MedicineToday 2013; 14(1): 20-27

PEER REVIEWED FEATURE
POINTS: 2 CPD/2 PDP

Treating resistant hypertension now and in the future

YUSUKE SATA MD; JIANZHONG XU MD; DAGMARA HERING MD; MARKUS SCHLAICH MD

Treatment of resistant hypertension is a priority because patients with nonoptimal blood pressure are at high risk for major cardiovascular events. Pharmacological advances include the use of aldosterone antagonists and the development of several new strategies. Device-based therapies such as catheter-based renal denervation and electrical stimulation of baroreceptors are showing promising results.

Key points

- Resistant hypertension is blood pressure above target levels despite adherence to lifestyle modification and treatment with at least three antihypertensive agents at optimal doses.
- Contributing lifestyle factors and potentially reversible causes should be identified and treated.
- Medications and other substances interfering with efficacy of antihypertensives should be discontinued or minimised.
- Beta blockers, α-blockers, centrally acting sympatholytic agents and direct vasodilators are fourth-line treatments.
- Many experts now consider aldosterone antagonists a fourth-line treatment.
- Potential pharmacological strategies include aldosterone synthase inhibitors, neutral endopeptidase inhibitors and endothelin receptor antagonists.
- The device-based therapy catheter-based renal denervation is available in Australia.

Hypertension is the most common cardiovascular disease worldwide and is responsible for approximately 7.5 million deaths each year. Despite continued advances in the pharmacological therapy of hypertension, control rates remain unsatisfactory with almost half of treated hypertensive patients not achieving blood pressure (BP) targets.[1,2] Noncompliance and nonadherence with prescribed medication and physician inertia are among the several significant contributors to this situation. In this context, it should be noted that most hypertensive patients require two or more antihypertensive drugs to control BP to target levels. The availability of single pill combinations of two or even three antihypertensive agents, with varying doses of each compound, has been useful in improving compliance and reducing costs. Importantly, the prevalence of hypertension continues to increase, mostly due to an ageing population and increasing rates of overweight and obesity.[3]

The growing number of patients in whom BP cannot be controlled despite the use of three or more antihypertensive medications in adequate doses is another significant clinical problem. This phenomenon is typically referred to as resistant hypertension. This article briefly reviews the prevalence and patient characteristics of resistant hypertension and then discusses lifestyle and pharmacological treatment strategies and promising new therapeutic options for this patient cohort.

Dr Sata is a Postdoctoral Fellow, Dr Xu is a Postdoctoral Fellow, and Dr Hering is a Postdoctoral Fellow at the Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne. Professor Schlaich is Head of the Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart and Diabetes Institute and at the Heart Centre, Alfred Hospital, Melbourne, Vic.

RESISTANT HYPERTENSION AND PSEUDORESISTANCE

Resistant hypertension is defined as BP that remains above the target value despite adherence to lifestyle modification and treatment with at least three antihypertensive agents at optimal doses, ideally including a diuretic, as summarised in a scientific statement of the American Heart Association.[4] The recommended treatment target BP is below 140/90 mmHg in average risk hypertensive patients, and below 130/80 mmHg in patients with atherosclerotic cardiovascular disease, diabetes mellitus or chronic kidney disease.[4,5]

Apparent resistance to pharmacological treatment can be due to poor compliance and adherence with prescribed pharmacotherapy (often referred to as pseudoresistance), physician inertia, lifestyle factors (overweight and obesity, smoking, dietary salt excess and excessive alcohol intake) and use of concomitant therapies that may interfere with the efficacy of blood pressure lowering agents, such as NSAIDs and sympathomimetics. White-coat hypertension is another major cause of pseudoresistance, with a prevalence of 20 to 30% in general hypertensive patients.[4] Out-of-office BP monitoring can identify white-coat effects, with home and 24-hour ambulatory BP monitoring being the most useful diagnostic approaches.[6]

Noncompliance and nonadherence with prescribed medication is an important problem and often a major cause of failure to achieve BP control. Approximately half of medications prescribed for chronic disease in the USA are not taken, and about 40% of patients with newly diagnosed hypertension discontinue the prescribed drugs.[4,7]

The steps in the diagnosis of resistant hypertension are outlined in the box on page 22.[4]

PREVALENCE AND CHARACTERISTICS

Although the precise prevalence of resistant hypertension within the total hypertension population is unknown, analysis of observational databases as well as of patients enrolled in clinical trials suggest the proportion of patients with resistant hypertension to be between 25 and 35%. Given the major public health problem of hypertension (estimated to affect almost half of the adult population by 2025), even a small percentage of patients being resistant represents a large overall burden to the community.

