Indian Journal of Clinical Medicine



REVIEW

# Clinical Perspective on the Management of Hypertension

Muzaffar Iqbal

College of Pharmacy, King Saud University, Riyadh, KSA.
Corresponding author email: muziqbal@gmail.com; muziqbal@ksu.edu.sa

**Abstract:** Hypertension is an important medical and public health issue all over the world. It is one of the most prevalent conditions seen today by clinicians in both developed and developing countries. Depending upon progression of systolic and diastolic blood pressure it is classified into stage 1, 2 and 3 hypertension. Life style modifications may be helpful in initial stage but pharmacological treatment is necessary when it become difficult to control it. In routine practice, pharmacological treatment is being selected from diuretics, β-blockers, calcium channel blockers and renin angiotensin system inhibitors either alone or in combination for both initial and maintenance therapy. Choice of drug depends upon favourable effects in specific clinical setting. Thiazide type diuretics are being preferred for most patients with uncomplicated hypertension whereas β-blockers show strong benefits in patients with a variety of cardiovascular complications. ACE-Inhibitors and ARBs are superior to other class in patients with multiple risk factors like obesity, insulin resistance or diabetes. CCBs compared with other class of hypertensive drugs demonstrate similar blood pressure lowering effects and similar reductions in cardiovascular morbidity and mortality but higher incidence of heart failure and fatal myocardial infarction in some patients. Despite the continued decrease in mortality and morbidity rate by these antihypertensive drugs, some documented increasing prevalence of cardiac failure and end stage renal disease remains to be explained.

**Keywords:** hypertension, diuretics, β-blockers, angiotensin inhibitors, calcium channel blockers

*Indian Journal of Clinical Medicine* 2011:2 1–17

doi: 10.4137/IJCM.S5475

This article is available from http://www.la-press.com.

## Introduction

Hypertension is an important worldwide public-health challenge because of its high frequency and concomitant risks of cardiovascular and kidney disease.[1] It has been identified as the leading risk factor for mortality, and is ranked third as a cause of disability-adjusted life-years.[2] The World Health Organization has concluded that hypertension is the major factor responsible for the most deaths worldwide (12.8% per year or more than seven million).[1] More than a quarter of the world's adult population-totalling nearly one billion (26%) had hypertension in 2000, and because a larger proportion of the world's population is expected to be older in 2025, this proportion has been projected to increase to 1.56 billion (≥29% prevalence by that time). However, there is considerable variation among countries and geographic regions for the reported prevalence of hypertension (≈5% to 70%) and hypertension control rates (≈5% to 58%).[2,3] The prevalence of hypertension increases with advancing age; for example, about 50% of people between the ages of 60 and 69 years old have hypertension, and the prevalence is further increased beyond age 70.[4] Although hypertension is more prevalent in economically developed countries, the larger population of developing countries results in a considerably larger absolute number of individuals affected.

Hypertension is a heterogeneous medical condition. In most patients (over 90% of individuals) it results from unknown pathophysiologics etiology (essential or primary hypertension). However a small percentage of patients (10%) have a specific cause of their hypertension (secondary hypertension). While essential hypertension cannot be cured, it can be controlled. Although it has frequently been indicated that the causes of essential hypertension are not known, this is only partially true because we have little information on genetic variations or genes that are over-expressed or under-expressed as well as the intermediary phenotypes that they regulate to cause high BP.[5] A number of factors increase BP, including 1) obesity, 2) insulin resistance, 3) high alcohol intake, 4) high salt intake (in salt-sensitive patients), 5) aging and perhaps 6) sedentary lifestyle, 7) stress, 8) low potassium intake, and 9) low calcium intake.[6,7] Furthermore, many of these factors are additive, such as obesity and alcohol intake.

Causes of secondary hypertension includes concurrent medical conditions or are endogenously induced (chronic kidney disease, cushing's syndrome, coarctation of the aorta, obstructive sleep apnea, parathyroid disease, pheochromocytoma, primary aldosteronism, renovascular disease, thyroid disease).[4] In most of these cases, renal dysfunction resulting from chronic kidney disease or renovascular disease is the most common secondary cause.[8] If the cause of secondary hypertension can be identified, hypertension in these patients can be cured.

## Worldwide Guideline for the Treatment of Hypertension

Different worldwide societies recommend guidelines for the management prevention and control of hypertension which are usually update as per need and requirement. The most recent update is as follows.

1. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[4] Published by High Blood Pressure Education Program (NHBPEP) Coordinating Committee of the National Heart, Lung, and Blood Institute (NHLBI).
2. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document, 2009.[9] Published by European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).
3. British Hypertension Society Guideline for Hypertension Management 2004 (BHS-IV).[10] Published by British Hypertension Society.
4. 2003 World Health Organization/International Society of Hypertension (WHO-ISH) Statement on Management of Hypertension. World Health Organization. International Society of Hypertension Writing Group.[11] Published by WHO.
5. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009).[12] Published by Japanese Society of Hypertension Committee.
6. CG34 HYPERTENSION-Management in adults in primary care: pharmacological update.[13] Published by NICE (National Institute for Health and Clinical Excellence Guideline).

7. The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension: part I—blood pressure measurement, diagnosis and assessment of risk and Part II-therapy.[14,15] Published by Canadian guidelines for the management of essential hypertension-Canadian Hypertension Education Program (CHEP).
8. Management of High Blood Pressure in Blacks.[16] Update of the International Society on Hypertension in Blacks (ISHIB) Consensus Statement. 2010.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) was published in 2003, and is still considered the gold standard. JNC 8 is currently being compiled and is expected to be published in 2011.

Classification of hypertension based on different guidelines is presented in Table 1. JNC 7 introduced the classification of BP between 120 to 139 mmHg systolic blood pressure (SBP) or 80 to 89 mmHg diastolic blood pressure (DBP) as "prehypertension" based on the risk of progression and associated CV risk. Stage 1 hypertension is defined as SBP between 140 to 159 mmHg and/or DBP between 90 to 99 mmHg. Another change in JNC 7 is the combining of stage 2 and stage 3 hypertension into a single stage 2 category refers to all levels of SBP > 160 and/or DBP > 100 mmHg.[4]

## Principle of Antihypertensive Therapy

The ultimate public health goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. It has been proven beyond a doubt that blood pressure reduction is associated with reduced cardiovascular morbidity and mortality. A meta-analysis of 61 prospective, observational studies covering 1 million adults and 12.7 million person-years at risk has substantiated that for every 2 mmHg decrease in mean SBP, there is a 7% reduction in the risk of ischemic heart disease mortality, and a 10% reduction in the risk of stroke mortality.[19] The long-term follow-up studies of the Multiple Risk Factor Intervention Trial have revealed that for the most patients it is the SBP rather than the DBP that most strongly predicts adverse events.[20] Additionally most persons with hypertension, especially those >50 years of age, will reach the DBP goal once the SBP goal is achieved, so the primary focus should be on attaining the SBP goal.

Major guidelines[4,11,12,16,18] on the management of hypertension recommend the initiation of antihypertensive drugs in all patients with a SBP 140 mmHg or more and/or a DBP 90 mmHg or more, and to adjust the treatment strategy in order for the patients to be below these values (Table 2). They further recommend drug treatment to be initiated within a lower BP range, that is, a SBP between 130 and 139 mmHg and a DBP between 85 and 89 mmHg in patients with diabetes or a history of cardiovascular or renal disease, aiming at achieving SBP/DBP values <130/80 mmHg. Treating SBP and DBP to targets that are <140/90 mmHg is associated with a decrease in cardiovascular disease (CVD) complications.[21–23] But despite use of combination treatment, reducing SBP to <140 mmHg may be difficult or more so if the target is a reduction to <130 mmHg. Additional difficulties should be expected in the elderly, in patients with diabetes,

**Table 1.** Classification of blood pressure.

| BP classification | JNC 7[4] | | JNC 6 1998,[17] EHS 2007,[18] BHS 2004,[10] JSH 2009[12] | |
|---|---|---|---|---|
| | SBP mmHg | DBP mmHg | SBP mmHg | DBP mmHg |
| Optimal | – | – | <120 | and <80 |
| Normal | <120 | and <80 | 120–129 | and/or 80–84 |
| High normal* | 120–139 | or 80–89 | 130–139 | and/or 85–89 |
| Stage 1 hypertension | 140–159 | or 90–99 | 140–159 | and/or 90–99 |
| Stage 2 hypertension | ≥160 | ≥100 | 160–179 | and/or 100–109 |
| Stage 3 hypertension | – | – | ≥180 | and/or ≥110 |
| Isolated systolic hypertension | – | – | ≥140 | and <90 |

**Note:** *Prehypertension in JNC 7.
**Abbreviations:** EHS, European Society of Hypertension; JNC, Joint National Committee; BHS, British Hypertension Society; JSH, The Japanese Society of Hypertension.

