Assessing Blood Pressure Responses to Noncardiovascular Drugs: The Beneficial Role of Ambulatory Blood Pressure Monitoring

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It has become apparent that noncardiovascular drugs can affect blood pressure (BP) in an off-target manner, either by raising or lowering pressure or by negating the beneficial hypotensive effect of concomitantly prescribed antihypertensives. This paper presents compelling evidence that ambulatory blood pressure monitoring (ABPM) should be used to detect BP effects during the development of noncardiovascular drugs. The requirements for standardizing ABPM to obtain the most information from the least number of participants and the many advantages of obtaining a 24-hour BP profile are discussed. The use of ABPM in trials of antihypertensive agents, though differing in purpose (the demonstration of BP-lowering efficacy) from the use of ABPM in trials of noncardiovascular drugs (the demonstration of any off-target effect on BP) nonetheless provides methodological similarities that can be applied in both contexts with advantage. The paper also considers whether there are lessons to be learned from a regulatory science approach that is designed to prospectively identify unacceptable off-target cardiac effects of noncardiac drugs and offers some thoughts on how a future paradigm of standardized use of ABPM to assess off-target BP effects during the development of noncardiovascular drugs might benefit patient safety. *J Clin Hypertens (Greenwich)*. 2013; 15:55–62. ©2012 Wiley Periodicals, Inc.

It has become clear that noncardiovascular drugs can raise or lower blood pressure (BP) in an off-target manner. The clinical relevance of small and transient, off-target drug-induced changes in BP to symptomatology, morbidity, or mortality is not known because the subject has not been systematically studied. However, Grossman and Messerli[1] recently observed that "severe hypertension involving encephalopathy, stroke, and irreversible renal failure have been reported." Off-target BP responses have therefore garnered increasing scientific and regulatory interest in recent years, being addressed at various conferences and in the literature (Table).[14,15] Considerable attention is now being paid to designing an appropriately informative assessment strategy that can be employed in noncardiovascular drug development programs to prospectively identify such BP responses.

While increases will likely attract more attention, decreases of certain magnitudes are also undesirable, particularly in some patient populations. Additionally, interactions between noncardiovascular drugs and antihypertensives that may either negate or potentiate hypotensive efficacy have received little study to date, but it can be reasonably assumed that many drugs either reduce or potentiate the BP-lowering effect of antihypertensive medication. For example, Grossman and Messerli[1] noted that rifampicin, a bactericidal antibiotic that induces CYP3A4 and P-glycoprotein, considerably reduces the plasma concentrations and the renin-inhibiting effect of aliskiren and some calcium antagonists by decreasing oral bioavailability. Sitagliptin, a dipeptidyl peptidase-IV inhibitor used to reduce hyperglycemia in diabetic patients, has been shown to attenuate the BP-lowering effect of high-dose enalapril by stimulating the sympathetic nervous system.[1]

One component of any assessment strategy formulated to prospectively identify BP responses of concern with noncardiovascular drugs is the methodology used to obtain BP data. This paper provides evidence to support the argument that ambulatory BP monitoring (ABPM) should be employed in this context. However, while appreciating the ability of ABPM to detect small drug-induced effects on BP at different periods of the 24-hour cycle, it is also recognized that the application of ABPM for this purpose demands a standardized methodology and stringent analysis of data.

LEARNING FROM ABPM APPLICATIONS IN THE DEVELOPMENT OF ANTIHYPERTENSIVE DRUGS

Traditionally, effects of drugs on BP have been assessed with conventional clinic BP measurement (CBPM) using the technique introduced into clinical medicine in 1896 by Riva-Rocci and Korotkoff. Despite being associated with many inaccuracies, this technique has survived largely unchanged for more than a century.[16,17] This, in turn, means that many pharmacologic studies of antihypertensives continue to rely on CBPM to assess drug-induced BP changes. While these studies may be well conducted and may indeed show an effect on BP at the "snapshot in time" at which a measurement is taken (which may only be at one point in a 24-hour cycle, typically during daytime hours), they cannot provide information on the duration of an effect on BP or its effect during the nocturnal period.

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Manuscript received: July 11, 2012; **revised:** August 12, 2012; **accepted:** August 22, 2012
DOI: 10.1111/jch.12023

By contrast, ABPM methodology confers several advantages over CBPM in demonstrating drug effects on BP. First, the "white-coat effect" in the clinic is now well established in the literature.[18] In contrast, the white-coat effect has little or no effect on average ABPM levels. Although 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),[19] the average BP measurements during daytime and nighttime periods are devoid of the white-coat effect. This is in contrast to all measurements obtained by CBPM, which are affected when this phenomenon is present. This has two consequences for investigations of drug-induced changes in BP. First, a rise in BP detected by clinic measurement may be erroneously attributed to the drug, whereas the rise is actually due to a white-coat reaction. Second, no effect on clinic pressure (or a reduction therein) may be mistakenly adjudged to be of little or no consequence, whereas the real reduction in BP would have been greater had it not been masked by the white-coat effect.

