UNIT NO. 6

RETHINKING THE STRATEGIES IN HYPERTENSION MANAGEMENT

Dr Akira Wu

ABSTRACT

The prevalence rates of hypertension are expected to increase globally. Hypertension accounts for the majority of stroke and at least half of heart attacks. Blood pressure lowering results in significant reduction in coronary artery disease events and stroke. Therapeutic intervention in high normal blood pressure delays the onset of hypertension but its long term benefits are uncertain. In hypertension with co-morbidities, the lower achievable blood pressure may not be better in view of concerns over the J curve effect of excessive blood pressure reduction. Hypertension predisposes to the onset of diabetes which may be accelerated by certain classes of anti-hypertensive agents, namely diuretics or beta-blockers. In the very elderly, the cardiovascular benefits of blood pressure lowering can be substantial. Improved cardiovascular outcomes are achieved by combination therapies which have clearly demonstrated pronounced blood pressure lowering and higher control rates. Certain drug components of the combination therapy may be preferred to improve cardiovascular outcomes. Dual renin-angiotensin aldosterone system blockade should not be routinely used but is indicated for hypertensive patients without heart severe heart failure or chronic renal disease with heavy proteinuria. The many advantages of single pill combination therapy will improve the overall management of hypertension.

Keywords: Etiologic consideration; Dual RAAS blockade; Diabetes; Single pill combination therapy

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INTRODUCTION

Approximately 26.4% of the adult population worldwide had hypertension in 2000, and this is expected to increase to 29.2% by 2025[1]. Hypertension accounts for approximately two-thirds of all strokes and 50% of heart attacks. There was a 22% reduction in coronary heart disease (CHD) events and a 41% reduction in stroke for a systolic BP reduction of 10 mm Hg or diastolic BP reduction of 5mmHg[2]. The slope of the relationship between blood pressure (BP) and stroke in individuals of the Asia-Pacific region is steeper than that observed in western populations[3]. It is anticipated that a better control of hypertension among Asians might have substantial beneficial effects on the cardiovascular morbidity and mortality. Unfortunately, blood pressure control rates are far from optimal in most populations [4, 5]. This mini-review will highlight some recent developments in hypertension research that may influence our strategies in improving management of hypertension.

AKIRA WU, Nephrologist and Physician,
Mount Elizabeth Medical Centre

ETIOLOGIC CONSIDERATION

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 such as nitric oxide, prostaglandins, endothelin, endothelium-derived hyperpolarising factor (EDHF), 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 [6]. Hypertensive patients can have chronically increased levels of renin despite feedback mechanisms [7]. 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 [8]. 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 [9]. Vasoactive substances synthesised in the vascular wall also play a vital role in the pathogenesis of hypertension. The key vasoactive substances are nitric oxide (vasodilation), prostaglandins (vaso-constriction), enthothelin I (ET)-1 which counters the effects of nitric oxide and EDHF which is vasodilating [10]. Some of the important co-morbidities in hypertensive patients are obesity and insulin resistance [11].

PRE-HYPERTENSION

Pre-hypertension is defined by JNC-7 as the blood-pressure range of 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic [12]. The condition heralds arterial hypertension and thus may be considered a starting point in the cardiovascular

disease continuum. Pre-hypertension is associated with excess morbidity and death from cerebrovascular causes [13, 14]. Unfortunately, current preventive strategies which aim at preventing the progressive rise in blood pressure using the recommended lifestyle modifications are weak.

Two trials [15, 16] involving pre-hypertensive individuals showed an angiotensin-converting enzyme inhibitor (ACEI) and an angiotensin receptor blocker (ARB) were able to lower blood pressure below 140/90 mmHg during therapy. However, blood pressure of most subjects rose above 140/90 mmHg following cessation of the drug. Pre-hypertension remains a useful designation to identify individuals at high risk of developing hypertension so that measures can be undertaken to prevent the disease from developing.

NEW CHALLENGES IN BLOOD PRESSURE GOALS

Most guidelines for the initiation of antihypertensive therapy advocate the target BP < 140/90 mmHg for patients with or without risk factors or target organ damage, or less than 130/80 mmHg for patients with diabetes or chronic kidney disease (CKD). However, there are some concerns over the possible existence of J-curve for lowering blood pressure too excessively in patients with pre-existing coronary artery disease [17, 18].

