

EDITORIAL COMMENT

Pulse Pressure

How Valuable as a Diagnostic and Therapeutic Tool?*

Stanley S. Franklin, MD, Nathan D. Wong, PhD



Cross-sectional and longitudinal studies of age-related increases in blood pressure (BP) have shown that mean diastolic blood pressure (DBP) levels off by approximately age 50 years and begins to decrease by age 60 years, whereas systolic blood pressure (SBP) continues to increase; this results in a slow widening of pulse pressure (PP) between the ages of 50 years and 60 years and more rapid widening thereafter as the decrease in DBP accelerates with more vascular aging (1,2). Elevated mean artery pressure (MAP), as a measure of steady-state resistance, is the dominant factor in the almost parallel increase in SBP and DBP during early adulthood; whereas widening PP as a marker of large artery stiffness is the dominant pulsatile force that contributes to vascular aging from middle age onward. Indeed, by middle age, isolated systolic hypertension (ISH) becomes the dominant form of hypertension (3). However, at any given SBP, the decrease in DBP adds to the risk of SBP (4). The potential clinical value of the widening of PP as a cardiovascular disease (CVD) factor was first suggested in a seminal publication by Darne et al. (5) in 1989. Since then, the Framingham Heart Study and others (6,7), using the combination of MAP and PP together, rather than any single BP component separately (SBP, DBP, MAP, or PP) improved the fit monotonically for predicting CVD collectively or coronary heart disease, heart failure, and stroke separately (7,8). Using the 7th Report of the Joint National Committee for CVD risk classification, a DBP <70 mm Hg can add ~20 mm Hg of SBP

risk, (i.e., a shift from prehypertension to stage 1 and from stage 1 to stage 2 hypertension) (7). During the past 20 years, there have been multiple observational studies and controlled trials showing the value of PP as an important risk factor for CVD and as a measure of early vascular aging. Moreover, the European Society of Hypertension has recognized widened PP as a distinct risk factor that is separate from elevated SBP in older individuals (9).

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It is with this background that the authors, using data from the Reduction of Atherothrombosis for Continued Health (REACH) registry examined the relationship between PP and adverse CVD events (10), published in this issue of the *Journal*. The novelty of the REACH registry is that it is the largest international patient population to study PP, which enabled the authors to adjust for a significant number of potential confounding factors, and to be able to perform several key subgroup analyses with substantial statistical power. The study consisted of >45,000 individuals (mean age: 68 years) from 45 countries who had clinical atherothrombotic disease or baseline CVD risk factors and subsequently had a 4-year follow-up for new CVD events. Eighty-one percent were receiving antihypertensive therapy. Univariable and multivariable regression analyses were used to determine the association between PP and CVD outcomes as continuous and categorical variables (i.e., by quartile with Forest plots). Not unexpectedly, a higher PP conferred increased risk for multiple CVD events although the increases in risk were modest at best. Furthermore, PP in subgroups of women, persons free of clinical CVD, and in treatment-naïve individuals, continued to predict increased CVD risk.

Sensitivity analyses showed: 1) PP was of strong prognostic value in the absence of prior CVD events; 2) PP was particularly useful in participants >60 years of

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From the Heart Disease Prevention Program, Division of Cardiology, University of California–Irvine, Irvine, California. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose. Clive Rosendorff, MD, served as Guest Editor for this paper.

age; 3) the degree of systolic hypertension was associated with increased risk for nonfatal myocardial infarctions and combined outcomes; and 4) antihypertensive treatment was associated with greater risk of hospitalization, myocardial infarctions, and combined events. In summary, the REACH registry authors concluded that PP was associated with multiple CVD outcomes that provided prognostic utility beyond that of MAP. On the other hand, this study should be interpreted within the context of its limitations.