**Table 2.** Blood pressure goals: consensus across treatment guidelines.

| Organization | Patient type | BP goals (mmHg) |
|---|---|---|
| JNC 7[4] | Uncomplicated hypertension | 140/90 |
| | With diabetes mellitus, chronic kidney disease | 130/80 |
| ESH 2007[18] | In all hypertensive patients | <140/90 |
| | Diabetes and clinical conditions (stroke, MI, renal dysfunction, proteinuria) | <130/80 |
| WHO-ISH[11] | Low risk for CVD | SBP 140 |
| | Presence of diabetes mellitus, target organ damage, or associated clinical conditions | <130/80 |
| ISHIB[16] | African Americans, low to moderate CVD risk | 140/90 |
| | High-risk CVD: diabetes mellitus,chronic kidney disease, prior CVD, stroke/TIA, target organ damage including MA | 130/80 |
| | Proteinuria >1 g/24 h | 125/75 |
| NKF[23] | Albuminuria (300 mg/d or 200 mg/g creatinine), with or without diabetes | 130/80 |
| | Proteinuria (protein to creatinine ratio 500–1000 mg/g) | "Consider even lower than 130/80" |
| ADA[22] | Diabetes | 130/80 |

**Abbreviations:** JNC, Joint National Committee; EHS, European Society of Hypertension; WHO-ISH, World Health Organization-International Society on Hypertension; ISHIB, International Society on Hypertension in Blacks; NKF, National Kidney Foundation; ADA, American Diabetes Association; MI, myocardial infarction; CVD, cardiovascular disease; TIA, transient ischemic attack; MA, microalbuminuria.

and in general in patients with cardiovascular (CV) damage. In order to more easily achieve goal BP, antihypertensive treatment should be initiated before significant CV damage developed.[18] Additionally guideline recommendations to lower BP less than 130/80 mmHg in patients with diabetes[21,24–29] or a history of cardiovascular disease is also not supported by incontrovertible trial evidence.[30–33]

Establishing the proper blood pressure goal for an individual patient is of obvious importance and it dependent upon comorbidities. Results of ongoing and future studies may modify the currently established target blood pressures and very likely when JNC 8 is published (expected in 2011), goal blood pressures will be different than those established by JNC 7.

Initial recommendations for therapy to achieve this goal very likely will continue to involve lifestyle modifications (non pharmacological treatment) as are recommended by JNC 7. If these fail or are inadequate, then pharmacologic therapy will be necessary.[4] Scope of this discussion will deal only with appropriate management for sustained hypertension. Management of hypertensive emergencies or resistant hypertension will not be addressed here.

## Nonpharmacological Treatment

Lifestyle modifications are the main stay interventions to prevent or delay the onset of hypertension and are essential concomitant therapy for those who require pharmacological drug treatment for hypertension.[15] Lifestyle measures should be instituted, whenever appropriate, in all patients, including those who require drug treatment. The purpose is to lower BP, to control other risk factors and to reduce the number or the doses of antihypertensive drugs.[18] JNC 7 also endorses the use of health-promoting lifestyle modifications as an "indispensable" part of treatment for all hypertensive and prehypertensive patients. These modifications include weight reduction in patients who are overweight or obese, physical activity, restricted sodium intake, the adoption of the Dietary Approaches to Stop Hypertension (DASH) diet, moderate alcohol consumption, and tobacco cessation. According to these guidelines, patients whose SBP and DBP falls between 130 and 139 mmHg and 80 and 89 mmHg, respectively, should follow lifestyle modification alone for a maximum of three months before receiving pharmacological agents.[4]

### Dietary modification

DASH-trial showed overall reductions in BP of 11.4/5.5 mmHg in hypertensive persons on a diet rich in fruits, vegetables, and low-fat dairy products, compared with control subjects on a so-called "usual American diet", while dietary sodium intake and weight were held constant.[34] Another two clinical

trials, one with a comprehensive food plan that supplied the recommended dietary allowances of all major nutrients and the other with a diet rich in fruits, vegetables, and low-fat dairy products and reduced in saturated and total fat produced reductions in BP comparable to or greater than those usually seen with monotherapy for stage 1 hypertension.[35,36]

Dietary salt intake has a linear association with blood pressure. Reduced sodium intake to approximately 100 mmol/day can prevent to develop hypertension.[37] The Dietary Approaches to Stop Hypertension (DASH)-Sodium feeding study showed that an even lower intake of sodium, approximately 60 mmol/day, further reduces BP in both normotensives and hypertensives.[38] High potassium intake is also associated with reduced BP. A meta-analysis showed that average SBP and DBP reductions associated with an increase in urinary potassium excretion of 2 g/day (50 mmol/day) were 4.4 and 2.5 mmHg in hypertensives and 1.8 and 1.0 mmHg in normotensives.[39]

Trials have also reported that reductions in alcohol intake can lower BP in normotensive and hypertensive men who are heavy drinkers (typically 3 or more drinks per day). A meta-analysis of 15 randomized controlled trials revealed that reduction in self reported daily consumption of alcohol, ranged from 16% to 100% (mean = 76%) was associated with a significant 3.3 mmHg reduction in SBP and a 2 mmHg reduction in DBP.[40] This reduction showed a dose-respone relationship between mean percentage of alcohol reduction and mean blood pressure reduction.

When determining dietary habits, clinicians should attempt to quantify sodium, carbohydrate, protein, and fat intake and assess the amounts of calcium, potassium, and magnesium contained in the diets of all patients.

### Weight loss and physical activity

Overweight (body mass index >25 kg/m$^2$) has been seen in epidemiologic studies to be an important risk factor for higher blood pressure, and there seems to be a linear relation between body weight and blood pressure.[41] Clinical trials have shown that weight loss, especially when combined with dietary sodium restriction, lowers blood pressure in hypertensive and also in normotensive patients. The Hypertension Prevention Trial showed that a 4% reduction in body weight over 3 years was associated with a 2.4 mmHg reduction in SBP and a 1.8 mmHg reduction in DBP.[37]

Increasing aerobic physical activity such as brisk walking, jogging, swimming or bicycling has been shown to lower BP. A meta-analysis of 54 randomized controlled trials showed a net reduction of 3.8 mmHg in SBP and 2.6 mmHg in DBP in individuals performing aerobic exercises, compared to controls.[42]

Evidence also demonstrates the benefits of device guided therapeutic breathing, smoking cessation, stress management, and patient education in controlling BP.[43–46] There is also growing evidence to support the use of several complementary and alternative medicine (CAM) activities to improve BP. These include yoga, certain relaxation techniques, and meditation. Because long-term compliance with lifestyle measures is low and the BP response highly variable, patients under non pharmacological treatment should be followed up closely to start drug treatment when needed and in a timely fashion.[18]

Life style modification have important role in hypertensive as well as nonhypertensive individuals. In hypertensive individuals, nonpharmacological strategies are recommended as successful primary and adjunctive treatment options for lowering blood pressure. Whereas in normotensives, it can reduce the incidence of hypertension and lower end-organ damage. Device guided breathing and patient education represent additional strategies to achieve sustained BP control with minimal risk or side effects. These strategies can also empower patients to take control of their health.

