Hypertension is the most common modifiable risk factor for cardiovascular disease and death; the increased risk associated with blood pressure (BP) elevation can be greatly reduced by treatment with antihypertensive drugs that lower both BP and related target organ damage. A total of 69 drugs in 15 different classes, many of which are also available in single pill combinations, have been approved for the treatment of hypertension in the United States. Despite this plethora of treatment options, a substantial portion of the hypertensive population has uncontrolled blood pressure. The unmet need of controlling blood pressure in this population may be addressed, in part, by developing new drugs and devices/procedures to treat hypertension and its comorbidities. In this Compendium Review, we discuss new drugs and interventional treatments that are undergoing preclinical or clinical testing for hypertension treatment. New drug classes, eg, inhibitors of vasopeptidases, aldosterone synthase and soluble epoxide hydrolase, agonists of natriuretic peptide A and vasoactive intestinal peptide receptor 2, and a novel mineralocorticoid receptor antagonist are in phase II/III of development, while inhibitors of aminopeptidase A, dopamine β-hydroxylase, and the intestinal Na+/H+ exchanger 3, agonists of components of the angiotensin-converting enzyme 2/angiotensin(1–7)/Mas receptor axis and vaccines directed toward angiotensin II and its type 1 receptor are in phase I or preclinical development. The two main interventional approaches, transcatheter renal denervation and baroreflex activation therapy, are used in clinical practice for severe treatment resistant hypertension in some countries. Renal denervation is also being evaluated for treatment of various comorbidities, eg, chronic heart failure, cardiac arrhythmias and chronic renal failure. Novel interventional approaches in early development include carotid body ablation and arteriovenous fistula placement. Importantly, none of these novel drug or device treatments has been shown to prevent cardiovascular disease outcomes or death in hypertensive patients. (Circ Res. 2015;116:1074-1095. DOI: 10.1161/CIRCRESAHA.116.303603.)

Key Words: blood pressure ■ drug ■ hypertension ■ interventional ■ treatment
estimated 10% to 15% of the general hypertensive population has resistant hypertension, defined as uncontrolled BP on ≥3 antihypertensive drugs of different classes, including a nonpotassium-sparing diuretic, at optimal doses, or requiring ≥4 drugs to achieve control. In addition, ≈0.5% of hypertensive patients have refractory hypertension, defined as uncontrolled BP on ≥5 drugs.5

Many more hypertensive patients are uncontrolled because of nonadherence or intolerance to available antihypertensive agents. Recent drug monitoring studies have revealed nonadherence to BP lowering therapy in 25% to 65% of patients with apparent treatment resistant hypertension (TRH).5–9 In 24% to 34.5% of these individuals, who were prescribed 3–5 antihypertensive medications, no antihypertensive medication was detected in blood or urine samples. The unmet need of controlling BP in these high-risk patients may be addressed, in part, by the development of new drugs and devices and procedures that are designed to treat hypertension and comorbidities, such as heart failure (HF), chronic kidney disease, and diabetes mellitus. This review will summarize recent development of novel drugs classes and interventional strategies for the treatment of hypertension and related target organ damage.

Part I. New Drugs

Anti-Aldosterone Agents

Aldosterone is a mineralocorticoid that regulates electrolyte and volume homeostasis in normal subjects and, when elevated, can contribute to the development of hypertension and a variety of related pathologies, including myocardial hypertrophy and fibrosis and HF.10 The principal effector of aldosterone action is the mineralocorticoid receptor (MR), a nuclear transcription factor that is expressed at high levels in the cortical collecting duct of the kidney (Figure 1). Activated MRs stimulate expression of sodium channels, resulting in increased sodium and water reabsorption and potassium loss, leading eventually to a volume expanded form of hypertension. Activation of MRs in extra adrenal tissues, particularly the heart and blood vessels, also promotes the development of hypertension and CVD by upregulating NADPH oxidase and increasing production of reactive oxygen species. This reduces the bioavailability of nitric oxide and leads to endothelial dysfunction and vascular disease.

Aldosterone is synthesized from 11-deoxycorticosterone in the zona glomerulosa of the adrenal cortex via the action of a mitochondrial cytochrome P450 enzyme, aldosterone synthase, which is encoded by the CYP11B2 gene (Figure 1). Aldosterone synthase catalyzes the final 3 rate-limiting steps of aldosterone synthesis (11β-hydroxylation of 11-deoxycorticosterone to form corticosterone, followed by 18-hydroxylation of corticosterone to form 18OH-corticosterone, and 18-oxidation of 18-OH corticosterone to form aldosterone). Cortisol synthesis, which occurs in the zona fasciculata of the adrenal cortex, is mediated by 11β-hydroxylase, which is encoded by the CYP11B1 gene.11,12 CYP11B2 has a high sequence homology with CYP11B1, and both CYP11B2 and CYP11B1 share an 11β-hydroxylase reaction, creating problems for those attempting to design selective aldosterone synthase inhibitors.13–14

Mineralocorticoid Receptor Antagonists

MRs have been therapeutic targets in hypertension treatment for over half a century: the first MR antagonist (MRA), spironolactone, appeared in the early 1960s.15 Although spironolactone monotherapy has modest BP lowering efficacy, it has had a recent resurgence as add-on therapy in patients with resistant hypertension16–19 and in the treatment of HF.20 Spironolactone use has been limited by its lack of selectivity for the MR, particularly at higher (>25 mg) doses. Because of its structural similarity to progesterone, spironolactone has significant progestogenic and antiandrogenic activity, leading to troublesome adverse effects in both men and women.21,22 The more selective MRA eplerenone lacks the antiandrogenic effects of spironolactone, but is less potent and has a shorter (3–4 h) half-life, leading to reduced antihypertensive efficacy and a requirement for twice daily dosing.22,23

The search for newer nonsteroidal MRAs that have superior selectivity and affinity for the MR began with the observation that some dihydropyridine calcium channel blockers compete with aldosterone for binding to the ligand binding domain of the MR and decrease aldosterone-mediated recruitment of transcriptional coactivators that are necessary for MR-directed DNA transcription.22,24,25 Optimization of MRA activity of dihydropyridine compounds led to the development of BAY 94-8862 (finerenone), a nonsteroidal MRA that has greater selectivity than spironolactone for the MR over other steroid hormone receptors, greater affinity than eplerenone for the
Finerenone was designed to have greater cardiac activity than the available steroidal MRAs to improve myocardial function without adversely affecting sodium-potassium homeostasis in the kidney. In preclinical models of hypertension-related HF and renal dysfunction, finerenone resulted in greater cardiorenal target organ protection than steroidal MRAs.28

The mineralocorticoid receptor antagonist tolerability study (ARTS) was designed to assess the safety and tolerability of finerenone in patients with HF with reduced ejection fraction and mild or moderate chronic kidney disease and to select doses for phase III clinical trials.29,30 ARTS (ClinicalTrials.gov: NCT01345656) is a multicenter, randomized, double-blind, parallel-group study divided into 2 parts: Part A tested the effects of finerenone (2.5, 5, or 10 mg once daily) in 65 patients with HF with reduced ejection fraction and mild chronic kidney disease (estimated glomerular filtration rate 60–90 mL/min/1.73 m²); Part B compared finerenone (2.5, 5, or 10 mg daily or 5 mg twice daily) with placebo or open-label spironolactone (25 or 50 mg daily) in 392 patients with HF with moderate chronic kidney disease (estimated glomerular filtration rate 30–60 mL/min/1.73 m²).30 Finerenone 5 to 10 mg/day was at least as effective as spironolactone 25 or 50 mg/day in decreasing biomarkers of hemodynamic stress (B-type natriuretic peptide [BNP] and amino-terminal proBNP) and albuminuria and was associated with lower incidences of hyperkalemia and worsening renal function. Adverse effects were infrequent and mostly mild. Finerenone may, therefore, offer target-organ protection with a reduced risk of electrolyte disturbances in HF patients. Finerenone is currently under investigation in 2 phase IIb clinical trials: (1) in patients with worsening chronic HF and type 2 diabetes mellitus and chronic kidney disease (ARTS-HF; ClinicalTrials.gov: NCT01807221) and (2) in patients with type 2 diabetes mellitus and diabetic nephropathy (ARTS-DN; ClinicalTrials.gov: NCT01874431).