A recent study used ambulatory BP monitoring to identify patients with resistant hypertension.[8] It found that of 68,045 patients treated with antihypertensive agents, 8295 (12.2%) had resistant hypertension defined as office BP equal to or greater than 140 mmHg systolic and/or 90 mmHg diastolic while being treated with three or more antihypertensive drugs, one of them being a diuretic. After ambulatory BP monitoring, 5182 patients (62.5%) were classified as true resistant hypertensives, the remaining 3113 (37.5%) having white-coat hypertension. Therefore, true resistant hypertension appears to be evident in about 8% of a treated hypertensive population.

Patients with resistant hypertension are more likely to have multiple cardiovascular risk factors, including chronic kidney disease or diabetes, left ventricular hypertrophy, obesity, hyperlipidaemia and sleep apnoea

STEPS IN THE DIAGNOSIS OF RESISTANT HYPERTENSION[4]

1. Confirm treatment resistance

- Office blood pressure (BP) greater than 140/90 mmHg in average risk hypertensive patients or 130/80 mmHg in patients with atherosclerotic cardiovascular disease, diabetes or chronic kidney disease
  and
  Patients prescribed three or more antihypertensive medications at optimal doses, including if possible a diuretic
  or
- Office BP at target but patient requiring four or more antihypertensive medications

2. Exclude pseudoresistance

- Is patient adherent with prescribed regimen?
- Obtain home, work or 24-hour ambulatory BP readings to exclude white-coat effect

3. Identify and reverse contributing lifestyle factors

Contributing lifestyle factors include:

- obesity
- smoking
- physical inactivity
- excessive alcohol ingestion
- high-salt, low-fibre diet

4. Discontinue or minimise interfering substances

Interfering substances include:

- NSAIDs, e.g. selective COX-2 inhibitors
- sympathomimetics, e.g. diet pills, decongestants, cocaine
- stimulants, e.g. methylphenidate, amphetamine, modafinil
- oral contraceptives
- cyclosporin
- erythropoietin
- natural liquorice
- some herbal compounds

5. Screen for secondary causes of hypertension

Secondary causes of hypertension include:

- obstructive sleep apnoea
- primary aldosteronism
- chronic kidney disease
- renal artery stenosis
- pheochromocytoma
- Cushing's syndrome
- aortic coarctation
- hyperparathyroidism
- intracranial tumour

(see the box on page this page).[4,9] These patients are therefore at greater risk of ischaemic heart disease, heart failure, chronic kidney disease and stroke, and management of their BP is more difficult.[9] Resistant hypertension is associated with a significantly increased risk of cardiovascular disease. A recent study of the prognosis of resistant hypertension demonstrated an almost 50% increase in cardiovascular events in those with resistant hypertension compared with those without, largely attributable to chronic kidney disease.[10]

CHARACTERISTICS OF PATIENTS WITH RESISTANT HYPERTENSION[4]

- Older age (over 65 years)
- Smoker
- High baseline blood pressure
- Obesity
- Excessive dietary salt ingestion
- Chronic kidney disease
- Diabetes
- Left ventricular hypertrophy
- Black race
- Female

SECONDARY CAUSES OF HYPERTENSION

Secondary causes of hypertension are rare in the general population but are more common in patients with resistant hypertension.[4] Clinicians should be aware of the most common causes of secondary hypertension, and be familiar with the appropriate diagnostic steps.[4] The more common causes are obstructive sleep apnoea (evident in up to 70% of patients with resistant hypertension), primary aldosteronism, renal artery stenosis and chronic kidney disease (renal parenchymal disease), and the less common causes include pheochromocytoma, Cushing's syndrome and aortic coarctation (see the box on page 24).[4]

EVALUATION

The evaluation of patients with confirmed resistant hypertension should focus on identification and documentation of end-organ damage, including retinopathy, left ventricular hypertrophy and kidney disease (including microalbuminuria).

