Wolters Kluwer

Increased pulse pressure

Author: Raymond R Townsend, MD
Section Editor: George L Bakris, MD
Deputy Editors: John P Forman, MD, MSc, Lisa Kunins, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2021. | **This topic last updated:** Jun 24, 2020.

INTRODUCTION

Typical blood pressure measurements include a systolic and diastolic value, which represent the extremes of pressure fluctuation within the circulation during the cardiac cycle. There has been much debate about which increased value alone, either systolic or diastolic hypertension, is more predictive of adverse cardiovascular outcomes in various patient populations. (See "Blood pressure measurement in the diagnosis and management of hypertension in adults".)

Mean arterial pressure measurements, which provide another indication of overall circulatory pressure load, have also been proposed as predictive for adverse cardiovascular outcomes. This is either determined directly by catheterization or can be estimated by formulas (such as diastolic blood pressure + 1/3 x [systolic pressure – diastolic pressure]). However, the mean arterial pressure provides less discriminatory power as patients age. The diastolic pressure peaks at and subsequently declines after the age of 55 years, while the systolic pressure rises relentlessly with each decade of life [1]. Thus, depending upon the respective changes in systolic and diastolic pressures with older age, the mean blood pressure may actually tend to change less as individuals age.

Since the diastolic pressure in a population rises until the sixth decade and then subsequently declines with increasing age, an elevation in the diastolic pressure alone is less useful as an outcome predictor in older patients. Increasing emphasis has therefore been placed upon systolic pressure alone as the most useful predictor of cardiovascular disease in these individuals. (See "Treatment of hypertension in older adults, particularly isolated systolic hypertension".)

Several guidelines have supported the use of systolic blood pressure (such as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC-7]) and strongly encourage the use of systolic blood pressure goals in antihypertensive treatment [2].

There is also an enhanced risk for cardiovascular events associated with increases in pulse pressure (systolic blood pressure minus diastolic blood pressure). This topic review will discuss the factors that determine pulse pressure and will present some of the evidence for and against the suggestion that there is an independent link between an increased pulse pressure and adverse cardiovascular outcomes.

CLINICAL PERSPECTIVE

The pulse pressure is **defined** as the systolic minus the diastolic pressure. This value appears, at least in some epidemiologic studies, to be superior in predictive value to the systolic or diastolic values alone. (See 'Increased pulse pressure and adverse outcomes' below.)

However, given the predictive information from the systolic and diastolic pressures, it is unclear, at first glance, that the pulse pressure provides additional independent information. Among patients with a diastolic pressure of 95 mmHg, for example, a higher pulse pressure simply means that there is a higher systolic pressure which itself is a risk factor for worse outcomes. The pulse pressure also must be considered in the context of the absolute values of systolic and diastolic pressures (eg, a blood pressure of 120/80 mmHg is not equivalent in risk to 160/120 mmHg) [3].

Pulse pressure and age — To better understand the purported associations among pulse pressure, systolic pressure, diastolic pressure, risk of cardiovascular disease, and increasing age, it is worthwhile to review age-related changes in blood pressure measurements and the risk for cardiovascular disease as individuals age.

In patients less than 55 years of age, the diastolic and systolic blood pressures are both predictive of adverse events from cardiovascular disease. However, because the diastolic blood pressure declines on average after the age of 55 years, its predictive value is diminished in older patients.

By comparison, the systolic pressure continues to rise with every decade of life, resulting in the maintenance of its predictive value for cardiovascular disease. Thus, in older patients, the association between an increased systolic pressure alone and cardiovascular disease becomes much stronger than that observed with the diastolic blood pressure alone.

With increasing age, the pulse pressure correlates more closely with the systolic pressure than with the diastolic pressure and is therefore also a good predictor of cardiovascular disease among older adults. An additional benefit of the pulse pressure is that it incorporates both the systolic pressure increase and the diastolic decrease that is observed with age. In some cases, this measurement has superior predictive power to that observed with the systolic pressure alone. (See 'Increased pulse pressure and adverse outcomes' below.)

FACTORS RESULTING IN INCREASED PULSE PRESSURE

Increases in the pulse pressure result from factors that increase and/or decrease the systolic and diastolic pressure, respectively. Since the changes in pulse pressure are mostly related to changes in systolic blood pressure, factors affecting systolic pressure are reviewed first.

