Diastolic Blood Pressure and Hypertension Phenotypes: The US Food and Drug Administration Has It Right

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I have not always been wrong.
—Sir Winston Churchill

It is often suggested that the US Food and Drug Administration (FDA) should not have chosen systemic arterial diastolic blood pressure (DBP) as the diagnostic criterion to be used to define the presence of hypertension in the approval process of antihypertensive drugs. Instead, many have argued that systolic blood pressure (SBP) would have been preferable because it better correlates with cardiovascular risk than does DBP. However, what is becoming apparent is that SBP and DBP identify different and distinct hypertension phenotypes. One must remember that hypertension is the disease (all types), while blood pressure is a biomarker.As has been previously defined:

> Hypertension…is a progressive cardiovascular syndrome arising from complex and interrelated etiologies. Early markers of the syndrome are often present before blood pressure elevation is sustained; therefore, hypertension cannot be classified solely by discrete blood pressure thresholds. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature and other organs and lead to premature morbidity and death.[1]

A disease that has multiple etiologies may have a variety of phenotypes. The necessary implication resulting from these considerations is that the appropriate treatment of hypertension will become more and more dependent on recognition of specific phenotypes of the syndrome and will attempt to accomplish at least two objectives: the reduction of the elevated BP, and the interruption of the pathophysiological process that accounts for the increase in BP and that contributes to target organ damage beyond that due to increased BP alone. Based on hemodynamic patterns, there are at least three phenotypes of hypertension.[2]

TYPE 1 HYPERTENSION

Type 1 hypertension is the phenotype initially selected by the FDA that is identified by increased DBP. In 1977, the first report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure Joint National Commission (JNC) defined hypertension as a DBP of 105 mm Hg, gave no recommendations regarding SBP, and suggested that treatment might be considered when DBP was between 90 mm Hg and 104 mm Hg.[3,4] DBP identifies this phenotype because the basic pathophysiology involves an increase in peripheral vascular resistance and mean arterial pressure. In assessing the area under the arterial BP curve, DBP is of greater importance than SBP (mean BP = [SBP + 2DBP]/3). Although a slight increase in cardiac output may be present, the loss of arterial vasodilatory mechanisms underlies the increase in BP. SBP should always be included as a secondary efficacy parameter since changes with therapy would alter cardiovascular risk.

TYPE 2 HYPERTENSION

In this type of hypertension, referred to as isolated systolic hypertension, the peripheral vascular resistance is normal or even reduced while the SBP is increased. It is now recognized that the pathophysiology of the increase in SBP is due to a decrease in proximal arterial compliance resulting from a loss of elastin fibers, often replaced with nondistensible type IV collagen. The development of type 2 hypertension appears to be age-dependent. Most antihypertensive drugs target the resistance vessels and therefore may not be suitable for the treatment of type 2 hypertension. Further, if a reduction in mean arterial pressure, especially diastolic perfusion pressure of the coronary arteries, occurs beyond that needed to maintain blood flow, an increase in adverse occurrences may ensue, ie, the so-called J curve.

TYPE 3 HYPERTENSION

Type 3 hypertension contains features of both types 1 and 2 hypertension. Thus, there is an increase in peripheral vascular resistance and therefore DBP, together with reduced proximal arterial compliance resulting in diastolic hypertension with a wide pulse pressure, as differentiated from type 2 hypertension, which is also characterized by a wide pulse pressure but with a normal to low DBP.

As more specific information becomes available regarding the above broad phenotypes, there will emerge increasing number of subtypes, eg, type 1a and type 1b. Thus, the FDA, by choosing a uniform phenotype for determination of efficacy of treatment, has established a clinically useful characterization for selection of certain patients for antihypertensive drug treatment. This approach is similar to diabetes mellitus where blood glucose, rather than BP, is the biomarker, but the pathophysiology and treatment of type 1 and type 2 diabetes, is different. Thus, the FDA must recognize that type 2 hypertension is a different entity than

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type 1 and evaluate drugs on the basis of efficacy in that particular group. It is likely that type 3 hypertension would be successfully treated with a combination of drugs effective for the treatment of types 1 and 2.

Any discussion of the diagnosis and treatment of hypertension is incomplete without consideration of the techniques of BP measurement. It is now apparent that office BPs, even when performed carefully, often overestimate BP (white-coat effect), and may even underestimate BP (masked hypertension). Thus, the FDA should require the use of ambulatory BP (ABPM) as the gold standard for recording BP in randomized clinical trials so that the phenotypes will be sharply delineated and the results devoid of the noise created by use of the BP recorded in the clinic setting.

References

1. Giles TD, Berk BC, Black HR, et al. Expanding the definition and classification of hypertension. *J Clin Hypertens.* 2005;7:505–512.
2. Izzo JL Jr, Giles TD, Matterson BJ. Defining the syndrome of hypertension. In: Izzo JL Jr, Sica DA, Black HR, eds. *Hypertension Primer*, 4th ed. American Heart Association, Lippincott Williams & Wilkins; 2008: 351–355.
3. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: a cooperative study. *JAMA.* 1977;237:255–261.
4. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The 1980 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med.* 1980;140:1280–1285.