Figure 1. Mechanism of action of anti-aldosterone agents. Aldosterone synthase inhibitors (ASIs), such as LCI699, inhibit the rate limiting step of aldosterone production. Mineralocorticoid receptor agonists (MRAs), such as finerenone, compete for the binding sites of aldosterone and effectively decrease blood pressure and aldosterone-mediated gene transcription. Both approaches have been shown to be useful in treating aldosterone-mediated hypertension and vascular disease. Aldosterone synthesis, green; cortisol synthesis, red; anti-aldosterone drugs, blue.
Four phase II studies of LCI699 have been performed in hypertensive patients. The first proof-of-concept study compared LCI699 to placebo in 14 patients with primary aldosteronism. LCI699 normalized plasma aldosterone and potassium but also increased 11-deoxycorticosterone and adrenocorticotropin levels and produced only modest reduction (4.2 mmHg) in 24-hour ambulatory systolic BP. The first randomized, double-blind, placebo-controlled trial of LCI699, performed in 524 patients with primary hypertension, compared the efficacy and safety of different doses of LCI699 with eplerenone. All doses of LCI699 produced significant reductions in office systolic BP that were noninferior to those seen with eplerenone. Plasma aldosterone levels were suppressed with LCI699 and increased with eplerenone; both agents were well tolerated, but adrenocorticotropin-stimulated cortisol release was blunted in ≈ 20% of the LCI699 group, likely as a result of inhibition of CYP11B1.

A subsequent study evaluated the effect of LCI699 on the cortisol response to adrenocorticotropin stimulation in 63 treated hypertensive patients to find the maximally tolerated dose in this patient population. LCI699 had a dose- and time-dependent inhibitory effect on both aldosterone- and adrenocorticosterone-stimulated cortisol synthesis, consistent with inhibition of 11β-hydroxylase (CYP11B1) activity. A fourth study evaluated the safety and efficacy of LCI699, compared with placebo and eplerenone, as add-on therapy in patients with resistant hypertension. BP lowering effects of LCI699 were inferior to those of eplerenone and plasma 11-deoxycorticosterone levels increased, confirming inhibition of 11β-hydroxylase and compensatory stimulation of adrenal steroidogenesis. The nonselectivity of LCI699 resulted in off-target inhibition of the 11β-hydroxylase activity of CYP11B1, thus stimulating the hypothalamic–pituitary–adrenal feedback axis and increasing adrenocorticosterone levels and adrenal steroidogenesis to compensate for the reduced cortisol secretion.

In the setting of aldosterone synthase (CYP11B2) inhibition, this resulted in up to a 10-fold increase in the biologically active aldosterone synthase substrate, 11-deoxycorticosterone,
which could activate the MR. These effects could account for the disappointing BP reductions seen at higher doses and with twice daily administration of LCI699.

Based on the results of the phase II trials, further development of LCI699 was discontinued, and the investigators outlined the mechanistic properties that would be required for a therapeutically successful aldosterone synthase inhibitor: (1) greater selectivity for aldosterone synthase inhibition on CYP11B2 over 11β-hydroxylase inhibition on CYP11B1; (2) a longer plasma elimination half-life than LCI699; and (3) preferential inhibition of the 18-oxidase step of aldosterone synthesis, thus preventing conversion of the weak mineralocorticoids 18-OH corticosterone and corticosterone to aldosterone. A series of novel pyridyl- or isoquinolinyl-substituted indolines and indoles have recently been synthesized using a ligand-based approach. These compounds are as potent and more selective than LCI699 for CYP11B2 over CYP11B1 and are currently being tested as treatments for mineralocorticoid-dependent CVD and renal disease.

**Activators of the Angiotensin-Converting Enzyme2/Angiotensin(1–7)/MAS Receptor Axis**

The classical renin–angiotensin system (RAS) has been studied extensively for decades and has yielded numerous effective therapies for hypertension and its complications. More recently, components of the RAS that play counterregulatory roles have been identified, characterized and put forward as therapeutic targets for hypertension and other forms of CVD. The carboxypeptidase angiotensin-converting enzyme 2 (ACE2) converts the decapeptide angiotensin I (Ang I) to the Ang(1–9) nonapeptide and the octapeptide Ang II to the Ang(1–7) heptapeptide. Ang(1–7) has been studied intensively and shown to activate the G-protein-coupled Mas receptor, triggering a signaling cascade that results in vasodilation, reduction in oxidative stress, and antihypertrophic and antifibrotic effects. ACE2 also mediates degradation of Ang II, likely contributing to the antihypertensive/vasoprotective effects of the counterregulatory RAS pathway.

Amplification of ACE2/Ang(1–7)/Mas signaling opposes the effects of the classical RAS and lowers BP and prevents or reverses related target organ damage in hypertensive animal models. Interestingly, inhibitors of the classical RAS, including ACE inhibitors and angiotensin receptor blockers (ARBs), increase circulating Ang(1–7) levels, and the Mas antagonist A-779 attenuates the effects of the ACE inhibitors and ARBs, indicating that the 2 RAS axes interact and provide further evidence for the therapeutic potential of the ACE2/Ang(1–7)/Mas axis in hypertension.

The more recently described Ang(1–9) has been shown to lower BP and reverse/ameliorate cardiovascular injury in animal models of hypertension by a mechanism that involves activation of the angiotensin type 2 receptor. Unlike Ang(1–7), Ang(1–9) does not activate the Mas receptor. The therapeutic potential of angiotensin type 2 receptor activation is being explored as a new therapeutic strategy for hypertension and other forms of CVD.

**Figure 2.** Drugs targeting the classical and counter regulatory renin angiotensin systems (RAS). Activation of the classical RAS pathway increases BP and target organ damage, and this pathway is the target for many currently available antihypertensive drugs, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Novel approaches to RAS inhibition, including vaccines targeting angiotensin II (Ang II) and the angiotensin II type 1 (AT1) receptor, are being evaluated in preclinical and clinical trials. In contrast, activation of the more recently described counter regulatory RAS pathway decreases blood pressure (BP) and target organ damage, and drugs that activate this pathway are beginning to be developed as antihypertensive agents. These include ACE2 activators, Ang (1–7) analogs, AT2 receptor agonists, peptide and nonpeptide activators of the Mas receptor, and alamandine complexed with cyclodextrin. Classical RAS, red; counter regulatory RAS, green; drugs, blue. ATR indicates AT1 receptor; MrgD, Mas-related G-protein-coupled receptor, member D; and rhACE2, recombinant human ACE2.
explored in preclinical studies. A selective nonpeptide angiotensin type 2 receptor agonist, compound 21(C21), has been found to have anti-inflammatory, antibacterial and antiapoptotic properties, but not to lower BP47 (Table). These findings suggest that C21 may be useful in preventing hypertension-induced target organ damage.

Interest in ACE2 as a therapeutic target has led to the synthesis of small molecule ACE2 activators, including XNFT52 and DIZE,53 which lower BP, improve myocardial function, and reverse myocardial and perivascular fibrosis in the spontaneously hypertensive rat (SHR; Table). Activation of ACE2 also decreases monocrotaline-induced pulmonary hypertension by a mechanism that involves Mas activation.54,55 As an alternative to pharmacological ACE2 activation, recombinant human ACE2 (rhACE2) has been shown to lower BP in SHR, to have anti-inflammatory effects in a model of lipopolysaccharide-induced lung injury,56 and to slow the progression of diabetic nephropathy in animal models57 (Table). A phase I study in healthy volunteers demonstrated sustained (>24 h) suppression of circulating Ang II levels after a single intravenous injection of rhACE2 with no effect on BP and no major adverse effects.58

Ang(1–7) has been administered in phase I/II studies as a putative antiproliferative and antiangiogenic agent to patients with advanced cancers refractory to standard therapy and as a hematopoietic agent to patients with multilineage cytopenias following chemotherapy.79,80 These studies were limited in scope, and native Ang(1–7) has not been developed further because of its abbreviated half-life in vivo. A cyclic Ang(1–7) analog containing a thioether bridge that makes it resistant to enzymatic digestion and a hydroxypropyl-β-cyclodextrin inclusion complex (alamandine/HPβCD) has been shown to enter the brain of SHR and DOCA (deoxycorticosterone acetate)-salt rats to inhibit brain APA activity and block the formation of Ang III and to normalize BP for several hours68,70,71 (Table). The oral bioavailability of alamandine/HPβCD has revived prospects for exploring the therapeutic potential of Ang(1–7)-related peptides.

**Centrally Acting Aminopeptidase Inhibitors**

Activation of the brain RAS plays an important role in the pathogenesis of hypertension in animal models.67,68 Two membrane-bound zinc metalloproteases, aminopeptidase A (APA) and aminopeptidase N (APN), are involved in the metabolism of brain Ang II and III, respectively (Figure 3). APA cleaves the N-terminal Asp from Ang II to form Ang III, and aminopeptidase N cleaves the N-terminal Arg from Ang III to form Ang IV. Ang II and Ang III have similar affinities for Ang II receptors and both peptides stimulate pressor responses by activating sympathetic nervous system activity, inhibiting the baroreflex at the level of the nucleus tractus solitarius and increasing release of arginine vasopressin into the circulation. Studies using selective APA (EC33) and aminopeptidase N (PC18) inhibitors have demonstrated that brain Ang III (not Ang II, as in the periphery) plays a predominant role in BP control in animal models and have identified APA as a potential therapeutic target for the treatment of hypertension66–71 (Table).

