The Burden of Blood Pressure-Related Disease
A Neglected Priority for Global Health

Vlado Perkovic, Rachel Huxley, Yangfeng Wu, Dorairaj Prabhakaran, Stephen MacMahon

The importance of high blood pressure as a major cause of common serious diseases has been recognized in most Western countries for ≈50 years. Before that, malignant hypertension was a frequent reason for hospital admission and a common cause of death.1 Safe and effective antihypertensive drugs were first developed in the 1960s and were shown to dramatically improve the prognosis associated with malignant hypertension.2,3 Over the next few decades, the widespread use of an expanding armamentarium of blood pressure–lowering drugs to patients at risk of malignant hypertension effectively eradicated this condition from most developed countries. Subsequently, the provision of blood pressure–lowering treatments to a much broader group of patients at risk of serious cardiovascular diseases, such as stroke and coronary heart disease, among whom blood pressure levels were often only modestly elevated, contributed importantly to the declines in stroke and coronary disease deaths rates experienced by most Western populations.4 However, the situation in higher-income countries stands in stark contrast to that experienced by their lower-income neighbors. The overall burden of blood pressure–related diseases is rapidly rising in countries such as India and China as a consequence of the aging population, increasing urbanization, and increases in age-specific rates of conditions such as stroke.5,6 Even war-torn countries and those ravaged by HIV/AIDS, such as some in sub-Saharan Africa, incur a huge burden of blood pressure–related diseases. In several such populations, cerebral hemorrhage is the leading cause of death in adults.7 Although safe and effective antihypertensive treatment could be provided in these regions with a range of generic products from <1 cent per person per day, the reality is that most people for whom such drugs are clearly indicated receive no treatment whatsoever. In this regard, the antihypertensive care available for a large proportion of the world’s population remains much as it was in the 1950s before the development of diuretics and β-blockers. In this review, we describe the global burden of blood pressure–related diseases, discuss some of the barriers to the implementation of effective preventive programs, and consider practical solutions that could be implemented in resource-poor settings.

Prevalence of High Blood Pressure in Higher- and Lower-Income Regions
There is now compelling evidence that the level of systolic blood pressure at which the risks of stroke and coronary heart disease begin to increase is ≈115 mm Hg.8–10 On this basis, the majority of adults in most higher- and lower-income populations have nonoptimal blood pressure.11,12 However, there are important regional variations in blood pressure distributions, even taking into account potential differences in the technique of blood pressure measurement. For example, in both sexes, for all ages >45 years, average blood pressure levels are highest in populations from Eastern Europe and Russia. Average levels are also particularly high in the Middle East, North Africa, and parts of sub-Sahara Africa.12 Classifications of hypertension vary, but on the basis of a single blood pressure measurement >140 mm Hg systolic or 90 mm Hg diastolic, ≈1 in 4 adults, worldwide, would be so classified (Table 1).13 Currently, this equates to ≈1 billion individuals, and this number is expected to grow to >1.5 billion (≈30% of the global population) by 2025, solely as a consequence of increases in both total population size and the proportions within populations reaching older ages. In higher-income regions, the number of hypertensive individuals is predicted to grow by 70 million people from 2000 to 2025, whereas in lower-income regions, the number is predicted to grow by >500 million over the same period. In China and India alone, the total number with a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg is expected to increase to >500 million by 2025.

Although demographic changes in populations will have the greatest short-term consequences for changes in population blood pressure distributions and hypertension prevalence, other factors are likely to augment these changes. In particular, progress in economic development, with consequent increases in obesity because of greater food availability and choice, and a reduction in physical activity can be expected to further increase mean blood pressure levels and
the proportion with high blood pressure in lower income regions such as China and India.14–16

Effects of Blood Pressure on Disease Burden in Higher- and Lower-Income Regions

Large-scale epidemiological studies have clearly demonstrated the enormous impact of nonoptimal blood pressure levels on the risks of major cardiovascular events in both higher- and lower-income regions.8,9,17 The Asia Pacific Cohort Studies Collaboration, which involved >500,000 individuals followed for several years on average, has demonstrated direct continuous associations of usual levels of systolic and diastolic blood pressure with the risks of coronary heart disease and stroke in both white and Asian populations.9,18 Overall, the association of blood pressure with stroke risk was about twice as steep as that with coronary disease risk, and whereas the association with coronary risk was identical in the Asian and white populations, the association with stroke risk was steeper among Asians (Figure 1). This appeared, in part, to be the consequence of the greater proportion of strokes that were hemorrhagic in the Asian population and the steeper association of blood pressure with hemorrhagic rather than ischemic stroke. There was also evidence of a steeper association of blood pressure with hemorrhagic stroke among Asians compared with whites.10

