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Current Issues On The Management Of Hypertension

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Summary

Hypertension is one of the most prevalent vascular diseases in the general population and is a major contributor to cardiovascular mortality and morbidity. Recent clinical trials have confirmed the benefits of treatment of hypertension to prevent stroke, congestive heart failure, and left ventricular hypertrophy. Despite the availability of many newer agent, blood pressure continues to be inadequately controlled in the majority of the hypertensive patients. There is still a lot of controversy in some of the issues in the management of hypertension. The present article summarizes some of the recent studies and published guidelines in the management of hypertension and provides some insight to these questions. Although the answers to some of these questions are still unclear, ongoing large scale studies should soon provide additional answers to these questions. (HK Pract 1996; 18 (4): 147-157)

摘要：

高血壓是常見的血管疾病，有極高的死亡和罹病率。最新的醫學研究證實適當地控制高血壓對減低「中風」，「充血性的心臟衰竭」和「心左室肥大」無容置疑。雖然已有多種新血壓藥面世，可惜還有很多病人得不到適當的治療，因此掀起了醫學界對高血壓治療方案作出激烈的爭論。本文介紹這方面的最新醫學研究和治療指引，令讀者能對此作更深入了解。大型的醫學研究將會繼續，替我們破解治療高血壓的疑惑。

Introduction

Hypertension continues to be one of the most common diseases treated by the general physician. Hypertensive individuals, even those with mild elevation of blood pressure, are at increased risk of cardiovascular disease, whether or not symptoms are present. The causes of essential hypertension which accounts for 90% of high blood pressure, have not yet been determined. Hypertension is defined as the level of blood pressure where investigation and treatment do more good than harm. Elevated arterial pressure is the only early indication of hypertension, i.e. the disease attributed to high blood pressure. The definition of elevated blood pressure is varying in different guidelines[1-3]. (Table 1) The

Table 1: Summary of guidelines for treating hypertension: (modified from ref. [1-3])

Year	WHO/ISH 1993	JNC 1992	BHS 1993
Definition of Hypertension	SBP>140 and/or DBP>90	SBP>140 and/or DBP>90	SBP≥160 and/or DBP≥90
Drug Treatment:			
– without other risk	SBP>160 and DBP≥95	BP≥150/95	SBP≥160 DBP≥100
– with other risk	SBP≥140 and/or DBP≥90	BP≥140/90	DBP≥90
Goal	BP≤130/80 BP<140/90 (elderly)	BP<140/90	DBP<90 and/or possibly SBP<160
First-line Treatment	D, BB, ACEI, CCB, AB AB	D, BB	D, BB or D, BB ACEI, CCB, AB

AB=α_1-blockers, ACEI=angiotensin converting enzyme inhibitor, BB=β-blocker, CCB=calcium channel blocker, D=diuretic
WHO=World Health Organization, ISH=International Society of Hypertension, JNC=Joint National Committee, BHS=British Hypertension Society

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conventional definition of hypertension is based on diastolic blood pressure (DBP). On the other hand, systolic blood pressure (SBP) elevation is associated with equally great or greater risk when compared to DBP[4]. In general, blood pressure is considered to be abnormal if the DBP is above 90 mmHg and the SBP is above 140 mmHg when measured at rest, relaxed condition. However, there are several common questions regarding the management of hypertension: 1. Why is hypertension treated? 2. What is the threshold for initiation of drug therapy? 3. How far should blood pressure be lowered? 4. What are the physiologic effects of long term hypertension control? 5. How should blood pressure be lowered? and 6. Is there a role for multiple drug therapy?

Some of the answers to these questions are not available and are important area of recent ongoing hypertensive research.

Why is hypertension treated?

