Review

High Blood Pressure and Cardiovascular Disease

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Abstract—Fragmented investigation has masked the overall picture for causes of cardiovascular disease (CVD). Among the risk factors for CVD, high blood pressure (BP) is associated with the strongest evidence for causation and it has a high prevalence of exposure. Biologically, normal levels of BP are considerably lower than what has typically been characterized as normal in research and clinical practice. We propose that CVD is primarily caused by a right-sided shift in the population distribution of BP. Our view that BP is the predominant risk factor for CVD is based on conceptual postulates that have been tested in observational investigations and clinical trials. Large cohort studies have demonstrated that high BP is an important risk factor for heart failure, atrial fibrillation, chronic kidney disease, heart valve diseases, aortic syndromes, and dementia, in addition to coronary heart disease and stroke. In multivariate modeling, the presumed attributable risk of high BP for stroke and coronary heart disease has increased steadily with progressive use of lower values for normal BP. Meta-analysis of BP-lowering randomized controlled trials has demonstrated a benefit which is almost identical to that predicted from BP risk relationships in cohort studies. Prevention of age-related increases in BP would, in large part, reduce the vascular consequences usually attributed to aging, and together with intensive treatment of established hypertension would eliminate a large proportion of the population burden of BP-related CVD.

High blood pressure (BP), cigarette smoking, diabetes mellitus, and lipid abnormalities are major modifiable risk factors for cardiovascular disease (CVD). Among these, high BP is associated with the strongest evidence for causation and has a high prevalence of exposure. However, there is considerable evidence that a biologically normal level of BP in humans is considerably lower than what has been traditionally employed in clinical practice and research, leading to an underrepresentation of the role that BP plays as a risk factor for CVD. We propose the following integrated theory for CVD causation that is supported by a robust body of coherent and consistent evidence: CVD in humans is primarily caused by a right-sided shift in the distribution of BP.

Theories abound in the current era of social networks, but few fulfill the basic requirements for causality. Scientific theories are most credible because they are structured and subject to refutation by systematic observation and experimental hypothesis testing.[1] Our theory fulfills virtually all of the criteria for causality proposed by Bradford Hill.[2]

Shift of BP Distribution in Humans: Uncovering a Selection Bias

At the end of the 19th century, Osler[3] did not mention the risks of high BP in his classic The Principles and Practice of Medicine textbook because, at that time, there was no practical way to measure BP using a noninvasive technique. Shortly after the development[4,5] and dissemination of noninvasive methods for BP measurement physicians and actuaries deduced that high BP could be a cause of disease, especially CVD events.[6,7] In 1913, Janeway[7] study of 7872 patients led him to conclude that an average BP above 160 mm Hg was pathological.

Despite the merits of early BP-CVD association reports, they compared the risk of CVD in adults identified as having a very high level of BP with the corresponding risk in counterparts with a lower but still high BP. The pioneers of BP measurement could not know that nearly all humans, including most of those in the lower BP category, had a level of BP above what is biologically normal and desirable. It took several decades before BP was measured in groups of humans with a true biologically normal BP because they were living in isolated unacculturated societies. Investigators discovered that almost all of those studied had an average BP that was substantially lower than the corresponding levels noted in studies that had been conducted in acculturated societies.[8–11]

There are potentially confounding differences between people living in acculturated societies and their counterparts living in isolated unacculturated societies. Most of these confounding variables were, however, controlled in a seminal study of 2 Amazonian tribes who had a similar background and cultural habits, with the exception of a difference in sodium intake.[8] The Mundurucus, whose lifestyle was influenced by the Franciscans, had incorporated salt into their diet as a means to preserve and season their food. In contrast, the Carajás had little contact with Westerners and consumed almost no salt. Average BP during adult life increased with rising age in the Mundurucus but not in the Carajás (Figure 1), whose mean systolic BP (SBP) and diastolic BP (DBP) remained about 110 and 60 mm Hg, respectively, throughout their adult lifespan.

