Assessment of Pressor Effects of Drugs

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Clinical/Medical
Revision 1

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I. INTRODUCTION

This guidance is intended to advise sponsors on the premarketing assessment of a drug's effect on blood pressure. Elevated blood pressure is known to increase the risk of stroke, heart attack, and death. The effect of a drug on blood pressure is, therefore, an important consideration in risk assessment and product labeling.

The recommendations in the guidance are generally applicable to new drugs with systemic bioavailability and to approved drugs for a new indication/population with a higher cardiovascular risk or when a new dosing regimen results in significantly higher or more prolonged exposure.

This guidance revises the draft guidance for industry *Assessment of Pressor Effects of Drugs* issued in May 2018. This revision provides greater detail about study design, including specific statistical powering recommendations that were not included in the original document. Furthermore, this revision provides recommendations on how to incorporate information about increased blood pressure in the prescribing information of drug product labeling.

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II. BACKGROUND

Data from multiple sources indicate that elevated systolic and diastolic blood pressures increase cardiovascular risk. Epidemiologic evidence demonstrates a monotonically increasing risk of

[1] This guidance has been prepared by the Division of Cardiology and Nephrology in the Center for Drug Evaluation and Research at the Food and Drug Administration.

stroke, heart attack, and death with increasing blood pressure; even a few millimeters of mercury (mmHg) can be clinically relevant. MacMahon et al. (1990) evaluated the relationship between diastolic blood pressure and the rates of stroke and coronary heart disease (CHD) events, defined as nonfatal myocardial infarctions and CHD deaths, in nine major, prospective, observational studies. Diastolic blood pressures that were lower by 5.0, 7.5, and 10 mmHg were associated with 34, 46, and 56 percent fewer strokes, respectively, and 21, 29, and 37 percent fewer CHD. Of note, the relative reduction in risk associated with a particular decrease in diastolic blood pressure was similar within the entire range of diastolic blood pressures evaluated (70 to 110 mmHg), including levels that would be considered normal. When the highest risk category of diastolic blood pressure (greater than or equal to 110 mmHg) was compared with the lowest risk category (less than or equal to 79 mmHg), the risk of stroke was about 10 to 12 times higher; the risk of CHD was about 5 to 6 times higher.

The incremental cardiovascular risk imparted by higher systolic blood pressure is a function of the underlying cardiovascular risk. Equations from pooled cohorts of 10-year atherosclerotic cardiovascular disease (ASCVD) event risk models can be used to describe the effect of a higher systolic blood pressure on the risk of developing an ASCVD event, defined as the occurrence of coronary death or fatal stroke, or the first occurrence of nonfatal myocardial infarction or stroke (Goff et al. 2014). FDA generated Figure 1 (see the Appendix) to show the expected increases in ASCVD events for a chronic elevation in systolic blood pressure (1 to 7 mmHg) in patients whose risks fall within three risk levels (low/borderline, intermediate, and high).

Results from controlled trials of antihypertensive drugs show that decreases in blood pressure led to decreased rates of stroke and cardiovascular deaths in populations with all levels of risk from other factors, such as elevated low-density lipoprotein cholesterol or smoking status. Maintenance of a reduction in blood pressure with antihypertensive drug regimens consistently reduced rates of stroke and cardiovascular death, with a less consistent effect on nonfatal myocardial infarction (see Table 1 in the Appendix). Furthermore, the beneficial effect on cardiovascular outcome occurs within a relatively short period of time (0.5 to 1 year), suggesting that an increased risk from elevated blood pressure would also occur relatively rapidly (Staessen et al. 1997; Veterans Administration Cooperative Study 1970). In the Systolic Hypertension in the Elderly Program (SHEP Cooperative Research Group 1991), for example, the reduced rate of stroke is clearly seen within 1.5 years (and perhaps earlier), and findings were similar in the European Working Party on High Blood Pressure in the Elderly trial (Amery et al. 1985).

This relationship of lower blood pressure to lower rates of stroke and cardiovascular death shown in Table 1 has been observed in outcome studies involving a wide array of antihypertensive drugs, including diuretics, reserpine, hydralazine, beta blockers, calcium channel blockers, and renin-angiotensin system inhibitors. FDA, with the concurrence of the Cardiovascular and Renal Drugs Advisory Committee,[2] considers this relationship to be sufficiently well-established to conclude that all antihypertensive drugs should be labeled with a cardiovascular risk reduction claim, even if a drug has not been evaluated in a cardiovascular outcome study (see the guidance

[2] Summary minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting for June 15, 2005, available at https://wayback.archive-it.org/7993/20170404055351/https://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4145M1.pdf.

for industry *Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims* (March 2011)).[3] This guidance now suggests that a drug-induced increase in blood pressure is likely to have similar deleterious effects, no matter the mechanism of the increase.