Hypertensive patients have increased overall mortality and increased incidence of other complications (**Figure 1**). Furthermore, it is clear that high blood pressure frequently coexists with other risk factors as part of a syndrome of cardiovascular, neuroendocrine and metabolic abnormalities (**Table 2**). Thus, hypertension is only one of a number of risk factors for cardiovascular diseases. It should not be treated in isolation from these other factors. Hence, the primary goal of treating hypertension and associated risk factors is to reduce the major cardiovascular mortality and morbidity i.e. stroke and coronary artery disease (CAD). As shown by the epidemiological studies and the treatment trials, lowering of DBP (5-6 mmHg) has resulted in a reduction in the incidence of stroke (38-40%), CAD (16%) and vascular mortality (21%) (**Table 3**)[5]. Treatment benefits

Figure 1: Diagram of the relationship between different risk factors and morbidity. DM = diabetes mellitus, MI = myocardial infarction, PVD = peripheral vascular disease

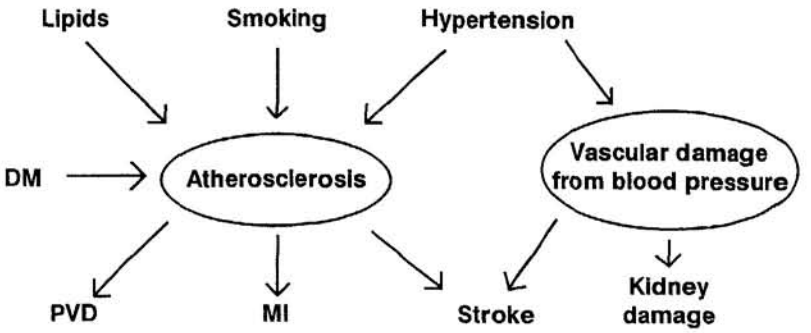

Table 2: The Hypertension Syndrome

High blood pressure
Dyslipidemias
Insulin Resistance
Truncal obesity
Microalbuminuria
Increased activity of coagulation factors
Reduced arterial compliance
Hypertrophy and altered diastolic function of left ventricle

Table 3: Summary of the effect of anti-hypertensive drug therapy on coronary artery disease, stroke, and vascular mortality from meta-analysis of 17 randomised studies (modified from ref. [5])

	No. of event, active therapy		No. of event, control		Risk reduction% (95% CI)	
	Death	Total	Death	Total	Death	Total
No. of patients	23847		23806			
Coronary artery disease	470	934	560	1104	16 (5-26)	16 (8-23)
Stroke	140	525	234	835	40 (26-51)	38 (31-45)
Total vascular mortality	768		964		21 (13-28)	

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relate to the degree of BP elevation and appear to be greater with larger reductions in BP. Several large studies also document treatment benefits for mild hypertension[6-8]. Furthermore, treatment benefits of isolated SBP elevation in elderly are also well documented[9-10]. Active therapy for elevated blood pressure has been shown to reduce relative risk equally in men and women with regard to stroke, CAD and other cardiovascular events[11]. Several studies have addressed the value of reducing blood pressure in the elderly and confirmed the benefits of treatment at least up to the age 75-80 years[9,10]. In summary, it appears that treatment benefits accompany reductions of SBP, DBP, and isolated systolic hypertension in both men and women and in elderly.

What is the threshold for initiation of drug therapy?

