UNIT NO. 5

THERAPEUTIC CONSIDERATIONS

Dr Akira Wu

ABSTRACT

Just over 50% of all strokes and about half of all ischemic heart disease are attributable to hypertension. Blood pressure lowering results in significant reduction in coronary artery disease events and stroke. Although all classes of antihypertensive agents are effective in blood pressure reduction, choice of drugs should be based on compelling indications, contraindications & patient factors. Single pill combination therapy can dramatically achieve BP targets and offer benefit in a high percentage of patients. Controlling blood pressure can sometimes be challenging in resistant hypertension. Recent introduction of renal sympathetic denervation therapy looks promising in the management of resistant hypertension.

Keywords: Single pill combination, sympathetic denervation therapy, hypertension, causes, resistant hypertension

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INTRODUCTION

According to the Global Burden of Disease 2000 study, approximately 54% of all strokes and 47% of all ischemic heart disease are attributable to high blood pressure (BP)[1]. Another interesting aspect of the report is that approximately one-half of the BP-attributable deaths were due to systolic BP levels between the optimal systolic BP level (defined in the report as ≤ 115 mm Hg) and the current therapeutic intervention threshold of ≥140/90 mm Hg as advocated in guidelines. Placebo-controlled trials have shown that reductions in BP of 10 to 20 mm Hg systolic and 5 to 6 mm Hg diastolic for a few years conferred relative risk reductions of 38% for stroke and 16% for coronary heart disease [2]. However, the blood pressure control rates in most countries are still sub-optimal. The purpose of this brief review is to highlight the role of single pill combination therapy and the minimally invasive renal denervation therapy in influencing the current therapeutic management of hypertension.

AKIRA WU, Nephrologist and Physician,
Mount Elizabeth Medical Centre

CAUSES OF HYPERTENSION

Although 90% of hypertension is essential or idiopathic, the rest is caused by kidney disease, vascular (arterial) stenosis, endocrinopathies, obesity and poly-pharmacy. An integral part of the assessment for hypertension should include the patient's cardiovascular (CV) risk and co-morbidities, and target organ involvement in the heart (LVH) or in the kidney (proteinuria).

Some of the key patho-physiologic considerations which may influence therapeutic approach, are volume regulation (sodium and fluid balance, ADH, aldosterone etc), sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), vasoactive substances (nitric oxide, prostaglandins, endothelium-derived hyperpolarizing factor [EDHF], endothelin), associated co-morbidities such as obesity, sleep apnoea and genetic factors. The kidney plays a pivotal role in salt and water intake and excretion which have a direct influence on volume status. The INTERSALT Study confirmed a direct relationship between sodium and mean blood pressure[3]. Hypertensive patients can have chronically increased levels of renin despite feedback mechanisms[4]. Aldosterone promotes hypertension by sodium retention contributing to volume expansion, up-regulation of angiotensin II (Ang II) receptors and potentiation of pressor responses of Ang II [5].

Over-activity of the sympathetic nervous system may contribute to hypertension. Alpha 1, alpha 2 and beta receptors mediate cellular responses to catecholamines. Activation of alpha 1 receptors results in vasoconstriction contributing to increased blood pressure[6]. Vasoactive substances synthesized in the vascular wall also play a vital role in the pathogenesis of hypertension. The key vasoactive substances are nitric oxide (vasodilation), prostaglandins (vasoconstriction), enthothelin (ET)-1 which counters the effects of nitric oxide and EDHF which is vasodilatory[7]. Some of the important co-morbidities in hypertensive patients are obesity and insulin resistance[8].

Table 1. ACCOMPLISH: Primary and secondary end points

End point	Hazard ratio (95% CI)
Cardiovascular morbidity / mortality*	0.80 (0.72-0.90)
Individual components	
• Cardiovascular mortality	0.80 (0.62-1.03)
• Fatal and nonfatal MI	0.78 (0.62-0.99)
• Fatal and nonfatal stroke	0.84 (0.65-1.08)
• Hospitalization for unstable angina	0.75 (0.50-1.10)
• Coronary revascularization	0.86 (0.74-1.00)
• Resuscitation after sudden cardiac arrest	1.75 (0.73-4.17)

*Primary end point

Jamerson K et al. N Engl J Med 2008; 359: 2417-2428.

Table 2. ONTARGET: Key results

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Outcome	Ramipril, n=8576 (%)	Telmisartan n=8542 (%)	Combination n=8502 (%)
CV death/MI/ stroke/ CHF hospitalization[a]	16.5	16.7	16.3
CV death /MI/stroke[b]	14.1	13.9	14.1
MI	4.8	5.2	5.2
Stroke	4.7	4.3	4.4
CHF hospitalization	4.1	4.6	3.9
CV death	7.0	7.0	7.3
Any death	11.8	11.6	12.5
Renal impairment	10.2	10.6	13.5

a. Primary end point
b. Primary end point in the HOPE trial

Yusuf S et al.N Engl J Med 2008: 358:1547-1559.

