A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension


Executive summary

Elevated blood pressure is the strongest modifiable risk factor for cardiovascular disease worldwide. Despite extensive knowledge about ways to prevent as well as to treat hypertension, the global incidence and prevalence of hypertension and, more importantly, its cardiovascular complications are not reduced—partly because of inadequacies in prevention, diagnosis, and control of the disorder in an ageing world.

The aim of the Lancet Commission on hypertension is to identify key actions to improve the management of blood pressure both at the population and the individual level, and to generate a campaign to adopt the suggested actions at national levels to reduce the impact of elevated blood pressure globally. The first task of the Commission is this report, which briefly reviews the available evidence for prevention, identification, and treatment of elevated blood pressure, hypertension, and its cardiovascular complications. The report focuses on how as-yet unsolved issues might be tackled using approaches with population-wide impact and new methods for patient evaluation and education in the broadest sense (some of which are not always strictly evidence based) to manage blood pressure worldwide.

The report is built around the concept of lifetime risk applicable to the entire population from conception. Development of subclinical and sometimes clinical cardiovascular disease results from lifetime exposure to cardiovascular risk factors combined with the susceptibility of individuals to the harmful consequences of these risk factors. The Commission recognises the importance of other cardiovascular risk factors—eg, smoking, obesity, dyslipidaemia, and diabetes mellitus—on antihypertensive treatment. However, as a Commission on hypertension, this report focuses mainly on issues and actions related to elevated blood pressure.

Previous action plans for improving management of elevated blood pressure and hypertension have not yet provided adequate results. Therefore, the Commission has identified ten essential and achievable goals and ten accompanying, mutually additive, and synergistic key actions that—if implemented effectively and broadly—will make substantial contributions to the management of blood pressure globally. The Commission deliberately has not listed these complementary key actions by priority because the balance between strength of evidence, feasibility, and potential benefit could differ by country.

Introduction

Background

Elevated blood pressure is globally the strongest modifiable risk factor for cardiovascular disease and related disability. Its prevalence and downstream detrimental impact on health are increasing because of longer life expectancy and increased exposure to risk in the population. Despite extensive knowledge about ways to both prevent and treat hypertension, its global incidence, prevalence, and (more importantly) cardiovascular complications are not reduced, partly because of inadequacies in prevention, diagnosis, and control of the disorder in an ageing world.
### Figure 1: Key actions

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### Aim

The **Lancet Commission on hypertension** aims to identify key actions to improve management of blood pressure at both the population and the individual level (figure 1), and generate a campaign to adopt the suggested actions at national levels to reduce the effect of elevated blood pressure worldwide. The first step of the work of the **Lancet Commission on hypertension** consists of this report, which briefly reviews the current evidence for prevention, diagnosis, evaluation, and treatment of elevated blood pressure, hypertension, and its cardiovascular complications. The report focuses on unsolved issues, rethinking these in the context of approaches with population-wide impact and new techniques for patient evaluation and education in its broadest sense, thereby suggesting new ways to manage blood pressure globally. Because new techniques will be an important part of the suggested solutions, our proposals will not always have a strong evidence base, but will highlight where further research might be most beneficial. Therefore, the aim of the **Lancet Commission will not be to conduct an extensive review of hypertension or rewrite current guidelines on its management, but to create the momentum for improved management of elevated blood pressure.**

### Structure

The report is built around the concept of lifetime risk starting with the entire population from conception. Development of subclinical and sometimes clinical cardiovascular disease (figure 2) corresponds with lifetime exposure to cardiovascular risk factors combined with the susceptibility of individuals to the harmful consequences of these risk factors. During the course of life, intervention is possible at different stages (figure 3), with primordial (before any risk factor elevation), primary, or secondary prevention strategies, on an individual or population level, through environmental changes, lifestyle changes, pharmacological treatment, or a combination of these approaches. On the basis of available evidence and future potential, we suggest new strategies for programme-oriented, system-oriented, and research-oriented actions. The **Lancet Commission on hypertension** recognises the importance of other cardiovascular risk factors such as smoking, obesity, dyslipidaemia, and diabetes mellitus on cardiovascular risk, which are very important to take into account for initiation and goals of antihypertensive treatment. However, as a **Commission on hypertension**, this report focuses primarily on issues and actions related to elevated blood pressure. Nevertheless, many of the identified problems and suggested actions are relevant for these other risk factors as well.

Different types of research methodology are needed to guide action. The use of randomised controlled trials is feasible in high-risk populations in which studies of short duration and relatively small cohort size allow for the assessment of statistically relevant outcomes, but not in relatively healthy populations in which long duration and large sample sizes are needed to observe the outcomes of interest.

We list ten mutually additive and synergistic key actions directed towards ten identified essential goals, divided into four categories bridging public health, health-care systems, and clinical practice (figure 1). The Commission deliberately has not ordered these key actions by priority, because they are complementary and the balance between strength of evidence and potential benefit is yet to be determined and varies based on country context.
Definition of hypertension
Because the relationship between blood pressure and cardiovascular risk is a continuum throughout the commonly observed range, there is no biological rationale to define a threshold from which normal blood pressure turns into hypertension. The definition of hypertension as a disease entity is relevant mainly for the initiation or change of treatment. However, the prognostic benefit of blood pressure reduction is dependent on both the overall cardiovascular risk of the patient and perhaps also how the reduction is accomplished. Therefore, initiation of treatment is dictated by an individual’s risk profile and set of comorbidities (ie, assessed cardiovascular risk) and the level of blood pressure above which there is clear evidence that treatment will improve prognosis.

Therefore, the Commission defines individuals as having hypertension when they consistently cross the blood pressure threshold above which there is robust scientific evidence that antihypertensive treatment will improve their prognosis. Generally—particularly if the cardiovascular risk of the individual is unknown—this threshold will be the traditional cutoff values of 140 mm Hg systolic, 90 mm Hg diastolic, or both. However, in some groups of individuals, other values are possible. Specifically, growing evidence from antihypertensive trials suggests that many individuals at high risk or with particular comorbidities should have different hypertension thresholds, as in patients with type 2 diabetes.1 However, among individuals at low risk, the support for targets below 160 mm Hg systolic, 100 mm Hg diastolic, or both, are primarily based on epidemiological data, which cannot directly be translated into evidence for pharmacological treatment. Inherently, the threshold used to define hypertension is very likely to be a shifting point of reference driven by emerging evidence, whereas the thresholds for treatment initiation and goals are likely to shift even more due to differences in resource availability and individual preferences.

Independent of how hypertension is defined, the prevalence of hypertension is strongly influenced by two opposite directed factors. On the one hand, age-specific blood pressure levels in high-income (and increasingly middle-income) countries are falling beyond what can be explained by improved detection and treatment of hypertension, but might partly be accounted for by improvements in early-life health and nutrition.2,3 On the other hand, this positive effect is partly counteracted by the ageing of the population worldwide, leading to an increase in the prevalence of hypertension among low-income and middle-income countries.4 Because of the force of ageing, even a marginal additional effect on blood pressure trends will have very large health benefits globally, especially in low-income and middle-income countries.5

Lifecourse approach
Throughout this report, the Commission tackles prevention and treatment of elevated blood pressure with a lifecourse approach. The evidence underpinning this approach is based on the need to consider early lifetime programming, long-term benefits, and changing priorities with ageing.

A large body of evidence suggests that up to 80% of cardiovascular early vascular damage can be prevented through a healthy lifestyle (sufficient physical activity, avoidance of obesity, moderate alcohol intake, healthy diet, and no tobacco or drug use).6 This finding has been consistently replicated even when the definition of a healthy lifestyle is narrowed or expanded to use different components such as sufficient sleep duration.5 Importantly, this evidence is derived from epidemiological surveys that query an individual’s habitual behaviour (or attitude), and the observed benefits thus result from the cumulative effects of health behaviour over an individual’s lifetime, not a change in lifestyle. However, it is important to emphasise that lifestyle is heavily influenced by socioeconomic factors, and therefore healthy lifestyles are not always available to all individuals, communities, or populations.

The Commission finds it likely that exposure to cardiovascular risk factors in childhood or even during fetal life promotes the development of vascular changes that launch the individual more towards the trajectory of so-called early vascular ageing, in which an accumulation of (still subclinical) vascular damage occurs already in early adulthood. In the Young Finns Study, risk factor load (defined as extreme quintiles for LDL cholesterol, HDL cholesterol, systolic blood pressure, body-mass index [BMI], and smoking) at age 3–18 years predicted intima-media thickening, increased arterial pulse wave velocity,7 elevated blood pressure,4 and loss of carotid distensibility8 on re-examination 21 years later in early adulthood (age 24–39 years). In this same cohort, more...
Figure 3: Early life effects and impact of preventive efforts in the management of elevated blood pressure

The insert shows the effects of genetic susceptibility and epigenetic imprinting during fetal life. Preventive efforts result in downward shifts in the life course curve, with earlier preventive efforts affecting life course trajectory more than later preventive efforts. CV=cardiovascular. QOL=quality of life. BP=blood pressure.

In terms of genetic evidence, findings from several large-scale studies have clearly shown that the random allocation of blood-pressure-related genetic variants (single nucleotide polymorphisms) is associated with a difference in both blood pressure and cardiovascular outcome. Within the context of a life course approach, the effect of a genetic variant on blood pressure seems to increase with ageing, suggesting a life course effect of accelerated ageing. Although lifestyle changes typically induce rather small reductions in blood pressure, they affect the large low-risk population and can act over decades, having the potential to improve cardiovascular outcome on a population level. By contrast, randomised controlled trials are typically designed to test large effects, in sick or high-risk populations over a few years. In this sense, genetic studies are highly informative because they provide information about the effect of small variations in blood pressure in the general population, in a fashion that is randomly allocated and blinded to the individual (who is usually unaware of their own genetic predisposition), avoiding the risk of bias inherent in epidemiological studies about lifestyle changes. Thus, natural genetic variation can hint at the effects that could be achievable with an intervention, provided it is both long term and free from off-target (ie, unwanted) effects. A 10 mm Hg decrease in systolic blood pressure is expected to reduce coronary heart disease risk by 17% on the basis of data from blood-pressure-lowering trials, by 25% on the basis of epidemiological data, and by more than 45% on the basis of modelling with genetic data. The much-lower benefit found in trials, probably related to off-target effects and poor adherence to therapy, underlines the importance that this type of evidence demonstrates net clinical benefit. Furthermore, all these expectations are based on the assumption that the relationship between blood pressure and outcome is exponential, although some data suggest a U-shaped association.

Prevention of functional impairment at older ages is also important. In individuals older than 75 years, in whom multiple diseases (primarily cardiovascular) coexist, a life course approach will be aimed at preservation of functional reserve, slowing disease progression, and mitigating complications to optimise quality of life, with the potential to decrease the demand on the healthcare system.

Arterial ageing has a complex relationship with increased blood pressure and cardiovascular risk, acting as a marker, an outcome, and a driver (figures 2, 3). As shown in the life course approach in figure 2, there are three avoidable thresholds on which preventive efforts should be focused: the development of elevated blood pressure, development of subclinical cardiovascular damage, and, finally, the development of overt cardiovascular disease leading to physical and cognitive disability, loss of autonomy, and loss of quality of life. Some individuals with early vascular ageing (red line) will cross these thresholds earlier in life. The optimum or ideal life course (green line) represents individuals who only develop elevated blood pressure or subclinical cardiovascular damage, but too late in the life course to substantially affect quality of life. The main goal of preventive efforts (small grey arrows) is to shift an individual’s life course towards the ideal life course. The dashed endings of the life course lines (specifically the ideal life course) are there to underscore that the goal of prevention is not necessarily avoidance of ever developing cardiovascular disease, but avoidance of premature cardiovascular disease. Furthermore, there is always uncertainty at the end of life, and an individual on the ideal life course can still suddenly develop cardiovascular disease. Depending upon genetic disposition and/or epigenetic imprinting during fetal life, individuals can start their life course higher or lower on the health–disease continuum (the enlarged insert), reflecting the so-called cohort effect. The orange dashed lines show the impact of a preventive effort, with a resultant downward shift in the life course curve. Early preventive efforts are likely to result in a substantial gain in time (x-axis) or reduction in disease progression (y-axis) compared with later preventive efforts.

Primordial, primary, and secondary prevention

The goal of primordial prevention is to maintain the state of cardiovascular health and optimal blood pressure, leading to an ideal life course maintained within the healthy range from birth to end of life. This goal necessitates a solid population-based strategy, combining...
policy and environmental change, behavioural (ie, lifestyle) incentives, education, and community-level actions aimed at minimising the risk factor burden for the population at large. Because these actions are not individualised (ie, individually tailored), the Commission defines these actions as population based although they reach individuals. Primary prevention (preventive actions after hypertension is diagnosed) aims to avoid cardiovascular complications. Secondary prevention (after subclinical end-organ damage or overt cardiovascular disease develops) aims to avoid further cardiovascular damage, cardiovascular events, and reduction in quality of life. By contrast with primordial prevention, these preventive actions are generally driven by an individual’s absolute risk. This approach necessitates a well functioning health system with the capacity to readily detect individuals whose risk or blood pressure surpasses a specific risk threshold for which a more individualised, clinical (often drug-based) approach is indicated, and to deliver this strategy superimposed on ongoing lifestyle interventions.

Policy makers, health-care systems, the pharmaceutical and food industries, and civil society are responsible for creating a healthy environment that removes barriers to health and empowers populations to practise healthy behaviours.

Summary of essential goals and key actions

Previous action plans to improve prevention and management of elevated blood pressure and hypertension have not yet had global impact. We identified several achievable goals and accompanying actions that, if implemented effectively and broadly, will make substantial contributions to improve outcomes related to elevated blood pressure worldwide. Recognising the inequitable distribution of financial and other resources across and within countries and regions, the Commission has further classified the goals and actions appropriate at two different levels. We denote as essential those actions recommended to be undertaken in all countries and regions, irrespective of income levels; the remaining actions are those that should be undertaken when additional resources permit.

The global perspective

Size of the problem

Because hypertension rarely causes symptoms in the early stages, it is a silent killer, causing accelerated atherosclerosis, damage to major organs, disability, and death from cardiovascular disease. Approximately one in four adults have hypertension (when defined as blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic) and by 2025, hypertension is projected to affect more than 1·5 billion people worldwide. In recent decades, there has been an epidemiological shift in the main cause of global disease burden from communicable to non-communicable disease, with hypertension being the leading risk factor. Although blood pressure is closely associated with different birth cohorts and mean age of the population, it is a largely preventable condition caused by lifestyles increasingly characterised by reduced physical activity, unhealthy diet, overweight, and obesity, together with a poorly understood genetically influenced susceptibility to cardiovascular risk factors. Social determinants of health such as socioeconomic disadvantage early in life drive related inequities in the burden of hypertension, morbidity, and premature death in specific populations.

Despite blood pressure measurements in more than 150 national population-based surveys in 97 countries, no fully reliable global or regional estimates of hypertension treatment coverage exist. Figure 4 shows the distribution of diagnosis and control of raised blood pressure in national surveys in selected countries that are not part of the Organization for Economic Co-operation and Development. In most of these surveys, at least half of adults with raised blood pressure had not been diagnosed with hypertension. Treatment coverage is therefore low, ranging from 7% to 61% among people who had presented with raised blood pressure in the household surveys (figure 5). Effective coverage is considerably lower than total coverage, ranging from 1% to 31%. Data from 11 national Demographics and Health Surveys disaggregated by wealth quintile suggest that coverage of hypertension treatment differs substantially across wealth quintiles in some but not all countries (figure 5). A consistent association between wealth and coverage is observed in Bangladesh, Benin, Egypt, Namibia, and Peru. In nine of the 11 countries,

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**Figure 4:** Adults with raised blood pressure or on medication for hypertension disaggregated by diagnosis and treatment status

STEPS=WHO STEPwise approach to surveillance. DHS=Demographic and Health Survey.
Effect of age on risk factors and treatment goals
The average age of the world population has increased in recent decades, contributing to hypertension increasing in importance relative to other risk factors. The number of Europeans older than 65 years is predicted to double during the next 50 years to about 150 million, and in roughly the same period people older than 90 years are expected to constitute roughly 12% of elderly people in Europe (up from 0·5% of the US population in 2000), increasing the prevalence of hypertension. Cardiovascular diseases are projected to increase by a quarter in the next 30 years, and the number of cases among those aged 75–84 years is estimated to double in the same period. Thus, age-related factors such as increased prevalence of type 2 diabetes and other cardiovascular risk factors should be considered within hypertension treatment plans for the future. Furthermore, it is important to realise that successful prevention does not necessarily avoid events, but usually delays them until a later time.

For the same elevation in blood pressure, risk of cardiovascular events increases with age, and treatment of hypertension in elderly people is therefore of particular importance. Most of the earlier trials showing prognostic benefits of antihypertensive treatment in elderly people were done in those with systolic blood pressure of 160 mm Hg or higher (a threshold greater than that proposed in most current guidelines). The Systolic Blood Pressure Intervention Trial (SPRINT) oversampled individuals aged 75 years or older without diabetes or a history of stroke, living outside of nursing homes and assisted living facilities, and showed benefits when treatment was targeted to a systolic blood pressure less than 120 mm Hg compared with a target of 135–139 mm Hg. These data should be interpreted against the background of the specific blood pressure measurement in SPRINT—which is known to result in values approximately 10 mm Hg lower than with standard office measurements—but nevertheless indicate benefits of tight blood pressure control in elderly people. However, attainment of low blood pressure targets might be associated with increased adverse drug reactions such as dizziness, electrolyte disturbances, and alteration of kidney function. This finding suggests that blood pressure targets might need to be individualised, particularly for elderly people, although it is also these individuals in whom antihypertensive treatment improves prognosis the most.

