health technology assessment

REPORT

MANAGEMENT OF MODERATELY ELEVATED BLOOD PRESSURE

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EXECUTIVE SUMMARY

1 INTRODUCTION

Hypertension is highly prevalent in both developed and developing countries. Persistent elevation of diastolic blood pressure by 5 mm Hg was associated with 34 % increased risk of stroke and a 21 % increased risk of coronary heart disease (MacMahon et al 1990). In Malaysia, it was found that many patients who have hypertension are under-diagnosed. 30% of them have never been diagnosed and present themselves to hospitals when complications arise. The findings from the National Health and Morbidity Survey are that 41% of hypertensive patients have never been on medication and present with life-threatening complications like stroke, heart disease, heart failure and kidney failure (Ministry of Health, 1997).

2. OBJECTIVES:

To study the effectiveness, safety, ethical, legal and cost implications of management of moderately elevated blood pressure

3. FINDINGS

There is sufficient evidence to indicate that moderately elevated blood pressure or mild hypertension should be diagnosed when the diastolic blood pressure is more than 90 mm Hg or systolic blood pressure exceeds 140 mm Hg.

The diagnosis of moderately elevated BP depends on the accurate measurement of blood pressure, taking into account physiological variations and other possible causes of elevated blood pressure. Individuals with borderline BP readings should have their BP monitored for at least 3-6 months before commencing therapy.

Treatment should begin with non-pharmacological interventions. There is evidence that drug therapy is beneficial in high risk subjects high normal BP of 130-139/85-89 mm Hg. However, for other patients the initiation of drug therapy will depend on the presence of risk factors, and the degree of blood pressure lowering achieved with non-pharmacological measures. These measures should be continued for at least 3 months for medium risk group patients, and for 6 months for low risk groups, before drug treatment is considered.

For non-pharmacological interventions, there is evidence of benefit of weight reduction, some evidence of benefit of sodium restriction, inconclusive evidence on potassium and calcium intake, some evidence on the benefit of a low fat diet rich in vegetables and fruits, good evidence of benefit of reduction of alcohol consumption, no evidence on benefit of stopping smoking, good evidence on benefit of exercise, and some evidence of benefit of combinations of non-pharmacological interventions.

For pharmacological treatment, diuretics, beta-blockers angiotensin-receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers have been found to be effective in the treatment of moderately elevated blood pressure.

4. RECOMMENDATION

A diagnosis of moderately elevated blood pressure or mild hypertension should be made if the systolic blood pressure exceeds 140 mm Hg or the diastolic blood pressure is more than 90 mm Hg. The blood pressure must be accurately measured, and further confirmed by monitoring the blood pressure. Management of these patients would depend on the level of blood pressure risk factors. Non-pharmacological interventions should be attempted before initiating therapy with drugs.

TABLE OF CONTENT

EXPERT COMMITTEE i
EXECUTIVE SUMMARY iii
1 INTRODUCTION 1
2 OBJECTIVES 1
3 METHODOLOGY 1
4 TECHNICAL FEATURES 2
4.1 Definition and Classification of Hypertension 2
4.2 Variation in Blood Pressure 2
4.2.1 Biological variation 2
(a) Physiological diurnal variation 2
(b) Activity related variation 3
(c) Postural adaptation 3
(d) Disease states, drug etc 3
4.2.2 Measurement variation 3
(a) White coat Hypertension 3
(b) Observer Error 3
(i) Systematic error 3
(ii) Terminal digit preference 3
(iii) Observer prejudice or bias 3
(c) Technical error 4
(d) Equipment errors 4
5 RESULTS 4
5.1 Classification, Definition And Recommendation For Initiating Drug Therapy 4
5.1.1 Joint National Committee (JNC) VII guidelines 4
(i) Definition and classification 4
(ii) Cardiovascular risk factors 5
5.1.2 World Health Organisation/International Society of Hypertension (WHO/ISH) Guidelines 6
(i) Definition and classification 6
(ii) Stratification of patients by absolute level of cardiovascular risk 7
(iii) Recommendation for initial therapy 10
5.1.3 Swedish Council on Technology Assessment in Healthcare (SBU) Health Technology Assessment on Moderately Elevated Blood Pressure 10
(i) Definition and Classification 10
(ii) Recommendation for initial therapy 10
5.1.4 British Hypertension Society Guidelines 10
(i) Definition and Classification 10
(ii) Recommendations for initial therapy 10
5.1.5 New Zealand Guidelines 11
(i) Definition and Classification 11
(ii) Recommendation for initial therapy 11
5.2 Benefits of Hypertension Therapy 12
5.3 Treatment 12
5.3.1 Non-pharmacologic management 13
(a) Weight reducation 13
(b) Mineral intake 14
Salt restriction 14
Potassium and Calcium intake 14
(c) Diet modification 14
(d) Alcohol intake 15
(e) Cessation of smoking/tobacco consumption 15
(f) Physical activity 15
(g) Combination of non-pharmacologic interventions 16
Combination of diet with exercise 16
Combination of diet with drugs 16
Combination of weight loss with sodium intake 16
Combination of reduced alcohol intake and weight loss 16
(h) Stress and relaxation 17
5.3.2 Pharmacological treatment 17
(i) Effectiveness 17
I Diuretics 17

(a) Monotherapy **17**
(b) Combination of Angiotension II receptor Blocker (ARBs) with Diuretics **17**
(c) Combination of ACE inhibitors with Diuretics **17**
(d) Cobination of calcium channel blocker with ACE inhibitors **17**
II Beta Blocker 18
III Angiotensin II Receptor (AT1 Subtyper) Blockers 18
(a) Candesrtan Cilexetil **18**
(b) Losartan **18**
(c) Telmisartan **19**
(d) Irbesartab **19**
(e) Eprosartan **19**
(f) Valsartan **20**
IV Angiotensin converting enzyme inhibitors (ACE Inhibitors) 20
(a) Enalapril **20**
(b) Ramipril **20**
(c) Benazepril **20**
(d) Imidapril **20**
(e) Quadropril **20**
(f) Trandopril **20**
(g) Lisinopril **20**
(h) Spirapril **21**
V Calcium Channel Blockers 21
(a) Amlodipine **21**
(b) Nisoldipine **21**
(c) Nifedipine **21**
(d) Reserpine **21**
(e) Barnidipine **22**
VI Alfa-1 Adrenorecptor Antagonists **22**
(a) Daxazosin **22**
(b) Terazosin **22**
(ii) Safety **22**
(a) Angiotensin II receptor blockers **22**
(b) Angiotension Converting Enzyme Inhibitors (ACE Inhibitors) **22**
(c) Calcium Channel Blockers **23**
(iii) Cost **23**
6. CONCLUSION **23**
7 RECOMMENDATION **24**
8 REFERNCES **36**

List of tables

Table 1 Classification of blood pressure for adults aged 18 and Above -JNV VII 5
Table 2 Cardiovascular risk factors 5
Table 3 Classification and Management of blood pressure for adults aged 18 years or older 6
Table 4 Definition and Classification of blood Pressure Levels (WHO/ISH) 7
Table 5 Factors influencing prognosis 8
Table 6 Stratification of risk to quantify prognosis 9
Table 7 Absolute risk and absolute treatment benefits of low to very high risk patients 9
Evidence Table 44
Appendix 1: Level of Evidence Scale 136

MANAGEMENT OF MODERATELY ELEVATED BLOOD PRESSURE

1. INTRODUCTION

Hypertension is highly prevalent in both developed and developing countries, constituting more than 30% of the adult population when a threshold value of 140/90 mm Hg is selected. In the United States, approximately 50 million (one in four) adults have hypertension. They use the medical services 50% more than normotensive individuals. Hypertension also represents one of the 3 leading causes of visits to primary healthcare centers, accounting for more than 5% of total deaths worldwide. Recent data from the Framingham Heart Study suggest that individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension (Chobanian et al, 2003).

Despite advances in detection and treatment of high blood pressure over the past 30 years, hypertension remains a source of morbidity and mortality in the United States. The presence of elevated values of both diastolic and systolic blood pressure is one of the most important risk factors for coronary heart disease, stroke and heart failure in patients with hypertension. Although pharmacological therapy is able to reduce blood pressure and decrease the risk of adverse cardiovascular events (Giannuzzi 2000). A review of nine major prospective studies with more than 420,000 subjects found that persistent elevation of diastolic blood pressure by 5 mm Hg was associated with 34 % increased risk of stroke and a 21 % increased risk of coronary heart disease (MacMahon et al 1990). In Malaysia, it was found that many patients who have hypertension are under-diagnosed. 30% of them have never been diagnosed and present themselves to hospitals when complications arise. The findings from the National Health and Morbidity Survey are that 41% of hypertensive patients have never been on medication and present with life-threatening complications like stroke, heart disease, heart failure and kidney failure (Ministry of Health, 1997).

The economic impact of hypertension is enormous - in the US it was about $US23.74 billion in 1995, and approximately $US1685 million in Spain in 1994. Direct costs contribute to more than 50% of the total costs of hypertension, of which 70% is from drug costs. There are still controversies mainly with respect to the long term versus short-term benefits of treatment of mild-to-moderate hypertension,

2. OBJECTIVES

To study the effectiveness, safety, ethical, legal and cost implications of management of moderately elevated blood pressure

3. METHODOLOGY

Electronic databases like MEDLINE, COCHRANE LIBRARY, OVID MEDSCAPE, nutritional web sites, as well as general web-sites like Yahoo were searched from 1980 to 2003, using the following keywords either singly or in combination: *Hypertension, Classification, Diagnosis, Epidemiology, Framingham Study trials in hypertension, clinical trials, treatment, race, gender, mild to moderate hypertension, borderline hypertension, non pharmacological intervention/management/approach, non drug intervention, alcohol consumption, diet, sodium intake, exercise, smoking cessation, tobacco cessation, pharmacological*

management/treatment/intervention, loop diuretic, potassium sparing diuretic, thiazide, chlorothiazide, JNC VII, beta blocker, moderate blood pressure.

In addition, hand searching was carried out of specific journals in the fields of hypertension, internal medicine, cardiovascular disease and epidemiology such as *American Journal of Hypertension, Journal of Hypertension, Circulation, Archives of Internal Medicine, Acta Med Scand, Journal of Internal Medicine, Diabetes Care, WHO Technical Report Series, American Journal of Epidemiology, Journal of Epidemiology and Community Health.*

Other than the above, the following guidelines and reports were reviewed: *Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (6th report, 1997), National Health and Morbidity Survey 1996 Malaysia, Clinical Hypertension, Norman Kaplan (6th edition), Medical Clinics of North America Essential Hypertension part 1 Sept 1997 & part 2 Nov 1997 and Cardiology Clinics Hypertension Nov 1995*, *1999 World Health Organization -International Society of Hypertension Guidelines for the Management of Hypertension*

4. TECHNICAL FEATURES

4.1. Definition and Classification of Hypertension

The threshold for hypertension can be identified by various approaches, the statistical approach based on the frequency of occurrence of high blood pressure (BP) reading in a population being one of the methods used. George Pickering as well as other authors together with studies in Bergen, Norway, Framingham, Massachusetts, Stockholm, Sweden, Tecumseh, Michigan, and Gothenburg has found that BP in a population follows a Gaussian (bell shaped) distribution. Consequently, BP readings falling beyond a certain portion of the curve, for example beyond the 95th percentile of the curve, are considered high. Another approach is using population studies, relating the level of blood pressure to increased risk of morbidity and mortality from cardiovascular diseases like coronary artery disease, stroke, as well as to total mortality. There is no clear threshold after which increased morbidity and mortality rises with increasing BP in a continuous graded curve. In most observational studies the risk curve increases somehow more over that level, therefore a diastolic blood pressure (DBP) of 90 mm Hg and Systolic blood pressure (SBP) of 140 mm Hg are chosen as the threshold for hypertension. (Collaborative Research Group, 1998; Antikainen 1998; O'Donnel 1997; Neilson 1997; Simons 1996; Kannel 1996; Howard 1995; MacMohan 1990; Selmer, 1992; Stamler 1993 1986; Lichtenstein 1985; Berglund, 1996; Shaper 1985; Svardsudd, 1997). The other method to define hypertension is by using data from clinical intervention trials to identify thresholds, by using benefits of therapy that outweigh the costs and side effects (Neaton 1993; SHEP Co operative Research Group, 1991; Dahlof 1991; MRC Working Party, 1985).

4.2 Variation in Blood Pressure

4.2.1 Biological variation

(a) Physiological diurnal variation

In normal subjects, SBP falls by an average of 16±9 mm Hg and DBP by 14± 7 mm Hg during sleep, regardless of the time of day. Blood pressure rises rapidly after waking. This "normal" adaptive response to the physiological needs of the body leads to the double- edged problem of coronary ischaemia during sleep hours, as a result of decreased perfusion pressure, and that of acute cardiovascular events during the first few hours after waking

(b) Activity related variation

There is SBP and DBP variation with both physical and mental activity and this effect is independent of the time of day at which it occurs. Whether the degree of activity related variation should be a therapeutic target is unknown

(c) Postural adaptation.

The normal adult BP rises an average of 10 – 20 mm Hg on standing. This reflects the need to measure BP with patient seated quietly for at least 5 minutes in a chair rather than on the examination table, with feet on the floor and arm supported at heart level, especially in those at risk of postural hypotension (Chobanian et al., 2003)

(d) Disease states, drugs etc.

Hypertension is occasionally caused by many primary disease states such as primary aldosteronism, phaeochromocytoma, renal parenchymal disease, renal artery stenosis, and acromegaly. Drug therapy, especially steroids, and the contraceptive pill is not uncommon, while pregnancy induced hypertension is a sub-specialty in itself. It is also noted that caffeine and tobacco cause a mild hypertensive response.

4.2.2 Measurement variation

(a) White Coat Hypertension

The blood pressure recorded may be influenced by behavioral factors that are related to the effects of the observer on the patient such as "white coat hypertension". This is a recognised phenomenon, which contributes to about 20% of labeled hypertension. It should also be noted that the white coat effect could be superimposed on bona-fide hypertensives (Redon, 1998; Staessen, 1997; White, 1993). Another widely recognised occurrence is that BP readings obtained by nurses are consistently lower than that of doctors. The presence of a physician caused an average rise of 22 /14 mm Hg in BP, and as much as 74 mm Hg in one study (Stephen, 1993).

(b) Observer Error

In 1964, Rose et al classified observer error into three categories as follows:

(i) Systematic error

Systematic errors could be intra-observer and inter-observer, and may be due to lack of concentration, poor hearing, confusion of auditory and visual cues, etc. The most important factor is failure to interpret the Korokoff sounds accurately, especially for diastolic pressure.

(ii) Terminal digit preference

This refers to the phenomenon whereby the observer rounds off the pressure reading to a digit of his or her choosing, most often to zero. It has been found that doctors have a 12-fold bias in favour of the terminal digit zero

(iii) Observer prejudice or bias

This is the practice where observers adjust the blood pressure to meet his or her preconceived notion of what the pressure should be. This usually occurs when an excess of pressure reading is recorded beyond the cut-off point for hypertension, reflecting the observer's reluctance to diagnose the individual as being hypertensive. Likewise, there might be observer bias in over-reading blood pressure to facilitate recruitment for a research project, such as a drug trial.

(c) Technical error

Technical error is use of an incorrect cuff size, in which an under-sized cuff tends to over-estimate blood pressure and gives a falsely elevated blood pressure reading, while an over-sized cuff may under- estimate blood pressure reading.

Other technical errors are the incorrect placing of the cuff, incorrect patient positioning or of the manometer in a busy clinic scenario. These may cause the values differ to depending on how much care each observer takes.

(d) Equipment errors

The mercury manometer is the most widely used device in practice and it needs regular cleaning. Dirt in the glass column can lead to "sludging" of the mercury against the column during inflation and deflation, resulting in false readings. Leaks or cracks or perishing of the rubber tubing, as well as defective control valves can cause a lack of air in the connection, leading to difficulty in controlling the mercury fall, leading to underestimation of systolic and overestimation of diastolic pressure.

The aneroid device is another new device for blood pressure reading, and this needs calibration. Compared with the mercury manometer, it frequently gives inaccurate readings.

The semi-automated electronic device is also used to measure blood pressure. It can be used for home recording by patients but this device has a fair degree of reliability.

5. RESULTS

5.1. Classification, Definition and Recommendations for Initiating Drug Therapy

Classification schemes for hypertension are helpful in defining the condition, quantitating risk factors, estimating the prognosis of disease, and guiding management**.** The continuous relationship between the level of blood pressure and the risk of cardiovascular events has been widely arbitrary in nature so that there is wide variation of the definition of hypertension by various national and international authorities. Currently the main classification schemes for hypertension are as follows:

5.1.1 Joint National Committee VII Guidelines

(i) Definition and classification

The Joint National Committee VII Guidelines (JNC VII)classification of high blood pressure for adults aged 18 and above is indicated in **table 1**. This classification is based on the mean of 2 or more properly measured seated BP readings on each of 2 or more office visits. In contrast with the classification provided in the JNC VI report, a new category designated pre-hypertension has been added, and stages 2 and 3 hypertension have been combined. Patients with pre-hypertension are at increased risk for progression to hypertension - those in the 130/80 to 139/89 mm Hg BP range are at twice the risk of developing hypertension as compared to those with lower values.

Table 1 Classification of blood pressure for adults aged 18 and above - JNC VII

BP Classification	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Normal	< 120	*and*	< 80
Pre-hypertension	120 -139	*or*	80-89
Stage 1 hypertension	140-159	*or*	90-99
Stage 2 hypertension	≥ 160	*or*	≥ 100

(ii) Cardiovascular risk factors

There is a consistent, continuous relationship between BP and risk of cardiovascular disease (CVD) events that is independent of other risk factors. The higher the BP reading, the greater the chances of getting myocardial infarction, heart failure, stroke, and kidney disease. For individuals aged 40 to 70 years, each increment of 20 mm Hg in systolic BP or 10 mm Hg in diastolic BP doubles the risk of CVD across the entire range of BP from 115/75 to 185/115 mm Hg as seen in Table 2 below:

Table 2: Cardiovascular risk factors* - JNC VII

Major Risk Factors	**Target Organ Damage**
Hypertension† Cigarette smoking Obesity (BMI 30kg/m^2) † Physical inactivity Dyslipidemia† Diabetes Mellitus† Microalbuminuria or estimated GFR < 60mL/min Age (< 55 years for men, > 65 years for women) Family history of premature cardiovascular disease (men < 55 years or women >65 years)	*Heart* Left ventricular hypertrophy Angina or prior myocardial infarction Prior coronary revascularization Heart failure *Brain* Stroke or transient ischemic attack Chronic kidney disease Peripheral arterial disease Retinopathy
** BMI indicates body mass index calculated as weight in kilograms divided by the square of height in meters; GFR , glomerular filtration rate* *†Components of the metabolic syndrome.*	

The presence of other cardiovascular risk factors like smoking, dyslipidemia, diabetes mellitus, age more than 60 years, men and postmenopausal women, family history of cardiovascular disease, women > 65 years old, or men <55 years old, target organ damage (TOD), and presence of clinical cardiovascular diseases, like left ventricular hypertrophy (LVH), angina/prior myocardial infarction, prior coronary revascularization, heart failure, stroke or transient ischemic attack, nephropathy, peripheral arterial disease and retinopathy, are also taken into consideration to assess and stratify the cardiovascular risk status in a hypertensive person. The importance of co-morbidity, risk factors and TOD are emphasized and treatment strategies recommended according to **Table 3** below**:**

Table 3: Classification and Management of blood pressure for adults aged 18 years or older - JNC VII

BP Classification	Lifestyle Modification	
		without compelling Indications
Normal	Encourage	
Prehypertension	Yes	No antihypertensive drug indicated
Stage 1 hypertension	Yes	Thiazide-type diuretics for most; may consider ACE inhibitor or ARB, β-blocker, CCB, or combination
Stage 2 hypertension	Yes	2-drug combination for most (usually thiazide-type diuretic & ACE inhibitor or ARB or β-blocker, or CCB)§

NOTE :
ACE: angiotension-converting agent; ARB: angiotensin-receptor blocker; BP: blood pressure; CCB: Calcium channel blocker
* Treatment determined by highest BP category
+ treat patients with chronic kidney disease or diabetes to BP goal of less than 130/80 mm Hg
§ Combined therapy should be used cautiously in those at risk for orthostatic hypertension

5.1.2. World Health Organization/International Society of Hypertension Guidelines

(i) Definition and classification

The World Health Organization/International Society of Hypertension Guidelines (WHO/ISH), to reduce confusion and for greater uniformity of guidelines, has adopted the definition and classification of hypertension of JNC VI. Hypertension is therefore defined as systolic blood pressure of 140 mm Hg/greater and diastolic blood pressure of 90 mm Hg/ greater in subjects who are not taking anti-hypertensive medication. The classification of blood pressure in adults over the age of 18 is provided in **Table 4.** Here, the term "Grade 1, 2 and 3 " has been chosen rather than the terms "Stage" 1, 2 and 3, as used in JNC VI

Table 4: Definitions and Classification of Blood Pressure Levels (WHO/ISH)

Category	Systolic (mm Hg)	Diastolic (mm Hg)
Optimal	< 120	< 80
Normal	<130	<85
High Normal	130-139	85-89
Grade 1 Hypertension (Mild)	140-159	
Subgroup: Borderline	140-149	90-99
Grade 2 Hypertension (Moderate)	160-179	90-94
Grade 3 Hypertension (Severe)	≥ 180	≥ 110
Isolated Systolic Hypertension	≥ 140	< 90
Subgroup : Borderline	140-149	< 90

(ii) Stratification of patients by absolute level of cardiovascular risk

Decisions on management of patients with hypertension are not based on the level of BP alone, but also on the presence of other risk factors of cardiovascular disease, concomitant diseases like diabetes, TOD and cardiovascular or renal disease and other patient's personal aspects like medical and social situations.

The main established predictors for estimate of level of cardiovascular risk are age, gender, smoking, diabetes, cholesterol, history of premature cardiovascular disease, the presence of target-organ damage and history of cardiovascular or renal disease (**Table 5).** This estimation is calculated from data on the average 10 year risk of cardiovascular death, nonfatal stroke or non-fatal myocardial infarction among participants with an average age of 60 years in the Framingham Study (Kannel 1996).

Table 5 Factors influencing prognosis (WHO/ISH)

Risk factor for CVD	(i)	Use for risk stratification
		* Level of SBP & DBP (grade 1-3)
		* Men > 55 years
		* Women > 65 years
		* Smoking
		* Total cholesterol > 6.5 mmol/l (250mg/dl)
		* Diabetes
		* Family history of premature cardiovascular disease
	(ii)	Other factors adversely influencing prognosis
		* Reduced HDK cholesterol
		* Raised LDL cholesterol
		* Micro-albuminuria in diabetes
		* Impaired glucose tolerance
		* Obesity
		* Sedentary lifestyle
		* Raised fibrinogen levels
		* High risk socio-economic group
		* High risk ethnic group
		* High risk geographic region
Target Organ Damage		* Left ventricular hypertrophy
		* Proteinuria and/ slight elevation of plasma creatinine concentration (1.2-2.0 mg/dl)
		* Ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac & femoral arteries, aorta)
		* Generalised or focal narrowing of the retinal arteries
Associated clinical conditions		*Cerebrovascular disease*
		* ischaemic stroke
		* cerebral haemorrhage
		* transient ischaemic attack
		Heart disease
		* myocardial infarction
		* angina
		* coronary revascularisationcongestive heart failure
		Renal disease
		* diabetic nephropathy
		* renal failure (plasma creatinine concentration 2.0 mg/dl)
		Vascular disease
		* dissecting aneurysm
		* symptomatic arterial disease

These absolute cardiovascular disease risks are further divided into four categories as low, medium, high and very high risk, representing a range of absolute disease risks, determined by the severity and number of risk factors present as shown in **Table 6 below:**

Table 6 Stratification of risk to quantify prognosis (WHO/ISH)

Other Risk Factors & Disease History	Blood Pressure (mm Hg)		
	Grade 1 (mild hypertension) SBP 140-159 OR DBP 90-99	**Grade 2 (moderate hypertension) SBP 160-179 OR DBP100-109**	**Grade 3 (severe hypertension) SBP>180 OR DBP >110**
I no other risk factors	Low risk	Medium risk	High risk
II 1-2 risk factors	Medium risk	Medium risk	Very high risk
III 3 or more risk factors or TOD* or diabetes	High risk	High risk	Very high risk
IV ACC*	Very high risk	Very high risk	Very high risk

Note
** TOD- Target organ damage*
**ACC- associated clinical condition including clinical cardiovascular disease or renal disease*

Each category represents a range of absolute disease risks, while the severity of hypertension and the number of risk factors present, and determine the risk of an individual. In low, medium, high and very high risk groups, the risk of a major cardiovascular event over the next 10 years is <15%, 15-20%, 20-30% and >30% respectively (**Table 7**). The estimated absolute treatment benefits range from <5 events prevented per 1000 patient years of treatment in low risk, to >17 events prevented per 1000 patient years of treatment in very high risk.

Table 7: Absolute risk and absolute treatment benefits of low to very high- risk patients (WHO/ISH)

Patient group	**Absolute risk (CVD events over 10 years)**	**Absolute treatment effects (CVD events prevented per 1000 patient-years)**	
		10/5 mm Hg (reduction BP-grade 1)	**20/10 mm Hg (reduction BP -higher grade)**
Low risk patients	<15%	<5	<9
Medium risk patients	15-20%	5-7	8-11
High risk patients	20-30%	7-10	11-17
Very high risk patients	>30%	>10	>17

(iii) Recommendations for initial therapy

The WHO/ISH Guidelines recommend that drug therapy should be initiated for patients who had been confirmed to have high BP and grouped in very high-risk groups. However, for patients in the medium and low risk groups, the initiation of drug therapy will depend on the

presence of risk factors, the degree of BP lowering achieved with lifestyle measures, and the availability of health resources. Therefore, for medium risk group patients, it is desirable to continue with lifestyle measures, and reinforce if necessary, for at least 3 months, and 6 months for low risk groups, before considering drug treatment. However, if targeted blood pressure is not achieved, drug treatment should be instituted within a 1-year period
The decision to lower the blood pressure of an individual is not based on the pressure alone, but also on the assessment of total cardiovascular risk.

5.1.3. Swedish Council on Technology Assessment in Healthcare Health Technology Assessment on Moderately Elevated Blood Pressure

(i) Definition and Classification

In 1990, the Swedish Council on Technology Assessment in Healthcare Health Technology (SBU) Health Technology Assessment on Moderately Elevated Blood Pressure (SBU, 1995), defined mild hypertension as DBP within the range of 90-104 mm Hg in individuals <70 years. However in 1993, classification was expanded to include elderly >70 years who had been diagnosed as being hypertensive if SBP>160 mm Hg and/or DBP>90 mm Hg.

(ii) Recommendation for initial therapy

The treatment goal is to reduce DBP <90 mm Hg and BP reading <160/90 mm Hg in the elderly. The aim is to prevent cardiovascular complications, and therefore all treatable risk factors like smoking, elevated lipids, diabetes etc. must be considered.
SBU recommended that treatment should begin with non- pharmacological methods for at least 3 months, followed by drug therapy, in the presence of the following conditions: (i) DBP reading >100 mm Hg, (ii) DBP> 95 mm Hg with the presence of other risk factors, (iii) SBP>180 mm Hg and/or DBP>100 mm Hg in the elderly with repeated reading of blood pressure (iv) SBP within the range of 170-180 mm Hg and DBP within range of 90-100 mm Hg in the presence of hypertension related organ involvement.

5.1.4. British Hypertension Society Guidelines

(i) Definition and Classification

The British Hypertension Society (BSH) classified BP into 3 categories, mildly elevated BP (DBP of 90-99 mm Hg), moderately elevated BP (DBP 100-109 mm Hg) and severely elevated (DBP>110 mm Hg).

(ii) Recommendations for initial therapy

BSH guidelines recommend that medication be used if DBP>100 mm Hg, despite initial non-pharmacological treatment. However, if other cardiovascular disease risk factors or organ involvement are present, medication is given even if DBP is 90-99 mm Hg.

In addition, the Systolic Hypertension in the Elderly Program (SHEP) and Medical Research Council (MRC) trials found that treatment of isolated systolic hypertension (SBP>160 mm Hg and DBP<90 mm Hg) is also beneficial in the elderly patients (SHEP Cooperative Research Group, 1991; MRC Working Party, 1985). By extrapolation, it seems reasonable to recommend that a threshold SBP of 160 mm Hg be considered for treatment in younger patients, irrespective of the DBP. Therefore the goal of treatment is get BP of <160/90 mm Hg.

