Circulation Research Compendium on Hypertension

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Giuseppe Mancia, Guest Editor

The Epidemiology of Blood Pressure and Its Worldwide Management

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Abstract: **Despite the vast amount of evidence on the benefits of blood pressure lowering accumulated to date, elevated blood pressure is still the leading risk factor for disease and disability worldwide. The purpose of this review is to summarize the epidemiological evidence underpinning the association between blood pressure and a range of conditions. This review focuses on the association between systolic and diastolic blood pressures and the risk of cardiovascular and renal disease. Evidence for and against the existence of a J-shaped curve association between blood pressure and cardiovascular risk, and differences in the predictive power of systolic, diastolic, and pulse pressure, are described. In addition, global and regional trends in blood pressure levels and management of hypertension are reviewed. (*Circ Res*. 2015;116:925-936. DOI: 10.1161/CIRCRESAHA.116.304723.)**

Key Words: blood pressure ■ epidemiology ■ hypertension ■ hypertension management

A Brief History of the Epidemiology of Blood Pressure (1900–2000)

Although the global excess of mortality caused by high blood pressure is now well recognized, knowledge of the link between high blood pressure and cardiovascular risk is a relatively recent development. In the early 1900s, high blood pressure was largely considered by physicians to be a natural consequence of aging and not a risk factor to be controlled.[1] In 1910, the US insurance industry recognized that insurance applicants with high blood pressure were at increased risk of death.[2] A 1925 report by the Actuarial Society of America provided some of the first quantitative estimates of the association between blood pressure and cardiovascular disease, concluding that the risk of death because of cardiovascular and other causes increases with increasing blood pressure.[3]

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Nonstandard Abbreviations and Acronyms

APCSC	Asian Pacific Cohort Studies Collaboration
CALIBER	CArdiovascular research using LInked Bespoke studies and Electronic health Records
CHD	coronary heart disease
DBP	diastolic blood pressure
HR	hazard ratio
IHD	ischemic heart disease
LICs	low-income countries
LMICs	low- and middle-income countries
MRFIT	Multiple Risk Factor Intervention Trial
OR	odds ratio
PSC	Prospective Studies Collaboration
PURE	Prospective Urban Rural Epidemiology Study
SAGE	Study on Global Aging and Health
SBP	systolic blood pressure

The Framingham Heart Study was one of the first epidemiological studies to both characterize the prevalence of hypertension and to analyze its consequences in a longitudinal prospective cohort.[4] Of 4469 participants who had their blood pressure measured between 1949 and 1952, 18% had hypertension, then defined as a systolic blood pressure (SBP)≥160 mm Hg. When followed >6 years, ischemic heart disease (IHD) events were ≈3× more common in hypertensive men than in normotensive men aged 45 to 62 years and 6-fold more common in hypertensive women than normotensive women of the same age group.[4,5]

Although, by 1960, epidemiological evidence was mounting that high blood pressure was associated with an increased risk of mortality, the majority of physicians continued to view blood pressure lowering as either useless or dangerous. The eminent cardiologist Friedberg[6] noted in the 1966 version of his textbook *Diseases of the Heart* that the treatment of individuals with a BP <200/100 mm Hg was not indicated. However, in the late 1960s, the first Veteran Affairs Cooperative Study, comparing a combination of antihypertensives (thiazide diuretic and reserpine) against placebo in hypertensive individuals, was halted because of an excess of morbid and mortal events in the placebo arm. This trial provided the first strong causal evidence that blood pressure lowering reduces the risk of death.[7]

In 1970, the National Heart and Lung Institute convened a task force to recommend ways to treat, prevent, and research atherosclerosis. One recommendation provided by the task force was to conduct a large randomized trial to test a complex intervention aimed at dietary change, halting of smoking, and treatment of high blood pressure.[8] In 1972, 350 000

Table 1. Large-Scale Observational Analyses of the Association of Blood Pressure With Cardiovascular Events

Study	Key Findings
Framingham[4]	• Men with hypertension (SBP ≥160 mm Hg or DBP≥95 mm Hg) had a 3-fold greater rate of CHD events than men with normotension (then defined as SBP<140 mm Hg or DBP<90 mm Hg) • Women with hypertension had a 6-fold greater rate of CHD events than normotensive women
MRFIT (1988)[11]	• Mortality within the MRFIT cohort was found to relate to blood pressure in a graded and continuous manner with no evidence of threshold down to 120 mm Hg systolic • Isolated systolic hypertension is associated with CHD mortality independently of DBP
MacMahon et al[10]	• DBP was continuously associated with risk of CHD and stroke events to a threshold of 70 mm Hg • A 10 mm Hg lower DBP was associated with 37% lower risk of CHD events and a 56% lower risk of stroke events
PSC[12]	• After accounting for regression dilution, a 20 mm Hg lower SBP was associated with a HR of 0.60 for IHD mortality (95% CI, 0.58–0.61) and a HR of 0.50 (CI, 0.48–0.52) for stroke mortality in the age group with the largest number of fatal events (70 to 79 y). • Although associations between vascular mortality and blood pressure are half as extreme in 80–89 as 40–49, absolute differences in risk are greater
Rapsomaniki (CALIBER)[13]	• 20 mm Hg lower SBP was associated with HR of 0.78 (CI, 0.75–0.80) for myocardial infarction, 0.74 (CI, 0.70–0.78) for ischemic stroke, 0.69 (CI, 0.63–0.76) for intracerebral hemorrhage • Hypertension (≥140/90 mm Hg) was associated with a mean 5 y lost from the age of 30 y • Although stable/unstable angina and myocardial infarction were associated with the greatest number of disease-free life years lost at the age of 30 y, by the age of 80 y, heart failure accounted for most of disease-free years lost

CALIBER indicates CArdiovascular research using LInked Bespoke studies and Electronic health Records; CHD, coronary heart disease; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; IHD, ischemic heart disease; MRFIT, Multiple Risk Factor Intervention Trial; and SBP, systolic blood pressure.

men without previous vascular disease were screened as potential participants for the Multiple Risk Factor Intervention Trial (MRFIT) and had a baseline blood pressure recorded. Although the trial itself did not show a significant benefit of the complex intervention, the MRFIT screening cohort formed one of the largest prospective individual patient cohort studies in blood pressure research. After 6 years of follow-up, mortality within the MRFIT cohort was found to relate to blood pressure in a graded and continuous manner with no evidence of threshold down to 120 mm Hg systolic (Table 1).[9,11] Similarly, in a 1990 overview of 9 prospective observational studies with 420 000 individuals, diastolic blood pressure (DBP) was continuously associated with risk of coronary heart disease (CHD) and stroke events to a threshold of 70 mm Hg.[10] Overall, a 10 mm Hg lower DBP was associated with 37% lower risk of CHD events and a 56% lower risk of stroke events.