SINGLE PILL COMBINATION THERAPY

The currently available antihypertensive agents and appropriate life style modification should be able to control BP in most hypertensive patients. Yet, most surveys showed only a minority of patients achieved optimal BP control, especially in those who need tight control. Reasons for poor control include poor adherence to therapy, side-effects of medications, clinical inertia, sub-optimal intensity, inappropriate selection and timing of therapy.

In complicated hypertension, more than 2 antihypertensive agents were usually required to reach goal BP levels as specified in various trials (ALLHAT, LIFE, ASCOT) on hypertension [9,10,11]. JNC7 was the first guideline advocating first-line combination therapy for those subjects requiring ≥0/10mmHg blood pressure reduction (stage 2 hypertension)[12]. The recognition of the need for several drugs to achieve control led to the development of single-pill combination therapies involving almost all newer classes of antihypertensive agents.

Single pill combinations offer many advantages which include ease of administration, minimisation of side effects due to lower doses of component drugs, synergistic mechanisms of drug actions, and improved compliance. However, if they include a patent-protected drug, the total cost to the patient may exceed that of 2 generics. The choice of drugs in a combination therapy is influenced by their favourable outcomes in clinical trials, their favourable effects on co-morbid conditions, expert committee recommendations, once daily therapy, compelling indications and other factors.

The recently published ACCOMPLISH trial [13] started to address the issue of the impact of different combinations of antihypertensive agents on the outcomes of hypertensive subjects at high risk. The combination of agents with different but synergistic mechanisms of action is most logical. The most rationale is a diuretic, an ACEI or ARB or DRI, and a CCB. For example, the activation of renin-release by a diuretic will potentiate the antihypertensive effect of any blocker of the RAAS such as ACEIs, ARBs and the DRI. When comparing against diuretics or BBs or ACEIs, all types of CCBs except for the short-acting agents, are effective in protecting against major CV events[14] .

In patients with high CV risk, ACEI and ARB are virtually identical in providing CV protection[15] . The renal data from the ONTARGET study suggest that an ACEI/ARB combination has no advantages and should not be routinely used for hypertensive patients without severe heart failure or chronic renal disease with heavy proteinuria. However, in hypertensive diabetic patients already treated with an ARB, the addition of a DRI-based treatment significantly reduced the mean urinary albumin/ creatinine ratio by 20% compared to the ARB-based treatment[16].

The importance of component drugs in single pill combination therapy is suggested by the ACCOMPLISH trial[13] which showed a significant ≈20% reduction in the primary CV end point in favour of the ACEI-CCB treated to the diuretic-CCB treated group (Table 2). Patients in both treatment arms received excellent blood-pressure control, with blood pressures of 132/73 mm Hg in the ACEI-CCB arm and 133/74 mm Hg in diuretic-CCB arm. More importantly, the blood pressure control rates of fixed drug combinations were superior to that achieved by free drug combinations. This study has established that combining a CCB with ACE inhibition, or presumably other forms of RAS blockade, is a very effective treatment option for high-risk patients with hypertension.

Antihypertensive treatment adherence varies with drug class as evident by a recent 17-study meta-analysis involving 935,920 patients with a mean age of 61.7 years. The results showed that the mean adherence to prescribed antihypertensive agents varied from 28% for beta blockers to 65% for ARBs. Patient adherence was greatest for ARBs, with rates 33% and 57% higher for this class than for ACE inhibitors and CCBs, respectively [17]. was greatest for ARBs, with rates 33% and 57% higher for this class than for ACE inhibitors and CCBs, respectively [17].

Resistant Hypertension

Resistant hypertension is defined as an elevated office blood pressure exceeding 140/90 mmHg in patients under 3 or more antihypertensive agents with an adequate dosage, including a diuretic. It is more common in the elderly, diabetics, obese and those with hypertensive heart disease or chronic kidney disease [18]. It is important to exclude pseudo-resistance such as white coat effect, blood pressure measurement problems, non-compliance, odd drug combinations, interfering drugs and under-dosing of anti-hypertensive agents. Every resistant hypertensive subject requires exclusion of a concealed undiagnosed cause of secondary hypertension, despite the lack of clinical clues to suspect it. This requires complex and expensive biochemical and radiological testing.

Primary aldosteronism has been documented in about 20% of resistant hypertension [19]. Standard triple drug regime for resistant hypertension is ACEI or ARB, diuretic preferably a thiazide and long acting CCB. Diuretics potentiate the effect of other antihypertensive agents, and contribute a specific effect to individuals with salt-sensitivity of blood pressure [20] . If blood pressure remains uncontrolled, other agents such as AAs (spironolactone, aldactone, eplerenone), vasodilating BBs, centrally acting agent or vasodilating agents (hydrallazine, minoxidil) may be added as last resort. Spironolactone may be particularly effective in obese subjects [21], on the basis of possible stimulation of inappropriate adrenal release of aldosterone by adipocyte secretagogues [22]. Although effective, these strategies are not devoid of risk, particularly in populations that are likely to have both resistant hypertension and risk for thiazide-inducedhyponatremia as in the elderly or for hyperkalemia which may affect subjects with diabetes, who commonly have renal tubular acidosis IV, and those with chronic renal insufficiency.