Orally administered RB150, a dimer of EC33, has been shown to enter the brain of SHR and DOCA (deoxycorticosterone acetate)-salt rats to inhibit brain APA activity and block the formation of Ang III and to normalize BP for several hours66,70,71 (Table). The RB150-induced depressor response was related to inhibition of arginine vasopressin release, resulting in a diuresis and reduction in volume, and a decrease in sympathetic tone, resulting in reduced vascular resistance. Systemic RAS activity was unaffected, and systemic administration of an ACE inhibitor potentiated the RB150-induced BP decrease, suggesting that centrally acting APA inhibitors might be used in combination with systemic RAS blockers to improve BP control and reduce cardiovascular disease risk in hypertensive patients.70

RB150 (renamed QGC001) has been administered in ascending doses (10–1250 mg) to 56 healthy male volunteers.72 QGC001 did not significantly change heart rate or BP at any dose and was safe and well tolerated in this phase Ia study, as well as in a phase Ib study where it was administered in single doses of ≤2000 mg and in multiple doses over a 7 day period.68 A proof-of-concept exploratory study is planned to evaluate the clinical efficacy of RB150/QGC001 for treating hypertension in humans.

**Vasopeptidase Inhibitors**

The zinc metalloprotease neprilysin (neutral endopeptidase 24.11) is a therapeutic target for hypertension and other forms of CVD because it degrades the natriuretic peptides atrial natriuretic peptide (ANP), BNP, and urodilatin,73 and the increase in circulating natriuretic peptide levels that results from neprilysin inhibition leads to natriuresis, vasodilation, renin–angiotensin–aldosterone system inhibition, reduced sympathetic drive, and antiproliferative and anti hypertrophic effects
on the heart and vasculature\textsuperscript{74} (Figure 4). However, nepri-
lysin inhibitors are ineffective in lowering BP, likely because nepri-
lysin also degrades vasooconstrictor peptides, for example, Ang II and endothelin-1.\textsuperscript{75,76} Thus, combining a nepri-
lysin inhibitor with an RAS blocker or an endothelin-converting enzyme
inhibitor offers the theoretical advantage of enhancing the fa-
vorable vasodilator/natriuretic effects of ANP and BNP and reducing the deleterious
vasoconstrictor effects of Ang II or endothelin-1 on BP and target organ damage.

Dual-Acting Angiotensin Receptor–Nephrilysin

Inhibitors

The first-in-class angiotensin receptor–nephrilysin inhibitor LCZ696 is a novel single molecule composed of the nephrilysin
inhibitor prodrug AHU377 (sacubitril) and the ARB valsartan
in a 1:1 ratio\textsuperscript{77} (Figure 4; Table). In a proof-of-concept ran-
domized, double-blind, placebo-controlled, active comparator
trial, graded doses of LCZ696 were compared with graded
doses of valsartan and to AHU377 in 1328 patients with mild
to-moderate hypertension.\textsuperscript{78} LCZ696 produced significantly
greater reductions than valsartan in office systolic and dias-
tolic BP and 24-hour ambulatory systolic BP and pulse pressure
over the entire dose range tested; AHU377 produced a BP re-
duction significantly greater than placebo but smaller than ei-
ther LCZ696 or valsartan. Plasma ANP and cyclic guanosine
monophosphate (second messenger for nephrilysin activity)
levels increased with LCZ696, but the changes in biomarker
levels were poorly correlated with BP responses. There were
no cases of angioedema, but the trial included only 8\% black
patients, a group prone to develop angioedema when treated
with a combined ACE–nephrilysin inhibitor,\textsuperscript{79} and 3\% Asians.

To address the lack of information about the efficacy and safety
of LCZ696 in Asian persons, a randomized, double-blind,
placebo-controlled study was performed in 589 hypertensive
patients in 5 Asian countries (Japan, China, Korea, Taiwan,
and Thailand).\textsuperscript{80} Reductions in systolic BP in clinic and night-
time ambulatory settings were 6 to 8 mm Hg greater than those
previously reported for Western patients.\textsuperscript{78} This was attributed
to the natriuretic effect of nephrilysin inhibition, as valsartan
monotherapy has been shown to be relatively ineffective in
controlling nighttime BP in Japanese patients.\textsuperscript{81} No cases of
angioedema or other serious adverse effects were noted. The
authors pointed out the potential benefit of this BP lowering
effect in prevention of stroke in Asian populations.

In light of its modest BP lowering effects in Western popula-
lations, LCZ696 is currently under development for treatment
of HF, resistant hypertension, and systolic hypertension in
the elderly, conditions that are mediated by a combination of
vasoconstriction, volume overload, and neurohormonal acti-
vation. A Phase II double-blind randomized controlled trial
(PARAMOUNT) compared the effects of LCZ696 to those of
valsartan alone in 301 patients with HF with preserved ejection
fraction.\textsuperscript{82} LCZ696 induced a greater reduction in systolic BP
(9 mm Hg) than valsartan (3 mm Hg), but the changes in bio-
markers (NT-proBNP), left atrial volume, renal function, and
functional class were independent of the BP lowering effect
of LCZ696.\textsuperscript{83} However, since BP was controlled in the majority
of participants at the time of enrollment in PARAMOUNT, a
BP-dependent effect of LCZ696 may have been seen in a dif-
f erent population with higher baseline BP.

The Phase III Prospective Comparison of angioten-
sin receptor–nephrilysin inhibitor with ACEI to Determine
Impact on Global Mortality and Morbidity in Heart Failure
(PARADIGM-HF) trial was a randomized double-blind trial
that compared the effects of LCZ696 (200 mg twice daily) to
enalapril (10 mg twice daily) in 8442 patients with class II,
III, or IV HF and an ejection fraction \(\leq 40\%\).\textsuperscript{84,85} The primary
outcome was a composite of death from cardiovascular cause
or hospitalization for HF. The trial was stopped early (medi-
an follow-up 27 months) because of overwhelming benefit.
There was a 20\% reduction in cardiac death, a 16\% reduc-
tion in total mortality and a 21\% reduction in hospitalization
for HF, all highly significant, in the LCZ696 arm compared
to the enalapril arm. Further, the symptoms and physical

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig3}
\caption{The brain renin angiotensin system (RAS) pathway. Activation of the brain RAS in response to oxidative stress and inflammation increases sympathetic nervous system outflow and arginine vasopressin (AVP) release and inhibits the baroreflex, thus raising BP. Angiotensin (Ang) III, which is generated from Ang II by aminopeptidase A (APA), is the predominant pressor peptide in brain in animal models, and APA is a therapeutic target for treatment of hypertension. The APA inhibitor RB150 (QGC 001) has been shown to pass the blood–brain barrier and lower BP in animal models; exploratory studies are underway in humans. Red, classical RAS; light blue, brain RAS pathway; blue, drugs, dotted arrows indicate crosstalk between the systems. APN indicates aminopeptidase N; AT1, angiotensin type 1; ATR, AT1 receptor; and ROS, reactive oxygen species.}
\end{figure}
limitations of HF were reduced with LCZ696. Mean systolic BP was slightly but significantly (3.2 mm Hg, P < 0.001) lower in the LCZ696 group, but this did not account for the outcome benefit. Safety concerns were minor: the LCZ696 group had more symptomatic hypotension, but this rarely required discontinuation of treatment, and more participants in the enalapril group stopped treatment because of other adverse events (most commonly cough or elevated serum potassium) or renal impairment. Angioedema was uncommon in both treatment groups, and the few cases that occurred did not cause airway compromise. However, the study had a run-in phase that excluded persons who were intolerant of an ACE inhibitor or ARB and enrolled few black patients, a group prone to develop angioedema in response to dual vasopeptidase blockade.\textsuperscript{79} Despite these caveats, the PARADIGM-HF trial has been hailed as revealing the first significant advance in HF therapy in nearly a decade and as offering new thresholds of hope for patients with chronic HF.\textsuperscript{86}

The ongoing prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin receptor blocker measuring arterial stiffness in the elderly (PARAMETER) study (EUDraCT ID:2012-002899-14; ClinicalTrials.gov: NCT01692301) compares the effects of LCZ696 versus the ARB olmesartan on aortic stiffness and central aortic hemodynamics in older (aged ≥ 60 years) patients with systolic hypertension.\textsuperscript{87} The central hypothesis of PARAMETER is that by simultaneously enhancing natriuretic peptide effects and inhibiting the RAS, LCZ696 will reduce aortic stiffness and characteristic impedance and improve central hemodynamics, perhaps via mechanisms that are independent of BP reduction. This concept will be examined in greater depth in a parallel study that will determine aortic distensability by MRI and retinal vascular remodeling by scanning laser Doppler flowmetry, respectively (www.ClinicalTrials.gov: NCT01870739). A novel aspect of both studies is assessment of mean aortic pressure and pulse wave velocity on a 24-hour basis using a novel cuff-based oscillometric ambulatory BP monitoring device.\textsuperscript{88}