Laboratory testing is warranted for the measurement of serum electrolyte and creatinine levels, estimated glomerular filtration rate, fasting glucose levels and urinalysis with estimation of proteinuria. Imaging studies may also be required for evaluation of renal artery stenosis, pheochromocytoma and other atherosclerotic diseases (especially peripheral artery disease, coronary artery disease or cerebrovascular disease).

TREATMENT OPTIONS

Treatment for patients with resistant hypertension is a priority because patients with nonoptimal BP are at high risk for major cardiovascular events.

Essential components of the treatment of resistant hypertension are the identification and treatment of both lifestyle factors contributing to treatment resistance and potentially reversible causes of secondary hypertension, and the discontinuation or minimisation of the use of concomitant therapies or other substances that may interfere with the efficacy of antihypertensive agents. Lifestyle modifications such as smoking cessation, dietary salt restriction, physical activity, body weight control and moderation of alcohol intake are all associated with antihypertensive therapeutic effects.[11]

PHARMACOLOGICAL THERAPY

Current strategies

The pharmacological treatment of resistant hypertension, by definition, involves combinations of three or more drugs, including a diuretic if tolerated. The choice of agents and their combination should maximise their clinical benefit and

SECONDARY CAUSES OF RESISTANT HYPERTENSION[4]

Common

- Obstructive sleep apnoea – snoring, witnessed apnoea, excessive daytime sleepiness
- Renal parenchymal disease – creatinine clearance <30 mL/min, microalbuminuria
- Primary aldosteronism – elevated aldosterone to renin ratio
- Renal artery stenosis – young, female, known atherosclerotic disease, worsening renal function

Uncommon

- Phaeochromocytoma – episodic hypertension, palpitations, diaphoresis, headache
- Cushing's disease – moon facies, central obesity, abdominal striae, interscapular fat deposition
- Hyperparathyroidism – hypercalcaemia, bone pain, multiple fractures
- Aortic coarctation – differential in brachial or femoral pulses, systolic bruit

reduce side effects, as recommended in current guidelines.[5]

Two- and three-drug combination therapies

Sympathetic hyperactivity and activation of the renin–angiotensin–aldosterone system both have important roles in hypertension and many other cardiovascular conditions (e.g. congestive heart failure and chronic kidney disease). Therefore, inhibition of neurohormonal overactivity is theoretically effective for the management of cardiovascular diseases.[12] The combination therapies of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists with dihydropyridine calcium channel blockers recommended by most guidelines as the most effective combinations for patients with hypertension exert their effect through neurohormonal activity modulation by different mechanisms of action.[13,14]

Addition of a diuretic is crucial as most patients with resistant hypertension have persistent volume overload that contributes to the treatment resistance of their hypertension and may not always be clinically detectable. In patients with an estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2, thiazide diuretics are less effective and loop diuretics (such as furosemide or bumetanide) may be necessary for effective volume control.[15]

Fourth-line options

Although current guidelines suggest that specialist advice is sought if BP control cannot be achieved with a combination of three or more medications, most GPs will be quite comfortable adding a fourth-line treatment option.

These medications include β-blockers (ideally vasodilating), α-blockers (which in high dose act as peripheral vasodilators), centrally acting sympatholytic agents and direct vasodilators. Some of these medications have significant adverse side effects, and certain combinations of them or their use in the presence of certain other conditions should be avoided – for example, combinations of the calcium channel blockers verapamil and diltiazem with β-blockers (to avoid higher degree heart block) and the use of α-blockers in patients with aortic stenosis (to avoid hypotension or syncope).