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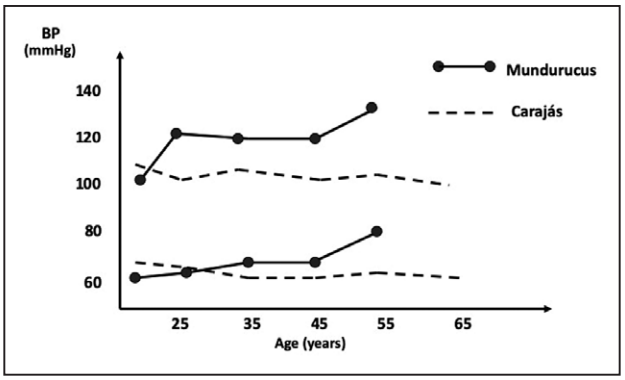

Figure 1. Blood pressure (BP) for men by age in Mundurucus and Carajás Indians, showing a rise with aging in the acculturated Mundurucus but not in the unacculturated Carajás. Reprinted from *The Lancet* (Lowenstein[8]) with permission. Copyright © 1961, Elsevier.

Another isolated society in Brazil, the Yanomamo Indians, with very limited access to salt also demonstrated little if any rise in BP with aging.[10] In addition to excreting very little sodium in their urine, they had high levels of plasma renin activity and aldosterone. These findings suggest biologically normal values of BP, renin activity, and aldosterone are very different compared with the relatively high levels of BP and low levels of plasma renin activity and aldosterone identified in acculturated societies, where there is exposure to high levels of dietary sodium. Animal model studies, population studies, and clinical trials provide evidence supporting the central role of excessive sodium consumption in causing age-related increases of BP.[12]

The consequences of 2 definitions for identification of an abnormally high BP are depicted in Figure 2. The left-hand panel depicts the rightward shift of SBP and DBP that occurs with acculturation. The shaded area in the distribution for unacculturated populations identifies high BP using a definition (SBP ≥120 mm Hg or DBP ≥70 mm Hg) is based on the BP distribution in observational studies. The corresponding shaded area in the distribution for acculturated populations is based on a definition of high BP (SBP ≥140 mm Hg or DBP ≥90 mm Hg) that has traditionally been used in acculturated populations. The shaded areas in the right-hand panel identifies high BP in acculturated societies using the SBP 120 mm Hg and DBP ≥70 mm Hg cut points.

Around 70% of those living in acculturated societies would be at higher risk of developing CVD according these values. Using the cut points proposed for diagnosis of hypertension in the 2017 American College of Cardiology/American Heart Association BP guideline (SBP ≥130 mm Hg or DBP ≥80 mm Hg),[13] around 63% of adults aged 45 to 75 years in the United States and 55% in China have hypertension.[14]

In recent decades, a leftward shift in the distribution of BP has been identified in high-income countries.[15] As expected, this downward shift in BP has been accompanied by a reduction in the incidence of CVD. The absolute number of individuals with hypertension in the world, however, has increased due to a rightward shift in the distribution of BP in low- and middle-income countries.[15]

Evidence From Cohort Studies

In an early cohort study, Keith et al[16] reported on BP-related risks, stratified by BP levels, symptoms, ECG abnormalities, albuminuria/hematuria, and optic fundi abnormalities. The mortality rate was proportional to severity of illness, being >80% over 1 year for participants who had BP resistant to treatment, bad general condition, an abnormal ECG, albuminuria, hematuria, and optical edema (characterized as class IV). Despite this and other observational reports published in the first half of the 20th century that suggested high BP caused CVD, many opinion leaders believed high BP was an inconsequential finding and use of the term benign essential hypertension was commonplace. White was in the group of influential leaders who believed high BP was a physiological compensatory mechanism and should not be manipulated by treatment.[17]