The use of ABPM in pharmacologic trials assessing the efficacy of BP-lowering drugs is now reasonably well established.[17,20]

An Example of Information Provided by the Employment of ABPM in a Substudy

Since the mechanisms determining BP may differ at different times within the 24-hour cycle, it is not surprising that drugs can vary in their effects in these windows of time.[21,22] The ability of ABPM to detect BP changes that CBPM had failed to identify has been well illustrated in the Heart Outcomes Prevention Evaluation (HOPE) study.[23–27] In the main study, the group receiving ramipril had approximately 35% fewer cardiovascular events, despite an insignificant mean reduction in systolic BP (SBP) of 3 mm Hg and in diastolic BP (DBP) of 2 mm Hg (3/2 mm Hg): the outcome benefit was attributed to angiotensin-converting-enzyme (ACE) inhibition, which was recommended in all high-risk individuals regardless of baseline BP. However, it became evident from a later analysis of the ABPM substudy that ramipril was actually taken in the evening while CBPM occurred around 10 to 14 hours later the following day.[26] The reported insignificant change in BP in the main study gave no indication of a "whopping 17/8 mm Hg reduction in BP during the evening hours," which translated into a 10/4 mm Hg average reduction over the entire 24-hour period.[27]

The HOPE study was designed to prove the beneficial effect of a drug on cardiovascular outcome, and were it not for the ABPM study, the interpretation of the results could have had a major impact on clinical practice. It is not unreasonable to make the case that a similar misinterpretation of BP effect for a noncardiovascular drug is possible if only CBPM is used to assess BP effect.

While the intents of trials examining on-target and off-target BP responses differ (ie, provide compelling evidence of efficacy for antihypertensives, and prospectively exclude unacceptable cardiovascular risk for noncardiovascular drugs), the methodological considerations for ABPM in the two contexts are very similar, as are the advantages conveyed.

ASSESSING BP RESPONSES TO NONCARDIOVASCULAR DRUGS

In an influential Letter to the Editor of the *Drug Information Journal*[28] in response to an Expert Commentary published in the same journal addressing the use of ABPM in trials of new antihypertensive agents,[16] Dr Norman Stockbridge (Division of Cardiovascular and Renal Products, US Food and Drug Administration) raised the question of "whether *all* systemically available drugs intended for chronic use merit a careful assessment of their effects on vital signs by ABPM."[28] This prescient question has since been discussed in sessions at several cardiovascular safety conferences that have subsequently been cited in the literature.[14,15]

ABPM provides a profile of BP behavior over a 24-hour period rather than simply providing a snapshot in time as is provided by clinic measurement. This profile allows assessment of the effects of noncardiovascular drugs not only aggregated over the entire 24-hour period but also during specific windows of this time cycle. For example, the circadian cycle can be divided into white-coat, daytime, siesta, vesperal (evening), nighttime, and matinal (morning) windows. A number of patterns may be observed in these windows: the white-coat effect; a siesta dip; dipping, nondipping, reverse dipping, and excessive dipping; and the morning surge in the nocturnal period. Dipping and nondipping are terms used to describe the most common nocturnal patterns of BP behavior; the majority of people show reduced BP at night (some excessively so when extreme dipping occurs), and about 30% of people have nondipping patterns, when BP remains similar to daytime BP, or occasionally rises above daytime BP (reverse dippers). Measurements of SPB and DPB, and also heart rate, can be analyzed to assess potential drug effects during each of these periods.[22]

The most important measures of circadian variation are the nocturnal dip and the morning surge.[22,29] Nocturnal hypertension (or a nondipping pattern) is the most important finding associated with increased target organ involvement and increased cardiovascular morbidity and mortality. An elevated nocturnal BP or a diminished nocturnal fall in BP is associated with poor cardiovascular outcome in populations[30,31] and also in patients with hypertension.[32–34] For example, 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 a 1 standard deviation elevation of the nighttime SBP and DBP increased cardiovascular

risk by approximately 20%, whereas daytime BP did not independently predict mortality outcomes, and was only weakly associated with cardiovascular, coronary, and stroke events.[29,35] Whatever the difficulties may be in implementing ABPM in clinical practice to facilitate diagnosis of elevated nocturnal BP, there can be no scientific justification for performing clinical trials without being able to detect the effect of drugs on nocturnal BP.[36,37]

Additionally, and independently from the fact that BP elevation in certain time windows may predict outcome, there is a tendency for cardiovascular events to occur more frequently in the early morning period.[38,39] Given the extensive evidence for the increased prevalence of cardiovascular events in the early morning hours, it becomes important to assess the possibility that noncardiovascular drugs might induce or accentuate this phenomenon. This period has been dubbed the "blind spot" in current clinical practice.[40]

Recently, BP variability has also been shown to be an important prognostic marker.[41,42] Its prognostic impact is largely dependent on the variability of BP over time, but the many measures of variability that may be obtained from ABPM facilitate the assessment of the effect of noncardiovascular drugs on this parameter.[43]