5.1.5. New Zealand Guidelines.

(i) Definition and Classification

The New Zealand Guidelines focuses on the importance of considering the overall risk profile of a patient to determine treatment. In general, patients with SBP of 150-170 mm Hg or DBP of 90-100 mm Hg or both should be given treatment to lower BP if the risk of a major

cardiovascular event in 10 years is > 20%. The Framingham Heart Study demonstrates a substantial increase in the absolute risk of cardiovascular disease events in individuals with SBP > 170 mm Hg and/or DBP >100 mm Hg. It also indicates the effect of other cardiovascular risk factors, TOD and symptomatic cardiovascular disease on prognosis. Unfortunately, the value of this classification system and the recommendations on treatment that follow are weakened, because the Framingham Heart Study risk predictions may not apply to other populations, and are not universally accepted or widely known enough to be used in individualized therapy. Implementation of these recommendations could result not only in a smaller proportion of people (<60 years), especially women, receiving treatment, but also an increased proportion of older people being treated. These guidelines also require a great deal of information to be provided for each patient, and would be too complicated for use

In conclusion, mild hypertension is diagnosed when DBP>90 mm Hg and SBP> 140 mm Hg. The New Zealand and the British Hypertension Society classifications have notably higher cut off points for SBP at 150 and 160 mm Hg respectively.

(ii) Recommendations for initial therapy

Positive treatment effects have been documented in patients with DBP>90 mm Hg and SBP>140 mm Hg, or SBP>160 mm Hg in older patients. In fact, recent studies have shown lower risks of cardiovascular events in diabetics with even lower DBP<80 mm Hg (The Hypertension Optimal treatment [HOT] Study) and DBP<82 mm Hg (United Kingdom Prospective Diabetes Study [UKPDS] 38).

The mode of therapy used ranges from lifestyle changes to drug therapy, the mode chosen depending on the total risk factor profile and severity of the hypertension. On the other hand, when diabetes or target organ damage or clinical cardiovascular disease is present, drug therapy is recommended even in subjects with a high normal BP of 130-139/85-89 mm Hg. Drug therapy is also advocated for more severe grades of hypertension (BP> 160/100 mm Hg). However, before starting drug therapy in individuals with borderline BP readings, they should be followed up for at least 3-6 months to monitor the BP. Treatment should begin with non-pharmacological interventions. Medication is prescribed when DBP>95 mm Hg, despite non-pharmacological treatment, and if other risk factors or target organ damage are present. Diabetes is an exceptionally serious risk factor and warrants more aggressive lowering of the BP to levels < 130/85 mm Hg. The indications for drug therapy increase with increasing age due to the greater absolute benefits that can be achieved.

The central issue with regards to the management of moderately elevated BP is the correct diagnosis of mild hypertension. All the large RCT to date with regards to hypertension intervention have used the "spot" clinic BP reading both as target and end-point. There remains the difficult problem of over treating patients who are true "white coat" hypertensives as well as under-treating hypertensives that do not have adequate 24 hour BP control despite drug therapy.

5.2. Benefits of Hypertension Therapy

The JNC VII report indicates that antihypertensive therapy has been associated with 35% to 40% mean reduction in stroke incidence, 20% to 25% in myocardial infarction, and more than 50% in heart failure. Treating patients with stage 1 hypertension (systolic BP, 140-159 mm Hg and/or diastolic BP, 90-99 mm Hg) and additional cardiovascular risk factors, to achieve sustained 12-mm Hg decrease in systolic BP for 10 years, will prevent 1 death for every 11

patients treated. In the presence of CVD or target-organ damage, only 9 patients would require this BP reduction to prevent a death (Chobanian et al., 2003).

A randomised, single blind placebo controlled study comparing the effects of therapy of mild hypertension in 17,354 patients with propanolol and diuretics versus placebo, found that CVS event rate was 4% in the placebo group vs 3.3% in the active treatment group at the end of the study. The main reduction in events was in the incidence of stroke, although there was no difference in the overall mortality or acute myocardial infarction (AMI) rates. (MRC Working Party, 1988) Another MRC trial of hypertension in older adults showed that active therapy of **Amiloride / Hydrochlorthiazide (HCTZ**) reduced both BP and clinical events like stroke, AMI and mortality by 25%, 19% and 17% respectively (MRC, 1992). A Swedish Trial in old patients with hypertension (STOP), showed that active therapy (diuretics and/ or beta blockers) reduce DBP more than placebo with a corresponding 40% reduction in CVS events and 43% reduction in mortality (Hanson 1991)

It was found in the HOT Trial that there was 43% reduction in strokes, and overall major CVS events by 15%, although the risk reduction in AMI was of borderline significance (Hansson 1998). Another study by the European Working Party on High Blood Pressure in the elderly (EWPHE) found that the overall mortality was the same, although the CVS mortality and particularly, stroke rate was reduced (Amery 1991). The Shanghai Trial of Nifedipine in the Elderly (STONE) found that total CVS events were reduced by 62%, the main reduction occurring in strokes, and although mortality was reduced, it did not reach statistical significance (Gong 1996). A 2 year SYS-Euro Trial demonstrated that SBP had fallen by 23 mm Hg with a corresponding fall of 42% in the stroke rate translating to a stroke rate of 13 per 1000 patient years, but the mortality rate was not significantly reduced (Staessen 1997) A meta-analysis by the Individual Data Analysis of Antihypertensive intervention trials (INDANA) Project Collaborators found that recurrence of stroke (fatal and nonfatal), was significantly reduced in active groups compared with controls. In addition, blood pressure lowering drug interventions reduced the risk of stroke recurrence in stroke survivors (Gueyffier, 1997). However, the Captopril Prevention Project (CAPPP) Trial found that overall CVS events were similar in both groups with greater cardiovascular protection with Captopril, although conventional therapy reduced strokes compared with ACE inhibitors. The protective effect of Captopril was most marked in patients with diabetes (Hansson et al., 1999).

5.3. Treatment

The goal of treatment inpatients with hypertension is to reduce blood pressure to a level where there is decreased risk of complications. Treatment of blood pressure encompasses non-pharmacological and pharmacological management, which may occur at home with close supervision by the health care provider, or in hospital.

5.3.1 Non-pharmacologic management

The non-pharmacologic therapy refers to non-drug interventions used in the management of hypertension, basically being synonymous with the interventions included under lifestyle modifications. These lifestyle modifications can at times be applied to the entire population, which do not require active participation of individual (JNC VI 1997; Chobanian et al, 2003).

Currently, the lifestyle modifications below are included in the non-pharmacologic approaches to the management of hypertension (JNV VI 1997; Reisin,1997; Chobanian et al, 2003).

(a) Weight reduction

Several epidemiological studies have revealed a close linkage between obesity and hypertension. Moreover, longitudinal studies have pointed to an increased prevalence of hypertension as weight and age increase (Frohlich 1983; Stamler 1978; Hsu, 1977). The pattern of deposition of excess fat, especially in the upper part of the body resulting in increase in the waist circumference of 85cm or greater in women, and 98cm or greater in men, has been shown to be a risk factor for hypertension (Pouliot 1994). BMI of 27 or greater was also associated with hypertension (JNC VI, 1997). Several studies have shown that weight loss by itself causes a drop in blood pressure (Ohashi et al 2001; Davis 1993; Schotte, 1990; MacMahon, 1986; Reisin 1982; 1978). A meta analysis found changes of about 5.2 mm Hg in mean systolic blood pressure with weight loss (Ebrahim 1998). A weight loss of 10kg was found to normalise blood pressure in 75% of obese hypertensive patients, and by maintaining their weight reduction for a year, they were able to maintain their blood pressure at the level of 140/90mm Hg (Reisin 1982).

The Dietary Intervention Study in Hypertension (DISH) found that weight loss of an average of 4.5kg without taking anti-hypertensive medication can normalise blood pressure in 60% of obese hypertensives (Langford 1985). The Trial on Anti-hypertensive Interventions and Management (TAIM) demonstrated that weight reduction by dietary intervention is an effective modality to maintain blood pressure in the normal range in overweight persons with mild hypertension (Davis 1993). It was also found that even obese patients who could not achieve or maintain their ideal body weight, but weight loss of 4.5kg had a positive effect on their blood pressure profile (Mertens 2000; Whelton et al 1998; JNC VI, 1997; Neaton 1993). In addition, people who lost at least 4.5 kg in 6 months and who had maintained this weight reduction for the next 30 months, had the greatest reduction in blood pressure (Steven, 2001). It was also found that maintaining BMI in the range of 18.5-24.9 was able to reduce systolic blood pressure approximately 5-20 mm Hg per 10 kg weight loss (Chobanian et al., 2003). A Cochrane Review found that the ranges of 3-9% of body weight are probably associated with modest blood pressure decrease of roughly 3 mm Hg systolic and diastolic (Brand,1998; Mulrow 2000; 2002), while a weight loss of 10% resulted in substantial improvement in BP (Kriketos 2001). The decrease in blood pressure could be sustained over the long term when lower weight is maintained (Reisin 1997). In patients who had maintained their weight reduction for a year, the systolic and diastolic blood pressure was found to be ≤ 140mm Hg and 90mm Hg respectively (Reisin 1982). A similar finding of lowered blood pressure if reduced body weight was maintained for one year was obtained in mild hypertensive obese subjects (Himeno 1999). Apart from this, it has also been found that even without changes in body weight, decreased percentage of body fat can decrease blood pressure significantly (Wada 1998).

A study of serotonergic agents, like Fenfluramine and Dexfenfluramine have been shown to cause a significant drop in systolic blood pressure (Weintraub 1992). Another study found that there is a significant reduction in systolic and diastolic blood pressure in patients treated with Dexfenfluramine for 6 months (O'Connor 1995). However, the safety profile of the currently available anorectic agents has not been proven, since some of these agents have been associated with an increase in blood pressure, valvular heart disease and pulmonary hypertension (Connolly 1997; Abenhaim 1996).

(b) Mineral intake

Salt restriction

There is a lot of debate on salt restriction in the management of blood pressure. Some studies show a direct relationship between sodium intake and the prevalence of hypertension (Cutler

1997), but others have pointed out the limitation of these studies that did not take other factors like weight and stress into consideration in arriving at their conclusions (Krotkieeski 1983). Another meta analysis concluded that mean systolic blood pressure changes by - 2.9 mm Hg with salt restriction (Ebrahim 1998). It has also been found that blood pressure was lowered due to sodium restriction (Conlin, 2001). Reducing daily salt intake to 5 g can also bring about a measurable reduction in blood pressure (Bonner, 1999; Korhonen, 1999). It was also found that reducing dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g sodium chloride) will reduce systolic BP to approximately 2-8 mm Hg (Chobanian et al., 2003)

However, one study found that salt reduction does not seem to the effect size when combined with other non-pharmacological interventions, and thus it has been suggested that dietary salt restriction should not be a basic component of anti-hypertensive therapy (Graudal 2000). This finding was support by a review that salt restriction may only be effective in blood pressure control in salt-sensitive individuals (Reisin, 1997). In fact, one observational study did suggest an adverse outcome in patients who were on salt restriction, but others were not able to verify this finding (Alderman et al., 1995)

A randomized controlled trial of 875 men and women with BP < than 145/85 mm Hg on antihypertensive drugs, found that by reducing sodium intake, antihypertensive drug therapy could be stopped in 92% subjects. However, only 38% were able to maintain BP less than 150/90 mm Hg after 30 months without presence of CVD (Whelton et al., 1998). A meta analysis of 56 randomized controlled trials found that sodium reduction can lower BP in hypertension trials, however sodium restriction may be effective for older hypertensives, but this is not supported as a universal recommendation (Midgley, 1996).

Potassium and Calcium intake

Epidemiological studies have shown that while we tend to excessive salt intake has been blamed as a major risk factor for hypertension, it is equally important to note that a diet poor in potassium and calcium may also contribute to the pathogenesis of hypertension (Ram 1981). Bearing in mind that potassium-rich foods can be expensive and can be easily lost if over cooked, the recommendation is to increase intake of fresh vegetables and fruits. A study done in China found that potassium was associated with a significant systolic BP reduction but not diastolic BP (Gu et al., 2001).

(c) Diet modification

It has been suggested that a diet rich in fruits, vegetables and low in fats may become first line treatment in hypertension, as this type of diet has been shown to cause a drop in both the systolic and diastolic blood pressure by 11.4mm Hg and 5.5 mm Hg respectively which is similar to the effect of single drug therapy (Peterson, 1998, Appel 1997).

A randomized controlled trial of the dietary approaches to stop hypertension (DASH) demonstrated that the combination diet (food rich in fruits, vegetables and low fat diary products, and low in total and saturated fat) is effective in lowering blood pressure of patients with high-normal or stage 1 hypertension. The DASH diet (rich in fruits and vegetables, potassium and calcium) has also been found to reduce systolic diastolic blood pressure (Kolasa,1999, Chobanian et al 2003). Another study found this reduction is more pronounced in those patients with high blood pressure (Conlin, 1999)

(d) Alcohol intake

Alcohol is an important factor in worsening of blood pressure (Stamler 1997). Moreover, alcohol also predisposes to strokes (Puddey et al., 1992). Further it causes resistance to antihypertensive medication (Gill et al., 1991).

A reduction in alcohol intake range from 1.3 - 5.7 drinks/day had resulting in significant reduction in SBP and DBP ranging from 0.9-8mm Hg/ 0.6 -6 mm Hg respectively (Rakic 1998; Cushman,1998; Puddey 1992; 1987; Parker 1994; Ueshima 1987; Puddey 1987). It was also shown that limiting consumption to not more than 2 drinks per day in most men and not more than 1 drink per day in women and lighter weight persons brings about a reduction of systolic BP of 2-8 mm Hg (Chobanian et al., 2003). Another study also found that reduction of alcohol intake can reduce 5 mm Hg and 3 mm Hg in systolic pressure and diastolic blood pressure respectively, which is unrelated to weight loss (Puddey 1992). A meta analysis of randomized controlled trials on the effect of alcohol reduction on blood pressure, also found that alcohol reduction was associated with significant reduction in mean systolic and diastolic blood pressure (Xin 2001). While some workers have shown that less than 15ml of ethanol per day may be associated with a low risk for coronary events, generally it has been suggested that alcohol consumption be discouraged or at least limited to less than 30ml of ethanol per day, where total abstinence is not possible (JNC VI, 1997).

(e) Cessation of smoking/tobacco consumption

Paradoxically, large epidemiologic studies have shown that smokers tend to have lower blood pressure than non-smokers (Green 1986). It has also been found that smoking cessation does not appear to have any positive effect on blood pressure (Green & Harah, 1995). Nevertheless, smoking is a major risk factor for coronary artery disease and avoidance of tobacco in any form is essential for the prevention of coronary heart disease ((JNVC VI, 1997).

While it has been found that there is higher increment in both systolic and diastolic blood pressure in those who had quit for >/= 1 year than current smokers, that there is progressive increase in blood pressure with prolongation of cessation in men, thus cessation of smoking may result in increases in blood pressure (Lee 2001). Another study found that smoking cessation has not been proven to decrease blood pressure levels but should nonetheless be recommended due to favourable effects on cardiovascular morbidity and mortality (Reisin 1997).

(f) Physical activity

Epidemiological studies suggest an inverse relationship between physical activity or fitness, and blood pressure. A meta-analysis of 48 studies found that heavy-intensity exercise training three times a week resulted in an average drop of 5.3 mm Hg and 4.8 mm Hg in systolic and diastolic pressures respectively (Fagard, 1995). Vigorous exercise like riding a bicycle ergometer at 60- 70 % of maximum work capacity for 45 minutes 7 times a week can lower systolic blood pressure by 16 mm Hg and diastolic by11 mm Hg. If the activity is carried out 3 times a week, it reduces systolic blood pressure by 11 mm Hg and diastolic pressure by 9 mm Hg (Nelson et al., 1986; Jenings, 1987). It was also found that engaging in regular aerobic physical activities such as brisk walking at least 30 minutes per day on most days of the week shows a reduction on systolic BP approximately 4-9 mm Hg (Chobanian et al., 2003)

However, low intensity endurance exercise appears to be effective in reducing blood pressure in elderly patients with moderate hypertension (Ehsani, 2001). Moderate intensity exercise appears to be as effective as high intensity training for reducing blood pressure (Hagberg, 2000, Kokkinos, 2000). Canadian guidelines on prevention of hypertension also indicate that moderate exercise 3 to 4 times per week for 50-60 minutes can reduce blood pressure more

effectively compared to vigorous exercise (Cleroux 1999). In one study it was found that physical exercise for 60 minutes 3 times a week for 10 weeks reduced blood pressure by 6-11 mm Hg (Uehara 1997). While the effect of exercise on blood pressure varies according to the intensity and duration of training bouts, moderate exercise levels may be optimal, and walking has also been found to be effective (Kingwell et al., 1993). A review of 15 studies indicate that exercise training decreases systolic and diastolic blood pressure on an average by 11 and 8 mmHg respectively (Hagberg et al., 2000). There is also other evidence that regular exercise can reduce blood pressure (Kokkinos 1995; Paffenbarger 1993) However, dynamic exercise is effective in lowering blood pressure only if it is performed regularly (Orbach 1998)

(g) Combinations of non-pharmacological interventions

combination of diet with exercise

One study found that a combined exercise training and dietary program could lower BP in patients with mild to moderate hypertension, but its long-term consequences on morbidity and mortality remain to be determined (Hoque 1998). Another study found that while exercise alone can lower blood pressure somewhat, when combined with weight reduction, blood pressure was substantially reduced (Reid,1994)

Combination of diet with drugs

The Anti-hypertensive Interventions and Management (TAIM) Trial demonstrated that weight reduction by dietary intervention in combination with diuretics or β- blockers is effective in maintaining blood pressure in the normal range in overweight persons with mild hypertension (Davis 1993). Moderate restriction in sodium combined with diuretics has been found to be effective and safe in managing hypertension (Ram 1981). A randomised control trial found that moderate salt reduction in the presence of ACE inhibitor is effective in lowering blood pressure (Singer 1995)

Combination of weight loss with sodium intake

Lowered sodium level (1500mg/d) coupled with the DASH diet has been found to decrease systolic BP when compared to the high sodium diet control alone (Fasc 2000)

Combination of reduced alcohol intake and weight loss

With reduction of alcohol intake combined with weight loss, it has been found that a decline of up to 10 mm Hg in systolic blood pressure and 7.5 mm Hg in diastolic pressure may occur. (Puddey et al., 1992)

(h) Stress and relaxation

There is no hard data at present to support the use of relaxation therapies to prevent or treat hypertension (JNC VI, 1997).

5.3.2. Pharmacological treatment

(i)Effectiveness

I Diuretics

(a) Monotherapy

A randomised control trial found that a combination of **amiloride** and **spironolactone** lowered SBP by ±1.6 mm Hg and DBP by ±1.2mm Hg, whereas either drug alone had no significant effect on BP (Pratt et al., 2001). Low dose hydrochlorothiazide is not recommended as monotherapy for patient with mild to moderate hypertension due to the fact that BP lowering effect is already attenuated at 6 months (Radevski et al., 2000). The Eurevie Study found that the loop diuretic piretanide 6 mg to be a potent antihypertensive drug without significant effect on serum electrolytes, plasma glucose and lipids (Charansonney et al., 1997).

(b) Combination of Angiotensin II Receptor Blockers (ARBs) with Diuretics

A combination of **Valsartan /hydrchlorothiazide (HCTZ)** was found to effectively lower blood pressure and was also well tolerated (Palatini et al., 2001).The combination of **Losartan and hydrochlorothiazide** was found to be significantly better in lowering blood pressure than monotherapy (Fasce et al., 1999; Manolis et al., 2000; Flack et al., 2001). It was also found that a fixed dose of **Losartan** combined with **HCTZ** is comparable to other classes of antihypertensive drugs in combination with **HCTZ** in lowering blood pressure in mild to moderate hypertension (Benedict, 2000). A combination of **Telmisartan 80mg/HCTZ** 12.5 mg was found to be more effective in reducing supine trough DBP and supine trough SBP than **Telmisartan** 40mg/**HCTZ** 12.5 mg (McGill & Reilly, 2001). **Irbesartan plus HCTZ** combined produced a greater reduction in BP than either drug alone (Kocher et al., 1999).

(c) Combination of ACE Inhibitors with Diuretics

A combination of **hydrochlorthiazide** with **angiotension-converting enzyme (ACE) inhibitor** was found to maintain antihypentensive effect up to 9 months (Radevski 2000). The reduction of both sitting and standing diastolic and systolic blood was found to be more pronounced with **Enalapril** combined with **HCTZ** than **atenolol,** achieving the targeted diastolic blood pressure < 90 mmHg (Os et al., 1997). **Quinapril** combined with **HCTZ** maintained its antihypertensive effect for up to 9 months (Radevski et al., 2000). Another study found that **Captopril** and **HCTZ** progressively reduced systolic and diastolic blood pressure (Santello, 1998). A randomised controlled trial found that a low dose combination of **perindopril** 2mg/**indapamide** 0.625 mg use as first line treatment for elderly over 1 year result in sustained blood pressure control (Chalmers et al., 2000). A study of combined antihypertensive therapy of **lisinopril** with **thiazide** diuretic in patients with essential hypertension found that it effectively lowered blood pressure (Ishimitsu et al., 1997)

(d) Combination of calcium channel blockers with ACE inhibitors

The combination of **nitrendipine** and **enalapril** was found to be superior to both monotherapies, in reducing mean and diastolic blood pressure (Roca-Cuschs et al., 2001). Another study found that a combination of **amlodipine** with **lisinopril** lowered blood pressure effectively (Naidu et al., 2000). **Nisoldipine** and **lisinopril** was found to be effective in controlling blood pressure in patients not controlled by monotherapy (Ruddy et al., 1997).

II Beta Blockers

The Joint National Committee (JNC) VII report found that beta blockers lower BP and will also reduce all the complications of hypertension (Chobanian et al., 2003). It has also been shown that beta blockers are effective as monotherapy (Pieniazek, Franczuk & Janicki, 2001). Beta-blockers have been shown to possess a satisfactory hypotensive effect without any adverse effects on glucose metabolism for long-term use (Owada et al., 2001). The Canadian recommendations for management of hypertension recommend that for adults less than 60 years of age with uncomplicated hypertension, the choice of initial therapy should be monotherapy with a thiazide diuretic, preferably at a low dose, or a ß-adrenergic antagonist. If the response is inadequate or there are adverse effects, another drug from the initial drug therapy group should be substituted. It is also recommended that combination therapy, with a thiazide diuretic and a ß- adrenergic antagonist should be used if there is only a partial response to monotherapy. For uncomplicated hypertension without contraindications in patients over the age of 60 years, beta blockers are not recommended as first line therapy, although ß-adrenergic antagonists may be useful as adjunctive therapy in elderly patients taking diuretics. It was also found that the benefits of ß-adrenergic antagonist therapy in hypertensive smokers remain uncertain, and are thus not recommended in the absence of target-organ damage or concurrent cardiovascular disease, in hypertensive patients who smoke (Feldman et al., 1999). The WHO/ISH Guidelines show that beta blockers are safe and effective for use as monotherapy or in combination with diuretics, dihydropyridine calcium antagonists and alpha blockers. Although it has been found that the standard dose of beta blocker is contraindicated in heart failure, however, there is emerging evidence that they may have a beneficial effect when used in very low starting doses in some of these patients. Beta blockers should be avoided in patients with obstructive airway disease & peripheral vascular disease (1999 WHO/ISH Guidelines).

III Angiotensin II Receptor (AT1 Subtype) Blockers

(a) Candesartan Cilexetil

Candesartan Cilexetil either alone or as add on therapy was found to reduce mean SBP/DBP by 18.7 mm Hg /13.1 mm Hg respectively(Weir et al., 2001)). Another study showed that a once daily dose of **Candesartan Cixeletil** effectively lowered blood pressure, and maintained its antihypertensive effect over a long period (Server, 1997). **Candesartan Cilexetil** added to other drugs like diuretics, calcium channel blockers, beta blockers, ACE inhibitors and alpha blockers was found to consistently reduce SBP/DBP.(Weir et al., 2001). One study found that **Candesartan Cilexetil** was as effective as **enalapril**, **almodipine** or **HCTZ**, (Kloner et al., 2001) while it was also found to lower seated blood pressure more than **enalapril** or **HCTZ** (Malmqvist et al., 2000). Another multicentre study found that **candesartan cixeletil** effectively lowered blood pressure more than **enalapril** at trough and on the following day after last dose (Himmelmann et al., 2001). **Candesartan** was also found to be more effective than **losartan** (Sever, 1997), and as effective as **amlodipine** in reducing systolic and diastolic BP, and controlled diastolic BP <90 mm Hg (Kloner et al., 2001).

(b) Losartan

A double blind randomised trial found that **Losartan** monotherapy was effectively in lowering SBP and DBP (Flack et al., 2001), while another study found that blood pressure was normalized with a daily dose of **losartan** (Zimlichman,1999).

Comparing the effectiveness of **losartan** with other classes of antihypertensives, **Losartan** effectively reduced DBP more than **enalapril** in a randomized controlled trial (Shobha et al., 2000). Another randomized controlled trial found that daily **Losartan** administration is effective in reducing blood pressure and is better tolerated than ER **Felodipine** (Hung et al.,

1999). A daily dose of **Losartan** was also found to effectively lower DBP and SBP as well as **Valsartan** (Elliott et al., 2001). In addition, **losartan** has been found to be as effective as **candesartan** in reducing DBP and SBP (Monalis, 2000; Monterroso et al., 2000; Hedner et al., 1999). A daily dose of **losartan** had greater antihypertensive effect than a daily dose of captopril (Roca-Cusachs et al., 1997).

(c) Telmisartan

The TEES Study on efficacy and safety of **telmisartan** compared with **enalapril** in elderly patients with primary hypertension found a reduction in mean supine diastolic blood pressure and supine systolic blood pressure (Karlberg et al., 1999). Another study found a reduction in SBP of 10 mm Hg or more in 80% of patients treated with **telmisartan** (Fretag, 2001). However, while there is reduction in blood pressure in all doses of **telmisartan**, it did not produce a first dose effect (Smith et al., 2000). The long duration of action of **telmisartan** was able to consistently control and sustains blood pressure over 24 hours and during the last 6 hours of the dosing interval (Littlejohn et al., 2000). Another randomised study of patients using **telmisartan** as monotherapy found that in 67% of patients DBP was under control(< 90mm Hg) (Neutal et al., 1999). It was also found that **telmisartan** 80 mg produced a greater reduction in both SBP and DBP over a 24 hour period, while **telmisartan** 40 mg reduced SBP and DBP only during the night (Mallion, 1999).

The reduction of blood pressure, including the 24 hour mean blood pressure, with **telmisartan** 40 mg and 80 mg was found to be greater than **losartan** 50 mg (Mallion, 1999). **Telmisartan** 40-160 mg was as effective as **atenolol** 50-100 mg or **lisinopril** 10 to 40 mg in significantly reducing systolic and diastolic blood pressure.; **Telmisartan** 80mg/day is more effective than **enalapril** 20mg/day, and a daily dose of **telmisartan** provided better control of diastolic BP for full dosing interval than **losartan** 50 mg or **amlodipine** 5 or 10 mg. (McClellan et al., 1998).

(d) Irbesartan

Irbesartan has been found to reduce effectively lower blood pressure, the sitting DBP 9.6 mm Hg from baseline and the sitting SBP by 10.1 mm Hg (Lacourciere, 2000). A daily dose of 150 mg to 300 mg reduces trough seated blood pressure and diastolic blood pressure (Chiou 2000). It also found in 7 RCT that the use of **irbesartan** was associated with significant reduction of incidence of headache (Hanson et al., 2000).

In a study comparing **irbesartan** and **losartan**, it was found that **irbesartan** lowers the mean SeDBP more than **losartan** (Oparil et al., 1998), similarly **irbesartan** 300 mg reducing trough SeDBP and SeSBP more than **losartan** 100mg, although there was no difference between **irbesartan** 150mg and **losartan** 100 mg (Kassler-Taub, 1998). Similar findings were obtained in a review where a daily dose of **irbesartan** 150-300 mg effectively controlled and reduced 24 hour BP similar to **enalapril**, **atenolol** and **losartan** (Gillis et al., 1997)

(e) Eprosartan

A daily dose of **Eprosartan** was found to maintain blood pressure for up to 24 months (Levine, 2001). It was also found in a review that **eprosartan** 400 - 800 mg/day either as a single daily dose or in 2 divided doses, can reduce trough sitting systolic blood pressure by 6.3 - 15 mm Hg and diastolic blood pressure by 4.1 - 9.7 mm Hg (Plosker, 2000).