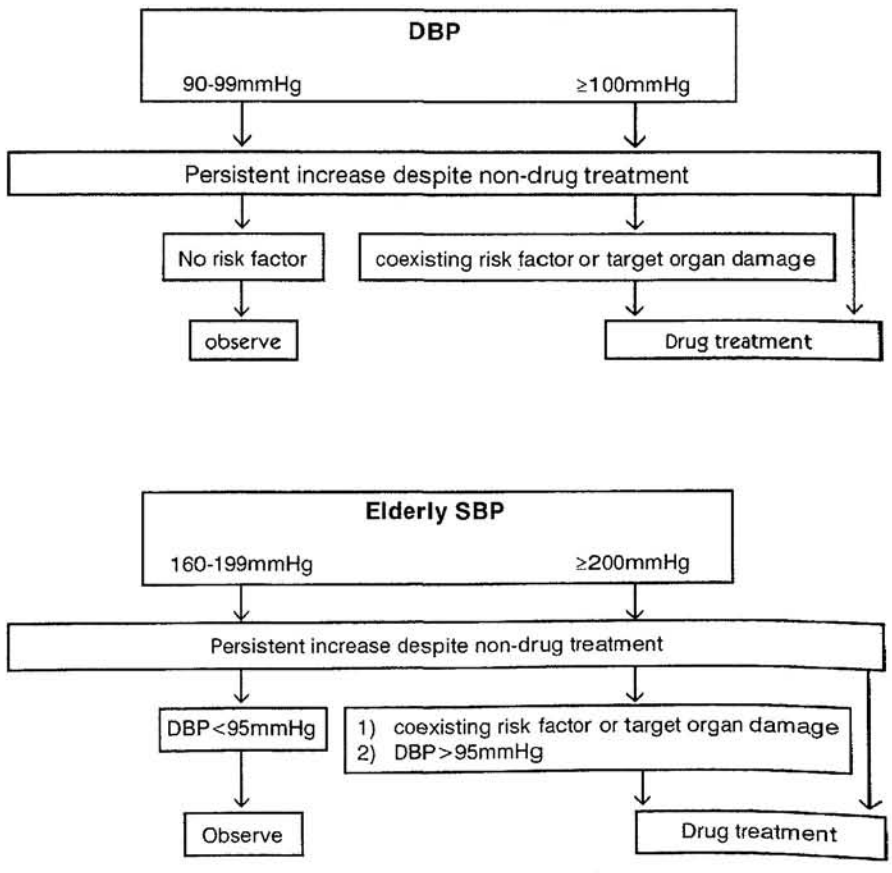
There is no clearly defined threshold level of blood pressure above which risk becomes apparent as shown by prospective observational studies. The long term risks for the development of cardiovascular disease increase with every increment of blood pressure. Within a range of diastolic pressure which many would consider normal, there is a doubling of risk of stroke and CAD[12]. Recently, guidelines on threshold for initation of drug therapy have been published and these are summarized in **Table 1**[1-3]. The question of when to administer drugs to young people with persistently raised DBP≥100 mmHg is now less controversial. Younger individuals with a DBP in the range of 90-99 mmHg should also be considered candidate for starting antihyertensive drug therapy especially if there is evidence of target organ damage or with coexisting risk factors (male, smokers, dyslipidaemia, diabetes, renal disease and strong family history of premature CAD)[3]. Individuals with borderline hypertension but otherwise healthy are at little short term risk and will not be endangered by postponement of drug therapy. They should be continued on non-pharmacological therapy and observed regularly. When blood pressure does not fall during continuing observation and non-pharmacological therapy, the case to start drug therapy is strong (**Figure 2**).

Similar to younger individuals, hypertension in the elderly is a major risk factor for cardiovascular mortality and morbidity. These risks are magnified in the elderly, probably because of the higher prevalence of associated cardiovascular risk factors and events[13]. Furthermore, systolic hypertension in elderly is not benign and is a more potent risk factor than increase in DBP[14]. Among elderly individuals (65-74 years), a sustained SBP of >160 mmHg is an indication for pharmacological treatment independent of the level of DBP[3]. Little is known about how best to manage hypertension in very elderly individuals (≥80 years).

How far should blood pressure be lowered?

This question is controversial. Epidemiological data indicate that the relationship between the blood pressure and cardiovascular risk is linear, i.e., the lower the DBP, the lower the risk of stroke and CAD[4,5]. Theoretically, it appears that the lower the blood pressure achieved by treatment, the better. However, a retrospective study

Figure 2: Management schemes of hypertension. DBP = Diastolic blood pressure, SBP = Systolic blood pressure. (modified from ref. [2])



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showed that aggressive lowering of DBP might lead to increase in coronary events in patients with established CAD. Thus concerns have been raised that lowering DBP may increase the risk of myocardial ischemia by lowering diastolic perfusion pressure in the coronary circulation, mainly in patients with left ventricular hypertrophy and CAD, the so-called J-curve hypothesis **(Figure 3)**[15,16] Diastolic blood pressure below 85 mmHg during treatment also has greater cardiovascular morbidity than patients in the 85-90 mmHg range[15]. An alternative explanation for increased morbidity in those with lower blood pressure on treatment is that patients in this subgroup have a lower pressure not only because of active anti-hypertensive treatment, but also because they have subclinical heart disease. Observation of the J-curve phenomenon in placebo or untreated groups of hypertensive patients may support this explanation. The absence of a J-curve in older patients with isolated systolic hypertension (SHEP)[9] suggests that treatment-related reduction in DBP to levels below 80 mmHg does not have to lead to increased morbidity from CAD. A tendency towards lower morbidity even in actively treated patients with low blood pressure is supported by TOMHS[17].