Increases in systolic pressure — Elevations in systolic pressure, particularly among older adults, are usually the result of stiffness in the large arteries as well as an early pulse wave reflection [4,5]. Although increases in peripheral vascular resistance appear to be a relatively more important component of hypertension in younger patients (30 to 49 years old), the role of peripheral vascular resistance in hypertension diminishes progressively with age [1,6]. Given the known effects of aging on vessel stiffness, increases in pulse pressure in older patients (eg, >55 years of age) result from aortic stiffening, while increases in younger patients (ie, <45 years of age) are more likely to result from increases in stroke volume. (See "Treatment of hypertension in older adults, particularly isolated systolic hypertension", section on 'Isolated systolic hypertension'.)

Decreases in diastolic pressure — Since stiffening of the aorta with age reduces the elastic reservoir capacity, more blood runs off from each stroke volume during systole, resulting in a reduced blood volume within the aorta at the onset of diastole. This factor, when combined with diminished elastic recoil and an increased pressure decay rate, causes a fall in the diastolic pressure with age [7]. These changes in diastolic pressure (both in normotensive and hypertensive patients) become evident after the age of 55 years [1].

Genetics — Increased pulse pressure may be a heritable trait [8-12]. As an example, a genome-wide association study that included more than 120,000 individuals of European ancestry found five loci that were significantly associated with pulse pressure, including three that had opposite effects on systolic and diastolic pressure [9]. One of these five loci, the fidgetin gene, was also associated with pulse pressure in an Asian cohort [8]. Other genetic studies have found a high degree of heritability (ranging from 20 to 40 percent) [10,11] with linkage to

chromosome 18 in all ethnic groups, chromosome 19 in whites, and chromosome 17 in Hispanics [10].

Other considerations — Since a portion of the systolic pressure depends upon the height of the patient, shorter patients tend to have a higher pulse pressure. In addition, slower heart rates result in a greater pulse pressure.

In general, women are shorter than men but tend to have faster heart rates. As a result, differences in pulse pressure with gender are generally lacking since the effect of height on pulse pressure may be counterbalanced by the effect of heart rate.

Increasing evidence suggests that patients with metabolic syndrome have stiffer vessels, resulting in an increased pulse pressure [13].

Although it is generally thought that the aorta increases in size with age, some studies suggest that increases in pulse pressure are associated with reductions, not increases, in aortic diameter [14]. In one study of more than a thousand non-diabetic individuals who were free of cardiac disease, aortic root diameter determined by echocardiography was inversely related to pulse pressure [14]. These data suggest that aortic dimensions may contribute to, rather than result from, increased pulse pressure.

INCREASED PULSE PRESSURE AND ADVERSE OUTCOMES

An increase in the pulse pressure places greater stress on arteries, resulting in fatigue and an increased fracture rate in the elastic components of the vessel wall. The vascular intima becomes prone to damage, thereby increasing the risk of atherosclerosis and thrombosis.

Pulse pressure and cardiovascular disease — In addition to damage to the vascular wall, an increased pulse pressure is associated with increased stress on the left ventricle, which can result in ventricular hypertrophy and failure [15,16]. Heightened pressure during systole increases myocardial oxygen need, and the lower diastolic value may become a limiting factor for coronary perfusion, resulting in ischemia.

The net result of these combined effects is that increases in pulse pressure may be a predictor of a variety of adverse cardiovascular outcomes. This association has been observed in numerous population-based cohort studies [3,17-26], among those undergoing coronary intervention [27], and in participants of randomized trials of hypertension treatment [28-30].

The following studies illustrate the range of findings from population-based cohorts, several of which included individuals with and without hypertension:

- In the Framingham Heart Study, for example, each 10 mmHg increment in pulse pressure was associated with a 23 percent higher risk of developing coronary heart disease (figure 1) [17]. This association with pulse pressure was primarily seen in patients over the age of 50 years, particularly over the age of 60 years [18]. The adverse outcomes observed with an elevated pulse pressure in patients over the age of 50 years appear to apply to both normotensive and hypertensive patients, including those with low diastolic but normal systolic blood pressure [19].

