DECADE IN REVIEW—HYPERTENSION

The past decade in hypertension—facts, hopes, and hypes

Thomas Unger

Hypertension research in the past decade has been a mixture of hope and hype. In the absence of new drug developments, clinical intervention procedures such as renal nerve ablation and baroreflex activation therapy have dominated the research, but the results have not yet fulfilled the great expectations.

Unger, T. *Nat. Rev. Cardiol.* **11**, 633–635 (2014); published online 2 September 2014;
doi:10.1038/nrcardio.2014.131

"A simple, brief, catheter-based procedure to ablate sympathetic nerves can be done safely without long-term complications and could result in persistent reductions of blood pressure."[1] Such was the hope 5 years ago after the publication of a study involving 45 patients by an international team of researchers who investigated the efficacy of catheter-based renal sympathetic denervation for resistant hypertension.[1] Indeed, initial findings suggested that resistant hypertension, which is refractory to pharmacological therapy, could be treated with an interventional approach. This study fuelled an outburst of studies on renal sympathetic nerve ablations for the treatment of hypertension. However, much to the disappointment of cardiologists worldwide, findings from the SYMPLICITY HTN-3 trial[2] released early in 2014 demonstrated no significant differences in systolic blood pressure between the renal-denervation group and the sham-controlled group after 6 months (Figure 1). Now that the hype surrounding renal sympathetic denervation has subsided, we must determine whether this procedure can offer permanent benefit to patients with hypertension and, most importantly, which treatment-resistant subgroups (age, ethnicity, sex, duration of hypertension, state of the sympathetic nervous system) are eligible for denervation.

Immunization against angiotensin II to reduce blood pressure represented another promising strategy to treat hypertension 6 years ago. The efficacy of this strategy was evaluated in a phase IIa trial involving 72 patients.[3] After a 14-week treatment period, a significant reduction in ambulatory blood pressure was observed in patients who received a higher dose of the vaccine, compared with placebo. However, these findings could not be reproduced in further clinical studies. Nevertheless, vaccinations against a population-wide disease such as hypertension might still be effective if an appropriate target can be identified, and the associated immunological problems can be overcome.

A third nonpharmacological approach for the treatment of hypertension has emerged for patients with resistant hypertension. Baroreflex activation therapy (BAT) involves the implantation of a device that permanently stimulates the baroreceptor reflex, which is usually attenuated in patients with hypertension. Although BAT for lowering blood pressure is no longer a novel concept, it has regained attention because of marked improvements in device technology. In a randomized trial published in 2011, 265 patients with resistant hypertension were assigned to either group A (BAT applied permanently for up to 12 months) or group B (BAT deferred until after 6 months).[4] No differences were apparent between the two groups after 6 months, but an ancillary analysis revealed a significantly higher percentage of patients (42% versus 24%, $P<0.005$) who achieved systolic blood pressure ≤140 mmHg in group A compared with group B.[4] A treatment regimen involving

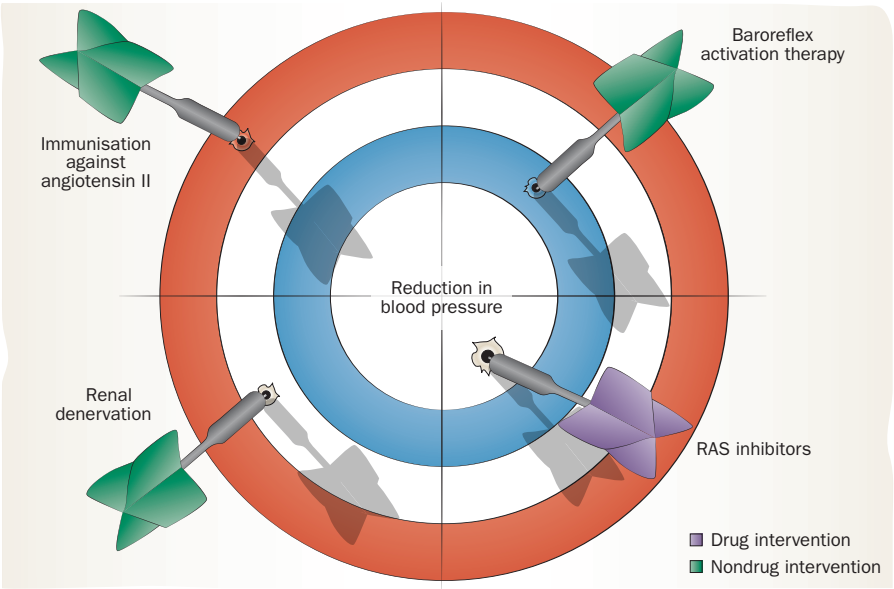

Figure 1 | The hits and misses in the development of blood-pressure lowering therapies during the past decade. The ARB telmisartan was shown to be as effective as the gold-standard ACE-inhibitor ramipril in the ONTARGET trial. However, nondrug interventions were less successful. Renal denervation failed to reduce systolic blood pressure in patients with resistant hypertension in the SYMPLICITY HTN-3 trial. Furthermore, initial findings that immunisation against angiotension II reduced ambulatory blood pressure could not be reproduced in subsequent clinical studies. Finally, baroreflex activation therapy did not significantly reduce systolic blood pressure after 12 months in a randomized controlled trial, but significantly increased the number of patients who achieved systolic blood pressure of ≤140 mmHg. Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; RAS, renin–angiotensin system.

surgical implantation of a device is unlikely to become standard therapy for all hypertensive patients, but this strategy might be suitable for selected patients who do not respond sufficiently to anti-hypertensive drug therapy.

