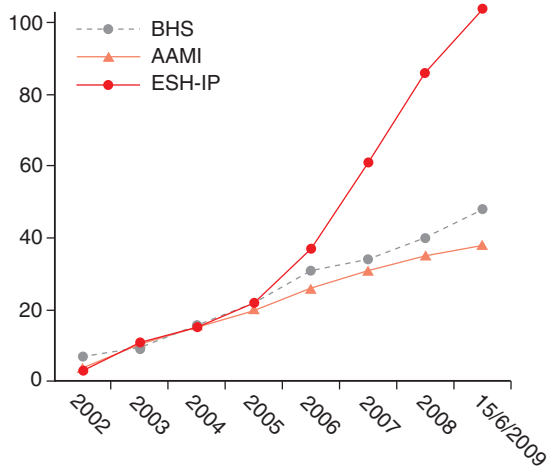

Figure 4. Cumulative graph of validation studies performed according to the European Society of Hypertension International Protocol (ESH-IP) compared with the British Hypertension Society (BHS) and Association for the Advancement of Medical Instrumentation (AAMI) protocols from 2002 (publication of ESH-IP) until June 2009. (Reproduced with permission from Stergiou G, Karpettas N, Atkins N, O'Brien E. European Society of Hypertension International Protocol for the validation of blood pressure monitors: A critical review of its application and rationale for revision. *Blood Press Monit* 2010;15:39-48)

FACILITATING USE IN CLINICAL TRIALS

The use of ABPM in both clinical practice and research has been hampered by both manufacturers and researchers having concentrated on the development and means of validating the accuracy of devices—the hardware—rather than directing attention to presentation and analysis of data—the software—so as to make the technique more user-friendly and acceptable to clinicians and researchers.

The Conway Institute, University College Dublin, in association with dabl Limited, has been endeavoring to redress this imbalance and has developed the dabl ABPM system to facilitate the wider use of ABPM in the clinical management of hypertension [1,45,46,69,145,223,224]. The use of this custom-designed software system for the analysis of ABPM has facilitated the application of ABPM in primary care by showing clearly on a standardized plot the windows of the 24-h profile, the normal bands for systolic and diastolic BP, the recorded levels of BP throughout the 24-h period, as well as a computer-generated interpretative report (**Figures 5** to **8**).

Together with central hosting of data, the dabl ABPM system has provided valuable demographic information in research [48,53,225], and it is now used in many centers internationally. The analysis of ABPM data and the reported diagnoses by the dabl ABPM system has been shown to be more accurate than reporting of ABPM data by expert observers [224].

As stated previously, the advantages of ABPM are such that there can be no scientific argument against ABPM being mandatory in all studies of drug efficacy. There are, however, practical obstacles, which have militated against the wider use of ABPM in such studies, especially in prospective multicenter trials. These include the lack of familiarity with the technique, the need for trained personnel, the need to standardize the methodology, the need for electronic collection and monitoring of data so as to be able to inform investigators in real-time as to the success or otherwise of ABPM recordings, and the cost of the procedure, which, though higher than conventional BP measurement, provides so much additional information that the benefits make the procedure very cost-effective. Finally, the goal levels for reduction of both daytime and nighttime BPs need to be determined and real-time analysis and transmission to the investigators of the target ABPM levels achieved have to be feasible.

The dabl ABPM system has now been developed to incorporate these requirements into the smooth performance of pharmacological trials. The preceding review has shown that the requirements for ABPM in studies of antihypertensive drug efficacy must include the following basic facilities:

Figure 5. Schema of ambulatory blood pressure.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
(Plot and report generated by dabl ABPM—© dabl 2010 [http://www.dabl.ie])