In a series of seminal reports, the Prospective Studies Collaboration pooled data from many cohort studies and accounted for the effects of regression dilution bias to generate precise estimates of the relationship between BP and CVD. Their most important report[18] was based on experience in 61 cohort studies that provided 12.7 million person-years of risk experience (56 000 deaths from coronary heart disease [CHD] and stroke). The risk of CVD increased steadily with progressively higher levels of baseline SBP and DBP, above a usual SBP and DBP of 115 and 75 mm Hg, respectively. For a 20 mm Hg higher level of SBP and 10 mm Hg higher level of DBP the risk of CVD was 2-fold higher (Figure 3, left, with log-transformed vertical axis). The corresponding pattern for

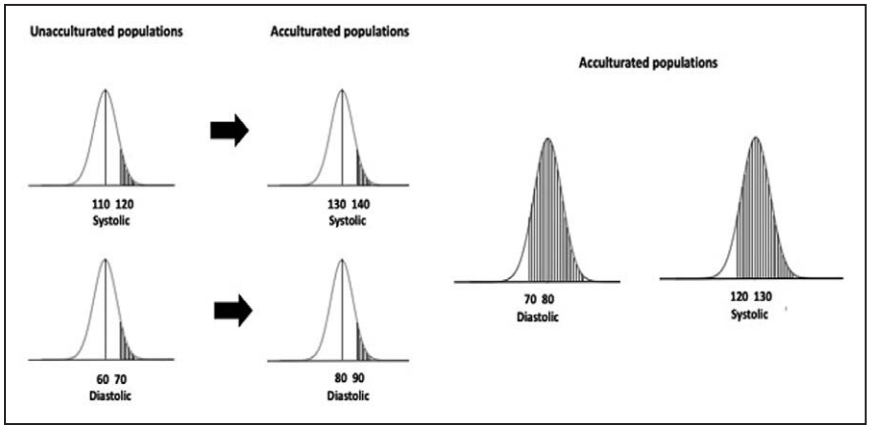

Figure 2. Left part depicts distribution of systolic and diastolic blood pressure (BP) in unacculturated and acculturated populations. Shaded areas identify distribution of a high BP definition (systolic BP ≥120 mm Hg or diastolic BP ≥70 mm Hg) for adults in unacculturated societies and for their counterparts living in acculturated societies using the traditional definition for diagnosis of hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg). Shaded areas in the **right** part highlight distribution of high systolic and diastolic BP applying the definition used for high BP in unacculturated societies (SBP ≥120 mm Hg or diastolic BP ≥70 mm Hg).