Early vascular ageing and subclinical cardiovascular damage
Hypertension is a systemic condition affecting the whole vasculature. In rat models of hypertension, capillary rarefaction has been found to precede the development of hypertension and microvascular changes such as capillary thinning are also characteristic of human hypertension. On a functional level, the ability of the endothelium to regulate vascular tone is altered during the development of hypertension, partly due to increased release of reactive oxygen species and reduced availability of endothelium-derived nitric oxide. In human beings, arterial stiffening precedes hypertension. At the same time, high blood pressure causes damage to large and small arteries, leading to further endothelial dysfunction, reduced vascular compliance, increased vascular stiffness, reduced lumen diameter, and formation of atherosclerotic plaques. From a clinical perspective (and, in part, irrespective of whether they are cause or consequence), hypertension is clearly associated with changes in vascular function and structure that are more...
pronounced than the changes that would be expected as part of a normal ageing process. This process is referred to as early vascular ageing. 

Findings from clinical studies have shown that subclinical vascular damage is associated with adverse outcome. For example, increased vascular stiffness is a predictor of cardiovascular events and all-cause mortality independent of traditional cardiovascular risk factors. 

The availability of devices and techniques to non-invasively assess subclinical changes in vascular structure and function has fuelled interest in vasculature properties as a surrogate marker of cardiovascular risk. This approach is attractive because it would shift clinical practice from the current concept of disease based on risk factors towards a more precise assessment of an individual’s position on the cardiovascular continuum. An individual’s vascular phenotype would be the result of the combined action of all known and unknown risk factors and provide a personalised assessment of vascular (and cardiac) risk.

However, although guidelines agree that some assessment of target-organ damage is required as part of the clinical assessment of patients with hypertension, the current evidence only supports rather crude and late assessment of target-organ damage as part of the cardiovascular continuum. 

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Different situations around the world

About 80% of all cardiovascular mortality occurs in low-income and middle-income countries, where the greatest burden of hypertension is observed. Although there has been a trend towards reduction in mean systolic blood pressure among adults in Europe, Australia, and North America between 1980 and 2008, systolic blood pressure increases have been observed in low-income and middle-income countries. WHO estimates that the prevalence of hypertension is highest in Africa (46% of adults older than 25 years), 35% in North and South America together, and 40% in the rest of the world, with extremely low levels of awareness and control. However, reliable data about frequency, rate of control, and efficacy of interventions are not known, especially in low-income and middle-income countries.

In addition to geographical differences, stark disparities exist within countries between specific populations and local areas, with marked socioeconomic differences. These differences have evolved or persisted even within the context of improved national indicators, and have been observed in countries of all income levels. For example, in the USA, although hypertension control improved for the population overall between 1999 and 2012, substantial differences between black populations and white populations in control of blood pressure have been reported. Within New York City, geocoded population surveys show that lower-income neighbourhoods have higher prevalence of hypertension than wealthier neighbourhoods. Although proximate and modifiable causes of hypertension include exposure to factors such as poor diet, excessive alcohol intake, and physical inactivity, social factors such as education, income, social norms, and attitudes (eg, racism and discrimination) are associated with health inequities including in hypertension.

During the past two decades, age-standardised mortality from cardiovascular disease has improved within urban environments in high-income countries, which might have resulted from improved access to medical care and the availability of healthier food options, smoke-free spaces, and access to opportunities for other healthier lifestyle options. In low-income and middle-income countries, however, rapid urbanisation is increasing population exposure to environments that are associated with a higher prevalence of hypertension than rural environments. Factors that contribute to increased blood pressure in cities include more sedentary work life, increased use of inactive transportation modes (such as driving or use of escalators), and intake of more calorie-dense and nutrient-poor processed foods compared with rural environments. Furthermore, inadequate financing and development of the primary health-care system in low-income and middle-income countries often leaves disease and risk factors undetected and poorly managed. Primary health-care centres in low-income and middle-income countries are often inadequately equipped with basic diagnostic tools, and health-care providers cannot match the demands for improved identification of patients with hypertension and for more aggressive treatment of the condition.

A common theme associated with prevention of disease and promotion of health is to create environments that make physical activity and healthy diets easily accessible, for example by building segregated bicycle infrastructure and implementing systems to ensure a range of affordable fresh fruit and vegetables in urban areas. Universal access to health-care services and low-cost, high-quality medications makes diagnosis, treatment, and control more likely. By contrast, in environments that deter these activities (for example, communities where roads are unsafe for pedestrian traffic, where healthy foods are unavailable to purchase, or where health-care facilities or health insurance are inadequate), individuals become disempowered to make healthy choices, resulting in less healthy behaviours and populations.
Hypertension in the years to come and technological developments

The steady increase in the prevalence of hypertension during recent decades seems likely to continue, especially in low-income countries. This growth has also led to substantial increases in mortality and morbidity due to suboptimal blood pressure, which is also likely to continue. The estimated number of blood-pressure-related deaths yearly has increased by 49% to 10·4 million in 2013, and the number of disability-adjusted life-years has increased by 45%.6 Most of this increase has probably occurred in low-income and middle-income countries.

As a result of increases in population, ageing, urbanisation, and obesity, the number of people with hypertension can be expected to increase in low-income countries and some middle-income countries if not counteracted by concerted action. However, in high-income countries, age-adjusted blood pressure is decreasing, thereby mitigating the effect of the ageing population on the prevalence of hypertension. It is, therefore, clear that not only prevention and detection but also treatment and control of hypertension should be top priorities that are currently not well addressed.

The impact of hypertension can be reduced through existing strategies.6,22 Cost-effective models of interventions appropriate to use in countries with few resources have been suggested,64 and would be expected to reduce the global burden of non-communicable disease (such as cardiovascular disease induced by high blood pressure) if implemented in countries of any income level.19 The emergence and rapidly growing uptake of technological innovations offer further opportunities to use these tools to improve outcomes. This Commission proposes several strategies to lower the global burden of blood-pressure-related disease in the future through the better use of advanced technologies and systems to improve individual characterisation, enhance population-level empowerment, and strongly address prevention across the lifecourse.

Prevention: lifestyle and environmental changes

Current evidence, problems, and perspectives

It is striking that all blood pressure guidelines73–78 agree that individual lifestyle modification is the cornerstone of prevention and is the first line of treatment. However, two important challenges emerge in terms of clinical hypertension guidelines. First, the guidelines are written mostly by clinicians, such as cardiologists and nephrologists with training and experience in the clinical management of hypertension and cardiovascular disease, who therefore focus on individual patient recommendations. Second, hypertension treatment guidelines are designed for patients already diagnosed with hypertension, although individual lifestyle modifications are often not achieved despite robust evidence for the effectiveness of a healthy lifestyle to lower blood pressure.77 Substantial community-wide benefits can be obtained in individuals who have not yet entered clinical care and have no immediately detectable risk but might be on a trajectory for high blood pressure on the basis of existing epidemiological trends, as well as those at high risk or with existing disease.

Improvements in the prevention of blood-pressure-related disease will be achieved not only by better clinical treatment strategies for people already receiving blood-pressure-lowering therapy, but also through systematic strategies that ensure low blood pressure levels across populations; up to half of blood-pressure-related morbidity occurs in people with a systolic blood pressure less than 140 mm Hg.22 Furthermore, the strongest risk factor for development of hypertension is a blood pressure just below the cutoff value for hypertension—also referred to as prehypertension. Successful population-based strategies will therefore reduce the risk for people at all blood pressure levels, preventing incident hypertension, delaying disease onset, and reducing risk in patients with existing disease. Tackling this large group should be at the forefront of preventive efforts, because a substantial part of blood-pressure-related disease burden originates from this nominally normotensive group.42

Despite this knowledge, the largest proportion of funding and research activities is still projected towards individual pharmacological and device-based treatment, such as the best combinations of antihypertensive therapy or new strategies to treat resistant hypertension. But within the global context, most individuals with hypertension are still unaware of their blood pressure. This discrepancy was evident in the Prospective Urban Rural Epidemiology study,31 which examined hypertension prevalence, awareness, treatment, and control figures among 142,042 individuals from low-income, middle-income, and high-income countries. The largest proportion of hypertensive individuals (53·5%) were unaware of their hypertension status, and of those with hypertension, only 13% were controlled (figure 6)—findings consistent with other global, regional, and national studies. The questions to be answered are why is detection so low, why is control suboptimal, and how can these factors be improved?

The answers must be found through focused research.

How could we target the global population with hypertension (including those who are still unaware of their cardiovascular risk), those who are prehypertensive (and, therefore, have increased risk but are not targeted for pharmacology intervention), and those who are normotensive? Individual-based pharmacological approaches in patients with hypertension are evidence based and should be enforced. However, considering that the cardiovascular risk attributable to blood pressure is a continuum, the most effective solution is probably to reduce blood pressure in the population as a whole, although neither the beneficial effect of this strategy or the suggested ways to accomplish it are strictly evidence based. These two very different approaches are complementary and might—if used together—increase the chance of success.
Effective incorporation of population-based approaches is embedded in the Open Working Group on Sustainable Development Goals endorsed by the UN General Assembly. One of the 17 Sustainable Development Goals is to “ensure healthy lives and promote well-being for all at all ages”. Included in this goal is a target to reduce premature mortality from non-communicable diseases by 33% by 2030, through prevention, treatment, and promotion of mental health and wellbeing, thereby extending the previous target of 25% reduction in premature mortality from non-communicable diseases by 2025. Several of the non-communicable disease global targets fit precisely within the sphere of primordial and primary prevention, referring to specific targets for alcohol use, physical activity, salt intake, tobacco use, and obesity.

Many of these factors can be addressed on a population level by governments taking action to develop the appropriate social and economic environments that would support the creation of communities where healthy choices are easy and readily available (such as tobacco legislation). Such environments will inherently shape the health behaviours of larger populations by encouraging individuals within those communities to take up healthy behaviour, actively participate in physical activity, or choose to cook healthy meals at home, with much greater chance of success than stand-alone interventions targeted at individual patients.

The global prevalence of obesity and diabetes underscores the need for effective prevention in high-income countries as well as in the many middle-income countries that now have high obesity levels. It is important to introduce such interventions in low-income and middle-income countries, where tobacco and alcohol use, poor nutrition, and subsequent obesity are increasing. However, low-income countries are often challenged with the dual epidemics of non-communicable and communicable diseases, which continue placing excessive financial burden on their health systems. Wide promotion and availability of unhealthy diets, including processed foods and sugar-sweetened beverages that are affordable and easily available, can hardly be counteracted by individual promotion of healthy lifestyle by health-care practitioners alone. Policy interventions to make healthy choices easier will enable and drive these broader—and more sustainable—population-wide changes. They will require governments to carefully consider the long-term and short-term effects of decisions related to the social, economic, food, and physical environments, and support evidence-informed approaches to creating health-promoting environments—for example, by encouraging the production and promotion of healthy foods, differential taxation approaches, and enforced clearer labelling, in a similar way to that achieved with tobacco. Translating successes and embracing new and stronger actions to change current directions is necessary.

Evidence-based health behaviours

Substantial evidence supports the effectiveness of specific health behaviours to improve blood pressure, cardiovascular morbidity, and mortality. In terms of dietary intake, extensive evidence supports the beneficial effects of the Mediterranean diet (with extra virgin olive oil or nuts) and Dietary Approaches to Stop Hypertension (DASH) diet as well as a reduction in salt intake and increased potassium intake. Significant blood-pressure-lowering effects have been shown for dietary nitrate (found in beetroot juice and green leafy vegetables). Convincing evidence also supports cardiovascular protection by physical activity and improved fitness, weight loss, tobacco cessation, and limited alcohol intake, and management of psychosocial stress. Importantly, not only do these preventive measures improve blood pressure and cardiovascular outcome, but also most have multiple cross-cutting benefits, resulting in prevention of non-communicable diseases in general. For example, lifestyle modification can be more effective than metformin to prevent type 2 diabetes.

The effects of some interventions on hard cardiovascular endpoints have not yet been formally tested to date in adequately powered randomised trials. However, a large trial assessing the effects of reducing sodium intake on stroke is underway in China (the China Salt Substitute and Stroke Study; NCT02092090). Similar cluster-based methods could allow evidence to be generated for other lifestyle interventions. Although debate continues in the absence of these types of outcome data, overall the blood pressure benefits achieved by lifestyle modification are
expected to translate into long-term cardiovascular benefits that will outweigh any putative associated risks.

The major challenge is to achieve sustainable changes in lifestyle and behaviour, especially when making use of individual-based approaches. Sustainability has proven difficult with clinical approaches, which require substantial resources over a long period of time, and therefore are only applicable to very high-risk individuals. Additionally, the effects of clinical lifestyle interventions do not persist. Finally, engagement and motivation of individuals across populations is not feasible with high-resource approaches. These problems might partly explain why these preventive measures have not been successfully scaled at a global level.

Hence, the conclusion of this report is to focus on population-based strategies that involve broad public-health and systems approaches. However, among individual-based approaches, some strategies could be worth undertaking. An important first step to mobilising population-wide action is probably awareness, as shown by findings from the PURE study. A global initiative will be required to achieve this goal. Emerging technologies using novel approaches include mobile technology, where the findings from the Tobacco, Exercise and Diet Messages trial demonstrated that advice, reminders, and support through text messaging effectively reduced systolic blood pressure, LDL cholesterol, BMI, and smoking, and increased physical activity. A systematic review further indicated that text messaging approaches more than doubled the odds of medication adherence, but long-standing effects have not yet been tested. In terms of health literacy, the medical community has the responsibility of training the trainers—ensuring quality and consistency of the health education curriculum in schools—but cannot be the primary vector to deliver the message on a sufficiently large scale. Patient empowerment could be one strategy that substantially improves adherence and thereby probably improves outcomes. Alternative and promising approaches include peer-group interventions based on elements of social cognitive theory and disclosure of a genetic risk score, where preliminary results suggest that this knowledge can be a positive driver to act on other modifiable risk factors. Unfortunately, the limitations of individual-based approaches in achieving behavioural change at a population level are highlighted by the worldwide obesity crisis, reflecting difficulties in achieving and sustaining lifestyle changes in individuals. This situation is mirrored by alarming hypertension prevalence, especially in low-income and middle-income countries. It is therefore clear that different approaches are required.

**Population-based approaches to improve cardiovascular health**

Individual approaches to long-term adherence to new health behaviours are far from optimal. Findings from a Swedish study showed that if all individuals followed a low-risk lifestyle, the risk of observed stroke would be reduced by 62% and the risk of observed myocardial infarction would be reduced by 79%. Evidence shows that specific health behaviours such as tobacco cessation, increased physical activity, reduction of overweight, and a healthy diet can reduce blood pressure and cardiovascular events. However, only 1% of the Swedish population was leading a low-risk lifestyle. Therefore, a different strategy which does not focus on the individual is necessary.

To improve population cardiovascular health, several approaches are suggested: (1) health-promoting environments are essential, and require strong leadership of an organisation with global reach—such as the UN—and intense involvement from multiple stakeholders; (2) according to WHO, an effective school health programme can be one of the most cost-effective investments a nation can make to simultaneously improve education and health; (3) Health education—continuing through the life course as cardiovascular risk increases and hypertension begins to develop—would improve health literacy at all ages (figure 2) and increase awareness and detection of hypertension. It will require the combined efforts of governments, teachers, and communities; (4) technology can indirectly improve population blood pressure by ensuring the availability of healthy foods such as fruit and vegetables throughout the year to wider communities and by increasing physical activity. Refrigerators can increase the availability of fresh foods and simultaneously reduce the use of potentially harmful additives, such as sodium nitrate. The videogaming industry, wearable technology (eg, fitness bands), and social media can increase physical activity and general knowledge about healthy behaviours; (5) wider implementation of successful governmental actions including smoke-free policies, marketing of foods and alcohol (eg, the banning of adverts for alcohol or unhealthy foods), sin taxes (eg, sugar taxes), and regulation of the sodium content of processed foods; (6) owing to population diversity (cultural and social environments), unique approaches might be necessary to ensure successful acceptable population activities. Furthermore, the global health environment is constantly changing, and traditional cardiovascular risk assessment based on large cohorts from the early 1990s might become less effective as smoking habits decrease and obesity increases. The additive value of new risk markers is unclear, especially regarding functional outcomes like cognitive impairment. Therefore, continued research is needed to develop more effective population-based cardiovascular prevention strategies; and (6) to empower the general population and medical community, professional societies and health-care experts should contribute to clear, evidence-based recommendations that are easily available on websites and apps.
Salt reduction in the population

Globally, average estimated salt intake is 7·5 g/day (sodium intake 3·0 g/day), ranging from 5·5 to 13·7 g/day (sodium intake 2·2 to 5·5 g/day). More than 75 countries have national strategies for salt reduction in place. Findings from randomised trials have demonstrated that salt restriction from high levels leads to clear reductions in blood pressure. In the absence of randomised studies on cardiovascular events, findings from observational studies and a long-term observational follow-up of the TOPH I and II trials have suggested that sodium reduction, including to less than 2300 mg per day, is likely to translate to cardiovascular benefits, while other observational studies have suggested that the relationship between sodium excretion and cardiovascular events might be U-shaped, because an increased risk was observed in people with a sodium excretion less than approximately 3 g/day when estimated from a morning fasting urine sample. However, observational studies are limited by their inability to determine causality. A trial assessing the effect of reducing salt intake on stroke is underway (the China Salt Substitute and Stroke Study, NCT02092090) and could provide further evidence. Additionally, data from large populations undergoing initiatives for salt reduction (such as the UK and more recently South Africa, the first country to legislate mandatory industry salt reduction in various processed foods) will also provide longitudinal information. The Commission finds that further research should be prioritised, including randomised controlled trials when feasible—and trials that help to determine the most effective population-level sodium-reduction strategies.