Table 1. Estimated Number of Individuals Aged ≥20 Years With Blood Pressure >140/90 mm Hg in 2000 and Predicted Number of Affected Individuals in 2025

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence 2000, Millions</th>
<th>Predicted Prevalence 2025, Millions</th>
<th>Increase, Millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established market economies</td>
<td>239.5</td>
<td>309.7</td>
<td>70.2</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>114.3</td>
<td>200.6</td>
<td>86.3</td>
</tr>
<tr>
<td>Former socialist economies</td>
<td>93.1</td>
<td>103.7</td>
<td>10.6</td>
</tr>
<tr>
<td>Middle East crescent</td>
<td>73.8</td>
<td>152.6</td>
<td>78.8</td>
</tr>
<tr>
<td>China</td>
<td>181.6</td>
<td>299.2</td>
<td>117.6</td>
</tr>
<tr>
<td>India</td>
<td>118.2</td>
<td>213.5</td>
<td>95.3</td>
</tr>
<tr>
<td>Other Asia and islands</td>
<td>71.4</td>
<td>129.4</td>
<td>58.0</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>79.8</td>
<td>150.7</td>
<td>70.9</td>
</tr>
<tr>
<td>Total</td>
<td>971.7</td>
<td>1559.4</td>
<td>587.7</td>
</tr>
</tbody>
</table>

Adapted from Kearney et al13 with permission from Elsevier.

Figure 1. The higher risk of (A) fatal and nonfatal coronary heart disease and (B) stroke, associated with higher systolic blood pressure (SBP) levels by age and region in the Asia Pacific Cohort Studies Collaboration.
There is little direct evidence about the effects of blood pressure on cardiovascular disease risks in other lower-income regions outside of Asia. However, on the basis of regional evidence about blood pressure distributions and the burden of death and disability from cardiovascular disease, the contribution of blood pressure to total cardiovascular disease burden can be estimated for all regions of the world. Those analyses showed that approximately two thirds of all stroke and half of all coronary disease can be attributed to nonoptimal blood pressure. This represents millions of deaths and 64 million disability-adjusted life years each year. Lower-income countries suffered approximately two thirds of the total burden of blood pressure–related disease. The 2 countries experiencing the greatest burden of blood pressure–related diseases were India and China. However, whereas stroke was the most common type of blood pressure–related disease in China, coronary disease was more common in India. Compared with higher-income regions, these and other lower-income regions had a greater proportion of blood pressure–related disease occur among people of middle age. In the poorest regions, including many in Africa, most blood pressure–related disease occurred among individuals aged 40 to 59 years.

The relationship between blood pressure levels and noncardiovascular diseases risk has been less well defined, although similar relationships between blood pressure levels and the risk of end-stage kidney disease have been described in large studies of white and Asian populations. Given the very large increases in diabetes (and the inevitable attendant increases in diabetic kidney disease) being experienced across the developing world, it is likely that nonoptimal blood pressure will be responsible for a large proportion of the resulting disease burden.

Effects of Blood Pressure Lowering on Disease Risks in Higher- and Lower-Income Regions

The effects of blood pressure lowering with a range of drug therapies have been demonstrated in a large series of clinical trials. Evidence from these trials has been synthesized by the Blood Pressure Lowering Treatment Trialists’ Collaboration and others, demonstrating that the magnitude of the blood pressure reduction achieved is a more important predictor of the cardiovascular benefits obtained than the choice of drug. In a wide variety of patient populations, blood pressure lowering reduced the risk of coronary heart disease and stroke by roughly the magnitude predicted from the observational evidence about the association of blood pressure with cause-specific cardiovascular events. In general, a 10-mm Hg reduction in systolic blood pressure produced approximately a 20% to 25% reduction in major cardiovascular events, with larger effects on stroke than coronary outcomes.

There was some evidence of relatively minor differences between drug classes in their effects on some cause-specific outcomes. For example, for any given blood pressure reduction, there appeared to be an ~10% greater reduction in coronary heart disease risk with angiotensin-converting enzyme inhibitor treatment than with other therapy. However, overall the net effects on total cardiovascular disease risk of all of the common drug classes were broadly equivalent. Indeed, treatment based on a diuretic, one of the least expensive drug classes, produced as much reduction in overall risk as did treatment based on any of the other more expensive drug classes. Because diuretics are available for as little as a few cents per week, they provide the most affordable basis for antihypertensive therapy in resource-poor settings.

