

# Assessment of drug-induced increases in blood pressure during drug development: Report from the Cardiac Safety Research Consortium

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This White Paper, prepared by members of the Cardiac Safety Research Consortium, discusses several important issues regarding the evaluation of blood pressure (BP) responses to drugs being developed for indications not of a direct cardiovascular (CV) nature. A wide range of drugs are associated with off-target BP increases, and both scientific attention and regulatory attention to this topic are increasing. The article provides a detailed summary of scientific discussions at a Cardiac Safety Research Consortium-sponsored Think Tank held on July 18, 2012, with the intention of moving toward consensus on how to most informatively collect and analyze BP data throughout clinical drug development to prospectively identify unacceptable CV risk and evaluate the benefit-risk relationship. The overall focus is on non-CV drugs, although many of the points also pertain to CV drugs. Brief consideration of how clinical assessment can be informed by nonclinical investigation is also outlined. These discussions present current thinking and suggestions for furthering our knowledge and understanding of off-target drug-induced BP increases and do not represent regulatory guidance. (*Am Heart J* 2013;165:477-88.)

On the basis of the principles of the US Food and Drug Administration (FDA) Critical Path Initiative, the Cardiac Safety Research Consortium (CSRC) ([www.cardiac-safety.org](http://www.cardiac-safety.org)) was created to facilitate collaborations among academicians, industry professionals, and regulators to develop consensus approaches addressing cardiac and vascular safety issues that can arise in the development of new medical products.<sup>1</sup> The CSRC convened a Think Tank meeting on July 18, 2012, at the FDA in Silver Springs, MD, to foster stakeholder discussion about drug-

induced, off-target blood pressure (BP) increases. This White Paper is the result of discussions at the meeting by a broad range of experts, now further extended by the CSRC writing group. It focuses on the current state of knowledge and controversial areas regarding the non-clinical and clinical assessments of drug-induced off-target BP liabilities. This White Paper is intended to assist pharmaceutical sponsors, scientists, clinicians, and regulatory authorities involved in the development of products with the potential for cardiac and vascular toxicity. The CSRC views expressed here do not represent regulatory policy.

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Submitted December 19, 2012; accepted January 4, 2013.

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0002-8703/\$ - see front matter

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<http://dx.doi.org/10.1016/j.ahj.2013.01.002>

## Background

In recent years, it has become evident that drugs can affect BP in an off-target manner.<sup>2-5</sup> In most instances, these drugs raise BP through known classical mechanisms including salt and water retention, activation of the sympathetic nervous system, inhibition of prostacyclin, or inhibition of vascular endothelial growth factor.<sup>4,6,7</sup> Although in most instances drug-induced off-target BP increases are relatively small, there are instances in which the increases may be moderate to extreme as well as sustained and can cause target organ injury.<sup>8,9</sup> Table I presents several examples of such off-target BP increases.

Off-target BP elevations have increasingly attracted scientific and regulatory interest, focusing attention on

**Table 1.** Examples of drug classes associated with increases in BP

Drug category	Effects and mechanisms of action
Antiangiogenic therapies for cancer	Antiangiogenic therapies that inhibit vascular endothelial growth factor induce mild to severe hypertension by increasing vascular resistance. Multiple mechanisms are likely, including reductions in the expression of endothelial and neuronal nitric oxide synthases in the kidney and enhanced synthesis of endothelin-1.
Antidepressants	Antidepressants raise SBP, DBP, and heart rate to varying degrees depending on subclass; changes are dose dependent. The primary mechanism is increased sympathetic nervous system activity (primarily by the serotonin-norepinephrine reuptake inhibitors).
Calcineurin inhibitors	Calcineurin agents such as cyclosporine and tacrolimus can induce significant peripheral and renal vasoconstriction leading to severe hypertension. The mechanisms by which the calcineurin inhibitors induce hypertension are multiple and include activation of sympathetic nervous system, enhanced production of endothelin 1, reduced nitric oxide (NO) activity, and impairment of renal sodium handling independent of the direct nephrotoxicity observed with these agents.
Erythrocyte-stimulating agents (ESAs)	ESAs such as erythropoietin increase BP in as many as 20% of patients with anemia of chronic kidney disease. The mechanism of hypertension appears to be independent of the effects of erythropoietin on red blood cell mass and blood viscosity. ESAs may induce endothelin-1 release and produce an enhanced mitogenic response in endothelial cells. In addition, production of the vasodilator prostacyclin is decreased, and the vasoconstricting prostanoid thromboxane is increased when ESAs are administered.
NSAIDs and analgesics	NSAIDs induce dose-dependent increases in BP by blocking the synthesis of vasodilatory prostaglandins as well as prostaglandins associated with natriuresis. Hence, the NSAIDs can induce an increase in BP by enhancing plasma volume and vasoconstriction. NSAIDs also attenuate certain antihypertensive therapies including diuretics, $\beta$ -blockers, and angiotensin-converting enzyme inhibitors, but are less likely to interfere with $\alpha_1$ -adrenergic inhibitors, calcium antagonists, and central-acting drugs.
Steroids (corticosteroids, estrogens, and progestins)	Steroid hormones produce hypertension by acting through renal type I mineralocorticoid receptors to produce salt and water retention. This is the case for some, but not all, corticosteroid preparations as well as pharmacologic doses of estrogens and progestins found in oral contraceptives and postmenopausal hormone agents. In addition, glucocorticoids have a variety of effects on the NO system, including inhibition of inducible NO synthase and endothelium NO synthase isoforms, inhibition of transmembrane arginine transport, and inhibition of synthesis of the NO synthase cofactor tetrahydrobiopterin. In general, progestins antagonize the vasoconstrictor effects of estrogens and may modify the BP effects seen with combination agents.
Stimulant and anorexic drugs	Stimulant drugs for the treatment of attention deficit hyperactivity disorder (amphetamine and dextroamphetamine, atomoxetine, methylphenidate) can significantly raise BP and HR. Some of these agents are similar to the sympathomimetic agents and stimulate both $\alpha_1$ - and $\beta_1$ -receptors, leading to vasoconstriction and tachycardia. Atomoxetine is a selective norepinephrine transporter blocker and could increase BP by elevating norepinephrine concentration in peripheral sympathetic neurons.
Sympathomimetic agents	This broad class of agents includes agents such as phenylephrine hydrochloride, dipivalyl adrenaline hydrochloride, epinephrine, phenylpropanolamine, pseudoephedrine hydrochloride, and methylphenidate, as well as drugs of abuse (amphetamine, methamphetamine, and cocaine). Sympathomimetics activate $\beta$ -receptors of the heart leading to increases in HR and $\alpha$ -receptors in vascular smooth muscle leading to vasoconstriction and increases in BP.

