Key advances in antihypertensive treatment

Ludovit Paulis, Ulrike M. Steckelings and Thomas Unger

Abstract | Although various effective treatments for hypertension are available, novel therapies to reduce elevated blood pressure, improve blood-pressure control, treat resistant hypertension, and reduce the associated cardiovascular risk factors are still required. A novel angiotensin-receptor blocker (ARB) was approved in 2011, and additional compounds are in development or being tested in clinical trials. Several of these agents have innovative mechanisms of action (an aldosterone synthase inhibitor, a natriuretic peptide agonist, a soluble epoxide hydrolase inhibitor, and an angiotensin II type 2 receptor agonist) or dual activity (a combined ARB and neutral endopeptidase inhibitor, an ARB and endothelin receptor A blocker, and an endothelin-converting enzyme and neutral endopeptidase inhibitor). In addition, several novel fixed-dose combinations of existing antihypertensive agents were approved in 2010–2011, including aliskiren double and triple combinations, and an olmesartan triple combination. Upcoming fixed-dose combinations are expected to introduce calcium-channel blockers other than amlodipine and diuretics other than hydrochlorothiazide. Finally, device-based approaches to the treatment of resistant hypertension, such as renal denervation and baroreceptor activation therapy, have shown promising results in clinical trials. However, technical improvements in the implantation procedure and devices used for baroreceptor activation therapy are required to address procedural safety concerns.

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Introduction

Hypertension is the most-prevalent controllable disease in the adult populations of developed countries and contributes substantially to morbidity and mortality.[1] The armamentarium of antihypertensive treatment comprises diuretics, calcium-channel blockers, β-blockers, and inhibitors of the renin–angiotensin–aldosterone system (RAAS) that act at various levels of the RAAS cascade.[2] Previously, we have speculated that novel therapeutic targets might still exist within the RAAS.[2] Indeed, the only new antihypertensive molecule approved in 2010–2011 was the angiotensin II type 1 receptor (AT_1R) blocker azilsartan (Table 1),[3,4] which increases the already broad choice of this class of agents. With such a modest advance in therapeutic options, the goals for new antihypertensive treatments remain unchanged: improvement of blood-pressure control; treatment of resistant hypertension; and possibly also reduction of cardiovascular risk factors other than blood pressure, such as myocardial hypertrophy, fibrosis, or increased arterial stiffness.[2] The approaches to achieve these goals include development of novel molecules or new formulations, of which eight are currently in clinical studies (Table 1);[5] intensive investigation of novel fixed-dose combinations, of which 10 were approved in 2001–2009[6] and two in 2010, one is pending clinical testing, and another is in phase II trials (Table 2); and finally, nonpharmacological strategies, such as renal denervation or baroreflex activation. In this Review, we focus on developments in these three strategies in the past 2 years (2010–2011).

Novel molecules

Only one novel molecule—the AT_1R blocker azilasartan medoxomil—has been approved for the treatment of hypertension in the past 2 years. However, eight new compounds are currently undergoing clinical testing (Table 1). Two are modified versions of currently used antihypertensive drugs: a controlled-release formulation of the α_2-adrenergic agonist clonidine and a modified-release formulation of the calcium-channel blocker lercandipine. The other six are novel molecules: two dual-action AT_1R blockers (known as LCZ 696, which also inhibits neutral endopeptidase, and PS 433540, which also blocks the endothelin A receptor), a dual endothelin-converting enzyme (ECE) and neutral endopeptidase inhibitor (known as daglutril), an aldosterone synthase inhibitor (known as LCI 699), a natriuretic peptide receptor A (NPRA) antagonist (known as PL 3994), and a soluble epoxide hydrolase inhibitor (known as AR 9281). This list of eight new compounds is considerably shorter than it was in 2009, when 28 distinct molecules were listed to be in the clinical phase of investigation.[2] Another novel molecule, the angiotensin II type 2 receptor (AT_2R) agonist compound 21, has shown promising results in animal models but has not yet been tested in clinical trials.

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AT_1R blockers

Strong evidence indicates that AT_1R blockers are at least as effective as β-blockers, calcium-channel antagonists, or angiotensin-converting enzyme (ACE) inhibitors in reducing cardiovascular morbidity and mortality.[7–9] The approval of azilsartan medoxomil in 2011 increased the number of currently available agents in this class to eight.[2] Approval of azilsartan was on the basis of randomized studies involving almost 6,000 patients with mild-to-severe hypertension,[10,11] which showed that an 80 mg dose of this agent was more effective than placebo and more effective than an active comparator therapy (valsartan 320 mg or olmesartan medoxomil 40 mg) in lowering 24 h mean blood pressure. The antihypertensive effect was sustained after 26 weeks of administration.[10,11] However, in common with other novel AT_1R blockers, insufficient long-term morbidity and mortality data are yet available for comparison with those of established compounds, such as valsartan, losartan, and telmisartan.