Most trials have been conducted in higher-income countries, and few have recruited enough patients from lower-income regions to provide reliable evidence about the effects of treatment in resource-poor settings. However, 2 studies have recruited large numbers of patients from Asia, in particular, China, as well as Western countries. In the Perindopril Protection Against Recurrent Stroke Study Trial of blood pressure lowering among patients with a history of cerebrovascular disease, participants recruited from Asian countries derived at least an equivalent benefit from the study therapy as did participants from Western countries (Figure 2). Similarly, in the Action in Diabetes and Vascular Disease Trial of blood pressure lowering among patients with type 2 diabetes, the effects of treatment were the same among participants recruited from Asia and those recruited from elsewhere. A few trials have been conducted exclusively in Asian populations (eg, the Felodipine Event Reduction Trial), and these studies have generally reported benefits that are similar to those typically observed in studies conducted in Western populations.

Although some higher-income countries may have the resources required to provide blood pressure–lowering treatment to most or all of those with hypertension, this is not affordable or practical for most lower-income countries. For example, for India or China to provide treatment for all of those with hypertension would require each of these countries to deliver such care to a population of ~200 million. For such countries, it is essential that treatment policy targets those most in need, for whom benefits will be greatest and costs easiest to justify. One approach that has been widely promulgated by the World Health Organization and European guidelines is to base treatment policies on estimated absolute disease risk rather than on blood pressure levels alone. If the target for blood pressure–lowering therapy was a 25% 10-year risk of a major cardiovascular event, then this

<table>
<thead>
<tr>
<th></th>
<th>Strokes</th>
<th>Placebo</th>
<th>Favors active</th>
<th>Favors placebo</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>116</td>
<td>182</td>
<td>39% (22,52)</td>
<td>22% (5,35)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>307</td>
<td>420</td>
<td>28% (17,38)</td>
<td></td>
<td></td>
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</tbody>
</table>
would imply the provision of treatment to ≈50 million people in of each China and India and ≈20 million people in each of Africa and South America (Figure 3). Such a treatment strategy has been assessed as being cost-effective for many lower-income regions.34 However, for some of the poorest countries, blood pressure–lowering treatment may need to be restricted to even higher-risk individuals, perhaps only those who have moderate-to-severe hypertension or a history of significant cardiovascular or renal disease.

Barriers to the Prevention of Blood Pressure–Related Diseases in Lower-Income Regions

Drug Costs
There are many barriers to the provision of appropriate blood pressure–lowering therapy in resource-poor settings, but drug costs should not be one of them. For example, the diuretic hydrochlorothiazide can be purchased internationally for ≈0.3 cents per 25-mg tablet, the β-blocker atenolol for ≈1 cent per 100-mg tablet, and the angiotensin-converting enzyme inhibitor enalapril for 2 to 3 cents per 20-mg tablet (Table 2). On this basis, 1 year’s supply of hydrochlorothia-

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Example Agent, Dose, mg</th>
<th>Median Supplier Price, US Cents per Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blocker</td>
<td>Atenolol, 50</td>
<td>1.1</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>Nifedipine sustained release, 20</td>
<td>1.9</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Hydrochlorothiazide, 25</td>
<td>0.3</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>Enalapril, 20</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Data are from McFadyen,35 ACE indicates angiotensin-converting enzyme.

Figure 3. Total number of individuals (in millions) with an estimated 10-year risk of cardiovascular disease of ≥25% according to World Health Organization region. AFR indicates Africa; AMR, the Americas; EMR, Eastern Mediterranean; EUR, Europe; SEAR, Southeast Asia; WPR, Western Pacific Region; A, very low child mortality and very low adult mortality; B, low child mortality and low adult mortality; C, low child mortality and high adult mor-
tality; D, high child mortality and high adult mortality; E, high child mortality and very high adult mortality. Developed by Dr A. Rodgers from data collected for Ezzati et al.19

America. Assuming that such treatment reduced the 10-year risk of a major cardiovascular event from 25% to 20%, the drug costs for the prevention of each fatal or serious event would be approximately $200. Such costs are within the financial capacity of all but the very poorest countries. However, as experience in sub-Saharan Africa has shown with respect to donated or heavily subsidized antiretroviral drugs, the absence of functional primary health care services in many countries means that even a free or inexpensive drug cannot be reliably provided to those in need.36 In addition, whereas the cost of some generic drugs from wholesalers may be low, the price at which the same drug is provided to a patient is often grossly inflated. Moreover, there are often financial incentives for healthcare providers to selectively prescribe more expensive drugs despite there being no clear advantage over cheaper drugs, such as diuretics.