how well these increases are described during drug development and their potential impact on benefit-risk relationships. Although acknowledging that off-target BP reductions and drug-drug interactions may also be important, these topics are beyond the scope of this article. In addition, this paper does not address special populations including children and adolescents, where increases in BP may warrant different considerations.

## The clinical importance of drug-induced off-target increases in BP

There is powerful epidemiologic evidence showing that as BP increases in a population, the risk of cardiovascular (CV) events increases.<sup>10,11</sup> In addition, multiple placebo-controlled clinical trials over the past 4 decades have demonstrated that treating hypertension reduces the risk of CV events, particularly stroke and the development of congestive heart failure.<sup>12-15</sup> The reductions in CV events were not mechanism specific. It is

estimated that differences of as little as 3 mm Hg in systolic BP (SBP) in hypertensive middle-aged to older populations may have meaningful clinical relevance, including nearly 10% differences in stroke over a period of several years of observation.<sup>16,17</sup>

Small drug-induced BP increases in a population represent a public health concern, particularly when the patient population is being treated on a chronic basis or has enhanced CV risk based on age, CV comorbidities, or traditional CV risk factors. An informative example is the experience with the CV outcome analyses from the comparative trials of nonselective anti-inflammatory drugs (NSAIDs) including the cyclooxygenase-2 inhibitors. The NSAIDs, particularly ibuprofen and rofecoxib, at high daily doses for up to 1 year of exposure have been associated with clinically important increases in SBP (3-6 mm Hg)<sup>18,19</sup> and increases in CV events including myocardial infarction and heart failure with rofecoxib<sup>18,20</sup> and stroke with high-dose ibuprofen.<sup>19</sup> Although it is not completely established whether the CV

risks with these agents are mediated by the BP changes or whether increases in BP may be a marker of other pathologic mechanisms produced by the drugs, the epidemiologic evidence suggests the former mechanism.

In addition to the possible risk associated with small changes in BP with some compounds, there are also classes of compounds and therapeutic indications that present a substantial increase in BP in individual patients. Tyrosine kinase inhibitors have been reported to have such an effect in some cases. Such BP increases have been proactively managed during treatment exposure to the compound. However, the applicability of such an approach to small BP increases is questionable. It is recognized that in some populations, such as those with ischemic heart disease, low BPs may not necessarily be beneficial, perhaps because of reduced coronary perfusion pressure during diastole.<sup>21</sup> Given this acknowledgment and the relative lack of steepness of the CV risk-to-BP relationship at normotensive BPs,<sup>22</sup> it might be argued that modest drug-induced off-target BP elevations within the normotensive range may not be associated with increased cardiac events in some populations. Still, offsetting the possible coronary disadvantages of lower BPs is evidence that stroke events are increased at higher BP levels within this range.<sup>23</sup>

From the current perspective, a more consistent approach to the prospective assessment of BP increases and the detection of unacceptable drug-induced BP increases is needed. In determining the level of risk associated with BP increases, it is also relevant to take into consideration the therapeutic indication and benefit to the patient population. For example, agents for the treatment of cancer that raise BP may be reviewed quite differently from a new drug for the treatment of analgesia because of the potentially favorable impact on mortality in the oncologic indication. In addition, the expected duration of treatment, the potential for treating drug-induced hypertension, and evidence of the reversibility of the BP increase with drug discontinuation are all of clinical importance.

### **Assessment of CV risk as a function of mean BP vs BP variability**

There are at least 3 sources of BP variability. The first is intrinsic variability: BP varies from minute to minute, from day to day, and from month to month because of physical activity and environmental effects as well as for reasons that are not well understood. A second source of variability in BP comes from the imprecision of measurements, although this can be partly ameliorated by ambulatory BP monitoring or other careful or frequent measurement strategies. Third, there is the BP variability caused by the intended or unintended effects of drug interventions, which may be difficult to discern because of the other sources of variability. There are mixed

findings as to whether BP variability is a source of increased CV risk. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), visit-to-visit variability in SBP was a strong predictor of subsequent stroke, independent of the mean BP.<sup>24</sup> In contrast, in a population sample of nearly 3000 Belgians monitored for a median period of 12 years, mean SBP was a predictor of fatal and nonfatal CV events, independent of BP variability.<sup>25</sup> Similarly, when the BP is already modestly elevated or occurs in a lower-risk population, BP variability may play a lesser role in inducing CV target organ damage than the mean BP.<sup>26</sup>