Despite their efficacy, the large number of AT_1R blockers already available and the strong competition in this field is likely to discourage the launch of new compounds in this class. Perhaps for this reason, several compounds that have shown promise in animal models, such as PF-03838135 and K-868,[12] have not yet entered the clinical phase.

Aldosterone synthase inhibitors

The recognition of aldosterone as a downstream effector of some deleterious angiotensin II effects, and the growing awareness of the role of aldosteronism in resistant hypertension,[13,14] have promoted the use of aldosterone antagonists in patients with hypertension. The currently available aldosterone antagonists, spironolactone and eplerenone, act on the mineralocorticoid receptor. Their blood-pressure-lowering effects are comparable in hypertensive patients with and without increased aldosterone levels,[15–18] and both these agents seem to reduce mortality in a blood-pressure-independent manner in patients with heart failure.[19–22] Although the antihypertensive effect is somewhat greater, milligram for milligram, for spironolactone than eplerenone,[16] spironolactone is associated with an increased rate of progesterone-dependent and testosterone-dependent adverse effects, mainly gynecomastia and breast tenderness.[23]

Inhibition of aldosterone synthase should prevent the reactive increase in aldosterone levels that occurs in response to aldosterone antagonists, which triggers the undesired genomic, mineralocorticoid receptor-dependent effects (such as sodium/potassium exchanger or sodium/hydrogen exchanger activation) and nongenomic, mineralocorticoid receptor-independent effects (such as phospholipase C and JNK kinase activation) of these agents, leading to inflammation, hypertrophy and fibrosis.[2] LCI 699 could represent a first-in-class aldosterone synthase inhibitor. Initial results in 14 patients with primary aldosteronism showed that twice-daily administration of 0.5 mg or 1.0 mg of LCI 699 lowered 24 h ambulatory systolic blood pressure and supine plasma aldosterone concentrations after 4 weeks.[24] In a phase II study in patients with primary hypertension, 0.25 mg, 0.5 mg, or 1 mg once daily, or 0.5 mg twice daily of LCI 699 reduced ambulatory systolic and diastolic blood pressure as well as mean sitting systolic blood pressure.[25] However, the most profound reductions were observed with the 1 mg once daily dose, which was the only regimen that also reduced mean sitting diastolic blood pressure. This dosage achieved a blood-pressure reduction comparable to that obtained with 50 mg eplerenone twice daily (the highest approved dose). The occurrence of adverse events and hyperkalemia was low and comparable in all active treatment groups.[25] Despite the short half-life of LCI 699 (about 4 h), and the fact that more detailed data on its effect on blood pressure, such as trough to peak ratio, need to be published, these data suggest that this drug might be suitable for once-daily dosing. As once-daily dosing is associated with improved compliance with therapy,[26] this feature might represent an additional advantage over eplerenone, which is administered twice daily at the highest approved dose.

However, aldosterone synthase inhibitors would not prevent epithelial adverse effects, such as sodium retention and potassium excretion leading to hypertension, or nonepithelial adverse effects, such as downregulation of nitric oxide synthase and promotion of inflammation, proliferation and fibrosis. These adverse effects are mediated by cortisol, which in an altered redox state might act on the mineralocorticoid receptor.[27] Data from the phase II studies showed that LCI 699 did not affect baseline morning cortisol levels but did suppress adrenocorticotropic hormone-stimulated release of cortisol in ~20% of patients, probably owing to partial inhibition of 11β-hydroxylase, which catalyzes the final step of cortisol synthesis.[24,25] Thus, these findings raise the question of whether this suppressive effect might interfere with a clinically useful response to stress (such as in acute injury) and compromise the safety of LCI 699, which could lead to suspension of its clinical development. These concerns suggest that aldosterone synthase inhibitors with greater specificity than LCI 699, such as SPP 2745,

Key points

- In 2010–2011, one novel antihypertensive—azilsartan—as well as several novel fixed-dose combinations of existing antihypertensive agents, including aliskiren double and triple combinations and an olmesartan triple combination were approved
- Novel antihypertensive compounds in clinical development include an aldosterone synthase inhibitor, a natriuretic peptide agonist, and a soluble epoxide hydrolase inhibitor
- An angiotensin II type 2 receptor agonist—compound 21—is in preclinical development
- Novel antihypertensives with dual activity, including an angiotensin-receptor blocker and neutral endopeptidase inhibitor, an angiotensin-receptor blocker and endothelin receptor A blocker, and an endothelin-converting enzyme and neutral endopeptidase inhibitor, are in clinical development
- Upcoming fixed-dose combinations of antihypertensives are expected to include calcium-channel blockers other than amlodipine, and diuretics other than hydrochlorothiazide (which are included in the current combinations)
- Nonpharmacological approaches for the treatment of resistant hypertension—renal denervation and baroreceptor activation—have shown promising results in clinical trials

Table 1 | Compounds* newly approved or in clinical trials for the treatment of hypertension

