
Assessment of Pressor Effects of Drugs Guidance for Industry

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

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Clinical/Medical**

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TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	1
III.	BLOOD PRESSURE ASSESSMENT: SHORT-TERM USE VS. CHRONIC USE OF A DRUG	4
	A. Drugs Intended for Short-Term Use	4
	B. Drugs Intended for Chronic Use	4
IV.	RECOMMENDED USE OF AMBULATORY BLOOD PRESSURE MONITORING	5
V.	STUDY DESIGN ISSUES IN ASSESSING BLOOD PRESSURE EFFECTS FOR DRUGS INTENDED FOR CHRONIC USE.....	6
	A. Control Group.....	6
	B. Study Design.....	6
VI.	REGULATORY CONSIDERATIONS	7
	REFERENCES.....	8

Assessment of Pressor Effects of Drugs Guidance for Industry¹

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I. INTRODUCTION

The purpose of this guidance is 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 can therefore be an important consideration in benefit-risk assessment.

This guidance is intended to address precision of blood pressure measurements in the assessment of the effects of a drug in development. This guidance recommends systemic characterization of the effect of a drug on blood pressure during drug development.

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II. BACKGROUND

Information from multiple sources indicates that elevated systolic and diastolic blood pressures increase cardiovascular risk. Epidemiologic evidence demonstrates that even a 2- to 3-millimeter of mercury (mm Hg) increase in existing high blood pressure increases rates of stroke, heart attack, and death. MacMahon et al. (1990) evaluated the relationship between diastolic blood pressure and rates of stroke and coronary heart disease (CHD) in nine major, prospective, observational studies. Diastolic blood pressures that were lower by 5, 7.5, and 10 mm Hg were associated with 34 percent, 46 percent, and 56 percent less stroke, respectively, and 21 percent, 29 percent, and 37 percent less CHD. Of note, within the range of diastolic blood pressure studied (70 to 110 mm Hg), the relative reduction in risk associated with a particular decrease in diastolic blood pressure was similar across all levels of diastolic blood pressure, including levels

¹ This guidance has been prepared by the Office of Drug Evaluation I in the Center for Drug Evaluation and Research at the Food and Drug Administration.

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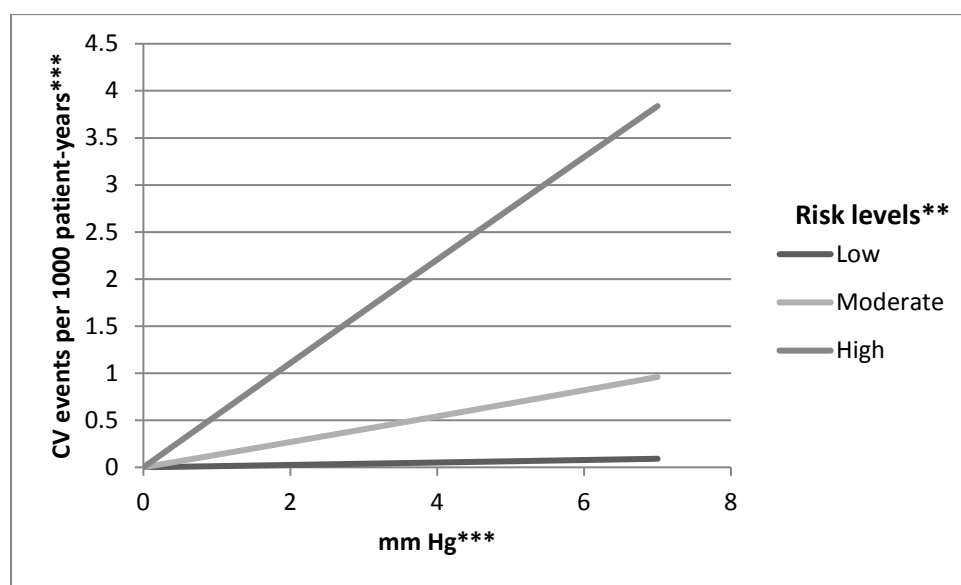
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44 that would be considered normal. Comparing the highest risk category of diastolic blood pressure
45 (greater than or equal to 110 mm Hg) to the lowest risk category (less than or equal to 79 mm
46 Hg), the risk of stroke was about 10 to 12 times higher; the risk of CHD was about 5 to 6 times
47 higher.