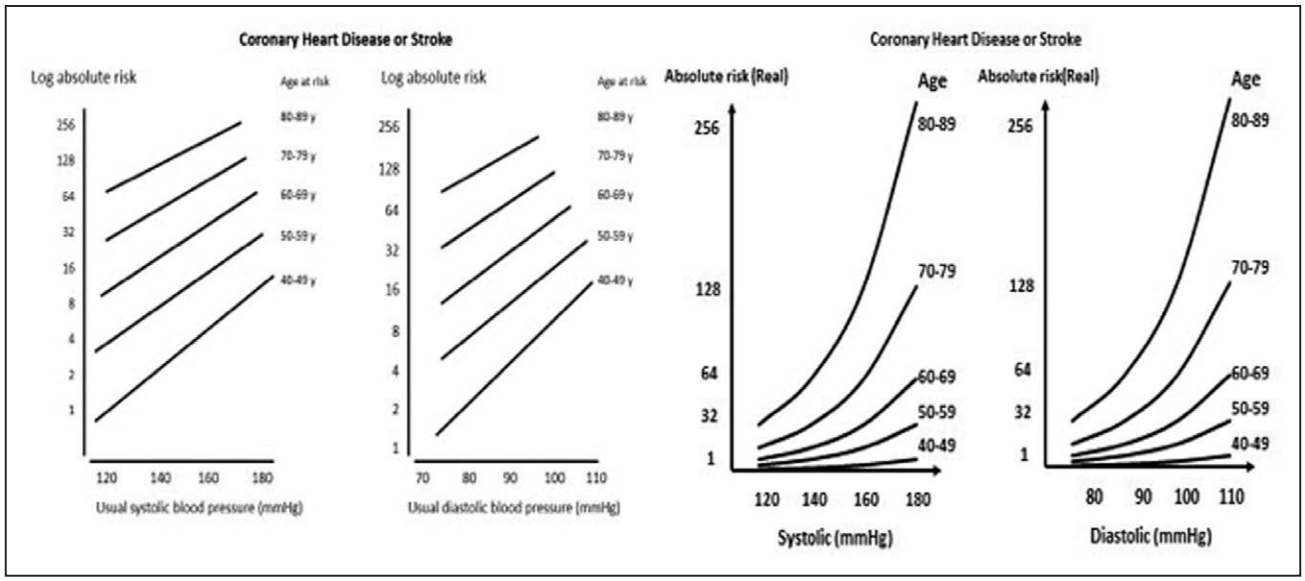

Figure 3. Log transformed (**left**) and untransformed (**right**) absolute risk of coronary heart disease or stroke in adults, by systolic and diastolic blood pressure, stratified by age. Reprinted from *The Lancet* (Lewington et al[18]) with permission, copyright © 2002 Elsevier; and reprinted from Fuchs[19] with permission, copyright © 2018, Springer International Publishing.

BP-related absolute risk of CVD (Figure 3, right), revealed an exponential association between increased BP and risk for CHD and stroke. It identified a relatively small increment in absolute risk of CVD with increasing BP levels at lower BP values and at younger age, which likely explains why individual studies in young and middle-aged participants have only identified a CVD risk at higher values of BP.[19]

Most of the early observational studies were focused on BP complications (stroke and CHD) which usually occur earlier than other BP clinical consequences and are especially prominent at higher levels of BP. At older age, stroke and CHD are accompanied by several complications that develop over a longer period of exposure to high BP, either because the target organs are more resistant or because more modest BP elevations have been present for a prolonged period of time. The complications of high BP can be classified as short- and long-term consequences (Table). Consistent observational evidence suggests high BP is the leading cause of long-term consequences such as heart failure, with and without preserved ejection fraction,[20] atrial fibrillation,[21] valvular heart disease,[22,23] peripheral arterial disease and aortic syndromes,[24] chronic kidney disease and end stage renal disease,[25,26] dementia,[27,28] and Alzheimer Disease.[29] Diabetes mellitus,[30] erectile dysfunction,[31] and age-related macular degeneration[32] are other conditions that likely have high BP as one of their causes.

Centenarians

The primary reason that centenarians reach 100 years of age is an unusually low burden of CVD and cancer. CHD, stroke, dementia, and hypertension are less frequent in centenarians compared with individuals who die at a younger age[33] (Figure 4). Vascular aging is directly associated with level of BP and not inexorable. Prevention of age-related increases in BP would substantially reduce the vascular consequences usually attributed to aging. Individuals who develop hypertension late in life are not at increased risk for CVD earlier in life.[34] Centenarians may be resistant to dietary sodium loads having the ability to excrete sodium in the absence of high-pressure natriuresis.

Cartesian Evidence

Experimental studies, the highest hierarchical method for demonstration of causality, provide strong support for our theory of CVD causation. The 1967 Veterans Administration Cooperative Study Group on Antihypertensive Agents,[35] SHEP trial (Systolic Hypertension in the Elderly Program)[36] and SPRINT (Systolic Blood Pressure Intervention Trial)[37] are 3 of

Table. Short-Term and Long-Term Consequences of High BP

Short and long-term consequences
Stroke
Coronary heart disease
Heart failure
Cardiovascular death
Long-term consequences
Hypertensive cardiomyopathy
Heart failure with preserved ejection fraction
Atrial fibrillation
Valvular heart disease
Aortic syndromes
Peripheral arterial disease
Chronic kidney disease
Dementias
Diabetes mellitus
Erectile dysfunction

BP indicates blood pressure.