This hypothesis is supported by the observation that some drugs that produce sustained increases in blood pressure (e.g., rofecoxib, sibutramine, torcetrapib, celecoxib) have been associated with adverse cardiovascular effects. In light of these findings, it is reasonable to expect that chronic use of drugs that increase blood pressure measured by either ambulatory blood pressure monitoring (ABPM) or clinically will increase cardiovascular risk, with an absolute increase in risk related to the baseline risk, the baseline blood pressure, the duration of treatment, and the magnitude of the blood pressure increase.

Although nearly every drug development program has some assessment of the drug's blood pressure effects, the methods used for assessing blood pressure are not consistent and not always adequate. As a result, small increases in blood pressure that could be relevant to the risks of a drug may not be reliably detected in some drug development programs.

Several factors can influence the importance of blood pressure effects to the benefit-risk assessment, including the magnitude of the blood pressure increase, the seriousness of the condition being treated, the effect of the drug on the condition, the underlying cardiovascular risk in the patient population most likely to use the drug, the availability of other effective therapies that do not raise blood pressure, strategies that can be used to mitigate the blood pressure effects, and the anticipated duration of drug treatment.

For a drug that increases blood pressure, differences in blood pressure effects across subgroups of the patient population may exist, just as differences across subgroups may exist in response to a blood pressure–lowering treatment. Characterizing such differences is important.

III. BLOOD PRESSURE ASSESSMENT: DRUGS INTENDED FOR SHORT-TERM VERSUS CHRONIC USE

Whether a drug is intended for short-term or chronic use is a significant factor for determining how to assess blood pressure during a clinical trial.

A. Drugs Intended for Short-Term Use

There is little concern about a drug indicated for short-term use that has small effects on blood pressure because the cardiovascular risk of small, short-term elevations in blood pressure does not appear to be meaningful. FDA's analysis of placebo-controlled hypertension trials less than 12 weeks in duration (most were shorter) did not find an increased risk of cardiovascular events in the placebo groups (DeFelice et al. 2008). Large blood pressure increases are of concern, however, even with drugs intended for short-term use. Therefore, in general, careful assessment

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

of blood pressure using clinic blood pressure measurement during routine study visits (section IV. B.) is recommended.

B. Drugs Intended for Chronic Use

There is greater concern with the effects of a drug on blood pressure when the drug will be used chronically. As noted above, the risk related to blood pressure is a continuous function, and sustained increases in blood pressure correlate with long-term increases in the risk of cardiovascular events. It follows that drug-induced sustained elevations in blood pressure, even if small, would have such effects. Sponsors, therefore, should include a thorough blood pressure assessment for any drug intended for chronic use. FDA recommends use of ABPM for this assessment, as ABPM is capable of detecting small, but potentially relevant, blood pressure effects (see section IV). ABPM also assesses effects over a 24-hour period, which is more informative than assessment at a single time point (Pickering 2000).

IV. TYPES OF BLOOD PRESSURE ASSESSMENT

A. Clinic Blood Pressure Measurements

Clinic blood pressure measurements can be used for three purposes: to assess the effects of drugs intended for short-term use, to characterize the dose or exposure-response relationship for drugs that increase blood pressure, and to serve as part of the overall safety assessment to identify patients with large increases in blood pressure.

The accuracy of clinic blood pressure measurement can be improved by collecting triplicate measurements of sitting blood pressure in all subjects at baseline (predose), at several visits (at least two visits before the end of the trial), at the end of the interdosing interval (trough measurement; predose), and at peak concentration of test drug or active metabolites. Measurements should be made approximately 1 to 3 minutes apart, using the same arm at each visit. For studies with entrance criteria that include specific blood pressure ranges or cutoffs, separate predose measurements should be obtained; screening measurements should not be used as the baseline.

If a large blood pressure effect is not detected by clinical blood pressure measurements in early, small studies, FDA recommends an ABPM study for drugs intended to be used chronically.