(f) Valsartan

Studies have found that **valsartan** 40-80 mg inhibits the pressor of angiotensin II for 24 hours (McInnes, 1999), there is good or satisfactory hypotensive effect with daily dose of 80 -160 mg

valsartan (Ivleve Ala et al., 1999), it consistently reduces blood pressure over 24 hours and up to 36 hours after dosing in those who missed the dose (Lasko et al., 2001) and at 4 and 8 weeks compared to placebo (Hedner et al., 1999). It has also been found the **valsartan** 80 mg reduces the clinic sitting systolic and diastolic blood pressure at 2, 4 and 6 weeks (Monterroso et al., 2000; Botero et al., 2000). It has also been found that treatment with **valsartan** for 2 weeks resulted in a significant fall in both systolic and diastolic blood pressure; this hypotensive effect was enhanced with 8 weeks treatment (Zakirova et al., 1997).

IV Angiotensin converting enzyme inhibitors (ACE Inhibitors)

(a) Enalapril

Various studies found that **enalapril** significantly reduces systolic and diastolic blood pressure (Cuocolo et al., 1999) by 10 mm Hg and 5 mm Hg respectively in one study (Dziak 1999), while other studies found that it reduces SBP in the range of 5.0 - 14.8 mm Hg and DBP by 10.1 - 20.1 mm Hg. (Smith et al., 2000; Lacouciere 2000; Botero et al, 2000; Chiou et al, 2000;Gtuitard et al, 1997; Karlberg et al, 1999). Another randomised controlled trial found that **enalapril** 10-20 mg lowers seated blood pressure by 12/8 mm Hg at 6 weeks and 13/9 mm Hg at 12 weeks treatment while 51 % of patients achieve DBP < 90 mm Hg after 12 weeks treatment (Malmqvisk et al, 2000). **Enalapril** 20 mg twice daily produced significant reductions in arterial pressure at rest and during exercise by 8 weeks' treatment which was maintained during 5 years treatment (Gonzalez-Juanatey, 1995).

(b) Rimipril

A randomised controlled trial found that **rimipril** was able to lower systolic and diastolic blood pressure for a 24 hour period (Kukushkin et al, 1998).

(c) Benazepril

Benazepril decreased mean sitting DBP from 100.5 ± 5.5 to 86.7 ± 7.5 mm Hg at 4 weeks and 82.5 ± 6.5 mm Hg at 8 weeks, while SBP was lowered from 169.5 to 150.5 ± 13.1 mm and to 145.0 ± 10.9 mm Hg (Hazizi et al, 1998).

(d) Imidapril

The administration of **Imidapril** 5-10 mg /day resulted in clinical decrease in blood pressure after 2 weeks treatment (van der Does & Euler, 2001), while it was also found to reduce sitting systolic blood pressure and standing blood pressure (Dews & VandenBurg, 2001).

(e) Quadropril

Quadropril once daily resulted in a reduction of systolic and diastolic blood pressure and this hypotensive effect remained stable (Shal'nova et al, 2000).

(f) Trandopril

It has been found that **trandopril** 2 mg/day significantly reduces both systolic and diastolic pressure, and hypotensive effect was maintained for 24 hours. (Kohlmann , Jardim & Orgman, 1999).

(g) Lisinopril

A randomised controlled trial demonstrated that **lisinopril** produced constant blood pressure lowering effect and maintained circadian rhythm in a 24 hour period (Ruddy & Fodor 1997), while another trial found that 10 mg **Lisinopril** given as monotherapy was able to achieve target blood pressure (Oi'binskaia et al, 1999). It was also found that DBP of most patients was able to be controlled with **Lisinopril** (Neutel 1999), and **Lisinopril** once daily was able to

achieve a diastolic blood pressure of 90 mmHg or less (Abengowe, Exedinchi & Balogun, 1997).

(h) Spirapril

Spirapril 6 mg once daily as initial or maintenance dose resulted in reduction SBP at both peak and trough (Guitard et al, 1997), and was effective in lowering blood pressure, although a dosage of 1-4 mg/day was less effective (Hayduk et al, 1999)

V Calcium Channel Blockers

(a) Amlodipine

It has been found that **Amlodipine** 5 mg daily reduced systolic BP and achieved diastolic BP < 90 mm Hg (Kloner et al., 2001;Whitcomb et al., 2000; Sowunmi et al, 1996)., although in one trial the anithypertensive effect decreased by the 8th week of therapy (Shal'nova et al, 2000). The reduction in BP as found to be greater in younger patients and in those with BMI > 30 kg/m^2 (Yosefy et al, 1999). **Amlodipine** 10 mg given as monotherapy was able to achieve target blood pressure (Naidu 2000). There was a decrease in seated systolic and diastolic blood pressure by 23/17, after 8 weeks of treatment with **Amlodipine** and blood pressure was controlled to 90 mmHg or 10 mmHg or less from the baseline (Cheung, Lau & Wu, 1998). A RCT in patients with mild to moderate hypertension found that there is benefit only by increasing the dose after 6 weeks of treatment (Hayduk, Adamezak & Nowitzki, 1999).

A randomised controlled trial comparing **Amlodipine** and long acting diltiazem in treatment of mild or moderate hypertension indicated that **Amlodipine** caused greater reduction in sitting and standing systolic and also diastolic pressure, and 24 h ambulatory systolic and diastolic pressure than diltiazem (Horwitz, Weinberger & Clegg, 1997). Compared with **Felodipine**, patients on **Amlodipine** has significantly greater fall in systolic ambulatory BP although there was no difference in diastolic ambulatory BP (Hoegholm et al, 1995).

(b) Nisoldipine

A study found that **Nisoldipine** reduces mean, systolic and diastolic blood pressure (Whitcomb, et al, 2000), and it produced 24 h period constant blood pressure lowering effect and maintained the circadian rhythm (Ruddy & Fodor, 1997)

Nisoldipine was found to demonstrate similar antihypertensive efficacy as **HCTZ** in mild to moderate hypertension (Fodor, 1997)

(c) Nifedipine

Nifedipine was found to be effective in lowering SBP and DBP (Manyemba, 1997), the effect lasts over 24 hours (Toal, 1997), and it also induced regression in ventricular hypertrophy (Lopez et al, 1997).

A randomised cross over study comparison of **Nifedipine** and **Felodipine** with 24 hour ambulatory blood pressure found that both drugs had a similar antihypertensive effect (Tverner, Marley & Tonkin, 1999).

(d) Reserpine

An open randomised crossover drug trial found that **Reserpine** reduced SBP by 15.9 mm Hg and DBP by 11.1mm Hg. (Manyemba, 1997)

(e). Barnidipine

Barnidipine has been found to be effective in controlling blood pressure (Kalke et al, 1999), and the antihypertensive effect is durable (Nakajima, Akioka & Miyazaki, 2000). It has also been found that **Benidipine** also increases urinary sodium excretion (Ohya et al, 2000)

VI Alfa –1 Adrenorecptor Antagonists

(a) Daxazosin

A clinical trial found that **Doxazosin** reduced supine and standing blood pressure (Sanz Guajardo et al, 1997), and another study found that it achieved the target BP (Os et al, 1999).

(b) Terazosin

A multicentre randomised controlled trial found that there was a strong dose-response relationship between fall in blood pressure and the **Terazosin** dose, as well as a plateau of response for **Terazosin** doses above 10 mg, so that the maximum antihypertensive response was 10.7 mmHg for systolic and 8.0 mm Hg for diastolic blood pressure (Achari et al, 2000).

(ii) Safety

(a) Angiotensin II receptor blockers

The adverse event rates for angiotension receptor blockers were low.. The most common adverse effects of **Candesartan Cilexetil** are headache and dizziness, and rare serious adverse effects like orthostatic hypotension (Weir et al, 2001). Other adverse events, appear during the first 3 months but decrease steadily with time (Sever & Holzgreve, 1999). As for **Losartan** most of the adverse effects were effects like headache and dizziness (Freytag et al, 2001; Manolis et al, 2000; Shoba et al, 2000; Zimlichman, 1999; Hedner et al, 1999; Roca-Cusachs et al, 1997). There were no severe adverse effects like peripheral oedema reported with **Telmisartan** compared to **Amlodipine** treated patients (Kloner et al, 2001), but mild or moderate adverse events were reported with **Telmisartan**, with a few patients experiencing fatigue and male impotence (Freytag et al., 2001). A few patients experience dry cough with **Candasartan** or **HCTZ** rather than with **Enalapril** (Malmqvist, Kahan & Dahl 2000). While drug related effects are the most common (Monalis et al, 2000), these do not cause patients to discontinue treatment (Neutal et al, 1999).

Patients treated with **Eprosartan** had a safety profile similar to placebo, the most common reported adverse effects being upper respiratory infection (Levine, 2001). A review found that high propensity of persistent nonproductive cough does not occur in **Eprosartan** treated patients (Plosker et al, 2000).

The most common side effects reported in **Valsartan** are treatment related effects like dry cough, headache and dizziness (Lasko et al, 2001; Botero et al, 2000; Hedner et al, 1999).

(b) Angiotensin Converting Enzyme Inhibitors (ACE Inhibitors)

Adverse effects of administration of ACE inhibitors were minimal, the most common being drug related effects like cough, headache, malaise and dizziness (van der Does & Euler 2001; Dews &VandenBurg, 2001; Lacouciere, 2000; Chio et al, 2000; Malmqvisk et al, 2000; Botero et al, 2000; Shal'nova et al, 2000; Neutal et al, 1999; Kukushkin et al, 1998; Spinar & Vitovec, 1998; Ol'binskaia et al, 1999; Hazizi et al, 1998; Guitard et al,1997; Roca-Cusachs et al, 1997; Ruddy & Fodor, 1997). For the **Benazepril** group, asthenia, nausea, raised serum creatinine levels, angioedema, and hepatitis were reported (Hazizi et al, 1998).

(c) Calcium Channel Blockers

The side effects usually reported in patients treated with calcium channel blockers are pedal swelling, dizziness, headache, flushing, fatigue, and heaviness in the head (van der Does et al,

2001; Kloner et al, 2001; Whitcomb et al, 2000; Yosefy et al, 1999; Kalke et al, 1999; Cheung et al, 1998; Sanz Guajaardo & Espejo Martines, 1997; Sowunmi, Walker & Salako, 1996), while peripheral edema has been reported in patients treated with nisoldipine (Ruddy, & Fodor,1997).

(iii) Cost

A cost comparison found that **Nisoldipine** is more economical than **Amlodipine**.in treating patients with hypertension.(Whitecomb et al, 2000).

A meta analysis found that the treatment cost to prevent major hypertension complications using diuretics and beta blockers are much lower than ACEI < CCB or alpha blockers especially in middle aged patients (Perce et al, 1998).

6. CONCLUSION

There is sufficient evidence to indicate that moderately elevated blood pressure or mild hypertension should be diagnosed when the diastolic blood pressure is more than 90 mm Hg or systolic blood pressure exceeds 140 mm Hg. Decisions on management of these patients should be based on the level of blood pressure, the presence of other risk factors of cardiovascular disease, concomitant diseases like diabetes, target organ damage and cardiovascular or renal disease and other patient's personal aspects like medical and social situations.

The diagnosis of moderately elevated BP depends on the accurate measurement of blood pressure, taking into account physiological variations and other possible causes of elevated blood pressure. Individuals with borderline BP readings should have their BP monitored for at least 3-6 months before commencing therapy.

Treatment should begin with non-pharmacological interventions. There is evidence that patients who had been confirmed to have moderately elevated blood pressure and belong to very high-risk groups benefit from drug therapy - when diabetes or target organ damage or clinical cardiovascular disease is present, drug therapy is beneficial in subjects with a high normal BP of 130-139/85-89 mm Hg. However, for patients in the medium and low risk groups, the initiation of drug therapy will depend on the presence of risk factors, and the degree of blood pressure lowering achieved with non-pharmacological measures. These measures should be continued for at least 3 months for medium risk group patients, and for 6 months for low risk groups, before drug treatment is considered.

For non-pharmacological interventions, there is evidence of benefit of weight reduction, some evidence of benefit of sodium restriction, inconclusive evidence on potassium and calcium intake, some evidence on the benefit of a low fat diet rich in vegetables and fruits, good evidence of benefit of reduction of alcohol consumption, no evidence on benefit of stopping smoking, good evidence on benefit of exercise, and some evidence of benefit of combinations of non-pharmacological interventions.

For pharmacological treatment, diuretics, beta-blockers angiotensin-receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers have been found to be effective in the treatment of moderately elevated blood pressure.

7. RECOMMENDATIONS

A diagnosis of moderately elevated blood pressure or mild hypertension should be made if the systolic blood pressure exceeds 140 mm Hg or the diastolic blood pressure is more than 90 mm Hg. The blood pressure must be accurately measured, and further confirmed by monitoring the blood pressure. Management of these patients would depend on the level of blood pressure, as well as other factors like risk of cardiovascular disease and concomitant disease. Non-pharmacological interventions like weight reduction, dietary interventions including sodium restriction, reduction of alcohol consumption, exercise, should be attempted before initiating therapy with drugs like diuretics, beta-blockers angiotensin-receptor blockers, angiotensin converting enzyme inhibitors and calcium channel blockers.

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EVIDENCE TABLE - BP CLASSIFICATION GUIDELINES

No	Title, Author, Journal, Year, Volume, Number, Page No	Study design, Study sample, Follow up	Characteristics & outcome	Grades & Comments
1.	The Sixth Report of the Joint National Committee) on Prevention, Detection, Evaluation and Treatment of High BP. (1997 *Arch Intern Med*,157, pp 2413-2446	Evidence based medicine from population studies and outcome data from randomized controlled trials.	Hypertension defined as BP >140/90 mmHg. Emphasis on absolute risk. Risk stratification used in treatment strategy	Fair.
2.	Guidelines for the management of mild hypertension: Memorandum from a WHO/ISH meeting. (1993) *J. Hypertension*, 11, pp 905-918	Evidence from population and cohort studies.	Hypertension defined as BP >140/90 mmHg. Moderate hypertension defined as SBP ≥ 180 and DBP ≥ 105mmHg. Presence of TOD and other risk factors emphasized.	Fair
3.	WHO-ISH Guidelines for the Management of Hypertension. (1999) *J. Hypertension*, 17, pp 151-183	Evidence from population and cohort studies including Framingham studies.	Hypertension defined as BP ≥ 140/90. Moderate (Grade 2) hypertension defined as SBP 160-179 and DBP 100-109mmHg. Presence of TOD and other risk factors and associated clinical conditions emphasized. Risk stratification to quantify prognosis. Risks of BP and other risk factors extrapolated. Studies in populations from Asia, Africa and Latin America lacking	Fair
4.	The Swedish Council on Technology Assessment SBU Moderately elevated BP (1995) *J. Int. Med*, 238 (Supp.737), pp13-17	Evidence from population studies in Sweden.	Hypertension defined as DBP>90 mm Hg in individuals <70 years and SBP>160 mm Hg +/- DBP>90 mm Hg in the elderly >70 years.	Fair
7	MacMahon S et al (1990) Blood pressure, stroke and coronary heart disease . *Lancet*,335, pp 765-74.	9 major prospective observational studies. N= 420 000 individuals. 843 strokes, 4856 CHD events. F/up: 6-25 years.	Differences in DBP of 5, 7.5, and 10 mmHg respectively associated with 34%, 46% and 56% less stroke and 21%, 29%, 37% less CHD. DBP 70-110mm Hg studied.	Fair

No	Title, Author, Journal, Year, Volume, Number, Page No	Study design, Study sample, Follow up	Characteristics & outcome	Grades & Comments
8	Selmer R (1992) Blood pressure and 20 year mortality in the city of Bergen, Norway. *Am. J. Epidemiol*, 136, pp428-40.	Prospective observational study. BP survey with MMR screening in 1963. N= 52 064 participants men and women. F/up: 20 years.	Increased BP related to increased mortality in CHD stroke and all causes in all age groups except oldest.	Fair -large sample size -Representative population -men and women -100% Follow-up -Participation 77%
9	Stamler J et al (1993) BP systolic and diastolic and cardiovascular risks. *Arch Intern Med*, 153, pp 598-614	US prospective population studies on blood pressure and cardiovascular risks from MRFIT, Chicago heart Association, Detection Project in Industry, Chicago People's Gas Study, Western Electric Study, Framingham Study, Honolulu Heart Study, LRC study and NHANES F/up20 years	SBP and DBP have, continuous, graded, strong, independent relationships to CAD, stroke, and all cause mortality for all age groups both men and women. Hypertension defined as BP > 140/90 mmHg High normal SBP 130-139. DBP 80-99 mmHg.	Fair <u>1. Chicago Peoples' Gas Study.</u> -Long follow-up, 14 years. -100% follow-up -Sample size 1465 -Only men involved 2. W. Electric Co. Study -Long follow-up, 24 years of 98% people -Only men
10	Kannel WB. et al. (1996) Epidemiologic Assessment of the role of BP in Stroke. The Framingham Study. *JAMA*, 276, pp 1269-1278	Ongoing prospective longitudinal study of factors related to cardiovascular disease and stroke since 1949. N=5209 men and women 30-62 years F/up: 14 years	Hypertension defined as BP>160/95 mm Hg, was associated with a 4 fold risk of atherothrombotic brain infarction compared to normotensives(BP< 140/90 mm Hg)	-large sample, 5209 men and women. -long follow-up, started 1948. Ongoing. population not representative of Asians, Africans and non-westerners
11	Collaborative Research Group.(1998)	Prospective observational study	Overall mean BP was 124/78 mm Hg. Each 5 mm Hg lower DBP was associated with a lower risk of haemorrhagic and	Fair

No	Title, Author, Journal, Year, Volume, Number, Page No	Study design, Study sample, Follow up	Characteristics & outcome	Grades & Comments
	BP, cholesterol and stroke in Eastern Asia. Eastern Stroke and Coronary Heart Disease *Lancet*, 352, pp 1801-1807	N= 124 774 male and female participants from China and Japan. F/ up: 7 years.	non-haemorrhagic stroke. Association between BP and stroke seems stronger than Western populations; a population wide reduction of 3mm Hg DBP should decrease the number of strokes by a third. Decreasing cholesterol levels showed a decease in non-haemorrhagic stroke.	
12	Svardsudd K (1997) Mortality and morbidity during 13.5 years follow-up in relation to BP. The Study of Men Born in 1913. . *Acta Med. Scand,* 205, pp 483	Randomized prospective study. N=973 of fifty year old men. F/up : 13.5 years.	BP strongly associated with all cause mortality and morbidity from myocardial infarction, stroke and angina pectoris. SBP >175 mm Hg DBP > 105 mm Hg	Fair -Representative sample of Gothenburg men born in 1913. -Long follow-up, 13 years. -100% follow-up. -Small sample size -Only men
13	O'Donnell CJ et al. (1997) Hypertension and borderline isolated systolic hypertension increase risk of cardiovascular disease and mortality in male physicians. *Circulation*, 95(5), pp 1132-7	Prospective cohort study. N=18 682 healthy US men participating in the physician's health study. Randomized on low dose aspirin and beta carotene. F/up: 11.7 years	Hypertension and increased risks of cardiovascular disease – MI and stroke. Hypertension defined as BP> 160/90 or having treatment for hypertension. Borderline ISH is SBP =140 to159 and DBP<90 mm Hg. Normal BP < 140/90mm Hg	Fair -Long follow-up, 11 years. -Morbidity follow-up, 99.2% -Mortality follow-up, 100%. -Only men -Self reported measures of BP and BP treatment may have led to misclassification
14	SHEP Co-operative research group.(1991)	Multicenter randomized, double blind, placebo controlled.	Stroke incidents and major cardiovascular events reduced with active treatment with Chlorithaledone/ Atenol/Reserpine	Good -Large population of elderly.

No	Title, Author, Journal, Year, Volume, Number, Page No	Study design, Study sample, Follow up	Characteristics & outcome	Grades & Comments
	Prevention of stroke by anti-hypertensive drug treatment in older persons with ISH. *JAMA*, 265, pp3255-3264.	N= 4 736 persons, age >60 yrs. F/up : 4.5 years.	ISH defined as SBP > 160 and DBP < 90 mm Hg	-Men and women including blacks(14%), Hispanics and others. -Well designed study -Follow-up short, 4.5 years -35% assigned to placebo took anti-hypertensive treatment during trial .
15	Dahlof B et al (1991) Mobility and mortality in the Swedish trial in old patients with hypertension (STOP-hypertension). *Lancet*,.338, pp 1281-1284	Prospective randomized double blind intervention study N=1 627 patients at 116 health centres in Sweden. F/up: 25 months.	Anti-hypertensive treatment in males and females 70-84 years had decreased cardiovascular mortality and mobidity and total mortality. SBP 180-230 and DBP >90 mm Hg or a DBP=105-120 mm Hg	Fair -Large population -Representative of old people. -Short follow-up -Trial stopped prematurely due to positive outcome for active treatment -Very old patients who may have other causes of death.
16	Neaton JD. et al (1993) Treatment of Mild Hypertension Study(TOMHS). *JAMA* 270, pp 713-724	Randomized double blind placebo controlled trial. N=902 individuals (male and female aged 45-69 years) F/up: 4.4 years.	Drug treatment in combination with nutritional hygienic intervention more effective in preventing cardiovascular and other clinical events than hygienic treatment alone. DBP= 90-99 mm Hg or antihypertensive treatment with DBP < 95 mm Hg	Fair -Fairly long follow-up -Small sample size -Small percentage of patients on drug treatment had major CVD event than placebo (5.1% against 7.3%)
17	MRC working party (1985) MRC trial of treatment of mild hypertension: principle results	Single blind randomized trial. N=17 354 patients (male and female), 85 572 patient years of observation.	Groups that benefited most from anti-hypertensive treatment are the oldest patients with the highest BP. Treatment decreased stroke and all CVD events but no change in CHD events and all cause mortality. Mild hypertension defined as DBP=90-109 mm Hg	Fair -Selection bias of population towards upper social economic group-Limited to small

No	Title, Author, Journal, Year, Volume, Number, Page No	Study design, Study sample, Follow up	Characteristics & outcome	Grades & Comments
	BMJ 291, pp 97-104	F/up: 4.5 years.		town practice areas. -Screening BP initially by nurses, later by GPs. -Withdrawals and lapses from follow-up, high. (30-43%)
18	Antikainen R et al (1998) SBP, ISH and risk of CHD, strokes, cardiovascular disease and all cause mortality in the middle aged population *J Hypertens*. 16, pp 577-583	Prospective 15 year cohort study of 2 independent cross sectional random samples of subjects participating in baseline surveys in 1972 and 1977 in east Finland. N=10 333 men and 11 160 women aged 25-64 years. F/up data on deaths due to CHD, CVD from government statistics agency.	CHD, stroke, cardiovascular disease and all cause mortality increased with increasing SBP. ISH defined as SBP > 160, DBP < 95 mmHg Hypertension defined as BP>160/90 mmHg	Fair -Large sample, &-Long follow-up, 15 years -Self administered questionnaire on smoking and medical history -BP data based on single measurements leads to over-estimation of hypertension prevalence and underestimates risks of hypertension during follow-up.
19	Nielson et al. (1997) Is diastolic hypertension an independent risk factor for stroke in the presence of normal SBP in the middle aged and elderly. *Am J Hypertens*, 10(6), pp 634-639	Prospective population based study from the Copenhagen City Heart Study. N=6 545 subjects aged 50-80 years. F/up: 12 years.	Subjects with elevated SBP had a significant increased risk of future stroke. ISH defined as SBP>160, DBP<90 mmHg. Borderline ISH, SBP<160, DBP<90 mmHg.	Fair -Large sample size, -Long follow-up
20	Lichtenstein MJ et al (1985) Systolic and diastolic blood pressures as predictors of CHD mortality in the Whitehall study.	Prospective observational cohort study N=18 403 male civil servants aged 40-64.	Top quintile of SBP (>151 mmHg) identify 5% more men at risk of death from CHD than for the top diastolic quintile (>95 mmHg)	Good -Large sample size -Only men -Not representative population (public officials in London

No	Title, Author, Journal, Year, Volume, Number, Page No	Study design, Study sample, Follow up	Characteristics & outcome	Grades & Comments
	BMJ, 291(6490), pp243-245	F/up: 10 year mortality.		only) -Participation 80%
21	Berglund G (1996) Cardiovascular risk groups and mortality in urban Swedish male population: The Malmo preventive project. *J Intern Med*, 239 (6), pp 489-497	Prospective observational study. N=22 444 men. F/up 12.2 years.	Hypertension in 13% hypercholesterolaemia in 19%, diabetes in 2.6%, smoking in 49% of the subjects. Multiple risk factors found in 17% of the cohort. Despite intervention, all cause mortality increased 3 fold in smokers and hypercholesterolaemia, 4 fold in hypertension and 5 fold in diabetes. Hypertension defined as BP>160/100 mmHg	Fair
22	Shaper AG et al (1985) Risk factors for Ischaemic Heart Disease: The Propsective Phase of The British Regional Heart Study. *J Epidemiol Community Health*, 39 (3), pp 197-209	Randomize prospective. N=7735 men from general pratices in 24 British towns. F/up: 4.2 years.	Serum cholesterol, HDL cholesterol, triglycerides, SBP and DBP, smoking, BMI are all associated with increased risk of IHD. Evidence of IHD initially is strongly associated with increased risk of subsequent IHD. SBP>148 mmHg confers 2 times risk. DBP>92 mmHg confers 3 times risk	Fair. -Large sample size -Representative population sample -Follow-up 99% -Only men -Stratified samples from mid-size cities in UK
23	Simons LA et al (1996) Predictors of mortality in the prospective Dubbo study of Australian elderly. *Aust NZ J Med,* 26(1), pp 40-48	Prospective study in non-institutionalized Australian study N= of 1236 men and 1569 women aged above. 60 F/up : 62 months.	Significant predictors of mortality were older age, being married, smoking, alcohol, prior CHD, hypertension, diabetes and cholesterol. Blood pressure increased mortality <75 years. For men with DBP>90 mmHg overall age adjusted CHD death is 79%>men with DBP<90 mmHg.	Fair
24	Stamler J et al. (1986) Prevalence and prognostic significance of hypercholesterolaemia in men with hypertension. MRFIT study.	Prospective cohort study N= 361,662 screened in 18 cities in the MRFIT study. F/up: 6 year	For men with high BP, serum cholesterol related to CHD in a strong graded way. Smoking associated with a doubling of the mortality at any level of cholesterol. High BP defined as DBP>90 mmHg.	Fair -Large sample size -Long follow-up -Not representative population sample -Door to door in

No	Title, Author, Journal, Year, Volume, Number, Page No	Study design, Study sample, Follow up	Characteristics & outcome	Grades & Comments
	Am J Med,14(80), pp .33-39			residential areas of several US cities. -Only men
30	Howard BV et al. (1995) CHD prevalence and its relation to risk factors in American Indians. The Strong Heart study. *Am J Epidemiol*, 142(3), pp 254-68	Cross-sectional study N=13 Indian communities in USA.	Prevalence of CHD among American Indians was significantly and independently related to age, diabetes, hypertension, albuminuria, percentage of body fat, smoking, high plasma insulin and low HDL. Diabetes was the strongest risk factor. Hypertension defined as BP>140/90mmHg	Fair

EVIDENCE TABLE: PHYSIOLOGICAL VARIATION IN BLOOD PRESSURE –

No	Author, Title, Journal, year. Volume, number, page no	Study Design, Sample Size. Follow up	Outcome & Characteristic	Grade & comment
1.	Redon-J (1998) Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension*., 31(2), Feb, pp 712-8	Prospective study F/up: 49 months (range, 6 to 96). .	While significant differences in systolic and diastolic ambulatory blood pressures were observed among groups, no differences were observed at either the beginning or at the time of the last evaluation for office blood pressure. Twenty-one of the patients had a new cardiovascular event; the incidence of events was significantly lower for the LT group (2.2 per 100 patient-years) than it was for the MT group (9.5 per 100 patient-years) or for the HT group (13.6 per 100 patient-years)	Fair
2.	White-WB (1993). Twenty-four-hour blood pressure load as a surrogate end-point in assessing antihypertensive therapy.	Data were obtained from a study of 15 men with moderate to severe essential hypertension who had been treated with a placebo followed by 6-8 months of carvedilol	In studies of office or 'white-coat' hypertensives, ambulatory blood pressure has proved a better predictor of target organ involvement than casual (clinic) pressure. Blood pressure loads of > 50% for systolic pressure and > 40% for diastolic pressure are superior to clinic pressures, and also to the usual ambulatory monitoring parameters of mean 24-h, awake and sleeping blood pressure, in	Fair