**Dual-Acting Endothelin Converting Enzyme–Neprilysin Inhibitors**

Orally active dual inhibitors of neprilysin and endothelin-converting enzyme have been developed, and one of these (duglutril, SLV-306) has been studied in rodent models of diabetes mellitus and in patients with hypertension, HF, and type 2 diabetes mellitus (Table). Duglutril is a prodrug that is hydrolyzed after oral administration to the active metabolite KC-12615, a mixed inhibitor of neprilysin and endothelin-converting enzyme.\textsuperscript{89} In diabetic rat models, duglutril and a similar compound have been shown to reduce
BP and proteinuria and prevent nephrosclerosis as effectively as the ACE inhibitor captopril. Dalgutril has also been shown to be safe and well tolerated in healthy volunteers, and biomarker measurements confirmed dual suppression of nephrilysin and endothelin-converting enzyme activity in these subjects. Data from a multicenter, randomized controlled trial performed in 75 patients with HF showed that dalgutril reduced pulmonary and right atrial pressures without affecting systemic arterial pressure, cardiac output, or heart rate. Dalgutril has also been shown in a small randomized, double-blind, placebo-controlled crossover trial to lower BP but not to reduce albuminuria in patients with type 2 diabetes mellitus and nephropathy.

Natriuretic Peptide Receptor Agonists
Natriuretic peptide receptor agonists are being developed as an alternative approach to inhibiting the degradation of endogenous natriuretic peptides for the treatment of HF and refractory or resistant hypertension. The natriuretic peptide receptor A (NPR-A) agonist PL-3994 is a synthetic molecule that contains an amino acid mimetic and has reduced affinity for the natriuretic peptide clearance receptor (NPR-C) and increased resistance to nephrilysin, resulting in a prolonged half-life after subcutaneous administration (Table). A phase I trial of a single subcutaneous dose of PL-3994 in healthy volunteers showed increased natriuresis and diuresis, elevation in plasma cyclic guanosine monophosphate levels, and reduction in systemic BP compared with placebo. A phase II trial in volunteers with hypertension who were receiving ≥1 antihypertensive medications demonstrated a reduction in systemic BP compared with placebo. In particular, PL-3994 appeared to act synergistically with ACE inhibitors, suggesting that it could be administered as an adjunct to standard therapy in patients with refractory or resistant hypertension or HF. No safety concerns were raised in either trial (ClinicalTrials.gov: NCT00686803).

C-ANP<sub>4-23</sub> is a ring deleted analog of ANP that is selective for NPR-C and decreases the enhanced expression of G<sub>Î»</sub> proteins that has been implicated in the pathogenesis of hypertension in animal models (Table). Intraportal injection of C-ANP<sub>4-23</sub> has been shown to decrease BP in SHR by inhibiting enhanced expression of G<sub>Î»</sub> proteins and reducing nitrosative stress, not by modulating the eNOS/cyclic guanosine monophosphate pathway. This study revealed a novel function of NPR-C, which has generally been considered a clearance receptor for natriuretic peptides and has raised the possibility that NPR-C agonists, such as C-ANP<sub>4-23</sub>, could be useful for the treatment of hypertension and related CVDs.

Soluble Epoxide Hydrolase Inhibitors
Soluble epoxide hydrolase (s-EH) catalyzes the conversion of multiple lipid epoxides to the corresponding dihydroxy lipids. Substrates of s-EH include members of the arachidonic acid family, for example, epoxycosatetraenonic acids, and the effects of s-EH inhibitors have been attributed to increased epoxycosatetraenonic acid levels. Preclinical studies have shown that inhibitors of s-EH lower BP, prevent and reverse pressure overload–induced cardiac hypertrophy, attenuate ischemic and ischemia-reperfusion injury of the brain and heart, prevent atherosclerosis and aneurysm formation, and attenuate insulin resistance in animal models.

AR9281 is a potent and selective inhibitor of human s-EH that has been shown to lower BP, improve vascular function, and reduce renal damage in a rat model of Ang II-induced hypertension and to improve glycemic parameters in a mouse model of diet-induced obesity (Table). The metabolic effects of AR9281 were absent in mice with diet-induced obesity due to deletion of the Ephx2 gene, which encodes s-EH, validating the mechanism of the AR9281 effect. Randomized double-blind, placebo-controlled studies in healthy volunteers have shown that AR9281 dose-dependently inhibits s-EH at doses that are well tolerated. A randomized double-blind, placebo-controlled dose-ranging phase II study in patients with mild to moderate hypertension and impaired glucose tolerance was terminated in November 2009, and no efficacy results have been reported, suggesting that it was ineffective in lowering BP (ClinicalTrials.gov: NCT00847899). However, s-EH inhibitors have other promising therapeutic applications, for example, inflammation, pain, and CVD that warrant future investigation.

Vasoactive Intestinal Peptide Receptor Agonist
Vasoactive intestinal peptide (VIP) is a neuropeptide with vasodilator and positive inotropic/chronotropic properties that are mediated via the G-protein-coupled receptors VPAC1 and VPAC2. Deficiency in VIP and alterations in properties of VPAC1 and 2 have been described in various forms of cardiopulmonary disease, and VIP is a therapeutic target for hypertension, both systemic and pulmonary, as well as HF. To overcome the abbreviated half-life (<2 min) of VIP, vasomera (PB1046), a stable long-acting form of VIP that is selective for VPAC2, has been developed by fusing an analogue of VIP with an elastin-like polyepitide that reduces the potential gastrointestinal side effects associated with activation of VPAC1. Vasomera reduces BP and improves inotropic and lusitropic properties of the heart in animal models of hypertension and HF and has been shown to be safe and well-tolerated after single subcutaneous or intravenous injections in phase I studies in patients with essential hypertension (ClinicalTrials.gov: NCT01523067, NCT01873885). The pharmacodynamic activity of subcutaneous vasomera is supportive of a once weekly dosing regimen that could allow for chronic use in the home setting. Intravenous dosing of vasomera is being evaluated for short-term treatment of HF in the hospital setting.

Intestinal Na<sup>+</sup>/H<sup>+</sup> Exchanger 3 Inhibitor
Excessive sodium intake and impaired sodium excretion plays an important role in the pathogenesis of hypertension and its complications, including HF and chronic kidney disease. Electroneutral Na<sup>+</sup>/H<sup>+</sup> exchangers, for example, NHE2, NHE3, and NHE8, that are expressed in the apical regions of the enterocyte transport sodium from the intestinal lumen into enterocytes, and have shown that AR9281 dose-dependently inhibits s-EH at doses that are well tolerated. A randomized double-blind, placebo-controlled dose-ranging phase II study in patients with mild to moderate hypertension and impaired glucose tolerance was terminated in November 2009, and no efficacy results have been reported, suggesting that it was ineffective in lowering BP (ClinicalTrials.gov: NCT00847899). However, s-EH inhibitors have other promising therapeutic applications, for example, inflammation, pain, and CVD that warrant future investigation.

Intestinal Na<sup>+</sup>/H<sup>+</sup> Exchanger 3 Inhibitor
Excessive sodium intake and impaired sodium excretion plays an important role in the pathogenesis of hypertension and its complications, including HF and chronic kidney disease. Electroneutral Na<sup>+</sup>/H<sup>+</sup> exchangers, for example, NHE2, NHE3, and NHE8, that are expressed in the apical regions of the enterocyte transport sodium from the intestinal lumen into enterocytes, and have shown that AR9281 dose-dependently inhibits s-EH at doses that are well tolerated. A randomized double-blind, placebo-controlled dose-ranging phase II study in patients with mild to moderate hypertension and impaired glucose tolerance was terminated in November 2009, and no efficacy results have been reported, suggesting that it was ineffective in lowering BP (ClinicalTrials.gov: NCT00847899). However, s-EH inhibitors have other promising therapeutic applications, for example, inflammation, pain, and CVD that warrant future investigation.