Maternal health and fetal programming

Fetal programming refers to the concept that environmental conditions during pregnancy can predispose to disease during adulthood. A substantial body of evidence links maternal health and the fetal environment to future health of offspring. In particular, epidemiological evidence indicates that low birthweight (defined by WHO as <2500 g) increases risk of developing hypertension and cardiovascular disease in later life. A reduced number of nephrons and abnormal vascular development have been proposed as possible explanations for this relationship, although the underlying mechanisms responsible for fetal programming towards hypertension are incompletely understood. Epidemiologically, blood pressure has been falling in high-income countries for decades well before major lifestyle interventions such as taxation on tobacco, promotion of physical activity, and restriction of salt intake, and the same blood pressure decline has also begun in some middle-income countries. The blood pressure declines have both cohort and period effects, suggesting that the changing determinants are a combination of social changes (affecting specific cohorts) and technological or structural changes. A large part of the cohort effect can be explained by improvements in maternal health influencing fetal programming and changes in early-life diet. The precise mechanisms are unknown but epigenetic changes might be one of several possible mechanisms.

Irrespective of the mechanism, the fetal environment is a crucial determinant of hypertension and efforts should be made to improve maternal and fetal health globally. Indeed, in low-income and middle-income countries an estimated 27% of all livebirths were small for gestational age with approximately 15% of all births being classified as low birthweight. Maternal malnutrition, smoking, alcohol abuse, pre-eclampsia, and diabetes all represent possible targets to stop fetal programming of hypertension.

Summary of possible actions

Primordial and primary prevention of hypertension should be applied full circle throughout the lifecourse of populations by creating and enabling sound economic and social environments that would directly result in health-promoting environments (table 1). The cross-cutting benefits to all non-communicable diseases are immense, and can only be achieved by strong leadership and intense cooperation between multiple stakeholders (including governmental and non-governmental organisations, food and fitness industries, educational systems, media outlets, mobile technology companies, and employers), with full engagement of a global body such as the UN; the European Union pledge for responsible marketing of food and beverages to children is an example of such international leadership. We should further improve applications of technology to strengthen health and food monitoring systems, as well as food delivery and storage, but also use novel technology and the mobile industry that might aid in achieving this goal. Awareness should be emphasised throughout, including equal basic access to validated blood pressure monitors in low-income and middle-income countries. Task sharing can be effective, as demonstrated by the Feed Me Better campaign introduced by celebrity chef Jamie Oliver at schools in the UK, which achieved multiple benefits including improved bodyweight, micronutrient intake, and better educational performance.

Diagnosis and evaluation

Introduction to diagnosis and evaluation

Improved characterisation of patients, including accurate diagnosis, is the primary requisite to guide therapy, management, and follow-up in hypertension. A (more) specific diagnosis of hypertension is fundamental to tailor therapy (eg, non-pharmacological, drug class or classes, and dose). Failures or weaknesses in this diagnostic
process can result in inappropriate treatment, potentially leading to increased adverse drug reactions (particularly in older individuals), inappropriate discontinuation of therapy, greater cardiovascular risk due to poor blood pressure control, or failure to treat the right patient.

Increased availability of new technologies has led to opportunities on the one hand, but to substantial challenges on the other. Measurement devices for blood pressure have never been so available and affordable, but many might not be validated according to scientific standards. Many devices to investigate novel parameters of potential pathophysiological relevance and risk stratification are now available. Similarly, techniques to measure different omics (circulating biomarkers) are now available for individuals, but the huge amount of data generated has little relevance for clinical practice at this stage. One of the main hurdles in the implementation of novel diagnostic tools is that alone they do not improve outcomes and thus often lack evidence for clinical benefit; improved outcomes (and thus evidence for use) can only be achieved for any type of testing if combined with treatment in a diagnostic-therapeutic strategy.

**Diagnostic difficulties**

A key objective of this Commission is that every person should have their blood pressure measured. Although blood pressure monitors now available include oscillatory, aneroid, and hybrid (with a mercury-like column) devices. Each has specific problems in terms of maintenance and calibration, and their accuracy can be questioned in particular settings (including among patients with arrhythmia or stiff arteries). Ideally, devices should comply with the validity guidelines of scientific societies, rather than just internal testing by the manufacturer, and this information should be clearly available for the customer. Correct cuff size is important for device accuracy. Appropriately sized cuffs for children, thin individuals, and (more importantly) obese individuals are underused in medical practice, although about 40% of people with hypertension require a blood pressure cuff bigger than the standard adult size.

Moreover, traditional cylindrical cuffs substantially overestimate blood pressure compared with trunco-conical cuffs in those with a pronounced trunco-conical shape of the upper arm.

Major difficulties exist in accurate determination of an individual’s true blood pressure. The small number of blood pressure measurements taken in the physician’s office, commonly used to establish the diagnosis and initiate treatment of hypertension, cannot account for marked spontaneous variability in blood pressure. The existence of white-coat and masked hypertension justify the use of out-of-office and automated, unobserved measurements, but office blood-pressure measures can still be used as a crude indication of blood pressure control and are preferable to no measure at all. Ideally, diagnosis, initiation, and titration of treatment should be guided by ambulatory, home, or automated, unobserved blood pressure, the latter potentially being applicable in resource-restricted environments.

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**Table 1: Identified problems and corresponding goals and actions relating to prevention**

<table>
<thead>
<tr>
<th>Goals</th>
<th>Actions</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low awareness of hypertension</td>
<td>Every adult should know their blood pressure*</td>
<td>Measurement access</td>
</tr>
<tr>
<td>Exposure to an unhealthy environment</td>
<td>Maximise multi-sectoral collaboration to create health-promoting environments†</td>
<td>Health-promoting environment</td>
</tr>
<tr>
<td>Lack of understanding regarding the impact of unhealthy lifestyles on hypertension</td>
<td>Universal education about healthy lifestyles over the life course*</td>
<td>Healthy behaviours</td>
</tr>
<tr>
<td>Knowledge gaps in the effectiveness of prevention programmes, policies, and use of new technologies</td>
<td>Resource allocation for research into action-oriented prevention</td>
<td></td>
</tr>
</tbody>
</table>

*Essential goals. †Related to research.
White-coat and masked hypertension are phenotypes not identified by clinic blood-pressure measurement. White-coat hypertension is defined as a persistently elevated office measurement of blood pressure concomitant with normal blood pressure outside the office. It represents about 30% of all patients diagnosed with hypertension and is associated with lower cardiovascular risk than sustained hypertension. The condition might not require treatment with anti-hypertensive drugs in the absence of associated risk factors and organ damage, but this strategy remains to be definitively tested. Home or ambulatory blood factors and organ damage, but this strategy remains to be definitively tested.18,19 Home or ambulatory blood-pressure monitoring helps to confirm or exclude white-coat hypertension, at least in people with mild hypertension at low or moderate total cardiovascular risk. Masked hypertension is the opposite of white-coat hypertension (normal office blood pressure and elevated out-of-office blood pressure), affecting about 5–10% of the general population but higher among people with untreated diabetes (29%) and is associated with higher cardiovascular risk than white-coat hypertension. People with normal or high-normal office blood pressure together with organ damage or at high cardiovascular risk should be offered home or ambulatory blood-pressure monitoring, to exclude masked hypertension. Both home and ambulatory blood pressure are complementary methods and, when measured and recorded according to protocol, might offer substantial advantage beyond physician-measured blood pressure in the office environment. Several international guidelines recommend the use of home blood-pressure monitoring as a method that has good reproducibility, is well tolerated by patients, is more widely accessible than ambulatory blood-pressure monitoring, and is a relatively inexpensive option for improved management of hypertension. Some limitations of home monitoring can be overcome through the use of memory-equipped devices, as well as by taking advantage of telemonitoring (transmission of blood pressure measurements directly to the doctor) and smartphone applications. Further, ambulatory monitoring might provide more information on key issues such as blood pressure values during sleep and routine daily activities. However, studies are still needed to clarify whether antihypertensive treatment tailored on the basis of out-of-office blood pressure, as compared with conventional office measurements, will result in stronger prevention of cardiovascular complications.

A practical and time-efficient method of blood pressure measurement could be achieved with automated, unobserved, in-clinic measurement, which provides blood pressure values close to out-of-office values and also limits white-coat effects. This method was used in the SPRINT study in which repeated blood pressure measures were recorded with an automated device after 5 min of rest while the participant was seated and alone. By using this refined blood-pressure-measurement method, SPRINT showed that lower blood-pressure targets were more attainable than those generally achievable using traditional office measurements, and these lower blood-pressure levels were associated with better outcomes in people with high cardiovascular risk. Nonetheless, for all out-of-office methods, some adaptation of the threshold values might be necessary because they provide lower values than physician-measured blood pressure.

An additional challenge in refining the risk associated with elevated blood pressure is that blood pressure values can vary substantially with time: beat to beat, minute to minute, hour to hour, day to night, over different days, or between clinic visits over weeks, months, and even years. Day-to-night variability provides important clinical information; a reduced (non-dipping pattern) or inverted (reverse dipping pattern) fall in blood pressure from day to night is an established marker of adverse prognosis. Such patterns are associated with increased activity of the sympathetic nervous system, secondary hypertension, or orthostatic hypertension. Ambulatory blood-pressure monitoring is best suited to explore day-to-night changes in blood pressure, although nocturnal self-measurement of blood pressure is also feasible. Long-term, visit-to-visit variability in blood pressure is gaining interest as a potential prognostic marker for stroke, cardiovascular disease, and all-cause mortality, although evidence is conflicting.

Haemodynamic characterisation

Haemodynamic characterisation of hypertension (particularly as it pertains to pulsatile haemodynamics) is a field of growing interest. Blood pressure is the result of the flow generated by the left ventricle and the complex impedance to that flow imposed by the arterial tree. One approach to haemodynamic characterisation of patients with hypertension involves the assessment of central systolic blood pressure, which variably differs from the conventionally measured brachial systolic blood pressure. There are conflicting observations regarding the incremental prognostic value of central compared with brachial blood pressure. However, it should be emphasised that considerable differences in central systolic blood pressure can occur among people with similar brachial systolic blood pressure, and that antihypertensive therapy can affect central and brachial systolic blood pressures differently. Because central blood pressure (and how it changes in response to drug therapy) seems to relate more strongly to end-organ damage than brachial blood pressure, precise estimation of central blood pressure is expected to improve management decisions in hypertension, as suggested by findings from a randomised trial. Methods to measure central blood pressure might be particularly useful in elderly people with high prevalence of white-coat hypertension, and among young individuals with isolated systolic hypertension.
It should be emphasised that the study of central haemodynamics can yield much more information than brachial or central (peak) systolic blood pressure. For any given peak left ventricular pressure, late systolic load (as opposed to early systolic load) promotes more left ventricular hypertrophy, fibrosis, dysfunction, and failure. Dimensionless measures of wave reflections and late systolic load derived from the pressure waveform are much stronger predictors of outcomes (particularly heart failure) than central or peripheral pressures, with statistically significant incremental prognostic value. The quantitative assessment of pulsatile haemodynamics continues to evolve, and will probably yield improved understanding of the underlying abnormalities leading to target-organ damage in hypertension. Similarly, as technology evolves, assessments of central haemodynamics are becoming increasingly feasible in ambulatory settings, enhancing the ability to characterise patients during daily activities.

Finally, characterisation of traditional haemodynamic parameters—including peripheral resistance and volume status—using non-invasive techniques (such as impedance cardiography) could provide useful information for tailored management of hypertension. The growth in the development of wearable devices offers promise as potentially widely used tools that could facilitate detailed information along these lines as the associated technology develops. However, these devices will only be relevant in selected groups because of practical reasons.

Markers of subclinical cardiovascular damage
Markers of subclinical cardiovascular damage or of vascular health integrate the effects of long-term exposure to a highly variable risk factor such as blood pressure with other cardiovascular risk factors, superimposed on an individual’s genetic background. This time-integrative characteristic combined with the ability to reflect both known and unknown risk burden make these markers highly attractive. Elevated urine albumin–creatinine ratio, suggesting microvascular damage, and left ventricular hypertrophy on electrocardiography (ECG), suggesting cardiac damage, predict cardiovascular events independently of traditional risk factors. They are relatively inexpensive methods, and easy to measure and implement, making them feasible globally.

In hypertension, the target organs include the brain, heart, kidneys, and arteries. Because arteries are implied in the pathogenesis of target-organ lesions, they are logical candidates as useful markers of subclinical damage. Arteries adapt themselves to high blood pressure by the walls becoming stiffer and thicker. Aortic stiffness, measured as carotid-to-femoral pulse wave velocity, has been associated with cardiovascular risk even after adjustment for blood pressure and other classic risk scores in more than 24 longitudinal studies, as confirmed in meta-analyses of individual participant data. Because a wide range of baseline reference values exists, and the measurements are non-invasive and well standardised, routine clinical measurements of aortic stiffness could be helpful in deciding which patients are at increased risk despite only mildly elevated blood pressure, potentially aiding treatment decisions. However, simplification of the technology will help to minimise operator variability and maximise utility. Importantly, reference values for aortic stiffness only exist at present for white populations, emphasising the need for networks for research collaboration to generate multiethnic reference values. More research into new inexpensive methods to measure or estimate aortic stiffness is also needed.

The use of markers of subclinical cardiovascular damage for population-level screening cardiovascular risk is not recommended because these markers usually lack specificity for future cardiovascular events, at least in the short term. Thus, a high number of false-positive diagnoses might be expected (ie, patients falsely classified at high risk). Whether these are true false positives or whether these individuals could benefit from intervention has yet to be proven, and the cost-effectiveness of such an approach is also unknown. However, increased aortic stiffness is predictive of the future occurrence of hypertension in the general population. Thus, if it were easier and less time consuming to measure, aortic stiffness might be useful as first-line screening in certain populations.

People at moderate risk or patients with established cardiovascular risk factors are typically the target population for the use of markers of subclinical cardiovascular damage; the markers can be used to reclassify individuals from moderate to high risk, and thereby inform primary prevention, or help to decide treatment choice and intensity. However, whether this use of markers leads to improved outcomes for patients is still unclear. In any case, subgroup analyses from the Heart Outcomes Prevention Evaluation (HOPE-3) study provide new perspective on the possible value of blood-pressure-lowering therapy even among adults with borderline elevated blood pressure and average risk, irrespective of detailed measures of subclinical cardiovascular damage.

For patients with advanced target-organ damage or overt cardiovascular disease and already at high risk, other biomarkers could help to diagnose and stratify disease severity, or to guide treatment. For instance, N-terminal prohormone of brain natriuretic peptide has proven high value for the diagnosis of heart failure in patients with acute dyspnoea, and N-terminal prohormone of brain natriuretic peptide response to treatment is indicative of outcome.

Risk factor interactions
Risk factors cluster together, and since 1994 the prevention of cardiovascular disease has become more
focused on the assessment of (and the adoption of accurate tools to quantify) total cardiovascular risk. Very few patients with hypertension have isolated high blood pressure independent of other risk factors, and a synergistic effect of multiple cardiovascular risk factors (eg, lipid, glucose, etc) contributes to a total cardiovascular risk that is greater than the sum of the risk carried by each risk factor alone. Control of hypertension in patients with multiple cardiovascular risk factors is more difficult in high-risk than in lower-risk patients.

The relatively poor control of hypertension in patients with multiple risk factors despite effective anti hypertensive and cardioprotective drugs demonstrates that risk-factor clustering affects not only the cardiovascular risk but also the efficacy of the antihypertensive treatment. In this context, even though the metabolic syndrome is not a unique entity, it has been associated with masked hypertension, arterial remodelling, inflammation, and increased odds of cardiovascular events in middle-aged and older individuals, with neurogenic abnormalities playing a crucial role. Therefore, detailed characterisation of the so-called phenotype of the individual patient with hypertension might be essential, not only for risk stratification and type of antihypertensive drug, but also for the intensity of the antihypertensive treatment. The different clusters of metabolic syndrome components have varying effects on arterial ageing and risk for cardiovascular disease, with differing prevalence across Europe and the USA consistently shown in cohorts participating in the Metabolic Syndrome and Arteries Research Consortium (eg, in populations with differing genetic factors, lifestyle, or influence of medical treatment). Notably, differences in blood pressure levels among the clusters of components did not account for differences in the likelihood of having extremely stiff arteries. Thus, the burden of elevated blood pressure differs according to the specific associated cardiovascular risk factors and not just by the number of associated cardiovascular risk factors.

The best way to integrate multiple risk factors for treating hypertension is still a matter of discussion. The 2013 European Society of Hypertension guidelines grade interventions according only to the number of risk factors, not to specific clusters. These scores to identify high cardiovascular risk lose accuracy in different ethnic groups. Additionally, the risk scores were constructed largely from cohort studies done two or three decades ago, thus reflecting different levels of cardiovascular risk factors in the population. Last, but not least, whether the scores correctly estimate the total cardiovascular risk associated with multiple risk factors in the increasing population of elderly individuals with comorbidities is uncertain.

