Hypertension is now endemic at a global scale, affecting 1 billion patients, and is no longer limited to developed countries. Based on current evidence, 7.6 million premature deaths (about 13.5% of the global total), 54% of strokes, and 47% of cases of ischaemic heart disease are attributable to high blood pressure (BP) worldwide. The estimated annual cost of hypertensive disease for the nations’ economies is considered tremendous; for the United States alone it reaches $66 billion. At the same time, despite the availability of more than 75 antihypertensive agents in 9 classes, BP control in the general population is at best inadequate. Thus, future antihypertensive strategies should be directed, apart from using the right combination of current drugs at optimum doses, towards clinical use of novel drugs, individually tailored gene-polymorphism directed therapy and development of new modalities such as immunotherapy.

Given the excitement of witnessing the emergence of new classes of drugs, one should firstly focus on direct renin inhibition. After solving the problems of bioavailability and poor efficacy, eventually the first non-peptide, orally active renin inhibitor has now been launched as a treatment for hypertension. It is likely to be as effective at lowering BP as other means of inhibiting the renin system in monotherapy, but with fewer side effects. Another field of research is the exploration of pathways responsible for the activation of guanylate cyclase, which increases cyclic guanosine monophosphate levels in target tissues, resulting in vasodilation and antiproliferation. An oral stimulator of guanylate cyclase lowers blood pressure, reduces cardiac hypertrophy and fibrosis in experimental models, but might inhibit platelet aggregation and prolong the bleeding time. Phase II and III trials will investigate the safety and efficacy of this agent, which would be most suitable for older patients with isolated systolic hypertension as well as for diabetics with stiff conduit arteries. On the same attractive template, targeting one of the major mechanisms for the augmented vascular wall stiffness, which is the accumulation of advanced glycation end-products, provides another therapeutic option. Nowadays, there are advanced glycation end-product breakers, such as alagebrium, which result in marked improvements in endothelial function and central aortic pressure when administered twice daily. These drugs may play a more central role in the near future due to the emerging notion that the sole arbiter of treatment efficacy in hypertension should not be just brachial BP, but also the improvement of aortic functional characteristics that are interrelated with diverse mechanisms of atherosclerosis progression and adverse outcome. Finally, NADPH oxidases have been shown to contribute to the pathogenesis of hypertension; thus, the development of specific inhibitors of these enzymes has focused attention on their potential therapeutic use. Two of the most specific inhibitors, gp91ds-tat and apocynin, decrease BP in animal models of hypertension, whereas other substances, including diphenylene iodonium, aminoethyl benzenesulfonyl fluoride, protein kinase C inhibitors, and VAS2870, have shown promise for antihypertensive efficacy only in vitro. Nevertheless, while we await the clinical implementation of specific targeting of the NADPH homologues, the currently available antihypertensive agents, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, along with statins, inhibit NADPH oxidase activation.
ing the BP lowering effect of statins, a recent meta-analysis showed that they exert a significant effect on systolic pressure, especially in patients with higher levels of BP at baseline, independently of age and lipid alterations.\(^8\)

Many maintain that the pharmacological approaches have reached a plateau, necessitating newer innovative strategies based on genetics and immunotherapy. Although not yet available for clinical practice, antisense gene therapy is a conceptually valid way of approaching hypertension control and may be applicable to human hypertension. Towards this end, injection of antisense oligodeoxynucleotides against tyrosine hydroxylase reduced blood pressure,\(^9\) while intracardiac administration of a retroviral vector containing angiotensin II type I receptor antisense gene prevented the development of hypertension and cardiac hypertrophy in experimental animal models.\(^10\) Furthermore, DNA testing for genetic polymorphism and genotyping may predict a pronounced response to a certain antihypertensive agent.\(^11\) One of the most remarkable reports in the current year is one regarding the effects of vaccination targeting angiotensin II in hypertensive individuals.\(^12\) After 14 weeks, patients exhibited a significant reduction of systolic BP by 9 mmHg and a remarkable drop in morning pressure surge by 25/13 mmHg. Although intriguing as a concept, questions have been raised concerning long-term safety and cost; thus, later stage studies will be needed to show efficacy, especially in broader hypertensive populations with comorbidities and a different cardiovascular disease burden.

It seems that the mythical “Pandora’s box” of antihypertensive treatment is now opened and provides diverse compounds and strategies that widen the armamentarium available to combat hypertension. Only future research and solid evidence from clinical trials will define which of the therapeutic approaches will remain in the land of myth and which will find their place in the “cruel and real” world of hypertensive disease.

### References