Intestinal Na<sup>+</sup>/H<sup>+</sup> Exchanger 3 Inhibitor
Excessive sodium intake and impaired sodium excretion plays an important role in the pathogenesis of hypertension and its complications, including HF and chronic kidney disease. Electroneutral Na<sup>+</sup>/H<sup>+</sup> exchangers, for example, NHE2, NHE3, and NHE8, that are expressed in the apical regions of the enterocyte transport sodium from the intestinal lumen into enterocytes, and have shown that AR9281 dose-dependently inhibits s-EH at doses that are well tolerated. A randomized double-blind, placebo-controlled dose-ranging phase II study in patients with mild to moderate hypertension and impaired glucose tolerance was terminated in November 2009, and no efficacy results have been reported, suggesting that it was ineffective in lowering BP (ClinicalTrials.gov: NCT00847899). However, s-EH inhibitors have other promising therapeutic applications, for example, inflammation, pain, and CVD that warrant future investigation.
extracellular volume expansion, lowers BP, and reduces albuminuria and cardiac and renal injury in the 5/6 nephrectomy rat model of sodium-dependent hypertension. Tenapanor also enhances the BP lowering and organ protective effects of the ACE inhibitor enalapril in this model. These findings suggest that reducing sodium transport in the gut could provide a useful alternative or adjunct to dietary sodium reduction or diuretics in the treatment of hypertension and related target organ damage.

Dopamine β-hydroxylase (DβH) Inhibitor

Dopamine β-hydroxylase (DβH), the enzyme that catalyzes the hydroxylation of dopamine to form noradrenaline in the sympathetic nervous system, is a therapeutic target for treatment of hypertension and other cardiovascular disorders characterized by sympathetic activation, for example, HF.110 Inhibition of DβH offers theoretical advantages over adrenergic receptor blockade: (1) it causes gradual sympathetic slow-down instead of acute inhibition and (2) it increases dopamine availability, thus causing renal vasodilation, natriuresis, and diuresis. First, second, and early third generations DβH inhibitors, for example, disulfiram, fusaric acid, and nepicastat, either lacked potency or selectivity for DβH or caused severe CNS-related adverse effects and thus were not clinically useful. Etamicastat (BIA 5–453) is a potent and reversible inhibitor of DβH that does not pass the blood brain barrier and thus is selective for peripheral DβH when administered orally (Table).111 Etamicastat lowers BP in the SHR, but not in normotensive WKY (Wistar Kyoto) rats, and prolongs survival in animal models of HF.112 Studies in healthy men and men with mild to moderate hypertension showed good tolerability and statistically significant dose-dependent decreases in 24-h ambulatory blood pressure (ABP).113 These emerging preliminary results warrant further testing in broader populations.

Vaccines

Vaccines targeting renin for the purpose of treating hypertension have been available for over 50 years.113 Although a renin vaccine successfully lowered BP in animal models, it induced autoimmune disease of the kidneys and further development was suspended.114 An Ang I vaccine also lowered BP in animal models,115,116 but was ineffective in a randomized, double-blind, placebo-controlled clinical trial.117 Further, a vaccine raised in response to an Ang II–derived peptide conjugated to a virus-like particle derived from the bacteriophage Qβ (AngQb) was effective in producing anti-Ang II antibodies and reducing BP in SHR, despite increasing circulating Ang II levels118 (Figure 2; Table). In a placebo-controlled, randomized phase I trial, 12 healthy volunteers received a single injection of AngQb,119 Ang II–specific antibodies were raised in all subjects, and the AngQb antigen was well tolerated. A subsequent double-blind, randomized, placebo-controlled phase IIa trial tested the effects of immunization with 2 doses of AngQb (also named CYT006-AngQb) on ambulatory BP in 72 patients with mild-to-moderate hypertension.119 Mean ambulatory daytime BP and the early morning BP surge were reduced significantly (by 9/4 and 25/13 mm Hg, respectively) in the high dose group. Changes from baseline in nighttime BP were not significantly different from placebo in either group, and the diurnal pattern of BP response to the vaccine paralleled the diurnal rhythm of RAS activity, with higher levels in daytime than nighttime, and the highest levels of all during the early morning surge in BP. Most observed adverse events were not serious and similar to those seen with other vaccines, that is, mild, transient reactions at the injection site and influenza-like symptoms. The induced antibody response was reversible, with a half-life of ≈4 months, a time course that is compatible with a treatment regimen of 3 to 4 injections per year, which could coincide with regular clinic visits for hypertension management. The authors commented that the immunization strategy could reduce the need for daily dosing of antihypertensive medications, thus enhancing adherence. However, the study was limited by inclusion of a small number of otherwise healthy hypertensive participants, and later stage clinical trials will be needed to evaluate efficacy and safety in a broader hypertensive population.

A subsequent study that used an accelerated immunization schedule in an attempt to induce higher antibody titers, and thereby, greater BP reduction was successful in boosting the antibody titer 5-fold, but resulted in smaller BP reductions.120,121 Antibody affinities were significantly lower, and the amount of Ang II sequestered in the blood of vaccinated persons was significantly less than in the previous study.119 Changes in daytime ambulatory BP correlated with individual antibody affinities and, in particular, with measures of off-rates (how long Ang II is bound to the antibodies). Thus, persons whose antibodies had higher affinity and bound Ang II for a longer period of time showed greater BP reductions. These findings suggest that an accelerated immunization regimen leads to antibody responses with higher titers but lower affinities, perhaps related to disruption in the β-cell antibody affinity maturation process, thereby creating a lower capacity for sequestering Ang II in the blood, resulting in less BP reduction. The authors concluded that a better understanding of how differences in dose and timing of immunizations affect antibody titers, affinities, and BP is crucial for the successful development of an effective vaccine therapy for hypertension. Ongoing phase II trials in patients with mild-to-moderate hypertension are exploring these issues.122 Preclinical studies are evaluating in hypertensive rodent models the safety and efficacy of vaccines against various peptide sequences within the Ang II type 1 receptor, ATRQb-001 and ATR12181,123,124 against Ang II conjugated via the N-terminus to keyhole limpet hemocyanin125 and against a chimeric protein (pHAV–4 Ang IIs) that presents 4 successive repeated Ang II sequences as the functional epitope on the surface of the hepatitis A virus-like particle126 (Figure 2; Table). In all cases, significant BP reductions were achieved, keeping alive the concept that vaccine therapy might be useful in the treatment of human hypertension and its complications.

Novel Approaches to Preeclampsia Treatment

Immunologic approaches are also being explored for the treatment of preeclampsia. Endogenous digitalis-like factors (EDLFs) are a family of circulating Na/K-ATPase inhibitors, including marinobufagenin, that are elevated in preeclampsia and contribute to its pathogenesis by mediating...
vasoconstriction and vascular fibrosis and inhibiting proliferation and invasion of the cytotrophoblast.\textsuperscript{127–130} An antidi- 
goxin antibody fragment (Digibind, Ovine Digoxin Immune 
Antibody) has been shown to attenuate the inhibitory effects of 
EDLFs on Na/K-ATPase, to lower BP in animal models of 
volume-dependent hypertension and to reduce maternal BP 
and preserve renal function in women with preeclampsia\textsuperscript{131,132} 
(Table).

A randomized, double-blind, placebo-controlled trial, 
Digibond Efficacy Evaluation in Preeclampsia, demonstrated 
beneficial effects on renal function and a trend toward reduc- 
tion in antihypertensive drug usage but no prolongation of 
pregnancy or improvement of maternal outcome overall in 
women with severe preeclampsia.\textsuperscript{129,133} A secondary analysis of 
Digibond Efficacy Evaluation in Preeclampsia stratified patients by circulating levels of EDLF activity and found 
that the beneficial effects of Digibond on renal function and on 
utilization of antihypertensives, as well as some maternal and 
fetal/neonatal outcomes, were greater in women who were 
EDLF positive.\textsuperscript{129} Digibind production was terminated by its 
manufacturer in 2010, and DigiFab, affinity purified Fab frag- 
ments of antidigoxin antibody, became the only antidigoxin 
antibody available for clinical use.\textsuperscript{130} DigiFab has similar effects 
as Digibind on EDLFs derived from the blood of women 
with preeclampsia. Ongoing expedited phase II studies are 
evaluating the safety and efficacy of digoxin-immune Fab for 
treatment of preeclampsia (Table).

Antithrombin replacement is a novel approach for the treat- 
ment of early onset severe preeclampsia that has been shown 
in small uncontrolled studies to lower BP, reduce protein- 
uria, and improve coagulation parameters.\textsuperscript{134} The Prospective 
Randomized Evaluation of the Safety and Efficacy of 
Recombinant Antithrombin in Very Preterm Preeclampsia 
(PRESERVE-1; ClinicalTrials.gov: NCT02059135) is an on- 
going phase III randomized placebo controlled trial of recom- 
binant human antithrombin (ATryn) for the treatment of early 
(24–28 weeks) onset preeclampsia (Table). The primary end 
point is the increase in gestational age from randomization 
to delivery; secondary end points include a large number of 
maternal and fetal outcomes.