B. Recommended Use of ABPM

FDA recommends the use of ABPM rather than routine clinic blood pressure measurement for drugs intended to be used chronically, as ABPM provides more accurate measurements of blood pressure throughout the day.

Several factors influence the ability to detect small changes in blood pressure. First, blood pressure naturally varies throughout the day (diurnal variation), as well as with meals, activity, and changes in response to stress, including the stress of having one’s blood pressure measured

(white coat hypertension). In addition to these true variations in blood pressure, clinic blood pressure measurement is associated with measurement error (e.g., calibration error, improper auscultation, rounding). Given these variations, blood pressure assessment using a small number of measurements may not reliably detect small, but potentially relevant, increases in blood pressure. Moreover, increased nocturnal blood pressure has been recognized recently as an important predictor of cardiovascular risk (Parati et al. 2014; Whelton et al. 2017).

The advantages of ABPM over clinic blood pressure measurements include the following:

- Assesses blood pressure effects over a 24-hour period
- Provides insight into the nocturnal blood pressure response
- Allows a more precise measure of an individual's blood pressure throughout the day
- Can be programmed to collect measurements at specified times or to capture a standardized schedule of measurements over 24 hours
- Is free of potential investigator bias, including tendencies to round up or down

V. BLOOD PRESSURE ASSESSMENT: STUDY DESIGN CONSIDERATIONS FOR DRUGS INTENDED FOR CHRONIC USE

A. Control Group

ABPM studies of less than 12 weeks suggest there is little or no change on placebo; whether to include a placebo group may depend on a number of factors (Harrison et al. 2020). For example, changes in blood pressure with time may obscure drug effects, making inclusion of a placebo group desirable in studies with longer duration. A placebo control group can also be desirable when design elements other than drug treatment (e.g., lifestyle modifications) could affect blood pressure.

An active control is generally not needed but can provide useful information if, for example, the investigational drug is a member of a chemical or therapeutic class of compounds that are known to increase blood pressure. Including a member of the same class as an active control could be used to compare the blood pressure effects between drugs with appropriate sample size and statistical power.

B. Population

The ABPM study should be performed in the patient population for which the drug is being developed, either in a targeted study or as part of a larger study already being conducted for other purposes. The study may also be performed in a related patient population with characteristics similar to those of the intended target patient population (i.e., similar demographic and disease-specific characteristics).

C. Study Design

In general, the study should be powered to exclude a 3-mmHg increase in 24-hour average systolic blood pressure using an upper bound of the two-sided 95% confidence interval assuming the true effect is 0 mmHg. Such an increase would lead to an increase of approximately 0.5 to 1 cardiovascular event per 1,000 patient years in patients with intermediate to high cardiovascular risk at baseline (see Figure 1) using the ASCVD risk model. Sponsors and the review division should consider the underlying cardiovascular risk in the patient population and the perceived benefit of the drug when selecting an appropriate effect to be ruled out.

Blood pressure should be measured at least twice an hour over 24 hours using ABPM at baseline and on-treatment to assess the overall effect; on-treatment measurements should be performed only after the drug has reached its steady state effect on blood pressure. Based on a meta-analysis of antihypertensive agents, which showed that maximal effect was not observed until 4 weeks of treatment, we recommend that ABPM trials be of at least 4 weeks' duration (Lasserson et al. 2011).

In general, sponsors should present the results as 24-hour average as well as the daytime (awake) and nighttime (asleep) averages. Other presentations may be appropriate depending on the mechanism of action and the expected pharmacokinetic and pharmacodynamic properties of the drug. Results may suggest that blood pressure elevations are related to drug concentration exposure, which could, in turn, relate to dose and dosing interval. Sponsors should collect pharmacokinetic samples at appropriate time points in an effort to demonstrate treatment compliance and to explore the relationship between blood pressure increases and drug exposure.

If the drug increases blood pressure in the overall patient population, sponsors should obtain additional information about the effects of the drug in relevant subsets of the population with potentially larger blood pressure effects, if applicable (e.g., patients with preexisting hypertension, patients with impaired renal status, patients at increased cardiovascular risk, older patients).