In the past 2 decades, the development of drugs for the treatment of hypertension and other cardiovascular diseases has been largely dominated by inhibitors of the renin–angiotensin system, reflected by many comparative drug studies with large patient cohorts. A prime example is the ONTARGET trial,[5] in which the efficacy of the angiotensin receptor blocker (ARB), telmisartan, was compared with the gold-standard angiotensin-converting-enzyme (ACE) inhibitor, ramipril, in patients with coronary artery disease or diabetes mellitus, in addition to other cardiovascular risk factors, including hypertension. After a mean follow-up period of 5 years, telmisartan was noninferior to ramipril in terms of the composite primary end point of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure, and was better tolerated than the ACE inhibitor. A combination of the two drugs did not provide further benefit, but in fact increased the risk of hypotension, syncope, renal dysfunction, and hyperkalaemia. In the parallel TRANSCEND trial[6] involving 5,926 patients who were unable to tolerate ACE inhibitors, telmisartan was superior to placebo treatment only when hospitalization for heart failure was removed from the combined primary end point.

At first glance, these two trials do not seem to have conveyed any new knowledge; however, on further inspection, many lessons can be gained from them. Firstly, the conventional strategy of clinical trials in cardiovascular disease (that is, to extract marginally significant benefits of one drug versus another) will be questioned because the gain in clinical evidence is disproportionate to the time and financial expenditure of such a trial. In the future, mega-trials on therapeutic regimens will have to be replaced by smaller, better defined, and more individualized clinical studies. Secondly, the long-debated efficacy of ACE inhibitors versus ARBs in treating cardiovascular disease can now be considered settled; each is noninferior to the other, but ARBs are generally better tolerated. Thirdly, in the TRANSCEND trial,[6] a combination of two different classes of renin–angiotensin inhibitors was not beneficial for patients at high cardiovascular risk. For these reasons, the ONTARGET–TRANSCEND trial[5,6] was a hallmark study of the past decade, and will probably be the last mega-trial of this kind in cardiovascular therapy.

Concerning the pathophysiology of hypertension, two seminal publications have aroused much interest in the past decade. An article describing hydrogen sulphide (H_2S) as a physiological vasorelaxant was published in 2008.[7] Genetic deletion of the H_2S-generating enzyme cystathionine γ-lyase markedly reduced H_2S levels in serum and tissue. Mutant mice lacking this enzyme showed pronounced hypertension, together with diminished endothelium-dependent vascular relaxation. These results strongly indicate a physiological role for H_2S as a vasodilator and blood-pressure regulator. In 2011, a paper examining the association between angiotensin II-induced hypertension and vascular injury, and its relationship with T-regulatory lymphocytes was published.[8] The investigators convincingly showed that T-regulatory lymphocytes suppressed angiotensin II-mediated vascular injury through their anti-inflammatory actions,[8] adding support to the hypothesis that immune mechanisms modulate the various physiological and pathophysiological actions of angiotensin II. This notion is consistent with the pathological concept that 'undercurrents', such as immune mechanisms, inflammation, proliferation, and fibrosis, are important in disease processes, forming a link between various pathologies (such as those involving the kidneys, heart, and blood vessels).[9]

Finally, we should not forget genetics. The findings from a study published in 2009 offered an early insight into the genetic basis of hypertension, and the identified loci might be new targets for the reduction of blood pressure.[10] After decades of heavy spending and international collaborative endeavours to unveil the complex genetic background underlying hypertension, we might be moving away from the general 'one-size-fits-all' approach and towards more personalized methods of diagnosis and treatment.

At present, the future of hypertension research is somewhat diffuse. The golden age of hypertension research appears to have come to a temporary end, as most of the large pharmaceutical drug companies have stopped developing new anti-hypertensive therapies. Despite this, new areas of research are emerging; scientists are beginning to view hypertension as a pathological interface in the development of disorders involving the blood vessels, heart, and kidneys, and will develop strategies to target common pathological 'undercurrents' such as inflammation, fibrosis, and proliferative processes.

CARIM School for Cardiovascular Diseases, Maastricht University, PO Box 616, 6200 MD Maastricht, Netherlands.
t.unger@maastrichtuniversity.nl

Competing interests
The author declares no competing interests

1. Krum, H. *et al.* Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* **373**, 1275–1281 (2009).
2. Bhatt, D. L. *et al.* A controlled trial of renal denervation for resistant hypertension. *N. Engl. J. Med.* **370**, 1393–1401 (2014).
3. Tissot, A. C. *et al.* Effect of immunisation against angiotensin II with CYT006-AngQb on ambulatory blood pressure: a double-blind, randomised, placebo-controlled phase IIa study. *Lancet* **371**, 821–827 (2008).
4. Bisognano, J. D. *et al.* Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled Rheos Pivotal Trial. *J. Am. Coll. Cardiol.* **58**, 765–773 (2011).
5. Yusuf, S. *et al.* Telmisartan, ramipril, or both in patients at high risk for vascular events. *N. Engl. J. Med.* **358**, 1547–1559 (2008).
6. Yusuf, S. *et al.* Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* **372**, 1174–1183 (2008).
7. Yang, G. *et al.* H_2S as a physiologic vasorelaxant: hypertension in mice with deletion of cystathionine gamma-lyase. *Science* **322**, 587–590 (2008).
8. Barhoumi, T. *et al.* T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. *Hypertension* **57**, 469–476 (2011).
9. Hess, K., Marx, N. & Lehrke, M. Cardiovascular disease and diabetes: the vulnerable patient. *Eur. Heart J. Suppl.* **14**, B4–B13 (2012).
10. Newton-Cheh, C. *et al.* Genome-wide association study identifies eight loci associated with blood pressure. *Nat. Genet.* **41**, 666–676 (2009).