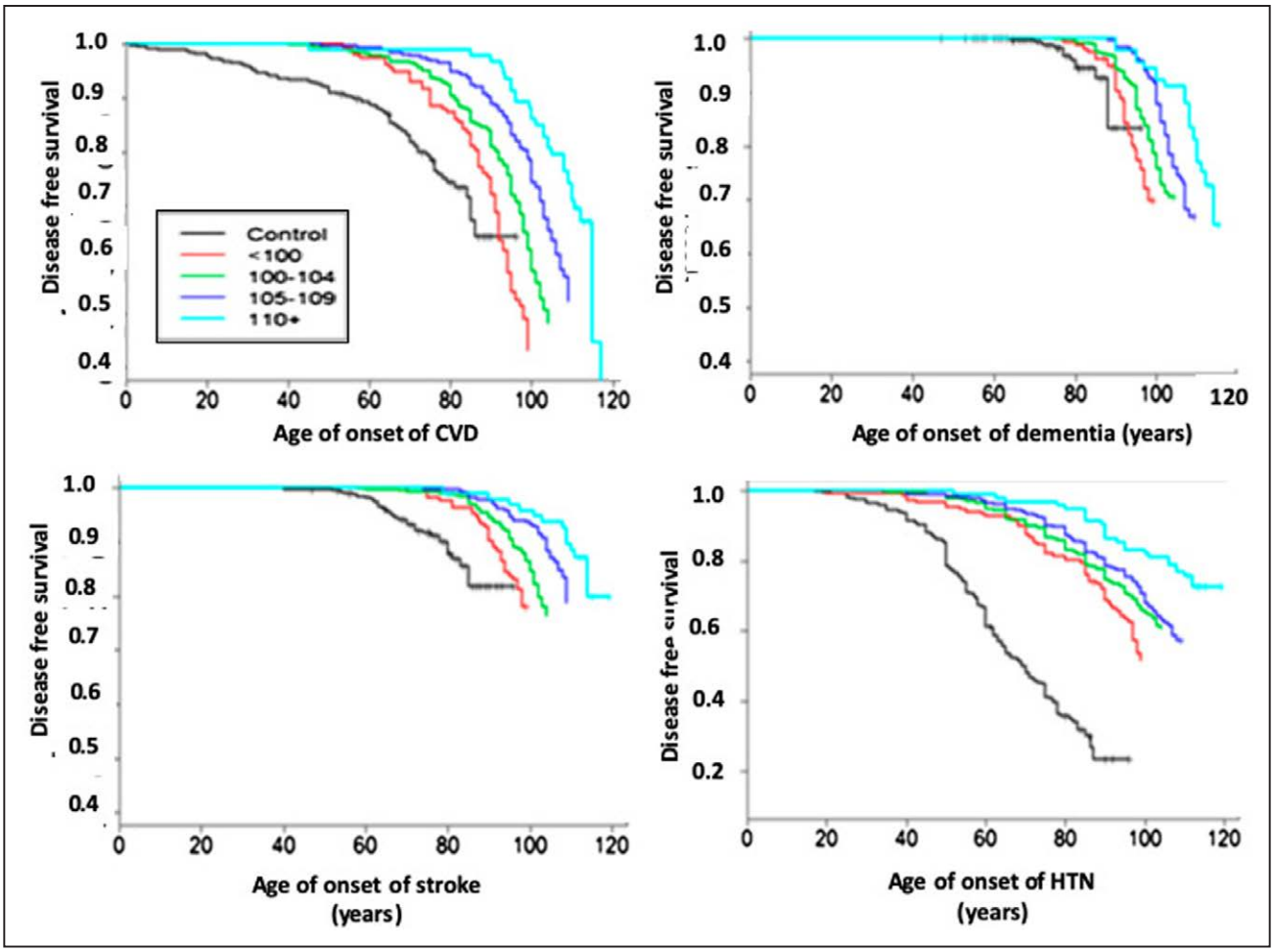

Figure 4. Disease-free age survival for cardiovascular disease (CVD), dementia, stroke, and hypertension (HTN) in controls (individuals without a familial predisposition for exceptional longevity (black line), and centenarians (color lines), stratified by age in years at death. The data demonstrate a consistent delay in onset of CVD, dementia, and stroke when HTN starts late in life. Reprinted from Andersen et al[33] with permission. Copyright © 2012, The Author. Published by Oxford University Press on behalf of The Gerontological Society of America.