VI. REGULATORY RISK ASSESSMENT

Large drug-induced elevations in blood pressure are relevant for all drugs, even for those intended for short-term use. Smaller sustained elevations of blood pressure of even a few millimeters of mercury are a concern when the drug is intended for chronic use, particularly when the target population is at increased cardiovascular risk. As noted above, the increment in proportional risk for a given blood pressure increase appears to be similar across the range of blood pressures, including normal blood pressure. Conversely, the increase in absolute risk would be very small for a person at low baseline risk (e.g., age 25, normal low-density lipoprotein and high-density lipoprotein, not diabetic, and normotensive) and becomes progressively greater as the number and severity of risk factors increase, as shown in Figure 1. Sponsors should consider Figure 1 when formulating their approach to assessing the importance of the pressor effect of a particular drug.

The finding that a drug increases blood pressure and the magnitude and pattern of that increase should be factored into the overall risk assessment for the drug. This assessment should include consideration of any steps that could be taken to mitigate the risk of increased blood pressure, such as patient selection, pretreatment assessments, blood pressure monitoring in some or all patients, and expectant use of blood pressure–lowering treatments.

VII. LABELING CONSIDERATIONS

The ABPM study results should be generally summarized in the *Pharmacodynamics* subsection in the CLINICAL PHARMACOLOGY section of labeling. A brief description of the ABPM study design and study population should be included regardless of whether the drug was shown to increase blood pressure. If the drug is associated with an increase in blood pressure from clinic blood pressure measurements or ABPM, this subsection should include the following, as appropriate:

- Effects on systolic and/or diastolic blood pressure with the doses studied
- The distribution of blood pressure effect sizes
- The dose or exposure response
- The time course of the blood pressure effect
- Important subgroup differences in blood pressure response (e.g., demographics, concomitant illness, concomitant treatments)

If a drug has been shown to increase blood pressure from clinic blood pressure measurements or ABPM, the adverse reaction must be included in the ADVERSE REACTIONS section.[4]

If the drug is associated with a clinically significant increase in blood pressure (see section V.C.), then the following should be included in the WARNINGS AND PRECAUTIONS section:[5]

- A description of the blood pressure increases (e.g., mean observed blood pressure effect, distribution of blood pressure increases, adverse events of hypertension and related terms).

- Clinical implications (e.g., increased risk of major adverse cardiovascular reactions, including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death)

- Steps to take to prevent, mitigate, monitor for, or manage the blood pressure increases (e.g., recommendations for checking blood pressure before and during drug treatment, for use of the drug in patients at higher risk of major adverse cardiovascular reactions or

[4] See 21 CFR 201.57(c)(7) and the guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (January 2006).

[5] See the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011) and 21 CFR 201.57(c)(6).

those taking other drugs that increase blood pressure, and for continued use of the drug in patients who develop hypertension or who have exacerbation of preexisting hypertension)

Clinically significant increases in blood pressure should also be described in other sections of labeling as appropriate (e.g., BOXED WARNING, CONTRAINDICATIONS).

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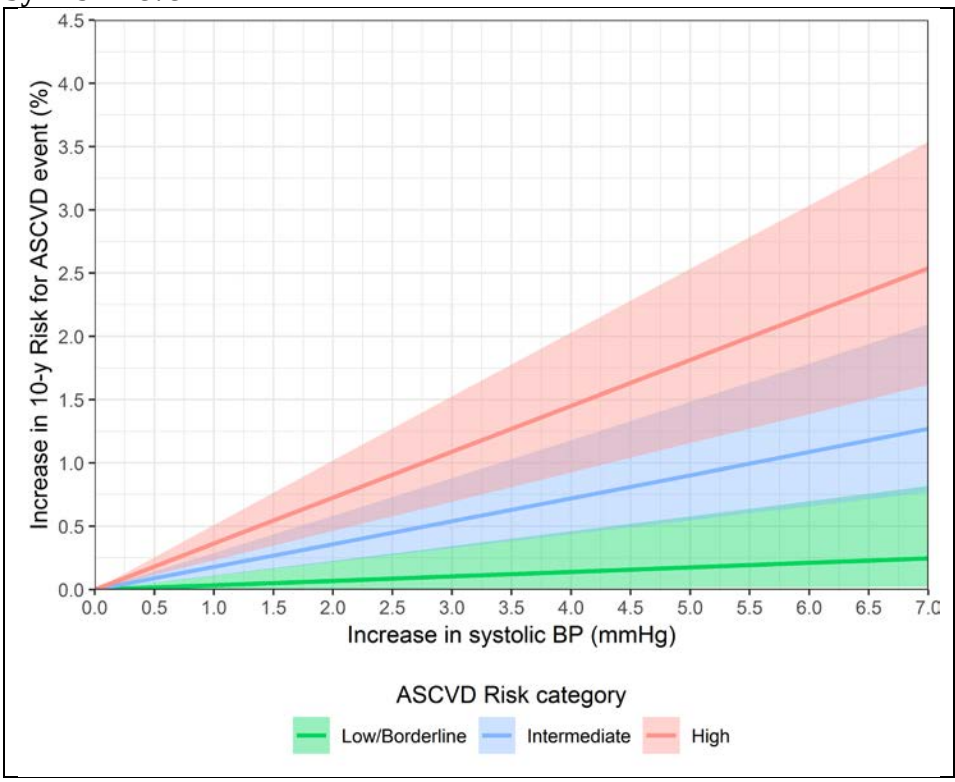
APPENDIX