## Pharmacological Treatment

As blood pressure increases, it become more difficult to control it at the target level through life style modifications alone and treatment with antihypertensive drugs become necessary. Guidelines also recommend the use of antihypertensive drugs in patients with grade 1 hypertension at low or moderate cardiovascular risk, that is, when BP is between 140 and 159 mmHg SBP and/or 90 and 99 mmHg DBP, provided nonpharmacological treatment has proved unsuccessful. However, it should be recognized that the evidence in favour of this recommendation is scant because older trial of 'mild hypertension' focused on patients whose BP could be higher than those defining grade 1 hypertension[47] and also in FEVER trial[48], where entry level means BP was just below 160 mmHg (159 mmHg). Although Canadian

Guideline recommends that antihypertensive therapy should be prescribed for average DBP of 100 mmHg or higher (grade A), or average SBP of 160 mmHg or higher (grade A) in patients without macrovascular target organ damage or other cardiovascular risk factors.[14]

Guidelines also point out that the BP threshold for drug treatment is not related to age and recommend starting antihypertensive drugs at SBP at least 140 mmHg or DBP at least 90 mmHg in the elderly as well. However, there is no single trial on elderly hypertensive patients that recruited patients with a SBP in the grade 1 hypertension range (ie, <160 mmHg).[49] Therefore, it can be concluded that current guidelines recommendations on BP values at which to initiate drug treatment in the elderly are not based on results from trials, but derived from other findings and perhaps encouraged by the large benefits of antihypertensive therapy in all available trials in the elderly, admittedly at higher initial blood pressures.

## Choice of antihypertensive drug

Based on reviewed of the large number of randomized trials of antihypertensive therapy it was concluded that the main benefits of antihypertensive treatment are due to lowering of BP per se, and are largely independent of the drug employed.[18] Similarly meta-analysis of large clinical studies have shown that the prevention of cerebrovascular and cardiovascular disorders is proportionate to the degree of decrease in blood pressure, rather than the class of antihypertensive drugs.[50,51] The antihypertensive drug with the greatest hypotensive effect and suited for various accompanying condition should be selected for each hypertensive patient. Although JNC 7 recommends thiazide type diuretics as preferred initial agent in patients without compelling indications and for Stage 1 hypertension (SBP 140 to 159 mmHg, DBP 90 to 99 mmHg).[4]

Several classes of antihypertensive drugs are available today. Among these, the drug to be used as a first line of treatment is being selected from calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, diuretics and β-blockers. All these drugs are suitable for the initiation and maintenance of antihypertensive treatment either as monotherapy or in some combination with each other. All these drugs, alone or in combination, show a sufficient hypotensive effect and tolerability in hypertensive patients and extensive evidence for suppression of the occurrence of cerebrovascular and cardiovascular disease are also accumulated. The results of large clinical studies suggest that these classes have positive indications and contraindications so the appropriate drugs should be selected for patients having certain conditions. For example, a β-blocker is not necessarily the first choice for elderly patients without complications or for hypertensive patients with abnormal glucose or lipid metabolism.[52,53] Some reports have recommended renin-angiotensin (RAS) system inhibitor (ARBs, ACE-inhibitors) if there is no complicating condition, or a β-blockers for young patients and a diuretic or a CCB for elderly patients because of age-related differences in the mechanism of hypertension[54,55] but another report has refuted the difference in antihypertensive effect according to age.[56] At any rate, the frequency with which the target control level can be achieved using a single drug is low.[55] Since each drug class has contraindications as well as favorable effects in specific clinical settings, therefore choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third and subsequent choice, with average patients as reference, has now little scientific and practical justification and should be avoided. Similarly it is generally also not possible to predict the responses of individuals with hypertension to any specific drug. For example, for some antihypertensive drugs, on average about two-thirds of patients will have a meaningful clinical response, whereas about one-third of patients will not respond to the same drug.[57]

Despite the large armamentarium of available blood pressure-lowering agents, the need remains for safer and more effective antihypertensive treatment.[58]

## Diuretics

The advent of newer drugs for the treatment of hypertension like the CCBs and ARBs resulted in a decreased use of diuretics. The steady introduction of newer agents and their heavy promotion by the industry made physicians switch away from use of diuretics as first line agents in the treatment of mild to moderate hypertension.

The ALLHAT study compared the long-term effects of antihypertensive treatment with a diuretic chlorthalidone, the ACEI lisinopril, or the CCB amlodipine, or an α-receptor blocker doxazocin when each drug is used as initial treatment with step-up drugs added as needed in more than 40000 hypertensive individuals. Results demonstrated that thiazide types of diuretics are unsurpassed in lowering blood pressure and reducing the clinical events. Evidence from this study also proved that thiazide type of diuretics offer better reduction of blood pressure with lesser incidence of coronary revascularization and heart failure as compared to other drugs like CCB, ACEI or ARB.[59] The evidence from the SHEP study emphasizes the value of a low-dose thiazide-type drug as initial therapy for isolated systolic hypertension in older patients.[60] Clinical trial data also indicate that diuretics are generally well tolerated.[59,61] However due to negative metabolic effect of thiazide diuretics, there remains some controversy as to whether a thiazide-type diuretic should be the initial treatment for all hypertensive patients. Because in ALLHAT, serum cholesterol did not increase from baseline in any group, but it was 1.6 mg/dL lower in the CCB group and 2.2 mg/dL lower in the ACE inhibitor group than in diuretic-treated patients.[59] Thiazide induced hypokalemia could contribute to increased ventricular ectopy and possible sudden death, particularly with high doses of thiazides in the absence of a potassium sparing agent.[62] Similarly, the diabetogenic role of β-blockers and diuretics is difficult to discriminate, and when it has been dissociated diuretics appear worse than β-blockers.[63] Diuretics have rarely been studied in depth for their capacity to regress organ damage, and when tested have often been found inferior to calcium antagonists or ACE inhibitors.[64–66] Furthermore, all large studies that have explored the tolerability of various classes of antihypertensive agents on persistence to therapy have found diuretics to be, together with β-blockers, the least tolerated compounds[67] or those accompanied by the least persistence on treatment.[68,69] Finally, a recent meta-analysis has reported outcome benefit for low-dose but not for high-dose diuretics.[70] In addition, the results of the ACCOMPLISH trial have raised doubts as to whether thiazides are always the best protective component of combination therapy.[71] ACCOMPLISH trial was stopped early because treatment with antihypertensive combination therapy of ACE inhibitor benazepril plus the calcium-channel blocker amlodipine was more effective than treatment with the ACE inhibitor plus thiazide diuretic hydrchrorothiazide.

In spite of those diuretics is at least as efficacious as other antihypertensive drugs in preventing combined cardiovascular outcomes in a wide range of hypertension severity, age, gender, race and presence of other comorbidities, such as diabetes mellitus. Probably due to their more efficacious blood pressure lowering effect, they are superior to other drugs in preventing some outcomes, such as cerebrovascular disease and heart failure. In the case of heart failure, their unique preload reducing effect among the antihypertensive drugs may be another reason to explain their superiority. The consistent findings of some of the previous clinical trials[72] and ALLHAT trial,[59] together with their ease of administration, infrequent side effects and low price, recommend diuretics as the first option in the management of hypertension. JNC 7[4] report also has stated that thiazide type diuretics should be used for most patients with uncomplicated hypertension, either alone or in combination with drugs from other classes.

