

Hypertension: treatments, diabetes, and developing regions

Despite major progress in prevention and treatment, hypertension is the leading risk factor for cardiovascular disease and mortality.^{1,2} Worldwide, more than 7 million deaths can be attributed directly or indirectly to the effects of hypertension. This major cause of morbidity and mortality affects between 20% and 50% of adults, depending on nationality and age.³ At age 65 years, individuals have a 90% chance of developing hypertension by the time they reach 80 years of age. In the USA, the annual cost of care for hypertension is estimated to be about US\$90 billion. More importantly, complications of hypertension have a substantial effect on quality of life because they affect the heart, brain, kidneys, and eyes. Hypertension affects not only adults but children as well, and although fewer children have hypertension than do adults, treatment costs are high and hospital stays are almost double the length, particularly if the child also has chronic kidney disease.⁴

To diagnose hypertension, treat, and follow-up patients, or investigate the mechanisms of hypertension and action of antihypertensive agents, blood pressure has to be reliably measured. Moreover, reliable measurement of blood pressure is indispensable to study of the prevalence and control of hypertension in populations, and to the assessment of health programmes and efficacy of health policies. More than 100 years after the invention of the sphygmomanometer, measurements of blood pressure are still variable and unreliable, largely because strict guidelines for blood pressure measurement are seldom followed adequately in the hurried assessment of patients in busy offices and hospitals.⁵ The variability with which the technique of measurement of blood pressure is undertaken⁵ might explain why prevalence and control of hypertension are reported to vary so substantially between countries, even those with similar cultures and lifestyles.⁶

*The Lancet's Series on hypertension*⁷⁻⁹ examines important aspects related to high blood pressure that are a cause for concern. Despite progress in the development of powerful antihypertensive agents and expansion of our mechanistic understanding of the disease, at best 50% of patients in developed countries have their blood pressure controlled to goal.⁶ Accordingly, Stéphane Laurent and colleagues⁷ examined new treatments for high blood pressure. Innovations in hypertension therapeutics have

become more rare over the past 5 years than during the previous two decades, which saw the development and initial clinical use of angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, a renin inhibitor, calcium-channel blockers, and new β blockers, and large multicentre randomised controlled trials to assess these drugs' effects on hard endpoints. Difficult to treat, resistant hypertension in patients—who often also have diabetes, chronic kidney disease, sleep-disordered breathing, or other disorders—has become easier to control because mineralocorticoid receptor blockers are now used.¹⁰ Although these drugs are relatively weak antihypertensive agents on their own, they are much more potent when added to triple therapy consisting of a renin-angiotensin blocker, a calcium-channel blocker, and a thiazide-like diuretic.¹⁰ This increased efficacy adds to the risk of hyperkalaemia, which needs particular surveillance in people with diabetes who might also have hyporeninaemic hypoaldosteronism or chronic kidney disease (or both). More frequent use of the thiazide-like diuretic chlorthalidone—that was, until recently, almost abandoned—has also helped to control the blood pressure of patients with resistant hypertension¹¹ and is specifically recommended by the UK's National Institute for Health and Clinical Excellence guidelines.¹² However, patients with refractory hypertension can still be unresponsive to four or more drugs. For these patients, a new treatment—catheter-based radiofrequency ablation of renal sympathetic nerves—is available. Although data

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from patients followed up for 2 years suggest that this approach is safe,¹³ its long-term effects are unknown. Appropriate selection of patients is crucial, and guidelines are only now starting to define which population of patients should be considered for this procedure. Additionally, several molecules in development are described in Laurent and colleagues' article⁷ that target the renin-angiotensin-aldosterone or endothelin systems or combinations thereof, including combinations of neprilysin inhibitors and drugs that release nitric oxide. Hopefully their development will result in safe and therapeutically effective antihypertensive drugs that not only lower blood pressure but also reduce morbidity and mortality.