**Obstructive sleep apnoea and inadequate sleep hygiene**

Impaired sleep quality unfavourably alters circadian blood-pressure profile and autonomic cardiovascular regulation. Available evidence indicates that habitual short sleep duration (less than 6 h per night) induces a sustained increase in blood pressure in normotensive and prehypertensive adolescents and adults, increasing the risk of developing hypertension. Although the direct association between sleep changes (eg, sleep deprivation, short sleep duration, insomnia) and elevated blood pressure is not entirely understood, and involves numerous factors (eg, stress exposure, activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis, inflammation), the incidence and prevalence of hypertension related to inadequate sleep seems to be most important in adults younger than 60 years, especially women. Moreover, insufficient sleep has been linked to weight gain and metabolic abnormalities, which are implicated in the development of hypertension.

In addition to sleep disruption and abnormal breathing pattern during sleep, patients with obstructive sleep apnoea commonly present with a non-dipping blood pressure profile. The prevalence of obstructive sleep apnoea is increasing, and its presence and severity are strongly associated with obesity. The alarmingly high prevalence of excess bodyweight among children and adolescents suggests that obesity-related health conditions will probably increase in younger populations, leaving them at high risk for adverse health problems throughout their life course. Arterial hypertension, particularly resistant hypertension, often occurs in patients with obstructive sleep apnoea, and they share multiple pathophysiological mechanisms resulting in adverse consequences on various organs. Elevated sympathetic activity is evident in patients with obstructive sleep apnoea, and further augmentation of sympathetic drive elicited by recurrent episodes of apnoea during sleep could contribute to hypertension and cardiovascular events. Despite the epidemiological association between obstructive sleep apnoea and hypertension, the reductions in blood pressure noted in clinical studies of continuous positive airway pressure have been remarkably small (roughly 1–3–0 mm Hg in systolic or diastolic blood pressure). The small size of this effect might be explained by similar overlapping pathophysiological pathways linking obesity and obstructive sleep apnoea to hypertension, or because diagnosis of obstructive sleep apnoea and treatment with continuous positive airway pressure is often started late after lengthy exposure to high blood pressure that has already remodelled the arterial tree. Findings from a randomised trial showed that a weight loss intervention combined with continuous positive airway pressure therapy resulted in greater reduction in systolic blood pressure (14·1 mm Hg) than did weight loss (6·8 mm Hg) or continuous positive airway pressure (3·0 mm Hg) alone at 24 week follow-up among individuals who adhered to treatment. Findings from another trial indicated that treatment with continuous positive airway...
pressure, but not nocturnal supplemental oxygen, reduced 24 h mean blood pressure in patients with obstructive sleep apnoea and controlled hypertension.248

With available evidence suggesting that continuous positive airway pressure is useful for the treatment of obstructive sleep apnoea, targeting of obesity is essential to properly address cardiovascular risk in this population. Weight loss is clearly effective in reducing the adverse metabolic consequences of obesity, sympathetic activity, hypertension, and obstructive sleep apnoea. Low-cost, effective weight loss interventions in this population are needed. Additionally, immediate global action and policies to reduce physical inactivity, promote outdoor activities, and institute prevention programmes to control obesity are clearly warranted to reduce the global burden attributable to hypertension.

**Secondary hypertension**

A key objective of the Commission is to increase the diagnosis rate of secondary hypertension, which remains underdiagnosed.1,249 Secondary hypertension (caused by endocrine, renal, or vascular disorders, rare monogenic diseases, or a drug or toxic agents) represents a rare opportunity for curative antihypertensive therapy, accounts for up to 5–10% of patients with hypertension, and affects millions of people worldwide.1,250

To reduce the delay of diagnosis, decisional algorithms should be simplified. General practitioners should be educated to suspect secondary hypertension in every patient with juvenile, resistant, or severe hypertension.1,249 Initially, medical history, physical examination (eg, an abdominal bruit might reveal renal artery stenosis), and simple laboratory tests—including estimated glomerular filtration rate (for detection of chronic kidney disease) and electrolytes (hypokalaemia might indicate an endocrine hypertension)—should be examined. If abnormalities are detected, physicians should be able to request appropriate additional investigations. Endocrine hypertension is mainly due to adrenal disorders causing an excess of hormones which affect blood pressure regulation. Primary aldosteronism (Conn’s syndrome or bilateral adrenal hyperplasia) is the most common form of secondary hypertension. The diagnostic algorithm is sequentially based on biochemical tests (serum potassium, aldosterone–renin ratio, urine aldosterone secretion, and confirmatory tests in the absence of intake of products derived from liquorice and other agents that affect aldosterone–renin ratio) followed by adrenal CT scan or MRI and adrenal venous sampling to discriminate unilateral or bilateral disease.251–253

Catecholamine-secreting tumours (pheochromocytoma or extra-adrenal paraganglioma) are severe disorders, sometimes revealed by life-threatening emergencies or in the form of a hereditary predisposition (up to 40% of affected patients carry a mutation in a susceptibility gene). Evidence-based guidelines recommend measurement of metanephrines, genetic testing, and imaging studies253 as well as long-term follow-up after surgery.248 Renovascular hypertension, due to fibromuscular dysplasia (typically in young women) or atherosclerotic stenosis of renal arteries (typically in elderly people with cardiovascular risk factors) can be diagnosed by CT or MRI.251

Although education of general practitioners is essential, evaluation of patients by a multidisciplinary team in centres experienced in dealing with secondary hypertension should be favoured. Creation of dedicated registries at the international level should be promoted to produce and validate robust and cost-effective diagnostic algorithms. Development of next-generation sequencing methods in the routine diagnostic setting would improve diagnosis for monogenic forms of hypertension and catecholamine-secreting tumours. Development of non-invasive imaging techniques able to differentiate fibromuscular dysplasia from atherosclerotic stenosis, to quantify the degree of stenosis and to appreciate its effect on renal function should be encouraged. Given the substantial efforts often required to accurately identify secondary hypertension, diagnosis of secondary hypertension cannot be the highest-priority goal in low-income and middle-income countries. However, an action for the future should be to increase the availability of relevant investigations in communities with few resources.

**New cardiovascular biomarkers and omics**

A biomarker is a characteristic that can be objectively measured and evaluated, and acts as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions.256

In hypertension, blood pressure is an almost ideal biomarker. Blood pressure is causally related to the development of the condition, defines the condition, predicts the outcome, is the target of therapeutic interventions, and serves as a surrogate marker to assess the benefit of therapies. Therefore, the role that other biomarkers could have in hypertension requires careful thought. We discuss three relevant scenarios briefly.

First, and bearing in mind the Commission’s definition of the condition, hypertension is not merely persistently elevated blood pressure; we see the potential for a new definition of hypertension based on a molecular phenotype characterised by complex biomarkers. Genetic polymorphisms have been identified with highly significant associations with blood pressure, but the proportion of variance explained by these genetic markers is only about 3–5%.257 The specific composition of proteins in hypertension assessed by proteomic techniques258 and the description of the metabolome associated with hypertension259 could potentially redefine hypertension at a molecular level. At present, little research in this area has been done, but the potential of proteomics260 and other comprehensive molecular techniques should be fully exploited to better characterise the condition termed hypertension.
Second, biomarkers could help in the prediction of the risk of developing hypertension. In this scenario, raised blood pressure would again be a symptom that points towards the underlying pathology, most likely changes in the resistance of small and large arteries. Blood pressure therefore only rises after functional and structural changes in the vasculature have already occurred, before diagnosis of hypertension. There are good reasons to believe that prediction and preventive treatment before the onset of hypertension have the potential to further reduce hypertension-associated morbidity and mortality.

Third, in patients with hypertension, biomarkers can be used to refine or reclassify cardiovascular risk. We would assume that complex molecular biomarkers based on omics techniques will provide better individual prediction than traditional unidimensional biomarkers such as lipids or markers of cardiac damage (eg, the cardiac troponins). Limited data are currently available about risk prediction in hypertension with omics-based biomarkers.258,259,261

The so-called higher omics techniques—eg, proteomics and metabolomics—will be best suited to describe the current state of an individual, whereas genetic and genomic biomarkers are better suited as risk markers. In fact, because of the complex interplay between genes and environment, the association between genetic and phenotypic variants is not always very tight. Nevertheless, findings from genome-wide association studies and other genetic studies have robustly identified candidate markers associated with the risk of having hypertension.24,257

Functional analysis of regulated pathways that emerge from these studies emphasises the importance of renal salt and water handling (eg, in the form of natriuretic peptides) and signalling.262 Whether these genetic variants are also associated with the risk of developing hypertension and associated organ damage in a truly prospective fashion remains to be explored.

### Summary of possible actions

In summary, the Commission identifies two basic problems. First, fundamental phenotyping of individuals with elevated blood pressure—including blood pressure measurements, basic cardiovascular risk stratification, and screening for secondary hypertension—is often not done systematically. Second, further research is needed to determine the additive beneficial effect of more advanced phenotyping. In table 2, the different subproblems with corresponding goals and actions are listed, classifying the three actions dealing with the fundamental phenotyping of individuals with elevated blood pressure as essential.

#### Pharmacological prevention and treatment

**Current evidence and problems**

There is strong evidence that blood-pressure-lowering drugs are beneficial for the prevention of major events such as stroke, myocardial infarction, kidney failure, and cardiovascular death. Compelling data are few, however, concerning the role of antihypertensive treatment—in

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**Table 2: Identified problems and corresponding goals and actions relating to diagnosis**

<table>
<thead>
<tr>
<th>Goals</th>
<th>Actions</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor measurement of blood pressure</td>
<td>Improve the quality of blood pressure measurement* Increase the availability of standardised blood pressure monitors*</td>
<td>Certification and validation of monitors and endorsement of protocols for measuring blood pressure by professional societies Develop simple and inexpensive blood pressure monitors Give preference for home, ambulatory, and automated unobserved measurements to office measurements Measurement quality</td>
</tr>
<tr>
<td>Poor identification of people at high cardiovascular risk</td>
<td>Improve awareness of absolute cardiovascular risk as a target for treatment* Improve detection of clusters of cardiovascular risk throughout the life course (eg, MetS)* Improve detection of obstructive sleep apnoea*</td>
<td>Promote education on cardiovascular risk of patients, doctors, and health professionals Reinforce targeting global cardiovascular risk rather than single risk factor Empowerment</td>
</tr>
<tr>
<td>Lack of diagnosis or delayed diagnosis of secondary hypertension</td>
<td>Increase the diagnosis rate of secondary hypertension by doctors*</td>
<td>Promote simple and robust algorithms for detecting secondary hypertension Increase the availability of relevant investigations in communities with few resources Favour management by multidisciplinary teams with appropriate expertise Secondary hypertension</td>
</tr>
<tr>
<td>Lack of data on blood pressure, cardiovascular risk, and arterial ageing from childhood to adulthood</td>
<td>Address the birth-cohort effect† Update cardiovascular risk algorithms†</td>
<td>Capitalise on recent large existing cohorts, develop novel cohorts including biomarkers, and adequate follow-up to ascertain cardiovascular outcomes†</td>
</tr>
<tr>
<td>Poor assessment of vascular ageing in routine clinical practice</td>
<td>Promote the concept of early vascular ageing for monitoring cardiovascular health</td>
<td>Promote the use of aortic stiffness as a robust and simple marker of early vascular ageing Develop simple and affordable devices to measure aortic stiffness† Reference values for different ethnicities†</td>
</tr>
<tr>
<td>Uncertainties about the clinical use of omics-based biomarkers</td>
<td>Evaluation and validation of the diagnostic and prognostic value of omics-related markers</td>
<td>Capitalise on large existing cohort with adequate follow-up and ascertained cardiovascular events†</td>
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*Essential goals. †Related to research.
middle-aged and older individuals—to prevent dementia or in slowing the progression of cognitive impairment.

In early trials into diastolic and systolic–diastolic hypertension, blood-pressure-lowering drugs reduced, on average, diastolic blood pressure by 5 mm Hg, the risk of stroke by 42%, and the risk of coronary events by 14%. In subsequent trials on systolic hypertension in individuals aged 60 years or older, the average reduction in systolic blood pressure was 10 mm Hg, and the overall risk reduction was 30% for stroke and 23% for coronary events. Similar trends were observed in patients aged 80 years or older in the Hypertension in the Very Elderly Trial who were actively treated aiming for a systolic blood pressure lower than 150 mm Hg. The beneficial effects of blood-pressure-lowering therapies to reduce stroke, myocardial infarction, heart failure, and death have also been shown in meta-analyses.263

Very recent evidence from the SPRINT trial and the subsequent meta-analysis suggest that, at least in at-risk populations without diabetes or a history of stroke, blood pressure targets as low as 120 mm Hg systolic are associated with further improved outcomes, although this blood pressure target is associated with substantial adverse effects. The lower target achieved in SPRINT should, however, be interpreted in the context of the protocol for blood pressure measurement used. Trials in patients with type 2 diabetes that used a similar approach to aggressively lower blood pressure including ACCORD and ADVANCE showed smaller benefits on event rates than did SPRINT. This was confirmed by findings from meta-analyses.

Drug treatment to achieve blood pressure of less than 140/90 mm Hg still seems to reduce all types of fatal and non-fatal cardiovascular events, even in individuals with mild hypertension and in those at low-to-moderate cardiovascular risk. However, absolute risk reductions with blood-pressure-lowering treatment are greater in patients at higher levels of cardiovascular risk, and a higher level of baseline risk is associated with a higher absolute residual risk on treatment. It therefore remains unclear whether patients with mildly elevated blood pressure, in particular those at a younger age (ie, younger than approximately 40 years of age in men and 50 years of age in women), need pharmacological treatment. Although reserving antihypertensive treatment for higher-risk patients with hypertension maximises the cost–benefit ratio, only treatment of patients at low-to-moderate risk might prevent the increasing number of treatment failures associated with late initiation of treatment. Furthermore, antihypertensive treatment in people with mild hypertension and at intermediate risk without known cardiovascular disease has recently been supported by a predefined subanalysis of the blood-pressure-lowering part of the HOPE-3 trial. Individual treatment decisions that take patients’ preferences into account will be the best approach in some—but not all—health-care systems.

Some evidence suggests that the antihypertensive drugs recommended by current guidelines (namely angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics) achieve similar global cardiovascular prevention. Nonetheless, some of these drug classes have benefits in addition to blood pressure reduction. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are particularly indicated in the presence of chronic kidney disease, diabetes mellitus, or chronic heart failure. β-blockers are indicated in the presence of coronary heart disease and chronic heart failure, but tend to be less effective in the prevention of stroke. By contrast, calcium channel blockers provide more protection against stroke, but less protection against heart failure in overall analysis and in several single active-comparison trials. The combination of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers could be detrimental in clinical conditions other than chronic heart failure, and hence is discouraged in the management of hypertension. The combination of β blockers and diuretics increases the risk of new-onset diabetes mellitus. Findings from two trials have suggested that the combination of angiotensin-converting enzyme inhibitors and calcium channel blockers might be superior to combinations of diuretics with either angiotensin-converting enzyme inhibitors or β blockers, at least in white populations.

Although many large and well designed randomised controlled trials are available on the benefits of antihypertensive treatment, there is still insufficient evidence on several clinically relevant questions for the management of hypertension. Whom should we treat? How should we treat? To which level should we treat and how? How long should treatment continue? These are all important questions that need to be addressed by further research. The Commission therefore strongly suggests that decisions about treatment should be made with the lifecourse framework in mind, whereby not only immediate cardiovascular benefits but also long-term remote target-organ or metabolic harms are taken into account in a unifying concept of lifecourse net clinical benefit. Although all classes of antihypertensive drugs reduce cardiovascular events, clinical trials and observational data suggest not only differences across antihypertensive drug classes with regard to general efficacy and specific cardiovascular outcomes but also differences regarding the risk of new-onset diabetes and atrial fibrillation and the potential for renal protection in specific clinical scenarios. It is possible that the...
metabolically neutral class of angiotensin-converting enzyme inhibitors is associated with greater life course benefit than the diabetogenic class of diuretics, but in the absence of trial data with event horizons of 20–30 years this proposal is purely speculative. The potential of big data to fill in this knowledge gap cannot be overstated. The Commission strongly recommends research into the life course net clinical balance between benefits and harms of different antihypertensive drugs and of different blood pressure targets.

**General treatment and adherence**

Detection and management of hypertension in high-risk populations, most notably in low-income and middle-income countries, remains suboptimal. Despite clear evidence for the benefits of blood pressure reduction using low-cost and safe drugs, most individuals with hypertension in the world are undetected, untreated, or poorly controlled (figure 6). Accordingly there is an urgent need to ensure access to affordable, high-quality medicines globally. Indeed, the best-documented antihypertensive therapies are now off patent and can, therefore, be manufactured at very low cost, which will be crucial in overcoming limitations to access, including regulatory, political, and corporate factors.

Most patients with hypertension require more than one drug to control their blood pressure. Single-pill combinations of two or more antihypertensive drugs, therefore, have the potential to reduce the number of tablets that patients have to take, as demonstrated in the ACCOMPLISH trial and generally lead to improved blood-pressure control. However, whether these combinations are cost-effective and improve adherence to therapy remains debated. Available combination pills are based mainly on proprietary agents. The complex licensing legislation for new formulations and combinations makes it commercially unattractive to develop combination pills based on less expensive, off-patent compounds.

Until more definitive data are available, we propose the use of simplified algorithms supported by e-health technologies both for initiation of drug monotherapy in mild hypertension and combined therapy in more severe grades. To facilitate drug therapy in patients with hypertension worldwide, a core set of affordable, efficient, evidence-based, high-quality drugs must be widely available. The primary health-care team has to be extended beyond physicians and should involve allied health professionals and community workers to improve hypertension management and to put into practice a communication strategy with emphasis on prevention and control of hypertension.