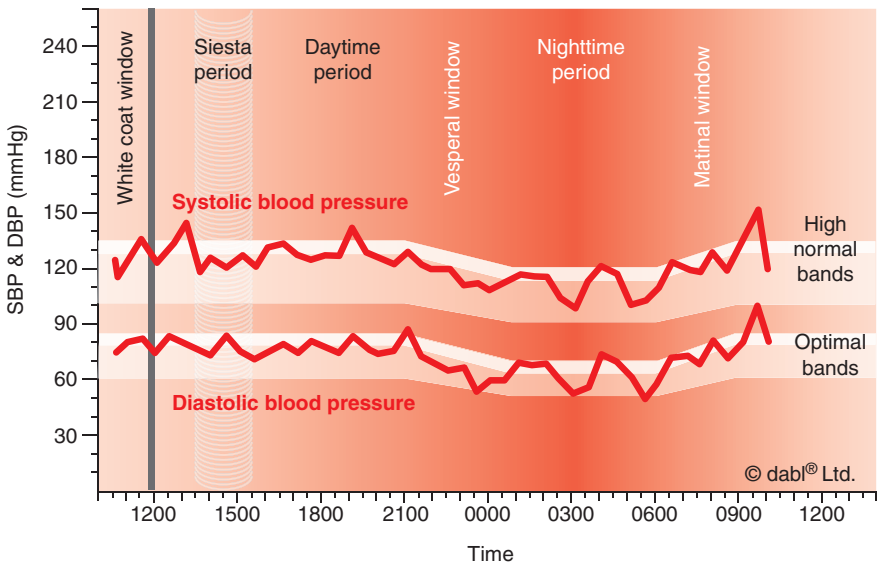

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Figure 6. Ambulatory blood pressure monitoring shows white coat hypertension (175 mmHg/95 mmHg) with otherwise normal 24-h systolic blood pressure (SBP; 133 mmHg daytime, 119 mmHg nighttime) and optimal 24-h diastolic blood pressure (DBP; 71 mmHg daytime, 59 mmHg nighttime). Normal dipping pattern.
(Plot and report generated by dabl ABPM—© dabl 2010 [http://www.dabl.ie])

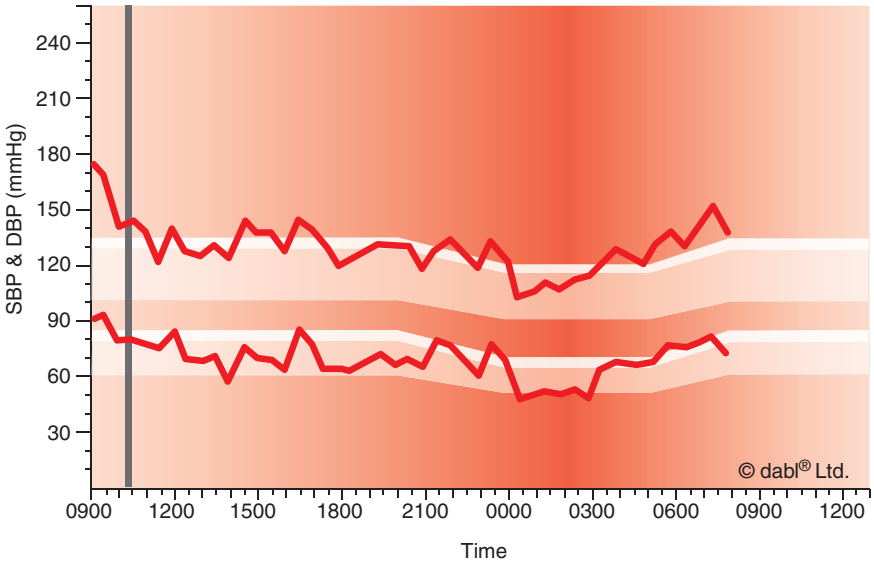


Figure 7. Ambulatory blood pressure monitoring shows mild daytime systolic hypertension (150 mmHg), borderline daytime diastolic hypertension (87 mmHg), borderline nighttime systolic hypertension (123 mmHg) and normal nighttime diastolic blood pressure (68 mmHg) with a white coat effect (187 mmHg/104 mmHg). Normal dipping pattern.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
(Plot and report generated by dabl ABPM—© dabl 2010 [http://www.dabl.ie])