CONSIDERATION OF AN EXISTING REGULATORY LANDSCAPE

While there is currently no regulatory guidance published on the assessment of circadian BP changes induced by noncardiovascular drugs, it is of interest to consider the potential nature of such documentation. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E14, entitled "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs,"[44–46] constitutes a regulatory landscape that initially might suggest itself as informative in the current context. It employs a combination of clinical, statistical, and regulatory science to address an issue involving off-target responses to noncardiac drugs.[47] The guideline describes the Thorough QT/QTc (TQT) study, a dedicated trial that rigorously assesses an investigational drug's proarrhythmic liability by characterizing drug-induced QT/QTc interval prolongation as a cardiac safety biomarker for arrhythmogenesis. A regulatory "threshold of concern" for drug-induced QT/QTc interval prolongation is provided by ICH E14. However, breaching this threshold does not equate by itself to failure to secure marketing permission no matter what. At the time of marketing application, the greater the severity of the drug's indication and the fewer currently available treatments there are for it, the more likely a drug is to be approved for a given degree of QT/QTc prolongation. If approved, the drug's labeling will carry information concerning its degree of QT/QTc prolongation.[48,49]

With the exception of a relatively small number of test drugs for which a classical TQT study is not feasible[50] (and for which the most thorough evaluation feasible still must be conducted), the TQT can be meaningfully regarded as a "one study fits all" scenario. However, several considerations suggest that a similarly styled "Thorough BP Study" (TBP study) would not be appropriate in the current context. First, as opposed to the singular measure of magnitude of change in the TQT study (waveform morphology is also of interest, but is currently not as quantifiable as the TQT interval and hence is not addressed to the same extent), several measures of BP are candidates for assessment: SBP and DBP individually, the pattern of SBP and DBP change, pulse pressure, and perhaps characteristics such as pulse wave velocity. Second, the participants employed in TQT studies are typically healthy young adults. Given the physiological complexities of BP determination, it is feasible that results from a purported TBP study would not be representative of responses to the drug in certain patient populations, eg, the more elderly. Such considerations would argue for BP assessments in phase II trials where the participants would be representative of the target population of patients should the drug be approved.

Third, BP alterations can result from a variety of mechanisms of action. As Grossman and Messerli[1] observed, "Some agents cause either sodium retention or extracellular volume expansion, or activate directly or indirectly the sympathetic nervous system. Other substances act directly on arteriolar smooth muscle or do not have a defined mechanism of action. Some medications that usually lower BP may paradoxically increase BP, or an increase in pressure may be encountered after their discontinuation." Thus, a given BP increase can result from various underlying patterns of physiological response, and thought must therefore be given to the potential significance of different routes of arriving at the same BP change and to the degree of desirability of assessing these patterns. Whatever approach crystallizes for regulators (some thoughts on this topic are offered later in the paper), it seems reasonable to expect that, in contrast to the TQT study, a one-size-fits-all TBP study approach is unlikely to be chosen. However, should regulators in certain jurisdictions choose to recommend a TBP study approach, these authors would strongly advocate for the use of ABPM in such a study.

It would still be expected, however, that, as for QT/QTc prolongation liability, benefit-risk analysis would be a crucial aspect of regulators' deliberations at the time of marketing application. More rigorous assessment of the benefit-risk balance is receiving increasing interest.[51,52] It is now well acknowledged that striking the right balance between maximization of efforts to ensure drug safety to the greatest degree possible before approval in a transparent manner while doing everything possible to avoid discouraging therapeutic innovation and new drug development is a major challenge.[53]

FINANCIAL, PRAGMATIC, AND STATISTICAL IMPLICATIONS OF EMPLOYING ABPM

Since this paper addresses the use of ABPM in a novel setting (ie, assessments of the cardiovascular safety of noncardiovascular drugs) it is difficult to provide definitive commentary on its cost effectiveness at this point in time. However, some degree of insight can perhaps be gleaned from assessments of the cost-effectiveness of ABPM in clinical practice. Cost-benefit analyses have shown that ABPM is cost-effective in both primary care and specialist services and hence cost effective for the diagnosis and management of newly diagnosed hypertension.[54–56] Recently, the UK's National Institute for Health and Clinical Excellence (NICE) undertook the most detailed ABPM cost-benefit analysis ever conducted and clearly demonstrated that the use of ABPM would result in substantial savings to the UK National Health Service. This analysis indicated that ABPM is the most cost-effective method of confirming a diagnosis of hypertension in a population suspected of having high BP based on a conventional BP screening measurement >140/90 mm Hg.[57,58]