One of the main causes for non-control of hypertension is a lack of adherence by the patient. Low medication adherence is common in patients with hypertension, especially those with resistant hypertension; indeed, the prevalence of poor adherence is reported to be as high as 25–50% in patients with apparent resistant hypertension. Low adherence to antihypertensive treatment has been consistently associated with poor blood pressure and adverse cardiovascular prognosis. There are significant differences in discontinuation of therapy between antihypertensive drug classes, with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blockers showing the best adherence. Significant heterogeneity in adherence to antihypertensive therapy has also been reported between drugs belonging to the same drug class. Objective assessment of adherence to therapy is possible by testing for the presence drug metabolites in body fluids, particularly urine. Measurement methods such as high-performance liquid chromatography coupled to tandem mass spectrometry are sensitive, reproducible, relatively inexpensive, and could help treatment decisions, particularly in patients with difficult-to-control hypertension. However, these drug metabolite screens provide only snapshot information and—especially if done without informing the patient—could substantially undermine the relationship between doctor and patient. These extensive efforts to assess adherence objectively are primarily for research and only feasible in high-income countries.

The Commission is convinced that it is very important for treatment adherence that the patient can see a clear relationship between increase in antihypertensive treatment and decrease in blood pressure. Therefore, we recommend use of either ambulatory, home, or automated unobserved blood pressure to initiate and titrate treatment (rather than the highly variable office blood pressure, which could mask the effectiveness of a drug).

A growing body of evidence suggests that a multidisciplinary approach to improve adherence is needed. This approach includes task sharing and involvement of non-physician health workers and family members, as well as educating the patient and reminders to reinforce the importance of treatment adherence. Different approaches can be used depending on the economic, cultural, and social context (see section on Empowerment as a tool).

Side-effects of antihypertensive treatment are another major factor contributing to poor blood-pressure control. Drug and drug-class-specific side-effects such as cough associated with use of angiotensin-converting enzyme inhibitors, peripheral oedema with dihydropyridine-type calcium channel blockers, and tiredness with β-receptor blockers are well recognised and cause treatment failure in a proportion of patients with hypertension. Notably, the combination of dihydropyridine calcium channel blockers with angiotensin-converting enzyme inhibitors significantly reduces the occurrence of peripheral oedema, the most common adverse drug reaction usually leading to discontinuation of the calcium channel blockers (irrespective of their efficacy in lowering blood pressure).

Hypotension—as a side-effect of antihypertensive therapy—occurs largely independently of the choice of antihypertensive drug class. In fact, especially in older
individuals, episodes of systolic hypotension are extremely common, affecting roughly 55% of patients aged 75 years and older.\textsuperscript{109} There is a complex interplay between hypotension, cerebral hypoperfusion, and poor adherence to therapy as a result of impaired cognition that add to the challenges of antihypertensive therapy, especially in elderly people.

**Pharmacological prevention**

Antihypertensive therapy has a major role in the primary and secondary prevention of cardiovascular and renal diseases, both in the general population and in at-risk populations such as those with diabetes or chronic inflammatory diseases. Antihypertensive drugs are therefore part of a concerted treatment strategy to tackle cardiovascular risk factors such as hypertension, obesity, dyslipidaemia, and hyperglycaemia. Preventive treatment often starts with the assessment of biomarkers such as blood pressure, bodyweight, cholesterol, and glucose levels, followed by the targeted prescription of individual drugs to address these risk factors. By contrast, the notion of a polypill containing fixed doses of preventive drugs such as antihypertensive drugs, statins, and aspirin, which is prescribed irrespective of the exact individual risk but rather depending on average population risk (eg, based on an age threshold)\textsuperscript{302,303} has gained attention, especially in low-income and middle-income countries where the burden of cardiovascular diseases is high, resources for diagnostic tests are scarce, and inexpensive and standardised treatments are more likely than individualised therapies to be taken up in clinical practice.\textsuperscript{304} The beneficial effect of lipid-lowering treatment with statins in patients with high cardiovascular risk is well supported by several studies,\textsuperscript{305,306} but findings from the HOPE-3 study\textsuperscript{307} showed that lipid-lowering statin treatment also reduced cardiovascular events in individuals with intermediate risk and no known cardiovascular disease independently of blood pressure and antihypertensive treatment. However, there is an ongoing debate about indications, cost-effectiveness, and composition of the polypill, making translation of this concept into clinical practice very difficult.\textsuperscript{307}

Primordial prevention of hypertension can be achieved by prescribing antihypertensive drugs at a stage when blood pressure is still within the normal range. The classification as high normal blood pressure\textsuperscript{113} for blood pressure ranges of 130–139 mm Hg systolic and 85–90 mm Hg diastolic has been introduced because individuals in this range are more likely to progress to hypertension compared with those with normal or optimal blood pressure. Studies in individuals with high normal blood pressure have shown with short follow-up periods (2 years in TROPHY\textsuperscript{109} and up to 3 years in PHARAO\textsuperscript{109}) that incident hypertension can be prevented or at least delayed. However, because of insufficient long-term follow-up data, primordial prevention of hypertension is open for further research. Such treatment is, however, well tolerated and provides a basis for prevention trials in high-risk patients such as those with atherosclerosis\textsuperscript{110} or chronic renal failure,\textsuperscript{110} for whom there is some evidence that treatment of normotensive individuals to systolic blood pressures below 130 mm Hg can be associated with beneficial outcomes. However, another approach was tested in the blood-pressure-lowering part of the HOPE-3 trial\textsuperscript{308} in which people with intermediate risk without known cardiovascular disease were randomly assigned to candesartan 16 mg plus hydrochlorothiazide 12·5 mg versus placebo for 5–6 years. Significantly improved outcome, however, was only observed in people with baseline systolic blood pressure greater than 143·5 mm Hg (ie, in the top tertile of systolic blood pressure among trial participants), thus not supporting antihypertensive treatment in normotensive individuals at intermediate cardiovascular risk—although the study was not powered to detect benefits among different subgroups defined by baseline blood pressure. Therefore, the evidence base is not sufficiently robust for primordial prevention to be universally accepted.\textsuperscript{311}

**Management of elderly individuals with hypertension**

More than 30% of people older than 65 years fall at least once annually,\textsuperscript{305,310,311} and antihypertensive treatment is a major (and modifiable) risk factor for falls.\textsuperscript{314,315} The risk is particularly high when more than three defined daily doses of antihypertensive drugs are taken and is independent of specific drug classes such as diuretics or β blockers.\textsuperscript{315} Aggressive treatment of older people with hypertension might not only increase their risk of falls via episodes of hypotension, but also lead to poor adherence to therapy and increased adverse drug reactions.\textsuperscript{316} However, in the SPRINT trial\textsuperscript{317} there was no increase in falls-related injuries requiring hospital evaluation or admission. A useful strategy could be to monitor blood pressure more carefully with automated devices (when the patient is alone and relaxed), use systematic home or 24 h ambulatory blood-pressure measurements, and include standing blood pressure in elderly people to identify patients with clinically significant hypotension before any falls occur.

Another relevant aspect in older people with hypertension is cognitive impairment, with the prevalence of dementia increasing from 7% in subjects older than 65 years to 30% in subjects older than 80.\textsuperscript{317} Subjective reports of memory loss begin about 2–3 years before onset of dementia.\textsuperscript{318} Elevated blood-pressure levels in middle-age have been associated with increased risk of dementia in older age.\textsuperscript{318} Elevated blood pressure provokes early damage of cerebral white matter microstructure\textsuperscript{319} and is associated with poor cognitive performance, even at young ages.\textsuperscript{312} Thus, cerebrovascular injury should be considered and monitored as target-organ damage in hypertension in its own right\textsuperscript{320} to prevent the onset of clinical overt dementia, to slow the progression of cognitive decline, and to postpone the onset and
exacerbation of behavioural symptoms that can often lead to loss of independent living of patients and can be devastating for caregivers. Antihypertensive treatment can improve cerebral microcirculation through reduced blood pressure and protective effects on arteries of specific antihypertensive drugs. However, as with falls, treatment that is too aggressive can result in hypotension and cerebral hypoperfusion, thereby accelerating the progression of cognitive decline in older individuals.

We should acknowledge the lack of strong evidence from randomised controlled trials on the protective role of blood pressure reduction on cognitive dysfunction. Clinical trials that include cognition as primary endpoint are needed. The randomised controlled trials should include predominantly older individuals and adopt accurate and cost-effective tests to screen for cognitive impairment. Such trials might clarify whether the association between hypertension and cognition is causal and which antihypertensive drugs are the most effective in slowing progression of cognitive impairment and postponing the onset of overt clinical dementia. Furthermore, improved characterisation of pathways linking hypertension to cognitive decline and dementia could help to identify novel drug targets such as accelerated arterial ageing, clearance of cerebral parenchymal waste products (including β-amyloid) via the perivascular circulation, and the response of the cerebral vasculature to injury.

**Ethnic and cultural differences**

With a few exceptions, most mortality and morbidity trials into hypertension management have been done in individuals of European descent, and limited trial data are available to inform treatment specifically for those of Asian, African, or Middle Eastern origin.

The challenges in understanding the ethnic and cultural differences in cardiovascular disease are substantial. Ethnicity is difficult to define and classify. The biology of individuals is driven by complex sets of gene–gene, environment–environment, and gene–environment interactions, and some clear physiological differences are apparent across ethnic groups (eg, decreased renin concentrations and endothelial nitric oxide bioavailability among those of African origin). Among the environmental influences are socioeconomic issues, but issues including widespread differences in stress handling, smoking habits, nutrition, and caloric intake can have pronounced effects on the prevalence of hypertension and development of target-organ damage, including overt cardiovascular disease. As a consequence, the results of hypertension research in individuals of European descent might not apply directly to those of non-European ancestry.

As the world becomes more connected and increases in prosperity, lifestyles characterised by reduced levels of physical activity and unhealthy diets rich in fat, salt, and sugar are more common everywhere. As a result, the prevalence of hypertension and diabetes mellitus increases, with predictable adverse effects on cardiovascular outcomes. To better manage the already high but expanding need for antihypertensive treatment in people of non-European descent, more ethnically specific research is needed concerning genetic adaptation as a promotor for cardiovascular risk factors, development of target-organ damage, and, crucially, the optimal pharmacological management of raised blood pressure. However, ethnic differences in culture and lifestyle and underlying socioeconomic conditions probably affect cardiovascular events more than do genetics.

**Lifestyle modifications**

Nearly all guidelines recommend non-pharmacological therapy or lifestyle modification as a first-line approach to hypertension management. Lifestyle modification offers universal appeal as an intervention because the costs, in motivated individuals, are minimal and can lead to drug step-down or withdrawal. However, in the absence of self-motivation, achievement-sustained lifestyle modifications require substantial resources over a longer period. Furthermore, although the benefits of lifestyle modification in cardiovascular prevention are clear, evidence to guide the use of individual-based lifestyle modification as a stand-alone or add-on therapeutic intervention is lacking, which is perhaps most evident for dietary modifications. For example, investigators of the DASH-Sodium trial and others have established that a low-sodium diet can lead to substantial improvements in blood pressure. Long-term follow-up data from the Trials of Hypertension I and II also suggested that the long-term risk of cardiovascular events might be reduced with sodium reduction. Similarly, high potassium intake has been purported to reduce blood pressure. Restriction of salt intake has been demonstrated to reduce blood pressure and cardiovascular events more in patients with hypertension than in those without hypertension.

Evidence of varying quality suggests that particular foods (eg, beetroot, nitrate-containing foods and beverages, garlic, and flaxseed) can reduce blood pressure levels. However, the usefulness of such foods to lower blood pressure remains to be proven in large cohorts. Ultimately, further research—including interventional studies—are needed to guide the use of dietary modification in the treatment of hypertension.

Increased physical activity is another lifestyle modification for which there is reasonable consensus on value as a preventive intervention but less guidance for its use as therapy. Most recommendations suggest increased physical activity in the management of hypertension and extend logically from the large bodies of observational data showing associations between decreased physical activity and cardiovascular risk. Findings from meta-analyses also suggest that exercise training reduces blood pressure in healthy individuals and those with hypertension. Even in patients at high cardiovascular risk, the benefits of
regular exercise could outweigh any risks by improvement in cardiac structure and function. Nonetheless, there remains a paucity of data about the optimal form (eg, aerobic vs resistance or isometric training), type (eg, swimming vs running), and thresholds at which maximum benefit are achieved. Moreover, there is a pressing need for strategies to optimise uptake of recommendations.

Finally, the evidence supporting the use of most lifestyle modifications in therapy is typically from studies that looked at these modifications individually. In practice, however, lifestyle modification should be systematic, and assessment of the efficacy of multiple lifestyle modifications given together will be crucial. Indeed, although the effects of individual lifestyle modifications on blood pressure might be small, the effect of several modifications together might prove more effective than pharmacotherapy, at least in some patients.

Meta-analyses for this are already underway. Irrespective of the evidence gaps, the general consensus is that people should be encouraged to engage in some form of regular exercise to improve their cardiovascular risk profile.

Targeting pathophysiology
Pathophysiology-based approaches to secondary hypertension
Many of the factors that regulate blood pressure through the key mechanisms of cardiac output, volume status, and vascular tone are known and include the sympathetic nervous system, the renin–angiotensin–aldosterone system, and renal function. In primary (essential) hypertension, a large number of factors with fairly small effects act together, whereas in secondary hypertension, one or very few well defined factors with substantial contributions to blood pressure dominate.

Individualised treatment that targets the specific cause of hypertension substantially improves blood pressure control in most patients with secondary hypertension and even cures hypertension in at least a fifth of such patients. In patients with primary aldosteronism, adrenalectomy in cases of unilateral production of aldosterone and medical therapy including aldosterone antagonists for bilateral hyperaldosteronism are therapeutic options to control blood pressure. Surgical resection can cure hypertension in patients with a catecholamine-producing tumour. Although renal percutaneous transluminal angioplasty is indicated in the first instance in patients with fibromuscular dysplasia, randomised trial data have shown no benefit of surgical revascularisation or stenting compared with medical therapy in patients with atherosclerotic stenosis of renal arteries. In patients with rare forms of monogenic hypertension, such as Liddle’s syndrome and Gordon’s syndrome, blood pressure control can be achieved and hypertension can be controlled with lifelong treatment with a single drug such as amiloride (Liddle’s syndrome) or a thiazide-type diuretic (Gordon’s syndrome).

However, despite decades of research, the indication for adrenal surgical resection versus medical therapy for primary aldosteronism is still controversial, especially in very elderly patients, and the benefit of interventional treatment of renal artery stenosis remains under debate. International randomised clinical trials are still required to develop evidence-based indications for medical or interventional therapies in different categories of secondary hypertension.

Personalised treatment and management by multidisciplinary teams with appropriate expertise are essential to achieve favourable outcomes in patients with secondary hypertension. Lifelong specialised follow-up is indicated, and in some cases (including catecholamine-producing tumours caused by germline mutations of SDHB) follow-up includes not only the patient (who is at risk of recurrence and development of metastases) but also their relatives (when genetic testing offers the possibility to detect and treat asymptomatic disease in family members). However, the profound knowledge of the natural history of the different forms of secondary hypertension and specific prognosis biomarkers needed to precisely refine follow-up recommendations is still lacking.

Pathophysiology-based approach to essential (primary) hypertension
The mechanisms underlying the pathophysiology of essential hypertension are complex and multifactorial. Lessons learned from the treatment of patients with secondary forms of hypertension can, however, inform therapeutic approaches to those with essential hypertension. Activation of the sympathetic nervous system, which occurs in patients with phaeochromocytoma, also plays an important part in the initiation and maintenance of elevated blood pressure and associated adverse effects in many patients with essential hypertension. The close association between the sympathetic nervous system and the renin–angiotensin system in the pathophysiology of hypertension has led to the development of mechanisms-based approaches to hypertension treatment, including drugs and invasive procedures targeting the neurogenic component of hypertension; however, further investigation is needed before introduction of these therapies into the clinical setting. With available evidence linking excess aldosterone to disease progression, resistant hypertension, and mortality, further studies to improve selectivity and tolerability of drugs directly aimed at the aldosterone pathway are needed. A reduction in blood pressure and sympathetic activity has been demonstrated with invasive therapeutic strategies such as baroreflex activation therapy and renal denervation in treating patients with truly resistant hypertension or those whose hypertension is uncontrollable in the absence of other treatment options. However, in the light of the similar blood-pressure responses to renal denervation and sham control found in the Symplicity Hypertension-3 trial, a better
understanding of underlying pathophysiology is needed before using these treatment approaches (for example, insufficient ablation of the renal sympathetic nerves might explain the lack of difference in blood pressure noted in the trial). An approach which ablated a combination of nerves, including the main renal artery and branches, resulted in the greatest reduction in renal sympathetic activity in an animal model, indicating that renal denervation done in all arteries including accessory renal arteries produced a greater reduction in blood pressure and sympathetic nerve activity compared with ablation in the main renal artery alone in patients with resistant hypertension. These findings might substantially improve efficacy of renal denervation and reduce the variability in blood pressure response to the procedure, which should be assessed further in randomised, sham-controlled clinical studies.

Although pathophysiological principles should be explicitly considered within personalised management of hypertension control, the contribution of individual pathophysiological factors to a patient’s elevated blood pressure is difficult to assess in clinical practice, where comprehensive assessment of the sympathetic nervous system and renin–angiotensin system to the same standard as in clinical research studies is not feasible. However, findings from the PATHWAY-2 study showed that the blood pressure response to classes of antihypertensive drugs could be predicted by plasma renin concentration, a crude measure of the activity of the renin–angiotensin system. Additionally, assessment of haemodynamic profiles with non-invasive devices that are simple to use seems to help in deciding on initiation of treatment, choice of drugs, and monitoring of therapy.