Despite this historical research that collectively shaped the basis of our knowledge about the positive association between blood pressure with risk of cardiovascular mortality, several important questions about the strength of this association in different patient groups and for different clinical outcomes remained unanswered until recently, and some are still subject to ongoing investigations.

Blood Pressure as Risk Factor for Several Diseases

Blood Pressure and Cardiovascular Disease

In 2002, the Prospective Studies Collaboration (PSC) reported results from a meta-analysis of prospective observational studies of the association between blood pressure and vascular mortality.[12] Although previous analyses had largely associated measured blood pressure with cardiovascular risk, random measurement error and time-dependent regression to the mean are expected to reduce the calculated association between measured blood pressure and cardiovascular risk (an effect termed regression dilution bias). This large meta-analysis (based on 100 000 deaths among 1 million participants without a history of vascular disease, recruited into 61 prospective cohort studies between 1950 and 1990) controlled for regression dilution bias and, therefore, provided reliable evidence on the association between usual blood pressure (baseline blood pressure unaffected by measurement error and temporal variation) and cardiovascular risk. It found a continuous log–linear relationship between blood pressure and vascular mortality, that is, for a given absolute difference in blood pressure, the proportional difference in risk of vascular death was similar at all blood pressure levels investigated (Table 1).[12] More specifically, irrespective of the baseline blood pressure, a 20 mm Hg lower SBP was associated with a hazard ratio (HR) of 0.60 for IHD mortality (95% confidence interval [CI], 0.58–0.61) and a HR of 0.50 (CI, 0.48–0.52) for stroke mortality in the age group with the largest number of fatal events (70–79 years).

Other vascular causes of mortality that were investigated exhibited similar associations with a 20 mm Hg reduction in SBP. The age-standardized HR for heart failure was 0.53 (CI, 0.48–0.59), whereas that for aortic aneurysm was 0.55 (CI, 0.49–0.62). Mortality from atherosclerosis and hypertensive heart disease were found to have HRs of 0.48 (CI, 0.42–0.55)

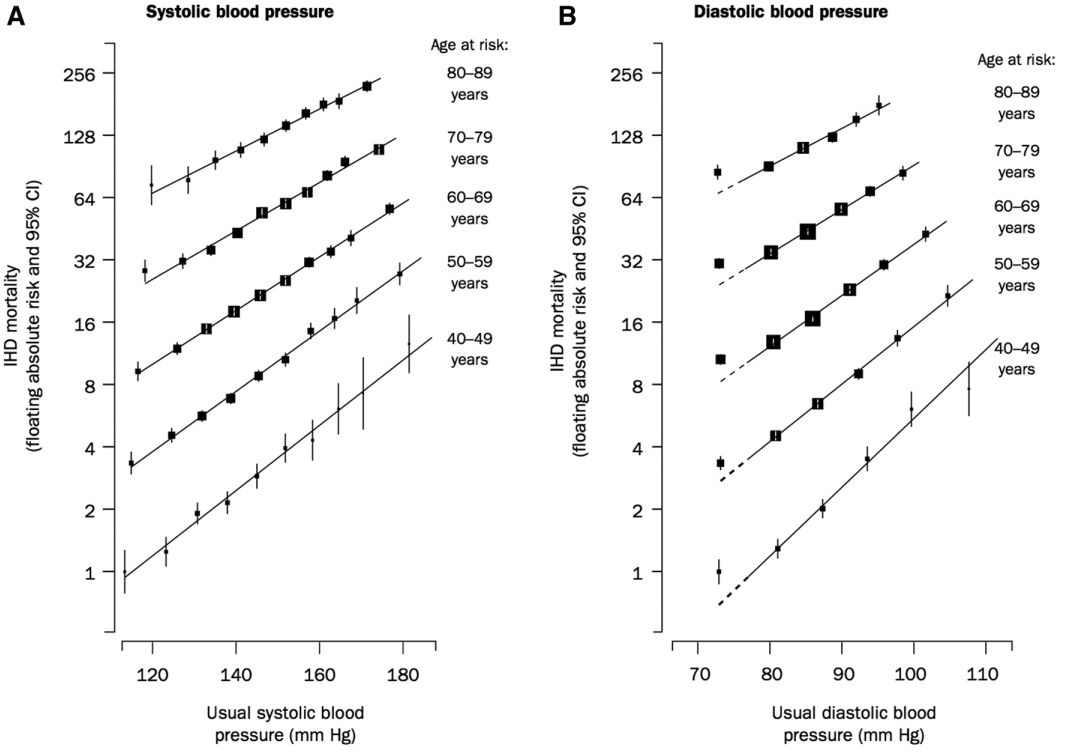

Figure 1. Ischemic heart disease (IHD) mortality in each decade of age vs usual blood pressure at the start of the decade. CI indicates confidence interval. Adapted from the Prospective Studies Collaboration (Lewington et al[12]) with permission of the publisher. Copyright ©2002, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