48
49 The absolute risk of cardiovascular events is related to multiple risk factors. Data from the
50 Framingham Heart Study have been used to describe the effect of a higher systolic blood
51 pressure (1 to 7 mm Hg) in patients at three risk levels. Figure 1 shows expected increases in
52 cardiovascular events for a chronic elevation in systolic blood pressure in patients whose risks
53 fall within three risk levels (low, moderate, and high).

54
55 **Figure 1: Relationship of CV Events to Chronic Elevations in Systolic Blood Pressure by**
56 **Risk Level***

57



58
59 * D'Agostino RB et al., 2008, General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart
60 Study, *Circulation*, 117(6):743–753; data available at Framingham Heart Study Cardiovascular Disease (10-Year
61 Risk) web page at <https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/>.

62 ** Low risk = age 25, total cholesterol of 161, high-density lipoprotein (HDL) of 55, untreated systolic blood
63 pressure (SBP) of 125, nonsmoker, nondiabetic.

64 Moderate risk = age 40, total cholesterol of 205, HDL of 45, untreated SBP of 135, nonsmoker, diabetic.

65 High risk = age 70, total cholesterol of 225, HDL of 39, treated SBP of 150, nonsmoker, diabetic.

66 *** CV – cardiovascular; mm HG – millimeter of mercury.

67
68 Results from trials show that elevated blood pressure leads to increased cardiovascular events in
69 populations with all levels of risk from other factors, such as elevated low-density lipoprotein
70 (LDL) cholesterol or smoking status. Maintenance of a 5- to 6-mm Hg reduction in diastolic
71 blood pressure with antihypertensive drug regimens typically produces risk reductions of
72 approximately 40 percent in stroke and 15 percent in CHD. Furthermore, the beneficial effect on
73 outcome first occurs within a relatively short period of time, around 6 to 12 months, suggesting
74 that an increased risk from elevated blood pressure would also occur relatively rapidly (Staessen
75 et al. 1997; Veterans Administration Cooperative Study 1970). In the Systolic Hypertension in
76 the Elderly Program (Prevention of Stroke 1991), for example, the reduced rate of stroke is

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77 clearly seen within 1.5 years (and perhaps earlier), and similar findings were seen in the
78 European Working Party on High Blood Pressure in the Elderly trial (Amery et al.1985).
79

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81

FDA encourages sponsors to seek further discussion to understand the temporal relationship
82 between changes in blood pressure and changes in risk.
83

84

85

This relationship of lower blood pressure to lower rates of stroke and CHD has been observed in
86 outcome studies involving a wide array of antihypertensive drugs, including diuretics, reserpine,
87 hydralazine, beta blockers, calcium channel blockers, and renin angiotensin system inhibitors.

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guidance for industry *Hypertension Indication: Drug Labeling for Cardiovascular Outcome
Claims.*³

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Furthermore, some drugs that produce sustained increases in blood pressure (e.g., rofecoxib,
96 sibutramine, torcetrapib) have been associated with adverse cardiovascular effects. It is therefore
97 reasonable to expect that chronic-use drugs that increase blood pressure will increase
98 cardiovascular risk, with the absolute increase in risk related to the baseline risk, the baseline
99 blood pressure, the duration of treatment, and the magnitude of the blood pressure increase. In
100 the Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or
101 Naproxen Ambulatory Blood Pressure Measurement (PRECISION-ABPM) trial, ibuprofen was
102 associated with a 3.7-mm Hg increase in ambulatory systolic blood pressure compared to
103 celecoxib and a 1.9-mm HG increase compared to naproxen, leading to an increase in
104 cardiovascular event rates (Ruschitzka et al. 2017). The overall PRECISION trial showed that
105 there were numerically more cardiovascular events in ibuprofen-treated patients, compared with
106 those who received naproxen or celecoxib (Nissen et al. 2016).

108

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FDA encourages sponsors to seek further discussion on whether the results and interpretation of
the PRECISION study are relevant in the context of this guidance.

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116

Although nearly every drug development program has some assessment of the effect of a drug on
blood pressure, the methods for assessing blood pressure vary. As a result, the precision of blood
pressure measurement differs widely, such that small increases in blood pressure that could be
relevant for the overall assessment of the risks of a drug may not be reliably detected in some

² See the 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>.

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/RegulatoryInformation/Guidances/default.htm>.