Structural Barriers
The prevention of blood pressure–related diseases requires a primary health care system that can identify those at high risk, ensure regular monitoring of their health status, and provide an uninterrupted appropriate and affordable treatment supply. Each of these poses its own unique challenges in many lower-income regions. With respect to identifying those at high risk, algorithms developed for Western populations typically require laboratory blood tests for total, low-density lipoprotein, and high-density lipoprotein cholesterol and fast-
ing blood glucose.37 In many resource-poor settings, labora-
tory access can be difficult and expensive. In regions in which HIV and hepatitis B infection are common, there may also be professional and community concerns about screening programs that involve phlebotomy. Therefore, screening algo-
rithms are required that take special account of these factors. For example, a screening algorithm that includes gender, age, cardiovascular disease history, blood pressure, weight and height, and a urine dipstick test for glucose and protein is likely to be more practical and may well provide much of the predictive value of more complex blood-based assessments.32 In addition, such algorithms should, wherever possible, use regional data on morbidity and mortality, because back-
ground rates vary considerably between regions.38 Although
there are few data available about the proportion of high-risk individuals who are aware of their status, there are more data available about the proportion aware of having high blood pressure. For example, in lower-income regions such as India, only a minority of all those with high blood pressure are aware of their condition (Table 3).\(^{39-43}\) Improving the identification of individuals at high risk of blood pressure–related diseases will require educational programs aimed at both healthcare providers and consumers. The provision of provider incentives for screening and risk assessment is likely to be an important determinant of success.

The capacity to provide long-term monitoring of those at high risk is an essential criterion for the effective prevention of blood pressure–related diseases. In many situations, primary healthcare services have provided only episodic care with little record kept of previous visits.\(^{44}\) In part, this reflects the priority given to the management of acute conditions, such as infections, trauma, and childbirth, over chronic conditions that require treatment over many years. It is now clear that primary healthcare services in resource-poor settings must be adapted to provide long-term care, not only for communicable diseases but also for the management of HIV infection with long-term antiretroviral therapy.\(^{44}\) Central to this is an improvement in the quality of medical charts, which are required for continuity of care. Once again, provider incentives are likely to be helpful in achieving acceptable levels of monitoring and follow-up.

Continuity of care also requires access to an uninterrupted and affordable drug supply. In many situations, neither is available. Drug distribution chains in many rural regions can be unreliable, to the degree that even hospitals can often be without blood pressure–lowering drugs for the treatment of hypertensive emergencies. In other regions, drug distribution chains are more reliable, but the involvement of several distributors can inflate costs significantly. Finally, in many lower-income countries, there is no separation between prescription and supply to avoid drug selection being affected by financial rewards to the prescriber. In these circumstances, practical guidelines designed specifically for use in resource-poor settings are required in place of the complex and largely impractical international guidelines developed primarily with higher-income countries in mind. Guidelines for lower-income regions should be developed with due regard to the important role played by nonphysician health workers, who provide a large proportion of primary healthcare services in countries such as China. Again, incentives to reward the prescription of guideline-based blood pressure–lowering therapy are likely to be helpful.

### Policy Barriers

In many countries there are policy barriers to the implementation of blood pressure–lowering treatment programs. Most common is the restrictive focus of prevention programs on infectious disease and sometimes on HIV/AIDS alone. Many lower-income countries face a double burden of communicable and noncommunicable disease, yet few allocate resources to demands on the basis of cost-effectiveness or even disease burden. Multilateral organizations, such as the World Health Organization and the World Bank, have been partly responsible for this unbalanced approach through the setting of Millennium Development Goals\(^{45}\) that excluded any mention of chronic disease prevention and through the setting of implausibly high targets for antiretroviral therapy implementation.\(^{46}\) Notably, the failure to achieve these targets\(^{47}\) at least in part reflected the failure to deploy effective strategies to create the primary healthcare networks required to deliver any form of chronic care.