## Beta Blockers

The exact mechanism by which β-blockade reduces blood pressure is not completely understood. Hemodynamically, these drugs decrease cardiac output; and the slowing of heart rate was originally thought to be of clinical importance, particularly in hypertensive patients with tachycardia. But, at the same time, peripheral resistance is increased slightly and sodium reabsorption by the kidney is increased. The ability of β-blockers to inhibit activity of the RAS by reducing the release of renin from the juxtaglomerular cells of the kidney may contribute to their blood pressure lowering effects, especially in patients with medium or high levels of plasma renin activity.[73] β-Adrenergic receptor antagonists may lower blood pressure by other mechanisms also, including alteration of the control of the sympathetic nervous system at the level of the CNS, altered baroreceptor sensitivity, altered peripheral adrenergic neuron function, and increased prostacyclin biosynthesis.[74]

Over time, β-blockers became widely accepted for the treatment of hypertension, and one of the reasons for the acceptance of this drug class by clinicians was

that these agents appeared to be better tolerated than many of the drugs previously available for treating hypertension.[75] The benefit of β-blockers compared with that of other antihypertensive agents has been questioned on the basis of the results of two large randomized trials, the LIFE study[52] and the ASCOT study,[53] both of which showed superiority of ARB and CCB over therapy initiated by a β-blocker as far as stroke (LIFE) or stroke and mortality (ASCOT) were concerned. These two large trials have strongly influenced a following meta-analysis[76] which concluded that β-blocker initiated therapy is inferior to others in stroke prevention, but not in prevention of MI and reduction in mortality. On the basis of a similar meta-analysis, the NICE in the United Kingdom has advised the use of β-blockers only as fourth line antihypertensive agents[13] which was further supported by a meta-analysis in which the tolerability of β-blockers relative to other antihypertensive medications has been assessed, and worse outcomes in comparison with CCBs, renin-angiotensin system inhibitors, and thiazide diuretics reported.[77] There is also no doubt that β-blockers as well as diuretics (especially when combined) have adverse metabolic effects and facilitate new-onset diabetes.[78,79] It may also produce adverse metabolic changes and the older agents also have adverse effects on the lipid profile: they decrease blood concentrations of high-density lipoprotein cholesterol and increase plasma triglyceride concentrations.[80]

A recent meta-analysis of 147 randomized trials (the largest meta-analysis so far available) reports only a slight inferiority of β-blockers in preventing stroke (17% reduction rather than 29% reduction with other agents), but a similar effect as other agents on preventing coronary events and heart failure, and a higher efficacy than other drugs in patients with a recent coronary event.[81] Furthermore, the publication of a 20-year follow-up of the UKPDS trial[82] comparing atenolol and captopril in diabetes has found the incidence of cardiovascular outcomes to be similar in patients on the β-blocker or the ACE inhibitor, with a reduction in all-cause mortality favoring the β-blocker. Interpolation of ASCOT data on stroke in the meta-regression analysis of the Blood Pressure Lowering Treatment Trialists' Collaboration makes it clear that β-blocker/diuretics is not systematically inferior to calcium antagonist/ACE inhibitor treatments in their ability to reduce BP.[83]

Although it is well established, that the traditional β-blockers may produce adverse metabolic changes, diabetogenic and also have adverse effects on the lipid profile. But it is plausible that these β-blocker effects on glucose and lipid metabolism could at least partly explain the clinical outcomes differences between these agents and other drug classes.[75] Furthermore it is still unclear whether drug-induced diabetes carries the same negative prognosis as naturally occurring diabetes, with some authors emphasizing studies showing that trial patients with new onset diabetes do not have a higher incidence of cardiovascular outcomes during the trial and several year thereafter,[84] whereas others underline the opposite conclusion in other studies.[85,86]

Compared to other agents in trials using subclinical damage as an endpoint, β-blockers may have been shown to be less powerful than ACE inhibitors, ARBs and CCBs and this may be supposed to result in less cardiovascular protection in the long run. But it should not be ignored that there are not a homogeneous class of β-blocker and that vasodilating class of β blockers such as carvedilol, nebivolol and celiprolol appears not to share some of the negative properties described for other compounds. Carvedilol is a nonselective β-blocker with additional α-blocking activity that has been available in the United States for several years. Nebivolol is a highly selective $\beta_1$-blocker with the additional property of increasing the availability of vascular nitric oxide. Celiprolol lowers aortic stiffness and central pulse pressure.[87] These vasodilating drugs have metabolic and hemodynamic properties that distinguish them from their predecessors in the β-blocker class. These agents do not have the inhibitory effects on exercise tolerance that have previously been reported with β-blockers.[88] Carvdilol and nebivolol has been shown to have survival benefits in patients with heart failure, including patients who are elderly and have heart failure but preserved systolic function.[89]

In many ways, β-blockers have demonstrated strong benefits in patients with a variety of cardiovascular conditions. Over time, the evidence of symptomatic and metabolic adverse effects, together with concerns over major clinical outcomes, have led to some questioning of the use of older types of

β-blockers for the routine treatment of hypertension, especially in elderly patients without heart disease. But the emergence of the newer types of vasodilatory β-blockers should have the effect of reinvigorating interest in the β-blocker class.

## Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Antagonists and Renin Inhibitors

Inhibitors of the renin-angiotensin system (RAS), including ACE- inhibitors, ARBs and now direct renin inhibitor (DRI) are commonly used in the treatment of hypertension.[90] ACE-inhibitors modulate blood pressure by inhibiting ACE mediated conversion of angiotensin I to angiotensin II. ARBs modulate blood pressure by inhibiting the activation of the $AT_1$ receptor by angiotensin II.[91] Aliskiren, a direct renin inhibitor, is the first of a new class of antihypertensive drugs that block the RAS further upstream. Its antihypertensive effect, safety, and tolerability are comparable with ARBs and ACE inhibitors; however, its long-term data is awaited.[92]

Inhibition of the RAS, when utilized along with other antihypertensive medications has been particularly effective in hypertensive patients with type 2 diabetes, chronic kidney disease, and vascular disorders and so consensus group guidelines have reflected this in their treatment recommendations.[93] The RAS plays an important role in blood pressure regulation, and ACE inhibitors & ARBs have been shown to be effective, first line drugs to treat arterial hypertension caused by various disease conditions. According to the EHS 2007 guidelines, ACE inhibitors and ARBs are superior to other classes of agent in patients with multiple risk factors including the metabolic syndrome and its major components, ie, abdominal obesity and insulin resistance or manifest diabetes mellitus.[18]

In 40% to 60% of patients with mild-to-moderate hypertension, ACE inhibitor monotherapy produces a satisfactory reduction in blood pressure.[94] In this population, ACE inhibitors contribute to reversal of cardiac hypertrophy, and do so with significantly greater efficacy than β-blockers.[95] In patients with congestive heart failure, ACE inhibitors relieve pulmonary congestion by a balanced reduction in cardiac preload and afterload. They appear to induce venous vasodilation, which increases peripheral venous capacitance and reduces right atrial pressure, pulmonary arterial pressure, capillary wedge pressures, and left ventricular filling volumes and pressures.[95]

Large studies such as the HOPE (Heart Outcomes Prevention Evaluation [96] and EUROPA (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease)[97] studies have shown that ACE inhibitors reduce cardiovascular mortality and morbidity in patients with established coronary artery disease without left ventricular dysfunction. Data from the HOPE Study show that ACE inhibitor therapy can reduce the incidence of acute coronary syndrome in patients with vascular disease. The data from HOPE and EUROPA were pooled with those of the PEACE (Prevention of Events with Angiotensin Converting Enzyme inhibition),[98] and QUIET (QUinapril Ischaemic Event Trial)[99] studies in a meta-analysis by Pepine and Probstfield, which included a total of 31,555 patients[100] showed that ACE inhibitor therapy produced 14% reductions in all-cause mortality and MI, a 23% reduction in stroke, and a 7% reduction in revascularization procedures compared with placebo.