There are 2 interventional approaches that are being developed for patients with resistant hypertension. The Rheos® Hypertension Therapy system (CVRx, Inc; Minneapolis, Minnesota) is an implantable device that has been shown in clinical trials to lower blood pressure through activation of carotid baroreceptors [23]. The renal sympathetic denervation is a catheter-based interventional procedure which has been shown to be effective and can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients [24]. The substantial reduction in BP was sustained out to 2 years of follow-up, without significant adverse events [25].

RENAL DENERVATION THERAPY

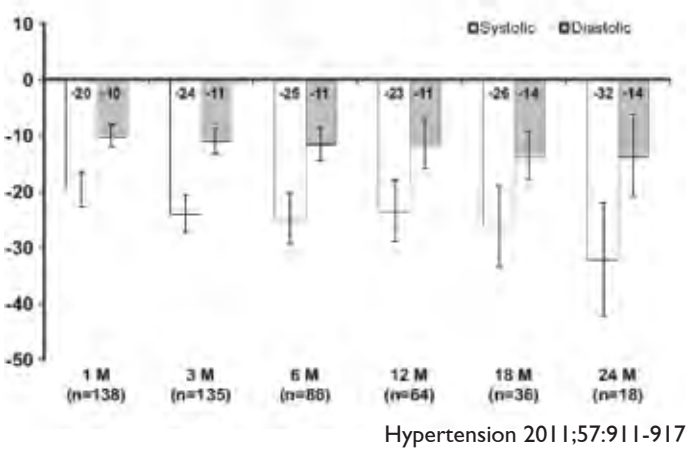
The sympathetic innervation of the kidney is implicated in the pathogenesis of hypertension through effects on rennin secretion, increased plasma rennin activity that leads to sodium and water retention, and reduction of renal blood flow (RBF) [26,27]. Complete bilateral renal denervation decreases the level of blood pressure in several experimental models, such as spontaneously hypertensive rats, DOCA hypertensive rats, two-kidney one-clip rats, obesity-induced hypertensive dogs, and aortic coarctation dogs [26]. Renal denervation, a minimally invasive procedure that disables sympathetic nerves located in the renal artery walls. The system consists of a generator and a flexible catheter. The catheter is introduced through the femoral artery in the upper thigh and is threaded up into the renal artery near each kidney. Once in place, the tip of the catheter delivers low-power radio-frequency (RF) energy according to a proprietary algorithm, or pattern, to affect the surrounding sympathetic nerves. The procedure does not involve a permanent implant.

Results from SYMPLICITY HTN-2 [24], a randomized, controlled clinical trial of 106 patients in Europe, Australia and New Zealand, showed that patients with resistant hypertension (systolic BP ≥160 mm Hg on ≥3 antihypertension drugs, including a diuretic) randomized to renal denervation achieved a mean blood pressure reduction of 32/12 mmHg at 6 months, whereas the patients in the control group randomised to anti-hypertensive medications alone had blood pressures that did not vary from baseline (1/0 mmHg). The overall occurrence of adverse events did not differ between groups.

In the recently published 24-month follow-up of 153 patients in SYMPLICITY HTN-2 (38), post-procedure office BPs were reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively (Figure 1). The median time from first to last radiofrequency energy ablation was 38 minutes. The procedure was without complication in 97% of patients (149 of 153). The 4 acute procedural complications included 3 groin pseudoaneurysms and 1 renal artery dissection, all managed without further sequelae.

Based on the findings of Symplicity HTN-1 [24], the indications for renal denervation therapy are systolic blood pressure of 160 mmHg or greater on 3 or more antihyper tensive medications and eGFR >= 45 mL/min. The contra-in dications are renal artery abnormalities and known secondary hypertension attributable to a cause other than sleep apnea.

Figure 1. Mean systolic and diastolic BP changes after renal sympathetic denervation procedure over 24-months of follow-up



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CONCLUSIONS

In conclusion, hypertension is a significant but modifiable risk factor for atherosclerotic events and mortality. Early achievement of target BP levels maximizes cardiovascular protection. Multiple antihypertensive agents are often required to achieve target BP levels in hypertension with co-morbidities. Multi-mechanism therapies offer many advantages over free pill combinations. Single pill combinations are becoming the

therapy of choice for optimal management of hypertension. The renal sympathetic denervation therapy looks promising in controlling blood pressure in multi-drug resistant hypertension.

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LEARNING POINTS

- **Blood pressure lowering results in significant reduction in coronary artery disease events and stroke.**
- **Multiple antihypertensive agents are often required to achieve target BP levels in hypertension with co-morbidities.**
- **Single pill combinations are becoming the therapy of choice for optimal management of hypertension.**
- **The renal sympathetic denervation therapy looks promising in controlling blood pressure in multi-drug resistant hypertension.**