FDA generated Figure 1 to show the expected increases in ASCVD events for a chronic elevation in systolic blood pressure (1 to 7 mmHg) in patients whose risks fall within three risk levels (low/borderline, intermediate, and high).

Figure 1: Relationship of ASCVD Events to Chronic Elevations in Systolic Blood Pressure by Risk Level



Risk categories:

- Low/borderline: <7.4% 10-year risk for ASCVD event (n=10,686)
- Intermediate: 7.5% to 19.9% 10-year risk for ASCVD event (n=4,880)
- High: ≥20% 10-year risk for ASCVD event (n=5,391)

FDA created Figure 1 by applying the ASCVD risk model to the demographic, vital sign, and laboratory data for each subject (age ≥30 years) collected in the National Health and Nutrition Examination Survey 2003–2018[1] and calculating the ASCVD risk after increasing the systolic blood pressure by 1-mmHg increments for each subject. Solid lines are the median increases in ASCVD risk, and the shaded area represents the increases in ASCVD risk for the 5th and 95th percentiles within each risk category (see Arnett et al. 2019 for risk categories).

[1] The National Health and Nutrition Examination Survey datasets can be found at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

The relationship of lower blood pressure to lower rates of stroke and cardiovascular death are shown in Table 1 below.

Table 1: Reduction in Blood Pressure and Cardiovascular Events with Antihypertensive Drugs in Placebo-Controlled Trials

Source	Intervention	Number of Subjects	Mean Follow-Up (years)	Mean Change from Baseline in SBP / DBP (mmHg)*	Number of Events (%) [Event Rate, 1,000 patient-years]		
					Nonfatal Stroke	Nonfatal Myocardial Infarction	Cardiovascular Death
Veterans Administration Cooperative Study Group on Antihypertensive Agents (1970)	Active	186	3	-27 / -17	5** (2.7%) [NR]	5 (2.7%) [NR]	8 (4.3%) [NR]
	Placebo	194		+4 / +1	20** (10.3%) [NR]	2 (1.0%) [NR]	19 (9.8%) [NR]
European Working Party on High Blood Pressure in the Elderly Trial (Amery et al. 1985)	Active	416	3***	-33 / -16	13 (3.1%) [9]	19 (4.6%) [14]	42 (10.1%) [30]
	Placebo	424		-11 / -6	24 (5.7%) [20]	12 (2.8%) [9]	61 (14.4%) [48]
Systolic Hypertension in the Elderly Program (SHEP Cooperative Research Group 1991)	Active	2,365	4.5	-27 / -9	96 (4.1%) [NR]	50 (2.1%) [NR]	90 (3.8%) [NR]
	Placebo	2,371		-15 / -5	149 (6.3%) [NR]	74 (3.1%) [NR]	112 (4.7%) [NR]
Systolic Hypertension in Europe (Syst-Eur) Trial Investigators (Staessen et al. 1997)	Active	2,398	2	-23 / -7	34 (1.4%) [5.7]	26 (1.1%) [4.4]	59 (2.5%) [9.8]
	Placebo	2,297		-13 / -2	57 (2.5%) [10.1]	31 (1.3%) [5.5]	77 (3.4%) [13.5]

Abbreviations: DBP = diastolic blood pressure; SBP = systolic blood pressure; NR = not reported.
*Obtained using routine clinic blood pressure measurements.
**Cerebral vascular accident defined as either a thrombosis (clinical diagnosis) or a transient ischemic attack with objective neurological signs.
***Results presented for the double-blind part of trial.