There is evidence that out-of-office BP predicts CV outcomes better than in-clinic monitoring from prospective cohort studies<sup>27,28</sup> that have long-term follow-up periods. This is true for both the daytime (diurnal) and nighttime (nocturnal) BPs.<sup>29</sup> Data from the International Database on Ambulatory Blood Pressure in relation to Cardiovascular Outcomes (IDACO) program<sup>29</sup> in which more than 7,000 people have been observed for 10 years or more demonstrate the impact of out-of-office BP on CV outcomes. In one recent evaluation from IDACO, the adjusted hazard ratio and 95% CIs for CV events (both fatal and nonfatal) based on daytime SBP was 1.33 (1.25-1.42) per increase in the SD (15.5/9.3 mm Hg) of the daytime BP, and that for nighttime SBP was 1.31 (1.24-1.38) per increase in the SD (15.5/9.3 mm Hg) of the nighttime SBP. In adjusted models, clinic BP lost its predictive value, whereas both the daytime and nighttime BPs retained their prognostic significance.<sup>27</sup> The difference in these results between clinic and ambulatory BP measurements is primarily the result of increased clinic BP variability, a factor that requires consideration when assessing the practicality of treating drug-induced increases in BP in individual patients. Furthermore, these findings support broader use of out-of-office BP monitoring to assess the impact of drugs that might affect BP because their results could translate into improved predictors of CV harm.

In the evaluation of the impact of a non-CV drug on BP, attempts must be made to evaluate and reduce the non-drug-related sources of BP variability in a clinical trial. This includes reduction of measurement error or bias by observers through measurement training programs,<sup>30</sup> use of automated digital devices in the clinical trial with enduring data output capture at the time of measurement,<sup>31</sup> and ambulatory BP monitoring.<sup>32</sup> Although these measures help immensely to reduce intrinsic BP variability in clinical trials, it is not entirely removed as a source of variation that might be attributed to the unintended effects of a non-CV drug.

### **Central tendencies or outlier assessments for BP**

It is well known that small increases in the mean or median values of BP—even if statistically significant—

could encompass patients with large BP increases, some with no changes at all, and others with decreases in BP.<sup>33</sup> Hence, it is pertinent to determine whether the entire exposed population receiving the drug is at risk for BP increases or whether a subgroup, defined by demographic characteristics, concomitant therapies, and CV baseline risk is at particular risk. This is a key issue for drug development and one that often cannot be resolved without large numbers of patients who have had appropriate BP assessment, particularly if the central tendency is small or if the BP effect is heterogeneous.

It may be difficult, even impossible, to precisely define the CV risk of a non-CV drug with small mean or median increases in BP because the risk of a CV adverse event is dependent on multiple factors including the underlying age and CV risk of the population, the baseline BP, and the length of treatment. Although there is a lack of robust data, small central tendency increases in BP in a population with such risk factors are likely to predispose to future CV events. Outliers who present with large increases in BP are typically more obvious to physicians and may lead to an intervention by the prescriber. It is therefore prudent that the drug label should assert whether a potential BP effect might be expected and how to deal with it appropriately (such as discontinuation or down-titration of the drug vs initiating or intensifying antihypertensive therapy if the efficacy and benefit are of sufficient importance to justify continuation). Owing to BP variability and other factors, it is not likely that all at-risk patients with significant BP increases would receive sufficient medical intervention to restore them to their pretreatment BP levels.

As discussed in the following text, data from nonclinical and each phase of preapproval clinical development should be collected and analyzed to inform the prescriber of the BP signal using the most precise methodology, the potential risk depending on the distribution of the CV risk of the population being treated, and how to mitigate risk with appropriate antihypertensive therapy or with discontinuation of the offending agent.

## Nonclinical development

The nonclinical evaluation of drug effects on BP can involve multiple approaches ranging from *in vitro* subcellular assays to fully integrated *in vivo* animal models. Early exploratory safety pharmacology studies may involve receptor-binding assays (often followed by function-based assays) to identify potential off-target effects of drug candidates at sites recognized for modulating vascular tone (eg, angiotensin-,  $\alpha$ -,  $\beta$ -, adenosine-, and endothelin receptors) as well as potential mechanisms to alter kidney sodium handling (eg, renin, atrial natriuretic factor, brain natriuretic peptide, and distal convoluted tubule sodium transporters) and might have a role in lead selection. *In vitro* isometric

contraction studies with aortic rings (measuring tension) and pressurized vessels (measuring vessel diameter) may also prove useful in identifying potential vasoactive substances and mechanisms and might be most useful if receptor studies identify potential issues. Subsequent studies may use direct measures of BP, cardiac function (contractility), and regional hemodynamics using smaller mammals such as instrumented rats. In addition, despite their well-known low BP measures, guinea pig models may also provide useful information.<sup>34</sup>

The use of anesthetized animals provides for higher exposures and more extensive instrumentation, enabling a more thorough hemodynamic evaluation (including assessment of vascular resistance, myocardial contractility, and cardiac output); anesthesia may also increase response sensitivity.<sup>35</sup> The nonclinical characterization of dose-dependent effects (including supratherapeutic exposures) supports pharmacokinetic (PK)/pharmacodynamic (PD) modeling useful in designing early clinical studies to validate CV effects.

Dedicated CV studies are required before first-in-human studies for noncytotoxic small-molecule drug candidates.<sup>36</sup> Typically, these studies evaluate acute effects of drugs in conscious, telemetered dogs, or nonhuman primates involving continuous recording of BP and heart rate using indwelling catheters (considered to be the criterion standard). The use of telemetry systems may also prove useful for detecting secondary (or delayed) effects, or those resulting from metabolites, and complements clinical 24-hour ambulatory BP studies. A recent study of noninvasive and implanted telemetric approaches in conscious beagle dogs showed that noninvasive approaches (oscillometric tail cuff with jackets) can be used to acquire BP data in freely moving jacketed dogs but require further technique refinement to improve system sensitivity to detect smaller changes in BP.<sup>37</sup> The use of trained animals and well-controlled environments can increase the sensitivity and precision of CV evaluations.