Agent	Mechanism of action	Status
Azilsartan medoxomil	AT_1R blocker with peroxisome proliferator-activated receptor γ activity	Approved in 2011 by EMA and FDA
LCI 699	Aldosterone synthase inhibitor	Phase II
LCZ 696	Dual AT_1R blocker and neutral endopeptidase inhibitor	Phase II (phase III for heart failure)
PS 433540	Dual AT_1R and endothelin A receptor blocker	Phase II
Daglutril	Dual endothelin-converting enzyme and neutral endopeptidase inhibitor	Phase III
PL 3994	Natriuretic peptide receptor agonist	Phase II (also phase II for congestive heart failure)
AR 9281	Soluble epoxide hydrolase inhibitor	Phase II (also phase II for diabetes mellitus type 2)
Lercandipine, modified release	Calcium-channel antagonist	Phase II
Clonidine, controlled release	Centrally acting α_2-adrenergic agonist	Phase III

*Only compounds approved by the FDA in 2010–2011[3,4] or listed as clinically investigated by the Pharmaceutical Research and Manufacturers of America website[5] on 1 December 2011 are included. Abbreviation: AT_1R, angiotensin II type 1 receptor; EMA, European Medicines Agency.

could be useful as antihypertensive agents. However, the development of SPP 2745 was stopped following a company merger, despite previous promising reports on its specificity and cardioprotective, renoprotective, and vasculoprotective effects. Further studies are needed to demonstrate whether aldosterone synthase inhibitors can deliver blood-pressure-independent, organ-protective effects comparable to those of mineralocorticoid receptor antagonists.

In addition to the specific aldosterone antagonists, some calcium-channel blockers can block mineralocorticoid receptors[28–30] or inhibit aldosterone synthesis.[31–33] These early data suggest that nonsteroid agents with double or triple actions on calcium channels, mineralocorticoid receptors, and aldosterone synthase could potentially be developed.[6]

Natriuretic peptide receptor A agonists

The endogenous factors atrial natriuretic peptide and brain natriuretic peptide already serve as important markers of cardiovascular risk. These proteins have natriuretic, vasorelaxant, and antiproliferative effects; the pathways responsible for their action include NPRA stimulation and guanylyl cyclase activation, with subsequent accumulation of cyclic GMP, which has putative beneficial effects in hypertension, heart failure, nephrosclerosis, and stroke.[34] Knockdown or knockout of NPRA results in reduced formation of cyclic GMP and increased blood pressure,[35] whereas administration of atrial natriuretic peptide elicits endothelium-dependent vasorelaxation.[36] The NPRA antagonist PL 3994 is currently in a clinical phase of investigation in patients with heart failure and hypertension.[5] In phase I trials, PL 3994 dose-dependently increased cyclic GMP levels, reduced blood pressure, and induced natriuresis on the day following treatment in healthy volunteers.[37] Similar results (an increase in cyclic GMP and a reduction in blood pressure) were shown in a phase IIa study in patients with adequately controlled essential hypertension.[38] In this study, patients treated with ACE inhibitors experienced the largest blood-pressure-reducing effect, which suggested synergism between NPRA agonism and ACE blockade.[38]

Soluble epoxide hydrolase inhibitors

Soluble epoxide hydrolase was identified as a novel therapeutic target for blood-pressure control because its inhibition (by a derivate of urea) had a blood-pressure-lowering effect in spontaneously hypertensive rats, which have angiotensin-II-induced hypertension,[39] but not in normotensive Wistar rats.[40] Inhibition of this enzyme also had antiproliferative effects.[41] AR 9281 is the first soluble epoxide hydrolase inhibitor that has advanced to clinical trials. This agent is lipophilic, it can be administered orally, and it lowered blood pressure, improved vascular function, and reduced renal damage in rats with angiotensin-II-induced hypertension.[42–43] By contrast, AR 9281 did not cause any blood-pressure-lowering effects in healthy human volunteers, although it inhibited soluble epoxide hydrolase and was well tolerated in an 8-day, dose-ranging study of single-dose and multiple-dose treatment.[44] Nevertheless, elevated activity of soluble epoxide hydrolase was observed in patients with hypertension and diabetes mellitus,[44] outlining the possible role of AR 9281 in these indications.

Angiotensin II type 2 receptor agonists

Our research group identified AT_2R as a possible therapeutic target for hypertension treatment.[2] Stimulation of AT_2R opposes many aspects of AT_1R stimulation by mediating vasodilatory, antiproliferative, and anti-inflammatory effects.[45] The nonpeptide AT_2R agonist compound 21[46] has been used to investigate the direct effects of pharmacological AT_2R stimulation. This compound improved myocardial function independently of blood pressure after myocardial infarction in normotensive Wistar rats,[47] and suppressed inflammation and NF-κB activity in primary murine and human dermal fibroblasts.[48] Despite this evidence of the cardioprotective potential of compound 21, the usefulness of

Table 2 | Combinations* newly approved or in clinical trials for the treatment of hypertension