In the absence of studies which document that a reduction of DBP to below 85-90 mmHg increases the efficacy of treatment, the goal for DBP reduction cannot be more closely specified than below 90 mmHg. Documentation is even less complete with regard to optimal treatment goals for SBP. Among middle aged hypertensive patients it appears reasonable to aim for a SBP below 140 mmHg. For elderly patients, a target SBP below 160 mmHg can be suggested. Different guidelines[1-3] have different target blood pressures **(Table 1)**. An appropriate aim therefore is to reduce the DBP to <90 mmHg and SBP to <140 mmHg for young patients or <160 mmHg for elderly. Reductions of blood pressure beyond 125/85 mmHg are a matter of clinical judgement. In certain patients, such as those with diabetes mellitus, blood pressure should be reduced as much as possible to reduce renal complications (e.g. 120/70 mmHg), but those with CAD should not. The Hypertension Optimal Treatment (HOT) study, which randomises patients to different target blood pressure, is expected to clarify the target blood pressure for anti-hypertensive therapy[18].

Figure 3: The "J-shaped" curve of drug treatment of DBP. (modified reference [16]) DBP = Diastolic blood pressure, MI = myocardial infarction

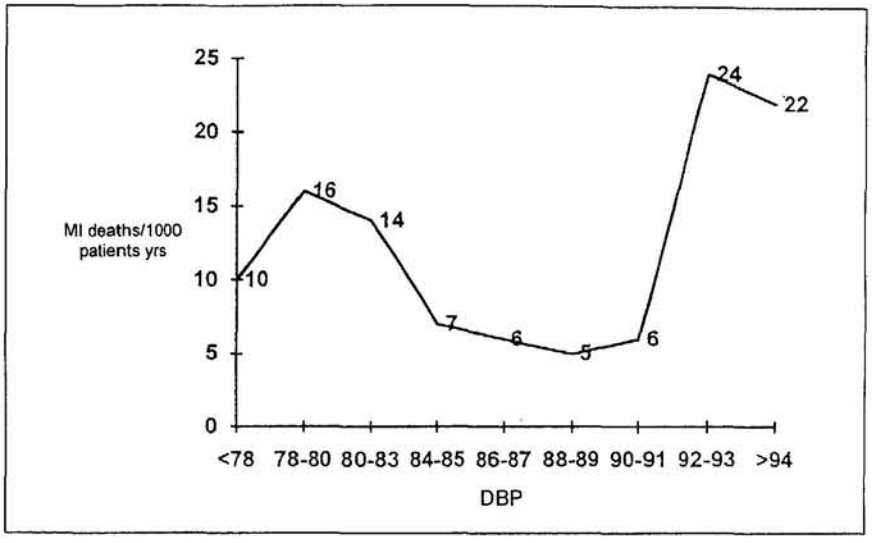

Table 4: Lifestyle modification for hypertension control and/or overall cardiovascular risk (modified from ref. [2-3])

- **Lose weight if overweight**
- **Avoid excessive alcohol**
- **Exercise (aerobic) regularly**
- **Reduce sodium intake**
- **Maintain adequate dietary potassium, calcium and magnesium intake**
- **Stop smoking and reduce dietary satured fat and cholesterol intake**

How should blood pressure be lowered?

Pharmacological antihypertensive therapy should be instituted only when sustained hypertension has been confirmed and non-drug measures fail. Lifestyle changes **(Table 4)** are effective and are recommended for both hypertensive and normotensive individuals with a strong family history. Risk factors such as diabetes and dyslipidaemia should also be controlled. The choice of antihypertensive agent remains ill defined. Diuretics and β-blockers have less than ideal side-effect profiles but have been proven in many primary prevention trials to reduce cardiovascular morbidity and mortality[6,7]. Although newer agents are better tolerated and have fewer metabolic side-effects, their preventive efficacy remains to be proven. The best approach is to tailor therapy to the patient with the consideration of coexisting diseases, side effect profile and presence or absence of

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contraindication. Diuretics, β-blockers, α_1-blockers, calcium antagonists or angiotensin converting enzyme (ACE) inhibitor can be used as first line agent when appropriate (**Table 5**).