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117 drug development programs. Several factors can influence the importance of an effect on blood
118 pressure, including the seriousness of the condition being treated, the effect of the drug on the
119 condition, the underlying cardiovascular risk in the patient population most likely to use the
120 drug, the availability of other effective therapies that do not raise blood pressure, strategies that
121 can be used to mitigate the blood pressure effects, and the anticipated duration of treatment with
122 the drug.

123
124 For a drug that increases blood pressure, subset (and individual) differences in increases in blood
125 pressure response can possibly exist, just as differences among subsets exist in response to blood
126 pressure-lowering treatment. Characterization of such differences is important.

127 128 III. BLOOD PRESSURE ASSESSMENT: SHORT-TERM USE VS. CHRONIC USE 129 OF A DRUG

130
131 The decision of how blood pressure is assessed during a clinical trial depends on whether a drug
132 is intended for short-term use or chronic use.

133 134 A. Drugs Intended for Short-Term Use

135
136 There is little concern about a drug indicated for short-term use that has, at most, small effects on
137 blood pressure, because the cardiovascular risk of small short-term elevations in blood pressure
138 is not thought to be significant. FDA's analysis of placebo-controlled hypertension trials of less
139 than 12-week durations (most were shorter) did not find an increased risk of vascular events in
140 the placebo groups (DeFelice et al. 2008). Large blood pressure-increasing effects are of
141 concern, however, even with drugs intended for short-term use. Therefore, in general, careful
142 assessment of blood pressure using cuff sphygmomanometry (cuff blood pressure measurement)
143 during routine study visits should be adequate to assess the blood pressure effect of drugs
144 intended for short-term use.

145
146 When use of clinic blood pressure measurements is appropriate, accuracy can be improved by
147 collecting triplicate measurements of sitting blood pressure in all subjects at baseline (predose),
148 at several visits (at least two visits before the end of the trial), at the end of the interdosing
149 interval (trough measurement; predose), and at peak concentration. Measurements should be
150 made at least 1 minute apart using the same arm at each visit.

151
152 It is important that measurements be recorded to the nearest even number in mmHg.⁴

153 154 B. Drugs Intended for Chronic Use

155
156 There is greater concern with the effect of a drug on blood pressure when the drug will be used
157 chronically. As noted above, epidemiologic studies show that risk is related to blood pressure as
158 a continuous function, and that sustained increases in blood pressure correlate with long-term
159 increased risk of cardiovascular adverse events. It follows that even small, sustained increases in
160 blood pressure (2 to 3 mm Hg) chronically would be expected to have such an effect. Thus,
161 detecting such changes is important for drugs intended for chronic use, and for this reason, a

⁴ Recommendations are available on proper measurements of blood pressure (see Whelton PK et al. 2017).

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162 sponsor should include a thorough blood pressure assessment, as described in this guidance, for a
163 drug intended for chronic use. As discussed in section IV. Considerations for Ambulatory Blood
164 Pressure Monitoring, FDA recommends use of ABPM for this assessment, as ABPM is capable
165 of detecting small, but potentially relevant, blood pressure effects. ABPM also assesses effects
166 over a 24-hour period, more relevant than a single time point (Pickering 2000).

167
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IV. RECOMMENDED USE OF AMBULATORY BLOOD PRESSURE MONITORING

170
171

172 Several factors influence the ability to detect small changes in blood pressure. First, blood
173 pressure naturally varies throughout the day (diurnal variation) and with meals and activity and
174 changes in response to stress, including the stress of having one's blood pressure measured
175 (*white coat hypertension*). In addition to these true variations in blood pressure, measurement
176 error is associated with use of a cuff blood pressure measurement (e.g., calibration error,
177 improper auscultation, rounding). Given these variations, blood pressure measurement using a
178 small number of cuff sphygmomanometry measurements may not reliably detect small, but
179 potentially relevant, increases in blood pressure (i.e., 2 to 3 mm Hg). Therefore, FDA
180 recommends the use of ABPM as it provides the precision and accuracy needed to detect these
181 smaller changes in blood pressure. ABPM has several advantages over cuff blood pressure
182 measurements including the following:

183

- 184 • ABPM allows the assessment of blood pressure effects over a 24-hour period.
- 185
- 186 • ABPM allows for a more precise measurement of an individual's blood pressure than can
187 be achieved through the use of cuff blood pressure measurements.
- 188
- 189 • ABPM devices can be programmed to collect measurements at specified times.
- 190
- 191 • ABPM is free of potential investigator bias, including tendencies to round up or down.
- 192
- 193 • ABPM provides a large number of blood pressure measurements throughout the day,
194 providing both a more precise assessment of average change and greater ability to
195 describe individual variation.