Fortunately, in recent years both World Health Organization\(^{48}\) and the World Bank\(^{49}\) have recognized the importance of chronic diseases, including blood pressure–related diseases, as a cause not only of premature death and disability but also as a threat to social and economic development. This may herald the beginning of a rebalancing of investment priorities for health care in at least some lower-income countries. However, the prioritization of blood pressure control as a strategy to improve health status will require evidence that worthwhile benefits can be achieved at a price that is affordable. This requires a markedly different approach to that adopted in higher-income countries in which treatment programs are primarily physician centered and often use expensive diagnostic procedures (eg, 24-hour blood pressure measurement or echocardiography) and on-patent drugs. As indicated above, lower-income regions require approaches that can be implemented by nonphysician healthcare workers using simple assessment tools and low-cost drugs. They also require a targeted focus on a select group of individuals at particularly high risk of cardiovascular or renal diseases. Goals that involve the identification and treatment of all of those who might be classified as hypertensive, irrespective of disease risk, are unrealistic and, as a consequence, counterproductive. Different strategies are probably required in urban and rural areas, but both require outreach programs to access disadvantaged population subgroups.

### Table 3. Prevalence, Awareness, and Treatment Status of Hypertension (≥140/90 mm Hg) in Studies Conducted Among Nonrepresentative Indian Subpopulations

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence, %</th>
<th>Awareness, % of Prevalent</th>
<th>Treatment, % of Prevalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddy et al, 2006(^{40})</td>
<td>27.7</td>
<td>37.3</td>
<td>30.3</td>
</tr>
<tr>
<td>Prabhakaran et al, 2005(^{41})</td>
<td>30.0</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>Deepa et al, 2003(^{42})</td>
<td>22.1</td>
<td>37.3</td>
<td>18.7</td>
</tr>
<tr>
<td>Hypertension Study Group, 2001(^{39})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>70</td>
<td>46.6</td>
<td>41.6</td>
</tr>
<tr>
<td>Rural</td>
<td>55</td>
<td>61.4</td>
<td>53.0</td>
</tr>
<tr>
<td>Gupta et al, 1995(^{43})</td>
<td>30.9</td>
<td>13.1</td>
<td>8.0</td>
</tr>
</tbody>
</table>
Research Relevant to the Prevention of Blood Pressure–Related Diseases in Lower-Income Regions

Strategies to reduce the burden of blood pressure–related diseases in lower-income countries requires research. Although most requirements are for operational research, there is still a need for research that will provide evidence about the effects of novel interventions for disease prevention that may be of special relevance to particular populations. Research into region-specific strategies targeting important determinants of blood pressure, such as salt intake or obesity, may yield useful information. However, the greatest current need is for operational research to determine how best to implement affordable drug-based preventive programs that have proven effective in reducing blood pressure–related diseases, such as stroke and coronary heart disease. Novel approaches are required, because the models developed for use in higher-income countries are neither affordable nor practical given current and foreseeable resource constraints.

One research strategy that may have particular merit is the conduct of cluster-randomized trials of new healthcare delivery strategies for the prevention of blood pressure–related diseases. This could involve the development of regionally tailored packages of interventions targeted to healthcare providers and designed to increase the identification of high-risk individuals and to improve their treatment according to evidence-based, resource-sensitive algorithms. Key components of such a package would need to include healthcare provider training, simple algorithms for screening, treatment and follow-up, and reliable drug supply. Intervention packages targeted to consumers could also be assessed. Components might include free or subsidized drugs, health education about blood pressure and cardiovascular disease, and community programs aimed at increasing self-referral for risk assessment. Although such research programs are challenging to implement and require significant resources, they are still likely to be much less expensive than the trial programs required for the development and registration of new antihypertensive drugs and of much greater potential benefit for the prevention of blood pressure–related diseases globally.

Perspectives

Nonoptimal blood pressure is the leading cause of death globally, responsible for 7 million deaths annually. Most of these deaths and most of the disability caused by blood pressure–related diseases are suffered by people in lower-income countries. The resulting burden threatens already fragile health systems, as well as social and economic development. Yet, very few people receive blood pressure–lowering therapy in many lower-income countries. The reasons for this are complex but largely involve the limitations of primary healthcare systems to deliver effective and affordable care. The solutions are also complex and will not be easily found in the approaches adopted by most higher-income countries given the costs involved. Specific solutions are required for different regional circumstances. These need to reflect competing disease burdens, financial resources, human resources, and cultural and societal values regarding the relative importance of strategies focused on disease prevention as opposed to treatment. Novel research strategies are required to identify the optimal path toward this goal.

Acknowledgment

We gratefully acknowledge the contribution of Associate Professor Bruce Neal to this work.

Sources of Funding

This work was supported in part by a program grant from the National Health and Medical Research Council of Australia. V.P. is a recipient of a National Heart Foundation of Australia Astra Zeneca Fellowship and a Royal Australasian College of Physicians Pfizer Cardiovascular Research Fellowship.

Disclosures

None.

References