The potential cause and underlying mechanisms of unresponsiveness to antihypertensive drugs in patients who adhere to treatment need to be addressed in future clinical trials. The role of lifestyle modifications including stress management in the treatment of hypertension and the question of whether behavioural and procedure-based therapies can favourably modulate neurogenic mechanisms and ultimately prevent hypertension and its cardiovascular consequences still need to be explored systematically.

**Treatment of hypertension beyond the treatment of elevated blood pressure**

Treatment of hypertension currently focuses on blood-pressure-lowering measures. However, in the future, we suggest that additional therapeutic strategies beyond the mere lowering of blood pressure will have to be explored and applied. Recent data suggest that the pathophysiology of hypertension is more complex than originally thought and involves processes such as endothelial dysfunction, inflammation, altered sodium handling, and oxidative stress. Targeting of these mechanisms will, in most cases, not immediately reduce blood pressure but rather counteract the substantially altered vascular phenotype that truly characterises hypertension. The potential to develop a cure for hypertension that at the same time treats the phenotype of persistently elevated blood pressure should be the ultimate aim.

In addition to traditional and emerging risk factors, molecular biomarkers will help to characterise the phenotype of hypertension in individual patients, pointing towards the specific dysregulated pathways that can be targeted with specific therapies, thereby paving the way for personalised medicine in hypertension. In this sense, biomarkers—for example, subclinical cardiovascular phenotypes and target-organ damage—can be a target of antihypertensive therapy, not as a symptom to be minimised but as a definition of the condition that is altered when it has been successfully treated.

**Targeting haemodynamics**

Haemodynamic assessment might help in the choice of antihypertensive therapy by identifying individuals who might benefit more from ad-hoc regimens (based on matching the haemodynamic action of drugs with the haemodynamic pattern of hypertension) and assisting in the titration of the intensity of therapy to specific goals. To achieve this goal, new methods that assess arterial pressure and flow dynamics, beyond focus on conventional upper-arm blood pressure, are needed.

Antihypertensive medications can have different haemodynamic effects in the large central arteries (eg, aorta, carotids) compared with the brachial artery where the blood pressure cuff is applied. For instance, organic nitrates lower central aortic systolic blood pressure more than systolic brachial blood pressure. By contrast, β blockers (primarily atenolol) less effectively lower central aortic systolic blood pressure but have similar effects on brachial systolic blood pressure compared with calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers. Thus, assessment of left ventricular hypertrophy and geometry and arterial pressure waveforms to determine haemodynamic and volume status, and central aortic loading conditions, can efficiently refine hypertension management decisions, as supported by findings from two randomised trials. The BEAUTY study compared haemodynamic monitoring using impedance cardiography (combined with a drug selection algorithm) versus conventional drug selection for the treatment of uncontrolled hypertension. Both strategies resulted in similar reductions in ambulatory daytime and office systolic blood pressure, although therapy based on impedance cardiography was associated with more use of diuretics and fewer side-effects than conventional management.

Blood pressure variability has been recognised as a prognostic factor independent of the level of blood pressure per se. Most of the evidence, however, relates blood pressure variability with the risk of stroke, whereas the association with other cardiovascular events seems to...
be less robust. Different ways to calculate blood pressure variability, different modalities of variability (short term, long term, day–night, and others86), and little evidence about therapeutic approaches specifically directed to change blood pressure variability hinder the translation of a potentially useful concept to clinical practice. Different effects of various drug classes on blood pressure variability have, however, been described87,88 and could form a basis for prospective evaluation in clinical trials.

At this point, it is clear that measurements of haemodynamic patterns of hypertension are of interest to elucidate mechanisms related to the pathophysiology of hypertension in individual patients, and hold promise as a therapeutic strategy in hypertension. However, further investigations are needed before they can be recommended for routine clinical use. In particular, trials designed to target specifically central blood pressure at any given level of brachial blood pressure are required.

Targeting subclinical organ damage
Targeting of biomarkers might be useful if improvements in biomarker profiles are associated with improved outcome.89 Left ventricular hypertrophy in hypertension has previously been considered as adaptive, but the presence of left ventricular hypertrophy is associated with increased cardiovascular risk. More importantly, treatments such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers90,91 decrease in left ventricular hypertrophy, which is predictive of improved prognosis.92,93 It remains unclear whether treatment guided by the level of left ventricular hypertrophy adds incremental benefit over blood-pressure-targeted treatment.

For detection of vascular and renal damage, urine albumin–creatinine ratio is the most robustly studied parameter. When increased, it is associated with atherosclerotic disease, myocardial infarction, and cardiovascular risk. Furthermore, any substantial reduction is associated with improved prognosis,94 especially in diabetes in some95 but not all trials.96 The major challenge related to urine albumin–creatinine ratio is the variability of this parameter with time and intervention.97,98 For other subclinical markers, the evidence is more scarce.

Markers of large artery structure and function,99 especially carotid-to-femoral pulse wave velocity100 and carotid distensibility,211,212 have demonstrated their added value against cardiovascular risk scores. They appear simple to use and are applicable in large groups. Reference values are available101,102 and efforts have been made to standardise measurements, but whether arterial markers can be used to target therapy remains unclear. Similarly, early brain damage can be detected by MRI through white matter hyperintensities.213 However, by contrast with left ventricular hypertrophy and urine albumin–creatinine ratio, whether intervention can reverse these lesions is unclear. Further information is needed before considering cerebral lesions a target for therapy.

An important problem is that target-organ damage is slow to respond to treatment,97,98 thereby reducing its value as a monitoring tool in the acute care of patients. However, changes in target-organ damage can detect failure or success of therapeutic strategies before the development of myocardial infarction, stroke, or cardiovascular death. Whether targeting of subclinical organ damage rather than or in addition to blood pressure provides additional benefit to the patient or to society remains to be clearly demonstrated. For example, the ongoing SPARTE trial103 will address the question of whether arterial stiffness assessed as carotid-to-femoral pulse wave velocity can be used as a surrogate endpoint. The demonstration that such monitoring of treatment is advantageous over the classic approach based on blood pressure measurement should be tested in clinical trials.

Summary of possible actions
There is a large arsenal of effective pharmacological agents with established efficacy in the treatment of hypertension. To improve the pharmacological management of hypertension globally, a crucial first step is to ensure universal access to affordable, high-quality therapeutics. However, even with this access, therapy is not always given optimally. We therefore recommend the development of evidence-based decisional algorithms to inform health-care professionals precisely on the required diagnostic and therapeutic steps. Such algorithms should be based on the most current evidence, be clear and simple, and aim to standardise the diagnostic work-up and therapy of almost all patients with hypertension. Such algorithms will probably include predominant use of generic drugs from major antihypertensive classes, combination therapy as an initial treatment approach, and measures to monitor treatment and improve adherence. When coupled with better identification of hypertensive individuals with the help of “more hands” in health service through task sharing, these actions will greatly improve blood pressure control and reduce the global burden of hypertension and related cardiovascular complications not only in individual patients but in whole populations.

In addition to these recommendations, research is needed to better understand the potential of targeted therapy depending on age, ethnicity, and cardiovascular risk on treatment, the utility of lifestyle modification in therapy, and the benefits of monotherapy versus combination therapy as an initial treatment strategy. It will also be important to assess whether treatment based on targets such as left ventricular hypertrophy, haemodynamics, and biomarker-based approaches are superior to blood pressure control for reduction of cardiovascular risk in hypertension. Prior to the development of hypertension, preventive therapeutic strategies including the use of polypills or targeting prehypertension also have the potential to delay the
natural lifespan of hypertension, but require evidential support.

Finally, the Commission sees a continued need for the development of new drugs, both those that act on new therapeutic targets and those that target existing pathways but have improved pharmacokinetic or pharmacodynamics profiles (table 3).

### Empowerment as a tool

#### Introduction to empowerment

Education and empowerment are related tools that offer great potential to improve the global management of elevated blood pressure. Abundant evidence suggests that early health education improves outcomes in terms of primordial prevention; education can also be tailored to improve interactions between patients, doctors, health-care providers, pharmacists, and key participants in the management of hypertension to maximise its effectiveness.

Patient empowerment more specifically refers to the process of shifting a patient’s mentality from a passive recipient of health care towards an active role where they understand their condition and their role in the health-care process, and take self-initiated actions to benefit their health.395,396 The many strategies for patient empowerment include shared decision making, self-led lifestyle modifications, self-administered treatment and monitoring, and the provision of health information (eg, biochemistry) directly to the patient. Irrespective of the method, strategies that foster patient empowerment have consistently been shown to increase patient satisfaction, encourage adherence, and improve outcomes in chronic diseases including hypertension.396–398

A complementary and essential relative of patient empowerment is community empowerment, the process of empowering communities of people—defined by geographic proximity, shared common interests, or even disease (eg, hypertension)—to take control over their conditions and improve the quality of their lives and collectively overcome inequities.399,400 Strategies for community empowerment include provision of education, technical information, and tools necessary for action, ultimately enabling the community to define the problem, determine the best solution, and implement the response.399,401 However, a community-based programme that includes stakeholders from the community is not necessarily a community empowerment approach. In community empowerment, an essential component is leadership and control of the process by the community, coupled with availability of essential resources and capacity to act. An empowered community is confident, inclusive, organised, cooperative, and influential. All of

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<td>Lack of antihypertensive drug availability</td>
<td>Improve availability of affordable, high-quality, and effective antihypertensive agents worldwide*</td>
<td>Universal availability of at least one of each class of antihypertensive drug Availability of single-pill combinations where resources permit Development of novel therapeutics based on improved knowledge of pathophysiology†</td>
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<td>Lack of available health-care professionals for management</td>
<td>Increase capacity for management of hypertension worldwide*</td>
<td>Train community health workers to detect, initiate, and monitor treatment of hypertension Expand health-care workforce by facilitating task sharing in the management of hypertension</td>
</tr>
<tr>
<td>Lack of stratified approaches to the treatment of hypertension</td>
<td>Optimise treatment initiation, goals, and combinations according to age, ethnicity, and cardiovascular risk*</td>
<td>Harness existing data to provide rational information on optimisation of targets, treatment initiation, and therapy based on age, ethnicity, and cardiovascular risk Support randomised controlled trials that focus on optimisation of BP targets, treatment initiation, and therapy†</td>
</tr>
<tr>
<td>Poor adherence to treatment</td>
<td>Improve approaches to overcome poor adherence</td>
<td>Harness information technology tools to facilitate patient adherence Identify determinants of poor adherence Develop treatment approaches targeting causes of poor adherence†</td>
</tr>
<tr>
<td>Limited information on how to use lifestyle modification as therapy</td>
<td>Establish defined approaches to incorporate culture-specific lifestyle modification into management of hypertension</td>
<td>Integrate existing knowledge into management strategies Randomised controlled trial to determine optimal lifestyle modification approaches to hypertension management</td>
</tr>
<tr>
<td>Brachial blood pressure might be a suboptimal measure to guide treatment</td>
<td>Determine whether treatment to alternative targets improves cost efficacy and effectiveness of antihypertensive treatment</td>
<td>Assess the relative benefit of management based on target-organ damage† Assess the relative benefit of management based on biomarkers†</td>
</tr>
<tr>
<td>Uncertain effect of empowering patients to take control of their antihypertensive management</td>
<td>Assess the benefits and determine optimal implementation of self-treatment</td>
<td>Randomised controlled trials to assess the effectiveness of self-treatment†</td>
</tr>
<tr>
<td>Physician inertia in increasing antihypertensive medication</td>
<td>Counteract physician inertia</td>
<td>Promote education of doctors and health-care professionals through the availability of simple guidelines for daily management of hypertension</td>
</tr>
</tbody>
</table>

*Essential goals. †Related to research.

Table 3: Identified problems and corresponding goals and actions relating to pharmacological treatment
these aspects, when brought to bear on preventing and controlling hypertension, can result in effective and sustainable changes in a community’s health trajectory.

**Education**

In addition to population-wide education strategies, patients and individuals at risk of hypertension represent an audience potentially receptive to more focused educational initiatives. Education in such populations might be expected to improve communication between provider and patient, and ultimately empower the patient to play an active role in managing their risk factors and disease. Indeed, abundant and long-standing evidence suggests that patient education improves outcomes in hypertension. Physicians who spend more time with patients and engage more in lifestyle and prevention education generally prescribe less medication. However, long-term follow-up of this strategy is needed to measure the effect on patient outcome. Despite this evidence, and the fact that virtually all practice guidelines for hypertension advise lifestyle modifications as first-line treatment, educational initiatives are not universally implemented, even in patients with hypertension. In one study, only 55% of young adults with hypertension had documented evidence of lifestyle education after diagnosis.

A major gap in knowledge is the lack of clarity about what constitutes effective lifestyle counselling for hypertension. For example, how many sessions, of what duration, over what period of time, and in what format are most effective? Systematic reviews of educational interventions in patients with hypertension are underway and could ultimately provide some clarity in this area. In addition to this consideration, health-care delivery systems are unlikely to adequately deliver patient education in the clinical environment. Conventionally, physicians are seen as being central to oversee lifestyle change, but this strategy might not be the best approach. The World Development Indicators on Health Systems indicate that there are only 0.1 physicians and 0.5 nurses for every 1000 people in low-income countries, and even in high-income countries the available 3.1 physicians and 8.6 nurses per 1000 are insufficient to carry out this important task effectively. It is, therefore, understandable that major reports and guidelines on prevention of cardiovascular disease state the importance of an integrated approach or shared responsibility involving numerous stakeholders to ensure successful implementation of preventive strategies.

Community health workers, pharmacists, nurses, physiotherapists, dietitians, and other allied health professionals are probably better positioned than medical doctors to provide consistent and substantive lifestyle education. Introducing or strengthening community linkages and resources creates new opportunities for the delivery of health information and patient-centred disease management. In parallel, continuing education of all health workers remains crucial to ensure delivery of optimal care based on current knowledge. Experience with trained non-physician community health workers in Pakistan, South Africa, and Iran has shown that lay health workers could effectively deliver health-promotion materials, detect high blood pressure, and reduce blood pressure levels in the population. Indeed, team-based care and task sharing with nurses, pharmacists, and medical assistants are effective in improving blood pressure control, particularly when coupled with education on medication, which could also be extended to other professions.

Primary-care physicians must also ensure that they are applying best practice based on the best available knowledge. For future physicians, the university medical training curriculum must sufficiently address current guidelines and also include novel approaches such as patient empowerment, self-treatment, and the use of new technologies. International and national professional societies should also work together to produce consistent guidelines, because real or perceived inconsistencies are a likely cause of therapeutic inertia.

**Self-monitoring of blood pressure**

Self-monitoring empowers individuals to engage in their own management of blood pressure, leading to many possible benefits, including more active treatment by doctors, facilitation of discussion with doctors, improved patient–doctor relationships, greater possibility for adhering to antihypertensive therapy, and reduction of blood pressure. Self-monitored blood pressure must be done with a standardised protocol to minimise the potential for erroneous readings from extrinsic (eg, device validation) and intrinsic (eg, level of relaxation) factors affecting reading quality. The widespread availability of educational material on self-monitoring should make this information easily accessible to patients and doctors. Despite all the potential advantages of self-monitoring, there are still evidence gaps relevant to both patients and clinicians. Patients lack education about what they should be concerned about and how to act; physicians have insufficient clarity about how to optimise the use of self-monitoring in the clinical encounter, and need better guidance in interpreting self-monitored values (including how to handle differences from clinic blood-pressure measures). Future developments in wearable devices that are appropriately validated could overcome some of these hurdles. For health-care systems, an expanding number of monitors now include technology for the immediate communication of a patient’s home-measured blood pressure reading to the doctor’s office or another third party. Clinical protocols, capacity, and response systems need to be developed to support timely, appropriate, and meaningful feedback to patients to improve control. The use of these devices in self-titration is described further below.

**Self-administered treatment**

Self-administered treatment provides an important opportunity to improve management of chronic diseases
such as hypertension. This approach seeks to shift patients from mere receivers of drugs prescribed by the physician to active participants in the shared decision making regarding their treatment. For this approach to be effective, patients should be given advice based on the best available scientific evidence, with alternative approaches and outcomes presented so they can choose the treatment strategy that is most suitable for them. The patient’s individual goals are prioritised while ensuring that they understand the short-term and long-term consequences of their choices.

Only a few studies have assessed self-management and self-titration in hypertension. One pilot study assessed the effectiveness of self-management and self-titration with a web-based system; blood pressure was effectively reduced, but there were barriers to implementation of the protocol, including the patients’ lack of trust in the system. Findings from the SETHI and TASMINH trials further showed that self-monitoring and self-titration could engage patients in their treatment, resulting in improved blood-pressure control and reductions in cardiovascular risk up to 12 months after initiation. Further clinical trials will be necessary to better identify the target populations, develop algorithms or procedures for drug adjustment, and evaluate the most effective duration of the intervention. There is also a need for specific training for both patients and doctors and to monitor progress regularly. It is possible that self-titration could reduce clinical inertia (ie, resistance to change), but this notion remains to be proven.

Technology

Mobile and internet technologies already play an important role in the management of hypertension by educating patients and supporting disease management; this role is expected to grow alongside a global increase in availability.

App and web-based content provide an opportunity to reach both the patient and the general population, especially in low-income and middle-income countries. By providing resources that are available to patients at all times, there is increased opportunity to educate and influence a patient’s lifestyle outside of the clinic at times when they are more receptive to change. However, such approaches must adhere to current clinical recommendations. Investigators of a study who assessed whether internet content accurately reflected the American Academy of Paediatrics recommendations for infant sleep safety found that less than half of all high-traffic websites were consistent with recommendations, with a substantial influence of low-accuracy retail-product sites and blogs. Accordingly, the hypertension community will need to guard against the circulation of outdated or erroneous educational material within the plethora of available health-related content. One possible approach would be for international and national professional societies to collaborate in endorsing a consistent message through the creation of a universally recognised seal of approval to ensure confidence in the quality of the content.