No	Author, Title, Journal, year. Volume, number, page no	Study Design, Sample Size. Follow up	Outcome & Characteristic	Grade & comment
	J-Hypertens-Suppl, 11(4), Jun, pp S75-80	monotherapy (25-75 mg/day). Blood pressure was evaluated by 24-h ambulatory monitoring.	predicting left ventricular hypertrophy. In the carvedilol study, the mean awake systolic blood pressure load fell from 94 to 43% and the diastolic blood pressure load fell from 84 to 27% with carvedilol treatment (P < 0.001 in both cases). Of the patients treated with carvedilol monotherapy, 60% fell into the lower risk category (< 50% systolic blood pressure and < 40% diastolic blood pressure load).	
3.	Stephan-D (1993) Ambulatory or single measurement of blood pressure: comparison in a controlled trial in patients with hypertension *Ann-Cardiol-Angeiol-Paris.* 42(1), Jan, pp: 45-9	Acebutolol or enalapril were given double-blind to 17 patients with uncomplicated moderate essential hypertension.	With treatment, the fall in DBP by single measurement was significant only at the first month with enalapril and at the third month with acebutolol while the effects of both drugs were significant on ambulatory systolic blood pressure (SBP) and DBP by the first month. Ambulatory BP revealed a superior antihypertensive action of acebutolol on SBP at the third month but this was not shown by single BP measurements. These results confirm the specificity of trial protocols of antihypertensive drugs based upon ambulatory BP measurements.	Fair
4.	Staessen, Amery (1997) APTH (Ambulatory Blood Pressure and Treatment of Hypertension)Trial. *JAMA* 278(13): 1065-72	Randomised, double blind for 6 months then open design. 419 patients recruited with DBP of 80 – 89 mm Hg. Randomly assigned to either target BP 80 – 89 mmHg (office BP) or AMBP target of daytime mean of 80 – 89 mm Hg.	Median follow up 182 days (range 85 – 258 days) The average CBP was 144 / 90 mm Hg, average ABP was 130 / 79.5 mm Hg. Symptoms and LV mass regression were similar however more patients with ABP had stopped drug therapy c/w ABP (26.3% vs 7.3%) Overall costs between groups were similar	Good

EVIDENCE TABLE: BENEFITS OF HYPERTENSION THERAPY

No.	Author; Title, Journal,	Study design, Sample size, follow up	Characteristics & outcome	Grades & Comment
1	Medical Research Council Study – MRC Working Party	Randomised, placebo controlled single blind study	CVS event rate was 4% in the placebo group vs 3.3% in the active treatment group at the end of the study. The main reduction in events	Good

No.	Author; Title, Journal,	Study design, Sample size, follow up	Characteristics & outcome	Grades & Comment
	(1988) Randomised, placebo controlled single blind study comparing the effects of therapy of mild hypertension in middle aged adults with propanolol and diuretics versus placebo *BMJ* pp 59	N= 17,354 patients F/up : over 5.5 years. DBP at baseline 90 – 109 mm Hg	was in the incidence of stroke, however there was no difference in the overall mortality or AMI rates. The mortality rate in women on treatment was significantly higher, the converse was true for men.	
2	MRC trial of hypertension in older adults–MRC Working party (1992) Randomised single blind placebo controlled trial in older adults (65 – 74 years). Active therapy consisted of Amiloride / HCTZ or Atenolol or both *BMJ* pp 304	Randomised single blind placebo controlled tria N=4 396 patients F/up :over a mean of 5.8 years. SBP at baseline 16- - 209 mm Hg.	Active treatment with diuretics reduced both BP and clinical events (stroke, AMI and mortality – 25%, 19% and 17% respectively). Atenolol did not alter the rates of CVS adverse events compared with placebo	Good
3	Hanson, Dahloff et al (1991) STOP Hypertension – *Lancet* pp 328	Randomised, double blind placebo controlled. N=1627 patients between 70 - 84 years were randomised to active therapy (diuretics and / or beta blockers) and F/up: mean period of 25 months.	Active therapy reduce DBP more than placebo with a corresponding fall in CVS events (40% reduction in CVS events and 43% reduction in mortality)	Good
4	Hansson, Zanxhetti et al (1998) HOT Trial -	Randomised treatment trial N=18 790 patients	Benefit was demonstrated in the lowest BP (< 80 mm Hg) target group c /w the group assigned to DBP < 90 mm Hg. There was a 43% reduction in strokes however the risk reduction in AMI was of borderline significance. The benefits were most marked in the	Good

No.	Author; Title, Journal,	Study design, Sample size, follow up	Characteristics & outcome	Grades & Comment
	Lancet June, pp 351,	F/up 3.8. years	diabetic sub-group. Aspirin was also found to reduce AMI by 36% and overall major CVS events by 15%.	
5	Amery et al (1991) EWPHE – *AM J Med*, pp 90	RCT. N=840 patients over 60 years F/up: 4 years	After a mean follow up of 4 years, the overall mortality was the same however CVS mortality and particularly, stroke rate was reduced	Good
6	Gong, Zhang et al (1996) STONE (Shanghai Trial of Nifedipine in the Elderly)Trial *Journal of Hypertension,* 14, (4), Oct, pp 1237-45	Randomised single blind placebo controlled trial.] N=1 632 patients (60 – 79 years).	Nifedipine reduced SBP by 21 mm Hg c/w placebo (12 mm Hg). The DBP fell by 13 mm Hg and 7.5 mm Hg respectively. Total CVS events were reduced by 62%. 77 events occurred in the placebo group, 32 in the Nifedipine group. The main reduction occurred in strokes, mortality was reduced but did not reach statistical significance.	Good
7	Staessen et al (1997) SYS-Euro Trial *Lancet* pp 350	N= 4 695 patients with SBP 160 – 219 mm Hg and DBP < 95 mm Hg were randomised to Nitrendipine or placebo with adjunctive therapy of Enalapril and HCTZ. .	After a median follow up of 2 years, SBP had fallen by 23 mm Hg in and 23 mm Hg in the placebo and active therapy groups respectively with a corresponding fall of 42% in stroke rate but no fall in overall mortality. The absolute stroke rate in the placebo group was 3.3% over the median follow up of 24 months (range 1 – 97 months). This translates into a stroke rate of 13 per 1000 patient years. The trial was terminated prematurely due to the significant reduction in events	Good
10	Gueyffier (1997) Effect of anti-hypertensive treatment in patients having already suffered from stroke. Gathering the evidence. The INDANA (Individual Data Analysis of Anti-hypertensive intervention trials) Project Collaborators. *Stroke*,c; 28(12): 2557-62	Meta-analysis trials of hypertensive patients included a small proportion of stroke survivors (536 patients); 1 trial included stroke survivors, whether hypertensive or not (5665 patients)	The recurrence of stroke, fatal and nonfatal, was significantly reduced in active groups compared with control groups consistently across the different sources of data (relative risk of 0.72, 95% confidence interval: 0.61 to 0.85). There was no evidence that this intervention induced serious adverse effect. Blood pressure lowering drug interventions reduced the risk of stroke recurrence in stroke survivors.	Good

EVIDENCE TABLE : NON PHARMACOLOGICAL TREATMENT

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
Weight Loss				

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
1.	The Sixth Report of the Joint National Committee on Prevention Detection, Evaluation and Treatment of High Blood Pressure (1997) *Archives of Internal Medicine* 157, pp 2413-46.	Position statement	Weight loss of as little as 10 lbs (4.5 kgs) reduces blood pressure in large proportion of overweight person with hypertension	Poor
2	Frohlich ED, Messerli FH, Reisin E et al (1983) The problem of obesity and hypertension. *Hypertension*. Sept-Oct, 5 (5 pt2) 11171-8	Review	Hypertemsion and obesity are two disorders that have been closely related. Each occurring in greater freuency with the other than in an otherwise normal population their coincidence carries increased risk of cardiovascular morbidity and mortality	**Poor**
3	Pouliot MC, Despres JP, Lemieux S et al (1994) Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal and visceral adipose tissue accumulation and related cardiovascular risk in men and women. *American Journal of Cardiology.*73(7), Mar 1, pp 460-8	Observational study N=151 subjects	Data suggest that waist circumference values above approximately 100cm, or abdominal sagittal diameter values > 25 cm are most likely to be associated with potentially “atherogenic” metabolic disturbances	Fair
4	Stamler R, Stamler J, Riedlinger WF et al (1978)	Community observational study	Emphasize the importance of overweight in relation to hypertension	**Poor**

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	Weight and blood pressure findings in hypertension screening of 1 million Americans *JAMA*, 240(15), Oct 6, pp 1607-10	N=1 million subjects		
5	Hsu PH, Mathewson FAL, Rabkin SW (1977) Blood pressure and body mass index pattern: *Journal of Chronic Diseases.* 30(2), feb, pp 93-113	Longitudinal study. Prospective Cohort study N=3054 subjects F/up: 27 years	Illustrates the correlation between body mass index with systolic and diastolic blood pressure	Fair
6	MacMahon SW, Wilcken DEL, MacDonald GJ. (1986) The effect of weight reduction on left ventricular mass: a randomised controlled trial in young overweight hypertensive patients. *New England Journal of Medicine* ,314(6), Feb 6, pp 334-9	Randomised controlled trial N= 41 subjects F/up: 21 weeks	Weight reduction decreases left ventricular mass in overweight hypertensive patients and that control of obesity is important not only for the treatment of hypertension but also for the prevention of left ventricular hypertrophy	Good Small sample
7	Reisen E, Frohlich ED (1982) Effects of weight reduction on arterial blood pressure *Journal of Chronic Disease*. 35(12), pp 887-91	Randomised Controlled Trial N= 107 subjects F/up: 18 months	Weight loss with hypocaloric diet without reducing sodium intake resulted in considerable fall in blood pressure in overweight hypertensive patients	Good
8	Davis BR, Blaufox MD, Oberman A, Wassertheil-Smoller S, Zimbaldi N, Cutler JA, Kirchner K,	Randomised Controlled Trial N= 587 subjects	Weight reduction is an effective long-term therapy for maintaining blood pressure in the normal range when used as mono-therapy Weight loss should be recommended for the management of obese	Good

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	Langford HG.(1993) Reduction in long-term antihypertensive medication requirements *Archives of Internal Medicine*,153, pp 1773-82	F/up: 5 years	individuals with mild hypertension	
9	Reisin E, Abel R, Modan M et al (1978) Effect of weight loss without salt restriction on the reduction of blood pressure in overweight hypertensive patients. *New England Journal of Medicine*, 298, pp 1	Randomised Controlled Trial N=107 subjects F/up: 6 months	Weight reduction has a direct significant reduction in blood pressure.	Good
10	Langford GH, Blaufox MD, Oberman A et al (1985) Dietary therapy slows the return of hypertension after stopping prolonged medication *JAMA*, 153, pp 657	Randomised Controlled Trial N= 496 subjects	Data demonstrates that weight loss or sodium restriction, in hypertensives controlled for five years, more than doubles success in withdrawal of drug therapy	Good
11	Ohashi H, Odno H; Ohno M Watanabe S (2001) Weight reduction improves high	N= 25 patients - group A =10 patients wt loss at least 5% - Group B 15 patients without	Blood pressure rate were significantly decrease in group A. Reduction of arterial blood pressure significantly correlated with the fall in body weight Blood pressure rate in hypertension patient with obesity significantly	Poor

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	blood pressure and microalbuminuria in hypertension patients with obesity *Nippon Jinzo Gakkai Shi,* 43(4), May, pp 339-9	wt loss Body mass index (BMI) of over 25 were prescribe low calorie diet (25 kcal./kg)	decreased with weight reduction.	
12	Stevens VJ; Obarzanek E Cook NR et al (2001) Long-term weight loss and changes in blood pressure: results of the trials of hypertension prevention; Phase II *Ann International Medicine;* 134(1), Jan 2, pp 1-11	Multicentre clinical trial N=1191 patient Weight loss - 595 Control- 596 F/up 3-4 year	Blood pressure was significantly lower in the intervention group than in the control group at 6, 18 & 36 months Participant who lost at least 4.5 kg at 6 months and maintained this weight reduction for the next 30 months had the greatest reduction in blood pressure and a relative risk for hypertension of 0.35 (CI 0.20 to 0.59) Clinically significant long-term reduction in blood pressure and reduced risk for hypertension can be achieved with event modest weight loss	Fair
13	Mertens IL; VanGaal LF (2000) Overweight, obesity; and blood pressure: the effects of modest weight reduction *Obes Res*, 8(3), May, pp 270-8	Review	Modest weight loss can normalize blood pressure levels even without reaching ideal weight. In Patient with high normal blood pressure, modest weight loss can prevent the onset of frank hypertension Conclusion: modest weight loss can be maintained over a longer period of time is a valuable treatment goal in hypertension patients	Poor
14	Brand MB, Mulrow CD, Chiuette E, Ngel L, Cornell J, Summerbell C, Anagnostelis B, Grimm R Jr.(1998)	Systematic Review	Modest weight loss in the range of 3-9% of body weight and probably associated with modest blood pressure decreases of roughly 3 mmHg systolic nd diastolic	Good

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	Weight reduction through dieting for control of hypertension in adults *Chorance Systematic Reviews,*vol4			
15	Mulrow CD et al (2000) Dieting to reduce body weight for controling hypertension in adults *Cochrane Database Systematic Review,* (2):CD000484	Systemtic Review	Weight loss in the range of 3-9% of body weight and are probably associated with modest blood pressure decrease of roughly 3 mmHg systolic and diastolic. Weight reducing diets may decrease dosage requirement of person taking antihypertensive medications.	Good
16	Mulrow CD et al (2002) Dieting to reduce body weight for controlling hypertension in adults *Cochrane Review*	Systematic Review	Modest blood pressure of roughly 3 mmHg systolic and diastolic was associated with weight loss in the range of 3-9% of body weight Weight diets decrease dosage requiment of taking antihypertensive medications	Good
17	Himeno E; Nishino K et al (1999) A weight reduction and weight maintenance program with long-lasting improvement in left ventricular mass and blood pressure *Am J Hypertension* 12 (7), Jul, pp 682-90	N= 36 - 22 normatension obese subject and 14 mild hypertension	Reduce body weight was maintained for 1 year after 12 weeks supervised weight reduction program in both normotensive and mild hypertensive obese subjects. Reduce left ventricular mass was maintained for a long period in both normotensive and mild hypertensive obese subjects and lowered blood pressure was maintained in the mild hypertensive obese subjects.	Poor
18	Schotte D E, Stunkard AJ (1990) The effect of weight reduction on blood pressure in 301 obese patient *Arch Internal Medicine* ,150 (8),	N=301 obese patient	Weight reduction was associated with significant reductions in systolic and diastolic blood pressure	Poor

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	Aug, pp 1701-4			
19	Ebrahim S; Smith GD (1998) Lowering blood pressure: a system review of sustained effects of non-pharmacological intervention *J Public Health Med*, 20(4), Dec, pp 441-8	Meta analysis	Mean systolic blood pressure changes is - 5.2 mmHg (CI -8.3 , -2.0) in weight loss	Good
20	Wada T, Ikeda Y (1998) Longitudinal studies to determine the effect of body fat rate reduction on blood pressure *J Med System*, 22(1), Feb, pp19-25	Review	If the body weight had not changed, blood pressure had decreased significantly when %BF had decreased significantly	Fair
21	Reisin E (1997) Non-pharmacologica approaches to hypeertension: weight; sodium, alcohol, exercise and tobacco consideration Me*d Clin North Am*, 81(6), Nov, pp 1289-303		Weight loss decrease blood pressure, and this change can be sustained over the long-term when the lower wt is maintained	Poor
22	Neaton JD, Grimm RH Jr, Prineas RJ et al (1993) Treatment of Mild Hypertension Study: final results	Randomised Controlled Trial. N= 892 subjects F/up; 4.4 years	As an initial regimen, drug treatment in combination with nutritional-hygienic intervention was more effective in preventing cardiovascular and other clinical events than was nutritional/hygienic treatment alone.	Good

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	JAMA, 270, pp 713-24			
23	Kriketos AD, Robertson RM, Sharp TA, Drougas H, Reed GW, Storlien LH, Hill JO. (2001) Role of weight loss and polyunsaturated fatty acids in improving metabolic fitness in moderately obese, moderately hypertensive subjects *J Hypertens*, 19(10) Oct, pp 1745-54	Clinical Trial Randomized Controlled Trial	Weight loss (10%) in obese hypertensive subjects resulted in substantial improvements in BP, Si and lipid profile. There was no additional effect on the reduction in BP by the type of FA consumed in the diet. Following weight loss, there was a trend for omega-3 FAs to have a protective effect on fat-free mass loss and a trend to further enhance Si. There were significant improvements in circulating lipid profiles independent of the dietary FA intervention following the weight loss. The improvements in BP and body composition were maintained during the weight-loss maintenance period. The type of fat consumed had minor differential effects on some of the measured metabolic outcomes. CONCLUSION: These results provide strong support for modest weight loss as a treatment for hypertension.	Good
24	Weintraub M, Sundaresan PR, Modan M et al (1992) Long-term weight control study III (Weeks 104-156). *Clinical Pharmacological Therapeutics,* 51, pp 104-156,181	Randomised Controlled Trial N=56 subjects F/up: 156 weeks	Drugs were effective in weight reduction	Good
25	O'Connor HT, Richman RM, Steinback KS et al (1995) Dexfenfluramine treatment of obesity: a double-blind trial with post trial follow-up	Randomised Controlled Trial N=60 subjects F/up: 1 year	It supported the use of dexfenfluramine in the use of chronic obesity. Collectively showed an improved cardiovascular risk profile	Good

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	International Journal of Obesity, 19, pp 181			
26	Connolly HM, Crary JL, McGoon MD, et al.(1997) Valvular heart disease associated with fenfluramine-phentermine. *New England Journal of Medicine*, 337, pp581-88	Routine screening and clinical observation. N= 24 subjects F/up: 12.3/.7.1 months	The paper expresses great concern on the possibility of valvular damage in patients whose obesity is treated with fenfluramine-phenpermine	Poor
27	Abenhaim L, Moride Y, Brenot F et al (1996) Appetite suppressant drugs and the risk of pulmonary hypertension *New England Journal of Medicine*, 335, pp 609-16	Case-control study 95 patients. 355controls. . F/up: 3 months	Use of anorexic drugs was associated with the development of primary pulmonary hypertension	Poor
28	Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH Jr, Kostis JB, Kumanyika S, Lacy CR, Johnson KC, Folmar S, Cutler JA (1998) Sosium reduction and weight loss in the treatment of hypertension in	Clinical Trial N= 975	Weight loss constitute a feasible, effective and safe nonpharmacologic therapy of hypertension in older person	Fair

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	older persons: a randomized controlled trial of non-pharmacologic interventions in elderly (TONE) . TONE Collaborative Research Group *JAMA* 279(11), Mar 18, pp 839-46			
29	Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ (2003) The Seventh Report of the joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure JAMA, 389 (19), May 21, pp 2560 – 72	JNC VII report	Maintain normal body weight BMI 18.5-24.9, approximate reduce systolic BP range from 5 –20 mmHg/10kg weight loos	Good to fair
Mineral intake ***Salt (sodium) restriction***				
30	Conlin PR (2001) Dietary modification and changes in blood pressure C*urr Opin Nephrol Hypertension;* 10(3), May, pp 359-63	Review	Blood pressure lowering effects of sodium restriction Consumption of diets that are low in fat and enriched in fruits and vegetables and the sustained effects of weight reduction	Poor

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
31	Graudal N Galloe A (2000) Should dietry salt restriction be a basic component of antihypertensive therapy? *Cardiovascular Drug Therapy*, 14(4), Aug, pp 381-6	Review	Salt reduction does not seem to add to the effect size when combined with other nonpharmacological interventions Dietary salt restriction should not be a basic component of antihypertisivetherapy	Fair
32	Bonner G (1999) Fat control- an effctive antihypertensive strategy. Special recommendations for therapy of the overweight patients *MMMW Fortschr Med*, 141(46), Nov 18, pp 34-6		Reducing daily salt intake to 5 g can also bring about measurable reduction in blood pressure	
33	Ebrahim S; Smith GD (1998) Lowering blood pressure: a system review of sustained effects of non-pharmacological intervention *J Public Health Med*, 20(4), Dec, pp 441-8	Meta analysis	Mean systolic blood pressure changes is - 2.9 mmHg (CI -5.8 , 0.0) in salts restriction	Good
34	Reisin E (1997) Non-pharmacologica approaches to hypeertension: weight; sodium, alcohol, exercise and tobacco consideration *Med Clin North Am*, 81(6), Nov, pp1289-30	Review	Salt restriction may be effective in blood pressure control only in salt-sensitive individual	Poor

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
35	Korhonen MH, Litmanen H, Rauramaa R Vaisanen SB, Niskanen L, Uusitupa (1999) Adherence to the salt restriction diet among people with mildly elevated blood pressure *Eur J Clin Nutr*, 53 (11), Nov, pp 880-5	Controlled Clinical trial N= 39	Salt intake of 5 g per day , there was a significantly decline in systolic and diastolic blood pressure level of during the salts restriction diet	Fair
36	Cutler JA, Follmann D, Allender PS (1997) Randomised trial of sodium resriction: an overview *American Journal of Clinical Nutrition*. 65 (supp 2), Feb, pp 643S-651S	Meta analysis N=2 635 subjects from 32 trials	There is no evidence that sodium reduction is hazardous. This overview suggests that reduction of cardiovascular morbidity and mortality is possible from reduction of sodium intake	Good
37	Krotkiewski M, Bjornstorp P, Sjostrom L, et al. (1983) Impact of obesity on metabolism in men and women importance of regional adipose tissue distribution *Journal of Clinical Investigation*, 72, pp1150	Observational study N= 930 middle aged men and women	Male abdominal type obesity shows susceptibility to the effect of excess body fat on lipid and carbohydrate metabolism.	Poor
38	Alderman MH, Madhavan S, Cohen H Sealey JE, Laragh JH (1995) Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men *Hypertension* 25(6), Jun, pp	Case-Control study N= 2 937 subjects F/up: 3.8 years	24-hr urinary excretion of sodium was inversely related to subsequent MI, cardiovascular morbidity and mortality, and all-cause mortality but not to non-CVD mortality (particularly in men)	Fair

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	1144-52			
39	Reisin E. (1997) Nonpharmacologic approaches to hypertension. Weight, sodium, alcohol, exercise, and tobacco considerations. *Med Clin North Am*, 81(6), Nov, pp 1289-303	Review	Salt restriction may be effective in blood pressure control only in salt-sensitive individuals	Poor
40	Midgley JP, Mathew AG, Greenwood CM, Logan AG (1996) Effect of reduced dietary sodium on blood pressure: 1 meta analysis of randomised controlled trial *JAMA*, 275(20) May 22-29, pp 1590-7	Meta analysis	Dietary sodium restriction for older hypertension individual might be considered, but the evidence in the normal population dose not support vurrent recommendation for unversal dietary sodium restriction.	Good
41	Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH Jr, Kostis JB, Kumanyika S, Lacy CR, Johnson KC, Folmar S, Cutler JA (1998) Sosium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of non-pharmacologic interventions in	Clinical Trial N= 975	Sodium reduced intake constitute a feasible, effective and safe nonpharmacologic therapy of hypertension in older persons	Fair

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	elderly (TONE) . TONE Collaborative Research Group *JAMA* 279(11), Mar 18, pp 839-46			
Potassium Intake				
42	Ram CVS, Grarret BN , Kaplan NM (1981) Moderate sodium restriction and vrious diuretic in the treatment of jypertension *Archives of Internal Medicine*, 141(8), Jul, pp 1015-9	N=12 patient	Changes in total body potassiam level and blood pressure were detemined in multiple studies on 12 hypertensive subject ingesting a diet either moderately restricted or higher in sodium	Poor
43	Gu D, He J, Wu X, Duan X, Wheletron PK (2001) Effect of potassium on blood pressure in Chinese, randomized, placebo controlled trial *J Hypertension*, 19(7), Jul, pp 1325-31	Randomised, double blind placebo controlled trial N= 150	Potassium was associated with systolic blood pressure reduction but not the diastolic blood pressure	Good
Diet Modification				
44	Appel LJ, Moore TJ, Obarzanek E et al (1997) The effects of dietary patterns on blood pressure *New England Journal of Medicine* 336 (16), Apr 17, pp 1117-24	Randomised Controlled Trial N= 459 subjects F/up: 8 weeks	A diet rich in fruits, vegetables and low fat dairy food and with reduced saturated and total fat can substantially lower blood pressure	Good

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
45	Conlin PR (1999) The dietary approaches to stop hypertension (DASH) clinical trial: implications for lifestyle modifications in the treatment of hypertensive patients *Cardio Rev*, 7(5), Sept-Oct, pp 284-8	Clinical trial, Multicentre Study; Randomized controlled trial N= 459 participants for 11 weeks	The combination diet (food enrich in fruits, vegetables and low fat diary products and low in total & saturated fat) is effective for lowering blood pressure in patients with high-normal or stage 1 hypertension.	Good
46	Kolasa KM (1999) Dietary Approaches to Stop Hypertension (DASH) clinical practice: primary care experience *Clin Cardio,* 22(7 suppl), Jul,:pp 1116-22	Review	Dash diet (rich in fruit, vegetables, nuts and low-fat dairy foods, with reduce saturated and total fats) reduce of 6 mmHg systolic and 3 mmHg diastolic blood pressure. Those with high blood pressure systolic dropped by 11 mmHg and diastolic dropped by 6 mmHg	Poor
47	Peterson LA (1998) Recent Advances: General Medicine *Br Med J* 317, pp 792-95			
48	Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ (2003) The Seventh Report of the joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure JAMA,389(19), May 21 pp 2560 – 72	JNC VII report	Adopt DASH eating plan , consume a diet rich in fruits, vegetables, and low fat dairy products with a reduced content of saturated and total fat approximately reduce systolic BP range from 8 – 14 mm Hg	Good to fair

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
A cohol intake				
49	Puddey IB, Parkar M, Beilen LI et al (1992) Effects of alcohol and caloric restrictions on blood pressure and serum lipids in overweight men *Journal: Hypertension* 20(4), Oct, 99 533-41	Randomised Controlled Trial N=86 subjects F/up: 18 weeks	Calorie reduction and alcohol restriction resulted in reduction in both systolic and diastolic blood pressure	Good
50	Xin X; He J; Frontini MG; Ogden LG; Motsomai OI; Whelton Pusat Kesihatan (2001) Effect of alcohol reduction on blood pressure: a meta analysis of randomized controlled trials *Hypertension*, 38(5), Nov, pp1112-7	Meta analysis N=2234 participants	Alcohol reduction was associated with significant reduction in mean (95%CI) systolic & diastolic blood pressure of -3.31 mmHg (-2.52 to -4.10mmHg) and -2.04 mmHg (-1.49 to -2.58 mmHg) respectively	Good
51	Stamler J, Caggiula AW, Grandits GA (1997) Relation of body mass and alcohol, nutrient, fibre and caffeine intakes to blood pressure in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. *American Journal of Clinical Nutrition*. 65 (supp 1), Jan, pp 338S-65S	Regression analysis of MRFIT Trial F/up: 6 years	Confirm direct independent relationship of body mass index, alcohol intake, dietary starch, sodium, and ratio of sodium and potassium to both systolic (SBP) and diastolic blood pressure (DBP) and an inverse relationship of serum potassium, magnesium, dietary fiber and caffeine intake to both SBP and DBP; Dietary saturated fatty acid and cholesterol has direct relationship to DBP; Dietary protein, polyunsaturated fatty acids, simple carbohydrate inversely related to DBP.	Poor

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
52	Cushman WC, CulterJA Hanna E et al (1998) Prevention and treatment of hypertension study (PTHS): effects of an alcohol treatment program on blood pressure *Arch Intern Med*, 158(11), Jun 8, pp1197-207	Randomised Controlled Trial N=641 outpatient veterans	The 1.3 drinks per day average produced only small non significant effects on blood pressure. The results from the prevention and treatment of hypertension study (PASTHS) do nbnot provide strong support for reducing alcohol consumption in nondependent moderate drinkers as a sole method for the prevention or treatment of hypertension	Good
53	Parker M, Puddey IB, Beilin LJ, Vandongen R.(1994) Two-way factorial study of alcohol and salt restriction in treated hypertensive men. A*m J Hypertens* 7(9 Pt 1), Sep, pp 814-23	Clinical Trial Randomized Controlled Trial	those who reduced their alcohol intake there was a fall in both systolic blood pressure (-5.4 mm Hg supine, p less than 0.01) and diastolic blood pressure (-3.2 mm Hg supine, p less than 0.01)	Poor
54	Ueshima H, Ogihara T, Baba S, Tabuchi Y, Mikawa K, Hashizume K, Mandai T, Ozawa H, Kumahara Y, Asakura S, et al.(1987) The effect of reduced alcohol consumption on blood pressure: a randomised, controlled, single blind study. *Hum Hypertens*, 1(2), Sep, pp 113-9	Randomized Controlled Trial N=50	whose alcohol consumption had reduced, showed decreases of 5.8 and 7.1 mmHg in SBP during the the first and second week	Good