ERRORS OF DIAGNOSIS

The authors note that there was zero-digit preference bias in 58% for SBP and 60% for DBP, when the expected number was 20%. This highlights the almost universal poor technique of BP measurement by physicians and nurses in an office setting that result in errors in calculating PP accurately. Importantly, in a recent International Database on Ambulatory Blood Pressure Monitoring (ABPM) in Relation to Cardiovascular Outcomes study of older persons (mean age: 74 years) with ISH, there was a 73% inaccurate diagnosis by exclusive use of conventional clinic or office BP measurements; failure to diagnose white-coat hypertension falsely widened PP, whereas failure to correctly diagnose masked hypertension falsely contracted PP (11).

Indeed, as the authors of the REACH registry noted, ABPM with measurement of daytime, nighttime, and 24-h measurements is the gold standard for accurate diagnosis of all BP components. However, a less expensive fully automated office device, which takes multiple readings with subjects resting quietly alone results in improved measurement of all BP components including PP (12). Thus, such misclassification, while not unique to REACH, can result in observed effects on PP that may be less than what may be present with greater accuracy in measurement. In addition, the high prevalence of treatment in the REACH population suggests that widened PP may have been more prevalent in the absence of treatment, given the greater SBP lowering effect (relative to DBP lowering) from antihypertensive treatment. The relatively modest hazard ratios (even those in the 4th quartile of PP) may be due to the older age of the cohort, the many comorbidities, and/or being on antihypertensive treatment. The J-shaped curve of PP with CVD mortality is also not surprising and probably represents reversed causality.

ERRORS OF TREATMENT

Considering PP in isolation can result in errors of treatment. For example, a PP of 75 mm Hg corresponds

to either a BP of 165/90 mm Hg with an elevated MAP of 115 mm Hg or 140/65 mm Hg with a MAP of 90 mm Hg. Focusing on PP alone does not clarify which physiologic component of elevated BP is contributing to CVD risk, and therefore what approach should be taken to reduce risk, (i.e., treatment may be directed at reducing MAP in the first person and reducing arterial stiffness in the second person with minimal further reduction in MAP). Moreover, there is evidence of a DBP J-curve of increased CVD risk in individuals with ISH and DBP <70 mm Hg, which occurred in ~30% of untreated older persons with ISH in the National Health and Nutrition Examination Survey (13). There was a 3-fold greater prevalence of CVD events from the highest to the lowest strata in untreated ISH. Advanced age, female sex, and diabetes mellitus, but not treatment status was associated with the low DBP and widened PP. Lastly, the elderly hypertensive person with ISH and widened PP, with or without excessively low DBP, should be classified as being either robust or frail. Indeed, ABPM may detect *de novo* orthostatic hypotension and/or precipitated by post-prandial and/or post-micturition states; thus, various degrees of frailty would dictate the limits of treatment in persons with ISH and widened PP. Importantly, although elevated PP provides useful prognostic information, the ultimate goal of therapy is dictated by how low to go in reducing SBP. The recently published SPRINT (Systolic Blood Pressure Intervention Trial), utilizing an automated BP measuring device, will undoubtedly have a bearing on the establishing of new SBP but not PP guidelines for the treatment of hypertension (14). Therefore, the relationship of PP with CVD risk should always be examined in the context of (e.g., stratified by) levels of SBP and ideally in a more treatment-naïve population.

In summary, as shown in the REACH registry study, a widened PP can be a reliable prognostic indicator of CVD risk and the authors are to be applauded for conducting a thorough and comprehensive analysis of this issue. However, a widened PP represents a “double-edged sword” in terms of potential pitfalls in making diagnostic and therapeutic decisions. In future hypertension guideline development there should be continued discussion of the potential role of PP in further risk stratification beyond traditional staging based on SBP and DBP.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Stanley S. Franklin, Heart Disease Prevention Program, Division of Cardiology, C240 Medical Sciences, University of California–Irvine, Irvine, California 92607-4079. E-mail: ssfranklinmd@earthlink.net.

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