Many experts now consider aldosterone antagonists such as spironolactone and eplerenone as a fourth-line treatment for resistant hypertension, their action being to block mineralocorticoid receptor activation and the resulting BP increase. Spironolactone often provides significant antihypertensive benefit when added to conventional drug regimens of resistant hypertension, with typical doses being between 12.5 and 50 mg per day.[16-18] However, it is important to monitor patients for potentially serious side effects of aldosterone antagonists, such as hyperkalaemia. This is particularly important in patients with impaired renal function and potassium levels above 4.5 mmol/L, in whom dose adjustment or cessation of the medication may be required. Other common side effects include gynaecomastia, breast tenderness and abdominal discomfort.

Potential future pharmacological strategies

Aldosterone synthase inhibitors

Inhibiting the production of aldosterone is another approach to blocking the BP-increasing effects of mineralocorticoid receptor activation. This can be achieved by inhibiting the enzyme aldosterone synthase (CYP450 1B2), which is involved in the synthesis of aldosterone. Selective aldosterone synthase inhibitors have been developed and are now undergoing preclinical evaluation.

One advantage to this approach may be the absence of reflex activation of the renin–angiotensin system as occurs with specific aldosterone receptor blockers, where there is upstream activation of renin and angiotensin II to overcome the blockade. Further study is required to determine the extent of the BP-lowering efficacy and safety blockade of this approach.

Neutral endopeptidase inhibitor

The development of a novel group of antihypertensive agents that simultaneously block two key pathways, namely the renin–angiotensin system by ACE inhibition or angiotensin receptor blockade and the natriuretic peptide system by neprilysin (also known as neutral endopeptidase) inhibition, is another promising approach in the treatment of hypertension. Dual inhibition effectively decreases vasoconstriction and increases the concentrations of vasodilators such as natriuretic peptide, bradykinin and adrenomedullin, thereby potentially

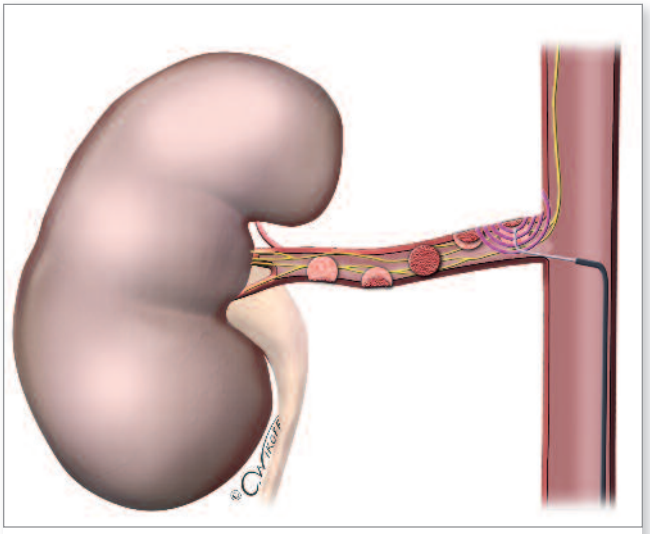

Figure 1. Catheter-based renal denervation. The tip of the treatment catheter is placed in the distal renal artery via vascular access through the femoral artery. Radiofrequency energy is applied via the tip of the catheter to target the renal nerves in the surrounding adventitia. Four to six ablations are performed in each artery and separated both longitudinally and rotationally to achieve circumferential coverage. This therapy is available in major centres in Australia.