Combination	Mechanism of action	Status
Olmesartan, amlodipine, and hydrochlorothiazide	AT_1R antagonist, calcium-channel blocker, and diuretic	FDA and German‡ approval in 2010
Aliskiren, amlodipine, and hydrochlorothiazide	Renin inhibitor, calcium-channel blocker, and diuretic	FDA approved in 2010, EMA approved in 2011
Aliskiren and amlodipine	Renin inhibitor and calcium-channel blocker	FDA approved in 2010, EMA approved in 2011
Azilsartan medoxomil and chlortalidone	AT_1R antagonist and diuretic	Preregistration
Candesartan cilexetil and nifedipine	AT_1R antagonist and calcium-channel blocker	Phase II

*Only combinations approved by the FDA in 2010–2011[3,4] or listed as clinically investigated by the Pharmaceutical Research and Manufacturers of America[5] on 1 December 2011 are included. ‡Approval via the European decentralized procedure. Abbreviation: AT_1R, angiotensin II type 1 receptor; EMA, European Medicines Agency.

AT_2R stimulation as a treatment for arterial hypertension was not clearly established by these studies. However, the results of chronic treatment with compound 21 in two different animal models of hypertension were reported during 2011. In stroke-prone spontaneously hypertensive rats, 6 weeks of treatment with compound 21, alone or in combination with an AT_1R blocker (losartan), resulted in improved vascular stiffness and reduced collagen concentration in the aorta and myocardium. The combination treatment also improved endothelium-dependent relaxation of resistance mesenteric arteries.[49] In rats with L-NAME-induced hypertension, caused by nitric oxide synthase inhibition, compound 21 alone or in combination with olmesartan reduced pulse wave velocity. Moreover, only the combination treatment completely prevented collagen accumulation in the aorta, which resulted in a profound reduction of aortic stiffness.[50] Most interestingly, the effects of AT_2R stimulation in both these studies seemed to be independent of the changes in blood pressure, suggesting that combinations of this agent with antihypertensive treatment might lead to vasculoprotective effects even beyond the blood-pressure-reducing effect.

Dual inhibitors

AT_1R blockade and vasopeptidase inhibition

Neutral endopeptidase is a metallopeptidase that metabolizes various vasodilatory and vasoconstrictive substances, leading to variable effects on blood pressure.[51] However, if this enzyme is inhibited in the presence of concomitant vasoconstrictor blockade, the effect of reduced degradation of vasodilatory substrates might outweigh that of vasoconstrictive substrates, leading to a net vasodilatory effect.

The OCTAVE and OVERTURE trials of the dual ACE–neutral endopeptidase inhibitor omaptrilat were encouraging in terms of efficacy in hypertension and heart failure. However, they highlighted an increased incidence of angioedema after treatment with dual ACE and neutral endopeptidase inhibitors compared with the ACE inhibitor enalapril.[52,53] Consequently, attention has shifted to dual AT_1R and neutral endopeptidase antagonism. The putative first-in-class dual AT_1R and neutral endopeptidase antagonist LCZ 696 achieved a blood-pressure reduction comparable to an AT_1R blocker (valsartan) in a phase II, randomized, double-blind, placebo-controlled, and active-treatment-controlled clinical trial in patients with mild-to-moderate essential hypertension.[54] After 8 weeks of treatment, the two highest doses of LCZ 696 (200 mg and 400 mg) achieved a larger reduction in sitting systolic and diastolic blood pressures than was achieved using comparable doses of valsartan (160 mg and 320 mg). The 400 mg dose of LCZ 696 also resulted in superior blood-pressure control and pulse-pressure reduction compared with valsartan. In contrast to the results of trials of dual ACE and neutral endopeptidase inhibitors, no angioedema was reported in this study.[54] With these encouraging data, LCZ 696 is now the most promising dual AT_1R and neutral endopeptidase inhibitor in clinical trials for the treatment of hypertension, as the development of the dual AT_1R and neutral endopeptidase antagonist VNP 489 seems to be halted (no novel data on VNP 489 have been reported in the past 2 years).

AT_1R and endothelin A receptor blockade

Endothelin is one of the most-potent vasoconstrictors, and also has prominent roles in fibrogenesis, inflammation, oxidative stress, atherosclerosis, salt and water homeostasis, and pulmonary hypertension.[55–57] Several endothelin receptor antagonists have been investigated for the treatment of hypertension. The selective endothelin A antagonist darusentan achieved promising blood-pressure reductions in patients with resistant hypertension in the DAR-311 (DORADO) trial,[58] and a larger reduction in mean 24 h systolic and diastolic blood pressure than either placebo or the sympatholytic antihypertensive agent guanfacine in the DAR-312 (DORADO-AC) trial.[59] However, adverse effects—salt and water retention and the development of peripheral edema—limit the tolerability of endothelin A receptor blockers[58–61] and probably contributed to the decision to put development of darusentan on hold. Nevertheless, these findings raise the question of whether dual-specificity AT_1R and endothelin A receptor antagonists (such as PS 433540, which is currently under clinical investigation as a treatment for hypertension) could be more effective and better tolerated than specific endothelin A receptor blockers. In a phase IIb, randomized, double-blind, placebo-controlled, and

active-treatment-controlled trial in patients with stage 1–2 hypertension, PS 433540 (at doses of 200 mg, 400 mg, and 800 mg) reduced systolic and diastolic blood pressures more effectively than placebo, with the highest dose achieving a greater reduction than the AT_1R blocker irbesartan. In addition, compared with irbesartan, all doses of PS 433540 were associated with improved rates of blood-pressure control (<140/90 mmHg) at 12 weeks.[62] Although these results were encouraging, they have not been published in a peer-reviewed journal, and clinical development of this agent has been suspended until a commercial partner is found.[63]