Again, in the clinical context (detecting white-coat or masked hypertension, determining the presence or absence of nocturnal dipping status, and evaluating BP control in patients on antihypertensive therapy), White and Maraka[59] observed that "While the advantages of ABPM are apparent from a clinical perspective, its use should be considered in relation to the cost of the equipment, data evaluation, and staff training as well as the possible inconvenience to the patient." Moving now to the clinical trials arena, employment of ABPM will have financial implications in terms of the cost of the equipment, data evaluation, and staff training and pragmatic implications in terms of potential inconvenience to participants. However, the authors of this paper would posit the argument that a sponsor simply cannot afford not to employ ABPM in at least part of a drug's clinical development program and hence in the creation of an integrated portfolio of cardiovascular safety evaluations. Should a drug receive marketing approval but then be withdrawn for postmarketing safety concerns, the financial ramifications can be considerable. If, however, the sponsor spends some financial resources doing good assessments in phase II using ABPM, there are two possible scenarios. First, they find out early that the drug has a BP liability of sufficient magnitude that its benefit-risk balance is unlikely to be favorable and they decide that termination of the drug's development program is judicious. Second, they gain information on the mean magnitude of, and importantly the intersubject variability in BP response that allows them to most efficiently decide how many participants should be monitored with ABPM in phase III (the lower the magnitude and the lower the variability, the smaller the number of participants for whom ABPM data are likely needed to assuage regulatory concerns and demonstrate a favorable benefit-risk balance). A related argument is that if a small company wants to take a compound to somewhere in phase II and then sell it to a large company to take it the rest of the way to marketing application, the small company can likely negotiate a more advantageous financial agreement if it is able to demonstrate at least initial evidence that the compound is not associated with a BP liability, again justifying the cost of performing at least some ABPM in phase II.

Consider now statistical implications of employing ABPM as they relate to the sample size required in clinical trials to provide compelling evidence of a drug's lack of BP liability. Campbell and colleagues[60] observed that while the reproducibility of ABPM is superior to CBPM in middle-aged patients, little is known in older age groups. They therefore conducted a study to compare the long-term reproducibility of ambulatory and office BP readings in patients older than 75 years. Their results demonstrated that the long-term reproducibility of ABPM is superior to CBPM for very elderly patients. The authors concluded that "In a clinical trial involving this age group, far fewer patients would be required if 24-hour BP was the primary efficacy endpoint rather than the office BP."[60] Taken together with the fact that ABPM provides a much richer dataset of multiple parameters, it is reasonable to argue in the context of cardiovascular safety assessments that, while the cost of ABPM per participant will be undeniably greater than CBPM, fewer participants undergoing ABPM would be needed to provide compelling evidence of a lack of drug-induced BP liability than would be needed if relying on CBPM data.

THOUGHTS ON A POTENTIAL FUTURE PARADIGM: MORE STANDARDIZED TESTING OF DRUG CARDIOVASCULAR SAFETY VIA ABPM

Based on discussions in this paper to date, some brief thoughts are offered on how a future regulatory landscape for more standardized testing of BP liability associated with a noncardiovascular drug might look.

Questions of interest include the following. Is a pattern of change in both SBP and DBP more important than a (potentially greater) change in either one of them? It is reasonable to argue that changes induced by drugs taken chronically are of greater concern than those induced by short-term pharmacotherapy, but do changes of concern vary by other variables such as sex and age? Is an increase of X mm Hg from a baseline of Y mm Hg more, less, or equally concerning than an increase of X mm Hg from a baseline of Z mm Hg? It might also be reasonable to ask whether an increase of X mm Hg from a baseline of Y mm Hg or Z mm Hg is more relevant in the nocturnal period (when risk of cardiovascular events is greatest) than in the daytime period. The answers to these questions are not readily apparent at the time of writing this paper. However, the authors believe that the answer to the question "Should ABPM figure prominently in such assessments?" is a straightforward "Yes."

TABLE. Noncardiovascular Drugs Implicated in Raising Blood Pressure (BP)