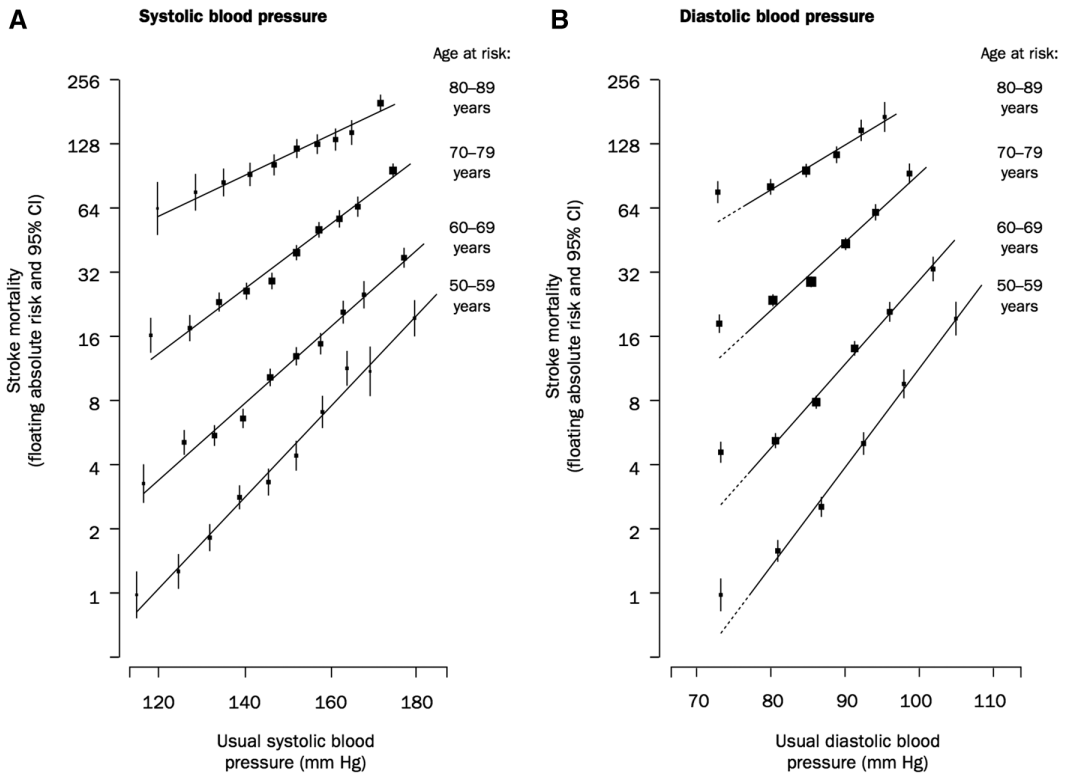

Figure 2. Stroke mortality in each decade of age vs usual blood pressure at the start of the decade. CI indicates confidence interval. Adapted from the Prospective Studies Collaboration (Lewington et al[12]) with permission of the publisher. Copyright ©2002, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

and 0.22 (CI, 0.20–0.25), respectively. This study also found no evidence for an increased risk of nonvascular mortality with lower blood pressure. In fact, each 20 mm Hg lower SBP was associated with a modestly lower risk of nonvascular mortality (age-standardized HR, 0.88; CI, 0.87–0.89), most probably explained by misclassification of vascular diseases rather than a valid association between blood pressure and risk of nonvascular mortality.

The large number of events in the PSC meta-analysis provided statistical power for more detailed analyses than had previously been possible. In particular, the collaboration was able to reliably investigate the relationship of blood pressure and vascular mortality by age. When stratified into different age groups, a continuous log–linear relationship was observed at all ages. However, the slope of the association differed significantly between the different age groups (Figures 1 and 2). For every 20 mm Hg lower SBP, the HR for death from IHD declined from 0.49 in the age group of 40 to 49 years to 0.67 in the age group of 80 to 89 years (Figure 1). For stroke mortality, the HR for a 20 mm Hg lower SBP declined from 0.36 in the age group of 40 to 49 years to 0.67 in the age group of 80 to 89 years (Figure 2; Table 1).[12] Despite the diminishing strength of the associations between vascular death and blood pressure with increasing age, the absolute annual differences in death rates associated with a given difference in blood pressure were found to be higher in the older age categories. This was because the absolute risks of vascular disease increased steeply with increasing age (Figures 1 and 2).[12] This evidence supported the notion that blood pressure control is likely to prevent substantial numbers of vascular events up to old age.

PSC also investigated differences in proportional risks by sex and showed modest differences between men and women. The proportional risk of IHD mortality per 20 mm Hg lower SBP were slightly smaller in men than in women, with HRs of 0.62 (CI, 0.60–0.64) for men and 0.55 (CI, 0.53–0.58) for women in the largest age group. For stroke, HRs for a 20 mm Hg lower SBP were similar, although possibly slightly attenuated in women, with HRs of 0.53 (CI, 0.49–0.56) for women versus 0.48 (CI, 0.46–0.51) for men in the age group of 70 to 79 years.

A few studies have also investigated differences in associations by ethnicity or geographical regions. In the Asian Pacific Cohort Studies collaboration (APCSC), risk of IHD was similar in Australian and Asian populations and steeper in younger than older people. A slightly stronger relationship between blood pressure and stroke was found in Asian populations (HR, 0.59; CI, 0.58–0.60) than in Australian populations (HR, 0.70; CI, 0.63–0.78).[14] In the PSC, similar HRs for IHD and stroke mortality were found in different regional populations. For IHD mortality, an age-standardized HR of 0.57 (CI, 0.56–0.58) was observed in Europe, 0.54 (CI, 0.51–0.56) in the United States/Australia, and 0.55 (CI, 0.48–0.63) in Asia. For stroke mortality, HRs were 0.49 (CI, 0.48–0.51) in Europe, 0.50 (CI, 0.47–0.53) in the US/Australia, and 0.42 in Asia (CI, 0.39–0.46).[12] However, in neither collaboration were reliable data available on stroke subtypes, and there was,

therefore, a possibility that any real difference in the strength of association in Asian and non-Asian populations could reflect differences in the ratio of stroke types.

The PSC and APCSC analyses were based on epidemiological studies that, in large part, preceded the introduction of major public health and medical interventions for blood pressure control. In addition, these collaborations largely focused on fatal stroke and fatal IHD and had little information on nonfatal vascular events. A recent study, however, was able to use data from linked healthcare records for 1.25 million patients in England who were registered with their primary care doctors between 1997 and 2010. In this contemporary cohort studied in the CArdiovascular research using LInked Bespoke studies and Electronic health Records (CALIBER) project, investigators reported the association between measured blood pressure (without formally controlling for regression dilution) and risks of fatal and nonfatal vascular events, including angina, heart failure, peripheral vascular disease, and abdominal aortic aneurysm.[13] A 20 mm Hg lower SBP was associated with an HR of 0.71 (CI, 0.68–0.74) for stable angina, 0.80 (CI, 0.76–0.85) for unstable angina, 0.78 (CI, 0.75–0.80) for myocardial infarction, 0.79 (CI, 0.76–0.81) for heart failure, 0.74 (CI, 0.70–0.78) for ischemic stroke, 0.69 (CI, 0.63–0.76) for intracerebral hemorrhage, and 0.79 (CI, 0.78–0.80) for total cardiovascular disease. Similar to PSC and APCSC, the strength of the association of SBP with cardiovascular disease attenuated significantly in older age groups (Table 1). For example, in the age group of 30 to 59 years, 20 mm Hg higher SBP was associated with a HR of 0.62 (CI, 0.58–0.66) for stable angina, but was associated with a HR of 0.78 (CI, 0.68–0.88) in the age group of >80 years. Similarly, for ischemic stroke, 20 mm Hg lower SBP was associated with an HR of 0.64 (CI, 0.56–0.72) in the age group of 30 to 59 years but an HR of 0.86 (CI, 0.77–0.96) in the age group of >80 years.