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
55	Puddey IB, Beilin LJ, Vandongen R (1987) Regular alcohol use raises blood pressure in treated hypertensive subjects. A randomised controlled trial. *Lancet*, 1(8534), Mar 21, pp 647-51	RCT N=44	Mean systolic and diastolic blood pressures were significantly lower during the last 2 weeks of the low-alcohol period than during the normal-alcohol period, the mean difference in the supine readings being 5.0 (1.4) and 3.0 (0.9) mm Hg, respectively. Regression analysis suggested that reduction in alcohol intake contributed to the fall in both systolic and diastolic blood pressures independently of changes in weight. Thus, curtailing alcohol intake may lead to improved blood-pressure control and may reduce the need for antihypertensive drugs.	Good
56	Rakic V, Puddey IB, Burke V, Dimmitt SB, Beilin LJ (1998) Influence of pattern of alcohol intake on blood pressure in regular drinkers: a controlled trial. *Hypertens*, 16(2), Feb, pp 165-74	A randomized, controlled cross-over trial N=55	Baseline ambulatory systolic blood pressure in weekend but not in daily drinkers was 2.4 mmHg higher on Monday than it was on Thursday ($P = 0.02$). This Monday-Thursday difference was lost during intervention. When subjects switched from the high-alcohol to the low-alcohol period the falls in ambulatory systolic blood pressure in weekend (3.1 mmHg, $P < 0.001$) and daily drinkers (2.2 mmHg, $P < 0.001$) were similar. Most of the fall was evident during week 1 of the low-alcohol period for weekend drinkers but not until week 4 for daily drinkers	Fair
57	Gill JS, Shipley MJ, Tsementzis et al (1991) Alcohol consumption—a risk factor for hemmorrhagic and non-hemmorrhagic stroke. A*merican Journal of Medicine* 90(4), Apr, pp 489-97	Case control study N= 1 194 subjects	Low level of alcohol consumption may have protective effect upon cerebral vasculature whereas heavy consumption predisposes to hemorrhagic and non hemorrhagic stroke.	Fair
58	J The Sixth report of the Joint national Committee on Prevention, Detection, Evaluation and Treatment o High Blood Pressure	Report	Limit drink beverages containing alcohol to their daily intake to no more than 1 ounces of ethanol, 24 ounces of beer, 10 ounces of wine 2 ounces of 100 proof whiskey. Significant hypertensuion may develop during abrupt withdrawl fom heavy alcohol consumption	Good to fair

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	NIH publication Nov 1997		but recedes a few day after alcoholk consumption is reduced	
59	Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ (2003) The Seventh Report of the joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure JAMA, 389 (19), May 21, pp 2560 – 72	JNC VII Report	Limit cinsumption to no more than 2 drinks per day (1 oz or 30 ml ethanol (eg 24 oz beer , 10 oz wine, or 3 oz 80 proff whiskey) in most men and no more than 1 drink per day in women and lighter weight person. Approxaimately reduce systolic BP range 2 –4 mm Hg	Good to Fair
Cessation of smoking /tobacco consumptions				
60	Green MS, Juscha E, Luz E (1986) Blood pressure in smokers and non-smokers. Epidemiological findings *American Heart Journ*al 111(5), May, pp 932-40	Epidemiological study	The data are highly suggestive of lower blood pressure among smokers compared with nonsmokers, whereas ex-smokers have blood pressure similar to those of nonsmokers	Poor
61	Green MS, Harari G. (1995) A prospective study of the effects of changes in smoking habits on blood count, serum lipids and lipoproteins, body weight and	Population based prospective study N=987 subjects	Cessation of smoking had little effect on serum lipid or blood pressure	Fair

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	blood pressure in occupationally active men. The Israeli Cordis Study. *Journal of Clinical Epidemiology* 48(9), Sep, pp 1159-66	F/up: 2.5 years		
62	Lee DH; Ha MH; Kim JR Jacobs DR (2001) Effects of smoking cessation on changes in blood pressure and incidence of hypeertension: a 4 year follow up study *Hypertension*, 37(2), Feb, pp 194-8	N=8170 healthy male F/up: 4 years	The adjusted increment in both systolic and diastolic blood pressure were higher in those had quit for >/= 1 year than in current smoker Progressive increase in blood pressure with the prolongation of cessation in men Conclusion : Cessation of smoking may result in increases in blood pressure.	Poor
63	Reisin E (1997) Non-pharmacologica approaches to hypertension: weight; sodium, alcohol, exercise and tobacco consideration *Med Clin North Am*, 81(6), Nov, pp 1289-303	Review	Smoking cessation has not been proven to decrease blood pressure levels but should nonetheless be recommended because of its favour effects on cardiovascular morbidity and mortality	Poor
64	The Sixth report of the Joint national Committee on Prevention, Detection, Evaluation and Treatment o High Blood Pressure NIH publication Nov 1997	Report	Cigarette smoking is risk factor for cardiovascular disease, and avoidance of tobacco in any form is essential. A significant rise in blood pressure	Good to Fair

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
Physical Activities				
65	Fagard RH (1995) The role of exercise in blood pressure control: supportive evidence *Hypertension* 13(11), Nov, pp 1223 -7	Review	Overall results suggest that dynamic aerobic training may lower conventional and daytime blood pressure in adults with elevated blood pressure at baseline	Poor
66	Paffenbarger RS Jr, Hyde RT, Wing AL et al. (1993) The association of changes in physical-activity level and other lifestyle characteristics with mortality among men *New England Journal of Medicin*e 328(8), Feb 25, pp 538-45	Randomised controlled trial N=46 subjects	Diastolic blood pressure remained significantly low after 32 weeks of exercise. Reduction of medication was possible	Fair
67	Kokkinos PF, Narayan P, Colleran JA et al. (1995) Effects of regular exercise on blood pressure and left ventricular hypertrophy in African-American men with severe hypertension *New England Journal of Medicine*, 333, pp1462-7	Randomised controlled trial N=46 subjects F/up:32 weeks	Regular exercise reduce blood pressure and left ventricular hypertrophy in African-American men with severe hypertension	Good Small sample
68	Cleroux J, Feldman RD, Petrella RJ (1999) Lifestyle modification to prevent and control hypertension 4 Recommendations on Physical	Guidelines	Physical sctivity of moderate intensity involving rhythmic movement with the lower limb for 50-60 minute, 3 or 4 time per week, reduce blood pressure and appear to be more effective than vigorous exercise	Good

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	Exercise Training, Canadian Hypertension Society, Canmadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Healt Canada, Heart and Stroke Foundation of Canada *CMAJ*, 160(9 suppl), May 4, pp S21-8			
69	Uehara Y, Arakawa K (1997) Non Pharmacological therapy inhypertensive patients – effect of physical exercise on hypertension *Nippon Rinsho,;* 55(8), Aug pp 2034-8	Review	Intensity cycle ergo meter (60 min x 3 times a week x 10 week) reduce blood pressure by –11.6/-6 mmHg.	Poor
70	Jennings G Nelson L, Korner P, Esler M (1987) The place of exercise in the long term treatment of hypertension *Nephron*, 47 Suppl 1, pp 30-3	Randomised controlled trial N=13 untreated hypertension patients	Had average fall in BP of 11/9 and 16/11 mmHg after 1 month each of 3/weeks and 7/weeks exercise respectively	Good
71	Nelson L, Jenings GL, Eslver MD, Korner PI (1986) Effect of changing levels of physical activity on blood pressure and haemodynamics in essential hypertension *Lancet*, 2 (8505), Aug 30 , pp473-6	Randomised Controlled Trial N= 13 untreated hypertension patients	45 minutes bicycling at 60-70% of maximum work capacity 3 time /week and 45 min bicycling 7 times/weeks reduce blood SBP by 11/9 mmHg with 3/week exercise and by 16/11 mm Hg with 7/week exercise	Good
72	Kingwell BA, Jenings GL	Randomised controlled trial	Moderate intensity cycling produced the greatest blood pressure	Good

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	(1993) Effects of walking and other exercise programs upon blood pressure in normal subjects *Med J Australia*, 158(4), Feb 15, pp 234-8	N=14	reduction Walking induce smaller blood pressure reduction High intensity cycling did not changeblood pressure	
73	Hagberg JM, Park JJ, Brown MD (2000) The role of exercise training in the treatment of hypertension: an updated *Sports Med,* 30(3), Sep, pp 193-206	Review	Exercise training decrease blood pressure in approximately 75% of individulswith hypertension, with systolic and diastolic BP reduction averaging approximately 11 & 8 mm Hg respectively Women may reduce BP more than men, and midle aged people had greater benefits than ypung or older people. Low to moderate intensity training appears to be as , if not more, beneficials as higher intensity training innreducing BP Asian and Pacific Island patients reduce BP especialy systolic BP, more consistently than Caucasian patients, the minimaldata also indicate that African-merican patients reduce BP with exercise trainingS	Poor
74	Ehsani AA (2001) Exercise in patient with hypertension *Am J Geriatric Cardiology* 10(5), Sep-Oct, pp 253-9, 273	Review	Endurnce exercise trining can lower blood pressure in older adults with mild (grade I) hypertension. Exercise training alone is likely to be ineffective in loweing blood pressure sufficiently in older adults with moderate to severe (grade II and higher) hypertension. Low intensity endurance exercise appears to be most effective in reducing blood pressure in older hypertension adults	Poor
75	Orbach P' Lowenthal DT (1998) Evaluation and treatment of hypertension I active individuals *Med Sci Sports Exerc,* 30(10 suppl), Oct, pp S354-66	Not stated	Dynamic (aerobic) exercise is effective in lowering blood pressure (BP) only if perform regularly	
76	Kokkinos PF & Papademetriou A (2000)	Review	Mild to moderate intensity exercise may be more effective in lowering blood pressue than higher intensity exercise.	Fair

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	Exercise and hypertension Coron Artery Dis 11(2), Mar , pp 99-102			
Combination of diet with exercise				
77	Reid CM, Dart AM, Dewar EM, Jennings GL (1994) Interactions between the effects of exercise and weight loss on risk factors, cardiovascular haemodynamics and left ventricular structure in overweight subjects. *J Hypertension* 12(3), Mar, pp 291-301	Randomized, parallel-group, crossover study design N=30	The results indicate that the effects of exercise and weight reduction on blood pressure are additive, although a positive interaction may exist with respect to lipids. Despite lowering blood pressure, exercise and weight loss had no effect on cardiac left ventricular structure or function in these overweight individuals.	Good To Fair
78	Hoque MS, Ali SM; Waiz A (1998) An exercise training combined with dietary program for patients with hypertension *Bangladesh Med Res Counc Bull*, 24(1), Apr, pp14-9	Clinical Trial 28 patients- distolic BP < or = 110 mmHg -hypertensive group 28 patients diastolic BP < or = 90 mmHg -control group	Combined exercise training and dietary program could lower BP in-patient with mild to moderate hypertension, but its long-term consequences on morbidity and mortality remain to be determined.	Poor Diet + exercise
Combination diet with drug				
79	Ram CVS, Garret BN, Kaplan NM (1981) Moderate sodium restriction and various diuretics in the treatment of hypertension: effects on potassium wastage and blood pressure control	Case Controlled Study N=12 subjects F/up: 4 weeks	Moderate restriction in sodium in combination with diuretics is effective and safe in hypertension	Fair

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	Archives of Internal Medicine, 141(8), Jul, pp 1015-9			
80	Davis BR, Blaufox MD, Oberman A, Wassertheil-Smoller S, Zimbaldi N, Cutler JA, Kirchner K, Langford HG. (1993) Reduction in long-term antihypertensive medication requirements *Archives of Internal Medicine.* 53, pp1773-82	Randomised Controlled Trial N= 587 subjects F/up: 5 years	Weight reduction is an effective long-term therapy for maintaining blood pressure in the normal range when in combination with either thiazide diuretics or β blockers. Weight loss should be recommended for the management of obese individuals with mild hypertension	Good
81	Singer DR, Markandu ND, Cappuccio FP et al.(1995) Reduction of salt intake during converting enzyme inhibitor treatment compares with addition of a thiazide. *Hypertension* 25(5), Sep, pp 213-6	Randomised controlled trial N=11 subjects	Moderate salt reduction is effective in lowering blood pressure in the presence of ACE inhibitor	Good
Combination reduction alcohol intake with weight loss				
82	Puddey IB, Parker M, Beilin LJ, Vandongen R, Masarei JR.(1992) Effects of alcohol and caloric restrictions on blood pressure and serum lipids in overweight men. *Hypertension*, 20(4), Oct, pp	Randomized Controlled Trial N=86	Calorie reduction and alcohol restriction were associated with decreases in systolic blood pressure of 5.4 (p less than 0.001) and 4.8 (p less than 0.01) mm Hg, respectively, and in diastolic blood pressure of 4.2 (p less than 0.001) and 3.3 (p less than 0.01) mm Hg, respectively.	Good

No	Author, Title Journal	Type of Study, Sample size, Follow-up	Characteristics & Outcome	Grade & Comments
	533-41			
Stress and relaxation				
83	The Sixth report of the Joint national Committee on Prevention, Detection, Evaluation and Treatment o High Blood Pressure NIH publication Nov 1997	Report	Emotopma; stress can raise blood pressure acutely. Rexalation therapies and biofeedback have been studied in multiple controlled trials with little effect beyond that seen in the control groups Significant decrease in SBP and DBP in 3 months	Fair

Evidence Table: Pharmacological Treatment -

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
Diuretic				
Effectiveness				
1.	Pratt JH, Eckert GJ, Newman S, Amrosius WT (2001) Blood pressure response to small doses of amiloride and spironolactone *Hypertension* 38(5), Nov, pp 1124-9	Randomised controlled trial	Combination of amiloride and spironolactone lowered SBP by 4.6 +/- 1.6 mmHg and DBP 2.2 +/- 1.2 mm Hg Whereas either drug alone had no significant effect on BP	Good
2.	Radevski IV, Valtchanova ZP, Candy GP, Hlatswayo MN, Sareli P (2000) Antihypertensive effect of low-dose hydrochlorothiazide alone or in combination with quinapril in black patients with mild to moderate hypertension. *J Clin Pharmacol* 40(7), Jul, pp 713-21	N= 49 black South African patients F/up : 12 months	Overall, profound and sustained BP reduction was observed at the end of the study. The 24-hour BP decreased from 151 +/- 14/98 +/- 7 to 136 +/- 15/87 +/- 9 mmHg ($p < 0.0001$ at end of study vs. baseline); the mean day BP decreased from 155 +/- 14/104 +/- 7 to 140 +/- 15/91 +/- 10 mmHg ($p < 0.0001$ at end of study vs. baseline). The overall control (mean day DBP < 90 mmHg) and response (decrease in day DBP > or = 10 mmHg) rates were 49% and 61%, respectively. At the end of the study, only 2 patients (4%) remained on treatment with HCTZ. Out of the initial 12 patients controlled on HCTZ at 3 months (12/49, 24%), 5 patients remained controlled at 6 months and only 1 patient at 12 months. In contrast, quinapril/HCTZ combinations maintained their antihypertensive effect up to 9 months, with a significant number of patients (22/49, 45%) requiring the highest dose of the combination (20/25 mg daily). In conclusion, low-dose HCTZ should not be recommended as monotherapy in black patients with mild to moderate hypertension due to the fact that the BP-lowering effect is attenuated already at 6 months of treatment, with most patients requiring the addition of the ACE inhibitor.	Poor
3.	Charansonney OL, Liever M, Laville M, Lion L, Derobert E, Visele N,	Clinical Trial	PIR proves to be a potent antihypertension drug without significant effect on serum electrolytes, plasma glucose, lipids. HCT was slightly more	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Decourt S, de Rusunan MP, Luciana J, Vasmant D, Boissel JP, Grunfeld JP (1997) The Eurevie Stuyd: Contrasting Effect of piretanide and thiazides in mild to moderate hypertension *Therapie* 52(3), May-Jun, pp 169-77		potent but induced a fall in serum potassium with a significant risk of hypokalaemia. The addition of SP to ALT led to a more potent diuretic with a higher level of serum potassium and plasma creatinine disturbances.	
ANGIOTENSIN II RECEPTOR BLOCKER WITH DIURETIC				
Effectiveness				
Valsartan + HCTZ				
4	Palatini P Malacco E; Fogari R Carretta R et al (2001) A multicenter, randomised double blind study of valsartan/hydrochlorothiazide combination versus amlodipine in patients with mild to moderate hypertension *Hypertensions*, 19(9), sep, pp 1691-6	Multicenter, randomised double blind study N=690 patients -	Both treatment approaches decrease systolic blood pressure and diastolic blood pressure to the same extent. Valsartan base treatment had slightly lower incidence of adverse events (1.5 vs 5.5% p=0.006) Conclusion The result demonstrate that the valsartan/hydrochlorothiazide combination and amlodipine are equally effective in lowering blood pressure and that the combination is better tolerated	Good
Losartan + HCTZ				
5	Flack JM, Saunders E, Gradman A, Kraus We et al (2001)	Multicenter, double blind randomised parallel-group,	Losartan monotherapy lowering in mean SiDBP by 6.6 mm Hg compared with placebo	Good

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Antihypertensive efficacy and safety of losartan alone and in combination with hydrochlorothiazide in adult African Americans with mild to moderate hypertension *Clinical Therapy,* 23(8), Aug, pp 1193-208	placebo-controlled study N=440 patient -188 – placebo;-193 losartan monotherapy (50 -150 mg);59 - Losartan/HCTZ F/up - 12 weeks	Placebo group a mean SiDBP reduction of 3.9 mm Hg. The losartan/HCTZ group with reduction in SiSBP & SiDBP of 16.8 mm Hg & 10.8 mm Hg respectively (P, or = 0.01 vs placebo & losartan monotherapy) Conclusion Losartan monotherapy was significantly more effective than placebo in lowering SiSBP and SiDBP. Moreover, the losartan/HCTZ combination regimen resulted in significant & clinically meaningful additional reduction in SiSBP & SiDBP compared with losartan monotherapy or placebo	
6	Fasce E; Waggwmann H (1999) Antihypertensive efficacy of monotherapy in increasing doses versus therapy associated in low doses *Rev Med Chil,* 127(8), Aug, pp 911-8	N= 73 patients	81 % did so with the combination of losartan & HCTZ. Combination resulted in a better blood pressure lowering than monotherapy (33.2 +/- 3.2 & 29.5 +/- 3.4 mm Hg SBP respectively; 16.4 +/- 3.2 & 13.2 +/- 3.4 mm Hg DBP, $p<0.05$) Conclusion: combination therapy achieved better blood pressure levels than monotherapy .	Poor
7	Manolis AJ, Grossman E, Jelakovic B, Jacovides A, Bernhardi DC, Cabrera WJ, Watanabe LA, Battagan J, Matadamas N, Mendiola A, Woo KS, Zhu JR, Mejia AD< Bunt T, Dumortier	Multicenter, double blind, randimised parallel group study N=1161patients-Losartan 50 mg QD, titrated to 100 mg QD (n =461)	Combination of Losartan 50 mg & HCTZ 12.5 mg reduced SiDBP & SiSBP significantly more of -14.3/-18.0 mm Hg . During the last 6 weeks, showed a greater reduction in SiDBP/SiSBP (-14.5 mmHg /-18.7 mm HG)	Good

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	T, Smith RD (2000) Effects of losartan and candesartan monotherapy and losartan/hydrpchlorothiazide combination therapy in patients with mild to moderate hypertension. Losartan Trial Investigators *Clin Ther* 22(10) Oct, pp 1186-203	Candesartan 8 mg D, titrated to 16 mg D (n- 468) Losartan plus HCTZ 12.5 mg QD- at 6 weeks if SiDBP not reaching < 90 mm Hg were titrated as described, whereas patients achieving this goal continuted with low-dose monotherapy. F/up 12 weeks		
8	Benedict CR. (2000) Safe and effective management of hypertension with fixed-dose combination therapy: focus on losartan plus hydrochlorothiazide. *Int J Clin Pract*, 54(1), Jan-Feb, pp 48-54	Not Stated	Treatment of hypertensive patients with fixed-dose combination therapy consisting of losartan and hydrochlorothiazide (HCTZ) has several potential benefits over monotherapy with each of the individual components: more effective blood pressure control, a reduction in the likelihood of adverse effects, and facilitation of patients staying on therapy due to a simple once-daily regimen. Losartan plus HCTZ fixed-dose combination therapy lowers blood pressure in mild to moderate or severe hypertensive patients to a level comparable with other classes of antihypertensive drugs in combination with HCTZ. Fixed-dose combination therapy with losartan plus HCTZ is therefore an excellent choice for hypertensive patients in whom combination therapy is necessary to achieve additional blood pressure reductions.	
Telmisartan +HCTZ				
9	McGill JB, Reilly PA (2001) Cobination treatment with telmisartan and hydrochlorothiazide in black patients with mild to moderate hypertension	Randomized controlled Trial 222 patients once daily treatment with one of 20 different double-blind combination telmisartan (0, 20, 40,80, 160 mg) and HCTZ (0, 6. 25,	Telmisartan 80mg/HCTZ 12.5 mg reduced supine trough diastolic blood pressure (DBP)- primary efficacy parameter by 13.3 mm Hg and supine trough systolic blood pressure (SBP) by 21.5 mm Hg. Telmisartan 40mg/HCTZ 12.5 mg reduced supine trough SBP/DBP by 14.3/10.0 mm Hg	Good

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Clin Cardiol , 24(1), Jan, pp 66-72	12.5, 25 mg) F/up: 4 weeks	Conclusion Telmisartan 80 mg combine with HCTZ 12.5 mg is effective and well tolerated in black patients with mild to moderate hypertension, providing greater antihypertension activity than the corresponding monotherapies.	
Irbesartan + HCTZ				
10	Kochar M, Guthrie R, Triscari J, Kassler-Taub K, Reeves RA (1999) Matrix study of irbesartan with hydrochlorothiazide in mild-to-moderate hypertension. *Am J Hypertens,* 12(8 Pt 1), Aug, pp 797-805	N=683 patients were randomized to receive once-daily dosing with one of 16 different double-blind, fixed combinations of irbesartan (0, 37.5, 100, and 300 mg irbesartan) and HCTZ (0, 6.25, 12.5, and 25 mg HCTZ) for 8 weeks.	At Week 8, mean changes from baseline in trough SeDBP (mm Hg) ranged from -3.5 for placebo, -7.1 to -10.2 for the irbesartan monotherapy groups, -5.1 to -8.3 for the HCTZ monotherapy groups, and -8.1 to -15.0 for the combination groups. Irbesartan plus HCTZ produced additive reductions in both SeDBP and seated systolic BP, with at least one combination producing greater BP reduction than either drug alone (P < .001). All treatments were well tolerated; there were no treatment-related serious adverse events. Irbesartan tended to ameliorate the dose-related biochemical abnormalities associated with HCTZ alone. In conclusion, the combination of HCTZ in doses up to 25 mg with irbesartan, in doses up to 300 mg, is safe and produces dose-dependent reductions in BP.	Fair
COMBINATION OF ACE INHIBITORS WITH DIURETI				
Effectiveness				
11	Os I, Hotnes T, Dollerup J, Mogensen CE (1997) Comparison of the combination of enalapril and a very low dose of	Triple blind, parallel active controlled study 74 patients - enalapril/HCTZ (10/6 mg) with atenolol (50 mg) after 4	Enalapril/HCTZ as well as atenolol reduce both sitting & standing diastolic & systolic BP (P<0.001) but enalapril/HCTZ had a more pronounced effect than atenolol on sitting BP (p=0.019), there was a trend toward more patients achieving target diastolic BP (< 90 mm Hg, P=0.53)	Fair

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	hydrochlorothiazide with atenolol in patients with mild to moderate hypertension. Scandinavian Study Group *Am J Hypertensions* , 10(8), Aug, pp 899-904	weeks placebo baseline period		
12	Radevski IV, Valtchanova ZP, Candy GP, Hlatswayo MN, Sareli P (2000) Antihypertensive effect of low-dose hydrochlorothiazide alone or in combination with quinapril in black patients with mild to moderate hypertension. *J Clin Pharmacol,* 40(7), Jul, pp 713-21	49 black South African patients12 months	Overall, profound and sustained BP reduction was observed at the end of the study. The 24-hour BP decreased from 151 +/- 14/98 +/- 7 to 136 +/- 15/87 +/- 9 mmHg ($p < 0.0001$ at end of study vs. baseline); the mean day BP decreased from 155 +/- 14/104 +/- 7 to 140 +/- 15/91 +/- 10 mmHg ($p < 0.0001$ at end of study vs. baseline). The overall control (mean day DBP < 90 mmHg) and response (decrease in day DBP > or = 10 mmHg) rates were 49% and 61%, respectively. At the end of the study, only 2 patients (4%) remained on treatment with HCTZ. Out of the initial 12 patients controlled on HCTZ at 3 months (12/49, 24%), 5 patients remained controlled at 6 months and only 1 patient at 12 months. In contrast, quinapril/HCTZ combinations maintained their antihypertensive effect up to 9 months, with a significant number of patients (22/49, 45%) requiring the highest dose of the combination (20/25 mg daily). In conclusion, low-dose HCTZ should not be recommended as monotherapy in black patients with mild to moderate hypertension due to the fact that the BP-lowering effect is attenuated already at 6 months of treatment, with most patients requiring the addition of the ACE inhibitor.	Poor
13	Santello JL, Mion Junior D.(1998) Captopril combined with hydrochlorothiazide in mild and moderate hypertension. A Brazilian multicenter study *Arq Bras Cardiol*, 71(5), nov, pp 713-6	Open, multicenter and non-comparative study	Initial systolic and diastolic pressures were 156 +/- 16 and 103 +/- 11 mmHg and after 14 days of placebo were 156 +/- 15 and 103 +/- 9 mmHg ($p > 0.05$). Systolic/diastolic pressure after 4, 8 and 12 weeks of treatment reduced progressively ($p < 0.05$) to 143 +/- 14/95 +/- 11, 140 +/- 13/91 +/- 9 and 134 +/- 11/86 +/- 8 mmHg. Blood pressure control was observed in 45, 67 and 88% ($p < 0.05$) of patients after 4, 8 and 12 weeks. Cough was the most important symptom, registered in 7% of patients under placebo and 12% in patients under treatment. The tolerance was considered good for 98% of patients. The association of captopril with hydrochlorothiazide is effective with good tolerance, being indicated as a once a day monotherapy for mild and moderate hypertension.	Fair

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
14	Chalmers J, Castaigne A, Morgan T, Chastang C (2000) Long term efficacy of new fixed, very low dose angiotensin converting enzyme inhibitor/diuretic combination s first line therpy in elderly hypertension patients *Hypertension* , 18 (3), Mar, pp 37-37	Multicentre Study Randomised controlled trial N= 193	Very low dose combination of perindopril 2mg/indapamide 0.625 mg result in sustained blood pressure control when used as first line treatment for elderly hypertensive patients over 1 yer and is well tolerated .	Good
15	Ishimitsu T, Yagi S, Ebihara A, Doi Y, Domae A, Shibata A, Kimura M, Sugishita Y, Sagara E, Sakamaki T, Murata K (1997) Long-term evaluation of combined antihypertensive therapy with lisinopril and a thiazide diuretic in patients with essential hypertension. *Jpn Heart J.* 38(6), Nov, :831-40.	Clinical Controlled Trial N=466 F/up: 1 year	The average blood pressure was effectively lowered to below 150/90 mmHg in both the monotherapy and the combination therapy groups throughout the study period. The average maintenance dose of lisinopril was lower when combined with thiazide than when given alone (9.8 vs. 11.5 mg/day, $p < 0.001$). Dry cough was the major side effect of lisinopril; no severe adverse effects were observed. The incidence of cough was not significantly different between the monotherapy group (13.1%) and the combination therapy group (11.3%). The increase in serum potassium observed in the monotherapy group was reversed by the concurrent use of the thiazide diuretic in the combination therapy group. Fasting blood glucose was significantly reduced in the monotherapy group; the reduction observed in the combination therapy group was not significant. Thus, the present results provide useful information as to the effectiveness and safety of combined antihypertensive therapy with lisinopril and a thiazide in comparison with monotherapy with lisinopril.	Poor
COMBINATION OF CALCIUM CHANNEL BLOCKER WITH ACE INHIBITOR				
Effectiveness				
16	Roca-Cusacs A, Torres , Horas M , Rios J, Calvo G, Delgadillo J, Teran M (2001) Nitrendipine and Enalapril combination therapy in mild to moderate hypertension assessment of Dose-Response Relationship by a clinical Trial of Factorial Design	Multicenter, randomized, double blind, factorial design, parallel group clinical trial comparing placebo, nitrendipin (5, 10 & 20 mg) and enalapril (5, 10 & 20 mg) alone or in combination -496 patients after 2 weeks placebo run in period, 414 patient with BP range between 90-109 mm Hg were randomly assign	The combination of nitrendipine & enalapril, particularly regime of nitrendipine 20 mg & enalapril 5 or 10 mg were significantly superior to both the monoterapies, mean diastolic blood pressure reductions from baseline to last visit were -12.5 & -14.3 mm Hg respectively Conclusion the antihypertensive efficacy of the combination was found to be superior to both monoterapies at any dose. The dose combination achieving the greatest blood pressure reduction was nitrendipin 20 mg & enalapril 10 mg	Good