Vasopeptidase and ECE inhibition

Endothelin is produced by another metallopeptidase, ECE. The dual ECE and neutral endopeptidase inhibitor daglutril (SLV 306, a prodrug for the active compound KC 12615) reduced both proteinuria and glomerulosclerosis in rats with streptozotocin-induced diabetes to an extent comparable to the ACE inhibitor captopril,[64] an effect previously not observed with sole ECE inhibition.[65] Although daglutril reduced pulmonary and right atrial pressure in patients with congestive heart failure,[66] this study was published in 2004 and more-recent data on this substance are not available. However, some other dual ECE and neutral endopeptidase inhibitors, such as SLV 338, are in preclinical pipelines. In stroke-prone, spontaneously hypertensive rats, SLV 338 treatment was well tolerated and associated with improved survival as well as a significantly lowered incidence of stroke. However, the treatment did not have a significant effect on blood pressure.[67]

Combination therapies

Currently a single pharmacologic agent is sufficient to achieve adequate blood-pressure control in only approximately one-third of patients with hypertension; another one-third will need two drugs, and the rest require at least three agents.[68] These requirements are reflected in the current European guidelines, which recommend the use of a combination of at least two antihypertensive drugs in patients with mild-to-severe (grade ≥2) hypertension.[69] Trials of antihypertensive therapy in patients with heart failure have demonstrated that mortality can be reduced progressively by the inclusion of additional antihypertensive agents in the treatment regimen; mortality was progressively reduced in the following trials: SOLVD (diuretic and ACE inhibitor), CIBIS II and RALES (diuretic, ACE inhibitor, and either β-blocker or spironolactone), and CHARM (diuretic, ACE inhibitor, β-blocker, and ARB).[70]

Combination therapy provides superior blood-pressure reduction because each agent typically blocks the counter-regulatory system activity triggered by the other[71] and might also attenuate its adverse effects. For example, the combination of a calcium-channel blocker (amlodipine) with an AT_1R antagonist (valsartan) was more effective in reducing blood pressure than either drug alone,[72] and the AT_1R blockade-induced dilatation at the venous capillary side reduced the occurrence of peripheral edema, caused by the calcium-channel blocker, in patients receiving the combination treatment compared with patients receiving amlodipine monotherapy.[72] Similarly, a meta-analysis of 43 randomized, controlled trials showed that addition of the diuretic hydrochlorothiazide to AT_1R antagonists resulted in enhanced blood-pressure reduction in hypertensive patients;[73] moreover, AT_1R-blockade-induced potassium retention might also counterbalance the potassium losses caused by diuretic administration.[74]

Interest in the development of combination therapies is increasing because of their superior efficacy and the potential to allow challenging blood-pressure targets to be met. In addition, patients prefer to take as few pills as possible,[26] and adherence to fixed-dose combinations of two agents given as a single pill is better than adherence to free combinations of the same agents.[75] Since 2000, 13 new fixed-dose combinations, including three triple therapies, have been approved for treatment of hypertension. Three of these agents, one double therapy and two triple therapies, were approved in 2010–2011 (Table 2).

The renin inhibitor aliskiren was approved as a monotherapy in 2007. Three combination therapies involving this agent are now available: aliskiren plus hydrochlorothiazide (approved in 2008), aliskiren plus amlodipine, and aliskiren plus amlodipine plus hydrochlorothiazide (both approved in 2010). The aliskiren plus amlodipine combination achieved greater blood-pressure reduction than either component alone in patients with mild-to-severe hypertension after 8 weeks of treatment.[76]

The approval of aliskiren (300 mg) in a fixed-dose triple combination therapy with amlodipine (10 mg) and hydrochlorothiazide (25 mg) was on the basis of the results of a double-blind, active-treatment-controlled trial in patients with moderate-to-severe hypertension. These data showed that the triple combination achieved a greater mean blood-pressure reduction than three two-drug combinations: aliskiren plus hydrochlorothiazide (9.9/6.3 mmHg), amlodipine plus hydrochlorothiazide (7.2/3.6 mmHg), and aliskiren plus amlodipine (6.6/2.6 mmHg).[77] Although none of these combinations included an AT_1R antagonist or an ACE inhibitor, such a combination was investigated in the ALTITUDE trial, which was designed to determine whether the addition of aliskiren (300 mg once daily) to conventional treatment (including AT_1R antagonist or an ACE inhibitor) of patients with type 2 diabetes, reduced cardiovascular and renal morbidity and mortality compared with placebo.[78] However, this trial was halted prematurely because of an increase in adverse events and no apparent benefits among patients randomly assigned to aliskiren.[79] These data suggest that the combination of aliskiren with an AT_1R antagonist or an ACE inhibitor might be dangerous and should not be used.