The proportional reductions per 20 mm Hg lower SBP observed in CALIBER were attenuated relative to those observed in PSC and APCSC. For example, in PSC, the HR for IHD mortality per 20 mm Hg lower SBP was 0.57 (in European populations), whereas an HR of 0.78 was observed for myocardial infarction in CALIBER. There are several potential explanations for these diverging findings. First, while PSC and APCSC adjusted for regression dilution, CALIBER did not, although multiple blood pressure measurements for individuals were averaged when available. Accounting for regression dilution increased the strength of observed associations 1.5- to 2-fold in PSC, when comparing usual blood pressure with measured blood pressure. Second, although PSC contained cohort studies that were conducted before the widespread introduction of antihypertensive therapy, CALIBER contained records from 1997 to 2010, after the widespread introduction of antihypertensive therapy in the United Kingdom. Although the CALIBER analysis adjusted for baseline usage of antihypertensive therapy, such interventions are likely to have been introduced for many individuals during the follow-up duration. Consequently, their cardiovascular risk would be reduced relative to what it would be if there baseline blood pressure had remained constant, reducing the association between cardiovascular risk and blood pressure over a range of blood pressures (from normotensive to hypertensive). Finally, the CALIBER cohort, whereas slightly larger than PSC, was of significantly shorter follow-up duration (median of 5.2 years versus mean of 12 years in PSC), included nonfatal vascular events (which may be less influenced by usual blood pressure and not captured reliably in routine databases) and may have differed in age from PSC. Ongoing studies will examine which, if any, of these factors affect the association between blood pressure and vascular risk.

The observed associations between 20 mm Hg lower SBP and cardiovascular risk in PSC are broadly consistent with randomized evidence of blood pressure lowering. In a meta-analysis of 147 blood pressure lowering trials, a 20 mm Hg reduction in SBP was associated with a 39% reduction in CHD events (HR, 0.61; CI, 0.53–0.69) and a 65% reduction in stroke events (HR, 0.35; CI, 0.27–0.45).[15] In the age group of 60 to 69 years (the mean age for the trials included in the meta-analysis), a 20 mm Hg lower SBP was associated with a 46% lower rate of CHD events (HR, 0.54; CI, 0.53–0.55) and a 57% lower rate of stroke events (HR, 0.43; CI, 0.41–0.45). Although IHD estimates and stroke estimates from PSC differ slightly than those from randomized trials, estimates from PSC lie within CIs of estimates from randomized trials.

In summary, large-scale epidemiological studies have provided overwhelming evidence that high blood pressure, in all age groups and in both the sexes, is associated with an increased risk of IHD mortality, stroke mortality, vascular mortality and a range of other fatal and nonfatal vascular events without any evidence for excess harm and no evidence of material heterogeneity by different ethnicities (Table 1).

Is There a Threshold Below Which These Observed Associations Do Not Hold?

There is no doubt that a physiological threshold must exist below, which blood pressure levels are associated with increased cardiovascular mortality. However, where this physiological threshold lies and whether it differs by subgroups of patients and types of outcomes is still subject to controversy and research. The large sample size in the PSC allowed for an examination down to 115 to 124 mm Hg for SBP and 75 to 84 mm Hg for DBP.[12] Within this range, no threshold was identified, at which a lower blood pressure was no longer associated with reduced vascular mortality, although there was a suggestion of tapering for the DBP curves in the 75 to 84 mm Hg category. These findings were also consistent with the MRFIT cohort (which was included in PSC). In the MRFIT cohort study, the lowest decile of SBP (<112 mm Hg in men) had the lowest risk of CHD mortality. Similarly, the lowest decline of DBP in men (<71 mm Hg) was associated with the lowest risk of CHD mortality.[9] The recent CALIBER report confirmed these earlier reports in a contemporary cohort of 1.25 million patients who had 83 098 cardiovascular events during 5.2 years median follow-up.[13] No evidence was found for a threshold for risk of ischemic stroke, intracerebral hemorrhage, stable angina, or myocardial infarction, with the SBP category of 90 to 114 mm Hg having the lowest risk of cardiovascular outcomes.

However, despite the evidence for the lack of a J-shaped association from these large-scale analyses, controversy over possible thresholds, in particular for DBP, has continued.[16] Over 20 different observational analyses have suggested that

a J-shaped curve exists between DBP and myocardial infarction, stroke, total mortality, or noncardiovascular events, with the nadir of the curve ranging from 60 to 95 mm Hg DBP depending on the analysis.[16] The physiological rationale for a J-curve relating DBP to CHD events relies on the unique physiology of the coronary vessel bed.[17] Although most vessels beds are filled during systole, the coronary bed is filled during diastole. Consequently, a reduction in DBP, at least in theory, could lead to myocardial ischemia and infarction.[16] Alternatively, in elderly patients with isolated systolic hypertension, decreased DBP may indicate increased arterial stiffness leading to an increased pulse pressure. An analysis of the Systolic Hypertension in the Elderly Program (which included only patients with isolated systolic hypertension) observed that time-dependent reductions in DBP in the active treatment group, but not the placebo group, were associated with an increased rate of cardiovascular events. The authors postulate that this may be because of patients with isolated systolic hypertension being treated to a level that uncovers subclinical disease.[18]

However, many of the studies reporting a J-shaped association included patients with IHD at baseline, which would raise the possibility of the disease itself leading to lower blood pressure levels, and not the opposite (reverse causality). For example, in an analysis of 5000 men with a history of myocardial infarction, a J-shaped curve was observed between blood pressure (SBP and DBP) and risk of all-cause and CHD mortality in the first 2 years of follow-up.[19] However, after 2 years, the association between cause-specific and all-cause mortality was linear and graded (implying the observed J-shaped curve in the first 2 years was because of reverse causality). Indeed, a systematic review of 13 studies that concluded there was a J-shaped curve, also noted that only 3 of the included studies excluded patients with cardiovascular disease.[20] Of the 27 observational studies included in another report, many also observed a J-curve between DBP and risk of stroke,[16] easily explainable by reverse causality but less so through a physiological mechanism. Similarly, observational analysis have also observed a J-shaped curve between SBP and CHD events, again consistent with reverse causality but less consistent with diastolic filling of coronary arteries.[21] Because PSC and CALIBER excluded individuals with a known history of vascular disease at baseline, the risk of reverse causality was minimized in their analysis. This is evidently not the case for observational analyses of randomized trials of individuals with pre-existing CHD.[21]

In summary, based on large (>500 000 participants) studies that were able to mitigate the risk of cofounding rigorously, there is no evidence to suggest a J-shaped association between SBP or DBPs and cardiovascular risk down to blood pressure categories of 90 to 114 mm Hg and 60 to 74 mm Hg, respectively. However, it is important to recognize that this broad category does not exclude the existence of a nadir within the 90 to 114 mm Hg range in people with no apparently known previous vascular disease. It is at least plausible that such a nadir may exist for myocardial infarction, stroke, or nonvascular death. Larger studies that specifically aim to determine whether such a nadir exists, through curve fitting, and whether the nadir differs in different clinical scenarios and for different outcomes are currently underway to investigate this question further. Large-scale trials and meta-analyses of these which compare a more versus a less aggressive blood pressure–lowering strategy, in particular, when achieved blood pressure levels in the treatment group are well below the commonly recommended targets, would ultimately clarify to which extent SBP and DBP can be lowered, whereas still maintaining a net clinical benefit (see separate article on evidence from randomized controlled trials).