Drug/Drug category	Effects
Antidepressants	Several antidepressant agents may increase BP by activating the sympathetic nervous system, and these changes may be more pronounced in older patients and may be dose-dependent.[1]
Anti-HIV therapy	Highly active antiretroviral therapy can cause a rise in BP but not usually before 6 months. Patients taking lopinavir/ritonavir had the highest risk, and patients receiving atazanavir had the lowest risk of developing elevated BP.[1]
Drugs activating the sympathetic nervous system (SNS)	Drugs that activate the SNS and cause hypertension include phenylephrine hydrochloride, used as an upper respiratory decongestant and in ophthalmic drops; dipivalyl adrenaline hydrochloride, used in ophthalmic drops (which may cause severe hypertension); epinephrine, used as a bronchodilator and decongestant and for antihemorrhoidal treatment; phenylpropanolamine, used as an anorexic agent and upper respiratory decongestant; pseudoephedrine hydrochloride, used as an upper respiratory decongestant; tetrahydrozoline hydrochloride, used as ophthalmic vasoconstrictor drops; naphazoline hydrochloride, used as an ophthalmic vasoconstrictor and as nasal decongestant drops; and oxymetazoline hydrochloride, used as upper respiratory decongestant drops.[1]
Drugs for treating addiction	In moderate smokers, bupropion, transdermal nicotine, or bupropion associated with transdermal nicotine caused an elevation in BP after acute smoking interruption.[2] Disulfiram for the management of alcoholism may cause a slight increase in BP and severe hypertension may occur in patients with alcoholic-induced liver disease.[1]
Drugs for treating malignancy	Antivascular endothelial growth factor drugs for the treatment of various malignancies may cause hypertension. About 1% of all patients on antiangiogenic therapy develop a life-threatening hypertensive crisis.[1] Use of ambulatory blood pressure monitoring (ABPM) demonstrated that sunitinib induced hypertension more frequently than previously reported.[3]
Hypoglycemic agents	Metformin treatment decreased daytime ABPM recordings whereas Diane 35 Diario exerted the opposite effect.[4]
Immunosuppressive agents	The incidence of cyclosporine-associated hypertension after renal, bone marrow, and cardiac transplantation varies between 30% and 100%. It is also common in patients with autoimmune disease and in patients with psoriasis treated with cyclosporine. Cyclosporine-induced hypertension is characterized by disturbance of the circadian rhythm, with the absence or reversal of the normal nocturnal fall in blood pressure (which can only be detected with ABPM). Hypertension usually decreases after the withdrawal or substitution of cyclosporine immunosuppression but may not remit completely.[1] Cyclosporine A induces arterial hypertension and causes a nondipping nocturnal pattern on ABPM.[5] Mean systolic and diastolic ABPM was significantly increased and nocturnal dipping was reduced in children treated with cyclosporine A.[6]
Nonsteroidal anti-inflammatory drugs (NSAIDS) and analgesics	NSAIDs can induce an increase in BP and interfere with antihypertensive treatment, mitigating or abolishing their effect. NSAIDs interfere with some antihypertensive agents such as diuretics, β-blockers, and angiotensin-converting enzyme inhibitors, but do not interact with calcium antagonists and central-acting drugs. ABPM has been used to demonstrate significant BP elevation with acetaminophen in patients with coronary artery disease.[1,7] High-dose ibuprofen, an NSAID, had no significant effect on 24-hour ABPM.[8] Several studies have shown that allopurinol reduces arterial BP in animal models and in adolescent patients with newly diagnosed hypertension. In one study, allopurinol did not produce additional antihypertensive effects in patients with treated arterial hypertension assessed with ABPM.[9] Addition of low-dose aspirin to antihypertensive medications and statins in hypertensive and hypercholesterolemic patients can reduce both systolic blood pressure (SBP) and diastolic blood pressure by improving endothelial function.[10]
Recombinant human erythropoietin (r-HuEPO)	r-HuEPO, which is effective in correcting anemia in patients with end-stage renal failure and patients with malignancies, induces hypertension or worsens existing hypertension in 20% to 30% of patients.[1]
Sex hormones	Around 5% of women taking estrogen containing oral contraceptives develop hypertension and this does not occur with progesterone-only annovulant drugs. Any rise in BP is usually small and is reversible on cessation of therapy, but severe hypertensive episodes, including malignant hypertension, may occur. Hormone replacement therapy in postmenopausal women has minimal if any effect on BP in normotensive women.[1] Hormone replacement therapy in postmenopausal Japanese women had no significant effect on 24-hour ABPM.[11]
Steroids	Hypertension occurs in at least 20% of patients treated with synthetic corticosteroids in a dose-dependent fashion; oral cortisol at doses of 80–200 mg/d can increase SBP as much as 15 mm Hg within 24 hours.[1]
Stimulant and anorexic drugs	Stimulant drugs in children with attention deficit hyperactivity disorder significantly raised ABPM and heart rate values.[12] Sibutramine did not induce or exacerbate hypertension in normotensive and controlled hypertensive obese patients with ABPM.[13]

Given earlier discussions of the lack of suitability of assessments in healthy participants, ABPM assessments would likely commence in phase II. This phase of development might be particularly well suited for such investigation for two reasons. Since the size of phase II studies is relatively small (compared with phase III studies), they tend to involve less investigational sites. This makes implementation of tight experimental control feasible, which greatly enhances the trials' ability to detect relatively small but systematic drug-induced

BP changes. The question then becomes: How do data from phase II studies influence the degree of monitoring required in phase III? A statistically driven answer is that the smaller the intersubject variability, the fewer the number of participants who would need to be monitored to provide the same degree of assurance about the nature of the drug's influence on BP. It might also be the case that, for a given degree of variation, the lower the mean magnitude of response, the fewer the number of participants who would need to be monitored, since a lower mean would presumably indicate less concern than a higher one.

Moving into phase III, financial and pragmatic considerations may argue against ABPM for all participants, but using ABPM for a subset of participants in each trial is likely feasible and potentially very informative (recall earlier discussions concerning the HOPE trial substudy). An "Integrated Portfolio of ABPM Data" can then be constructed from phase II and phase III investigations, and a "totality of evidence" approach taken to their assessment.

Given the clinical importance of various aspects of the 24-hour BP profile, especially nocturnal and preawakening data,[61,62] these factors are likely to feature prominently in any landscape that develops.

REQUIREMENTS FOR ABPM HARDWARE AND SOFTWARE

Devices used for ABPM must be validated according to internationally accepted protocols. The International Protocol of the European Society of Hypertension[63,64] is now the protocol that is most used for the independent validation of devices,[65] and only devices that have been validated and recommended for clinical use should be acceptable for pharmacologic studies of noncardiovascular drugs.