**Part II. Interventional Treatments**

In the 2013 ESH/ESC\textsuperscript{135} Guidelines for the Management 
of Arterial Hypertension, interventional strategies are men- 
tioned as therapeutic options for severe TRH. In Part II of 
this Compendium Review, we focus on 2 main interventional 
approaches, that is, renal denervation (RDN) and baroreflex 
activation therapy (BAT) because these interventions are used 
in clinical practice in some countries. We also discuss briefly 
other interventional approaches to TRH.

**Renal Denervation**

This is a rapidly growing research field with numerous pub- 
lished papers dealing with RDN. In this Comprehensive 
Review, we have focused on clinical aspects and established 
catheter-based techniques of RDN, but also provide some in- 
sights into the emerging field of alternative techniques target- 
ing renal nerves.

Increased sympathetic activity plays an important role in the 
development, maintenance, and acceleration of arterial hyper- 
tension,\textsuperscript{136,137} especially in TRH. Activation of efferent sympa- 
thetic nerves to the kidney stimulates renin release, enhances 
tubular reabsorption of sodium and water, and decreases re- 
nal blood flow.\textsuperscript{138} In addition, activation of afferent sensory 
nerves, for example, stimulated by stretch, renal ischemia, hy- 
poxia, or other injury, increases central nervous system sympa- 
thetic outflow and, as a consequence, sympathetic activity in 
key organs, including the heart, kidney, and vasculature, in 
particular the small resistance vessels.\textsuperscript{138,139} Catheter-based 
RDN has been introduced as a new interventional approach 
targeting sympathetic nerve activity, and hence arterial hyper- 
tension in humans.

The first nonrandomized, proof-of-concept study (Symplicity HTN-1) of RDN patients with TRH (systolic BP ≥160 mmHg) was published in 2009.\textsuperscript{140} There was a BP re- 
duction of 27/17 mmHg at 6 months of follow-up, without 
any significant safety issues. In the subsequent randomized 
controlled Symplicity HTN-2 study, a 2 week observation 
period was required and baseline office BP had to be ≥160 
mmHg (or ≥150 mmHg in diabetics, respectively).\textsuperscript{141} A BP 
reduction of 32/12 mmHg was observed after RDN compared 
with the control group (1/0 mmHg) with no outstanding safety 
concerns. Long-term data (36 months follow-up) from both 
studies showed that BP reduction was maintained or even be- 
came greater, suggesting that clinically meaningful reinnerva- 
tion did not occur.\textsuperscript{142,143} However, concerns about the design of 
the Symplicity HTN-1 and HTN-2 studies have been raised, 
for example, lack of 24-h ambulatory blood pressure monitor- 
ing (ABPM), to confirm true resistant hypertension, (ie, white 
coat effect was not definitely excluded) and the unblinded de- 
sign of the studies.\textsuperscript{144}

To overcome these deficiencies and after the advice of the 
Food and Drug Administration of the United States, the 
prospective, single-blind, randomized, sham-controlled 
Symplicity HTN-3 trial was performed.\textsuperscript{145} The primary safety 
end point was met, but the prespecified primary efficacy end 
point (reduction in office BP) was not reached. There was sig- 
nificant BP reduction from baseline in both groups (P<0.001), 
but between the RDN and sham-control group, neither office 
(−2.29 mmHg, P=0.026) nor 24-h ABPM (−1.96 mmHg, 
P=0.98) was significantly different at 6 months of follow-up.\textsuperscript{145}

After publication of the primary findings of Symplicity 
HTN-3, it became clear that the results are difficult to inter- 
pret because of procedural shortcomings. Post hoc analysis 
of the imaging taken during RDN showed that only 19 pa- 
tients had complete 4 quadrant ablations (covering 360° of 
the renal artery) for both renal arteries and only 68 for one 
renal artery, respectively.\textsuperscript{146} These data indicate that 253 of 
the participants randomized to the active treatment arm of 
the study did not have circumferential ablation of both renal 
arteries, calling into question the completeness of RDN in the 
trial. Office systolic BP changes in the group with incomplete 
RDN of both renal arteries were −14.2±24 (N=253); in those 
with ≥1 complete RDN, −16.1±23 (N=68); and in those with 
complete RDN of both arteries, −24.3±23 mmHg (N=19). In 
addition, 60 of the 111 operators performed just 1 or 2 RDN
procedures, further questioning the quality of the RDN procedures in the trial.\textsuperscript{140} Although each procedure was supervised by an experienced proctor and performed per protocol instructions, the denervation achieved was thus incomplete in most cases, owing to an insufficient number of ablations, lack of 4-quadrant ablations, or other technical features that might explain the failure to lower BP significantly.\textsuperscript{147}

In contrast to previous trials, mainly conducted in Europe and Australia, approximately one-quarter of patients enrolled in the Symplicity HTN-3 study were African American and there appeared to be an interaction with race and change in office BP ($P$ for interaction $=0.09$). In African Americans, office systolic BP decreased by 15.5 in the RDN group and 17.8 mmHg in the control group ($P=0.641$). In Non-African Americans (nearly all were white), office systolic BP was reduced by 15.2±24 mmHg in the RDN group and 8.57±25 mmHg in the sham-control group, with a significant difference between the 2 groups of 6.63 mmHg (95% confidence interval, −11.81 to −1.44; $P=0.012$).\textsuperscript{145} Of note, randomization into the RDN and control groups was stratified by race (African American versus Non-African American), that is, the subgroup analysis is solid because randomization was maintained, in contrast to all other subgroup analyses included in the Symplicity HTN-3 article.\textsuperscript{145} Differences in the response to BP treatment according to race are well known, and hence many guidelines recommend differential antihypertensive drug strategies in African Americans versus other racial groups.\textsuperscript{148,149}

Further debate about the efficacy of RDN is related to the numeric differences between office BP reduction (eg, Symplicity HTN-2 32/12 mmHg, $n=49$) and 24-h ABP reduction (eg, Symplicity HTN-2 11/7 mmHg, $n=20$).\textsuperscript{141} In a pooled analysis, it was shown that in patients with TRH, both office BP and, to a lesser extent, 24-h ABP were significantly reduced, whereas in patients with white coat hypertension, only office BP was significantly reduced.\textsuperscript{150} This discrepancy in BP reduction between office BP and 24-h ABP has been observed repeatedly. In the largest reported clinical study, a registry-based analysis, it was found that the disproportionate decreases in office BP versus 24-h ABP were related to the pretreatment BP (which is higher with office BP readings compared with 24-h ABPM) and that the changes in office and 24-h ABPM were not related in a 1:1 fashion.\textsuperscript{151}

Most recently, 2 randomized (not sham) controlled trials of RDN in patients with TRH have been published. In the PRAGUE-15 trial, the antihypertensive effects of RDN were compared with those of intensified pharmacological treatment, including spironolactone.\textsuperscript{152,153} The reductions in office BP and ABP were comparable in the 2 groups, but 39% of the patients in the pharmacological therapy group experienced adverse events, for example, hyperkalemia and antiandrogen effects. In the French DENER-HTN study, 106 patients with TRH were randomized to RDN ($N=53$) or intensified drug treatment ($N=53$).\textsuperscript{154} Baseline-adjusted changes in daytime and nighttime ABP from baseline to 6 month follow-up were significantly greater in the RDN group than in the control group: systolic daytime BP −5.9 mmHg ($P=0.0329$), systolic nighttime BP −6.3 mmHg ($P=0.0296$), diastolic daytime BP −3.1 mmHg ($P=0.092$), and diastolic nighttime BP −3.2 mmHg ($P=0.051$).\textsuperscript{154} Both trials included patients whose hypertension was not truly treatment resistant because office BP and ABP were lowered significantly after uptitrating pharmacological therapy in the intensified drug treatment groups.

Although current knowledge of the effects of RDN is based largely on studies performed with the Symplicity Flex catheter, multi-electrode approaches may reduce the need for catheter manipulation and decrease procedure time. The effects of RDN with various catheters on BP are generally similar, and most of the published trials were uncontrolled (Figure 5).

An unresolved but critical issue in assessing the clinical utility of RDN is to identify a reliable predictor of BP response. Analyses that have focused mainly on clinical characteristics of the patients and technical aspects of the catheters and procedures have failed to identify consistent and reliable predictors, with the exception of baseline systolic BP.\textsuperscript{141,150} Baseline BP is positively related to the amount of BP reduction post-RDN according to Wilder’s law\textsuperscript{155} and regression to the mean effect.

Other clinical effects of RDN, which are at least in part beyond BP reduction, have been reported. These include improvement in glucose metabolism,\textsuperscript{156} beneficial effect on end-organ damage, for example, left ventricular hypertrophy,\textsuperscript{157} arterial stiffness\textsuperscript{158} and albuminuria,\textsuperscript{159} attenuation of decline in renal function, and improvement in functional status in patients with congestive HF.