Blood Pressure and Renal Disease

In the MRFIT cohort, a strong-graded association was observed between blood pressure and the risk of end-stage renal disease. Those with an SBP >210 mm Hg had a 22-fold risk for the development of end-stage renal disease relative to those with a SBP <120 mm Hg.[22] DBP was a weaker predictor than SBP. When considered together in a proportional hazards model, adjusted for covariates, the relative risk (RR) for a 20 mm Hg higher SBP was 2.1 (CI, 1.9–2.2) versus 1.5 for DBP (CI, 1.4–1.5).[22] An analysis of 11 000 black male veterans, followed up for a minimum of 14 years, also concluded that both DBP and SBP were associated with risk of end-stage renal disease. Specifically, a SBP >150 mm Hg after treatment was associated with a 3-fold risk of development of end-stage renal disease relative to those with an SBP <126 mm Hg.[23] A larger cohort analysis of 300 000 Kaiser Permanente members also observed a graded and continuous relationship between baseline SBP and risk of end-stage renal disease, adjusted for other covariates. A SBP >210 mm Hg was associated with a 4.25 (CI, 2.63–6.86) associated RR of renal disease. Subjects with possible kidney disease at baseline, identified on the basis of elevated serum creatinine measurement, were removed from the cohort.[24] In the APCSC, blood pressure was a major risk factor for renal death, with a 1 SD increase in SBP (19 mm Hg) associated with an 84% increase in mortality (HR, 1.84; CI, 1.60–2.12).[25] There is, therefore, compelling evidence that elevated blood pressure is a strong independent risk factor for renal disease.

Predictive Power of SBP, DBP, and Pulse Pressure

Epidemiological evidence began to accumulate in the 1980s that SBP was a stronger predictor of cardiovascular risk than DBP. In one of the first reports, an analysis of the MRFIT cohort indicated that SBP was more closely predictive of all-cause mortality and CHD events than DBP (RR of 1.27 and 1.39 per 1 SD change of SBP versus RR of 1.21 and 1.34 per 1 SD change in DBP, respectively).[11] In the PSC, the blood pressure measurement with the greatest predictive power was mid–blood pressure (mean of SBP and DBP). However, SBP had greater predictive power than DBP, with 93% of the predictive power of mid–blood pressure for IHD mortality, compared with 73% for DBP.[12] For stroke mortality, SBP was also found to have higher predictive power than DBP, although this difference was smaller than that for IHD mortality (predictive power of 89% for SBP, 83% for DBP compared with mid–blood pressure). On the contrary, although an analysis of 5200 individuals in the Framingham cohort similarly indicated SBP to be a greater predictor of cardiovascular risk than

DBP, no benefit was seen for the use of mid–blood pressure than SBP alone.[26]

In the PSC, pulse pressure (defined as SBP minus DBP) was found to have a relatively low predictive power, specifically 43% of the predictive power that mid–blood pressure had for IHD mortality.[12] When DBP and SBPs were introduced into the same model, DBP was positively related to vascular mortality at a given SBP. This contrasts with analysis of the Framingham cohort, which indicated that for a given SBP, increased pulse pressure (ie, lower DBP) was associated with increased cardiovascular risk.[27] Examination of the association of blood pressure with cardiovascular mortality within a 19 000 French male cohort also indicated that pulse pressure was associated with mortality independently of mean arterial pressure.[28] In the recent CALIBER report, pulse pressure was found to be positively related to stable angina, unstable angina, myocardial infarction, heart failure but negatively related to abdominal aortic aneurysm.[13] In APCSC, pulse pressure was similarly positively related to fatal stroke and IHD events.[29] However, neither the CALIBER nor the APCSC analyses controlled for SBP when determining the relationship between pulse pressure and cardiovascular risk.

With regard to the direction of the association between SBP and DBPs (when combined) and cardiovascular risk, one possible explanation for the divergent findings of PSC and individual cohort studies is that the age distribution of participants varies between studies. In the Framingham cohort, a linear increase in SBP was observed for participants from an age of 30 to 84 years. However, after an age of 50 to 60 years, DBP declined and pulse pressure rose steeply, providence evidence of changes in BP hemodynamics through the aging process.[30] Analysis of the MRFIT cohort indicated that for men aged 45 to 57 years, increased pulse pressure at a given SBP was associated with an increased risk of cardiovascular mortality. However, for men aged 35 to 45 years, decreased pulse pressure at a given SBP (ie, an increased DBP) was associated with an increased risk of cardiovascular mortality.[31] These results and similar results from Framingham[32] suggest that increased pulse pressure may be associated with increased cardiovascular risk in older but not in younger populations, perhaps, as a marker of arterial stiffness in populations with isolated systolic hypertension.[32]

There is also evidence that the relative strength of SBP and DBPs as a prognostic factor of cardiovascular disease varies by age. In Framingham, there was a gradual reduction in the strength of DBP as a predictor for CHD with increasing age, and an increase in the predictive power of SBP and pulse pressures.[32] Although this analysis claimed that DBP was a stronger predictor of CHD risk than SBP below the age of 50 years, coefficients were standardized per 10 mm Hg for both the SBP and the DBPs rather than per SD, preventing reliable analysis of this claim. In PSC, the greater predictive power of SBP relative to DBP for IHD mortality did not differ significantly by age group, from the age of 40 to 89 years, a discrepancy attributed to the greater power of PSC relative to Framingham. Thus, although there is strong evidence that SBP is the best predictor out of SBP, DBP, and pulse pressure, and some evidence to suggest that the association between pulse pressure and vascular mortality varies with age, it is unclear whether the strength of the association between SBP and DBPs and vascular mortality differs by population, age or cardiovascular outcome.