The results on the efficacy of aliskiren in dual or triple combination therapies for hypertension are in line with previous data on other RAAS blockers in combination therapies. For example, a study that evaluated the efficacy of combinations of valsartan, amlodipine, and

hydrochlorothiazide in patients with hypertension (mean sitting diastolic blood pressure >100 mmHg) showed that the triple drug combination lowered blood pressure by 40/25 mmHg. This reduction was significantly greater than that achieved by treatment with two-drug combinations of valsartan and hydrochlorothiazide, valsartan and amlodipine, or amlodipine and hydrochlorothiazide, which lowered blood pressure by 32/20 mmHg, 34/22 mmHg, and 31/19 mmHg, respectively.[80]

A triple combination of olmesartan (40 mg), amlodipine (10 mg), and hydrochlorothiazide (25 mg) was approved in 2010 on the basis of the TRINITY results in patients with hypertension.[77] The triple combination treatment lowered blood pressure by 37/22 mmHg, which was superior to the blood-pressure reductions in the double-drug arms (30/17 mmHg with olmesartan and hydrochlorothiazide, 30/18 mmHg with olmesartan and amlodipine, and 28/15 mmHg with amlodipine and hydrochlorothiazide).[77]

To date, only triple combinations that include amlodipine as the calcium-channel blocker and hydrochlorothiazide as the diuretic have been investigated. The available data from the ACCOMPLISH[81] trial and comparisons of data from the double-agent arms of other triple therapy trials suggest that combinations of a RAAS blocker and a calcium-channel blocker might have superior efficacy to combinations that include a diuretic. However, this finding might be an artifact resulting from the choice of hydrochlorothiazide (a relatively weak diuretic), and the use of relatively low doses of this agent. The efficacy data for other fixed-dose dual therapies being investigated in clinical studies are, therefore, highly anticipated, as chlorthalidone[82] and nifedipine[83] are being used as the diuretic and calcium-channel blocker, respectively.

Nonpharmacological therapies

Renal sympathetic denervation

Although renal sympathectomy was an early method used to reduce blood pressure, it was abandoned after effective pharmacological therapies were introduced. However, the development of novel, minimally invasive, catheter-based approaches and the need to develop effective therapies for treatment-resistant hypertension have revived the strategy. The current procedure involves percutaneous radiofrequency ablation of sympathetic nerve fibers surrounding the renal arteries, via an intra-arterial catheter (Figure 1).[84,85] This method of renal denervation was initially evaluated in a cohort study of 45 patients with treatment-resistant hypertension. Renal epinephrine spillover decreased by 47% and office blood pressure was reduced by 14/10 mmHg, 21/10 mmHg, 22/11 mmHg, and 27/17 mmHg at 1, 3, 6, and 12 months, respectively, after the procedure. Adverse events included one intraprocedural renal-artery dissection before ablation, and one femoral-artery aneurysm without further complications.[86]

The safety and efficacy of catheter-based renal denervation for blood-pressure reduction was investigated further in the Symplicity HTN-2 Trial,[87] which included

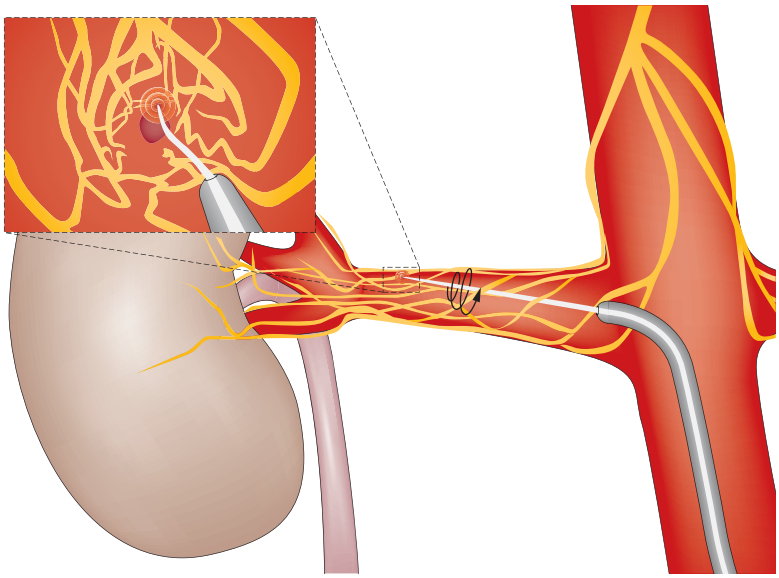

Figure 1 | Schematic representation of renal sympathetic denervation. An ablation catheter is guided into each main renal artery. On activation, the catheter generates a spherical region of increased temperature that burns an area approximately one-quarter of the circumference of the artery. Catheter rotation, with up to six burns, provides a full circumferential ablation and effective destruction of the sympathetic nerve fibers (yellow) surrounding the renal artery. Permission obtained from Oxford University Press, © Krum, H. *et al.* Novel procedure- and device-based strategies in the management of systemic hypertension. *Eur. Heart J.* **32**, 537–544 (2011).