Information and communications technology systems are a potential key to empowerment in hypertension care. These technologies can empower patient-centred medicine with enhanced access and continuity of health care, management planning according to the best available scientific evidence through computerised decision-support technology, and tools to promote self-management including patient-guided services such as electronic or mobile health applications and telemedicine. Information and communication technologies can also reduce medical errors and improve response to adverse events. There is also emerging evidence that telehealth and e-counselling services could be effective addenda to pharmacological interventions or as a preventive strategy in hypertension.

Finally, we have to consider the potential of mobile and wearable technologies, which are increasingly integrated into life, to enhance self-monitoring and treatment. Wearable technologies that assist in fitness monitoring are increasingly popular and could motivate individuals to improve their overall lifestyle. Hypertension-specific wearable technology is now emerging and could ultimately increase awareness, engagement, and, potentially, self-monitoring. To fully engage patients, this technology should be easy to use, without the need for complicated access or operation, while providing feedback on hypertension control in real time. One successful model of such an approach was deployed by Logan and colleagues, who used a system of Bluetooth home blood-pressure monitoring connected to a pre-programmed smartphone working through a central server to receive messages to inform the patient about the status of their blood pressure control. In patients with diabetes and hypertension, this system significantly reduced systolic and diastolic blood pressure compared with patients who were only controlled by home blood-pressure measurement after 1 year. Interestingly, the higher rate of blood pressure control was not related to higher use of blood pressure medications. The system seemed to be well accepted by patients and did not increase the number of visits to the doctor. There are also some promising results about the efficacy of mobile technologies for blood pressure control even for patients with low literacy living in low-income or middle-income countries, who reported a high level of satisfaction with care.

Summary

It is clear that there are several approaches to the management of hypertension that encourage patient engagement and empowerment and improve dialogue between patient and provider. An important consideration for such strategies will be the need for both educated patients and responsive health-care teams and providers to ensure the persistence of empowered behaviours.
It should be noted that, to date, the benefits of these patient empowerment strategies have typically been evaluated only over fairly short periods of time (ie, <2 years). The effects of these interventions could conceivably diminish over extended periods of time. Accordingly, for chronic diseases such as hypertension it will be important to assess the long-term feasibility, cost-effectiveness, and benefits of any approach. It will also be important to incorporate empowerment and technology into hypertension management within the context of available resources. Pioneering approaches, particularly those involving expensive technology in resource-rich locations, can inform future universal application.

**Blood pressure and health systems**

**The economics of managing blood pressure**

Blood pressure control was identified as a leading target of the 2013 WHO Global Monitoring Framework to reduce deaths from non-communicable diseases by 25% by 2025. Elevated blood pressure is a main indicator of high risk for cardiovascular disease, and many premature deaths can be averted cost-effectively through community and clinic-delivered interventions. Because most deaths related to non-communicable disease are projected to occur in the future in low-income and middle-income countries, specific consideration of the benefits and costs of hypertension prevention and control in resource-limited countries is warranted. However, a comprehensive health system initiative to prevent and treat hypertension would need to encompass efforts to address other important cardiovascular risk factors such as smoking, excessive alcohol intake, unhealthy diet, hyperlipidaemia, obesity, and inactivity.

Economic analysis can guide priority setting related to blood pressure management. Hypertension management can be cost-effective, with an estimated annual cost per person of implementing simple population management programmes (including distribution of base blood pressure diagnostic tools and at least one of eight essential medicines to lower cardiovascular disease risk in medium-risk or high-risk patients) of less than US$1 in low-income countries, less than US$1.50 in lower-middle-income countries, and US$2.50 in upper-middle-income countries. A multidrug package targeting hypertension and cardiovascular disease in 23 low-income and middle-income countries has been estimated to reduce cardiovascular death rates by 1.5-5% per year at an average annual cost of US$1.08 per person. With a large proportion of the population in low-income and middle-income countries having elevated blood pressure, hypertension management for even half of patients at moderate to high risk in these settings could avert an estimated 0.77 million deaths, or 15.4 million disability-adjusted life-years at a ratio of US$23 in benefits per $1 spent. Population-level drug treatment for elevated blood pressure is highly cost-effective, based on the assumption of a linear relationship between reduction in blood pressure and cardiovascular events reduction estimated to be cost saving. Salt reduction was identified by WHO as a “best buy” for non-communicable disease prevention and control, particularly as some of the relevant strategies can be implemented at very low cost. South Africa, Brazil, Argentina, and Chile are countries with industry agreements to reduce salt in processed food, and approaches to change behavioural patterns can be used where salt is added at the table, as in India.

**Health systems in relation to elevated blood pressure**

A health system is a broad term that includes elements from population surveillance to clinical care to public health infrastructure, as well as the financing to support it. The population-level impact of interventions pertaining to blood pressure management depends on the strength of the health system that delivers them. In low-resource settings where primary care systems are underdeveloped, public systems will need to incorporate new capacity for hypertension management, and explore efficiencies by linking with existing systems for addressing other diseases, such as HIV/AIDS, which might help alleviate administrative and delivery costs. Even in high-income countries where delivery systems for primary care are already established, these systems have to be updated through financing and delivery reform to ensure they remain effective and can deliver improved outcome. For chronic diseases to be managed successfully, delivery systems must be designed to avoid patterns of patient use that are episodic and acute in nature, supporting, instead, planned patient visits and continuity of care. There are hallmarks of health-care delivery systems that will improve the control of hypertension relevant to all health systems, high income or low. These include standardisation of treatment, team-based care, broad scale availability of affordable medications, and community engagement. The Innovative Care for Chronic Conditions Model proposed by WHO provides a framework for organising chronic care delivery, emphasising the importance of preventing the fragmentation of services from inpatient, to outpatient and pharmacy services, to prevention and community efforts. The Chronic Care Model, which emphasises proactive, planned, patient-centred, and team-based care, and connections between clinics and communities, has been shown to improve outcomes. Creating registries of patients with hypertension can allow for efficient management approaches across the continuum of care delivery points, allows for system accountability, and has been used in effective models. These aspects need to be implemented to achieve success in reducing the burden of blood-pressure-related disease.

Access to medication is another key requirement. Assuring sustained broad-scale access to affordable medications is challenging and approaches vary by country depending on health-system organisation and financing. In general, procurement and distribution processes should be carefully reviewed. Use of generic
formulations, simplified packages, or polypills, and wide distribution mechanisms such as primary health or outpatient facilities, can help scale up distribution in low-resource settings. In the Americas, the Pan American Health Organization’s Strategic Fund provides a model of regional support for drug availability by offering member states technical assistance with management of the drug supply chain and drug quality, creating a capital account to prevent stock-outs during emergencies, and negotiating favourable prices for drugs on their products list, including medications to treat hypertension.464

The promise and potential scale of universal health coverage throughout the world is expected to improve outcomes for non-communicable diseases. Universal health coverage is defined by WHO as “ensuring that all people have access to needed promotive, preventive, curative and rehabilitative health services, of sufficient quality to be effective, while also ensuring that people do not suffer financial hardship when paying for these services”.460 Universal health coverage involves three coverage dimensions—health services, finance, and population—and is a dynamic, continuous process that changes in response to shifting demographic, epidemiological, and technological trends, as well as people’s expectations.25

The 2013 WHO World Health Report encourages global adoption of universal health coverage, which has most recently been introduced in Thailand and Mexico, and is under consideration in India.461,462 The 2009 health reform in China emphasised the role of efficient health-care delivery for chronic diseases, including hypertension.463 The WHO and World Bank global monitoring report, Bringing universal health coverage (universal health coverage) into focus, for the first time quantified and tracked progress in universal health coverage in key areas of financial protection and health services coverage for populations as a whole, as well as subpopulations living in rural areas and the poor.

Strong health information systems are also necessary to advance the conditions for hypertension prevention, treatment, and control.464 Although there is no single cross-national surveillance system for cardiovascular disease and hypertension, several surveys, registries, cohort studies, and vital statistics can be used by different stakeholders to gather different kinds of information about these conditions. Technological advances in health-care systems and electronic health-care records can be used for surveillance and monitoring of health-care interventions in hypertension, including randomised trials testing the effects of different public health policies. As noted earlier in this Commission report, data necessary for even the most descriptive surveillance needs of prevalence are lacking. Government investment in health information systems at all levels is necessary to inform and advance efforts to prevent and control hypertension throughout the world. Monitoring the new objectives of the Sustainable Development Goals, for example promoting wellbeing and ensuring universal health coverage, presents an opportunity to focus on strengthening countries’ health information systems, using an integrated, comprehensive approach based on each country’s individual needs.465

In summary, national health systems can influence the global burden of hypertension. However, continuing commitment is needed by national governments to prioritise the protection and promotion of health and wellbeing of their citizens by ensuring best practices are implemented.466

Global health initiatives to reduce elevated blood pressure

Several initiatives are underway worldwide focusing on health systems improvement within the context of hypertension prevention, treatment, and control. Million Hearts is a national initiative from the USA to affect population health, aiming to prevent 1 million heart attacks and strokes in the USA by 2017 through health-system strengthening by increasing focus on cardiovascular prevention and by improving access to effective cardiovascular health care. The Centers for Disease Control and Prevention and Centers for Medicare & Medicaid Services, co-leaders of Million Hearts within the US Department of Health and Human Services, are collaborating with other federal agencies and private-sector organisations to make a long-lasting impact against cardiovascular disease. Million Hearts aims to prevent heart attacks and strokes by improving access to effective care and improving quality of care for the ABCS of heart health: aspirin (when appropriate), blood pressure control, cholesterol management, and smoking cessation. It focuses clinical attention on the prevention of heart attack and stroke, encouraging the public to lead a healthy lifestyle, and improving the prescription and adherence to appropriate medications for the ABCS.465,467

The Global Standardized Hypertension Treatment Project was originally developed across the Americas in 2012 with a focus on strengthening of clinical health systems. The initiative focused pharmacological management, with a core set of antihypertensive medications, ensuring their availability through efficient procurement mechanisms, using patient registries to monitor blood pressure control using standard treatment protocols, and encouraging team-based care and patient empowerment.468 Demonstration projects have been initiated in two countries, Barbados and Malawi, to improve control of hypertension through improved management in primary health-care settings in Barbados and using an existing HIV/AIDS platform in Malawi. Results from these projects are expected in 2017. The project framework and activities have been expanded to include lifestyle components, and it is being integrated into a global initiative, Global HEARTS.

China’s Shandong province (population 96 million), where hypertension and excessive sodium intake in adults are major public health problems, provides an example of hypertension control with population approaches such as sodium reduction through lifestyle changes. Most salt in
the diet is added at the table or during cooking. The Chinese Ministry of Health and the Shandong Government collaboratively launched the Shandong–Ministry of Health Action on Salt Reduction and Hypertension in 2011, introducing expanded blood-pressure screening and treatment, and driving changes in social norms by supporting health-promoting environmental policies. These strategies were implemented in concert with a surveillance system, funding mobilisations, and strengthening of local capacity of health services. Provincial and local government agencies and health-sector teams target interventions in household and educational settings such as elementary schools, and also prehypertension and hypertension populations from a representative study cohort selected by a complex, four-stage cluster sampling with strategic partners such as food industry, businesses, and restaurants to reduce sodium intake. Mid-term evaluation reported a decrease in the per-person seasoning salt intake in Shandong from 12.5 g to 11.58 g per day.468-470

By contrast, in the UK—where most dietary sodium consumption is through packaged and restaurant foods—a government-led initiative included a focus on reducing the amount of sodium in processed foods. Results are promising.471 The Institute of Medicine recommended a similar strategy to sodium reduction in processed foods in the USA. Areas of future research that could benefit low-income and middle-income countries in particular include country-specific cost–benefit analysis of different hypertension interventions. This strategy could help to optimise resource allocations in low-resource settings, and inform decisions to invest in strengthening of health systems (table 4).

**Key actions and implementation**

**Setting the scene for a multifaceted approach**

10-4 million people are estimated to die each year because of elevated blood pressure.41 The costs in terms of morbidity and mortality, as well as economic and societal costs, are substantial. The causes of hypertension are complex, as are the solutions. Hypertension is often the product of a lifelong interplay of individual and environmental factors, starting even before birth. Thus, the approach to this growing public health problem is multifaceted. First, there is a need to respond immediately to those at highest risk for related complications—those with evident hypertension and perhaps subclinical or even clinical cardiovascular disease—through evidence-based clinical treatment, delivered effectively by health systems designed to assure successful control for every patient. However, even if expertly delivered to all, such an approach is inefficient and does not thoroughly address the true breadth of the problem. The size of the hypertension problem, the previous relative failure of individual non-pharmacological prevention and the large proportion of undiagnosed and untreated patients with essential hypertension, underlines the need for solutions focused on population-based approaches including public health. The pipeline of future patients includes virtually every human being. Even those who reach middle-age without hypertension have a more than 90% chance of developing the condition during their remaining lifetime.472 Aggressive population-wide interventions that fundamentally include changes to the social and economic living environments will dynamically shape how populations behave, and will directly affect primordial and primary prevention. Such approaches are crucial and must be a part of any strategic approach that will successfully address the management of hypertension at the global level. Primary prevention will include early information on the importance of a healthy lifestyle and help to make appropriate lifestyle changes. However, for real impact, policies are required that will improve the socioeconomic environment, strategically framed on improving the population living environment as a whole. This approach must include intentions to reach people of all ages in the environments where they live, work, and play.

Population-level interventions will require multisectoral engagement from government, industry, non-governmental organisations, and civil society as a whole. The solutions we develop must be multidimensional, transforming the communities (reaching individuals indirectly) in which we live into health-promoting environments, and supporting innovations and improvements not

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<table>
<thead>
<tr>
<th>Goals</th>
<th>Actions</th>
<th>Keywords</th>
</tr>
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<tbody>
<tr>
<td>Lack of standardised, comprehensive knowledge about blood pressure levels</td>
<td>Endorse the WHO/World Health Assembly NCD Global Monitoring Framework</td>
<td>Health-system strengthening</td>
</tr>
<tr>
<td>Lack of system accountability for blood pressure control</td>
<td>Advocate for appropriate resourcing of surveillance systems</td>
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<tr>
<td>Health system collects, monitors, and responds appropriately to blood pressure levels</td>
<td>Create accessible reports</td>
<td></td>
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<tr>
<td></td>
<td>Develop efficient health-care delivery systems that monitor blood pressure levels for their populations and act appropriately</td>
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<tr>
<td></td>
<td>Develop task-sharing approaches that effectively deliver care in resource-constrained settings</td>
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</tr>
<tr>
<td></td>
<td>Connect health-care delivery centres with appropriate community points of blood pressure measurement</td>
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The action to endorse WHO/World Health Assembly NCD Global Monitoring Framework is closely connected to the key action on universal access to measurement of blood pressure, whereas the action to ensure accountability of the health system to collect, monitor, and respond appropriately to blood pressure levels is closely connected to the key action on expanding the capacity of the clinical workforce engaged in management of blood pressure. These two health-care system actions are later combined to one key action. NCD=non-communicable disease. *Essential goals.

Table 4: Identified problems and corresponding goals and actions relating to health systems
only in the health-care systems from which we access care, but also in the broader socioeconomic environment (eg, food systems and availability).

**Essential goals and related key actions**

The Commission has identified ten essential goals and related key actions that, not surprisingly, overlap to a large extent with current global health initiatives within the field of hypertension (table 5). The key actions are not prioritised among each other because they are complementary, and the balance between strength of evidence and potential benefits are inherently different between selective pharmacological intervention in high-risk patients versus broad implementation of health-promoting programmes. In essence, the key actions aim to stimulate goal-oriented dialogue, bridging concepts and strategies from public health, health-care systems, and clinical practice. The Commission approaches the hypertension problem at many different levels through improvement of public knowledge (to motivate healthy living including checking blood pressure); the environment (to support healthy living); education of health workers (to increase capacity and quality of detection and management); access to affordable, good-quality antihypertensive drugs; and health-care systems (to monitor and coordinate the actions).

**Key actions within prevention, in relation to current global initiatives**

**Introduction**

Many doctors consider preventive measures against hypertension to be ineffective, time-consuming, and with poor results. The time-pressed and stressful lifestyles that are increasingly the norm create environments that promote hypertension, encouraging easy or less expensive options such as sedentary behaviours and consuming cheap, salty, sugary, and fatty foods. Because many of the challenges required to address these challenges are social and political rather than medical, this report is not intended to be read exclusively by scientists and health-care professionals but instead aims for a broader audience—including various industries, policy makers, and civil society. Hence, the fundamental key action would be to strongly support policies and strategies that enhance changes in the broader socioeconomic environment with the greatest likelihood of population-wide benefits for cardiovascular health (figure 7).