many randomized controlled trials (RCTs) that have provided strong evidence regarding the effectiveness of BP lowering for prevention of CVD. Redefining the outcomes according a modern paradigm, the number needed to treat to prevent one major CVD event per year in the 1967 Veterans Administration trial was only 6 patients in those with a baseline DBP averaging 115 to 129 mm Hg.[38] Before publication of the SHEP results, many doctors believed isolated systolic hypertension was a natural and benign compensatory consequence of aging. The trial showed that chlorthalidone-based therapy reduced the incidence of stroke, the primary end point, by 36% compared with placebo.[36] SPRINT demonstrated that participants randomized to a SBP goal <120 mm Hg (intensive treatment) had an incidence of the primary composite CVD end point that was 25% lower compared with those randomized to a SBP goal <140 mm Hg (standard treatment).[37] There were reductions of 43% in CVD mortality and 27% in all-cause mortality. A similar benefit was demonstrated in the relatively large (N=2636) subgroup of participants 75 years or older at baseline, including those with frailty and reduced gait speed.[39]

High-quality meta-analyses have demonstrated the effectiveness of BP lowering for prevention of CVD. Additionally, studies have compared the observed benefit of BP reduction in RCTs with the expected benefit based on BP as a risk factor for CVD in observational studies.[40–42] In a study that included 147 RCTs, Law et al[40] calculated the CVD risk reduction for the average active treatment versus control trial difference in SBP (10 mm Hg) observed in their meta-analysis. As depicted in Figure 5, the reductions in stroke and CHD incidence rates were similar to the benefits expected on the basis of a 10 mm Hg difference in SBP in the Prospective Studies Collaboration meta-analysis of observational studies. Benefit for the same difference in BP was greater for stroke, reflecting the higher risk of elevated BP for cerebral vessels compared with the coronary circulation.

A similar benefit was observed in a network meta-analysis conducted by Bundy et al.[42] In this study, the relative risk reduction of major CVD events in trials where the participants had been treated to a SBP target between 120 and 124 mm Hg, compared with a corresponding target of 160 mm Hg or higher, was 64%, which is close to the hypothetical risk reduction of 75% for a 40 mm Hg SBP reduction in the Prospective Studies Collaboration meta-analysis.[18] The similarity between risk predicted in cohort studies and benefit demonstrated in RCTs fulfills one of the postulates of Descartes,[43] that is, that the sum of the angles of any triangle

