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

Philip Sager, MD, FACC, [a,n,o] **Jeffrey Heilbraun, MS,** [b,n,o] **J. Rick Turner, PhD,** [c,o] **Gary Gintant, PhD,** [d] **Mary J. Geiger, MD, PhD,** [e] **Peter R. Kowey, MD,** [f,g] **George A. Mansoor, MD,** [h] **Boaz Mendzelevski, MD,** [i] **Eric L. Michelson, MD,** [j] **Norman Stockbridge, MD, PhD,** [k] **Michael A. Weber, MD,** [l] **and William B. White, MD, FASH, FACP, FAHA** [m,o]

San Francisco, and Santa Clara, CA; Princeton, and Whitehouse Station, NJ; Durham, NC; Chicago, IL; Wynnewood, and Philadelphia, PA; London, United Kingdom; Wilmington, DE; Silver Springs, MD; Brooklyn, NY; and Farmington, CT

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 in 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) 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.[1] 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 nonclinical 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.

Background

In recent years, it has become evident that drugs can affect BP in an off-target manner.[2–5] 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.[4,6,7] 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.[8,9] 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

From the [a]Cardiac Safety Research Consortium, Sager Expert Consulting, San Francisco, CA, [b]CoreLab Partners, Princeton, NJ, [c]Quintiles, Durham, NC, [d]Abbvie, Inc, Chicago, IL, [e]Relypsa, Santa Clara, CA, [f]Lankenau Institute for Medical Research, Main Line Health, Wynnewood, PA, [g]Jefferson Medical College, Philadelphia, PA, [h]Merck Sharp & Dohme, Whitehouse Station, NJ, [i]CoreLab Partners, London, United Kingdom, [j]AstraZeneca LP, Wilmington, DE, [k]Division of Cardiovascular and Renal Drug Products, FDA, Silver Springs, MD, [l]SUNY Downstate College of Medicine, Brooklyn, NY, and [m]University of Connecticut School of Medicine, Farmington, CT.

[n]These authors' contributions to the article were equal.

[o]These authors comprised the core group of writers.

Disclaimer: The opinions and conclusions expressed in this article are solely the views of the authors and do not necessarily represent the regulations and policies or views of the US Food and Drug Administration or other authors' affiliations.

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

Reprint requests: William B. White, MD, FASH, FACP, FAHA, Division of Hypertension and Clinical Pharmacology, Calhoun Cardiology Center, University of Connecticut School of Medicine Farmington, CT 06030-3940.

E-mail: wwhite@nso1.uchc.edu

0002-8703/$ - see front matter

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

Table I. 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 erythropoetin 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 natruiuresis. Hence, the NSAIDs can induce an increase in BP by enhancing plasma volume and vasoconstriction. NSAIDs also attenuate certain antihypertensive therapies including diuretics, β-blockers, and angiotensin-converting enzyme inhibitors, but are less likely to interfere with α_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 α_1- and β_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 β-receptors of the heart leading to increases in HR and α-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.[10,11] 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.[12–15] 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.[16,17]

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)[18,19] and increases in CV events including myocardial infarction and heart failure with rofecoxib[18,20] and stroke with high-dose ibuprofen.[19] Although it is not completely established whether the CV