- The association between pulse pressure and cardiovascular mortality was analyzed in over 340,000 men in the Multiple Risk Factor Intervention Trial (MRFIT) aged 35 to 57 years without preexisting diabetes or coronary heart disease followed for 22 years [20]. Systolic and diastolic pressures were stronger predictors of cardiovascular death than pulse pressure. However, pulse pressure was independently associated with risk, particularly among older men (aged 45 to 57 years). Among men younger than 45 years, pulse pressure was associated with mortality only in those with hypertension; among older men, pulse pressure was associated with an increased risk of death at any level of blood pressure. As an example, there was a 22 percent increased risk of cardiovascular mortality in the highest compared with lowest quartile of pulse pressure in men aged 45 years or older who had optimal blood pressure (defined as less than 120/80 mmHg).

- Other studies, such as the second National Health and Nutrition Examination Survey (NHANES), found that pulse pressure added little predictive value compared with either systolic or diastolic pressure [3]. Among 7830 individuals followed for 15 years, a higher pulse pressure was associated with either increased, decreased, or no change in the risk of cardiovascular and all-cause mortality depending upon age, systolic, and diastolic pressure. However, a subsequent study of NHANES data found that, among 8356 young adults 18 to 40 years of age, higher pulse pressure was independently associated with an increased risk of mortality at 12 years [31].

An association between pulse pressure and cardiovascular endpoints has also been observed in hypertension treatment trials, as illustrated by the following [28,29]:

- In the Systolic Hypertension in the Elderly Program (SHEP) trial of older adult patients with isolated systolic hypertension, each 10 mmHg elevation in pulse pressure in the active treatment group was associated with increases in the risk for heart failure or stroke by 32 and 24 percent, respectively, after controlling for systolic pressure and other known risk factors [28]. However, pulse pressure was **not** associated with risk in patients assigned to placebo.

- Twenty-four-hour ambulatory blood pressure recordings were obtained in the Systolic Hypertension in Europe (Syst-Eur) trial, also of older patients with isolated systolic hypertension [29]. In the placebo group, the ambulatory pulse pressure predicted all cardiovascular endpoints and stroke, as each 10 mmHg increase in pulse pressure was associated with a hazard ratio ranging from 1.25 to 1.68. In contrast to the finding from the SHEP trial, this relation was **not** significant in patients assigned active treatment.

Pulse pressure and diabetes — The association between pulse pressure and the incidence of type 2 diabetes was examined in 2685 initially non-diabetic patients aged 20 to 84 years enrolled in the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial [32]. Higher pulse pressure was significantly associated with an increased risk of developing diabetes (relative risk 1.44 for each 16 mmHg higher pulse pressure, 95% CI 1.15-1.79). Similarly, the pulse pressure divided by the mean arterial pressure, as a measure of vascular stiffness, was directly associated with diabetes risk. The mechanism underlying this association is unclear.

Consistent findings were observed in a cross-sectional study of 528 hypertensive patients from Italy who had both clinic and 24-hour ambulatory blood pressure measurements [13]. Clinic pulse pressure was significantly higher in patients with the metabolic syndrome compared with patients without the metabolic syndrome (61 versus 49 mmHg); results were similar for 24-hour ambulatory pulse pressure. Higher pulse pressure was also associated with individual components of the metabolic syndrome, including higher fasting serum glucose.

Pulse pressure and progression of chronic kidney disease — Pulse pressure, as a reflection of arterial stiffness, may be an independent risk factor for progression of chronic kidney disease (CKD) [33-37]. The following studies illustrate the range of findings:

- The association between blood pressure components and risk of end-stage kidney disease (ESKD) was analyzed among 1513 patients with diabetic nephropathy in a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial [35]. After controlling for multiple potential confounders, a 10 mmHg higher pulse pressure was significantly associated with a 17 percent higher relative risk of developing ESKD. A similar association was found for systolic but not diastolic pressure.

- In a study of 30,636 patients in Singapore followed for more than 11 years, higher pulse pressure was associated with ESKD even after adjusting for systolic and diastolic pressure (hazard ratio 1.28, 95% CI 1.11–1.47 for every 10 mmHg higher pulse pressure) [37].