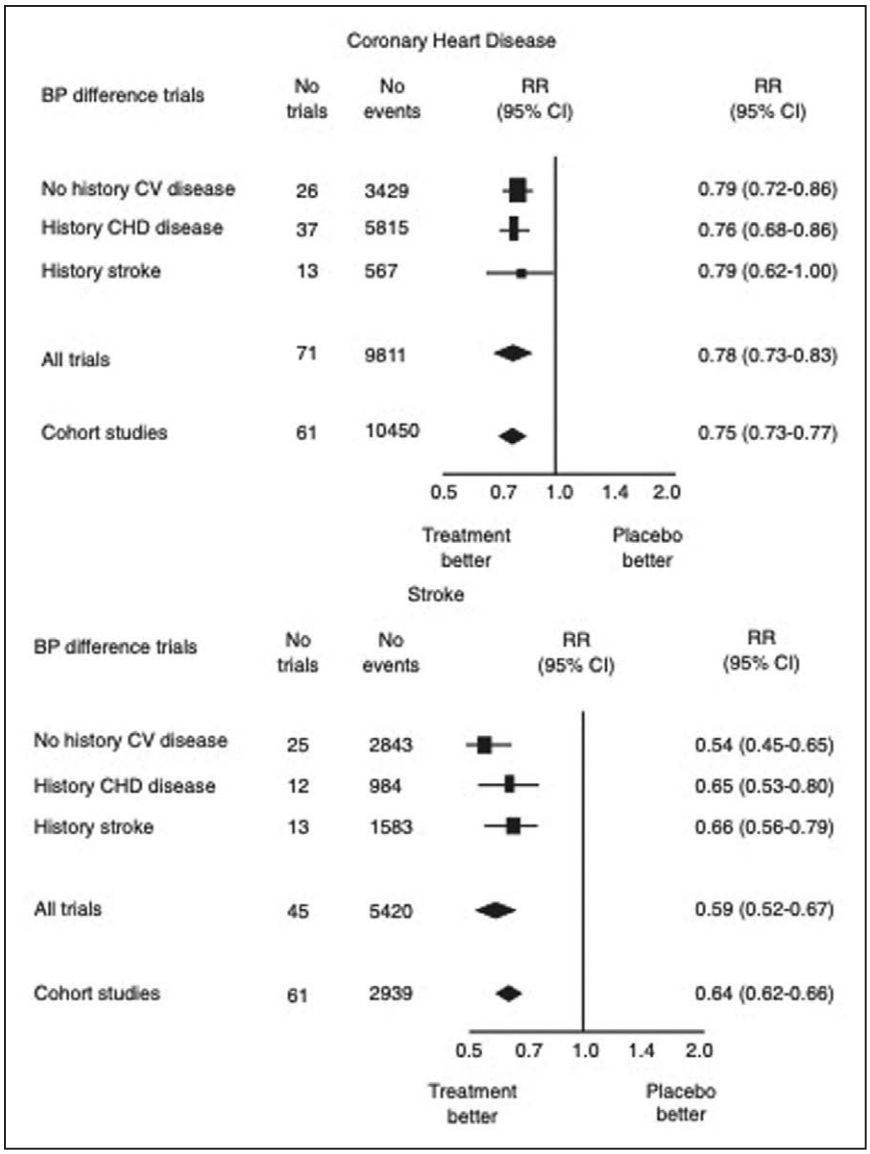

Figure 5. Relative risk estimates of coronary heart disease (**top**) and stroke (**bottom**) for systolic blood pressure (BP) reduction of 10 mm Hg or diastolic BP reduction of 5 mm Hg in clinical trials meta-analysis and corresponding difference in meta-analysis of observational cohort studies. CHD indicates coronary heart disease; CV, cardiovascular; and RR, relative risk. Reprinted from Law et al[40] with permission. Copyright © 2009, BMJ Publishing Group Ltd.

equals 180 degrees (2 right angles). The close approximation between the observed (clinical trials) and expected (observational cohort studies) benefits of BP lowering is impressive, since the expected estimate is based on imperfect measurements of a biological parameter.

Scant experimental evidence exists for prevention of the longer term consequences of high BP. Designing trials for these end points is challenging, because they require a longer duration of treatment than is necessary to demonstrate CVD benefit. Despite this, suggestive benefit of BP lowering in RCTs exists for some of these outcomes. For example, the composite outcome of mild cognitive impairment and dementia was significantly less common during long-term follow-up in the SPRINT study.[44,45]

The central role of BP levels has also been demonstrated by studies where BP has risen during treatment and resulted in CVD events. Examples come from studies using celecoxib,[46] sibutramine,[47] and torcetrapib.[48] In contrast, prevention of CVD events by inhibitors of sodium-glucose cotransporter 2 in adults with,[49,50] and without diabetes mellitus[51] may be due, in part, to BP-lowering.