Nonclinical studies of the BP effects of biologics may be investigated in separate CV safety pharmacology studies or incorporated into the design of toxicity studies after considering expression of the target receptor or epitope and tissue cross-reactivity.<sup>38</sup> Inappropriate target expression typically precludes testing in commonly used species, for example, rats and dogs.

Although larger changes in BP can easily be detected in nonclinical investigations, as noted, earlier smaller changes, especially in conscious animals, require careful attention to details of study design, experimental conduct, and data reduction and analysis. One such study (not necessarily typical of most studies conducted) demonstrated changes in SBP, diastolic BP (DBP), and mean arterial pressure of approximately 6, 4, and 5 mm Hg, respectively, with a 4-subject canine telemetry study.<sup>39</sup> A recent consensus study described multiple "best practices" for

the robust nonclinical assessment of BP effects of evolving drug candidates.<sup>40</sup>

To understand the translation of the effects of small molecules from nonclinical to early clinical studies, the Association of British Pharmaceutical Industries Animal Model Framework Initiative performed a meta-analysis comparing the effects of small molecules on DBP measured in conscious dog telemetry studies and the single-ascending-dose phase of first-in-human studies.<sup>41</sup> Preliminary non-peer-reviewed results suggest that a 5% change in DBP in dog telemetry studies would provide for 37% sensitivity (probability of dog correctly identifying a positive phase I outcome) and 60% specificity (probability of correctly identifying negative phase I outcome). Such studies are difficult to interpret, in part, because of the lack of uniformity in the nonclinical approaches and the variability in the rigor of the BP measurements in phase I studies. Further studies need to be performed to determine the translation of mean SBP (focusing on the negative and positive predictive accuracy) and to compare CV effects observed in healthy subjects in early phase I studies with those of patients with the disease of interest in later phases of drug development.

Careful interpretation of nonclinical data is advocated to avoid interruption of the development of useful agents based on faulty experiments or experimental models. An integrative approach to data interpretation would appear most desirable.

## Considerations for clinical evaluation of drug effects on BP

The clinical evaluation of drug impact on BP must involve multiple considerations based on the presumed mechanism of action of the off-target BP effects as well as the population that is being targeted for clinical use of the drug. In many instances, it may not be possible to construct a single BP study that comprehensively assesses these off-target effects. For example, identifying potential hemodynamic effects in young healthy participants with heightened sympathetic nervous system activity may not predict effects in an older population for whom the drug will be primarily used, owing to lower levels of sympathetic sensitivity in more elderly populations.<sup>42</sup> In the case of NSAIDs, the opposite concern is the case: the impact of sodium and volume retention on BP and other CV effects is much less in younger individuals with normal renal handling of sodium and water than in the targeted population for chronic use, that is, older people with osteoarthritis and pain in whom filtration fraction has fallen with age.<sup>6</sup> In addition, the evaluation of exposure and dose to determine thresholds in which a drug shows both benefit and off-target hemodynamic effects must be assessed in a participant population likely to mimic those eventually receiving the drug in clinical

practice. Questions remain regarding the clinical relevance of the duration of the increase and its magnitude, each of which should be incorporated into thorough analyses of drug effects on BP.

## Clinical BP monitoring in drug development

Blood pressure is one of the most commonly measured hemodynamic parameters throughout drug development. Despite this, there has been no uniformly agreed-upon methodology for how BP should be measured and what constitutes a clinically significant drug-induced off-target BP increase. Many factors enter into this analysis, including the overall benefit-risk profile of the drug, treatment indication, length of treatment, and the CV risk of the population. A BP effect might manifest as an increased incidence of new-onset hypertension, worsening of existing hypertension (eg, destabilization of treated hypertension), or simply a BP increase where BP remains in the normotensive zone. Detection of a drug-induced change is complicated by the fact that it may be influenced by the frequency and type of BP measurement during clinical trials and/or the length of the trial.

### Early clinical development

**Phase I.** Phase I studies often offer the highest exposures observed during clinical development and the general nature of phase I studies (small sample sizes, limited numbers of sites, marked reduction in activity caused by subject confinement, and short study duration) make it easier to perform intensive/frequent BP monitoring, to standardize BP equipment, and to collect timed samples for PK assessment to correlate with BP measurements, which is not the case in later trials.

The collection of repeated BP measures over time in these early studies provides the ability for central tendency analyses of change from baseline not only to the end point but also at various time points during dosing intervals. This can lend insight into overall dose-dependent BP effects, onset and offset and duration of action of the drug, positional effects, and corresponding heart rate changes observed along with BP effects. Potential PK/PD correlations can be assessed to determine BP effects at peak and trough drug concentrations.