106 patients with treatment-resistant hypertension. At 6 months after the procedure, office blood pressure decreased significantly, by 32 ± 23/12 ± 11 mmHg, in the renal denervation (plus ongoing therapy) group (52 patients), whereas it did not change from baseline in the control group (ongoing therapy only, 54 patients). Additionally, 84% of the patients who underwent renal denervation had a reduction in systolic blood pressure of ≥10 mmHg, compared with 35% of patients in the control group (P <0.0001). For some patients, the data from a 24-h ambulatory blood-pressure measurement at 6 months were available: in the renal denervation group (20 patients) a significant decrease from baseline was observed for both the mean systolic and diastolic blood pressure (by 11 ± 15/7 ± 11 mmHg), while no significant change was observed in the control group (25 patients). No serious procedure-related or device-related complications occurred.[87] A follow-up study of patients who underwent renal nerve ablation showed that postprocedure blood pressures remained below baseline, by 23/11 mmHg after 12 months (n = 64) and by 32/14 mmHg (n = 18) after 24 months, suggesting a persistent effect of the procedure.[88]

Although these results[87,88] are encouraging, further studies are required to clarify several factors that might affect the efficacy of renal denervation, including patient eligibility criteria, the need for continued drug treatment, the number of drugs required to keep blood pressure controlled, and the potential for achieving long-term blood-pressure reduction in view of the loss of renal sympathetic activity and the possibility of renal

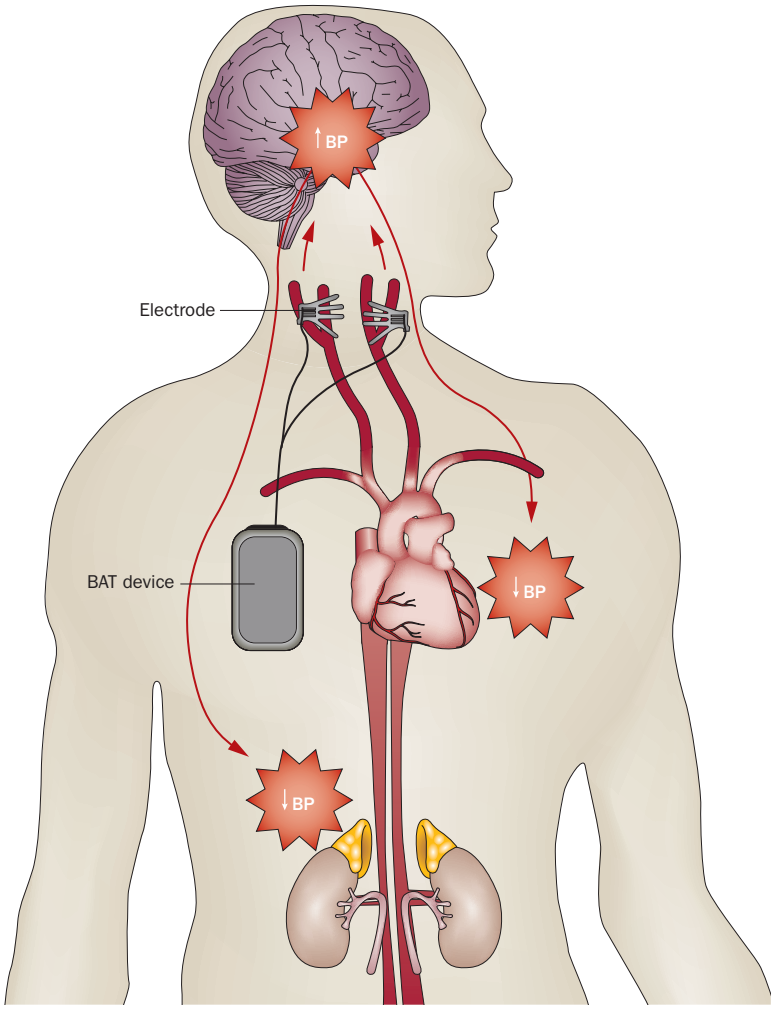

Figure 2 | Schematic representation of baroreflex activation therapy. The BAT device consists of an implantable pulse generator, bilateral carotid sinus leads delivering stimulation to the area of greatest response, and an external programmable device for noninvasive control of the pulse generator. Stimulation of the carotid sinus by this device supplies false information indicating hypertension to the blood pressure control centers of the central nervous system, leading to reflexive blood pressure lowering. Abbreviation: BAT, baroreflex activation therapy; ↓BP, signals resulting in decreased blood pressure; ↑BP, false signal indicating increased blood pressure. Permission obtained from Nature Publishing Group © Mearns, B. M. *Nat. Rev. Cardiol.* **8**, 540 (2011).

re-innervation. Initial data from animal experiments suggest that renal re-innervation might occur; in rats re-innervation was complete and functional at 8 weeks after renal denervation,[89] whereas in dogs functional re-innervation was complete 12–16 months after the procedure.[90] However, although it is evident that human kidney undergoes re-innervation after renal transplantation,[91] this re-innervation might be nonfunctional[92] and the extent to which re-innervation could affect the outcome of renal denervation in humans remains unclear. As the blood-pressure-lowering effect of the procedure persists 24 months after denervation,[88] a longer follow-up is required to answer this question and increase our knowledge of re-innervation in human kidney.

