



From epidemiological transition to modern cardiovascular epidemiology: hypertension in the 21st century

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In 1971, Omran formulated the theory of epidemiological transition to explain the shift in mortality and disease patterns worldwide.¹ The theory begins with the major premise that mortality is a fundamental factor in population dynamics. At the beginning of time was the age of so-called pestilence and famine. Mortality was high; life expectancy around 20–30 years; and famine, injuries, and infectious diseases were common causes of death. The first transition took place around 10 000 years ago which brought the world into the age of receding pandemics. Life expectancy increased to 40 years and tuberculosis, cholera, typhus, and the plague were responsible for deadly infectious pandemics. Populations shifted from foraging food to primary food production, and swelling populations, domestication of plants and animals, and progressively more sedentary lifestyles increased the prevalence of infectious diseases. The second transition happened in the 20th century when life expectancy reached 50 years. Profound changes in health and disease patterns took place in children and young women, and the primary cause of death shifted from infectious disease to chronic degenerative diseases.²

Although cardiovascular disease is the leading cause of death worldwide, death rates of people with cardiovascular disease have steadily decreased over the past three decades. In several industrialised countries, such as France, cardiovascular disease now ranks as the second most common cause of death after cancer, because of improved cardiovascular disease management rather than a rise in deaths caused by cancer. Improvements in cardiovascular mortality rates in industrialised countries are probably due to three major factors: an improvement in primary prevention of disease (better screening and treatment of cardiovascular risk factors and later onset of first events); more effective treatment of primary cardiovascular events that resulted in a considerable reduction in case-fatality over the past 30 years; and better secondary prevention with wider use of treatments with confirmed efficacy.³

Two major points stand out among cardiovascular causes of death. First, median age at death has risen over the past 30 years. Life expectancy has increased year by year and was 78 years in 2008 in France, when the median age of cardiovascular death was higher, for example, the median age of death from heart failure was 88 years.⁴ Second, whereas coronary heart disease and stroke are predominant causes of cardiovascular death, the proportion of deaths from heart failure and other end-stage cardiovascular diseases increases each year.⁴ Deaths caused by heart failure were as frequent as deaths caused by coronary heart disease and stroke in populations where

the average age of death is greater than 85 years.⁴ Findings from our prospective study⁵ in a population of very elderly people (mean age 87 years) showed that cardiac systolic dysfunction and atrial fibrillation were crucial risk factors for all-cause mortality in the later stages of life.

Hypertension is associated with stiffening and thickening of both vessel walls and ventricular walls,⁶ which can lead to clinical manifestations of cardiovascular and renal diseases, including coronary heart disease, stroke, arrhythmias, heart failure, and vascular dementia.

Coronary heart disease is a major cause of cardiovascular death. Hypertension, diabetes, dyslipidaemia, and smoking are all risk factors for myocardial infarction and other forms of coronary heart disease. Observational data from more than 1 million individuals showed that risk of death from both coronary heart disease and stroke increases progressively and linearly with blood pressure measurements from as low as 115 mm Hg (systolic) and 75 mm Hg (diastolic).⁷ Individuals with elevated blood pressure present more frequently with other risk factors for cardiovascular disease (diabetes, smoking, dyslipidaemia) and target organ damage. Potential interaction of risk factors increases the overall risk of patients with hypertension despite only mild or moderate blood pressure elevation.

Hypertension is the most important treatable risk factor for stroke. Stroke-related mortality in the USA over the past three decades has decreased, largely because of better blood pressure control, and achievement of specific targets of blood pressure levels for the prevention of primary and recurrent stroke remains an important goal.^{7,8} Hypertension is also the most prevalent, independent, and potentially modifiable risk factor for atrial fibrillation; up to 70% of patients with atrial fibrillation have a history of hypertension.⁹ Elevated blood pressure is also the most important risk factor for heart failure—roughly 75% of patients with heart failure have antecedent hypertension.⁸

The development of chronic kidney disease is associated with diabetes, hypertension, obesity, smoking, and low concentrations of HDL cholesterol.¹⁰ Along with diabetes, hypertension is a major risk factor for chronic renal disease and for progression to end-stage renal disease.

Finally, cognitive decline, one of the most devastating signs of ageing and vascular disease, is rapidly becoming a substantial cause of disability and mortality worldwide. Increasing evidence shows that hypertension, which causes damage to small and large cerebral vessels, is the most important, modifiable, vascular risk factor for the development and progression of cognitive decline and dementia.¹¹

Hypertension is, therefore, a major cause of coronary heart disease, stroke, arrhythmias, heart failure, renal disease, and dementia. Since the 1980s, mortality rates related to stroke and coronary heart disease have decreased in industrialised countries, partly because of improved blood pressure control. Life expectancy has increased, which provides the time and opportunity needed for the development of end-stage cardiovascular disease (such as arrhythmias, heart failure, renal disease, and dementia) and cancer.