However, although phase I studies offer many advantages, they also have limitations because of the small sample size, limited statistical power, and short duration of exposure. As noted earlier, participants are typically healthy (normotensive) young to middle-aged adults, and observed BP effects of a study drug may not be applicable to the intended treatment population. In addition, longer-term BP effects may go undetected. Nonetheless, these studies are often influential in decision making for continued development of a drug and typically define the clinical safety monitoring needed for future studies,

**Table II.** Points to consider in the determination of a drug-induced off-target BP effect

- Duration of action of the drug
- PK/PD relationship\*
- Timing of BP effect in relationship to the timing of administration
- Duration of the PD effect (increase in BP)\*
- Whether the BP effect is sustained, episodic, or transient\*
- Discontinuation rate during trials because of hypertension\*
- Reversibility of the BP effect\*
- Other cardiac effects (eg, reflexive heart rate changes or functional changes)\*
- Postural effects of the drug on BP (particularly if increased when supine)\*
- Intended use of drug for a short-term illness vs a chronic disease\*
- Targeted population's age and underlying CV risk\*
- Determination of whether BP effects are in the total study population or important subgroups (normotensives, controlled hypertensives, uncontrolled hypertensives)\*
- Interaction with antihypertensive medications\*
- Effect in populations of special interest, eg, impaired kidney function, concomitant medications known to increase the BP (eg, NSAIDs), older people, and hypertensives\*

\*Identifies those findings that are likely to impact the benefit-risk relationship.

although in at least the case of sodium-retaining mechanisms of a BP increase, this might be missed because of subjects' (relatively) normal renal function and the short treatment periods.

**Phase II.** Phase II is an opportune time to evaluate drug-induced off-target BP increases because these studies generally involve participants with the disease of interest, the concomitant use of drugs in the target indication, and more intensive vital signs monitoring compared with phase III, and they often evaluate a wider dose spectrum. Furthermore, standardization of BP equipment and technique in the context of current discussions remains feasible. Several factors are worth considering in the design of phase II studies, and a variety of means to perform BP monitoring can be considered, as shown in [Table II](#).

Blood pressure monitoring during phase II allows for confirmation of what was observed in a phase I program and expansion to the evaluation of the drug in a population intended for the study drug based on disease state, which, depending on the mechanism, might uncover a BP issue for the first time. Inclusion/Exclusion of participants with a wider range of baseline BPs and use of out-of-office measurements are desirable. Reversibility of any BP effects can be determined easily with programmed assessments after the active treatment period. Furthermore, the treatment duration is typically longer than that in phase I studies.

A major advantage of phase II trials is that placebo is the commonly used comparator, so assessment of BP changes on study drug can control for regression to the mean and other common confounders. Phase II is also an opportune time to perform dedicated BP studies that evaluate ambulatory BP recordings and/or other methodologies

for out-of-office measurement on varying doses and placebo. Unlike phase I studies, which have small samples and healthy participants, and phase III trials, which must mimic clinical practice as much as possible, phase II studies have reasonable numbers of participants with the disease of interest per treatment arm and are performed at sites in which enhanced rigor is expected.

Findings from phase II studies often determine the clinical safety monitoring needs for future studies, and, in particular, what, if any, additional CV evaluations or substudies might be needed during phase III and whether a more intensive examination of BP effects using ambulatory blood pressure monitoring (ABPM) in a larger sample size might be valuable later in the development program.

### Later-stage clinical development

**Phase III.** Intensive BP monitoring is less frequent in phase III, but standardization of BP equipment and measurement technique remains important for these studies. There are many variables in phase III that impact stringent definition of central tendency BP changes, and thus, phase III is more valuable for identifying outliers with large BP effects and adverse effects that might be attributable to BP increases. Depending on the presence of signals seen in phase I and/or II, self-monitoring of BP in some late-stage trials may provide a better assessment of the PDs of the drug's effect. Self-BP measurements can be taken at different times of the day, are reproducible, may improve patient compliance to treatment, and help overcome some of the issues with conventional BP monitoring (eg, the white-coat effect, ie, variance between clinic and self-monitored BP readings, and masked effects).<sup>43,44</sup> Out-of-office BP measurements increase the complexity of a phase III program but should be incorporated for both patient safety and to better characterize the drug if a signal was detected in phase I or II.

Assuming consistency of BP ascertainment during phase III trials, both individual study data and data pooled across all studies can provide additional useful insights regarding drug-induced BP effects or lack thereof, including the long-term effects of the drug, mean population effects (central tendency analyses), and assessment of outliers. Discontinuation rates, adverse event reports of hypertension, and changes in the frequency of concomitant antihypertensive medications can be compared between treatment groups. In a large phase III program, prespecified analyses may yield additional insights regarding important patient subgroups (eg, the elderly, those with treated hypertension, and African Americans). Understanding the potential mechanism of action of the observed effect is of interest but sometimes may require challenging mechanistic studies.

To optimize the interpretation of a drug's effect on BP, it is critical that BP be measured in a consistent fashion to allow for data integration and interpretation. The overall

**Table III.** Various technologies and methodologies to measure BP in clinical trials

BP methodology/ technology	Strengths	Limitations	Clinical phase applicability
Clinic BP measurement using auscultation by observer	Traditional standard used in epidemiologic and primary and secondary CV trials	Poor reproducibility caused by white-coat and masked BP effects, observer bias Concern regarding environmental mercury	Phases I-IV
Clinic BP measurement using noninvasive auscultation devices	Removes environmental concern regarding mercury, enhanced validation, and easier to read BP column	Poor reproducibility caused by white-coat and masked BP effects, observer bias	Phases I-IV
Clinic oscillometric BP measurement (digital)	Removes observer bias, select inflation sequence, improves reproducibility	Device precision can be a concern for certain devices, but probably improved compared with above modalities. White-coat and masked effects still occur.	Phases I-IV
Ambulatory BP Monitoring (ABPM)	Provides large number of readings over a 24-h period that enhances reproducibility Minimal placebo effect Obtains BP during sleep	Participant compliance related to multiple monitoring sessions can be problematic as well as a relatively high preponderance in some studies of technically unusable recordings. Expensive compared with other methods	Phases I-IV
Centralized office BP monitoring	Removes some observer bias, select inflation sequence, improves reproducibility Provides early visibility into BP trends in clinic	Same as other office-based measurements Study site education required to implement process	Phases I-III
Self-measured home BP (digital)	Removes white-coat and masked effects Provides out-of-office readings and can be timed to drug dosing Correlates to daytime ambulatory BP	Device precision can be a concern with some devices. Requires patient to transcribe BP values into logbook and patient training	Phases II-IV
Self-measured home BP measurement using telemonitoring	Removes white-coat and masked BP effects Avoids loss of data by participants Ability to transfer and process large amount of data easily, trend analysis, and alert criteria	Requires additional training and working with telecommunication providers to move to a data transmission focus	Phases II-IV