Table 5: Guideline for selecting initial therapy

Clinical situation	Preferred	Requires special monitoring	Relatively or absolutely contraindication
Cardiovascular			
– angina pectoris	BB, CCB		direct vasodilators
– bradyarrhythmia			BB, verapamil, diltiazem
– heart failure	D, AECI		CCB
– hypertrophic cardiomyopathy	BB, verapamil diltiazem		D, direct vasodilators
– peripheral vascular disease	CCB, ACEI		BB
– acute myocardial infarction	BB, ACEI		direct vasodilators
Renal			
– bilateral renal artery stenosis	CCB		ACEI
– renal failure	CCB, BB	ACEI	D*
Other			
– Asthma, COAD			BB
– DM	ACEI	BB, D	
– Dyslipidemia	AB, CCB	BB, D	
– Gout		D	

AB = α_1-blocker, ACEI = angiotensin converting enzyme inhibitor, BB = β-blocker, CCB = calcium channel blocker, D = diuretic. *Diuretic may have reduced efficaciousness.

Diuretics

Advantages. Diuretics remain important, they are cheap, effective and particularly useful in older patients and those with incipient heart failure. Low dose thiazide diuretic, especially in combination with a potassium sparing diuretic, has been extensively proven in primary preventive trials to reduce strokes. This therapy is especially useful in the elderly in the prevention of CAD as compared to a beta-blocker[6]. Primary cardiac arrest is also reduced with this therapy[19].

Disadvantages. Diuretic therapy requires monitoring for adverse effects on serum potassium, glucose and lipid levels.

β-blockers

Advantages. β-*blockers have* been used in large clinical trials with documented benefit. They have a particular role in younger individuals who are anxious, non-smokers, and patients with CAD in whom β-blockers are indicated for angina. They also have the additional benefits of a secondary preventive effect against death and re-infarction in patients who have suffered a myocardial infarction[20].

Disadvantages. β-blockers have adverse metabolic effects with worsening in insulin sensitivity and can cause glucose intolerance. Those without intrinsic sympathomimetic activity raise triglycerides and low density lipoprotein cholesterol level.

ACE inhibitors

Advantages. ACE inhibitors are efficacious, safe and have been shown to improve survival in patients with impaired left ventricular function[21] and delay the need for renal dialysis in patients with diabetic nephropathy[22]. More rapid reversal of left ventricular hypertrophy is observed compared with other hypertensive treatments (see below). ACE inhibitor is shown to prevent the progression and the development of diabetic nephropathy[23].

Disadvantages. ACE inhibitors cause bothersome dry cough in significant proportion of patients. Other side effects such as hyperkalemia, skin rash and renal impairment are relatively infrequent.

Calcium channel blockers

Advantages. The older calcium channel blockers such as verapamil, nifedipine and diltiazem have been extensively used and long acting once or twice daily formulations are now available. Second-generation agents which are newer dihydropyridine analogues, may have advantages over the first generation in terms of the potential for once-daily administration, vascular selectivity, and better side-effect profile.

Disadvantages. Ankle edema and headache are common complications. The long term safety of this group of drug is unclear. Recent data suggest that high dose, short acting preparation of nifedipine may be harmful and associated with two-fold increased risk of myocardial infarction in an uncontrolled study. However, they should not be considered as harmful until further proof from the other ongoing prospective randomized trials is available[24].

α_1-blockers

Advantages. α_1-blockers may be useful in patients with dyslipidemia as these agents tend to have either a neutral or beneficial effect on plasma lipid levels. They also are useful in patients with prostatism.

Disadvantage. Postural hypotension and dizziness are common side effects especially in elderly.

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What are the physiologic effects of long term blood pressure control?

The optimal management of hypertension extends beyond reduction of blood pressure to ultimate therapeutic goal of preventing target-organ damage, including left ventricular hypertrophy (LVH), atherosclerosis (CAD and stroke), and renal failure.

Left ventricular hypertrophy (LVH)

Echocardiographic studies have revealed that as many as 50% of asymptomatic patients who have mild-to-moderate hypertension have LVH[25,26]. The presence of LVH is a powerful predictor of cardiovascular morbidity and mortality, particularly for myocardial infarction, congestive heart failure, ventricular arrhythmia and sudden death[25]. Hemodynamic overload from long-standing systemic hypertension is the primary factor in the pathogenesis of LVH, but non-hemodynamic factors such as various growth factors, proto-oncogenes and cell growth-regulating gene, may play a significant role as well. Both the sympathetic nervous system and the renin-angiotensin system (RAS) may activate these cellular growth mechanism and contribute to LVH.