Other Measurements of Blood Pressure

Single blood pressure readings, measured in office by a clinician, had poor reproducibility. This is due both to error variance (resulting from imperfect blood pressure measurement) and true variance (resulting from real changes in blood pressure from one occasion to another). Consequently, several other approaches to the measurement of blood pressure have been devised in an effort to better determine the cardiovascular risk of an individual patient, including ambulatory measurements, home blood pressure measurement, and blood pressure variability. Please refer to other articles in this compendium for an overview of these measurements.

Worldwide Burden of Elevated Blood Pressure

Quantifying the disease burden associated with elevated blood pressure, the benefits derived from blood pressure lowering and the geographic variation in the management of elevated blood pressure can help to identify strategies for improving disease control.[33,34] Globally, elevated blood pressure (defined as SBP greater than the minimum risk category of 110–115 mm Hg) is the leading risk factor for mortality and morbidity, accounting for 7% (CI, 6.2–7.7) of global disability adjusted life years and 9.4 (CI, 8.6–10.1) million deaths in 2010.[33] The burden of elevated blood pressure is concentrated in older populations; 20% of all DALYs (disability adjusted life year) lost in individuals >70 years and 15% of those lost in individuals aged 50 to 69 years are because of elevated blood pressure. Global age-standardized blood pressure has decreased during the past 30 years, declining by 1 mm Hg each decade from 1980 to 2008.[35] However, the number of individuals with uncontrolled hypertension (defined as SBP≥140 mm Hg or DBP≥90 mm Hg) increased from 605 to 978 million because of population growth and aging.[35] As a result, high blood pressure (SBP>110–115 mm Hg) increased from the fourth ranked risk factor for burden of disease in 1990 to the leading risk factor in 2010.[33]

Significant regional heterogeneity underlies the global burden of disease posed by elevated blood pressure. The Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborative Group estimated age-standardized SBP in 199 countries using Bayesian hierarchical models and showed wide variations in blood pressure levels globally.[35] Age-standardized SBP among women was lowest in South Korea, with a mean SBP of 116.9 mm Hg.[35] Among women, the country with the highest age-standardized SBP was Sao Tome and Principe, with a blood pressure of 136.3 mm Hg. For men, the country with the lowest SBP was Papua New Guinea, with a mean pressure of 122.6 mm Hg, whereas the country with the highest was Niger, with a mean pressure of 139.4 mm Hg. Although East and Western African countries had the highest blood pressure for both men and women, the relative contribution of elevated blood pressure to disease is lower in these countries than in many high- and middle-income nations. This is largely because of the high burden of disease from other risk

factors, such as childhood underweight and household air pollution.[33] Overall, high blood pressure was the leading risk factor for disease in most of Asia, most of Latin America, North Africa, the Middle East, and Central Europe.[33] Indeed, >80% of the attributable global burden of elevated blood pressure is in low- and middle-income countries (LMIC), with only 20% in high-income nations.[36]

Although the burden of elevated blood pressure is overwhelmingly experienced by LMICs, the relevant epidemiological, preventive, and therapeutic research has largely been conducted in high-income countries. This research has demonstrated that variation in the burden of elevated blood pressure within high-income nations is substantial. For example, in the United States, black men have a rate of hypertension (defined as SBP≥140 mm Hg or DBP≥90 mm Hg) of 43%, compared with 34% for white men, whereas black women have a rate of hypertension of 45%, compared with 31% for white women.[37] This may be because of differences in the uptake and use of antihypertensive therapy, as well as differences in environmental factors.[38] Blood pressure and blood pressure control are highly related to socioeconomic status, independent of race. In a cohort of 27 000 women without hypertension at study entry, socioeconomic status, classified by either education or income, was associated with an increased risk of development of hypertension (defined as SBP≥140 mm Hg or DBP≥90 mm Hg) after 2 years of follow-up. For education, the HR for the development of hypertension was 0.84 (CI, 0.78–0.91) for women with a doctorate versus women with <2 years of health profession education.[39] For income, the HR for women with a salary of >$100 000 was 0.89 (CI, 0.83–0.96) relative to a woman with <20 000. However, when both variables (education and income) were included in the same model, only education was significant. A systematic review of the relationship between socioeconomic status and blood pressure in high-income countries found a consistent inverse relation among included studies (ie, lower socioeconomic status was associated with a higher blood pressure). However, the absolute differences in SBP between the highest and lowest socioeconomic group were relatively small (2–3 mm Hg) in studies included in the systematic review.[40]

A health-related factor that accounts for a large portion of hypertension in developed countries is excess weight. In an analysis of the Framingham cohort, the risk of new onset hypertension was 1.5 for overweight men (BMI, 25–29.9 kg/m^2) and 2.2 for obese men (BMI>30 kg/m^2), 1.7 for overweight women and 2.6 for obese women, relative to normal weight individuals (BMI<25 kg/m^2).[41] In fact, the population attributable risk for new onset hypertension for excess weight (both overweight and obesity combined) was 26% in men and 28% in women. Different rates of obesity may also explain racial differences in hypertension. In an analysis of trends of obesity among US adults from 1999 to 2008, non-Hispanic black men were 1.1-fold (OR, 1.13; CI, 1.01–1.27) and non-Hispanic black women 2.3-fold (OR, 2.26; CI, 2.02–2.51) likely to be obese relative to non-Hispanic white men and women, respectively.[42] However, in an analysis of the National Health and Nutrition Examination Survey, non-Hispanic blacks were 90% more likely (OR, 1.88; CI, 1.53–2.32) to have poorly controlled BP (SBP≥140 mm Hg or DBP≥90 mm Hg), even after adjustment for BMI and other health-related factors. These results indicate that, although differences in obesity may contribute to differential rates of hypertension, they cannot solely explain existing racial differences in hypertension.

The comparatively limited research conducted in LMICs, indicates that average blood pressure levels and rates of hypertension vary substantially between and within countries. For example, rates of hypertension among adults in Sudan and in rural Cameroon are <10%, whereas in Mozambique and in Burkina Faso rates are >30% and 40%, respectively.[43] In the World Health Organization Study on Global Aging and Health (SAGE), rates of age-standardized hypertension (SBP≥140 mm Hg or DBP≥90 mm Hg) among adults >50 years old were similar in magnitude in 6 LMICs as those observed in high-income countries. The overall hypertension rate among LMICs was 53%, varying from 32% in India to 78% in South Africa.[44] However, although blood pressure measurements in SAGE were performed by trained observers using standardized devices, significant variation between observers' measurements may hinder reliable comparisons in hypertension rates between different countries.