benefit-risk profile of the drug for the intended population and indication(s) must always be considered in the determination of clinical relevance, along with any known class effects. Likewise, it should be recognized that an observed BP population effect does not necessarily equate to the risk in an individual. Drug-induced BP increases do not necessarily preclude approval, which are always an issue of full regulatory review. Many therapies with known effects on BP are on the market: product labels reflect these findings and indicate where caution should be exercised (eg, in certain populations or when used concomitantly with other drugs). Additional patient monitoring could be recommended, particularly after initiation of therapy, and/or additional postmarketing studies may be requested to continue the longer-term assessment and impact of the reported BP finding. However, for small population-based increases in BP, the strategy of reducing patient risk by prescribing an antihypertensive medication may not be practical, and small BP increases in individual patients may not be recognized by health care professionals.

**Blood pressure monitoring methods: strengths and limitations.** The different modalities of BP measurement techniques are shown in Table III. In a drug development program where a possible BP signal exists,

multiple methodologies to measure BP should be used to allow an accurate assessment of the signal. Although the diagnosis of hypertension and the monitoring of BP during clinical trials are usually performed using manual BP readings taken at the clinical trial site by an observer, it is neither a precise nor an efficient process. Physician and nurse measurements are often inaccurate as a result of poor technique, often unrepresentative because of the white-coat effect, and rarely include enough readings made at any one visit. It is often not appreciated how large the variations in clinic BP can be. The practical limitation on the number of readings that can be taken at any one clinical visit, and on the number of visits, means that readings taken during clinic visits will almost always have relatively low intervisit reliability<sup>41</sup> and large variances. The technologies and methodologies shown in Table III provide a means for reducing BP variability during the trial and providing BP monitoring options that best fit the specific trial design, indication, study population, and development considerations. The different BP technologies are complementary, and based on the study design, the ideal approach can be defined and the primary methodology clearly defined.

**Home or self-monitored BP.** Home (or self-) BP monitoring avoids some of these limitations by enabling

larger numbers of readings to be taken in a more representative setting and plays an increasingly important role in the diagnosis and treatment of hypertension. Its use has been endorsed by guidelines such as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure<sup>45</sup> and the American Heart Association<sup>46</sup> in the United States and the European Society of Hypertension.<sup>47</sup> Home readings complement conventional clinic measurements and also 24-hour ABPM. The potential use of study participants having their BPs measured at home, by using self-monitoring or by having a family member make the measurements, has the theoretical advantage of being able to overcome 2 major limitations of clinic readings, that is, the small number of readings that are taken and the white-coat effect. Furthermore, self-BP monitoring improves patient compliance, and there is increasing evidence that it can predict CV outcomes better than office or clinic BP measurement.<sup>48</sup>

The limitations of home BP monitoring also need to be specified. First, readings tend to be taken in a relatively relaxed setting so that they may not reflect the BP occurring during stress. Second, patients may misrepresent their readings. Third, occasionally a patient may become more anxious as a result of self-monitoring. Using telemonitoring helps to improve the validity of self-measured BPs as data are transferred directly from the patient's home to a central server.<sup>49</sup> In addition, obtaining more numerous readings in a clinical trial with self-measured or ambulatory BP enhances reproducibility and allows for greater statistical power and hence reductions in sample size to rule out an effect size of clinical concern.<sup>50</sup>

**Twenty-four-hour ABPM.** In recent years, ambulatory BP monitors have become much more practical to use in clinical trials research. The devices are much smaller than in the past, simple to apply by a nurse or technician, and precise. These fully automatic, programmable recorders are capable of 100 to 200 BPs and pulse measurements from an energy source of 2 to 4 small batteries. Most devices measure BP by oscillometry rather than auscultation of Korotkoff sounds. The oscillometric methodology is accurate in individuals who have midrange BPs and hold their arms still during cuff inflation and deflation. Ambulatory BP recorders used in clinical research or practice should be independently validated using established criteria.<sup>51,52</sup>

Once a recording has been completed in an individual patient, the data are expressed as the mean 24-hour, awake and sleep SBPs and DBPs. Blood pressure during sleep is usually lower than the office pressure, whereas BP during wakefulness is similar to the values obtained in the office. Most consensus groups have used a 24-hour BP >130/80 mm Hg and an awake BP >135/85 mm Hg as abnormal based on several new outcome studies com-