Consequently, hypertension can lead to all stages of the cardiovascular continuum, independently of the previous stage. Hypertension left untreated could be considered as the origin of cardiovascular diseases. Research into future therapeutic strategies should give priority ranking to this epidemiological transition in hypertension.

Increases in life expectancy and end-stage cardiovascular disease events in patients with hypertension highlight the need for new risk-reduction strategies to reduce the burden of degenerative diseases. The following proposals all have little data at present and, therefore, need confirmation in dedicated therapeutic trials.

The first strategy is associated with the notion of residual risk in patients treated for hypertension.¹² Treated patients who reached the systolic blood pressure target of 140 mm Hg have a higher cardiovascular risk than do patients with a spontaneous systolic blood pressure reading of 140 mm Hg. This observation appears to substantiate the need for more ambitious target blood pressure levels for patients with hypertension, particularly within the first years of diagnosis.¹³ Intensive treatment at this early stage could reduce potentially irreversible arterial damage in individuals with hypertension, such as vascular and cardiac fibrosis.

The second proposal is that some of the residual risk could be attributable to the treatment that is too little and too late. Results from several studies suggest that prompt blood pressure reduction is preferable to delayed interventions,¹⁴ even in patients aged 80 years or older.¹⁵

The third strategy focuses on the optimum blood pressure measurement. Previous studies have established that treatment choice should be based on systolic blood pressure or pulse pressure in elderly people, rather than mean or diastolic blood pressure.¹⁶ Central blood pressure has been shown to relate more closely to white matter lesions, cognitive decline, and hypertension-related dementia than brachial blood pressure.¹⁷ Nevertheless, studies focusing on central blood pressure as the factor for titration of antihypertensive drugs are still lacking.

The fourth proposal is a fundamental shift. Existing guidelines suggest that the same baseline treatment be used for all patients with hypertension, that first-line treatment depends on baseline characteristics of the patient, or that no compelling factor exists in favour of one antihypertensive drug class or another.¹⁸ Not all

patients with hypertension are at the same risk of developing all potential complications, so why should the choice of antihypertensive drug not also focus on the diseases that are to be prevented? For example, renin-angiotensin-aldosterone system (RAAS) blockers probably prevent atrial fibrillation to a greater extent than blood pressure reduction.¹⁹

The fifth proposal is that antihypertensive drug combinations should be used more frequently, both as first-line and second-line treatments. In addition to easier and more rapid achievement of blood pressure goals when time is undoubtedly important,¹⁸ combination therapies could help to prevent disease to a greater extent than blood pressure reduction.^{18,19}

The sixth new strategy that we propose relates to the temporality of antihypertensive drug treatment. Hormonal systems are not constant throughout life. The RAAS, for example, is known to be affected by ageing,²⁰ and thus modifies the effects of antihypertensive drugs over time. This effect is seen with RAAS blockers and β blockers, which are both less effective with increasing age.¹⁸ If the choice of drug is affected by specific pathologies to be prevented, blood pressure lowering drug treatment should be modified during the life of the patient, independently of blood pressure control.

In summary, in terms of epidemiological transition, causes of cardiovascular death have clearly evolved over the past three decades: end-stage cardiovascular disease (atrial fibrillation, renal disease, dementia, and heart failure) is becoming more frequent than coronary heart disease and stroke. Because hypertension is the most prevalent cardiovascular risk factor for all these diseases, modification of antihypertensive strategies could have a considerable effect in delaying these degenerative diseases, thus further improving life expectancy. New strategies for the management of hypertension should focus on early initiation of blood pressure lowering drug treatment, more ambitious blood pressure goals in the initial stages of hypertension, and use of emerging technologies for blood pressure measurement. Maintenance of optimum blood pressure levels will prevent associated disorders, encourage wider use of blood pressure lowering drug combinations in all disease stages, and, finally, allow the application of the notion of temporality in blood pressure lowering treatment—ie, consideration of physiological changes over time as a factor in the choice of blood pressure lowering treatment.

Contributors

JB had the original idea and drafted this Viewpoint. All authors had substantial input to the content, reviewed the final version, and approved its publication.

Declaration of interests

JB has received research support from Servier; has served on advisory boards for Sanofi and Daiichi Sankyo; and has served as a speaker for Amgen, AstraZeneca, Bayer, Bouchara, Daiichi Sankyo, Menarini, MSD, Novartis, Pierre Fabre, Pileje, Sanofi, Servier, and Takeda. BIL has received research support from Servier, has served on advisory boards for Servier, and has served as a speaker for Bayer and Servier. J-JM has