Another paper by Ele Ferrannini and William Cushman⁸ addresses the important issue of hypertension and diabetes. 20% or more of people with hypertension have diabetes, and 80% or more of people with diabetes have hypertension.¹⁴ With the developing epidemics of obesity, metabolic syndrome, and diabetes,¹⁵ effective treatment for these patients with high cardiovascular risk is crucial. Although, until recently, evidence of how low to reduce blood pressure in these patients was not available, most guidelines recommended aggressive goals.^{16,17} However, the ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes—Blood Pressure) study¹⁸ has clearly shown that only a few patients benefit from lowering systolic blood pressure below 120 mm Hg, although those that do reach this goal reduce their risk of stroke, the most devastating and feared complication of hypertension. However, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation) trial¹⁹ suggested goals of around 135/85 mm Hg for patients with diabetes. Guidelines will probably go for the more conservative approach, and recommend achieving blood pressures of lower than 140/90 mm Hg, preferably around 135/85 mm Hg, and for the higher-risk patients close to 130/80 mm Hg, but not lower. For those at high risk of stroke, lower blood pressure goals might be recommended. Similar conservative goals will probably be recommended for patients with chronic kidney disease, and indeed guidelines²⁰ are already recommending a goal of 140/90 mm Hg or less, although these guidelines are still advising blood pressure goals of lower than 130/80 mm Hg for people with diabetes on the basis of the stroke benefit.²⁰

WHO has called attention to the fact that hypertension and other chronic diseases have become an important health problem in developing countries.²¹ As populations have become urban and westernised in culture, particularly their nutritional habits and lifestyle, hypertension has become increasingly prevalent in low-income and middle-income countries, as discussed by M Mohsen Ibrahim and Albertino Damasceno⁹ in their Series paper. Chronic disease and the cluster of hypertension, metabolic syndrome, diabetes, and dyslipidaemia, aggravated by the effects of tobacco use, need urgent state intervention in low-income and middle-income countries. Governments need to dedicate adequate funding to ensure that their citizens are appropriately educated about cardiovascular disease prevention and risk reduction through lifestyle changes, decreased salt intake, nutrition, and exercise. They must also ensure that high-quality affordable anti-hypertensive drugs are available, physically and financially, for affected populations. The participation of community organisations might be paramount to overcome barriers to access to health care. Adequate training of health professionals in the guideline-directed measurement of blood pressure and recommendations for evidence-based hypertension therapy adapted to resource-poor settings are both crucial, and means to enhance adherence to therapy need to be available. The International Society of Hypertension has increasingly developed educational activities in alliance with national and regional organisations in low-income and middle-income countries to help to achieve some of these objectives.²²

The task of controlling blood pressure undoubtedly remains a challenge, as shown by the poor control seen worldwide despite all that is known about the disease. However, communication of important aspects about hypertension, as discussed in *The Lancet's* hypertension Series, will surely contribute to the reduction of this important cause of heart disease, stroke, kidney disease, and death, and help to improve outcomes for patients with hypertension.

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Balancing the cardiometabolic benefits and risks of statins

Although the cardiovascular benefits of statins are unquestionable, concern has been raised about the potential diabetogenic effect of these drugs.^{1,2} This risk is most pertinent to the prescription of statins for people at low risk of cardiovascular disease—so-called primary prevention. In this setting, the absolute cardiovascular benefits of statins are less than in individuals at higher risk of cardiovascular disease and might be offset by drug side-effects, particularly new-onset diabetes.

In *The Lancet*, Paul Ridker and colleagues³ report from JUPITER (Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), a classic primary prevention study, that the incidence of diabetes (as reported by a physician) was higher in participants (with plasma C-reactive protein >2 mg/L) randomly allocated rosvastatin 20 mg daily compared with placebo during 5-year follow-up (hazard ratio [HR] 1.25, 95% CI 1.05–1.49, $p=0.01$). For participants

with one or more major diabetes risk factor (metabolic syndrome, impaired fasting glucose, body-mass index >30 kg/m², or glycated haemoglobin A_{1c} [HbA_{1c}] >6%) allocated rosvastatin, the primary endpoint (myocardial infarction, stroke, admission to hospital for unstable angina, arterial revascularisation, or cardiovascular death) was reduced by 39% ($p=0.0001$), venous thromboembolism by 36% ($p=0.08$), and total mortality by 17% ($p=0.15$), but incident diabetes was increased by 28% (HR 1.28, 95% CI 1.07–1.54, $p=0.01$) coupled with a significant increase in HbA_{1c}. In absolute terms, 134 total vascular events or deaths were avoided for every 54 new cases of diabetes. For participants without major diabetes risk factors allocated rosvastatin, the primary endpoint was reduced by 52% ($p=0.0001$), venous thromboembolism by 53% ($p=0.05$), and total mortality by 22% ($p=0.08$), with no increase in incident diabetes. In absolute terms, 86 total vascular events or deaths were

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