Chemical denervation with locally applied vincristine has also been suggested as a method of renal sympathectomy.[93] However, further data are needed to show whether this approach will be better tolerated by patients than radiofrequency ablation, and to determine whether the beneficial effect will be as durable.

Baroreceptor activation

Baroreflex activation therapy (BAT) is a device-based approach to treating hypertension that has been intensively investigated. The BAT device consists of an implantable pulse generator that activates the carotid sinus via an electrical signal, delivered by bilateral leads. The leads are implanted during open surgery and the electrodes are positioned at the areas of greatest response in the carotid sinus. Stimulation of the sinus by the BAT device supplies the blood pressure control centers with false information of increased blood pressure, leading to reflexive blood pressure lowering (Figure 2).[94]

Data from the DEBuT-HT trial,[95] which assessed BAT in 45 patients with hypertension, showed that 72% of patients had a reduction in systolic blood pressure of at least 30 mmHg after 4 years of treatment (mean reduction 53 ± 9 mmHg, P <0.001). The mean reduction in diastolic blood pressure at 4 years was 30 ± 6 mmHg (P <0.001) and the drop in heart rate averaged 5 ± 2 bpm (P = 0.02) against baseline. The average number of antihypertensive medications used decreased from 5.0 at baseline to 3.4 over the same time period.[96]

A large (n = 265) phase III, double-blind, randomized, prospective, multicenter, placebo-controlled study of the same device confirmed the efficacy and safety of BAT in patients with resistant hypertension. The results showed that target systolic blood-pressure values of <140 mmHg were achieved in 42% of patients who received 6 months of BAT, compared with 24% of patients who were implanted with the BAT device but did not receive stimulation during this period. A mean systolic blood-pressure reduction (from preimplant values) of 26 mmHg in patients who received BAT and 17 mmHg in patients who did not receive BAT (device implanted but not activated) was seen in the same time period. The mean blood-pressure decrease and proportion of patients who met the <140 mmHg blood-pressure goal had somewhat increased 12 months after BAT therapy, to 35mmHg and 53%, respectively.[97] Although these data were encouraging, and predefined efficacy, BAT safety, and device safety end points were met, the study did not meet the predefined procedural safety criteria of no implantation-procedure-related adverse effects in 82% of patients, as only 75% of patients did not experience adverse effects such as transient or permanent nerve injury, general surgical complications, and surgical wound infection. Several technical improvements are, therefore, likely to be required—most importantly device size reduction, and the development of a unilateral device with comparable efficacy to the bilateral version used in these studies.[95] To address these concerns, a smaller, second-generation unilateral BAT device was introduced in 2011. This device has been reported to offer improved procedural safety and comparable blood-pressure-reducing efficacy to the bilateral BAT device.[98]

Conclusions

Although development of new medications and treatment strategies for hypertension is still required, the investigation of novel therapeutic compounds for this indication (especially those with novel targets) seems to be losing momentum. Nevertheless, clinicians can remain optimistic that new antihypertensive drugs with novel mechanisms of action will be approved in the next 10 years. The aldosterone synthase inhibitors currently in drug-development pipelines seem to show particular promise, although problems of specificity and funding need to be addressed, and the development of novel molecules with dual activity (probably including AT_1R antagonism) is likely to continue. However, approvals for antihypertensive therapies in the near future will probably be dominated by new fixed-dose combinations, including a broader and more variable range of triple therapies. Device-based approaches to antihypertensive treatment have also advanced considerably and, as the technologies progress, they might represent a strategy to overcome the problem of treatment-resistant hypertension.

Review criteria

Drugs approved in 2010–2011 were identified using the CenterWatch and FDA databases, and those in clinical development were identified using the PhRMA database. Two nonpharmacological treatments, on which data were presented in 2010–2011, were also included. PubMed was searched using the following keywords: "azilsartan", "LCI 699", "PL 3994", "LCZ 696", "AR 9281", "PS 433540", "daglutril", "compound 21", "renal denervation" and "baroreceptor activation therapy", alone and in combination. Additional information was retrieved from the EBSCO database, Google Scholar, and Google searches. The reference lists of key review articles identified during these searches were also checked for additional relevant publications.

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Author contributions
L. Paulis and T. Unger researched the data for the article, provided a substantial contribution to discussions of the content, wrote the article and reviewed and/or edited the manuscript before submission. U. M. Steckelings provided a substantial contribution to discussions of the content, and reviewed and/or edited the manuscript before submission.