In patients with isolated systolic hypertension, an increase in stroke was observed when diastolic pressures were brought down from 90 mmHg to below 65 mmHg. CKD patients had an increase in strokes when systolic blood pressure was lowered below 120 mmHg [19]. Other studies [20, 21] have shown that systolic blood pressures of less than 120 mm Hg and diastolic blood pressures of less than 60 mm Hg have been associated with increased mortality. On the other hand, patients with pre-existing cerebrovascular disease had the greatest protection against recurrence if the systolic blood pressure was reduced below 120 mmHg [22]. The findings of a meta-analysis of seven randomised, controlled trials suggest the increased risk for events observed in patients with low blood pressure was not related to antihypertensive treatment. Poor health conditions leading to low blood pressure and an increased risk for death probably explain the J-curve [23].

Reduction of BP in patients with hypertension (>140/90 mmHg) and diabetes is known to reduce the risk of cardiovascular events [24, 25, 26]. An old mantra of hypertension management is that "the lower the blood pressure, the better". However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [27] of diabetic patients with hypertension, no significant difference in risk of nonfatal MI or cardiovascular-related death was observed when comparing the intensive-therapy (SBP < 120 mmHg) and standard-therapy (SBP < 140 mmHg) groups. However, a significant 42% reduced risk of total stroke and 38% reduced risk of nonfatal stroke were observed with intensive therapy. Significant adverse events attributed to antihypertensive therapy were significantly more frequent in the intensive treatment group. The ACCORD investigators concluded that their results provide no evidence that intensive BP control reduces the rate of a composite of major cardiovascular events, such as hypotension (most significant), bradycardia and hyperkalaemia. Adverse laboratory measures include hypokalaemia, increased serum creatinine and decreased glomerular filtration rate. Other adverse clinical measures were decreased high density lipoprotein and increased triglyceride.

Similarly, in The International Verapamil SR/ Trandolapril (INVEST) study [28], no difference was seen in diabetic patients with coronary artery disease when comparing the tight-control (SBP <130 mmHg) and usual-control (SBP 130 to < 140 mmHg) groups with regard to the rate of the primary outcome (first occurrence of all-cause death, nonfatal MI, or nonfatal stroke). However, a significant 8% increase was seen in the relative risk of all-cause mortality in the group with tight systolic control BP (P = 0.04), suggesting a J-shaped curve for the relationship between systolic blood pressure and mortality [29].

Furthermore, a retrospective analysis of outcomes in 25,588 high-risk subjects in ONTARGET [30] revealed no relationship between in-trial systolic blood pressure reduction and risk of myocardial infarction, heart failure, and cardiovascular mortality. On the basis of available evidence from placebo-controlled trials, randomised trials, and achieved BP analyses, it would appear that the target BP levels recommended in current guidelines (<130/80 mmHg) are not supported for the prevention of macrovascular outcomes in patients with diabetes.

The ongoing NIH-sponsored Systolic Blood Pressure Intervention trial (SPRINT) [31] will test the hypothesis that lowering of systolic blood pressure to <120 mmHg compared to <140 mmHg is more effective in reducing cardiovascular events in 9,250 high risk subjects with CKD, older age (> 55 years) or underlying cardiovascular disease.

In elderly patients (80 years or older) with hypertension (SBP >160 mmHg), the HYVET study [32] showed that reducing SBP to ≈143.5/75.4 mm Hg with active treatment and to 158.5/84 mm Hg with placebo resulted in a 39% significant reduction in the risk of fatal stroke. The active treatment studied was indapamide SR (1.5mg). Also, Perindopril 2-4mg was added when necessary, in order to achieve target blood pressure of SBP 150mmHg and DBP 80mmHg. There was also an impressive 64% reduction in the rate of heart failure, which was highly significant. The study was stopped prematurely after a median follow-up of 1.8 years because of a significant reduction in all-cause mortality of 21% in favour of active treatment. The HYVET study has provided unequivocal evidence that the benefits of BP lowering in the very elderly can be very substantial.

DUAL RAAS BLOCKADE

Several studies have suggested that combining an ARB with an ACEI may provide a more complete blockade of the RAAS in the treatment of diabetic and non-diabetic nephropathy and essential hypertension; in particular, it may lower BP and proteinuria further than monotherapy [33, 34]. In patients with high CV risk, ACEI and ARB are virtually identical in providing CV protection as shown in the ONTARGET study [35].

However, 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. The combined treatment with an ACEI and an ARB worsened renal outcome despite lowering proteinuria to a greater extent. Furthermore, the study has limited generalisation to the general diabetic nephropathy population, considering that only 13% had microalbuminuria and 31% were normotensive.