Effective anti-hypertensive therapy can prevent or even reverse established LVH. Regression of LVH leads to improved left ventricular filling and contractility, enhanced coronary reserve and reduce arrhythmia. The Framingham Study showed that LVH regression is associated with 25% risk reduction in cardiovascular events[26]. Meta-analyses showed that all drug groups-ACE inhibitor, β-blockers, calcium channel blockers and diuretics significantly reduced LVH[27]. Some drugs e.g. ACE inhibitor, may theoretically be more effective because they inhibit specific cellular mechanism in addition to blood pressure lowering. The large trials which used ECG criteria for LVH found that diuretics based therapy appears to have a favourable effect on more pronounced LVH. However, meta-analyses of echocardiographic studies for LVH showed that ACE inhibitors seem to be more effective than other agents[27]. Current ongoing large, well controlled, comparative studies (e.g. PRESERVE study) will provide a better answer concerning the long term effects of pharmacological blood pressure lowering therapy and its long term effects on LVH.

Atherosclerosis

Hypertension accelerates atherogenesis by altering the biology of the vascular endothelium and smooth muscle. Hypertension is also associated with abnormalities of lipid and insulin metabolism, impaired arterial compliance and increased production of vasoactive substances and growth factors that promote cellular metabolism[28]. Anti-hypertensive therapy may retard atherogenesis by reversing one or more of these factors through blood pressure lowering or other direct mechanism (**Table 6**).

Renal Failure

Hypertension is the leading cause of renal failure and tends to accelerate the progression of renal failure regardless of the underlying causes. Treatment of systemic hypertension is unequivocally beneficial in slowing the progression of diabetic nephropathy. Both ACE inhibitor and calcium channel blocker produce comparable reductions in proteinuria and a similar rate of decline in GFR[22,23,29]. Reduction in BP is an important factor in slowing the rate of progression of chronic renal failure. Theoretically, ACE inhibitors offer vasodilating effect and reduce intraglomerular capillary pressure, may have additional renoprotective effect. However, there is currently no data to suggest which agents may be more effective than others in this respect.

Is there a role for multiple drug therapy?

A recent study conducted in Europe reported that of over 11,000 hypertensive patients being treated by

Table 6: Summary of the effect of anti-hypertensive agents on factors related to atherosclerosis

	Lipids	RAS	Anti-proliferative effect	Insulin resistance	Arterial compliance	Overall effect
D	–	–	0	–	0	**Possibly-**
BB	–	0	0	–	+	?
CCB	0	0	+	0 or +	+	+
ACEI	0 or +	+	+	+	+	+
AB	+	0	+?	+	+?	+

Key: + = favorable effect, – = unfavourable, 0 = not effect.
AB = α_1-blockers, ACEI = angiotensin converting enzyme inhibitor, BB = β-blocker, CCB = calcium channel blocker, D = diuretic, RAS = Renin-angiotensin-system

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their general practitioners with monotherapy, only about one-third had a DBP <90 mmHg, leaving two-thirds inadequately controlled. This may seem surprising, but is by no means confined to Europe and is leading to reconsideration in the use of combination therapy, with an aim to increase efficacy but minimise side effects. Drugs have different primary actions, selective use of combination of therapy may have synergistic effect and counteract their own side-effects (**Table 7**). Furthermore, combination therapy may allow the use of lower dose of each drugs to reduce their side-effects. Thus, drugs for use in combination can maximise antihypertensive efficacy while minimising side effects, and we may be seeing fixed combination tablets for once or twice daily administration in wider use in the near future.

Table 7: Example of favourable and less desirable anti-hypertensive drugs combination

Drug Combination	Remarks
Favourable:	
BB+CCB/AB	BB reduces reflex tachycardia associated with some CCB/AB
ACEI+D	ACEI counteracts the secondary hyperaldosteronium due to D
ACEI + CCB	Synergistic action with increased efficacy
Unfavourable:	
BB+CCB	BB may aggravate bradyarrhythmias with some CCB
CCB + AB	Both are vasodilator and may lead to severe postural hypotension
ACEI+D	May lead to severe hyperkalemia when ACEI used with potassium sparing diuretics

AB = α_1-blocker, ACEI = angiotensin converting enzyme inhibitor, BB = β-blocker, CCB = calcium channel blocker, D = diuretic,

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