In addition to reduced glomerular filtration rate, pulse pressure is also independently associated with urine protein excretion [38,39].

PULSE PRESSURE AND ANTIHYPERTENSIVE THERAPY

Limited data suggest that antihypertensive agents differ in their effects on pulse pressure [40]. However, it is not appropriate to use pulse pressure as a factor in deciding which antihypertensive agent to employ or to use the measurement as a treatment endpoint itself [30,41].

- In the Losartan Intervention For Endpoints (LIFE) trial comparing an angiotensin receptor blocker (ARB; losartan) with a beta blocker (atenolol), the risk of the composite endpoint (stroke, myocardial infarction, and cardiovascular death) rose significantly as pulse pressure increased in the atenolol group [42]. In the losartan group, the risk of the composite endpoint also rose across the pulse pressure quartiles, but the increase was not significant.

- In a retrospective analysis of the Veterans Affairs Single-Drug for Hypertension Study including 1292 men with a diastolic blood pressure of 95 to 109 mmHg at randomization, after one year of treatment, hydrochlorothiazide reduced pulse pressure by 8.6 mmHg, clonidine by 6.3 mmHg, diltiazem by 5.5 mmHg, prazosin by 5 mmHg, captopril by 4.1 mmHg, and atenolol by 4.1 mmHg [43].

- In the Conduit Artery Functional Evaluation (CAFE) substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), 2073 participants underwent radial artery applanation tonometry and measurement of pulse wave velocity to calculate pulse pressure and central blood pressures [44-47]. The results suggested that atenolol had less central blood pressure reduction and improvement in pulse pressure, despite similar brachial artery blood pressure reduction, than a calcium channel blocker regimen [44-46]. Central pulse pressure was also associated with clinical outcomes [47].

- An analysis of data from clinical trials including more than 28,000 subjects suggested that the cardiovascular benefit of antihypertensive therapy was mostly linked to systolic blood pressure control [48]. In addition, the reduction in systolic pressure with treatment was found to be progressively larger than the reduction in diastolic blood pressure with increasing age (eg, greater fall in pulse pressure with increasing age) [48].

- In the REASON (P**re**terax in regression of **a**rterial **s**tiffness in a contr**o**lled double-bli**n**d) study, patients randomly assigned to the perindopril/indapamide regimen showed greater pulse pressure decreases with treatment when metabolic syndrome was present (10 to 11 mmHg) than when metabolic syndrome was absent (2 to 3 mmHg) [49,50].

- In a post hoc analysis of the Controlling and Lowering Blood Pressure With the MobiusHD (CALM II) trial, which compared lisinopril 40 mg to lisinopril 20 mg plus candesartan 16 mg daily in hypertensive diabetics, combination therapy produced a greater reduction in the pulse pressure compared with lisinopril alone as determined by ambulatory blood pressure monitoring (ABPM) [51]. The differences in pulse pressure were principally due to greater reductions in systolic pressure in the combination group. This study was not powered to assess outcome differences [51]. Further discussion of the CALM II trial can be found elsewhere. (See "Treatment of hypertension in patients with diabetes mellitus".)

Further prospective research is required to define pulse pressure as a predictor of cardiovascular outcomes and to determine whether pulse pressure is a better index of response to therapy [52,53]. The pulse pressure probably best serves as a tool in clinical trials, to better illustrate the pharmacodynamic effects of drugs, and possibly to provide a sharpened estimate of overall cardiovascular disease risk [52].

CONCLUSIONS

The literature appears to be divided on the prognostic values of the four measures of blood pressure: systolic, diastolic, mean, and pulse pressures. This arises in part because they are, basically, related to one another as they are all measures of the response in the circulation to each heartbeat. The value of one measure over another is strongly age-dependent and is also related to how variables are entered into statistical models that help predict cardiovascular outcomes.

The best use of pulse pressure at this time appears to be in providing help in revising the risk estimate of the systolic pressure in older individuals. Since systolic pressure predicts cardiovascular morbidity and mortality in older patients, clinicians are encouraged to revise upward the estimate of cardiovascular risk in older patients when the pulse pressure is increased [54]. A reasonable summation of our knowledge is that diastolic blood pressure is the best predictor of cardiovascular disease risk in the young (<50 years), all three blood pressure components are equally predictive at ages 50 to 59 years, and pulse pressure is the best predictor from age 60 years and beyond.