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	J Cardiovas Pharmacol, 38(6), Dec, pp 840-849	to treatment group		
17	Naidu MU, Usha PR, Rao TR, Shobha JC (2000) Evaluation of amlodipine, lisinopril, and a combination in the treatment of essential hypertension. Pos*tgrad Med J,* 76(896), Jun, 350-3	Clinical Trial Randomized Controlled Trial N=Twenty four patients	There was a significant additional blood pressure lowering effect with the combination when compared either with amlodipine or lisinopril alone.. The combination of 2.5 mg amlodipine with 5 mg lisinopril produced a much more significant lowering of blood pressure in a higher percentage of patients than that with an individual low dose.	Good Small sample
18	Ruddy TD, Fodor JG (1997) Nisoldipine CC and lisinopril alone or in combination for treatement of mild to moderate ysytemic hypertension. Canadian Nisoldipine CC Hypertension Trial *Cardiovasc Drug Ther,* 11 (4), Sep, pp 581-90	Randomised Controlled Trial N= 278 patients F/up:8 weeks	Combination of nisoldipine dan lisinopril was effective and well tolerated with blood pressure not controlled by monotherapy alone	Good

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
BETA BLOCKER				
19	Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, MatersonBJ, Oparil S, Wright JT, Roccella EJ (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure *JAMA*. 289	Guideline	Beta-blockers, prove to lowering BP, will all reduce the complications of hypertension.	Good
20	Pieniazek W, Franczuk P, Janicki K.(2001) [The comparison of clinical effectiveness of perindopril and acebutolol in the primary hypertension treatment] *Przegl Lek*, 58(5), pp 411-4.	Clinical Trial Randomized Controlled Trial Double blind, placebo controlled study performed in the group of 31 patients	Both perindopril and acebutolol proved to be effective in monotherapy of hypertension. After 3 weeks of the treatment we observed BP systolic and diastolic normalization, but more patients had systolic BP normalization after perindopril	Fair
21	Owada A, Suda S, Hata T, Miyake S. (2001) The effects of bisoprolol, a selective beta1-blocker, on glucose metabolism by long-term administration in essential hypertension. *Clin Exp Hypertens*. 23(4), May, pp 305-16.	Clinical Trial N-13 patient	beta-blocker possessing a satisfactory hypotensive effect without any adverse effects on glucose metabolism for long-term use, and is therefore a safe and useful drug for the treatment of essential hypertension.	Fair

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
22	Feldman, RD, Campbell N, Larochelle P, Bolli P, Burgess ED, Carruthers S. G, Floras JS, Haynes R. B, Honos G, Leenen, FHH, Leiter LA,. Logan AG, Myers MG, Spence JD, Zarnke KB, (1999) Canadian recommendations for the management of hypertension *CMAJ*, 161(12 Suppl), pp S1.	Guidelines	Initial therapy should be monotherapy with a thiazide diuretic, preferably at a low dose, a ß-adrenergic antagonist. Combination therapy, either with a thiazide diuretic and a ß- adrenergic antagonist should be used if there is only a partial response to monotherapy For uncomplicated hypertension without contraindication, the preferred therapy in hypertensive patients over the age of 60 years Although ß-adrenergic antagonists may be useful as adjunctive therapy in elderly patients taking diuretics, they are not recommended as first-line therapy The benefits of ß-adrenergic antagonist therapy in hypertensive smokers remain uncertain. Thus, ß-adrenergic antagonists are not recommended for hypertensive patients who smoke, in the absence of target-organ damage or concurrent cardiovascular disease	Good
23	1999 WHO/ISH Guidelines for the Management of Hypertension *J Hypertension, 17 pp 151-185*	Guidelines	Beta blocker are safe, effective for use as monotherapy or in combination with diuretic, dihydropyridine calcium antagonists and alpha blocker Whereas heart failure used to be a clear contraindication to the use of beta blokers in standard dose there is emerging evidence that they may have a beneficial effect when used in very low starting dose in some patient with heart failure Beta-blocker should be avoided in patient with obstructive airway disease & peripheral vascular disease.	Good
ANGIOTENSIN II RECEPTOR (AT1 SUBTYPE) BLOCKER COMBINE WITH ACE INHIBITOR				
Effectiveness				

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
24	Azizi M, Linhart A, Alexander J, Goldberg A, Menten J, Sweet C, Menard J. Pilot study of combined blockade of the renin-angiotensin system in essential hypertensive patients. *J Hypertens* 2000 Aug; 18(8) :1139-47	Multicenter, randomized, double-blind, parallel-group, pilot study. N=177 patients.	24-hour ambulatory mean DBP did not significantly differ between treatment groups although the combination tended to lower BP more. The combination therapy was more effective on clinic DBP measured at trough than was losartan by 3.2 mmHg [confidence interval (95%, CI) 0.7-5.7 mmHg, P = 0.012], and more effective than enalapril by 4.0 mmHg (95% CI, 1.5-6.4 mmHg, P = 0.002). In a subgroup of 28 patients, higher plasma active renin and angiotensin I levels during blockade by the combination therapy were observed. This finding confirmed that the combination of the two agents inhibited the renin-angiotensin system to a greater extent than did either agent alone. A combination of 10 mg enalapril daily and 50 mg losartan daily safely induces a supplementary, although modest, fall in clinic DBP in patients with mild-to-moderate essential hypertension.	
ANGIOTENSIN II RECEPTOR (AT1 SUBTYPE) BLOCKER				
EFFECTIVENESS				
Candasartan cilexetil				
25	Weir MR, Weber MA, Neutel JM, Vendetti J, Michelson El, Wang Ry (2001) Efficacy of candesartan cilexetil as add-on therapy in hypertensive patients uncontrolled on background therapy: a clinical experience trial. ACTION Study Investigators *Am J Hypertension,* 14(6 Pt 1), Jun, pp 567-72	Multicenter Study, Clinical Trial 6465 hypertensive patients- either untreated or uncontrolled hypertension (SBP 140 to 179 mm Hg or DBP 90-109 mm Hg inclusive baseline) despite a variety of antihypertensive medication including diuretics, calcium antagonists, angiotensin converting enzyme (ACE) inhibitors,, & alpha/beta blocker etiher singly or in combination.	The mean baseline blood pressure for the essential Hypertension Candesartan cilexetil as monotherapy reduce mean SBP/DBP by 18.7 mm Hg/13/1 mm Hg. As add on therapy to various background therapies. Candesartan cilexetil consistently reduced mean SBP/DBP further irrespective of the background therapy: Diuretic -17.8/11.3 mm Hg, Calcium antagonists 16.6/11.2 mm Hg, Beta blocker -16.4/10.4 mm Hg, ACE inhibitors - 15.3/10.0 mm Hg,Alpha blockers 16.4/10.4 mm Hg For the isolated systolic hypertension group. Candesartan cilexetil as monotherapy reduce mean SBP/DBP by 17.0 mm Hg/4.4 mm Hg. As add on therapy to various background therapies. Candesartan cilexetil consistenly reduced mean SBP/DBP further irrespective of the background therapy: Diuretic -17.4/5.1 mm Hg,Calcium antagonists 15.6/3.6 mm Hg,Beta blocker -14.0/4.8 mm Hg,ACE inhibitors - 13.4/4.3 mm Hg,Alpha blockers 11.6/4.5 mm Hg	Poor
26	Himmelmann A, Keinanen-Kiukaanniemi S, Wester A, Redon J, Asmar R, Hedner T (2001)	Multicenter, randomised double blind parallel group study 395 were randomised to an 8 week	There was a significant difference in the adjusted mean difference for the change from baseline to week 8 between candasartan cilexetil and enalapril 22 -24 h post dose by -3.5 mm Hg (95% CI :- 6.8 to -0.3 mm Hg p< 0.032)	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	The effect duration of candesartan cilexetil once daily, in comparison with enalapril once daily, in patients with mild to moderate hypertension *Blood press*;10(1), pp 43-51	double blind treatment period with either candesartan cilexetil 8-16 mg or enalapril 10-20 mg once daily, with force dose titration after 4 weeks	There was significant difference in adjusted mean daytime ambulatory blood pressure24 -36 h post dose by -4.2 mm Hg (95% CI: -6.8 to -1.6 mm Hg P< 0.002) / -3.5 mm Hg 95% CI: -5.1 to -1.8 mm Hg; p<0.001) Both drug was general well tolerated Conclusion In comparison with enalapril 20 mg , candasartan cilexetil 16 mg more effectively lowered blood pressure at trough and in particularly on the day following the dau after the last dose	
27	Sever P; Holzgreve H (1997) Long term efficacy and tolerability of candesartan cilexetil in patients with mild to moderate hypertension *J Hum Hypertens.* 11 (Suppl 2), pp :S69-73	Open label, prospective multicenter studies	4-16 mg of candesartan cilexetil once daily effectively lowered blood pressure and maintained its antihypertensive effect over a long term (< or 12 months). 81% patients showed a clinically significant response (reduction of SiDBP of or = 10 mm Hg or reduction to < 90 mm Hg) and 73.8% experienced normalization of SiDBP (< 90 mm Hg)	Poor
28	Malmqvist K, Kahan T, Dahl M.(2000) Angiotensin II type 1 (AT1) receptor blockade in hypertensive women: benefits of candesartan cilexetil versus enalapril or hydrochlorothiazide. *Am J Hypertens*, 13(5 Pt 1), May, pp 504-11	Clinical Trial Randomized Controlled Trial candesartan cilexetil, 8 to 16 mg (n = 140), enalapril, 10 to 20 mg (n = 146), or HCTZ, 12.5 to 25 mg (n = 143), for 12 weeks	Candesartan cilexetil lowered seated blood pressure by 17/11 and 19/11 mm Hg after 6 and 12 weeks of treatment, respectively. This reduction was greater (P < .01) than with enalapril (12/8 and 13/9 mm Hg) or HCTZ (12/7 and 13/8 mm Hg). The proportions of patients with controlled DBP (< 90 mm Hg) after 12 weeks of treatment with candesartan cilexetil, enalapril, or HCTZ were 60%, 51%, and 43%, respectively Conclusion, candesartan cilexetil reduced blood pressure more effectively and was better tolerated than enalapril or HCTZ in women with mild to moderate hypertension.	Fair
29	Kloner RA, Weinberger M, Pool JL, Chrysant SG, Prasad R, Harris SM, Zyczynski TM, Leidy NK, Michelson EL (2001) Comparative effects of candesartan	Clinical Trial Multicenter Study Randomized Controlled Trial N=251 adult patients (received candesartan cilexetil 16 mg (n = 123)	Overall, 79% of patients on candesartan cilexetil and 87% of those on amlodipine were controlled (diastolic BP <90 mm Hg) Candesartan cilexetil and amlodipine are both highly effective in controlling BP in patients with mild hypertension..	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	cilexetil and amlodipine in patients with mild systemic hypertension. Comparison of Candesartan and Amlodipine for Safety, Tolerability and Efficacy (CASTLE) Study Investigators. *Am J Cardiol*. ;87(6),ar 15, pp 727-31	or amlodipine 5 mg (n = 128) once daily.)		
Losartan				
30	Flack JM, Saunders E, Gradman A, Kraus We et al (2001) Antihypertensive efficacy and safety of losartan alone and in combination with hydrochlorothiazide in adult African Americans with mild to moderate hypertension *Clinical Therapy*. 23(8), Aug, pp 1193-208	Multicenter, double blind randomised parallel-group, placebo-controlled study 440 patient -188 - placebo -193 losartan monotherapy (50 -150 mg) - 59 - losartan/HCTZ,. F/up - 12 weeks	Losartan monotherapy lowering in mean SiDBP ny 6.6 mm Hg compared with placebo Placebo group a mean SiDBP reduction of 3.9 mm Hg. Conclusion Losartan monotherapy was significantly more effective than placebo in lowering SiSBP and SiDBP.	Fair
31	Shobha JC, Kumar TR, Raju BS, Kamath S, Rao M, Harwal, Babu A, Bhaduri J (2000) Evalution of efficacy and safety of losartan potasium in the treatment of mild to moderate hypertension as compared to enalpril	Randomised double blind controlled parallel & multicenter study 145 patient 72 patients - losartan potassium 50 mg	Losartan potassium reduced the DBP to < 90 mm Hg in 59% of patient at the end of 8 weeks compare to 45 % in the enalapril maleate group DBP was reduce by 10 or > 10 mm Hg in 89% of the patients with losartan as compared to the baseline whereas it was 80% in the enalapril group Conclusion Losartan potassium is an efficacious antihypertensive agent in mild to moderate hypertension. It also has fewer side effect when compare to	Good

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	J Assoc Physician India. 48(5), May, pp 497-500	73 patient - enalapril maleate 5 mg F/up: 8 weeks	enalapril maleate	
32	Elliott WJ, Calhoun DA, Delucca PT, Gazdick LP, Kerns DE, Zeldin RK (2001) Losartan versus valsartan in the treatment of patients with mild to moderate essential hypertension: data from multicenter, randomised, double blind 1 weeks trial *Clin Ther*. 23 (8), Aug, pp 1166-79	Radomized, multicenter, double blind parallel group equivalence study N= 495 patients 247 patient -losartan 50 mg 248 patient -valsartan 80 mg F/up :12 weeks	At stating and titrated doses, losartan & valsartan are similarly effective in reducing blood pressure in patient with mild to moderate hypertension. Losartan but not valsartan was associated with a decrease in serum uric acid levels.	Fair
33	Manolis AJ, Grossman E, Jelakovic B, Jacovides A, Bernhardi DC, Cabrera WJ, Watanabe LA, Battagan J, Matadamas N, Mendiola A, Woo KS, Zhu JR, Mejia AD< Bunt T, Dumortier T< Smith RD (2000) Effects of losartan and candesartan monotherapy and losartan/ hydrpchlorothiazide combination therapy in patients with mild to moderate hypertension. Losartan Trial Investigators *Clin Ther,* 22(10), Oct, pp 1186-203	Multicenter, double blind, randimised parallel group study N=1161patients-were F/up 12 weeks	Changes in SiDBP & SiSBP of -12.4/-14.4 mm Hg with losartan 50/100 mg and lower serum uric acid (0.13 mg/dl, 95 % CI, 0.04 to 0.23)	Poor
34	Hung Mj, Lin FC, Cherng WJ, Wang CH, Hung KC, Hsieh IC, Wen MS, Wu D.(1999) Comparison if antihypertensive efficacy and tolerability of losartan and extended-release felodipine in patients	Prospective, randomised, parallel study N= 44 patients 23- losartan 21- Felodipine	The mean reduction in sitting diastolic blood pressure at 6 and 12 weeks were significant with losartan (-8.6 & -11.8 mm Hg) respectively	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	with mild to moderate hypertension. *J Formos Med Assoc.* 98(6), Jun, pp 403-9	F/up:;12 weeks		
35	Roca-Cusachs A, Oigman, W Lepe L; Cifkova R, Karpov Ya, Harron DW (1997) A randomized double blind comparison of the antihypertension efficacy and safety of once daily losartan compared to twice daily captopril in mild to moderate essential hypertension *Acta Cardiol* 52(6), pp 495-506	Clinical Trial, Multicenter Study, Randomised Control Trial N= 192 – Losartan; 204- Captopril	Both treatment produced clinical important reductions SiDBP and SiSBP, The mean reduction (SiDBP & SiSBP) were significant.y greater in the losartan group (-11.5 & -15.4 mmHg respectively) than in the captopril group (-9.3 & -12.2 mm Hg respectively) (p=0.010 diastolic and p=0.023 for systolic) Once daily administration of losartan is effective treatment for patients with essential mild to moderate hypertension The antihypertensive efficacy of losartan is significantly greater than twice daily captopril.	Poor
36	Monterroso VH, Rodriguez Chavez V, Carbajal ET, Vogel DR, Aroca Martinez GJ, Garcia LH, Cuevas JH, Lara Teran J, Hitzenberger G, Leao Neves P, Middlemost SJ, Dumortier T, Bunt AM, Smith RD (2000) Use of ambulatory blood pressure	Multicenter, double-blind, randomized trial losartan 50 mg (n = 93) or valsartan 80 mg (n = 94) for 6 weeks were assessed through measurements taken in the clinic and by 24-hour ambulatory blood pressure	Both drugs significantly reduced clinic sitting systolic (SiSBP) and diastolic blood pressure (SiDBP) at 2, 4, and 6 weeks. Maximum reductions from baseline in SiSBP and SiDBP on 24-hour ABPM were also significant with the two treatments. The reduction in blood pressure was more consistent across patients in the losartan group, as indicated by a numerically smaller variability in change from baseline on all ABPM measures, which achieved significance at peak (P = .017) and during the day (P = .002). In addition, the numerically larger smoothness index with	Good

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	monitoring to compare antihypertensive efficacy and safety of two angiotensin II receptor antagonists, losartan and valsartan. Losartan Trial Investigators. *Adv Ther* ,17(2), Mar- Apr, pp 117-31	monitoring (ABPM)	losartan suggested a more homogeneous antihypertensive effect throughout the 24-hour dosing interval. The antihypertensive response rate was 54% with losartan and 46% with valsartan. Three days after discontinuation of therapy, SiDBP remained below baseline in 73% of losartan and 63% of valsartan patients. Both agents were generally well tolerated. Losartan, but not valsartan, significantly decreased serum uric acid an average 0.4 mg/dL at week 6. In conclusion, once-daily losartan 50 mg and valsartan 80 mg had similar antihypertensive effects in patients with mild to moderate essential hypertension. Losartan produced a more consistent blood pressure-lowering response and significantly lowered uric acid, suggesting potentially meaningful differences between these two A II receptor antagonists.	
37	Zimlichman R. (1999) Israeli experiences of treatment of hypertension with losartan (Ocsaar)--summary of the treatment of 421 patients in community health centers] Harefuah. 137(12), dec 15, pp 597-603, 680	Clinical Trial Controlled Clinical Trial Multicenter Study N=421 patients	After 4 weeks blood pressure was normalized in 344 and after 12 weeks in 363.	Poor
38	Hedner T, Oparil S, Rasmussen K, Rapelli A, Gatlin M, Kobi P, Sullivan J, Oddou-Stock P. (1999) A comparison of the angiotensin II antagonists valsartan and losartan in the treatment of essential hypertension.	Clinical Trial Randomized Controlled Trial	Valsartan produced a significantly higher number of responders (62%) than losartan (55%, P = .02) at the 8 week treatment endpoint. Valsartan (80/160 mg) monotherapy in this trial was as effective and well tolerated as 50/100 mg losartan in treating mild to moderate essential hypertension, and at 160 mg has a significantly higher responder rate than 100 mg losartan.	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Am J Hypertens 12(4 Pt 1), Apr, pp 414-7			
Telmisartan				
39	Karlberg BE, Lins LE Hermansson K (1999) Efficacy and safety of telmisartan, a selective AT1 receptor antagonist compared with enalapril in elderly patients with primary hypertension (TEES Study Group *J Hypertension.* 17 (2), Fweb 17, pp 293-302	Multicenter double blind, parallel group dosage titration study Randomised Controlled Trial N= 278 F/up 12 weeks	The adjusted mean changes from baseline in supine diastolic blood pressure at trough were -1.8 mm Hg for telmisartan and - 11.4 mm Hg for enalapril (P=0.074). Mean changes in supine systolic blood pressure were -22.1 mm Hg for telmisartan and -20.1 mm Hg for enalapril (P=0.350)	Good
40	Freytag F, Schelling A Meinicke T, Deichsel G (2001) Comparison of 26 week efficacy and tolerability of telmisartan and atenolol, in combination with hydrochlorothiazide as reuired, in the treatment of mild to moderate hypertension: a randomised, multicenter study *Clin Ther*. 23(1), Jan, pp: 108-23	Multicenter, randomized, double blind, double dummy, parallel group titration toresponse study compared doses of telmisartan (40mg titrated to 80mg titrated to 120 mg) with atenolol (50 mg tittrated to 100 mg). Open label hydrocglorothiazide (HCTZ) 12.5 or 25 mg . 346 receive telmisartan 174 receive atenolol	SBP/DBP reductions of 20.9/14.4 mm Hg were observed for the telmisartan regimen versus 16.7/13.3 mm Hg for the atenolol regimen. Only the difference in SBP was significant (P=0.005) Reduction from baseline in SBP of > or = 10 mm Hg was achieved by 80 % of telmisartan treated and 68 % of atenolol treated patients (P=0.003) Conclusion Telmisartan appears to be at least as effective as atenolol in the treatment of mild to moderate hypertension and may be better tolerated.	Fair
41	Smith DH, Matzek KM, Kempthorne Rawson J (2000) Dose response and safety of telmisartan in patient with mild to moderate hypertension *J Clin Pharmacol* 40 (12 Pt 1), Dec, pp1380-90	Randomised, Double blind, double dummy, placebo controlled, parallel-group study 207 patients - DBP 100 to 114 mm Hg, after 8 day placebo run in period. Patients were randomised to 28 day once daily, double blind treatment, double dummy treatement with	All doses of telmisartan and enalapril significantly reduce BP compared to placebo (p < or = 0.01) Mean +/- SE reductions in supine DBP after 28 days of treatment ranged between 7.9 +/- 1.3 mm Hg and 9.8 =/- 1.3 mm Hg in the telmisartan group and 1.5 mm Hg =/- 1.3 mm Hg with placebo Mean +/- SE reduction in SBP were 10.2 =/- 2.1 mm Hg with enalapril , placebo increase supine SBP by 3.5 =/- 2.1 mm Hg Conclusion All active treatment were well tolerated, with tolerability profiles similar	Good

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
		telmisartan 40, 80 or 120 mg. Enalapril 20 mg or placebo	to placebo and telmisartan did not produce any clinically relevant first dose effects.	
42	Littlejohn T, Mroczek W, Marbury T, VanderMaelen CP, Dubiel RF. (2000) A prospective, randomized, open-label trial comparing telmisartan 80 mg with valsartan 80 mg in patients with mild to moderate hypertension using ambulatory blood pressure monitoring.] *Can J Cardiol*. 16(9), Sep, pp 1123-32	Prospective, randomized, open-label, blinded end point, parallel group study. N=426 patients (n=214 telmisartan 80 mg; n=212 valsartan 80 mg))	Treatment with telmisartan was associated with a significantly greater mean reduction from baseline in the last 6 h ABPM mean for diastolic blood pressure compared with the valsartan-treated group (-7.5+/-0.6 mmHg versus -5.2+/-0.6 mmHg, respectively, P<0.01). Secondary analyses showed significantly greater efficacy with telmisartan 80 mg than with valsartan 80 mg, including greater mean reductions from baseline of ABPM (systolic blood pressure and diastolic blood pressure) during the daytime (06:00 to 21:59) and morning (06:00 to11:59) hours, and larger decreases in trough cuff blood pressure (P<0.01). Both treatments showed placebo-like tolerability profiles. CONCLUSIONS: Telmisartan 80 mg once daily was superior to valsartan 80 mg once daily in reducing diastolic blood pressure during the last 6 h of the 24 h dosing interval. These results may be due to telmisartan's longer plasma half-life or to a higher potency compared with valsartan, such that a higher dose of valsartan may produce effects similar to those of 80 mg telmisartan. These data confirm the long duration of action of telmisartan with consistent and sustained control of blood pressure over 24 h and during the last 6 h of the dosing interval. Both treatments were well tolerated; the adverse event data confirmed the excellent tolerability profiles of telmisartan and valsartan that have been reported previously.	Good to Fair
43	Neutel JM, Frishman WH, Oparil S, Papademitriou V, Guthrie G. (1999) Comparison of telmisartan with lisinopril in patients with mild-to-moderate hypertension. *Am J Ther* 6(3), May, pp 161-6	Randomized, multicenter, double-blind, double-dummy, parallel-group, dose-titration study N=578 patients 52-week	DBP control was achieved on monotherapy by 67% and 63% of the telmisartan and lisinopril patients, respectively. At the end of the maintenance period, supine DBP was controlled in 83% and 87% of the telmisartan and lisinopril patients, respectively, with systolic blood pressure over DBP reductions of 23.8/16.6 mm Hg for telmisartan and 19.9/15.6 mm Hg for lisinopril. The selective AT (1) receptor antagonist, telmisartan, is extremely effective in the treatment of mild-to-moderate hypertension both as monotherapy and in combination with HCTZ and is at least comparable in efficacy to lisinopril, with a tolerability profile that may offer advantages in terms of a reduced incidence of adverse events.	Good