**Table IV.** General consensus of the Think Tank for evaluation of drug-induced off-target BP effects

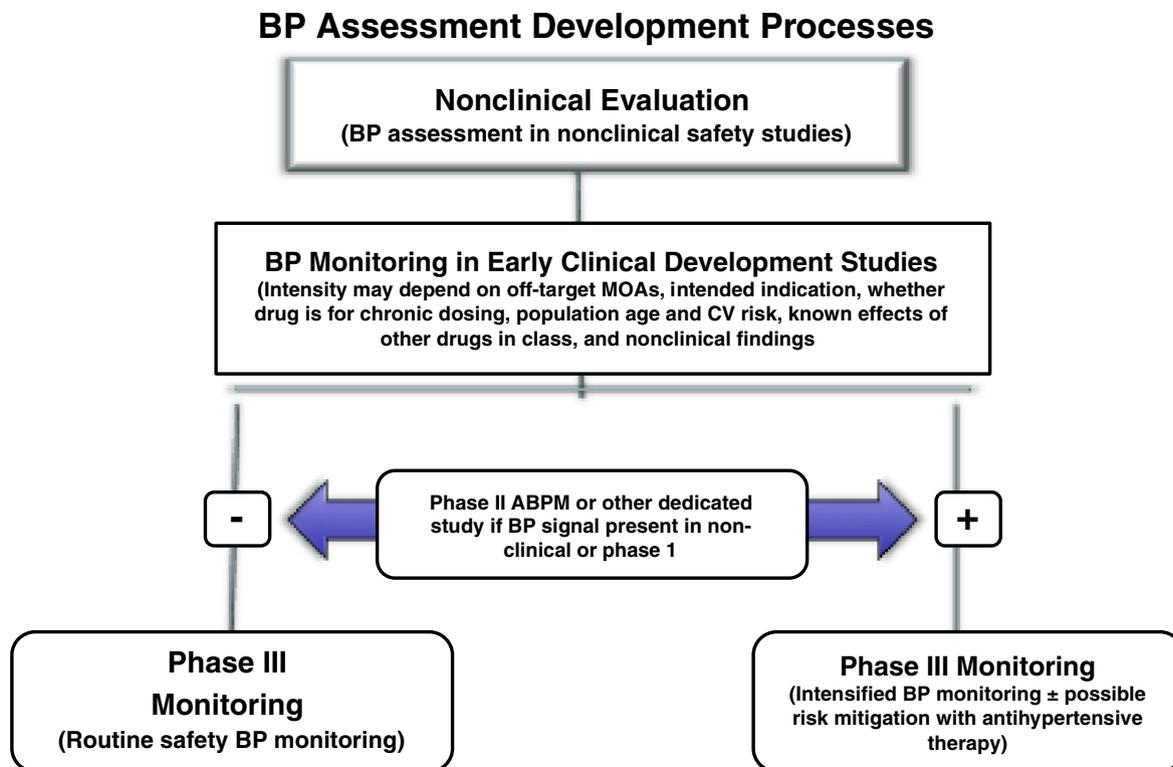
<p>Drug-induced BP increases: clinical implications and risk boundaries</p> <ul style="list-style-type: none"> <li>• Approach to BP assessment in drug development will be different from QT/QTc (TQT) approach because of the heterogeneity of mechanisms impacting different patient populations differently.</li> <li>• Changes in SBP across all levels are associated with increases in CV risk (particularly stroke and heart failure) with long-term therapy.</li> <li>• Methods of BP measurement may impact precision of the signal. ABPM is favored; automated methods can be useful in other settings.</li> <li>• Changes in BP (drug-induced off-target changes) differences should be evaluated according to baseline BP, age, sex, CV comorbidities, and mechanism.</li> <li>• Observational databases to estimate risk were found to have shortcomings but were useful overall, with the recognition that other methodologies do not exist at this time.</li> <li>• Central tendency increases are usually associated with outlier increases.</li> <li>• There are potential implications of a BP increase being theoretically mitigated by other actions of a drug on underlying risk, but the practical nature of this approach on an individual patient level for small BP increases is questioned.</li> <li>• BP increases may generally be hard to detect and treat by medical practitioners.</li> </ul>
<p>Drug-induced BP increases: technical aspects of BP measurement and need for a specific BP study</p> <ul style="list-style-type: none"> <li>• Devices used for clinical, self-, or ambulatory measurement should be independently validated for the population being studied (adults vs children, old vs young, etc). Overall, automated measurements have less variability and better accuracy.</li> <li>• Precision of BP signals in phase I studies has not been well studied; standardization of BP monitoring protocols should be enhanced in development programs.</li> <li>• Dedicated BP studies during phase II could have value, depending on the mechanism of action of the study drug, the population being studied, and the need to understand the need for safety monitoring during phase III.</li> </ul>

paring ambulatory vs clinic BP in patients with hypertension.<sup>53</sup> The key attributes of ABPM in clinical trials include the large number of readings per study, lack of a white-coat effect, the ability to obtain readings while patients are sleeping, the substantially better reproducibility than clinic BP, enhanced power to detect a BP increase, and the ability to obtain PD data in relation to a dose in the patients' home and work environments. The key limitations of ABPM are patient inconvenience and cost. However, for assessment of drug-induced BP effects, the benefits of ABPM far outweigh these limitations. These devices can be deployed once or multiple times during a clinical trial, depending on the design, and provide a reproducible and reliable metric.

## Concluding comments

Three areas of general consensus were reached at the Think Tank for the evaluation of drug-induced off-target BP responses (see Table IV). Although the concept of one study to fit the general requirements of assessing the BP effects of a new drug is attractive, it was concluded that this approach is not practical considering the potential heterogeneity of responses based on the

Figure



Assessment of BP changes during drug development.

mechanisms of action and the type of population that will be targeted for the drug. It was also clear that drug-induced changes in BP should be evaluated according to age, sex, baseline BP, and mechanism of action (if understood). Eventually during development, any off-target BP signal observed should be characterized according to CV and cardiorenal comorbidities. It was also noted that central BP tendency increases are likely to be accompanied by outlier increases such that careful statistical analyses are important to determine the extent of BP increases in the outliers. For drugs with substantial BP effects, it is possible that additional safety studies might be required for drugs that require long-term dosing, especially if intended for patients with significant CV risk factors or morbidities.