Large variations in rates of hypertension can also be observed between rural and urban populations. In the Prospective Urban Rural Epidemiology (PURE) survey, 160 000 adults from 17 countries (high, middle, and low income) were enrolled in a study designed to examine the association of societal factors with chronic noncommunicable diseases.[45] The pooled prevalence of hypertension among the 4 high-income countries included in the study was 41%. The prevalence among LMICs varied from of 27% in Iran to 67% in Poland.[46] Within the high-income countries, prevalence of hypertension was higher in rural populations than in urban populations (40% versus 36%; P<0.001). This was also the case in upper-middle–income countries (45% in urban versus 47% in rural; P=0.003) and lower-middle–income countries (35% in urban versus 39% in rural; P<0.001). However, in low-income countries (LICs), rural populations had significantly lower rates of hypertension than urban populations (44% in urban versus 32% in rural; P<0.001). In addition, although men had significantly higher rates of hypertension than women in high-income countries (44% versus 32%; P<0.001, respectively), women had slightly higher rates of hypertension in LICs than men (39% for women versus 37% for men; P=0.003). These results highlight the differing burden of hypertension in LICs relative to that in high-income countries and demonstrate the importance of conducting epidemiological research in LICs.

Worldwide Management of Hypertension

For several decades, there has been robust evidence from randomized trials of the benefits of blood pressure lowering. Moreover, many antihypertensive drugs are available generically, several at low price. Nevertheless, rates of awareness of hypertension remain low, with rates of adequate antihypertensive treatment and blood pressure control lower still (Table 2). In the Prospective Urban Rural Epidemiology study, rate of awareness among individuals with hypertension (defined as treatment with antihypertensive therapy or BP≥140/90 mm Hg), worldwide, was 47%. Although 41% of individuals with hypertension received antihypertensive therapy, only 13% of hypertensives

Table 2. Prevalence of Awareness, Treatment, and Control Among the Hypertensive Population (Self-Reported Hypertension With Treatment or BP ≥140/90 mm Hg) in Prospective Urban Rural Epidemiology Study

	No. (%) of Participants				
Income Level of Country	Overall	Aware	Treated	Controlled	Proportion With BP<140/90 mm Hg Among Those Receiving Treatment
HIC	6263	3070 (49.0)	2924 (46.7)	1189 (19.0)	1189 (40.7)
UMIC	18 123	9516 (52.5)	8761 (48.3)	2833 (15.6)	2833 (32.3)
LMIC	23 269	10 134 (43.6)	8595 (36.9)	2314 (9.9)	2314 (26.9)
LIC	10 185	4157 (40.8)	3230 (31.7)	1298 (12.7)	1298 (40.2)
All included countries	57 840	26 877 (46.5)	23 510 (40.6)	7634 (13.2)	7634 (32.5)

BP indicates blood pressure; HIC, high income country; LIC, low-income countries; LMIC, low- and middle-income countries; and UMIC, upper middle income country.

Data derived from Chow et al.[46]

achieve blood pressure control to levels <140/90 mm Hg.[46] Thus, although a large majority (87%) of individuals who were aware of hypertension also received antihypertensive therapy, only a minority of individuals (32%) receiving antihypertensive therapy had their BP controlled <140/90 mm Hg.

However, these global results mask significant variation in hypertension management at the country level and variation in management within countries. Although ≈47% of individuals with hypertension in high-income countries were treated, only 32% of hypertensives in LICs countries were treated. Similarly, 19% of hypertensives in high-income countries had their blood pressure controlled to a level <140/90 mm Hg, whereas only 13% of hypertensives in LICs achieved this. In a substudy of PURE, 7519 participants with either a previous CHD event or stroke were surveyed for use of cardiovascular event-preventing drugs (β-blockers, statins, antiplatelet therapy, or blood pressure–lowering drugs). Seventy-four percentage of participants in high-income countries were taking antihypertensive therapy for the secondary prevention of cardiovascular disease. This contrasts with 48% in upper-middle–income countries, 37% in lower-middle–income countries, and 19% in LICs (Figure 3).[47] Similarly, in the SAGE study, rates of effective blood pressure control among hypertensive individuals in LICs were low, ranging from 4% in Ghana to 14% in India.[44] Thus, there is a significant shortfall in the use of antihypertensive therapy worldwide, and a large gap in the rate of uptake between high- and low-income nations.

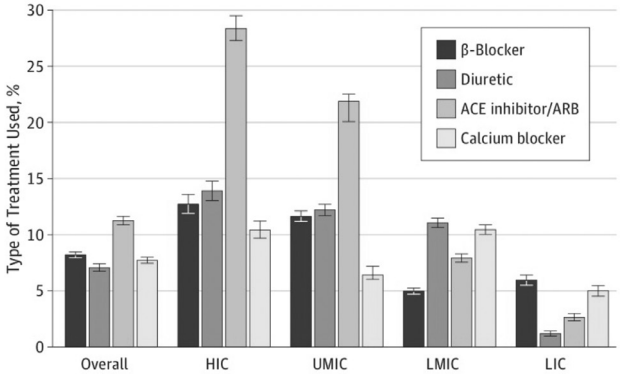

Figure 3. Types of treatments used for hypertension in countries overall and by income status. Percentage of treatment used refers to the proportion of participants with hypertension (on treatment or blood pressure [BP] ≥140/90 mm Hg) using a given blood pressure–lowering treatment. ACE indicates angiotensin-converting enzyme; LIC, low-income countries; and LMIC, low- and middle-income countries. Adapted from Chow et al[46] with permission of the publisher. Copyright ©2013, the American Medical Association. All rights reserved. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

The usage rates for drugs known to be effective are also highly variable within high-income countries and are on average low. In the United States, antihypertensive therapy usage among those with elevated blood pressure increased from 64% in 2001 to 77% in 2009. Usage of multiple combinations of antihypertensive agents, often needed for successful blood pressure control, also increased from 37% to 48%.[48] However, even with this improvement, 23% of hypertensive individuals in the United States are not taking any blood pressure–lowering drugs. In addition, only 47% of hypertensive individuals overall and 60% of treated hypertensive individuals had their blood pressure controlled (defined as a SBP<140 mm Hg).[48] In an analysis of 5 cross-sectional Health Surveys for England, conducted between 1994 and 2011, mean SBP among treated hypertensives has progressively improved from 150 mm Hg (SE of 0.59 mm Hg) in 1994 to 135.4 mm Hg (SE of 0.58 mm Hg) in 2011. However, this apparent improvement may reflect changes in the initial blood pressure of treated hypertensives, as individuals with mild hypertension (140–150 mm Hg) are more likely to be treated under current guidelines. In addition, only 37% of hypertensives had their blood pressure controlled to <140/90 mm Hg in 2011.[49]