Twenty-four-hour blood pressure control, rapid treatment response, and excellent tolerability profiles are 3 characteristics of ARBs that significantly contribute to its treatment success.[91] Significant antihypertensive effects and positive clinical outcomes have been noted after treatment with most ARBs (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan) in clinical trials having patients with varying degrees of hypertension and risk, including elderly patients, and patients with left ventricular hypertrophy, diabetes, severe hypertension, multiple risk factors, and target organ damage such as renal dysfunction.[52,101,102]

In patients with hypertension and left ventricular hypertrophy, ARB-based therapy, compared with β-blocker (atenolol)-based therapy with identical blood pressure control, has been shown to significantly reduce the composite risk of cardiovascular death, stroke, and MI and to decrease the rate of new-onset diabetes.[52] Similarly, ARB-based therapeutic regimens, compared with conventional therapy, have been shown to reduce the progression of nephropathy in patients with diabetic nephropathy (IDNT, RENAAL studies).[103,104] In patients with chronic heart failure, addition of an ARB, compared with

placebo, to conventional treatment has been shown to significantly reduce the risk of cardiovascular mortality and hospitalization (CHARM, Val-HeFT studies).[105,106] In high-risk post-MI patients, ARB therapy has been shown to reduce the risks of all-cause mortality, recurrent MI, sudden cardiac death, revascularization, coronary artery bypass grafting, or all-cause hospital admission to a degree similar to that of ACEI therapy (OPTIMAAL study).[107]

VALIANT, a good-quality trial in which valsartan compared with captopril (monotherapy and combination therapy) and examined patients with an acute myocardial infarction complicated by heart failure and/or left ventricular systolic dysfunction during median follow-up of 24.7 months. There was no significant difference in death rates, quality of life, and hospitalization rates between the valsartan and captopril groups. Valsartan was not inferior to captopril for mortality ($P = 0.004$) and for the composite endpoint of fatal and nonfatal cardiovascular events ($P < 0.001$).[105]

The overall data of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study which enrolled 25,620 patients over the age of 55 years with coronary heart disease or diabetes, plus additional risk factors, but without evidence of heart failure, telmisartan alone, or ramipril alone, was found to be equally effective in reducing the primary outcome of cardiovascular death, stroke, heart attack or hospitalization for new-onset heart failure, as well as each component of this composite endpoint. Despite the further lowering of SBP by 2.4 mmHg, combination therapy did not offer any additional benefit but was associated with a higher rate of hypotension-related side effects.[108,109] On the basis of the results of this analysis, dual blockade of the renin-angiotensin-aldosterone system should not be used for the treatment of hypertension, heart failure, and renal disease with perhaps the exception of diabetic nephropathy with albuminuria, until additional information is provided from ongoing studies.[110] However in the Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular Disease (TRANSCEND) study, telmisartan reduces cardiovascular events in high-risk patients with the exception of heart failure hospitalization and can be considered as the first-line therapy in those intolerant to ACE inhibitors.[111]

Aliskiren (DRI) is a new orally available, highly specific, and effective inhibitor of RAS activity. Clinical studies have provided convincing evidence that aliskiren controls RAS activity, reduces BP significantly, and displays good tolerability profile. Additionally, as with other RAS inhibitors, RAS blockade via direct renin inhibition has the potential to provide organ protection independent of BP reductions.[112] Single blockade of the RAS with an ACE inhibitor or ARB confers some cardiorenal protection; however, these agents do not extinguish the RAS as evidenced by a reactive increase in plasma renin activity (PRA), a cardiovascular risk marker, and incomplete cardiorenal protection. Dual blockade with an ACE inhibitor and an ARB also not offers additional benefit in patients with hypertension and normal renal and left ventricular function. But by blocking the first and rate-limiting step in the RAS, aliskiren reduces PRA by at least 70% and buffers the compensatory increase in PRA observed with ACE inhibitors and ARBs. The combination of a DRI with ARB or an ACE inhibitor is an effective approach for lowering blood pressure and available data indicate that such combinations favourably affect proteinuria, left ventricular mass index, and brain natriuretic peptide in patients with albuminuria, left ventricular hypertrophy, and heart failure, respectively.[113]

Aliskiren has been shown to be effective in lowering SBP and DBP in hypertensive patients when given in monotherapy at a single daily dose and is also effective in combination with a thiazide diuretic, CCB, ACE inhibitor or ARB.[114–116] A pooled analysis reported by Dahlöf et al[117] included 8,481 patients who participated in double-blind trials and received treatment with aliskiren monotherapy or placebo for 8 to 12 weeks. Once-daily aliskiren, 150 and 300 mg, produced reductions in mean trough sitting DBP of 10.1 and 11.8 mmHg, respectively, compared with 6.2 mmHg for placebo ($P < 0.0001$). In diabetic hypertensive patients with proteinuria, this drug in combination with ARB led to a greater reduction in urinary protein excretion than the administration of an ARB alone,[118] and in heart failure patients, this combination was significantly superior to ARB in causing a reduction in the plasma concentration of brain natriuretic peptide (a recognized prognostic marker for heart failure).[119]

Utility of ACE inhibitors for hypertension managements enhanced by paying careful attention to dose response and dose escalation to achieve better BP control and using ACE inhibitors in conjunction with classes of antihypertensive therapies that are additive (eg, diuretics and CCBs) rather than those classes which may yield only modest BP benefits. ARBs through their unique blockade of the renin-angiotensin system reduce morbidity and mortality associated with hypertension, and their excellent tolerability and ability to reduce blood pressure rapidly position them as choice of cardiovascular medications. Aliskiren antihypertensive potency is equivalent to those of ARBs, ACE inhibitors, and diuretics. However, clinical trials planned or in progress will address issues related to end organ protection and reduction in long-term cardiovascular end points and ultimately determine the place of renin inhibition in the treatment of hypertension.

## Calcium Channel Blockers

CCBs which include both dihydropyridines (DHPs) eg, nifedipine and amlodipine and non-dihydropyridines (verapamil and diltiazem), are among the most widely prescribed agents for the management of essential hypertension. Several large outcome risk trials and comprehensive meta-analyses have found that CCBs reduce the cardiovascular morbidity and mortality associated with uncontrolled hypertension, including stroke.[120] Conditions favoring the choice of a DHP CCB for hypertension include: advanced age, isolated systolic hypertension, angina pectoris, peripheral vascular disease, carotid atherosclerosis, and pregnancy. Whereas, diltiazem or verapamil should be considered for use in patients with angina pectoris or supraventricular tachycardia.

Several recent large clinical trials have confirmed CCBs efficacy not only in lowering blood pressure but also in reducing cardiovascular morbidity and mortality in hypertensive patients with a normal or high cardiovascular risk profile. In clinical trials such as ALLHAT, VALUE or ASCOT, an amlodipine-based therapy was at least as effective, when not slightly superior, in lowering blood pressure and sometimes more effective in preventing target organ damages than blood pressure lowering strategies based on the use of diuretics, β-blockers and blockers of the RAS.[121]

In ALLHAT trial which randomized 42,418 hypertensive patients aged 55 years or older, the differences in SBP and DBP with chlorthalidone vs. amlodipine were statistically, but not clinically significant. At a mean follow-up of 5 years, the differences were only 0.8 mmHg. The incidence of the primary outcome (fatal CHD or nonfatal MI, 6-year rate, 11.3% for amlodipine vs. 11.5% for chlorthalidone; $P = 0.65$) was similar between the groups.[59]

The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) Trial compared coronary heart disease outcome in two anti-hypertensive treatment strategies based on either an valsartan (ARB) or amlodipine (CCB). There were no differences in the primary composite endpoint of cardiac morbidity and mortality (which included interventional procedures, hospitalised heart failure, non-fatal MI and fatal coronary heart disease, however MI and stroke events occurred less commonly on amlodipine than on valsartan the former achieving statistical significance [$P = 0.02$ and $P = 0.08$ respectively]). There was a non-significant excess of hospitalized heart failure on amlodipine ($P = 0.012$). However, lower BPs early in the trial probably accounted for most of the observed benefits in favor of the CCB.[122]

In the International Verapamil SR-Trandolapril Study (INVEST), in 22,756 patients aged 50 years or older from 15 countries, BP control at 24 months was similar in patients receiving either sustained-release verapamil or atenolol as initial therapy. Both treatment strategies were equally effective for reducing the primary outcome (first occurrence of death [all cause], nonfatal MI, nonfatal Stroke).[123] The Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE trial demonstrated similar reductions in BP among 16,602 hypertensive patients with at least one additional risk factor for CV disease who were randomized to receive either controlled-onset, extended-release verapamil (plus other medications) or conventional treatment with either the β blocker, atenolol, or the diuretic, HCTZ. Both groups experienced similar incidences of the primary outcome (first occurrence of acute MI, stroke, or CV disease-related death; 4.5% in the verapamil group.[124]

Several meta-analyses have assessed the impact of CCBs on CV morbidity and mortality in hypertensive patients. Pahor et al[125] analyzed data from nine

clinical trials in which patients received CCBs or other antihypertensive agents (diuretics, β blockers, ACE inhibitors, or clonidine). The reduction in SBP and DBP was similar for all agents, and no differences were observed between CCBs and other agents for the end points of stroke and all-cause mortality; however, CCBs were associated with higher rates of MI, HF, and major CV events compared with other antihypertensive agents.