Non-catheter-based approaches of targeting the renal nerves have also been developed. In an adult swine model, a 3-needle delivery device was introduced and 3 different doses of ethanol (each $n=3$) were injected through the vessel wall into the peri-adventitial tissue in a circumferential manner. There was a dose-dependent decrease in renal parenchymal norepinephrine concentration (0.15 mL/artery, 54%; 0.3 mL/artery, 78%; and 0.6 mL/artery, 88%; all $P<0.05$) after 2 weeks. Histopathologic examination revealed no evidence of device or ethanol-induced intimal injury.\textsuperscript{160} An alternative ethanol-based approach was reported in one patient with TRH and end-stage renal disease. Percutaneous ethanol delivery was guided via computer tomography, and ethanol was injected around the renal arteries. After 1 month, office BP was reduced from baseline 172/84 to 143/70 mmHg. No data about 24-h ABPM, which is considered gold-standard, was provided.\textsuperscript{161}

The feasibility of a noninvasive approach to RDN by extracorporeal high-intensity focused ultrasound has been tested in a canine model. Compared with baseline, BP and renal parenchymal noradrenaline concentration were reduced (day 6, −50.1%; day 28, −55.4%; both $P<0.001$), whereas no significant change was observed in the sham-control group. Histopathologic examination demonstrated nerve fiber disruption at day 28 after RDN.\textsuperscript{162} The WAVE I trial tested Kona Medical’s ultrasound-based Surround Sound\textsuperscript{®} Renal Denervation System (Kona Medical, Menlo Park, CA) in 24 patients with TRH who were taking an average of 4.5 antihypertensive medications and had a mean baseline BP of 190/100 mmHg. Eighteen focused lesions were applied over 13 minutes to each artery, but for targeting and tracking reasons, a 5F intravascular renal artery catheter
had to be used. Office systolic BP was reduced by 29 mm Hg at 6 months after externally focused ultrasound RDN. The WAVE II study, using an optimized treatment protocol (14 externally focused lesions over 3 minutes were applied per side) has been completed, but not yet reported. The WAVE III study used an improved protocol of energy delivery without the need to have a guiding catheter inserted, thus achieving a fully noninvasive RDN approach in humans. First results (n=22), presented at the 2014 Transcatheter Cardiovascular Therapeutics (TCT) meeting, showed an office BP reduction of 29.6/11.8 mm Hg at 3 months after ultrasound RDN.163 The WAVE IV trial, a prospective, randomized sham-controlled study, in which office and ABP are to be obtained after 6 months, is underway (www.ClinicalTrials.gov: NCT02029885).

Baroreflex Activation Therapy
Knowledge of baroreflex regulation of BP goes back to ancient times. The arteries of the neck were named karotides, based on the Greek rout karos (heavy sleep) and karoun (to choke, to stupefy) because pressing on these arteries produced sedation. In the 20th century, the role of the carotid baroreflex was demonstrated for short-term BP regulation, but it was assumed to play no role in long-term BP control. However, based on several important studies in animals, interest in the role of the carotid sinus baroreceptor on long-term BP control has returned,164–166 and a surgical implantable device has been developed to administer BAT via electrical stimulation of the carotid baroreceptors.167 The prospective nonrandomized DEBut-HT trial was a multicenter European feasibility trial for the early-generation device (Rheos System; CVRx Inc., Minneapolis, MN) performed in 45 patients with TRH (systolic BP ≥160/90 mm Hg, despite ≥3 antihypertensive drugs, including a diuretic). In this proof-of-concept study, there was a reduction of 21±4/12±2 mm Hg (n=37) in office BP at 3 months, with further decreases of 30±6/20±4 (n=26) at 1 year and 33±48/22±26 mm Hg (n=17) at 2 years (all P<0.005), respectively. There was also a statistically significant reduction in 24-h ABP at 1 year follow-up. In contrast, no BP change was observed in 10 control patients who declined device implantation.167 In total, 8 serious adverse events (7 procedure-related and 1 device-related) were reported, a number comparable to published complication rates with carotid surgery.168,169 A substudy of 12 patients from the DEBut-HT trial demonstrated that muscle sympathetic nerve activity and BP were decreased after activation of BAT and increased without activation, providing evidence that reduction of sympathetic outflow is the primary mechanism for BP reduction with BAT.170

The double-blind, randomized, parallel-design Rheos Pivotal trial enrolled 256 patients with TRH. One month after Rheos device implantation, patients were randomized in a 2:1 manner to immediate BAT (device on) or delayed BAT (device remained off for 6 months). The prespecified acute primary efficacy end point (proportion of patients achieving BP reduction of ≥10 mm Hg after 6 months with a superiority margin of 20%) was not met, and the secondary efficacy end point (mean change in systolic BP after 6 months) failed statistical significance (group A [device on]: −16±29 versus group B [device off]: −9±29 mm Hg; P=0.08). There was an unexpected difference in systolic BP between preimplant (−1 month) and immediately postimplant (month 0) time points, prompting an additional post hoc analysis of the data. BP reductions from preimplant levels to 6 months postimplant were 26±30 mm Hg in the device on group versus 17±29 mm Hg (P=0.03) in the device off group. The sustained primary efficacy end point, defined as BP reduction of ≥10 mm Hg from months 0 to 12, with ≥50% of BP reduction seen at month 6 (primary end point) was reached. The procedural primary safety end point was not met, mainly because of surgical complications.
Carotid Body Ablation

Studies in animal models and human subjects have revealed enhanced carotid body (CB) sensitivity in hypertension, but the mechanisms of this abnormality are not known. CB hypersensitivity has been shown to precede the development of hypertension in SHR and in patients with white-coat hypertension. In a small, randomized, crossover, placebo-controlled study, deactivation of CB chemoreceptors by hyperoxia (respiration with 100% oxygen) attenuated the enhanced muscle sympathetic nerve activity in untreated hypertensive men, but no change was observed in controls. These data point to a potential pathogenetic role of enhanced chemoreceptor activity. Reductions in systemic vascular compliance and effective arterial volume may also improve arterial compliance, contributing to a reduced cardiac workload, despite increased cardiac output. Expected adverse effects are induction of venous stenosis and thrombosis and potential worsening/development of right ventricular failure. The Rox coupler system was originally developed for the treatment of patients with COPD. Early positive results extended the indication to patients with concomitant arterial hypertension. A subset of 24 COPD patients (NCT00832611 and NCT00992680) with an office systolic BP ≥130 mmHg when on antihypertensive treatment was retrospectively analyzed after the ROX coupler procedure was performed. Compared with baseline (145±12/86±13 mmHg), systolic and diastolic BP were significantly reduced after 6 (130±18/71±13 mmHg, P<0.01) and 12 months (132±18/67±13 mmHg, P<0.01), respectively. No clinical meaningful BP reduction was seen in normotensive COPD patients after creation of an AVF using the ROX coupler.

Based on this first evidence of efficacy of AVF in patients with COPD and coexisting arterial hypertension, the concept was further tested in a small prospective, nonrandomized study enrolling 8 patients with TRH, but without COPD. Compared with baseline, both office BP (175±19/87±14 versus 158±26/74±19 mmHg) and 24-h ABP (152±17/82±15 versus 142±18/69±14 mmHg) decreased at 6 months post creation of AVF. Subsequently, the European prospective, open-label, multi-center ROX CONTROL-HTN (NCT01642498) study was initiated to evaluate the ROX Coupler used along with standard drug therapy in 100 patients with TRH without COPD. In the ROX coupler group, office BP decreased by 26.3/20.1 mmHg (control group 3.7/2.4 mmHg) and ambulatory BP by 13.5/13.5 mmHg (control group 0.5/0.1 mmHg) after 6 months. Reductions were of similar magnitude in those with previous renal denervation.