One significant cause of poor hypertension management in developed countries and consequent increases in cardiovascular risk is a lack of adherence to therapy. In an analysis of 400 Italian primary care centers with 19 000 patients, only 8.1% of patients were classified as having high adherence to therapy (days with antihypertensive medication available ≥80%). Those with high adherence had a HR of 0.62 (CI, 0.40–0.96) for acute cardiovascular events relative to those with low adherence.[50] Similarly, in an analysis of national Finnish

registers, patients nonadherent to antihypertensive medication had 3× the odds of fatal stroke (OR, 3.01; CI, 2.37–3.83) compared with patients who were adherent to medication.[51] This evidence that nonadherence to antihypertensive medication is associated with increased cardiovascular risk is unsurprising considering the continuous relationship between usual blood pressure and cardiovascular events. In a multivariable analysis of the National Health and Nutrition Examination Surveys, nonpersistence of antihypertensive therapy after prescription of medication was associated with a younger age (OR, 2.61; CI, 1.69–4.02 for age group of 30–39 versus ≥50 years), Hispanic race (OR, 1.43; CI, 1.05–1.94 versus non-Hispanic), family income <$55 000 per year (OR, 1.96; CI, 1.35–2.83), no health insurance (OR, 1.88; CI, 1.24–2.83), and no medical visits in the past year (OR, 10.36; CI, 6.59–16.29),[52] suggesting potential characteristics to stratify patients by risk of nonadherence. However, considering evidence that as much as half of patients prescribed antihypertensive therapy in developed countries stop within a year,[53] broader approaches to improve adherence than the targeting of individual patients are needed.

Socioeconomic disparities in hypertension management are also common in developed and developing countries. In an analysis of randomly sampled black and white individuals in the United States, awareness of hypertension was significantly higher in black hypertensives than in white hypertensives (93% versus 89%; $P<0.0001$). In addition, treatment of hypertension was significantly higher among blacks than whites (91% versus 87%; $P<0.0001$). However, adequate control was significantly higher among whites than blacks (70% versus 62%; $P<0.0001$).[54] In LICs, a large divide exists between use of antihypertensive therapy in rural and in urban populations. In LICs, 36% of urban hypertensive individuals received antihypertensive therapy, whereas only 20% rural hypertensives received therapy.[46] Similarly, although 13% of urban hypertensives in LICs had their blood pressure controlled <140/90 mm Hg, only 7% of rural hypertensives had their blood pressure successfully controlled.

Although the provision of blood pressure–lowering drugs has typically been guided by the presence of hypertension, recent analyses have suggested that blood pressure–lowering treatment should preferably be guided by absolute cardiovascular risk, as is recommended for lipid-lowering therapy.[55] In a recent analysis from the Blood Pressure Lowering Treatment Trialists' Collaboration, patients were stratified into 4 cardiovascular risk categories. Blood pressure lowering resulted in a similar RR reduction of ≈15% in all 4 risk strata. However, although treatment of 1000 patients in each group for 5 years would prevent 14 cardiovascular events in the lowest risk category, treatment would prevent 38 cardiovascular events in the highest risk category, demonstrating that greater absolute benefits from blood pressure lowering can be observed in individuals at higher absolute risk.[56] Similarly, a simulation study of the American population found that benefit-based antihypertensive treatment (treatment based on absolute cardiovascular risk reduction) would prevent 900 000 more cardiovascular events than traditional target-based treatment >5 years.[57] There is thus growing evidence that blood pressure management should be guided by absolute risk rather than by levels of a single risk factor such as blood pressure. However, it is unclear how concordant current provision of blood pressure–lowering therapy is with a hypothetical absolute risk-based strategy on a global or regional level. Global surveys of cardiovascular risk management, such as PURE[46] and SAGE,[44] as well as regional analyses, such as the Health Surveys for England,[49] have largely examined usage of blood pressure–lowering therapy among individuals stratified by baseline blood pressure level, rather than cardiovascular risk. Future research is needed to examine how blood pressure therapy is provided to individuals of different cardiovascular risk strata, regionally and globally.

In combination, these results indicate that, globally, there remain major shortfalls in awareness of hypertension, uptake of hypertensive therapy, and blood pressure control. Increased awareness of hypertension does not necessarily imply increased uptake of antihypertensive therapy, whereas increased uptake of antihypertensive therapy does not imply increased blood pressure control. Research to identify the causes of these variations in hypertension management in both high-income countries and LICs could inform strategies to improve the care of patients with hypertension.

Conclusions

Since the initial recognition more than a century ago that elevated blood pressure is associated with a higher risk of mortality, the epidemiology of blood pressure has progressed substantially. It is now recognized that high blood pressure is a significant risk factor for a variety of cardiovascular and renal events (fatal and nonfatal), including myocardial infarction, stroke, atherosclerosis, aortic aneurysm, hypertensive heart disease, heart failure, peripheral artery disease, and end-stage renal disease. When considering the host of vascular diseases that elevated blood pressure is linked to, it is unsurprising that blood pressure (SBP>110–115 mm Hg) is now the leading determinant of morbidity and mortality worldwide, responsible for an even greater burden of disease than that conferred by smoking.[33]

Because of the continuous relationship between blood pressure and disease risk, a large component of the burden associated with nonoptimal blood pressure occurs among high-risk individuals who would not usually be classified hypertensive and, therefore, not considered for antihypertensive treatment. So strategies that focus on the treatment of hypertension alone will leave a large part of the burden unchecked. Although factors, such as obesity, high-salt intake, and physical inactivity are strongly implicated in the age-related rise on blood pressure, few interventions have been proven to produce prolonged reductions in either factor across a range of populations and social circumstances. So, until these interventions are developed, the only tool available to reduce the burden of blood pressure–related disease is antihypertensive therapy.

Although antihypertensive drugs are effective, and now inexpensive for most populations in the world, their use is far short of ideal. New measures of blood pressure may potentially allow for more accurate prediction of cardiovascular risk so that antihypertensive therapies are offered to those who are likely to have the greatest net benefit from it. However, understanding risks and benefits for groups and individuals will not

be sufficient to close the gap between evidence and practice. New models of care delivery, based on estimation of risks and benefits, are needed to overcome the challenge of cardiovascular risk management in the 21st century.[34]

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Disclosures

None.

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