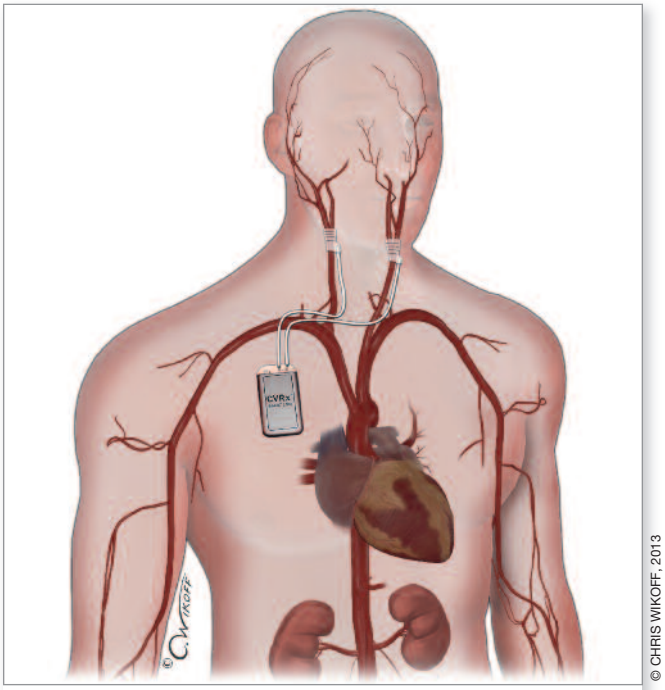

Figure 2. Baroreceptor stimulation therapy – the Rheos system (CVRx). An implanted pulse generator electrically stimulates the baroreceptors in the carotid arteries to induce blood pressure-lowering effects.

providing a pronounced BP-lowering effect and cardioprotective properties.

Studies are currently in progress to test this concept in resistant hypertension.

Endothelin receptor antagonists

Endothelin-1 is a powerful vasoconstrictor and has been implicated in vascular disease. Endothelin mediates its biological activity through the endothelin A and B receptors, thereby providing an additional therapeutic target to conventional antihypertensive treatment strategies.

Clinical experience exists with the selective endothelin A receptor antagonist darusentan, which has been evaluated in patients with moderate and resistant hypertension. Darusentan has been shown to provide supplementary reduction in BP in patients in whom optimal treatment with at least three antihypertensive agents at full dose, including a diuretic, failed.[19] It has also been shown to produce a significant dose-dependent reduction in seated clinic and 24-hour ambulatory BP compared with placebo.[20] The main side effects of darusentan are peripheral oedema, fluid retention, headache and flushing.

Assessment of the longer-term effects of endothelin receptor antagonists on renal parameters will help to determine their renal safety, especially in patients with chronic kidney disease, diabetic nephropathy and heart failure.

DEVICE-BASED THERAPY

In the past few years there has been considerable interest in the development of device-based therapies for resistant hypertension. Interestingly, these target sympathetic overactivity as a likely major contributor to the clinical scenario of resistant hypertension. Catheter-based radiofrequency ablation of the renal sympathetic nerves and electrical stimulation of the carotid sinus baroreceptors have shown promising results in this context (Figures 1 and 2).

Catheter-based renal denervation

Although renal denervation is approved by the TGA for use in Australia, its availability is limited to the major hypertension and cardiovascular centres. Local experts review each patient's suitability for renal denervation based on failure of lifestyle modification and appropriate pharmacological treatment to achieve BP targets, and suitable renal anatomy (exclusion of renal artery stenosis, multiple small renal arteries and others). Experienced interventional cardiologists typically perform the procedure and follow-up investigations include three-monthly reviews,

often by the GP, with thorough assessment of BP levels and laboratory markers such as electrolytes and renal function.

Background to the procedure

The sympathetic outflow to the kidney is often elevated in primary hypertension and most forms of secondary hypertension.[21,22] On the basis of surgical sympathectomy having been shown to prevent the development and ameliorate the severity of hypertension and the experience from splanchinectomy, selective renal denervation appeared as an attractive treatment modality.[21-26]

Catheter-based radiofrequency ablation of the renal nerves is an endovascular procedure to denervate the renal sympathetic nerves that run adjacent to the main renal artery within reach of ablative energy delivery (Figure 1). In an initial proof of concept study, significant reductions in BP (-32/14 mmHg) over 24 months were observed in patients with resistant hypertension who had received catheter-based renal denervation.[27] The Symplicity-HTN-2 trial showed that, at six months, renal sympathetic denervation significantly decreased the office BP compared with the control group (-33/11 mmHg).[24] Also, significantly more patients in the denervation group than in the control group achieved a primary efficacy goal of a systolic pressure of lower than 140 mmHg at six months' post-procedure (39% *vs* 6%).[24] The effects of this procedure were evident from the measurements of noradrenaline spillover from the denervated kidneys (a measure of renal sympathetic nerve activity), which on average were reduced by about 50% compared with baseline, indicating successful, albeit incomplete, renal denervation.[25]

Complications related to catheter-based renal denervation have been rare and primarily restricted to infrequent haematomas at the femoral artery access site, a renal artery dissection requiring renal artery stenting, a renal artery stenosis and three femoral artery pseudoaneurysms.[24,25,27,28] It is important to note that patients commonly experience moderate to severe pain during energy delivery, and analgesia and conscious sedation are therefore required throughout the procedure.