Attributable Risks

Estimation of the high BP contribution to causation of CVD has increased progressively as the definition of hypertension and analytic techniques have evolved. Early estimates of attributable risk were 25% for CHD and 50% for stroke.[52] Based on the risks identified by the Prospective Studies Collaboration,[18] the attributable risk for BP equal or >115/75 mm Hg was estimated to be 49% for CHD and 62% for stroke.[53] However, these estimates almost certainly understate the true contribution of high BP to development of CVD. In many of the cohort studies, residual bias in estimation is probable because the risk estimates have been based on only a few BP measurements. Vascular, cardiac, and renal damage results from an excessively high vascular load of beat-to-beat elevations in BP over long periods.[19] One or 2 BP measurements provide an insufficient estimate of vascular load. Other CVD risk factors, such as smoking, dyslipidemia and excess body weight, are subject to measurement error, but their estimation is much more precise compared to BP readings. More efficient methods for BP measurement, such as ambulatory BP measurement,[54] particularly at

nighttime,[55] home BP monitoring and automated office BP measurement provide more precise estimation of BP-CVD risk, including identification of risk at lower BP values compared to traditional office BP measurements.[54] Another reason for underestimation of BP-related risk is inclusion of intermediate consequences of high BP as causes of CVD in multivariate explanatory equations.[56] This is especially true for analyses that have included left ventricular hypertrophy or vascular wall thickening, but even overweight and obesity are CVD risk factors that are largely mediated by high BP.[57] Recognizing the potential for underestimation, other confounding risks increase concomitantly with BP, but in clinical trials the absolute risk reduction from BP-lowering accounts for nearly all of the predicted risk, leaving little residual risk to be explained by the other concomitant risks.

What Is Missing?

In adults without CVD, a strong BP-CVD risk association has been identified at lower levels of SBP (120–139 mm Hg) and DBP (80–89 mm Hg).[18] Individuals within this BP range are at increased risk for development of higher levels of BP over relatively short periods of follow-up[58,59] and already have evidence of target organ damage.[60,61] Moreover, meta-analyses of event-based RCTs have shown the benefit of antihypertensive treatment in adults with CVD (secondary prevention) and an average BP within the same range.[40,41] Trials have also shown that low-dose pharmacotherapy in adults without CVD and an average SBP of 130–139 mm Hg or DBP ≤89 mm Hg[62,63] and SBP 120–139 mm Hg or DBP 80–89 mm Hg[64] lowers BP and prevents incident hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg). The PREVER-Prevention trial additionally demonstrated that low-dose diuretic therapy (chlorthalidone and amiloride) in adults with a SBP 120–139 mm Hg or DBP 80–89 mm Hg prevented incident LVH estimated by ECG.[64]

Nonetheless, no BP-lowering trial has demonstrated prevention of CVD events in adults without CVD who have a SBP <140 mm Hg or DBP <90 mm Hg.

Despite strong evidence of a BP-lowering benefit in clinical trials and meta-analyses, direct documentation of intensive BP-lowering benefit is lacking in adults with high BP who have diabetes mellitus or a history of prior stroke. At least 2 event-based trials (one in Brazil and the other in China) are addressing this question in diabetics and one trial (in Brazil) is being conducted in stroke survivors.

Conclusions and Perspectives

Our proposal that CVD is predominantly caused by a rightward shift in the distribution of BP is supported by coherence and factual evidence. As a theory, it is open to refutation and formulation of alternative proposals. Among the existing theories, however, ours is the one that best meets Occam's razor premise, that is, it is the hypothesis with the fewest assumptions. Other risk factors, including lipid abnormalities, cigarette smoking, physical inactivity, and dietary influences other than sodium play an important role in CVD causation. Although elevated BP has the greatest effect on population health, prevention of CVD is best achieved by a comprehensive approach aimed at improving CVD risk factors at all stages of life.

Regardless of its exact contribution, high BP is a major risk factor for development of CVD. Prevention of the age-related increase in BP would substantially reduce the vascular consequences usually attributed to aging. It is time to focus greater attention on initiatives for prevention of the typical age-related increase in BP in addition to control of high BP in those with established hypertension. Even partial improvement in the age-related increase in BP would eliminate a large proportion of the existing burden of BP-related CVD.

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Disclosures

None.

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