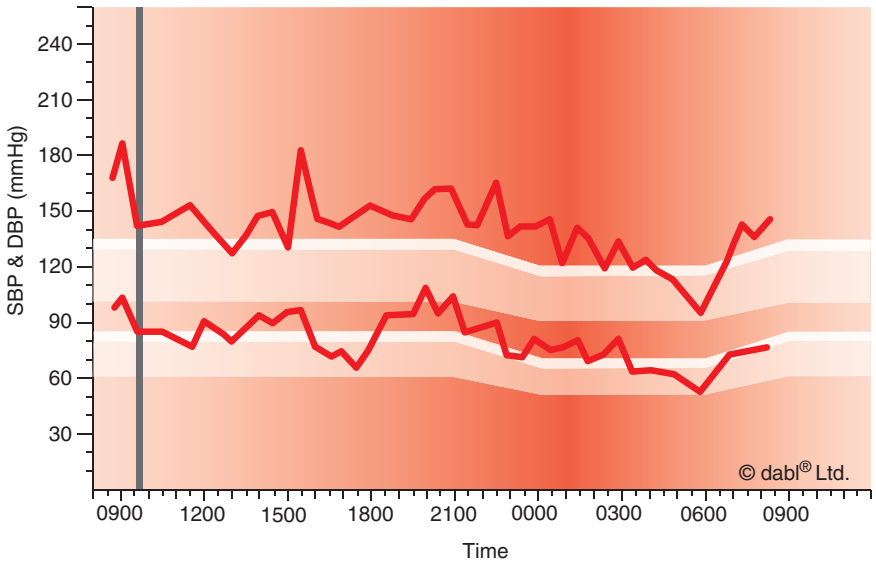
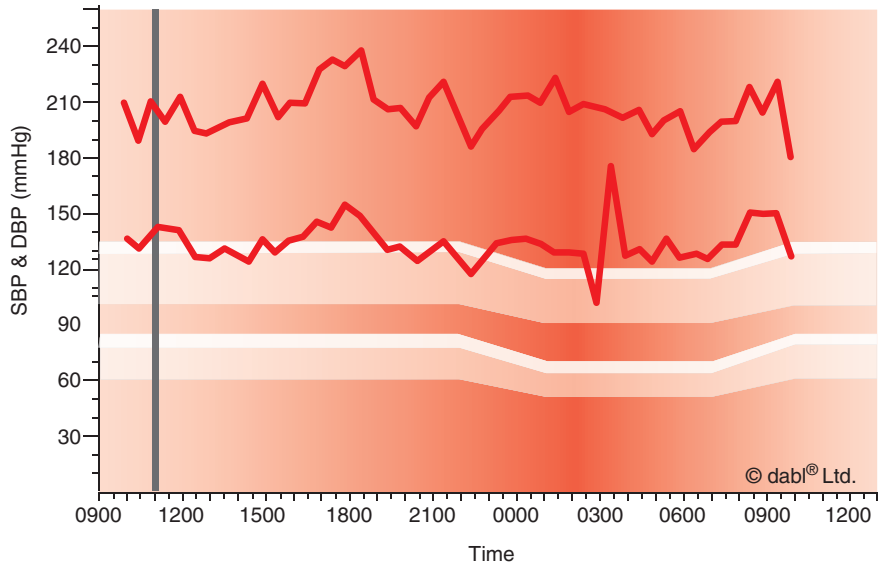


Figure 8. Ambulatory blood pressure monitoring shows severe 24-h systolic and diastolic hypertension (209 mmHg/135 mmHg daytime, 205 mmHg/130 mmHg nighttime). Nondipping pattern.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
(Plot and report generated by dabl ABPM—© dabl 2010 [http://www.dabl.ie])



1. 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
2. Provision of real-time analysis of ABPM data so as to be able to alert the investigator to the validity or otherwise of the ABPM
3. Organization of ABPM data so as to permit ongoing analysis
4. Flexibility of the system so that it can be adapted to accommodate studies of differing design

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.

CONCLUSIONS

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 sleeping pressure. Home measurement of BP, though 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. As noninvasive ABPM has a negligible placebo effect, it is now possible to consider efficacy studies, which need not have a placebo phase, thus simplifying the design of antihypertensive studies. Moreover, the provision of considerably more observations than is possible with clinic BP measurement, by reducing within-subject variability and increasing the power of studies, may reduce substantially the numbers of patients needed for such studies.

From the scientific viewpoint, it is now time to utilize the technique to obtain a fuller understanding of the patterns of drug-induced lowering of BP than was ever possible with conventional clinic BP measurement. The following was written in 1991: "The time has surely come when antihypertensive drug efficacy studies that do not assess blood pressure over 24 hours should no longer be acceptable." That this plea has not become reality some 20 years later must be seen as an indictment of clinical science [226].

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