Procedural complications related to arteriovenous coupler placement occurred in N=13 (31%) with venous stenosis occurring in N=12 (29%) of the 42 patients treated. In relation to worsening of hypertension, 5 hospital admissions for hypertensive crisis were reported in 3 (8%) of the 39 control patients, compared with none in the arteriovenous coupler group (P=0.0225).
Neurovascular Decompression

Animal studies have shown that pulsatile compression of the rostral ventrolateral medulla at the root-entry zone of cranial nerves IX and X increases both BP and sympathetic outflow,\textsuperscript{184,185} and clinical data suggest that neurosurgical decompression of the rostral ventrolateral medulla (used for neurological disorders) leads to BP reduction.\textsuperscript{186} A relationship between relief of hypertension and neurovascular decompression was demonstrated by Geiger et al, who observed improvement in BP control (7 out of 8 patients) 3 months after neurovascular decompression.\textsuperscript{187} Sympathetic nerve activity was significantly reduced after microvascular decompression in parallel with the BP decrement. Long-term effects were less promising, however, because hypertension relapsed, and 18 months post intervention, sympathetic nerve activity had increased to preoperative levels.\textsuperscript{188,189} Because no long-term clinically significant benefit has been demonstrated in a randomized controlled study and special postprocessing software for the analysis of MRI images of the rostral ventrolateral medulla (that are not commonly available) are required to qualify a patient for the procedure, microvascular decompression for treatment of TRH is restricted to compassionate use in patients with severe TRH and proven neurovascular compression using advanced imaging techniques.\textsuperscript{190}

Renal Artery Stenting (Revascularization)

Clinical indications for percutaneous transluminal angioplasty with stenting for renal artery stenosis are controversial. Recent clinical findings from large prospective randomized controlled trials revealed little or no benefit for BP control, preservation of kidney function, or prevention of cardiovascular or renal events, calling into question broad use of renal artery stenting in hypertensive patients with renal artery stenosis.\textsuperscript{191–193} In the ASTRAL trial, renal arterial revascularization did not result in a clinically relevant reduction in BP, but did cause a high incidence (17%) of adverse procedure-related complications.\textsuperscript{192} However, methodological questions have been raised regarding the inclusion criteria. To enroll a patient in the trial, physicians had to be uncertain whether the patient would profit from the intervention, thus excluding those patients with a clear indication for renal artery stenting and creating a selection bias. For example, 40% of the enrolled patients had <70% narrowing of the renal artery. The STAR trial showed that the primary endpoint, ≥20% decrement of estimated creatinine clearance, did not differ between medical therapy alone and medical therapy combined with revascularization.\textsuperscript{190} However, ≤30% of patients allocated to combined therapy did not undergo revascularization because at the time of angiography, the degree of stenosis was <50%.\textsuperscript{191} In the CORAL study of patients with atherosclerotic renal artery stenosis, hypertension, and chronic kidney disease,\textsuperscript{193} reduction in systolic BP over time was greater (−2.3 mm Hg; 95% confidence interval, −4.4 to −0.2; \(P=0.03\)) in the revascularization group, but this did not result in prevention of cardiovascular or renal events over a median follow-up of 43 months.

All of the studies of renal artery revascularization have been criticized on grounds that they did not critically evaluate the hemodynamic relevance of the renal artery stenosis.\textsuperscript{194,195} With the exception of subtotal occlusion of the renal artery, the angiographic degree of renal artery stenosis is a poor reflection of hemodynamic relevance.\textsuperscript{196} Hemodynamic relevance (to be suspected if stenosis is >80%) can be assessed by intraarterial pressure measurement or duplex sonography. A diminished resistance index in the cortical tissue reveals hemodynamic relevance, but measurement of blood flow velocity alone is not valid.\textsuperscript{197,198} In the CORAL study, translesional renal artery pressure gradients were obtained, but are not yet published.\textsuperscript{199} The ongoing controversy about the utility of renal revascularization is portrayed in many publications of pooled data, meta-analyses, and long-term follow-up data. In the absence of more convincing evidence of benefit (Figure 6),\textsuperscript{200} it may be wise not to stent as a primary therapeutic option in patients with atherosclerotic renal artery stenosis unless hemodynamic relevance can be demonstrated or rapid deterioration in kidney function or worsening BP is evident.\textsuperscript{201–203}

In contrast to atherosclerotic renal artery stenosis, a systematic review and meta-analysis of patients with fibromuscular dysplasia as cause of renal artery stenosis revealed that percutaneous transluminal angioplasty alone (without stenting) improves BP control or even cures hypertension.\textsuperscript{204} Further, BP outcome was inversely associated with age. Hence, the European consensus on the diagnosis and management of fibromuscular dysplasia proposes revascularization for hypertension because of fibromuscular dysplasia, especially in patients with recent onset hypertension or TRH.\textsuperscript{205}

Future

Published studies of interventional BP lowering treatments were performed almost exclusively in patients with severe TRH, defined as systolic BP ≥160 mm Hg (or ≥150 mm Hg in diabetics), despite treatment with an average of 5 different antihypertensive drugs. However, an expansion to broader populations of TRH (office BP ≥140/90 mm Hg) is being discussed.\textsuperscript{206} A small uncontrolled study of patients with true moderate TRH (office BP ≥140/90 mm Hg and 24-h ABP ≥130/80 mm Hg, despite treatment with ≥3 antihypertensive drugs, including a diuretic) showed reductions in office (13/7 mm Hg) and 24-h ABP (14/7 mm Hg) at 6 months after RDN,

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure6.png}
\caption{Renal artery revascularization: updated meta-analysis with the CORAL trial summary estimates of cardiovascular outcomes for revascularization vs medical therapy.}
\end{figure}
Despite a decrease in BP medication. In 51% of these patients, office BP was controlled to <140/90 mm Hg after RDN.\textsuperscript{207}

It is generally recognized that several pivotal steps must be taken before adopting RDN as a procedure for BP treatment outside the research setting. First, prospective, randomized, sham-controlled studies have to show the efficacy of RDN in lowering BP in TRH. In this regard, multi-electrode systems may provide more complete, and hence effective, RDN. Second, reliable tools have to be developed to assess the completeness of RDN. Third, because the BP response to RDN varies greatly from patient to patient,\textsuperscript{141,208,209} a reliable clinical predictor of BP response to RDN is needed to improve patient selection. Fourth, the efficacy of RDN in improving clinical outcomes has to be demonstrated. It is likely that global registry data will be needed to reach this final critical goal.\textsuperscript{210}

Acknowledgments

Samantha Giordano, PhD, Postdoctoral Fellow, Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham designed Figures 1–4 and assisted Suzanne Oparil with the literature searches.

Disclosures

S. Oparil reports individual and institutional payment related to board membership from Bayer, Daiichi Sankyo, Novartis, Medtronic, and Takeda; individual consulting fees from Backbeat, Bayer, Boehringer-Ingelheim, Bristol Myers-Squibb, Daiichi Sankyo, Eli Lilly, Medtronic, Merck, Pfizer, and Takeda; receipt of institutional grant funding from AstraZeneca, Daiichi Sankyo, Eisai Inc, Gilead, Merck, Novartis, Takeda, Takeda Global Research, and Development Inc; individual and institutional payment for development of educational presentations from American Society of Hypertension (ASH)/American Heart Association (AHA); individual and institutional payment for a new therapeutic strategy. J. Calhoun, A. McGlynn EA, Kalantar-Zadeh K, Jacobsen SJ. Characteristics of resistant hypertension in the United States, 2003–2008. \textit{Hypertension}. 2011;57:1076–1080. doi: 10.1161/HYPERTENSIONAHA.111.170508.

References


by guest on September 1, 2017 http://circres.ahajournals.org/ Downloaded from


Engl J Med
Senges J, Messerli FH, Zeymer U. Disproportional decrease in of-
sistant hypertension. Circulation
sure changes after renal sympathetic denervation in patients with re-

Engl J Med

members appointed to the Eighth Joint National Committee (JNC 8).

James P
Kandzari DE, O'Neill
BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-
Bhatt DL, Kandzari DE, O'Neill

A Europ J Hypertens (Greenwich)

J Med
Singh K, Katholi R, Esler MD. Percutaneous renal denervation in pa-

Krum H, Schaich M, Kindermann I, Ukena C, Cremers B, Brantd
MC, Hoppe UC, Vonend O, Rump LC, Sobotka PA, Krum H, Esler M, Böhm M. Effect of renal sympathetic denervation on glucose metabo-

Brantd MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Böhm M, Hoppe UC. Renal sympathetic denervation reduces left ventricular
jacc.2011.11.034.

Brantd MC, Reda S, Mahfoud F, Lenski M, Böhm M, Hoppe UC. Effects of renal sympathetic denervation on arterial stiffness and central hemo-
dynamics in patients with resistant hypertension. J Am Coll Cardiol.

jcardiac.2014.03.017.


Streithaf B, Gebauer B, Nickle P, Reinke P, Freyhardt P, Wiemers G, Hamm B, Günther RW. Percutaneous computer tomography-guided ethanol sympathicolysis for the treatment of resistant arterial hyper-

jcardiac.2014.03.017.

Armstrong JA, Anderson T, Brinton TJ, et al. TCT-412 non-invasive renal denervation using externally delivered focused ultrasound: early experi-


New Approaches in the Treatment of Hypertension
Suzanne Oparil and Roland E. Schmieder

Circ Res. 2015;116:1074-1095
doi: 10.1161/CIRCRESAHA.116.303603

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/116/6/1074

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/