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
44	Mallion J, Siche J, Lacourciere Y (1999) ABPM comprison of the antihypertension profiles of the selective angiotension II receptor antagonists telmisartan and losartan in patients with mild to moderate hypertension *J Hum Hypertension* 13(10), Oct, pp 657-64	Multinational, multicentre, randomised, double blind study F/Up 6 weeks N= 223 patients	Ambulatory blood pressure monitoring (AMBP) after 6 weeks showed that all active treatment produced significants reduction from baseline in 4 h mean SBP and DBP cpmpred with placebo During the 18-24 h period fter dosing the reduction in SBP/DBP with telmisatan 40 mg and 80 mg was greater than those observed for losartan 50 mg and losartan was no better than placebo 24 h men blood pressure,telmisartan 40mg and 80 mg were significantly better than losartan 50 mg. Compared with losartan, telmisaartan 80 mg produced significantly greater reductionin both SBP and DBP during all monitored period (10.01pm-5.59 am.) Telmisartan 40 mg and 80 mg once daily were effective and well tolerated in the treatment of mild to moderate hypertension, producing sustaine 24 h blood pressure control which favourably with losartan	Good to fair
45	Mc Clellan KJ, Markham A (1998) Telmisartan *Drug* 56(6), Dec, pp1039-44	Review	Administration of 40 -160 mg once daily of telmisartan to patient with mild to moderate hypertension, it significantly reduce systolic and diastolicBP compared with placebo and was at least as effective as atenolol 50 or 100 mg and lisinopril 10 -40 mg. Telmisartan 80 mg /day to be more effective than enalapril 20mg/day. Telmisartan 80 mg provide better control of diastolic BP for the full dosing terval than losartan potassium 50 mg or amlodipine 5 or 10 mg.	Fair
Irbesartan				
46	Lacouciere Y (2000) A multicenter, randomised, double-blind study of the antihypertensive eficacy and tolerability of irbesartan in patients aged > or = 65 years with mild to moderate hypertension	Clinical Trial Multicenter Study, Randomised Control Trial N= - 70 -daily dose of irbesartan 150 mg - 71 enalapril 10 mg F/up- 8 weeks	There was a mean reduction sitting DBP of 9.6 mm Hg for irbesartan . The mean reduction of sitting SBP was 10.1 mm Hg and for irbesartan Conclusion Irbesartan is an effective antihypertensive drug for elderly mild to moderate hypeertension	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Clin Ther 22 (10), Oct, pp 1213-24			
47	Chiou KR, Chen CH, Ding PY, Chen YT, Huang JL, Chiang AH, Liu CP, Tseng CJ, Chao CT, Chang MS (2000) Rnadomised, double blind comparison of irbesartan and enalapril for treatment of mild to moderate hypertension *Chung Huah I Hsuah Tsa Chih*, 63 (5), May, pp :368-76	Multicenter , double blind, randomise, parallel group study N= 116 patients F/up: 8 weeks	Irbesartan 150-300 mg provide reduction in trough seated systolic and diastolic blood pressure at week 8 of -16.5mm Hg and -7.2 mm Hg respectively	Fair
48	Hanson L Smith DH, Reeves R, Lapuert P (2000) Headache in mild to moderate hypertension and its reduction by irbesartan therapy *Arch Internal Medicine*. 160(11), Jun 1, pp1654-8	Review	Irbesartan was associated with significant reduction in the incidence of headache. Mild to moderate hypertension is not asymptomatic and that the incidence of hedache can be reduced by antihypertensive treatement with a favorable adverse effect profile.	Poor
49	Oparil S, Guthrie R, Lewin AJ, Marbury T, Reilly K, Triscari J, Witcher JA. (1998) An elective-titration study of the comparative effectiveness of two angiotensin II-receptor blockers, irbesartan and losartan. Irbesartan/Losartan Study Investigators. *Clin Ther*, 20(3), may -Jun, pp	Multicenter, randomized, double-masked, elective-titration study N=432- were randomly allocated to receive either irbesartan 150 mg once daily (n = 213) or losartan 50 mg once daily (n = 219).	The mean change in trough SiDBP at week 8, the primary efficacy end point, was significantly greater in patients receiving irbesartan monotherapy than in those receiving losartan monotherapy (-10.2 mm Hg vs -7.9 mm Hg, respectively). At week 12, reductions in trough SeDBP and seated systolic blood pressure were greater with irbesartan treatment than with losartan treatment (-13.8 mm Hg vs -10.8 mm Hg and -18.0 mm Hg vs -13.9 mm Hg, respectively), and a greater proportion of irbesartan patients responded to therapy (i.e., trough SeDBP < 90 mm Hg or reduction in trough SeDBP > or = 10 mm Hg) compared with losartan patients (78% vs 64%, respectively). Both regimens were well tolerated.	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	398-409			
50	Kassler-Taub K, Littlejohn T, Elliott W, Rudy T, Adler E (1998) Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan in mild to moderate hypertension. Irbesartan/Losartan Study Investigation *Am J Hypertension*. 11 (4 part 1), April 1, pp 445-53	Randomised Controlled Trial N=567 patients F/up: 8 weeks	After 8 weeks of treatment , reduction in trough seated diastolic blood pressure and trough systolic blood pressure with 300 mg irbesartan were greater than with 100 mg losartan. Throughout the study, the antihypertensioneffect of 150 mg irbesartan did not differ significantly from that of 100 mg losartan	Good to fair
51	Gillis JC, Markham A (1997) Irbesrtan : A review of its pharmacodynamic and pharmacokinetic properties and therapeutics use in the management of hypertension *Drug* 54(6), Dec, pp 885-902	Review	Once daily administration of irbesartan 150 -300 mg with or without adjunctive antihypertension agents , provide 24 hour BP control. Irbesartan reduced BP to a similar extent to enalapril and atenolol and to aa significantly greater extent than losartan.	Poor
Eposartan				
52	Levine B. (2001) Eprosartan provides safe and effective long-term maintenance of blood pressure control in patients with mild to moderate essential hypertension *Curr Med Res Opi.* 17(1), pp8-17	Clinical Trial Multicenter Study N=706 patients- from 55 centres in the USA and three centres in Canada were randomised to receive once-daily eprosartan (400-800 mg) alone or in combination with hydrochlorothiazide (HCTZ). The study consisted of five periods:	Once-daily eprosartan was well tolerated either alone or in combination with HCTZ, irrespective of the study dose administered. Patients treated with eprosartan had a safety profile similar to that reported in short-term placebo-controlled studies. The most frequently reported adverse event was upper respiratory tract infection, and although events increased with the addition of HCTZ, they were generally not severe. The beneficial effect on BP was maintained throughout treatment. In summary, eprosartan provides reliable blood pressure control in a high proportion of patients, with a safety profile similar to that seen with placebo in short-term, placebo-controlled trials. By providing long-term	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
		screening (day 1), run-in (2-4 weeks), titration (3-15 weeks), maintenance (12-24 months) and follow-up (5-7 days).	safety and efficacy, eprosartan may have the potential to increase patient compliance, a significant issue in the treatment of hypertension in all patient types.	
53	Plosker GL, Foster RH.(2000) Eprosartan: a review of its use in the management of hypertension. *Drugs.* 60(1), July, pp 177-201	Review N= > 100	Demonstrated that the antihypertensive efficacy of eprosartan (usually 400 to 800 mg/day as a single daily dose or in 2 divided doses) is significantly greater than that of placebo and at least as good as that of enalapril. In placebo-controlled trials, eprosartan achieved mean reductions from baseline in trough sitting systolic blood pressure of 6.3 to 15 mm Hg and in diastolic blood pressure of 4.1 to 9.7 mm Hg. Response rates associated with once daily administration of eprosartan 400 to 800 mg were approximately double those with placebo. Overall, eprosartan was well tolerated with a similar tolerability profile to that of placebo. In comparative trials, Conclusion, the angiotensin II receptor antagonist eprosartan is a well tolerated and effective antihypertensive agent that is administered once or twice daily without regard to meals.. Thus, eprosartan represents a useful therapeutic option in the management of patients with hypertension.	Poor
Valsartan				
54	Lasko BH, Laplante A, Hebert D, Bonnefis-Boyer S.(2001) Canadian valsartan study in patients with mild-to-moderate hypertension. Blood Press Monit 6(2), April, pp 91-9	single-blind, single-arm, multicenter study N=256 out-	The ambulatory blood pressure data support a consistent reduction of blood pressure with valsartan over a 24h period and for up to 32 h after dosing in those who missed a dose. The overall incidence of adverse experiences per person-year, treatment related or otherwise, was 6.3 and 10.6 for the valsartan and placebo study periods respectively. CONCLUSION: Antihypertensive treatment with valsartan for 8 weeks produced a significant decrease in diastolic blood pressure in hypertensive patients. In addition, the drug may be safely administered, and the results of 24 h/48 h ambulatory monitoring demonstrate that valsartan is a true once-a-day antihypertensive	Poor
55	Monterroso VH, Rodriguez Chavez V, Carbajal ET, Vogel DR, Aroca	Multicenter, double-blind, randomized trial	Both drugs significantly reduced clinic sitting systolic (SiSBP) and diastolic blood pressure (SiDBP) at 2, 4, and 6 weeks. Maximum	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Martinez GJ, Garcia LH, Cuevas JH, Lara Teran J, Hitzenberger G, Leao Neves P, Middlemost SJ, Dumortier T, Bunt AM, Smith RD (2000) Use of ambulatory blood pressure monitoring to compare antihypertensive efficacy and safety of two angiotensin II receptor antagonists, losartan and valsartan. Losartan Trial Investigators. *Adv Ther*, 17(2), Mar-Apr, pp117-31	losartan 50 mg (n = 93) or valsartan 80 mg (n = 94) for 6 weeks were assessed through measurements taken in the clinic and by 24-hour ambulatory blood pressure monitoring (ABPM)	reductions from baseline in SiSBP and SiDBP on 24-hour ABPM were also significant with the two treatments. The reduction in blood pressure was more consistent across patients in the losartan group, as indicated by a numerically smaller variability in change from baseline on all ABPM measures, which achieved significance at peak (P = .017) and during the day (P = .002). In addition, the numerically larger smoothness index with losartan suggested a more homogeneous antihypertensive effect throughout the 24-hour dosing interval. The antihypertensive response rate was 54% with losartan and 46% with valsartan. Three days after discontinuation of therapy, SiDBP remained below baseline in 73% of losartan and 63% of valsartan patients. Both agents were generally well tolerated. Losartan, but not valsartan, significantly decreased serum uric acid an average 0.4 mg/dL at week 6. In conclusion, once-daily losartan 50 mg and valsartan 80 mg had similar antihypertensive effects in patients with mild to moderate essential hypertension. Losartan produced a more consistent blood pressure-lowering response and significantly lowered uric acid, suggesting potentially meaningful differences between these two A II receptor antagonists.	
56	Botero R, Matiz H, Maria E, Orejarena H, Blanco M, Velez JR, Del Portillo H. (2000) Efficacy and safety of valsartan compared with enalapril at different altitudes. *Int J Cardiol* . 72(3), Feb 15, pp 247-54	Clinical Trial Multicenter Study Randomized Controlled Trial N= 142 adult Colombian outpatients receive either valsartan 80 mg once daily or enalapril 20 mg once daily for 8 weeks.	Both valsartan and enalapril reduced mean SDBP and SSBP with similar efficacy, independent of altitude. CONCLUSIONS: Valsartan 80 mg once daily is as effective as enalapril 20 mg once daily in reducing blood pressure, with tolerability profile at least as good as enalapril's.	Poor
57	McInnes GT. (1999)	Review	Valsartan is a specific angiotensin II receptor antagonist with high selectivity for the AT(1) receptor subtype. After oral administration of	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Clinical advantage of valsartan. *Cardiology* ;91 (Suppl 1), pp 14-8		single or repeated once-daily doses, valsartan 40-80 mg inhibits the pressor response to angiotensin II for 24 hours. In patients with mild-to-moderate hypertension, efficacy of valsartan appears to be independent of age, sex, and race, and is at least equivalent to that of calcium antagonists, ACE inhibitors, or thiazide diuretics. Response rate to valsartan 160 mg o.d. is significantly greater than after receiving losartan 100 mg o.d. Valsartan has additive effects with other antihypertensive drugs and combination therapy is effective in severe hypertension and in hypertension with renal insufficiency, where renal function is well maintained. Valsartan has good tolerability with a side-effect profile indistinguishable from placebo and superior to that of comparable drugs. Valsartan does not cause cough or adverse metabolic effects; first dose hypotension and rebound hypertension on abrupt withdrawal have not been encountered. Valsartan has clear clinical advantage in the management of hypertension. Its impact on prognosis in patients with a high risk of cardiovascular morbidity and mortality is under evaluation.	
58	Zakirova AN, Zakirova NE. (1999) Diovan efficacy and tolerance in mild and moderate hypertension] *Ter Arkh,* 71(4):41-4	N=20 patients	2-week treatment with diovan brought a significant fall of both systolic and diastolic blood pressure. In 8 weeks the hypotensive effect enhanced. Lowering of diastolic BP to 90 mm Hg or at least by 10% was achieved in 90% of the patients. Tolerance was good, unfavorable metabolic shifts were absent. CONCLUSION: Diovan proved to be effective and safe in therapy of patients with mild and moderate BH.	Poor
59	Hedner T, Oparil S, Rasmussen K, Rapelli A, Gatlin M, Kobi P, Sullivan J, Oddou-Stock P. (1999) A comparison of the angiotensin II antagonists valsartan and losartan in	Clinical Trial Randomized Controlled Trial	Valsartan produced a significantly higher number of responders (62%) than losartan (55%, P = .02) at the 8 week treatment endpoint. Valsartan (80/160 mg) monotherapy in this trial was as effective and well tolerated as 50/100 mg losartan in treating mild to moderate essential hypertension, and at 160 mg has a significantly higher responder rate than	Fair

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	the treatment of essential hypertension. *Am J Hypertens*. 12(4 Pt 1), Apr, pp 414-7		100 mg losartan.	
60	Ivleva AIa, Sokolova MA, Moiseev VS. (1999) The hypotensive effect and tolerance of valsartan (Diovan) in hypertension in a general clinical practice] *Ter Arkh.* 71(2), pp 67-70	N=20 patients	The hypotensive effect of Diovan in a dose 80 mg/day was satisfactory or good in 80% of patients. 15% of patients needed elevation of the dose to 160 mg/day. A complete resistance occurred in 1 patient. There were neither unwanted effects nor biochemical evidence of clinically significant renal or hepatic dysfunction due to valsartan. In stable BH correction, the rate of residual hypotensive effect reached 77.4% and 74.5% for systolic and diastolic BP, respectively. CONCLUSION: High effectiveness, good tolerance and safety of valsartan in single doses 80-160 mg/day allow to recommend it in monotherapy of mild and moderate hypertension.	Poor
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE inhibitors)				
EFFECTIVENESS				
Enalapril				
61	Dziak GV, Kolomiets SN, Minakov Ai Fushtei IM Iavorskii OG et al (1999) Treatment of mild to moderate hypertension with enalapril (multicenter study of enap and enap N in Ukraine) *Ter Arkh.* 7(11), pp 31-4	Multicenter study, Clinical Trial N=127 patients - Group 1-60 patient -enalapril (enap) 10mg/day/ 2 week -Bp not normalize raised to 20-40mg/day - Group 2 -67 patient - enalapril combine with hydrochlorotiaside a table/day/ 3 weeks, if Bp persistent higher	Blood pressure lowered under 140/90mm Hg in 66.7 % of group 1. Systolic pressure dropped by 10 mm Hg minimum & diastolic by 5 mm Hg minimum in 18 % of group 1 patient Enap N reduced blood pressure under 140/90 mm Hg in 65.7% of group 2 patients and systolic & diastolic pressure dropped respectively in 34.4 % patients. Conclusion Enap & Enap N tablets were found highly effective & well tolerated.	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
		than 140/90mm Hg treatment continue for 3 weeks with two table/day		
62	Karlberg BE, Lins LE Hermansson K (1999) Efficacy and safety of telmisartan, a selective AT1 receptor antagonist compared with enalapril in elderly patients with primary hypertension (TEES Study Group *J Hypertension*. 17 (2), Feb, pp 293-302	Multicenter double blind, parallel group dosage titration study Randomised Controlled Trial 278 patients randomized to either telmisartan or enalapril once /day. Telmisartan dosafe was increased from 20 tp 40-80 mg and that of enalapril from 5 to 10-20 mg at 4 weeks interval F/up 12 weeks	The adjusted mean changes from baseline in supine diastolic blood pressure at trough were -1.8 mmHg for telmisaratan and - 11.4 mm Hg for enalapril (P=0.074). Mean changes in supine systolic blood pressure were -22.1 mm Hg for telmisartan and -20.1 mm Hg for enalapril (P=0.350)	Poor
63	Smith DH, Matzek KM, Kempthorne Raw-son J (2000) Dose response and safety of telmisartan in patient with mild to moderate hypertension *J Clin Pharmacol*. 40 (12 Pt 1), Dec, pp 1380-90	Randomised, Double blind, double dummy, placebo controlled, parallel-group study 207 patients - DBP 100 to 114 mm Hg, after 8 day placebo run in period. Patients were randomised to 28 day once daily, double blind treatment, double dummy treatement with telmisartan 40, 80 or 120 mg. Enalapril 20 mg or placebo	All doses of telmisartan and enalapril significantly reduce BP compared to placebo (p < or = 0.01) Mean +/- SE reductions in supine DBP after 28 days of treatment ranged between 9.6 +/- 1.3 mm Hg with enalapril and 1.5 mm Hg =/- 1.3 mm Hg with placebo Mean +/- SE reduction in SBP 10.2 =/- 2.1 mm Hg with enalapril , placebo increase supine SBP by 3.5 =/- 2.1 mm Hg	Fair
64	Lacouciere Y (2000) A multicenter, randomised, double-blind study of the antihypertensive eficacy and	Clinical Trial Multicenter Study, Randomised Control Trial N= - 70 -daily dose of irbesartan 150	There was a mean reduction sitting DBP of 9.6 mm Hg and 9.8 mm Hg for irbesartan and enalapril respectively. The mean reduction of sitting SBP was 10.1 mm Hg and 11.6 mm Hg for irbesartan and enalapril respectively	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	tolerability of irbesartan in patients aged > or = 65 years with mild to moderate hypertension *Clin Ther.* 22 (10), Oct, pp 1213-24	mg - 71 enalapril 10 mg F/up- 8 weeks	Conclusion Irbesartan os an effective antihypertensive drug for elderly mild to moderate hypertension	
65	Malmqvist K, Kahan T, Dahl M. (2000) Angiotensin II type 1 (AT1) receptor blockade in hypertensive women: benefits of candesartan cilexetil versus enalapril or hydrochlorothiazide. *Am J Hypertens.* 13(5 Pt 1), may, pp504-11	Clinical Trial Randomized Controlled Trial candesartan cilexetil, 8 to 16 mg (n = 140), enalapril, 10 to 20 mg (n = 146), or HCTZ, 12.5 to 25 mg (n = 143), for 12 weeks	Candesartan cilexetil lowered seated blood pressure by 17/11 and 19/11 mm Hg after 6 and 12 weeks of treatment, respectively. This reduction was greater (P < .01) than with enalapril (12/8 and 13/9 mm Hg) or HCTZ (12/7 and 13/8 mm Hg). The proportions of patients with controlled DBP (< 90 mm Hg) after 12 weeks of treatment with candesartan cilexetil, enalapril, or HCTZ were 60%, 51%, and 43%, respectively. Conclusion, candesartan cilexetil reduced blood pressure more effectively and was better tolerated than enalapril or HCTZ in women with mild to moderate hypertension.	Poor
66	Botero R, Matiz H, Maria E, Orejarena H, Blanco M, Velez JR, Del Portillo H. (2000) Efficacy and safety of valsartan compared with enalapril at different altitudes. *Int J Cardiol* 72(3),Feb 15, pp 247-54	Clinical Trial Multicenter Study Randomized Controlled Trial N= 142 adult Colombian outpatients receive either valsartan 80 mg once daily or enalapril 20 mg once daily for 8 weeks.	Both valsartan and enalapril reduced mean SDBP and SSBP with similar efficacy, independent of altitude. CONCLUSIONS: Valsartan 80 mg once daily is as effective as enalapril 20 mg once daily in reducing blood pressure, with tolerability profile at least as good as enalapril's.	Poor
67	Cuocolo A, Storto G, Izzo R, Iovino GL, Damiano M, Bertocchi F, Mann J, Trimarco B. (1999) Effects of valsartan on left ventricular diastolic function in patients with mild or moderate essential hypertension: comparison with enalapril. *J Hyperten.* 17(12 Pt 1), Dec, pp	Double-blind, Crossover randomization N=24 scheme	In both subgroups, valsartan and enalapril induced a significant and comparable reduction of systolic and diastolic blood pressure.	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	1759-66			
68	Chiou KR, Chen CH, Ding PY, Chen YT, Huang JL, Chiang AH, Liu CP, Tseng CJ, Chao CT, Chang MS (2000) Randomised, double blind comparison of irbesartan and enalapril for treatment of mild to moderate hypertension *Chung Huah I Hsuah Tsa Chih* 20(6), Nov-Dec, pp 1159-69	Multicenter , double blind, randomise, parallel group study N= 116 patients F/up: 8 weeks	Enalapril 10 mg to 20 mg reduce systolic and diastolic blood pressure by-10.6 mm Hg and -5.0 mm Hg respectively	Fair
69	Guitard C, Lohmann FW, Alfiero R, Ruina M, Alvisi V. (1997) Comparison of efficacy of spirapril and enalapril in control of mild-to-moderate hypertension. *Cardiovasc Drugs Ther.* 11(3), Jul, pp 449-57	placebo-controlled, parallel-group study. N=251 patients	Compared with placebo, treatment with both spirapril and enalapril resulted in significant reductions ($p < 0.001$) in DBP and SBP. DBP was reduced to a greater extent with spirapril than with enalapril both at peak (-17.4 mmHg vs. -14.8 mmHg) and trough (-14.7 mmHg vs. -12.4 mmHg). Thus, although the trough/peak DBP ratios for spirapril and enalapril were very similar (84% vs. 82%), actual reductions in DBP were different. Spirapril and enalapril treatment resulted in similar reductions in SBP at both peak and trough levels. Conclusion, spirapril, 6 mg once daily, as the initial and maintenance dose, is at least as effective and well tolerated as enalapril individually titrated.	Poor
70	Gonzalez-Juanatey-JR (1995) Left ventricular systolic function after marked reduction of ventricular hypertrophy induced by 5 years' enalapril treatment [see comments] Eur-Heart-J.; 16(12), Dec, pp 1981-7	26 patients with previously untreated essential hypertension took enalapril 20 mg twice daily for 5 years. Cardiovascular parameters were determined by two-dimensionally guided M-mode echocardiography in a pre-treatment placebo phase, 8 weeks and 1, 3 and 5 years after the start of therapy, and	Significant reductions in arterial pressure at rest and during exercise were achieved by 8 weeks' treatment with enalapril and maintained during 5 years' further treatment, while a marked reduction in left ventricular mass took place progressively throughout the 5 year period. Reduction of myocardial hypertrophy by enalapril appeared to be beneficial rather than detrimental to cardiac pump performance.	Level 6 evidence

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
		8 weeks after drugs were discontinued		
Ramipril				
71	Kukushkin SK, Lebedev AV, Manoshkina EM, Shamarin VM. (1998) Ramipril effects on 24 hour profile of blood pressure in patients with mild and moderate hypertension] *Ter Arkh.*70(9), pp 69-71	21 single dose 2.5-10 mg/day. Captopril controls received 100 mg twice a day.	ramipril lowered systolic and diastolic blood pressure both for the 24-h period and in the day time; CONCLUSION: Long-term treatment with ramipril in the above regimen provides more effective control of BP than captopril in the above doses in patients with mild and moderate hypertension.	Poor
Benazepril				
72	Hazizi HM, Francillion A, Mottier D, Heintzmann F, Serrurier D (1998) Antihypertensive action and predictive factors of efficacy of benazepril in mild to moderate hypertension: clinical trial in general medical practice on 16,987 patients *Ann Cardiol Angeliol.* 47(1), jan, pp 33-41	Ramdomised control trial N=16,987 patients	In the intent to treat analysis 54.5% of patients, after 4 weeks, and 89.6% of patients after 8 weeks were controlled (DBP < 90 mmHg). Mean sitting DBP decreased from 100.5 +/- 5.5 mm Hg (baseline) to 86.7 =/- 7.5 mmHg after 4 weeks and to 82.5 =/- 6.5 mmHg after 8 weeks. Mean SBP decreased from 169.5 =/- 13.1 mm g to 150.5 =/- 12.5 mmHg after 4 weeks to 145.0 =/- 10.9 mmHg after 8 weeks	Good to Fair
Imidapril				
73	van der Does R, Euler R (2001)	Clinical Trial	After 2 weeks' treatment, clinically relevant decreases in blood pressure	Fair

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	A randomized, double-blind, parallel-group study to compare the anti-hypertensive effects of imidapril and nifedipine in the treatment of mild-to-moderate essential hypertension. *J Int Med Res* 29(3), may - jun, pp 154-62.	Multicenter Study Randomized Controlled Trial N= 320 patients- imidapril (n = 157) or nifedipine SR (n = 163).	were observed in both groups, with a trend towards further reductions until study end. These results show that imidapril is effective in the treatment of essential hypertension and is better tolerated than nifedipine SR.	
74	Dews I, VandenBurg M. (2001) A 24-week dose-titration study of the angiotensin-converting enzyme inhibitor imidapril in the treatment of mild-to-moderate essential hypertension in the elderly. *J Int Med Res.* 29(2), Mar-Apr, pp 100-7		After 24 weeks of treatment, there was a significant reduction in mean sitting diastolic blood pressure from 102.5 mmHg to 87.2 mmHg in the imidapril group (n = 226) and from 102.7 mmHg to 87.4 mmHg in the hydrochlorothiazide group (n = 123) (intent-to-treat population). There were corresponding reductions in sitting systolic blood pressure and standing blood pressure. Imidapril 5-20 mg is as effective and well tolerated as hydrochlorothiazide in the treatment of mild-to-moderate hypertension in elderly patients.	
Quadropril				
75	Shal'nova SA, Martsevich SIu, Deev AD, Kutishenko NP, Kukushkin SK, Manoshkina EM, Alimova EV, Semenova IuE, Lebedev AV, Koniakhina IP, Zagrebel'nyi AV. (2000) Comparative study of spirapril (quadropril) and amlodipine efficacy.	non-blind randomised parallel study N=80 patients -40 patients each. Patients of group 1 received monotherapy with quadropril, while those of group 2 were treated with amlodipine.	In the quadropril group baseline systolic BP reached 158.6 +/- 2.1 mm Hg, diastolic BP--101.8 +/- 0.8 mm Hg, heart rate was 74.3 +/- 1.6 beats/min. In the amlodipine group baseline systolic BP was 159.9 +/- 2.4 mm Hg, diastolic BP--101.8 +/- 1.0 mm Hg, heart rate was 71.3 +/- 1.0 beats/min. Systolic BP decreased at the end of quadropril therapy to 138.5 +/- 2.2 mm Hg, diastolic BP to 88.1 +/- 1.4 mm Hg. No significant change of the heart rate was observed. Under 5 mg of amlodipine systolic BP decreased to 137.9 +/- 2.5 mm Hg and diastolic BP to 87.1 +/- 1.6 mm Hg. Heart rate	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Results of randomized trial in patients with mild to moderate arterial hypertension] *Ter Arkh* 72(10), pp 86-9		increased to 73.3 +/- 2.2 beats/min. Under therapy with 10 mg amlodipine systolic BP decreased to 145.9 +/- 3.8 mm Hg, diastolic BP to 89.7 +/- 3.4 mm Hg. Heart rate increased to 77.3 +/- 4.0 beats/min ($p < 0.01$). The hypotensive effect of quadropril remained stable while the effect of amlodipine decreased by the 8th week of therapy ($p < 0.01$). CONCLUSION: Both quadropril and amlodipine demonstrated a comparable antihypertensive effect although in 11 of 40 patients in the amlodipine group a dose increase was necessary and tolerability of quadropril was better.	
Trandolapril				
76	Kohlmann Junior O, Jardim PC, Oigman W. (1999) Brazilian multicenter study on efficacy and tolerability of trandolapril in mild-to-moderate essential arterial hypertension. EMBATHE substudy with ambulatory blood pressure monitoring.] *Arq Bras Cardiol.* 72(5), may, pp 547-57	double-blind, placebo-controlled multicenter study Multicenter Study N=262 patients enrolled in this study, 127 were treated with trandolapril 2 mg/day for 8 consecutive weeks, and the remaining 135 patients received placebo for the same period of time.	Significantly reductions in both systolic and diastolic pressures were observed in patients treated with trandolapril when compared with those on placebo. Antihypertensive efficacy was achieved in 57.5% of the patients on trandolapril and in 42% of these normal values of BP were obtained. The efficacy of trandolapril was similar in all centers, regardless of the area of the country. In a subset of 30 patients who underwent ABPM, responders showed a significant hypotensive effect to trandolapril throughout the 24 hour day. CONCLUSION: Our results demonstrate, for the first time in a large group of hypertensive patients from different regions in Brazil, good efficacy and tolerability of trando-lapril during treatment of mild-to-moderate essential systemic hypertension.	Fair
Lisinopril				
77	Rudy TD, Fodor JG (1997) Nisoldipine CC and lisinopril alone or in combination for treatment of mild to moderate systemic hypertension.	Multicentre Study Rndomised Controlled Trial N= 278 patient	ABPM showed that both nisoldipine and lisinopril produced constant blood pressure lowering effect over 24 hours period and maintained circadian rhythm.	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Canadian Nisoldipine CC Hypertension Trial *Cardiovas Drug Ther.* 11(4), Sep, pp581-90	F/up: 8 weeks		
78	Ol'binskaia LI, Sizova ZhM, Zheleznykh EA, Fitilev SB, Sergeeva TE, Pukhlianko ME, Potapova GN. (1999) Antihypertensive efficacy, tolerance and safety of lisinopril (sinopril) and captopril (capoten) in patients with mild and moderate arterial hypertension] *Ter Arkh*, 71(11), pp 61-4		Sinopril produced good antihypertensive effect in 73.3% of patients (monotherapy) and 88.9% (combined therapy). For capoten it was 68.9 and 82.2%, respectively. The time of the beginning of the antihypertensive effect (4-20 days after the start of the treatment) for sinopril and copoten differed insignificantly and depended on hypertension severity (mild or moderate). CONCLUSION: Sinopril and capoten demonstrate high antihypertensive activity	
79	Neutel JM, Frishman WH, Oparil S, Papademitriou V, Guthrie G. (1999) Comparison of telmisartan with lisinopril in patients with mild-to-moderate hypertension. *Am J Ther*; 6(3), May, pp 161-6	Randomized, multicenter, double-blind, double-dummy, parallel-group, dose-titration study N=578 patients 52-week	DBP control was achieved on monotherapy by 67% and 63% of the telmisartan and lisinopril patients, respectively. At the end of the maintenance period, supine DBP was controlled in 83% and 87% of the telmisartan and lisinopril patients, respectively, with systolic blood pressure over DBP reductions of 23.8/16.6 mm Hg for telmisartan and 19.9/15.6 mm Hg for lisinopril The selective AT (1) receptor antagonist, telmisartan, is extremely effective in the treatment of mild-to-moderate hypertension both as monotherapy and in combination with HCTZ and is at least comparable in efficacy to lisinopril, with a tolerability profile that may offer advantages in terms of a reduced incidence of adverse events.	