Electrical stimulation of carotid sinus baroreceptors

The arterial baroreceptor reflex, or baroreflex, plays a role in arterial BP control and is known to reset to a higher input pressure range in hypertension.[29,30] Carotid sinus baroreceptor activation is, therefore, a logical approach to the treatment of hypertension and is currently being tested as an alternative therapy for resistant hypertension.[31] Baroreflex stimulation devices have been developed and several feasibility studies have shown reductions in BP after implantation of such devices (Figure 2).[32-34] Electrical baroreceptor stimulation therapy is currently not available in Australia, but is in Europe and the USA.

In the Rheos system pivotal trial, BP was significantly decreased at six months in patients receiving baroreceptor stimulation, but the predefined efficacy endpoint of systolic BP of 140 mmHg or lower could not be achieved, partly because half of the control group also reached this endpoint.[35] There were no negative effects on physiological baroreflex regulation but 35% of patients had a procedure-related nerve injury within initial one month of surgery. In most patients, however, adverse events resolved spontaneously.[31] Further clinical evaluation is in progress to establish whether the BP lowering benefit is sufficient to outweigh the cost and invasive nature of the procedure, using newer, less cumbersome electrodes and with unilateral carotid sinus stimulation.

SUMMARY

Resistant hypertension is common and increasingly difficult to control despite pharmacological advances, including the use of aldosterone antagonists. All patients with resistant hypertension should be evaluated for the possible presence of secondary hypertension and have diet and lifestyle modification. Potential future pharmacological strategies include aldosterone synthase inhibitors, neutral endopeptidase inhibitors and endothelin receptor antagonists.

In patients with persistent uncontrolled hypertension, device-based therapies such as catheter-based renal denervation and electrical stimulation of baroreceptors have so far shown promising antihypertensive effects. Further studies are required, however, to confirm the long-term efficacy, tolerance and safety of these devices. MT

REFERENCES

References are included in the pdf version of this article available at www.medicinetoday.com.au.

COMPETING INTERESTS: Dr Sata and Dr Xu have no disclosures. Dr Hering has received consulting fees and/or lecture fees from Medtronic. Professor Schlaich is an investigator in the Symplicity HTN studies sponsored by Ardian/Medtronic and has received consulting fees and/or lecture fees from Medtronic, Novartis, Boehringer Ingelheim, AstraZeneca, Merck Sharp & Dohme, Abbott and Servier.