Nonclinical models are helpful in identifying and elucidating potential BP signals and the mechanism of action by which the BP might become elevated, and additional research is needed to assess their positive and negative predictive accuracy. These investigations may prove useful in translating into clinical studies that assess the impact of drug-induced off-target BP effects in patient populations likely to be candidates for the therapy. Hence, phase II might be considered the most appropriate time during development to assess the BP effects

because it can use individuals with the disease of interest rather than healthy participants and could allow for the exploration of a dose-response on BP in alignment with efficacy (see Figure).

Technical aspects of how BP data are acquired were deemed to be of substantial importance. Although standardized clinical assessments timed to drug dosing in a clinic setting such as a clinical pharmacology research unit have value, poor reproducibility in a short-term or intermediate-term trial limit their validity. Out-of-office BP monitoring techniques, particularly using 24-hour ambulatory devices, are more likely to detect BP signals of small to moderate size and have the ability to characterize the PD profile of the drug under evaluation better than static, clinic measurements.

Finally, the knowledge gained from a well-designed BP assessment portfolio during mid-development of a drug in which a signal has been detected can be used to efficiently evaluate the agent during phase III (see Figure). This includes not only standardized clinical assessments timed to drug dosing but also, if appropriate from a clinical perspective, a mitigation plan that may be useful in reducing BP increases induced by the drug that may later translate into recommendations for the post-registration period.

## Acknowledgements

The following are acknowledged for their contributions to the discussions and critical review that led to the development of this white paper: Robert Blaustein, MD; Alan Charney, MD; Preston Dunnmon, MD; Lorna Ewart, PhD; Robert Fiorentino, MD; James Hainer, MD; Luana Koplowicz, MD, PhD; James Keirns, PhD; Rajanikanth Madabushi, PhD; Tzu-Yun McDowell, PhD; James Neaton, PhD; Christopher O'Donnell, MD; Milton Pressler, MD; Ignacio Rodriguez, MD; Domenic Sica, MD; Lee Simon, MD; Robert Temple, MD; Douglas Throckmorton, MD; and Theresa Wright, MD.

## Disclosures/Conflicts of Interest

William B. White, MD, has declared no stock ownership and is not a member of any speakers' bureaus. He received research funding from the National Institutes of Health (National Institute of Aging, National Institute of Drug Abuse). He is a safety consultant (member of DSMB, CV end point committee, or advisory board) to Ardea Biosciences; Astra-Zeneca; Astellas, Inc; Bristol-Myers Squibb; Dendreon; Forest Research Institute; Nycomed-Takeda; Palatin Technologies; Roche, Inc; Shire Pharmaceuticals; Takeda Global Research and Development; and Teva Pharmaceutical Industries. He is the president of the American Society of Hypertension from 2012 to 2014. Philip T. Sager, MD, has a stock ownership in Merck, Aegerion. He is not a member of any speakers' bureaus and has declared no research funding. He is a safety consultant (member of DSMB, CV end point committee, consultant, or advisory board) to Shire Pharmaceuticals, PolyMedix, Pfizer, Theravance, Lilly, Milestone, Medtronic, Aerpio, Array, SK Science, Zalicus, Elan, Sanofi, and BioMarin. He is a member of FDA Cardiovascular and Renal Drugs Advisory Committee and Executive Committee Member, CSRC. J. Rick Turner, PhD, is the senior scientific director of Clinical Communications, Quintiles. He is not a member of any speakers' bureaus. He has declared no stock ownership, research funding, or consulting job (outside consulting as part of his regular full-time employment at Quintiles). Dr Turner has disclosed that he is a full-time employee of the CRO Quintiles. Their Cardiac Safety Services division already does, or is shortly to, start offering ABPM services to the biopharmaceutical industry in the specific context of assessing drug-induced off-target BP responses. Jeffrey Heilbraun, MS, is the director of Strategic Development, CoreLab Partners, Inc. He is not a member of any speakers' bureaus. He has declared no stock ownership, research funding, or consulting job. He is a full-time employee of the CRO CoreLab Partners, Inc; Cardiac Safety Services division provides BP monitoring services (including ABPM) services to the biopharmaceutical industry. Peter R. Kowey, MD, is the chairman

of the Cardiology, Lankenau Institute for Medical Research, Main Line Health and Jefferson Medical College. He has a stock ownership in Cardionet. He is not a member of any speakers' bureaus. He is a consultant to Ardea, AZ, Astellas, BMS, Dendreon, Theravance, Forest, Nycomed, Takeda, Palatin, Roche, Shire, Teva, J&J, Merck, Novartis, BI, Daiichi, Gilead, Lilly, Sanofi, Pfizer, and GSK. Norman Stockbridge, MD, PhD, is employed by the FDA, Silver Springs, MD and has no disclosures or potential conflicts of interest. Michael A. Weber, MD, is a professor of medicine of the State University of New York Downstate College of Medicine. He has declared no stock ownership. He is a member of the following speakers' bureaus: Daiichi Sankyo, Forest Pharmaceuticals, Novartis, and Takeda Pharmaceuticals. He is a consultant to Boehringer-Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, and Takeda Pharmaceuticals. Gary Gintant, PhD, is an employee of Abbvie, Inc, Chicago, IL. Mary Jane Geiger, MD, PhD, is an employee of Relypsa Pharmaceuticals, San Francisco, CA. She has declared a stock ownership in Eli Lilly Pharmaceuticals, Inc. George Mansoor, MD, is an employee and shareholder of Merck Inc. Boaz Mendzelevski, MD, is an employee of CoreLab Partners, Inc. Eric Michelson, MD is an employee and owns stock in AstraZeneca.

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