In the meantime, the addition of an ARB should be considered for patients with heart failure due to reduced left ventricular ejection fraction who have persistent symptoms, or a progressive worsening of symptoms, despite therapy with an ACE inhibitor and a β-blocker [36]. A recent trial found that of the 1750 patients (5.4% of the study population) who received combination therapy, 86.4% did not have trial-established indications such as heart failure or proteinuria [37].

Combining a direct renin inhibitor (DRI) with an ACEI or an ARB has been shown to produce additional blood pressure [38] or albuminuria [39] reductions respectively. The long-term benefits of combining a DRI and an ARB in diabetic patients with high CV and renal risk should be known when the results of ALTITUDE study [40] are available in the near future.

HYPERTENSION AND NEW-ONSET DIABETES

Individuals with hypertension are at increased risk of developing diabetes. Antihypertensive agents have a variable influence on the rate of development of diabetes with diuretics and beta-blockers accelerating, and ARBs slowing the process; calcium channel blockers (CCBs) appear neutral [41]. Whether or not drug-related, hypertensive patients who develop new-onset diabetes are at high cardiovascular risk [42].

A recent meta-analysis used 11 randomised, placebo-controlled clinical trials, with a total of 84,363 patients, to study whether the administration of ACEIs or ARBs reduced the incidence of new-onset diabetes[43]. The results showed that ARBs significantly reduced diabetes incidence (OR, 0.8; CI, 0.8-0.9; P < .01). Incidence was also lower for ACEIs (OR, 0.8; CI, 0.7-1.0) but was only marginally significant (P = .07). The findings of the this meta-analysis are consistent with the 2 trials, DREAM [44] and NAVIGATOR [45] which found lower but non-statistically significant diabetes incidence with ACEIs, and significantly lower incidence with ARBs. Pre-treatment plasma glucose is by far the most important predictor of new-onset diabetes and its excessive risk of CV events [46, 47]. Multi-factorial intervention remains the primary goal in patients at high risk of developing diabetes.

SINGLE PILL COMBINATIONS

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 [48, 49, 50]. JNC7 was the first guideline advocating first-line combination therapy for those subjects requiring ≥ 20/10mmHg blood pressure reduction (stage 2 hypertension) [51].

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. The other advantage of single pill combinations is to provide the opportunity for early achievement of blood pressure goals to impact positively on CV outcome as shown in the VALUE trial [52].

The recently published ACCOMPLISH trial [53] started to address the issue of the impact of different combinations of antihypertensive agents on the outcomes of hypertensive subjects at high risk. This study recruited 11,506 high risk hypertensive patients who were randomised to either ACEI/HCTZ combination or ACEI/CCB combination. The results showed ACEI/CCB was preferable to ACEI/HCTZ in significantly reducing CV events and mortality. In addition, significantly more patients in both arms achieved over 75% control rate with single pill combinations than with free combinations. However, a recent study [54] showed that the ARB/diuretic combination decreased urinary albumin:creatinine ratio (UACR) significantly more than the ARB/CCB combination, and this decrease in UACR was associated with a greater magnitude reduction in sleep SBP. Powerful epidemiological associations with even smaller amounts of albuminuria have been made with the risk of renal failure and cardiovascular events [55, 56].

CONCLUSIONS

In conclusion, the quest for higher rates of blood pressure control continues to be a challenge. Therapeutic reduction of high normal blood pressure delays the onset of hypertension but its long term benefits remain unproven. The ideal blood pressure goals for hypertensive patients remain uncertain as more randomised control trials are needed to address this issue. In the very elderly, the benefits of blood pressure lowering can be substantial. Dual RAAS blockade should only be used in hypertensive patients with certain co-morbidities. The combination of a RAAS blocker with a CCB appears to be an appropriate, and even superior, choice for the treatment of high-risk patients with hypertension. Single pill combinations are certain to play a more important role in the therapeutic management of hypertension.

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LEARNING POINTS

- **Blood pressure lowering results in significant reduction in coronary artery disease events and stroke.**
- **Hypertension predisposes to the onset of diabetes which may be accelerated by certain classes of anti-hypertensive agents, namely diuretics or beta-blockers.**
- **In the very elderly, the cardiovascular benefits of blood pressure lowering can be substantial. Dual renin-angiotensin aldosterone system blockade should not be routinely used but is indicated for hypertensive patients without heart severe heart failure or chronic renal disease with heavy proteinuria.**
- **The advantages of single pill combination therapy in hypertension offer the advantages of ease of administration, minimisation of side effects due to lower doses of component drugs, synergistic mechanisms of drug actions, and improved compliance.**