Treating resistant hypertension
now and in the future

YUSUKE SATA MD; JIANZHONG XU MD; DAGMARA HERING MD; MARKUS SCHLAICH MD

REFERENCES

1. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension 2011; 57: 1076-1080.
2. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. J Am Coll Cardiol 2008; 52: 1749-1757.
3. Ma J, Lee KV, Stafford RS. Changes in antihypertensive prescribing during US outpatient visits for uncomplicated hypertension between 1993 and 2004. Hypertension 2006; 48: 846-852.
4. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension 2008; 51: 1403-1419.
5. National Heart Foundation of Australia (National Blood Pressure and Vascular Disease Advisory Committee). Guide to management of hypertension 2008. Updated December 2010. National Heart Foundation of Australia; 2008–2010.
6. Head GA, McGrath BP, Mihailidou AS, et al. Ambulatory blood pressure monitoring in Australia: 2011 consensus position statement. J Hypertens 2012; 30: 253-266.
7. Viswanathan M, Golin CE, Jones CD, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Ann Intern Med 2012; Sep 11. Epub ahead of print. doi: 10.7326/0003-4819-157-11-201212040-00538.
8. de la Sierra A, Segura J, Banegas JR, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension 2011; 57: 898-902.
9. Pierdomenico SD, Lapenna D, Bucci A, et al. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. Am J Hypertens 2005; 18: 1422-1428.
10. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation 2012; 125: 1635-1642.
11. Frisoli TM, Schmieder RE, Grodzicki T, Messerli FH. Beyond salt: lifestyle modifications and blood pressure. Eur Heart J 2011; 32: 3081-3087.
12. Sata Y, Krum H. The future of pharmacological therapy for heart failure. Circ J 2010; 74: 809-817.
13. Olsen MH, Mallion JM, Rahn KH, et al. Agreement within Europe about antihypertensive treatment and education – results from the European Society of Hypertension questionnaire. J Hypertens 2010; 28: 1593-1594.
14. Jamerson KA, Bakris GL, Wun CC, et al. Rationale and design of the avoiding cardiovascular events through combination therapy in patients living with systolic hypertension (ACCOMPLISH) trial: the first randomized controlled trial to compare the clinical outcome effects of first-line combination therapies in hypertension. Am J Hypertens 2004; 17: 793-801.
15. Taler SJ, Textor SC, Augustine JE. Resistant hypertension: comparing hemodynamic management to specialist care. Hypertension 2002; 39: 982-988.
16. Chapman N, Dobson J, Wilson S, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension 2007; 49: 839-845.
17. Vaclavik J, Sedlak R, Plachy M, et al. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension 2011; 57: 1069-1075.
18. Watanabe M, Krum H. Eplerenone for the treatment of cardiovascular disorders. Expert review of cardiovascular therapy. 2012; 10: 831-838.
19. Black HR, Bakris GL, Weber MA, et al. Efficacy and safety of darusentan in patients with resistant hypertension: results from a randomized, double-blind, placebo-controlled dose-ranging study. J Clin Hypertens (Greenwich) 2007; 9: 760-769.
20. Weber MA, Black H, Bakris G, et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. Lancet 2009; 374: 1423-1431.
21. Kumagai H, Averill DB, Ferrario CM. Renal nerve activity in rats with spontaneous hypertension: effect of converting enzyme inhibitor. Am J Physiol 1992; 263: R109-R115.
22. Winternitz SR, Katholi RE, Oparil S. Role of the renal sympathetic nerves in the development and maintenance of hypertension in the spontaneously hypertensive rat. J Clin Invest 1980; 66: 971-978.
23. Smithwick RH, Thompson JE. Splanchnicectomy for essential hypertension; results in 1,266 cases. JAMA 1953; 152: 1501-1504.
24. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 2010; 376: 1903-1909.

25. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009; 373: 1275-1281.
26. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. N Engl J Med 2009; 361: 932-934.
27. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension 2011; 57: 911-917.
28. Williams B. Resistant hypertension: an unmet treatment need. Lancet 2009; 374: 1396-1398.
29. Chapleau MW, Hajduczok G, Abboud FM. Mechanisms of resetting of arterial baroreceptors: an overview. Am J Med Sci 1988; 295: 327-334.
30. Nosaka S, Wang SC. Carotid sinus baroceptor functions in the spontaneously hypertensive rat. Am J Physiol 1972; 222: 1079-1084.
31. Heusser K, Tank J, Engeli S, et al. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. Hypertension 2010; 55: 619-626.
32. Scheffers IJ, Kroon AA, Schmidli J, et al. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. J Am Coll Cardiol 2010; 56: 1254-1258.
33. Illig KA, Levy M, Sanchez L, et al. An implantable carotid sinus stimulator for drug-resistant hypertension: surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial. J Vasc Surg 2006; 44: 1213-1218.
34. Chapleau MW, Hajduczok G, Abboud FM. New insights into the influence of pulsatile pressure on the arterial baroreceptor reflex. Clin Exp Hypertens A 1988; 10 Suppl 1: 179-191.
35. Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. J Am Coll Cardiol 2011; 58: 765-773.