In a meta-analysis of six clinical trials, investigators reported similar rates of mortality (total and CV) and major CV events with CCBs compared with conventional therapy (β blocker or diuretic). Similarly CCBs were associated with a lower risk of nonfatal stroke by 16% ($P = 0.013$) and a higher (18%) risk of nonfatal MI ($P = 0.036$). After correction for multiple comparisons, these $P$ values became 0.052 and 0.144, respectively.[126] In the systematic overview by the Blood Pressure Lowering Treatment Trialists' Collaboration, BP control was comparable between CCBs and other active treatments. There were no significant differences between CCBs and other active treatments in the rates of CHD, major CV events, CV deaths, or total mortality.[127]

In recent meta-analysis of eighteen RCTs (14 dihydropyridines, 4 non-dihydropyridines) which included 141,807 participants, diuretics are preferred first-line over CCBs to optimize reduction of cardiovascular events. The review does not distinguish between CCBs, ACE inhibitors or ARBs, but does provide evidence supporting the use of CCBs over β-blockers. Many of the differences found in this current review are not robust and further trials might change the conclusions. So the authors recommended that the more well-designed RCTs studying the mortality and morbidity of patients taking CCBs as compared with other antihypertensive drug classes are needed for patients with different stages of hypertension, different ages, and with different co-morbidities such as diabetes.[128]

Considering all the evidence available today, CCBs compared with conventional antihypertensive drugs demonstrated similar blood pressure-lowering effects and similar reductions in cardiovascular morbidity and mortality, with the exception of a higher incidence of heart failure and fatal MI in some studies. However, these drugs should be considered safe for the treatment of the uncomplicated hypertensive patient in combination with other drugs. They can also be used as first-line therapy for older, stroke-prone hypertensive patients.

## Alpha$_1$ Receptor Antagonist

$\alpha_1$-adrenergic blocking drugs are effective in reducing blood pressure and do so in a fashion comparable to most other antihypertensive drug classes.[129] Initially, for many years $\alpha_1$-adrenergic antagonists had been considered suitable initial drugs for uncomplicated early-stage hypertension. But guidelines including the European Society of Hypertension/European Society of Cardiology and the authors of the JNC 7 no longer include $\alpha_1$-adrenergic antagonists as initial agents for the treatment of hypertension.[4,18] This removal of $\alpha_1$-adrenergic antagonists from initial therapy status is related to findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). In ALLHAT there was no difference in the primary outcome of fatal/nonfatal MI or all-cause mortality when the doxazosin- based regimen was compared with one utilizing chlorthalidone. But the doxazosin treatment arm of this study was terminated early due to increased CV end points in compared with chlorthalidone. There was a 19% excess stroke incidence with doxazosin and a highly significant increase (25%) in combined CV disease. There was also a 66% increase in fatal or hospitalized heart failure in the doxazosin group, which was a major contributor to the increase in combined CV disease.[130] $\alpha_1$-adrenergic antagonists may find their greatest use as add-on therapy to other antihypertensives as these compounds reduce BP significantly when added to multiple antihypertensive medication classes, oftentimes controlling BP in patients resistant to two or more therapies.[131,132]

## Other Agents

Central $\alpha_2$-agonists (clonidine, guanabenz, guanfacine, and methyldopa), vasodilators (minoxidil, diazoxide, hydralazine, sodium nitroprusside) and reserpine also come under classification of antihypertensive agent but they have limited therapeutic use. Methyldopa is a preferred drug for treatment of hypertension during pregnancy based on its effectiveness and safety for both mother and fetus.[74] Hydralazine is still widely used in developing countries due to its lower cost and in treatment of hypertensive emergencies in pregnant women (especially preeclampsia) on account of

extensive experience with the drug in that setting.[133] Minoxidil is best reserved for the treatment of severe hypertension that responds poorly to other antihypertensive medications, especially in male patients with renal insufficiency.[134]

## Current Hypertension Guidelines Recommendation

Based, in large part, on the results of ALLHAT,[59] JNC 7[4] recommends thiazide-type diuretics as initial therapy for most patients, either alone or in combination with ACE inhibitors, ARBs, β blockers, or CCBs. Since most patients will require two or more agents to achieve BP goals, ACE inhibitors, ARBs, β blockers, or CCBs are suggested as add-on therapy when needed or in combination with thiazide-type diuretics as initial therapy in the case of patients presenting with stage 2 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg). In addition, CCBs may be particularly useful in patients with comorbid Raynaud's syndrome.

The European Society of Hypertension-European Society of Cardiology guidelines, on the other hand, conclude that all major classes of antihypertensives (diuretics, β blockers, CCBs, ACE inhibitors, ARBs) are suitable for initial and maintenance therapy, either alone or in combination.[9] Like the JNC 7 Report, the World Health Organization/International Society of Hypertension statement on hypertension management recommends a thiazide diuretic as first choice in the absence of a compelling indication for another drug class. In addition, a thiazide diuretic should be a component of combination therapy in most cases. According to this group, an indication exists for initial use of DHP CCBs for isolated systolic hypertension in the elderly.[11]

## Current Challenge and Future Thought

In spite of having so many therapeutic alternatives, there is a clear need to address remaining questions regarding clinical management of hypertension. Despite use of available combination treatment, reducing SBP to <140 mmHg may be difficult or more so if the target is a reduction to <130 mmHg in patients with diabetes, target organ damage, or associated clinical conditions. Guidelines also recommend use of antihypertensive drugs in patients with grade 1 hypertension at low or moderate cardiovascular risk (BP between 140 and 159 mmHg SBP and/or 90 and 99 mmHg DBP), but benefit of treatment is not supported by clinical trial evidence.

Over the past four or five decades hypertension and cardiovascular medicine has experienced dramatic and innovative changes that have significantly reduced morbidity and mortality. But national and international guidelines dealing with the evaluation, diagnosis, and treatment of hypertension have documented the increasing prevalence of cardiac failure and end-stage renal disease, despite the continued decrease in the morbidity and mortality resulting from stroke and coronary heart disease.[4,135] Why this enigmatic occurrence takes place, despite the continued use of antihypertensive therapy, remains to be explained.

A vast array of new antihypertensive compounds has been developed that are able to affect the outcomes of many pathophysiologic mechanisms in patients with hypertension. In more recent years, much new information has appeared concerning the basis genetic and biologic mechanisms involved in cardiovascular and renal diseases. In addition, innovative approaches to drug evaluation will become elucidated through individual studies into disease and drug mechanisms.

## Conclusion

Lifestyle modifications can prevent or delay the onset of hypertension in normotensive, whereas concomitant therapy in hypertensive it can reduce BP and enhance antihypertensive drug efficacy. Findings of some of the previous clinical trials together with their easiness of administration, infrequent side effects and low price, diuretics still recommended as first suitable choice in the management of hypertension. Data on vasodilating β blockers such as carvedilol, nebivolol and celiprolol may expand the utility of β-blockers to patient populations traditionally considered not to be optimal candidates for β-blockers therapy. ACE inhibitors and ARBs are superior to other classes of agent in patients with multiple risk factors, and long-term outcome trial of aliskiren will determine its suitable place in the treatment of hypertension. Several large clinical trials and meta-analysis confirm CCBs efficacy not only in lowering blood pressure but also in reducing cardiovascular morbidity and mortality

in hypertensive patients with a normal or high cardiovascular risk profile.

## Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

## References


1. Ezzati M, Lopez AD, Rodgers A, Hoorn SV, Murray CJL and the Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet*. 2002;360:1347–60.
2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005; 365:217–23.
3. Kearney P, Whelton M, Reynolds K, Whelton P, He J. Worldwide prevalence of hypertension: a systematic review. *J Hypertens*. 2004;22:11–9.
4. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–52.
5. Luft FC. Molecular genetics of human hypertension. *J Hypertens*. 1998;16:1871–8.
6. INTERSALT Co-operative Research Group. Sodium, potassium, body mass, alcohol and blood pressure: the INTERSALT study. *J Hypertens*. 1988;6(Suppl 4):S584–6.
7. Sever PS, Poulter NR. A hypothesis for the pathogenesis of essential hypertension: the initiating factors. *J Hypertens*. 1989;7(Suppl 1):S9–12.
8. Dosh SA. The diagnosis of essential and secondary hypertension in adults. *J Fam Pract*. 2001;50:707–12.
9. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens*. 2009;27:2121–58.
10. Williams B, Poulter NR, Brown MJ, et al. the BHS guidelines working party, for the British Hypertension Society. *BMJ*. 2004;328:13.
11. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) Statement on Management of Hypertension. World Health Organization. International Society of Hypertension Writing Group. *Journal of Hypertension*. 2003;21:1983–92.
12. Ogihara T, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). Japanese Society of Hypertension Committee. *Hypertens Res*. 2009;32:3–107.
13. NICE- CG34 HYPERTENSION-Management in adults in primary care: pharmacological update. http://www.nice.org.suk/nicemedia/live/10986/30111/30111.pdf. Downloaded on October 2010.
14. Quinn RR, et al. The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension: part I—blood pressure measurement, diagnosis and assessment of risk. Canadian Hypertension Education Program. *Can J Cardiol*. 2010;26:241–8.
15. Hackam DG, et al. The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension: part 2—therapy. Canadian Hypertension Education Program. *Can J Cardiol*. 2010;26: 249–58.
16. Flack JM, Sica DA, Bakris G, et al. Management of high blood pressure in blacks. An Update of the International Society on Hypertension in Blacks (ISHIB) Consensus Statement. *Hypertension*. 2010;56:780–800.
17. Kaplan NM. The 6th joint national committee report (JNC-6): new guidelines for hypertension therapy from the USA. *Keio J Med*. 1998;47:99–105.
18. Mancia G, De Backer G, Dominiczak A, et al. Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007;25:1105–87.
19. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data of one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–13.
20. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med*. 1992;152:56–64.
21. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. *Lancet*. 1998;351:1755–62.
22. American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care*. 2003;26:S80–2.
23. National Kidney Foundation Guideline. K/DOQI clinical practice guidelines for chronic kidney diseas. Evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis*. 2002;39:S1–246.
24. ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370:829–840.
25. Heart Outcomes Prevention Evaluation (HOPE) Study investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICROHOPE substudy. *Lancet*. 2000;355:253–9.
26. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317:703–13.
27. Tuomilehto J, Rastenyte D, Birkenhäger WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med*. 1999;340:677–84.
28. Brenner BM, Cooper ME, de Zeeuw D, et al. RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–9.
29. Berthet K, Neal BC, Chalmers JP, et al. Perindopril Protection Against Recurrent Stroke Study Collaborative Group. Reductions in the risks of recurrent stroke in patients with and without diabetes: the PROGRESS trial. *Blood Press*. 2004;13:7–13.
30. PROGRESS Collaborative Study Group. Randomised trial of perindopril based blood pressure-lowering regimen among 6108 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033–41.
31. Nissen SE, Tuzcu EM, Libby P, et al. CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study—a randomized controlled trial. *JAMA*. 2004;292:2217–25.
32. Poole-Wilson PA, Lubsen J, Kirwan BA, et al. A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet*. 2004;364:849–57.
33. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet*. 2008;372:1174–83.
34. Carretero OA, Oparil S. Essential hypertension: Part II: Treatment. *Circulation*. 2000;101:446–53.
35. McCarron DA, Oparil S, Chait A, et al. Nutritional management of cardiovascular risk factors: a randomized clinical trial. *Arch Intern Med*. 1997;157:169–77.

36. Svetkey LP, Simons-Morton D, Vollmer WM, et al; for the DASH Research Group. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Arch Intern Med*. 1999;159:285–93.
37. Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure: the Trials of Hypertension Prevention, Phase II. *Arch Intern Med*. 1997;157:657–67.
38. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med*. 2001; 344:3–10.
39. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follman D, et al. Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA*. 1997;277:1624–32.
40. Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2001;38:1112–7.
41. Doll S, Paccaud F, Bovet P, Burnier M, Wietlisbach V. Body mass index, abdominal adiposity and blood pressure: consistency of their association across developing and developed countries. *Int J Obes Relat Metab Disord*. 2002;26:48–57.
42. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta analysis of randomized, controlled trials. *Ann Intern Med*. 2002;136:493–503.
43. Elliott WJ, Izzo JL. Device-guided breathing to lower blood pressure: case report and clinical overview. *Med Gen Med*. 2006;8:23.
44. McCraty R, Atkinson M, Tomasino D. Impact of a workplace stress reduction program on high blood pressure and emotional health in hypertensive employees. *Journal of Alternative and Complementary Medicine*. 2003;9:355–69.
45. Patel C. Stress management and hypertension. *Acta Physiology Scand Suppl*. 1997;640:155–7.
46. Clark MA, Hogan JW, Kviz FJ, Prohaska TR. Age and role of symptomatology in readiness to quit smoking. *Addicted Behaviors*. 1999;24:1–16.
47. Medical Research Council trial of treatment of mild hypertension: principal results. MRC Working Party. *BMJ*. 1985;291:97–104.
48. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A; FEVER Study Group. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. *J Hypertens*. 2005;23:2157–72.
49. Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. *J Hypertens*. 2009;27:923–34.
50. Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527–35.
51. Turnbull F, Neal B, Pfeffer M, et al. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-dependent and independent effects of agents that inhibit the renin–angiotensin system. *J Hypertens*. 2007;25:951–8.
52. Dahlof B, Devereux RB, Kjeldsen SE, et al; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet*. 2002;359:995–1003.
53. Dahlof B, Sever PS, Poulter NR, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.
54. William B, Poulter NR, Brown MJ. British hypertension Society. British Hypertension Society guidelines (BHS-IV). *J Fam Pract*. 2004;53:528–50.
55. Morgan TO, Anderson AI, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. *Am J Hypertens*. 2001;14:241–7.
56. Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet*. 1999;354:1751–6.
57. Garbers D, Dubois S. The molecular basis of hypertension. *Ann Rev Biochem*. 1999;68:127–55.
58. Ruddy MC. Unmet needs in managing hypertension: potential role of direct renin inhibition. *Postgraduate Medicine*. 2010;122:203–12.
59. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin converting enzyme inhibitor or calcium channel blocker versus diuretic: The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981–97.
60. Kostis JB, Wilson AC, Freudenberger RS, Cosgrove NM, Pressel SL, Davis BR. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. *Am J Cardiol*. 2005;95:29–35.
61. Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS, et al. Single-drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *N Engl J Med*. 1993;328:914–21.
62. Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Wicklund KG, Lin X, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med*. 1994;330:1852–7.
63. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369:201–7.
64. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A metaanalysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med*. 2003;115:41–6.
65. Simon A, Gariepy J, Moyse D, Levenson J. Differential effects of nifedipine and co-amilozide on the progression of early carotid wall changes. *Circulation*. 2001;103:2949–54.
66. Zanchetti A, Crepaldi G, Bond MG, et al; on behalf of PHYLLIS Investigators. Different effects of antihypertensive regimens based on fosinopril or hydrochlorothiazide with or without lipid lowering by pravastatin on progression of asymptomatic carotid atherosclerosis: principal results of PHYLLIS: a randomized double-blind trial. *Stroke*. 2004;35:2807–12.
67. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122:290–300.
68. Corrao G, Zambon A, Parodi A, et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *J Hypertens*. 2008;26:819–24.
69. Burke TA, Sturkenboom MC, Lu SE, Wentworth CE, Lin Y, Rhoads GG. Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. *J Hypertens*. 2006;24:1193–200.
70. Wright GM, Musini VM. First-line drugs for hypertension. *Cochrane Database Syst Rev*. 2009;3:CD001841. http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD001841/frame.html.
71. Jamerson K, Weber MA, Bakris GL, et al; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–28.
72. Fuchs FD. Diuretics: again the first step in the treatment of most patients with hypertension. *Curr Control Trials Cardiovasc Med*. 2001;2:244–8.
73. Buhler FR, Laragh JH, Baer L, et al. Propranolol inhibition of renin secretion: a specific approach to diagnosis and treatment of renin-dependent hypertensive disease. *N Engl J Med*. 1972;287:1209–14.
74. Hoffman BB. Therapy of hypertension. In: Goodman and Gilman, editors. *The Pharmacological Basis of Therapeutics*. 11th ed. 2006:Chapter 32.
75. Weber MA, et al. β-blockers in the treatment of hypertension: new data, new directions. *The Journal of Clinical Hypertension*. 2008;10: 238–42.
76. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet*. 2005;366:1545–53.