**Creating a health-promoting environment**

The key to global prevention and control of hypertension is to support global adoption of health-promoting diets high in vegetables, fruits, legumes, whole grains, and quality proteins, with no introduction to tobacco and no

<table>
<thead>
<tr>
<th>Essential goals and related key actions</th>
<th>Keywords</th>
</tr>
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<tr>
<td>Pharmacological prevention and treatment</td>
<td>Health system collects, monitors, and responds appropriately to blood pressure levels (accountability)</td>
</tr>
<tr>
<td>Lack of available health-care professionals</td>
<td>Universal availability of at least one of each class of antihypertensive drug</td>
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<tr>
<td>Lack of stratified treatment</td>
<td>Information about optimisation of blood pressure targets, treatment initiation, and therapy based on ethnicity, age, and risk</td>
</tr>
<tr>
<td>Blood pressure and health-care systems</td>
<td>Promote and ensure capacity and accountability of the health system to conduct surveillance and monitoring</td>
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Table 5: Summary of main problems and key actions

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<table>
<thead>
<tr>
<th>Problem</th>
<th>Key actions</th>
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<td>RCT=randomised controlled trial. †Related to research.</td>
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**Prevention: lifestyle and environmental changes**

| Unhealthy environment | Strategies and policies to accelerate socioeconomic improvements and development of health-promoting environments; accelerate the implementation of accepted health-promoting policies | Make healthy food choices easier, combat tobacco, and promote physical activity in daily living | Health-promoting environment |
| Lack of understanding about unhealthy lifestyle | Early and sustained education about healthy lifestyles and blood pressure (new technology) | Educate and empower health workers and teachers to instil healthy lifestyles | Healthy behaviours |
| Low awareness | Ensure universal access to blood pressure measurement through inexpensive monitors and surveillance | Tailored education about hypertension throughout the life course | Measurement access |

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**Diagnosis and evaluation**

| Poor measurements | Certification and validation of monitors and endorsement of protocols for measuring blood pressure by professional societies | Develop simple, inexpensive blood pressure monitors; preference for home, ambulatory, automated, and unobserved blood pressure measurement | Measurement quality |
| Poor cardiovascular risk assessment | Promote education of patients, doctors, and health professionals | Reinforce targeting of global cardiovascular risk rather than single risk factors | Empowerment |
| Poor or delayed diagnosis of secondary hypertension | Simple protocols for detecting secondary hypertension in communities with few resources | Improve the availability of relevant investigations | Secondary hypertension |
Health literacy
Governments and civic society should encourage community-based strategies that promote health literacy, including early and continuous education on hypertension as a so-called silent killer, and emphasise how a healthy lifestyle can help to avoid elevated blood pressure. Health-literacy education should empower teachers to encourage children, through education, to make healthy life choices, such as being active, avoiding smoking and alcohol, and eating fruits and vegetables regularly—all known to have a direct effect on cardiovascular health. Ideally, every child on the planet should finish school as a health-literate adult.

Technological applications in food systems, social media, and wearable and mobile technology
Much more could be done to apply technology in food systems: for example, such efforts could ensure the consumption of fruit and vegetables all year round. Especially in low-income and middle-income countries, advanced technologies to facilitate distribution of foods to all communities and basic technologies such as refrigeration will result in increased consumption of fresh, nutritious foods, known to be beneficial in improving vascular health. Technology already exists to enforce and monitor food regulations, but can be applied more widely to, for example, monitor the real-time measurement and transmission of contents of packaged foods. Social media offers unprecedented potential to affect systemic change in the understanding, prevention, and management of hypertension at all lifecourse stages. More than 3 billion people worldwide are active internet users, with about 70% maintaining social media accounts. Improved success of social media campaigns to educate, monitor, and control hypertension, but also to improve community health behaviour, can be achieved by improved collaboration between different health professional organisations (eg, specialists in hypertension, heart disease, stroke, kidney disease, cancer) and social-media public health platforms. For example, coordination of efforts to existing activities such as World Health Day and World Hypertension Day can also help to attract widespread engagement.

The Commission recommends a close collaboration between a wide range of stakeholders such as governments, the mobile communications industry, health-care professionals, the pharmaceutical industry, and professional societies to not only develop and distribute inexpensive, validated, and certified blood pressure monitors, but also to ensure correct use through simple mobile apps and online education endorsed by the professional societies. In parallel, the Commission proposes that governments and health-care systems respond to the national goals, targets, and indicators outlined in the Sustainable Development Goals and the WHO Global Monitoring Framework.

Key actions within diagnosis and evaluation in relation to current global initiatives
Better characterisation of individual phenotype will not only improve hypertension risk assessment and help guide the choice of intervention, but can also act to empower people towards greater ownership of their condition and adherence to recommended intervention. Enhanced phenotypic characterisation, including identification of secondary hypertension, will also serve to strengthen the quality of health information systems for hypertension prevention, treatment, and control. Thus, important goals will be to ensure widespread access to valid and endorsed blood pressure devices, as well as enabling greater focus on global cardiovascular risk
management instead of single risk-factor focus, and also simplifying protocols to improve detection of secondary hypertension (figure 8). A method to help achieve these goals will be to provide widely accessible and professional-society-endorsed educational material by dissemination to the general community and treating doctors.

Provider-led efforts in education, empowerment, and lifestyle interventions are often restricted to the time that a patient is in the clinic (when they might not be receptive to such efforts), whereas online resources have unlimited availability and provide great opportunity for widespread education. Endorsement and promotion of online educational material by professional societies related to hypertension should help to disseminate appropriate information and advocate against erroneous material. This endorsement should be consistent with national and international recommendations and can serve as a reassurance that the content being accessed is based on the most up-to-date clinical knowledge. Resources for patients and doctors about blood pressure measurement should be with preference for home blood pressure, ambulatory blood pressure, and automated, unobserved blood pressure methods.

In a similar manner, professional societies could also give consideration to providing a seal of approval or certification of blood pressure devices meeting appropriate accuracy standards, which is particularly important given the rapid developments in wearable technologies marketed without validation testing according to current international expectations. Active warnings on substandard devices can be provided. These options would help to safeguard measurement quality more broadly and might even provide a potential source of revenue for professional societies. The seal of approval could, in turn, be used by manufacturers for marketing. Mechanisms to manage cross-society coordination and harmonisation of messaging in these efforts will be needed. It will also be important to develop resources that are accessible and empowering to doctors, including simplified guidelines with truncated flow charts addressing management of global cardiovascular risk and identification of secondary hypertension to aid examination and treatment decisions. All material endorsed by professional societies related to hypertension should be produced with standardised instructions that are clear and easy to follow for the end user, to enable wide uptake into different health-care services beyond those that focus on cardiovascular disease (eg, HIV/AIDS services) and into under-resourced regions.

Key actions within pharmacological prevention and treatment in relation to current global initiatives

Introduction

Our recommendations relate to affordable therapies, monitoring and self-monitoring of treatment, composition of health-care teams, risk assessment, and decisional algorithms (figure 9). The Commission encourages the scientific community, health-care providers, funding bodies, and the pharmaceutical industry to join forces and address these issues jointly and urgently. Not all questions have been solved and a consensus on the exact research question or implementation steps has to be reached as a first step. We can therefore only highlight the areas that need urgent attention.

Ensure access to affordable, high-quality medicine worldwide

As the best-documented antihypertensive therapies are now off patent, a minimum recommendation is that at least one of each class of antihypertensive medication should be available to all individuals around the world. Limitations to access include regulatory, political, and corporate factors. Where resources allow, single-pill combination therapy should be available. Future research should focus on the development of novel therapeutic approaches based on improved understanding of underlying pathophysiology. Combination therapy should also be expanded. Within antihypertensive classes, there should be a focus on improving pharmacokinetic profiles. Such changes could further reduce side-effect profiles and improve adherence.

Modest investments in strategies to improve the availability and uptake of effective blood-pressure-lowering medications, including investments in the development of systems that identify people who will benefit from therapy and deliver appropriate treatment, promise huge benefits that would probably be extremely cost-effective. Global, concerted action between governments, industry, civil society, and international organisations has made HIV therapy available at affordable costs to patients in low-income and middle-income countries, and similar efforts are currently underway for treatment of hepatitis C.

There is no reason why concerted strategies with the goal

Figure 8: Key actions within diagnosis and evaluation

The blue line represents the general lifecourse. The horizontal black dotted lines represent three avoidable clinical thresholds. The three blue boxes represent the key actions within diagnosis and evaluation. QOL=quality of life. BP=blood pressure.

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to make quality treatment available worldwide should not be successful in hypertension.

**Extend health-care workforce task sharing**

An extension of existing health-care workforce capacity can be achieved at modest cost by promoting team-based care and task sharing. Especially in low-income and middle-income countries, where health-care professionals are too scarce to effectively reach the population at risk, it is crucial to engage communities and train community health workers to detect and initiate treatment of hypertension. Data showing this approach to be feasible and effective are accumulating. Even well-resourced countries have suboptimal recognition of blood-pressure-related cardiovascular risk, and inconsistent assessment and monitoring. Accordingly, more comprehensive strategies using approaches beyond opportunistic screening at medical visits for other purposes are required. The approaches successfully used in childhood vaccination for infectious disease offer lessons in this regard. New models need to be developed and carefully assessed in clinical trials. Through task sharing and alternative community points of blood pressure measurement, we need to develop efficient systems for health-care delivery that are held accountable for monitoring blood pressure levels in their populations and for acting appropriately.

**Evidence-based decisional algorithms and stratified treatment strategies**

Although the current management of hypertension is based on principles regarding assessment of absolute risk and blood pressure reduction that are supported by strong evidence, many important parts of antihypertensive treatment are often applied on the basis of individual provider experience. Examples of these provider-related choices are most promising lifestyle modifications; when to add pharmacological antihypertensive treatment; use of lifetime cardiovascular risk versus 10-year risk; initial medical treatment strategies (eg, choice of drugs, monotherapy vs combination therapy); titration strategies; and monitoring of treatment success (monitoring blood pressure alone or alongside target-organ damage). Algorithms developed by professional societies and health-care institutions based on the best evidence are rarely adopted or applied consistently across institutions by all providers.

This Commission sees the urgent need to develop and implement simple algorithms that inform health-care professionals precisely on the required diagnostic and therapeutic steps. Such algorithms should be evidence based, or evidence from pragmatic and prospective clinical studies could be used. The potential for cost savings through standardisation of diagnosis and therapy extends to the more targeted use of specialist services for the minority of patients with complex issues, whereas most patients could be managed by general practitioners and allied health-care professionals in partnership, with appropriate means for patient empowerment and self-monitoring.

Implementation of simple evidence-based algorithms that standardise evaluation and treatment of hypertension will indirectly identify areas with less evidence and create a perfect basis for investigator-initiated prospective studies on treatment strategies. The PATHWAY studies show that investigator-initiated studies of treatment strategies are possible and can lead to clear answers. This Commission, therefore, encourages the scientific community to develop and define treatment strategies and then test them in clinical trials. Furthermore, the knowledge of the effects of age, social background, culture, and ethnicity on antihypertensive treatment is scarce. Therefore, the Commission encourages establishment of international collaborations to combine existing population surveys and create large web-based registries—using cloud computing technology—based on data generated by patients’ use of widely available, easy to use, certified apps, following the simple evidence-based algorithms mentioned above.

**Key actions within health-care systems**

Reducing raised blood pressure is one of the key targets of the WHO Global Monitoring Framework aimed at decreasing deaths from non-communicable diseases globally. Strengthening health systems, which encompasses all of those structures responsible for advancing health from population surveillance to public health and clinical care delivery, is an essential overarching goal required not only for preventing and controlling hypertension but to advance population health at large. All of the key actions noted earlier in this report ultimately rely upon highly functioning health systems.
to be implemented successfully and sustainably. This includes actions related to creating health-promoting environments, to assure access to affordable quality medications, and to establish care delivery systems that produce equitable and accountable health outcomes. Universal health coverage, which ensures everyone access to the benefits of the health system without financial hardship related to payment, is a recognised prerequisite, and strongly supported by this Commission, WHO, and the UN. Many different actions have to be implemented in parallel to improve management of hypertension globally. Therefore, it is necessary to develop surveillance models, taking advantage of new technologies that can measure the needs of the population, assess the functioning of the health system, and guide improvements in the system. Government investment in health information systems at all levels is essential to combine these many streams of actions against hypertension in one comprehensive approach under the framework of health systems.

**A multifaceted approach to the key actions**

Hypertension and all its associated complications are products of a lifelong interplay of individual and environmental factors, and, therefore, a multifaceted approach to this growing global problem is essential. The key actions proposed by the Commission (figure 10) are targeted at different populations, age groups, groups of health professionals and social workers, and groups of individuals at different stages of hypertension; the actions are either dominated by programmes and system change when evidence is convincing and by research when evidence is missing.

The key actions of this report follow from the identification of the most pressing needs on a global level. Hypertension will—at some point in life—affect almost every individual in the world, many of whom live in countries with very few economic resources. Therefore, the key actions in this report are mostly key actions at the population level. Furthermore, in light of the massive burden of hypertension in low-income and middle-income

![Figure 10: Summary of all key action points](image-url)

The blue line represents the general lifecourse. The horizontal black dotted lines represent three avoidable clinical thresholds. The green, blue, or red boxes represent the key actions within prevention, diagnosis and evaluation, and pharmacological prevention and treatment. CV=cardiovascular. QOL=quality of life. BP=blood pressure.
countries, we have explicitly pursued a globally feasible approach, partly by leveraging new technologies.

Overall, the Commission suggests intervening in parallel throughout the spectrum of risk from population level to patients at high cardiovascular risk. The proposed interventions (the key actions) consist of a mixture of research, development, programmes, and system change all leading to the creation of a health-promoting environment (figure 1). They build on the idea of empowerment: empowerment of individuals through broad health education, which is a prerequisite for an individual to make informed choices and to take ownership of their condition; empowerment of communities with socioeconomic difficulties to offer medical care to all individuals at risk of developing hypertension and cardiovascular disease; and empowerment of the medical community by offering simpler and more efficient tools to manage hypertension.

Global technical package for hypertension

As noted in the introduction to this report, the ultimate aim of this Commission is to generate a globally unifying campaign to prevent raised blood pressure, improve the management of elevated blood pressure, and reduce the impact of hypertension across the world. The Commission has identified ten key actions that are additive and synergistic. They range from population-based environmental policies aimed at shifting the population distribution of blood pressure downward by supporting healthier lifestyles and behaviours, to more individualised approaches targeted at high-risk groups with hypertension and increased cardiovascular risk. Interventions aimed at individuals include effective and good-quality antihypertensive treatment with the aim to reduce the size of the upper population distribution tail of blood pressure. As such, the Commission recognises the importance of bridging public health, health-care systems, and clinical practice. The actions we have identified are many, and full implementation will require diligence and persistence over time.

Although the details of roll-out will be refined over time with input and leadership from a variety of stakeholders from local to global, we believe it is useful to reflect on approaches used by other major global efforts to advance health. Public health programmes, including smallpox eradication, tuberculosis control, tobacco control, polio eradication, and others, have made progress by addressing six key areas: innovation to develop the evidence base for action; a technical package of a small number of high-priority, evidence-based interventions that together will have a major impact; effective performance management, especially through rigorous, real-time monitoring, evaluation, and programme improvement; partnerships and coalitions with public-sector and private-sector organisations; communication of accurate and timely information to the health-care community, decision makers, and the public to effect behaviour changes and engage civil society; political and partner commitment to obtain resources and support for effective action including related health-system strengthening initiatives such as universal health coverage. In cardiovascular prevention it is crucial to reduce risk factors, including high blood pressure, tobacco smoking and second-hand smoke exposure, exposure to air pollution, high BMI, physical inactivity, alcohol use, and diets low in fruits and vegetables and high in sodium and saturated fats both at individual (clinical) and population levels. The Commission supports the WHO Global Monitoring Framework initiative to reduce the high-value prevention targets, which can be effectively addressed through implementing the so-called best buys for prevention of non-communicable diseases.

The Commission proposes a unifying implementation plan, articulated as a technical package, designed to support two general and interrelated areas: prevention and treatment. Each area will include selected high priority and scalable interventions that can mobilise, commit, and boost international and national capabilities.

The prevention-related technical package would cover improved public understanding of unhealthy and healthy lifestyles and blood pressure and its consequences, policy and environmental approaches to promote health and support healthy behaviours, and improved access to effective health-care delivery systems and use of preventive and clinical services, and better cross-talks between community programmes and clinical services. We envisage the treatment package to include standard protocols for investigation (diagnosis and risk stratification), treatment (stratified and risk based), and monitoring, and team-based care, task sharing, and workforce development, with decentralised, community-based, and patient-centred care, and training and capacity building. The treatment package should also include access to affordable medications, technology, and health care, with promotion of access to a high-quality core set of medications, including fixed-dose combination pills at affordable cost to improve adherence. Finally, the treatment package should include enhanced surveillance, patient registries, and information systems to monitor trends in hypertension management, ensure accountability and equitable outcomes, and promote interoperable information systems to monitor implementation needs and effectiveness of interventions.

Future plans after this report

It is the intention and the ambition of The Lancet and the Commission on hypertension that this report should be a step towards an enhanced collective action to implement suggested actions to improve the management of blood pressure and reduce the impact of elevated blood pressure globally. With this report in hand, the Commission will contact hypertension organisations including the international, regional, and national societies, as well as other relevant international agencies (including cardiology, neurology, and nephrology...
societies) to propose global alliance. With the support of these professional societies, together we will carry forward the mission to draw up a broad-based campaign of advocacy and action, involving governments, industry, civic and consumer organisations, and health professional bodies. The Commission will call for relevant international, national, and subnational agencies, policy makers, researchers, public-health practitioners, development agencies, and donors to champion the recommendations of the report. The campaign will not just be a health campaign, but a much broader multisectoral campaign, bringing together all elements of society to address the lifelong health burden of elevated blood pressure using the lifecourse strategy described in the report. This goal cannot be realised without accelerated and substantial commitment from donors and national governments.

Contributors
All authors contributed to strategic planning, literature search, data interpretation, and the writing and revision of the report.

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