196

197 FDA also recommends ABPM for any clinical study designed to describe blood pressure effects
198 over 24 hours. These ABPM measurements should be performed in the patient population for
199 which the drug is being developed, either in a targeted study or as part of a larger study already
200 being conducted for other purposes in this population. In light of the precision of ABPM, the
201 number of subjects needed for such clinical studies may not be very large.

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204 **V. STUDY DESIGN ISSUES IN ASSESSING BLOOD PRESSURE EFFECTS FOR**
205 **DRUGS INTENDED FOR CHRONIC USE**

206

207 **A. Control Group**

208

209 In general, it is desirable to include a placebo group as the control group. ABPM measurements,
210 as noted, are not influenced by observer bias and provide precision. Nevertheless, there can be
211 changes in blood pressure with time that could obscure drug effects, making inclusion of a
212 placebo group desirable.

213

214

FDA encourages sponsors to seek further discussion on this issue, including the arguments for
and against using a placebo group as the control in ABPM studies.

217

218

219 **B. Study Design**

220

221 The goal of this careful ABPM assessment of blood pressure is to determine whether a drug has
222 a meaningful effect on blood pressure. The protocol should specify whether systolic, diastolic, or
223 mean blood pressure will be evaluated.

224

225 In addition to the natural variability in blood pressure during the day, drug concentrations, and
226 therefore a drug's effect on blood pressure, may vary. To assess the overall effect, blood pressure
227 should be measured throughout the day using ABPM and should be done only after the drug has
228 reached steady state. In general, the results should be based on the integrated mean (i.e., area
229 under the curve, a time-weighted average of the blood pressure throughout the day). Results may
230 suggest that blood pressure elevations are related to drug concentration peaks, which could in
231 turn relate to dose and dosing interval.

232

233 The study should be carried out in a patient population with characteristics similar to the
234 intended target patient population (i.e., similar demographic and disease-specific characteristics).

235

236 If no blood pressure effect is detected by ABPM in early, small studies, subsequent studies (later
237 phase 2, phase 3) can utilize routine cuff blood pressure measurement monitoring, which would
238 detect large effects in specific individuals. Even though early, small studies will not be useful in
239 detecting subgroup effects, an absence of an overall blood pressure effect should provide
240 reassurance that a subset of patients does not have a large blood pressure effect. In this case,
241 routine cuff blood pressure measurements would be sufficient in phase 3 studies.

242

243 If the drug increases blood pressure in the overall patient population, the sponsor should obtain
244 additional information about the effects of the drug in relevant subsets of the population with
245 potentially larger effects (e.g., patients with pre-existing hypertension, patients with impaired
246 renal status).

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249 **VI. REGULATORY CONSIDERATIONS**

250
251 Large drug-induced elevations in blood pressure are relevant for all drugs, even for those
252 intended for short-term use. Smaller elevations of blood pressure of even a few mm Hg can also
253 be a concern when the drug is intended for chronic use, particularly when the target population is
254 at increased cardiovascular risk. As noted above, the proportional risk increase for a given blood
255 pressure increase appears to be similar for people with low and high blood pressure, but the
256 increase in absolute risk would be very small for a person at low baseline risk (i.e., age 25,
257 normal LDL and high-density lipoprotein, not diabetic, and normotensive) and becomes
258 progressively greater as the number and severity of risk factors increases, as shown in Figure 1 in
259 section II. Background.

260
261
262 FDA encourages sponsors to seek further discussion on the best regulatory approach to interpret
263 drug's blood pressure effect including asking the following: Is there a specific, identified
264 increase applied across development programs that is cause for concern, or should each
265 development program have its own threshold as it takes risk tolerance into consideration?
266

267
268 The approach outlined in this guidance—identifying drugs that increase blood pressure and
269 determining the size of the effect—should be factored into the overall benefit-risk assessment for
270 the drug, recognizing that increasing blood pressure can be acceptable or can be managed
271 satisfactorily in many circumstances. This assessment should include the consideration of any
272 steps that could be taken to mitigate the risk of increased blood pressure, such as patient
273 selection, pretreatment assessments, blood pressure monitoring in some or all patients, and
274 planned use of blood pressure-lowering treatments.
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