While it is essential that appropriate hardware is employed in clinical trials employing ABPM, it is equally (and arguably more) important that appropriately informative software is employed. ABPM monitoring fulfills its full promise when sophisticated software is employed to collate, interpret, analyze, and electronically transmit data for central hosting and analysis. Software employed should therefore provide for real-time, online transfer of data and the return of 24-hour ABPM analysis to the investigator, as well as be able to collate and store data for detailed analysis of the BP parameters and indices so that the maximum use is made of ABPM data at the end of the study.

As a case study of one approach that demonstrates the feasibility and utility of ABPM in the current context, The Conway Institute, University College Dublin, in association with dabl Limited, has developed the dabl ABPM system. This custom-designed software system provides visual printouts on a standardized plot that shows the time windows of the 24-hour profile, the normal bands for SPB and DBP, the recorded levels of these pressures throughout the 24-hour period, and a computer-generated interpretative report together with the facility for real-time online transfer of data to a centrally hosted site. While originally developed for clinical patient care, the system has now been developed to incorporate these requirements into the smooth performance of pharmacologic trials.[17]

For trials of noncardiovascular drugs it is important to capture not only the hemodynamic changes that may be induced by the drug being evaluated, but also to be able to assess these changes in relation to heart rate and rhythm. It is expensive and impractical to perform 24-hour Holter monitoring and 24-hour ABPM on separate days, and therefore it becomes necessary to combine these investigations in one system. Moreover, the detection of arrhythmogenic and BP off-target effects of noncardiovascular drugs is a desirable facility. To facilitate the sophisticated analysis required for the detection of drug effects in pharmacologic trials, dabl has explored and demonstrated the feasibility of recording, storing, retrieving, and analyzing data from simultaneous measurement of 24-hour ABPM, Holter, and activity monitoring. While all of the above circadian hemodynamic profiles are of interest in themselves, the integrated analysis of all three modalities in real time, so that the BP consequences of a disturbance of rhythm, such as paroxysmal atrial fibrillation, can be readily detected and analyzed, provides valuable data in the assessment of noncardiovascular drugs.

The system also allows storage of data for detailed analysis according to evidence-based definitions for time-weighted arithmetic and mean values for BP levels. Moreover, given recent evidence that BP variability may provide information over and above mean levels (recall earlier discussions) and that reduction in BP variability may be beneficial, time-weighted measures of variability (eg, standard deviations and coefficients of variation) and measures of white-coat hypertension, white-coat effect, nocturnal dip, and morning surge are also provided. The system also yields informative indices associated with outcome, including area under the curve calculations, BP load parameters, trough and peak levels, cusum-derived statistics, and the ambulatory arterial stiffness index, which has been shown to predict cardiovascular mortality in a large cohort of hypertensive individuals, particularly for stroke.[22]

Finally, as all hemodynamic changes are influenced by activity, the system is also capable of monitoring the activity status of the patient. Twenty-four–hour actigraphy monitoring is incorporated into a simultaneous 24-hour Holter and ABPM recording to provide statistics that include the duration of actigraphy recording and the mean activity per minute, with an overview plot for display on screen and in reports. The ability to monitor activity over the 24-hour period allows for the assessment of activity throughout the day and night and for the detection of likely periods of sleep.

CONCLUSIONS

CBPM is influenced by many factors that limit the applicability of the technique for research into

drug-induced off-target BP responses. Moreover, and more importantly here, CBPM cannot provide a comprehensive assessment of duration of effect of noncardiovascular drugs, nor of their effect on sleeping pressures. ABPM can readily assess BP alterations caused by noncardiovascular drugs throughout a 24-hour period, and, if combined with 24-hour Holter monitoring and activity monitoring, a much more complete hemodynamic profile can be obtained from one investigatory procedure. From the scientific viewpoint, we believe that it is now time to utilize the technique of ABPM to obtain a fuller understanding of the patterns of noncardiovascular drug-induced BP responses than was ever possible with CBPM. It will be of interest to many scientists to follow the evolution of a new regulatory landscape addressing this issue.

Acknowledgments: The authors wish to acknowledge multiple instructive conversations with Lawrence Satin, MD, on the topic of this paper. We also wish to thank the reviewers of the original manuscript, who provided extremely helpful comments.

Disclosures: Eoin O'Brien has disclosed that he is medical director, board member, and shareholder of dabl Limited, Dublin, Ireland, and has contributed financially to the development of the dabl ABPM software program for ambulatory blood pressure measurement. Rick Turner has disclosed that he is an employee of Quintiles. The authors report no specific funding in relation to this research. No editorial assistance was used.