77. Wiysonge CSU, Bradley H, Mayosi BM, et al. Beta-blockers for hypertension. *Cochrane Database Syst Rev*. 2007;1:CD002003. http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD002003/frame.html.
78. Mancia G, Grassi G, Zanchetti A. New-onset diabetes and antihypertensive drugs. *J Hypertens*. 2006;24:3–10.
79. Bangalore S, Parkar S, Grossman E, Messerli FH. A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. *Am J Cardiol*. 2007;100:1254–62.
80. Rizos E, Bairaktari E, Kostoula A, et al. The combination of nebivolol plus pravastatin is associated with a more beneficial metabolic profile compared to that of atenolol plus pravastatin in hypertensive patients with dyslipidemia: a pilot study. *J Cardiovasc Pharmacol Ther*. 2003;8:127–34.
81. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:1665–83.
82. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med*. 2008;359:1565–76.
83. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527–35.
84. Kostis JB, Wilson AC, Freudenberger RS, Cosgrove NM, Pressel SL, Davis BR. SHEP Collaborative Research Group. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. *Am J Cardiol*. 2005;95:29–35.
85. Mozaffarian D, Marfisi R, Levantesi G, et al. Incidence of new-onset diabetes and impaired fasting glucose in patients with recent myocardial infarction and the effect of clinical and lifestyle risk factors. *Lancet*. 2007;370:667–75.
86. Alderman MH, Cohen H, Madhavan S. Diabetes and cardiovascular events in hypertensive patients. *Hypertension*. 1999;33:1130–4.
87. Boutouyrie P, Bussy C, Hayoz D, et al. Local pulse pressure and regression of arterial wall hypertrophy during long term antihypertensive treatment. *Circulation*. 2000;101:2601–6.
88. Stoschitzky K, Stoschitzky G, Brussee H, et al. Comparing beta-blocking effects of bisoprolol, carvedilol and nebivolol. *Cardiology*. 2006;106:199–206.
89. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26(3):215–25.
90. Kaplan ML, et al. 2010. Renin-angiotensin system inhibition in the treatment of hypertension. http://www.uptodate.com/patients/content/topic.do?topicKey=~cdWdWOABEbBS2t7.
91. Ram CVS. Angiotensin receptor blockers: current status and future prospects. *The American Journal of Medicine*. 2008;121:656–63.
92. Gradman AH, Schmieder RE, Lins RL, et al. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation*. 2005;111:1012–8.
93. White WB, et al. Angiotensin-converting enzyme inhibitors in the treatment of hypertension: an update. *J Clin Hypertens*. 2007;9:876–82.
94. Ibrahim MM. RAS inhibition in hypertension. *J Hum Hypertens*. 2006;20:101–8.
95. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med*. 2003;1(15):41–6.
96. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145–53.
97. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782–8.
98. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004; 351:2058–68.
99. Pitt B, O'Neill B, Feldman R, et al. The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol*. 2001;87:1058–63.
100. Pepine CJ, Probstfield JL. A HOPE for PEACE? Update on the role of ACE inhibition in CAD patients, CME monograph, UF College of Medicine. *Vasc Biol Clin Pract*. 2004:6.
101. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363: 2022–31.
102. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens*. 2003;21:875–86.
103. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–60.
104. Brenner BM, Cooper ME, De Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–9.
105. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003;362:759–66.
106. Maggioni AP, Anand I, Gottlieb SO, et al. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol*. 2002;40:1414–21.
107. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet*. 2002;360:752–60.
108. Teo K, Yusuf S, Sleight P, et al. Rationale, design, and baseline characteristics of two large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J*. 2004;148:52–61.
109. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1615–6.
110. Chrysant SG. Current status of dual renin angiotensin aldosterone system blockade for the treatment of cardiovascular diseases. *The American Journal of Cardiology*. 2010;105:849–52.
111. De la Sierra A. Main results and clinical interpretations from the TRANSCEND study. *J Hypertens Suppl*. 2009;27(2):S22–5.
112. Stanton A. Therapeutic potential of renin inhibitors in the management of cardiovascular disorders. *Am J Cardiovasc Drugs*. 2003;3:389–94.
113. Epstein BJ. Aliskiren and valsartan combination therapy for the management of hypertension. *Vasc Health Risk Manag*. 2010;6:711–22.
114. O'Brien E, Barton J, Nussberger J, et al. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. *Hypertension*. 2007;49:276–84.
115. Villamil A, Chrysant SG, Calhoun D, et al. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens*. 2007;25:217–26.
116. Littlejohn TW 3rd, Trenkwalder P, Hollanders G, Zhao Y, Liao W. Longterm safety, tolerability and efficacy of combination therapy with aliskiren and amlodipine in patients with hypertension. *Curr Med Res Opin*. 2009;25:951–9.
117. Dahlöf B, Anderson DR, Arora V, et al. Aliskiren, a direct renin inhibitor, provides antihypertensive efficacy and excellent tolerability independent of age or gender in patients with hypertension (abstr). *J Clin Hypertens*. 2007;9(Suppl A):A157.

118. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med*. 2008;358:2433–46.
119. Seed A, Gardner R, McMurray J, et al. Neurohumoral effects of the new orally active renin inhibitor, aliskiren, in chronic heart failure. *Eur J Heart Fail*. 2007;9:1120–7.
120. Basile J. The role of existing and newer calcium channel blockers in the treatment of hypertension. *J Clin Hypertens*. 2004;6:621–31.
121. Burnier M, Pruijm M, Wuerzner G. Treatment of essential hypertension with calcium channel blockers: what is the place of lercanidipine? *Expert Opin Drug Metab Toxicol*. 2009;5:981–7.
122. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–31.
123. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al; for the INVEST Investigators. A calcium antagonist vs. a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. *JAMA*. 2003;290:2805–16.
124. Black HR, Elliott WJ, Grandits G, et al; for the CONVINCE Research Group. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA*. 2003;289:2073–20.
125. Pahor M, Psaty BM, Alderman MH, et al. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomized controlled trials. *Lancet*. 2000;356:1949–54.
126. Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. *J Am Coll Cardiol*. 2002;39:315–22.
127. Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively- designed overviews of randomised trials. *Lancet*. 2003;362:1527–35.
128. Chen N, Zhou M, Yang M, et al. Calcium channel blockers versus other classes of drugs for hypertension. *Cochrane Database Syst Rev*. 2010;8:CD003654.
129. Sica DA (2005). Alpha1-adrenergic blockers: current usage considerations. *J Clin Hypertens (Greenwich)*. 2005;7:757–62.
130. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension*. 2003;42:239–46.
131. Campo C, Segura J, Roldan C, et al. Doxazosin GITS versus hydrochlorothiazide as add-on therapy in patients with uncontrolled hypertension. *Blood Press Suppl*. 2003;2:16–21.
132. Black HR. Doxazosin as combination therapy for patients with stage 1 and stage 2 hypertension. *J Cardiovasc Pharmacol*. 2003;41:866–9.
133. Kandler MR, Mah GT, Tejani AM, Stabler SN. Hydralazine for essential hypertension. *Cochrane Database Syst Rev*. 2010;8:CD004934.
134. Campese VM. Minoxidil: a review of its pharmacological properties and therapeutic use. *Drugs*. 1981;22:257–78.
135. International Society of Hypertension Writing Group. International Society of Hypertension (ISH): statement on blood pressure lowering and stroke prevention. *J Hypertens*. 2003;21:651–63.