Limited data also suggest that antihypertensive agents differ in their effects on pulse pressure [40]. However, it is premature to use pulse pressure as a factor in deciding which antihypertensive agent to employ or to use the measurement as a treatment endpoint itself [41].

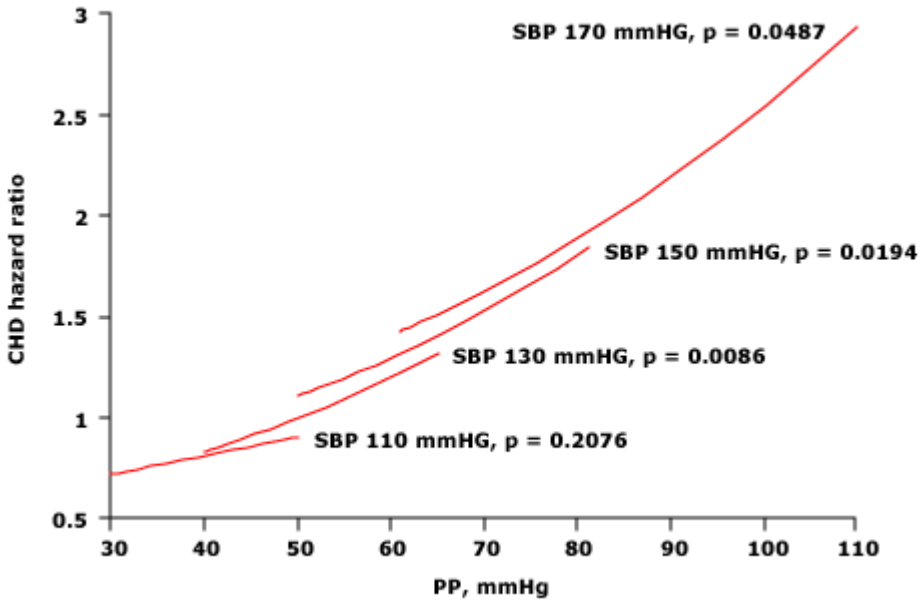
SUMMARY

- Pulse pressure is **defined** as the systolic minus the diastolic pressure. (See 'Clinical perspective' above.)
- Increased pulse pressure may be due to either or both an increase in systolic or a decrease in diastolic blood pressures. (See 'Factors resulting in increased pulse pressure' above.)
- Among older patients, increased systolic pressure results from increased stiffness in the aorta and other large arteries; among younger patients, increased stroke volume plays a more important role. (See 'Increases in systolic pressure' above.)
- Decreased diastolic pressure results from a reduction in aortic blood volume at the onset of diastole. This is related to the age-related decrease in elasticity of the aorta which causes more blood to run off during systole. (See 'Decreases in diastolic pressure' above.)
- The pulse pressure is a good predictor of cardiovascular events among older adult patients and in some cases has superior predictive capability to that provided by systolic pressure alone. The best use of pulse pressure is in revising upward the risk estimate provided by the systolic pressure in older individuals. (See 'Increased pulse pressure and adverse outcomes' above and 'Conclusions' above.)
- Limited data suggest that different hypertensive agents may have varying effects on pulse pressure. (See 'Pulse pressure and antihypertensive therapy' above.)

Topic 3858 Version 25.0

GRAPHICS

Pulse pressure is an independent risk factor for coronary heart disease



In the Framingham study of 1924 men and women followed for 20 years a higher pulse pressure (PP) at any level of systolic blood pressure (SBP) was an indepedent risk factor for coronary heart disease (CHD). Hazard ratios were determined from level of PP within SBP groups; hazard ratios were set to a reference value of 1.0 for SBP of 130 mmHg and PP of 50 mmHg. All estimates were adjusted for age, sex, body mass index, cigarettes smoked per day, glucose intolerance, and total cholesterol/HDL.

Data from Franklin, SS, Khan, SA, Wong, ND, et al, Circulation 1999; 100:354.

Graphic 74090 Version 1.0