References

1. Grossman E, Messerli FH. Drug-induced hypertension: an unappreciated cause of secondary hypertension. *Am J Med*. 2012;125:14–22.
2. Martins LC, Ferreira-Melo SE, Sabha M, et al. Acute effects of pharmacotherapies in blood pressure in normotensive moderate smokers. *Blood Press*. 2005;18:255–260.
3. Bamias A, Manios E, Karadimou A, et al. The use of 24-h ambulatory blood pressure monitoring (ABPM) during the first cycle of sunitinib improves the diagnostic accuracy and management of hypertension in patients with advanced renal cancer. *Eur J Cancer*. 2011;47:1660–1668.
4. Luque-Ramírez M, Mendieta-Azcona C, Alvarez-Blasco F, Escobar-Morreale HF. Effects of metformin versus ethinyl-estradiol plus cyproterone acetate on ambulatory blood pressure monitoring and carotid intima media thickness in women with the polycystic ovary syndrome. *Fertil Steril*. 2009;91:2527–2536.
5. Pilecki T, Paczek L, Senatorski G, et al. Effect of immunosuppressive treatment on diurnal profile of blood pressure. *Pol Merkur Lekarski*. 2002;13:37–40.
6. Wasilewska A, Zoch-Zwierz W, Tomaszewska B, Tenderenda E. The effect of cyclosporine A in steroid-dependent nephrotic syndrome in children. *Pol Merkur Lekarski*. 2005;18:168–172.
7. Sudano I, Flammer AJ, Periat D, et al. Acetaminophen increases blood pressure in patients with coronary artery disease. *Circulation*. 2010;122:1789–1796.
8. Wright JT, McKenney JM, Lehany AM, et al. The effect of high-dose short-term ibuprofen on antihypertensive control with hydrochlorothiazide. *Clin Pharmacol Ther*. 1989;46:440–444.
9. Kostka-Jeziorny K, Uruski P, Tykarski A. Effect of allopurinol on blood pressure and aortic compliance in hypertensive patients. *Blood Press*. 2011;20:104–110.
10. Magen E, Viskoper JR, Mishral J, et al. Effects of low-dose aspirin on blood pressure and endothelial function of treated hypertensive hypercholesterolaemic subjects. *J Hum Hypertens*. 2005;19:667–673.
11. Sumino H, Ichikawa S, Kumakura H, et al. Effects of hormone replacement therapy on office and ambulatory blood pressure in Japanese hypertensive postmenopausal women. *Hypertens Res*. 2003;26:369–376.
12. Samuels JA, Franco K, Wan F, Sorof JM. Effect of stimulants on 24-h ambulatory blood pressure in children with ADHD: a double-blind, randomized, cross-over trial. *Pediatr Nephrol*. 2006;21:92–95.
13. Gürsoy A, Erdoğan MF, Cin MO, et al. Effect of sibutramine on blood pressure in patients with obesity and well-controlled hypertension or normotension. *Endocr Pract*. 2005;11:308–312.
14. Satin LZ, Gutstein DE. Meeting report: 5th annual cardiovascular risk assessment summit. *Drug Inf J*. 2011;45:535–540.
15. Turner JR. Cardiovascular safety watch column. *J Clin Stud*. 2011; 3:10.
16. O'Brien E. Why ABPM should be mandatory in all trial of blood pressure-lowering drugs. *Drug Inf J*. 2011;45:233–239.
17. O'Brien E. The value of 24-hour blood pressure monitoring to assess the efficacy of antihypertensive drug treatment. *Hot Topics Hypertens*. 2011;4:7–23.
18. Stolarz-Skrzypek K, Thijs L, Wizner B, et al. From pioneering to implementing automated blood pressure measurement in clinical practice: Thomas Pickering's legacy. *Blood Press Monit*. 2010;15: 72–81.
19. Owens P, Atkins N, O'Brien E. Diagnosis of white coat hypertension by ambulatory blood pressure monitoring. *Hypertension*. 1999;34:267–272.
20. O'Brien E. First Thomas Pickering Memorial Lecture: ambulatory blood pressure measurement is essential for the management of hypertension. *J Clin Hypertens (Greenwich)*. 2012; doi: 10.1111/j.1751-7176.2012.00698.
21. O'Brien E. The circadian nuances of hypertension: a reappraisal of 24-h ambulatory blood pressure measurement in clinical practice. *Ir J Med Sci*. 2007;176:55–63.
22. O'Brien E. 24-hour ambulatory blood pressure measurement in clinical practice and research: a critical review of a technique in need of implementation. *J Int Med*. 2011;269:478–495.
23. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high risk patients: the Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145–153.
24. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145–153.
25. Williams B. The renin-angiotensin system and cardiovascular disease: hope or hype? *J Renin Angiotensin Aldosterone Syst*. 2000; 1:142–146.
26. Svensson P, de Faire U, Sleight P, et al. Comparative effects of ramipril on ambulatory and office blood pressures: a HOPE substudy. *Hypertension*. 2001;38:E28–E32.
27. Moutsatsos GD. More hype than HOPE. *Hypertension*. 2003;41:e4.
28. Stockbridge S. Letter to the Editor: ABPM part of FDA reviews. *Drug Inf J*. 2011;45:567.
29. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality. The Dublin Outcome Study. *Hypertension*. 2005;46:156–161.
30. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population. Follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation*. 2005;111:1777–1783.
31. Mancia G, Bombelli M, Facchetti R, et al. Long-term prognostic value of blood pressure variability in the general population. Results of the Pressioni Arteriose Monitorate a Loro Associazioni study. *Hypertension*. 2007;49:1265–1270.
32. Ben-Dov IZ, Kark JD, Ben-Ishay D, et al. Predictors of all-cause mortality in clinical ambulatory monitoring: unique aspects of blood pressure during sleep. *Hypertension*. 2007;49:1235–1241.
33. Fagard RH, Celis H, Thijs L, et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension*. 2008;51:55–61.
34. Muxfeldt ES, Cardoso CR, Salles GF. Prognostic value of nocturnal blood pressure reduction in resistant hypertension. *Arch Intern Med*. 2009;169:874–880.
35. Fan HQ, Li Y, Thijs L, et al. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. *J Hypertens*. 2010;28:2036–2045.
36. O'Brien E. Is the case for ABPM as a routine investigation in clinical practice not overwhelming? *Hypertension*. 2007;50:284–286.
37. Logan AG. Ambulatory blood pressure monitoring: it's time to move on! *J Hypertens*. 2010;28:2000–2002.
38. Rocco MB, Barry J, Campbell S, et al. Circadian variation of transient myocardial ischemia in patients with coronary artery disease. *Circulation*. 1987;75:395–400.

39. Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. *Stroke*. 1998;29:992–996.
40. Kario K. Time for focus on morning hypertension: pitfall of current antihypertensive medication. *Am J Hypertens*. 2005;18:149–151.
41. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905.
42. Rothwell PM, Howard SC, Dolan E, et al. Effects of β blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol*. 2010;9:469–480.
43. Dolan E, O'Brien E. Blood pressure variability: clarity for clinical practice. *Hypertension*. 2010;56:179–181.
44. ICH Guideline E14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. 2005. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf. Accessed June 20, 2012.
45. ICH Guideline E14 Questions & Answers Document, Revision 1. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: questions & answers. 2012. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Q_As_R1_step4.pdf. Accessed June 20, 2012.
46. Satin LZ, Durham TA, Turner JR. Assessing a drug's proarrhythmic liability: an overview of computer simulation modeling, nonclinical assays, and the Thorough QT/QTc Study. *Drug Inf J*. 2011;45: 357–375.
47. Turner JR. Integrated cardiovascular safety: employing a three-component risk exclusion model in the assessment of investigational drugs. *Appl Clin Trials*. 2010;19: June issue:76–79.
48. Highlights of prescribing information for crizotinib. http://labeling.pfizer.com/showlabeling.aspx?id=676. Accessed August 9, 2012.
49. Highlights of prescribing information for vemurafenib. http://www.gene.com/gene/news/news-events/zelboraf/pi.pdf. Accessed August 9, 2012.
50. Rock EP, Finkle J, Fingert HJ, et al. Assessing proarrhythmic potential of drugs when optimal studies are infeasible. *Am Heart J*. 2009;157:827–836, 836.e1.
51. Levitan BS, Andrews EB, Gilsenan A, et al. Application of the BRAT framework to case studies: observations and insights. *Clin Pharmacol Ther*. 2011;89:217–224.
52. Noel R, Hermann R, Levitan B, et al. Application of the Benefit-Risk Action Team (BRAT) Framework in Pharmaceutical R&D: results from a pilot program. *Drug Inf J*. 2012; doi:10.1177/0092861512458908.
53. Krucoff M. Focus on the cardiac safety research consortium. *Drug Inf J*. 2011;45:241–244.
54. Krakoff LR. Cost-effectiveness of ambulatory blood pressure: a reanalysis. *Hypertension*. 2006;47:29–34.
55. White WB. Expanding the use of ambulatory blood pressure monitoring for the diagnosis and management of patients with hypertension. *Hypertension*. 2006;47:14–15.
56. O'Brien E. Ambulatory blood pressure measurement. The case for implementation in primary care. *Hypertension*. 2008;51:1435–1441.
57. National Institute for Health and Clinical Excellence (NICE). Hypertension. The clinical management of primary hypertension in adults. Clinical Guideline 127. 2011. www.nice.org.uk/guidance/CG127. Accessed August 9, 2012.
58. Lovibond K, Jowett S, Barton P, et al. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. *Lancet*. 2011;378:1219–1230.
59. White WB, Maraka S. Is it possible to manage hypertension and evaluate therapy without ambulatory blood pressure monitoring? *Curr Hypertens Rep*. 2012;14:366–373.
60. Campbell P, Ghuman N, Wakefield D, et al. Long-term reproducibility of ambulatory blood pressure is superior to office blood pressure in the very elderly. *J Hum Hypertens*. 2010;24:749–754.
61. White WB. "The nighttime might be the right time" for cardiovascular event prediction. *Hypertension*. 2012;60:8–9.
62. White WB. The risk of waking-up: impact of the morning surge in blood pressure. *Hypertension*. 2010;55:835–837.
63. O'Brien E, Pickering T, Asmar R, et al. International protocol for validation of blood pressure measuring devices in adults. *Blood Press Monit*. 2002;7:3–17.
64. O'Brien E, Atkins N, Stergiou G, et al. European Society of Hypertension International Protocol for the validation of blood pressure measuring devices in adults. 2010 Revision. *Blood Press Monit*. 2010;15:23–38.
65. 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.