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
80	Abengowe CU, Exedinachi EN, Balogun MO (1997) An open trial of lisinopril in mild to moderate hypertension in Nigeria *West Afr Med,* 16(4), Dec, pp 218-32	Multicenter study N= 51	Lisinopril 10-40 mg once daily able to controlled the blood pressure to < or = 90 mm Hg	Poor
Spirapril				
81	Guitard C, Lohmann FW, Alfiero R, Ruina M, Alvisi V. (1997) Comparison of efficacy of spirapril and enalapril in control of mild-to-moderate hypertension. *Cardiovasc Drugs Ther*. 11(3), July, pp 449-57	Placebo-controlled, parallel-group study. N=251 patients	Compared with placebo, treatment with both spirapril and enalapril resulted in significant reductions ($p < 0.001$) in DBP and SBP. DBP was reduced to a greater extent with spirapril than with enalapril both at peak (-17.4 mmHg vs. -14.8 mmHg) and trough (-14.7 mmHg vs. -12.4 mmHg). Thus, although the trough/peak DBP ratios for spirapril and enalapril were very similar (84% vs. 82%), actual reductions in DBP were different. Spirapril and enalapril treatment resulted in similar reductions in SBP at both peak and trough levels. Conclusion, spirapril, 6 mg once daily, as the initial and maintenance dose, is at least as effective and well tolerated as enalapril individually titrated.	Poor
82	Hayduk K, Kraul H (1999) Efficacy and safety of spirapril in mild to moderate hypertension *J Crdiovasc Pharmacol* . 34 (Suppl 1), Aug, pp S 19-3	Review	In several studies, spirapril was given to patients with mild to moderate essential hypertension at doses of 1-24mg/day, there was an indentical blood pressure lowering effect at doses of 6-24 mg/day, doses of 1-3 mg/day were less effective. showed a	Poor
CALCIUM CHANNEL BLOCKER				
Effectiveness				
Amlodipine				
83	Hayduk K, Adamezak m, Nowitzki G (1999)	Single blind, randomized contrail trial	Diastolic and systolic blood pressure decrease steadily until the end of the 6 weeks of treatment in both groups, with no statistically significant	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Is initial dose titration of amlodipine worthwhile in patients with mild to moderate hypertension *Curr Med Res Opin* , 15(1), pp 39-45	115 patient – group I – amlodipine 5 mg once dly –10 weeks, group II – 5 mg once daily – 2 weeks increase to 10mg if DBP >90 mmHg	difference between the group.	
84	Kloner RA, Weinberger M, Pool JL, Chrysant SG, Prasad R, Harris SM, Zyczynski TM, Leidy NK, Michelson EL; (2001) Comparative effects of candesartan cilexetil and amlodipine in patients with mild systemic hypertension. Comparison of Candesartan and Amlodipine for Safety, Tolerability and Efficacy (CASTLE) Study Investigators. *Am J Cardiol,* 87(6), Mar 15, pp 727-31	Clinical Trial Multicenter Study Randomized Controlled Trial N=251 adult patients (received candesartan cilexetil 16 mg (n = 123) or amlodipine 5 mg (n = 128) once daily.)	Overall, 79% of patients on candesartan cilexetil and 87% of those on amlodipine were controlled (diastolic BP <90 mm Hg). Candesartan cilexetil and amlodipine are both highly effective in controlling BP in patients with mild hypertension.	Fair
85	Shal'nova SA, Martsevich SIu, Deev AD, Kutishenko NP, Kukushkin SK, Manoshkina EM, Alimova EV, Semenova IuE, Lebedev AV, Koniakhina IP, Zagrebel'nyi AV. (2000) Comparative study of spirapril (quadropril) and amlodipine efficacy. Results of randomized trial in patients with mild to moderate arterial hypertension]	non-blind randomised parallel study N=80 patients -40 patients each. Patients of group 1 received monotherapy with quadropril, while those of group 2 were treated with amlodipine.	In the quadropril group baseline systolic BP reached 158.6 +/- 2.1 mm Hg, diastolic BP--101.8 +/- 0.8 mm Hg, heart rate was 74.3 +/- 1.6 beats/min. In the amlodipine group baseline systolic BP was 159.9 +/- 2.4 mm Hg, diastolic BP--101.8 +/- 1.0 mm Hg, heart rate was 71.3 +/- 1.0 beats/min. Systolic BP decreased at the end of quadropril therapy to 138.5 +/- 2.2 mm Hg, diastolic BP to 88.1 +/- 1.4 mm Hg. No significant change of the heart rate was observed. Under 5 mg of amlodipine systolic BP decreased to 137.9 +/- 2.5 mm Hg and diastolic BP to 87.1 +/- 1.6 mm Hg. Heart rate increased to 73.3 +/- 2.2 beats/min. Under therapy with 10 mg amlodipine systolic BP decreased to 145.9 +/- 3.8 mm Hg, diastolic BP to 89.7 +/- 3.4 mm Hg. Heart rate increased to 77.3 +/- 4.0 beats/min ($p < 0.01$). The hypotensive effect of quadropril remained stable while the	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Ter Arkh. 72(10), pp:86-9		effect of amlodipine decreased by the 8th week of therapy ($p < 0.01$). CONCLUSION: Both quadropril and amlodipine demonstrated a comparable antihypertensive effect although in 11 of 40 patients in the amlodipine group a dose increase was necessary and tolerability of quadropril was better.	
86	Whitcomb C, Enzmann G, Pershadsingh HA, Johnson R, Ciuryla V, Reisin E.(2000) A comparison of nisoldipine ER and amlodipine for the treatment of mild to moderate hypertension. *Int J Clin Pract*. 54(8), Oct, pp509-13	Multicentre, double-blind, double-dummy, randomised trial N=161 patients.	The least squares mean reductions in systolic SBP/DBP (+/- standard error) for nisoldipine and amlodipine were -11.7/-9.3 +/- 1.4/0.8 and -14.3/-12.0 +/- 1.4/0.8 mmHg, respectively. The DBP treatment difference was 2.7 mmHg (90% confidence interval: 1.1 to 4.3 mmHg; $p = 0.005$). In summary, nisoldipine and amlodipine provide clinically equivalent antihypertensive efficacy; however, nisoldipine is more economical than amlodipine.	Fair
87	Yosefy C, Viskoper JR, Leshem Y, Rav-Hon Y, Rosenberg GI, Yaskil E. (1999) Multicenter community-based trial of amlodipine in hypertension in Israel *Harefuah*. 137(3-4), Aug, pp 89-93, 176	open non-comparative trial N=266 patients	In this major group BP was reduced from 165 +/- 15/101 +/- 4 to 139 +/- 11/83 +/- 5 after 12 weeks of AML ($p < 0.05$). The reduction was greater in those under 70 years, from 173 +/- 12/100 +/- 5 to 142 +/- 12/80 +/- 4 ($p < 0.05$). In those with BMI > 30 kg/m2, BP decreased from 165 +/- 15/101 +/- 5 to 140 +/- 12/83 +/- 5 ($p < 0.05$). Mean change in heart rate was -1.5 bpm ($p < 0.05$). Mean final AML dose was 5.5 mg/day. conclude that AML is an effective and well-tolerated antihypertensive suitable for most hypertensive patients.	Poor
88	Naidu MU, Usha PR, Rao TR, Shobha JC (2000) Evaluation of amlodipine, lisinopril,	Clinical Trial Randomized Controlled Trial N=Twenty four patients	5 mg amlodipine monotherapy achieved the target blood pressure in 71% patients.	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	and a combination in the treatment of essential hypertension. *Postgrad Med J*. 76(896) , Jun, pp 350-3			
89	Sowunmi A, Walker O, Salako LA.(1996) Amlodipine as monotherapy in hypertensive Africans: clinical efficacy and safety studies. *Afr J Med Med Sci*. .25(3), Sep, pp :213-6	Controlled Clinical Trial N=20 patients over a 10 week period	At the end of the trial, diastolic blood pressure was reduced to below 90 mmHg in all but four patients. However, these four patients had greater than 20 mmHg reduction in diastolic blood pressure. There was a slight, but insignificant increase in heart rateLaboratory tests, including plasma lipids done at the start and end of the trial, remained unchanged.	Poor
90	Cheung BM, Lau CP, Wu BZ. (1998) Amlodipine, felodipine, and isradipine in the treatment of Chinese patients with mild-to-moderate hypertension. *Clin Ther*. 20(6), Nov, Dec, pp 1159-69	amlodipine (n = 41), felodipine (n = 38), or isradipine (n = 39) for 8 weeks,	Mean seated systolic and diastolic blood pressure decreased by 23/17, 30/17, and 20/15 mm Hg after 8 weeks of treatment with amlodipine, felodipine, and isradipine, respectively. These reductions were all statistically significant. Blood pressure was controlled (defined as diastolic pressure < 90 mm Hg at the final visit or a decrease from baseline of > or = 10 mm Hg) in 85%, 74%, and 74% of patients receiving amlodipine, felodipine, and isradipine, respectively. There were no significant changes in heart rate, plasma lipid levels, or serum biochemistry markers with any of the three treatments. The results of this study indicate that all three drugs are highly effective in lowering blood pressure and are well tolerated in Chinese patients with mild-to-moderate hypertension.	Poor
91	Horwitz LD, Weinberger HD, Clegg L (1997) Comparison of amlodipine and long acting diltiazem in the treatment of	Multicenter study Rndomised controlled trial N= 123 patients	Amlodipine cused significantly greater reductions in sitting and standing systolic , standing diastolic blood pressure, and 24 h ambulatory systolic and diastolic pressure versus diltiazem Mlodipine was more effective than diltiazem in reducing systolic and diastolic blood pressure to the target pressure of , 140 mm Hg systolic nd ,	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	mild to moderate hypertension *Am J Hypertension.* 10(11), Nov, pp 1263-9	F/up : 10 weeks	90 mmHg diastolic over a range of doses widely used in clinical practice.	
92	Hoegholm A, Wiinberg N, Rasmussen E, Nielsen PE (1995) Office and ambulatory blood pressure: a comparison between amlodipine and felodipine ER. Danish Multicentre Group *J Hum Hypertension*. 9(8), Aug, pp 611-6	Multicentre Study, randomised controlled trial N=118 patient	The fall of ambulotry SBP was significantly greater in the patient treated with amlodipine compared with felodipine ER whereas there was no different between the groups with respect to ambulatory DBP.	Poor
Nisoldipine				
93	Whitcomb C, Enzmann G, Pershadsingh HA, Johnson R, Ciuryla V, Reisin E. (2000) A comparison of nisoldipine ER and amlodipine for the treatment of mild to moderate hypertension. *Int J Clin Pract* .54(8), Oct, pp509-13	Multicentre, double-blind, double-dummy, randomised trial N=161 patients.	The least squares mean reductions in systolic (S)BP/DBP (+/- standard error) for nisoldipine and amlodipine were -11.7/-9.3 +/- 1.4/0.8 and -14.3/-12.0 +/- 1.4/0.8 mmHg, respectively. The DBP treatment difference was 2.7 mmHg (90% confidence interval: 1.1 to 4.3 mmHg; p = 0.005). In summary, nisoldipine and amlodipine provide clinically equivalent antihypertensive efficacy; however, nisoldipine is more economical than amlodipine.	Poor
94	Rudy TD, Fodor JG (1997) Nisoldipine CC and lisinopril alone or in combination for treatment of mild to moderate systemic hypertension. Canadian Nisoldipine CC Hypertension Trial	Multicentre Study Rndomised Controlled Trial N= 278 patient F/up: 8 weeks	ABPM showed that both nisoldipine and lisinopril produced constant blood pressure lowering effect over 24 hours period and maintained circadian rhythm.	Fair

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
	Cardiovas Drug Ther. 11(4), Sep, pp581-90			
95	Foldor JG (1997) Comparative efficacy and tolerability of nisoldipine coat and hydrochlorothiazide in mild to moderate hypertension *Int J clin Pract.* 51(5), July - Aug, pp 71-5	Multicentre Randomised Controlled Trial	Nisoldipine 10 mg od reduced both diastolic and systolic blood pressure. At treatment endpoint, the change from baseline in SBP was 16.2 mmHg for the nisoldipine group nd 14.9 mmHg in HCTZ group	Poor
Nifedipine				
96	Manyemba J (1997) A randomised crossover comparison of reserpine and sustained-release nifedipine in hypertension. *Cent Afr J Med*. 43(12), Dec, pp 344-9	Open, randomised crossover drug trial N=32	Both second line drugs were effective in lowering SBP and DBP and there was no significant difference between them. Nifedipine reduced SBP by 18.9 mmHg (95% CI 12.1 to 25.7) and DBP by 9.6 mmHg (95% CI 7.2 to 12.0). Reserpine reduced SBP by 15.9 mmHg (95% CI 8.4 to 23.4) and DBP by 11.1 mmHg (95% CI 7.5 to 14.6). However, only two patients attained the target DBP of < or = 90 mmHg after each active treatment period. Since both agents were equally effective in reducing both SBP and DBP and reserpine is much cheaper than nifedipine	Poor
97	Toal CB (1997) Efficacy of low dose nifedipine GITS (20 mg) in patients with mild to moderate hypertension *Can J Cardiol*. 13 (10), Oct, pp 921-7	Randomised controlled trial N= 187 patients	Nifedipine 20 mg GITS is eeficacious in dcreasing BP, with goosd 24 hour control and an incidence of adverse event simir to that placebo treated patients	Fair

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
98	Lopez NC, Corral JL, Perozo M, Garcia P, Bustillio N, Arreaza MR, Arocha I (1997) Nifedipine in the treatment of moderate and severe arterial hypertension. Long term effect on arterial pressure and left ventricular *Rev Esp Cardio.* 50(8), Aug, pp 567-72	Randomised controlled trial N= 30 patients F/up: 1 years	70 % of the ptient blood pressure rech values of 140-90 mm Hg . 12 % reduction in left ventriculr mass was observed without modification in systolic function, monotherapy with nifidipine ws effective in reducing high blood pressure, induced regression in ventricular hypertrophy nd showed good tolerance in one years follow up.	Fair
99	Taverner D, Marley J, Tonkin AL. (1999) Cross-over comparison of nifedipine Oros and felodipine extended release with blind 24 h ambulatory blood pressure assessments. C*lin Exp Pharmacol Physiol* 26(11), Nov, pp 909-13	randomized cross-over design with a 2 week open placebo run-in phase and two observer-blind treatment periods N=23 subjects-	Compared with placebo, mean (+/- SD) 24 h DBP was reduced by 6.2 +/- 6.8 and 5.2 +/- 5.1 mmHg after nifedipine and felodipine, respectively. The 24 h mean systolic blood pressure (SBP) fell by 11.8 +/- 10.9 and 10.1 +/- 8.2 mmHg for nifedipine and felodipine, respectively, compared with placebo. There were no significant differences between the two active treatments in the reduction of DBP or SBP during the 24 h period, daytime or night-time. 6. Similar antihypertensive effects are achieved with nifedipine Oros and felodipine ER when doses are individually titrated, with no significant differences between the two treatments.	Fair
Reserpine				
100	Manyemba J (1997) A randomised crossover comparison of reserpine and sustained-release nifedipine in hypertension. *Cent Afr J Med*, 43(12), Dec, pp 344-9	Open, randomised crossover drug trial N=32	Both second line drugs were effective in lowering SBP and DBP and there was no significant difference between them. Nifedipine reduced SBP by 18.9 mmHg (95% CI 12.1 to 25.7) and DBP by 9.6 mmHg (95% CI 7.2 to 12.0). Reserpine reduced SBP by 15.9 mmHg (95% CI 8.4 to 23.4) and DBP by 11.1 mmHg (95% CI 7.5 to 14.6). However, only two patients attained the target DBP of < or = 90 mmHg after each active treatment period. Since both agents were equally effective in reducing both SBP and DBP and reserpine is much cheaper than nifedipine	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
Benidipine				
101	Kalke S, Shah BV, Nair KG, Gala D, Sood OP, Bagati A. (1999) Clinical trial of benidipine in mild to moderate hypertension. *J Assoc Physicians India* 47(2), Feb, pp195-7	N=34 patients	The blood pressure of 20 patients was controlled with benidipine 4 mg/day (effective rate 80%). Five patients with unsatisfactory control on 4 mg/day benidipine were put on 8 mg/day. Four of them were controlled and one was considered as failure (effective rate 80%). conclude that benidipine is well tolerated in the dose of 4-8 mg/day and is an effective antihypertensive agent for treatment of patients with mild to moderate hypertension.	Poor
102	Nakajima O, Akioka H, Miyazaki M.(2000) Effect of the calcium antagonist benidipine hydrochloride on 24-h ambulatory blood pressure in patients with mild to moderate hypertension in a double-blind study against placebo. *Arzneimittelforschung*. 50(7), Jul, pp 620-5	Clinical Trial Randomized Controlled Trial	The mean SBP and DBP fell to 135 and 88 mmHg, respectively, after dosing, which gave T/P ratios of 82% and 64%, respectively. The SIs for SBP and DBP were 1.82 and 0.76, respectively. These findings indicate that benidipine maintained a satisfactory and durable antihypertensive effect by once-a-day dosing.	Poor
103	Ohya Y, Abe I, Ohta Y, Onaka U, Fujii K, Kagiyama S, Fujishima-Nakao Y, Fujishima M. (2000) Natriuretic effect of barnidipine, a long-acting dihydropyridine calcium channel blocker, in patients with essential hypertension. *Int J Clin Pharmacol Ther*. 38(6), Jun, pp 304-8	Single-blinded study.	Blood pressure decreased from 161 +/- 4/92 +/- 2 mmHg to 146 +/- 4/85 +/- 2 mmHg ($p<0.05$) after 7-day-treatment with barnidipine. Barnidipine significantly increased urinary sodium excretion; the change was evident on the first day of administration (control period 41 +/- 3 mEq/day, and first day 59 +/- 3 mEq/day, $p < 0.05$). Drug discontinuation transiently decreased sodium excretion to 35 +/- 3 mEq/day. Cumulative sodium balance after 7-day-treatment reached 47 +/- 19 mEq. Urine volume, potassium excretion, and creatinine excretion did not change during the treatment period. The plasma levels of ANP tended to increase, but those of aldosterone did not change with barnidipine. Barnidipine administration for a week decreased the blood pressure and made the sodium balance negative by increasing the urinary sodium excretion in patients with essential hypertension. The natriuretic effect of this drug could contribute at least in part to its antihypertensive effect.	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
ALFA –1 ADRENORECPTOR ANTAGONIST				
EFFECTIVENESS				
Doxazosin				
104	Sanz Guajardo D; Espejo martines J (1997) Randomised, Comparative study to evaluate efficacy and safety of doxazosin verses nitrendipine in the treatment of mild to moderate hypertension *An Med Internal*. 14(1), pp 15-9	Clinical Trial, randomized Control Trial N= 61 patients : 31 patient received 1-16 mg of doxazosin and 30 patients assigned to 10-20 mg of nitrendipine F/up 14 weeks	Both treatment reduced supine and standing diastolic and systolic blood pressure ($p<0.01$ for all comparisons)	Poor
105	Os I, Stokke HP. (1999) Effects of doxazosin in the gastrointestinal therapeutic system formulation versus doxazosin standard and placebo in mild-to-moderate hypertension. Doxazosin Investigators' Study Group. *J Cardiovasc Pharmacol*; 33(5),May, pp 791-7	Clinical Trial Multicenter Study Randomized Controlled Trial N= 392 patients compared doxazosin GITS with doxazosin standard in 315 patients with mild-to-moderate hypertension	Approximately 64% of patients with doxazosin GITS (198 of 309 patients) and 68% with doxazosin standard (207 of 304 patients) achieved goal BP response at the final visit versus 36% with placebo (25 of 70 patients; $p < 0.05$). The majority with doxazosin GITS (60%) remained at the initial 4-mg starting dose. Doxazosin GITS was as effective as doxazosin standard, and both were more effective than placebo in controlling BP in mild-to-moderate hypertension. Whereas the efficacy of doxazosin GITS at 4 or 8 mg is equivalent to that of the standard regimen in this combined analysis, the GITS formulation appears to eliminate the need for titration in most patients.	Poor

No	Author, title, Journal	Study design, Sample size, Follow up	Outcomes & Characteristic	Grade & comment
Terazosin				
106	Achari R, Hosmane B, Bonacci E, O'Dea R. (2000) The relationship between terazosin dose and blood pressure response in hypertensive patients. *J Clin Pharmacol*. 40(10), Oct, pp :1166-72	Double-blind, randomized, placebo-controlled, multicenter study N=128 patients	There was a strong dose-response relationship between fall in blood pressure and the 1 to 10 mg terazosin dose, as well as a plateauing of response for terazosin doses above 10 mg. The maximum antihypertensive response (Emax) to terazosin was 10.7 mmHg for systolic blood pressure and 8.0 mmHg for diastolic blood pressure. The daily dose of terazosin, which produced 50% of the maximum response (ED50), was 3.0 mg for systolic blood pressure and 1.5 mg for diastolic blood pressure. The results of this study suggest that although some patients may benefit from terazosin doses of greater than 10 mg, doses up to 10 mg will maximize therapeutic benefit for most patients, with acceptable side effects.	Fair

EVIDENCE TABLE ; SAFETY

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
Angiotensin II Receptor Bocker				
1	Weir MR, Weber MA, Neutel JM, Vendetti J, Michelson El, Wang RY (2001) Efficacy of candesartan cilexetil as add-on therapy in hypertensive patients uncontrolled on background therapy: a clinical experience trial. ACTION Study Investigators *Am J Hypertension.* 14(6 Pt 1), Jun, pp: 567-72	Multicenter Study, Clinical Trial 6465 hypertensive patients-	Most common adverse effects is headache & dizziness Orthostatic hypotension was in infrequent	Poor
2	Sever P; Holzgreve H (1999)	Open label, prospective	12 % of adverse events were judged to be causally related to drug and only 5% of	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	Long term efficacy and tolerability of candesartan cilexetil in patients with mild to moderate hypertension *J Hum Hypertens.* 11 (Suppl 2), pp S69-73	multicenter studies	patients withdrew from therapy due to adverse events. The most common adverse events were typical of hypertensive patients in general. Most adverse events appeared during the first 3 months of treatment and their incidence decreased steadily with time	
3	Kloner RA, Weinberger M, Pool JL, Chrysant SG, Prasad R, Harris SM, Zyczynski TM, Leidy NK, Michelson EL (2001) Comparative effects of candesartan cilexetil and amlodipine in patients with mild systemic hypertension. Comparison of Candesartan and Amlodipine for Safety, Tolerability and Efficacy (CASTLE) Study Investigators. *Am J Cardiol* . 87(6), Mar 15, pp 727-31	Clinical Trial Multicenter Study Randomized Controlled Trial N=251 adult patients (received candesartan cilexetil 16 mg (n = 123) or amlodipine 5 mg (n = 128) once daily.)	Overall, 79% of patients on candesartan cilexetil and 87% of those on amlodipine were controlled (diastolic BP <90 mm Hg) Candesartan cilexetil and amlodipine are both highly effective in controlling BP in patients with mild hypertension. Candesartan cilexetil offers a significant tolerability advantage with respect to less risk of developing peripheral edema.	Poor
4	Malmqvist K, Kahan T, Dahl M. (2000) Angiotensin II type 1 (AT1) receptor blockade in hypertensive women: benefits of candesartan cilexetil versus enalapril or hydrochlorothiazide. *Am J Hypertens.* 13(5 Pt 1), May, pp 504-11	Clinical Trial Randomized Controlled Trial candesartan cilexetil, 8 to 16 mg (n = 140), enalapril, 10 to 20 mg (n = 146), or HCTZ, 12.5 to 25 mg (n = 143), for 12 weeks	Patients experienced less dry cough ($P < 0.001$) with candesartan cilexetil or HCTZ than with enalapril. No treatment differences were found in the incidence of dizziness and quality of life was well maintained in all groups. Compared with candesartan cilexetil and enalapril, HCTZ increased uric acid and decreased serum potassium ($P < .001$). Conclusion, candesartan cilexetil reduced blood pressure more effectively and was better tolerated than enalapril or HCTZ in women with mild to moderate hypertension.	Poor
5	Freytag F, Schelling A Meinicke T,	Multicenter, randomized, double	Percentage of side effect seen in losartan and enalapril group were 1 and	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	Deichsel G (2001) Comparison of 26 week efficacy and tolerability of telmisartan and atenolol, in combination with hydrochlorothiazide as required, in the treatment of mild to moderate hypertension: *Clin Ther*. 23(1), Jan, pp 108-23	blind, double dummy, parallel group titration N=346 receive telmisartan 174 receive atenolol	respectively. Conclusion It also has fewer side effect when compare to enalapril	
6	Manolis AJ, Grossman E, Jelakovic B, Jacovides A, Bernhardi DC, Cabrera WJ, Watanabe LA, Battagan J, Matadamas N, Mendiola A, Woo KS, Zhu JR, Mejia AD< Bunt T, Dumortier T< Smith RD (2000) Effects of losartan and candesartan monotherapy and losartan/hydrpchlorothiazide combination therapy in patients with mild to moderate hypertension. Losartan Trial Investigators *Clin Ther* 22(10), Oct, pp 1186-203	Multicenter, double blind, randimised parallel group study N=1161patients- F/up 12 weeks	6.9 % of patient treated with losartan 50mg /100 mg experiencing drug related adverse effect	Poor
7	Roca-Cusachs A, Oigman, W Lepe L; Cifkova R, Karpov Ya, Harron	Clinical Trial, Multicenter Study, Randomised Control Trial	The percentage of patients reporting a clinical adverse experience considered drug related by the investigator was 13% in the captopril group and 10 % in losartan	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	DW (1997) A randomized double blind comparison of the antihypertension efficacy and safety of once daily losartan compared to twice daily captopril in mild to moderate essential hypertension *Acta Cardiol* 52(6), pp 495-506	 N= 192 – Losartan; 204-Captopril	group. The incidence of drug related cough was 2.6 % in the losartan group and 4.4 % in the captopril group.	
8	Shobha JC, Kumar TR, Raju BS, Kamath S, Rao M, Harwal, Babu A, Bhaduri J (2000) Evalution of efficacy and safety of losartan potasium in the treatment of mild to moderate hypertension as compared to enalpril *J Assoc Physician India* 48(5), May, pp497-500	Randomised double blind controlled parallel & multicenter study 145 patient -72 patients - losartan potassium 50 mg, 73 patient - enalapril maleate 5 mg F/up: 8 weeks	Percentage of side effects seen in losartan and enalapril groups were 12 and 2 respectively. Conclusion It has fewer side effect when compare to enalapril maleate	Fair
9	Zimlichman R. (1999) Israeli experiences of treatment of hypertension with losartan (Ocsaar)--summary of the treatment of 421 patients in community health centers] *Harefuah* 137(12), Dec 15, pp 597-603, 680	Clinical Trial Controlled Clinical Trial Multicenter Study N=421 patients	Side-effects were minimal and treatment was effective in all age groups.	Poor
10	Hedner T, Oparil S, Rasmussen K, Rapelli A, Gatlin M, Kobi P,	Clinical Trial Randomized Controlled Trial	The incidence of adverse experiences (AE) was similar in all three groups, with headache and dizziness reported most often.	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	Sullivan J, Oddou-Stock P. (1999) A comparison of the angiotensin II antagonists valsartan and losartan in the treatment of essential hypertension. *Am J Hypertens* 12(4 Pt 1), Apr, pp 414-7			
11	Neutel JM, Frishman WH, Oparil S, Papademitriou V, Guthrie G. (1999) Comparison of telmisartan with lisinopril in patients with mild-to-moderate hypertension. *Am J Ther* 6(3), may, pp 161-6	Randomized, multicenter, double-blind, double-dummy, parallel-group, dose-titration study N=578 patients 52-week	Treatment-related side effects occurred in fewer telmisartan-treated patients (28%) than in lisinopril-treated patients (40%; P =.001). Significantly fewer patients (P =.018) receiving telmisartan experienced treatment-related cough (3% v 7%), and cough led to discontinuation significantly less often (P =.007) with telmisartan treatment than with lisinopril treatment (0.3% v 3.1%). In addition, two cases of angioedema were observed, both in the lisinopril group.	Poor
12	Levine B.(2001) Eprosartan provides safe and effective long-term maintenance of blood pressure control in patients with mild to moderate essential hypertension *Curr Med Res Opin.* 17(1), pp 8-17	Clinical Trial Multicenter Study N=706 patients-	Patients treated with eprosartan had a safety profile similar to that reported in short-term placebo-controlled studies. The most frequently reported adverse event was upper respiratory tract infection., and, although events increased with the addition of HCTZ, they were generally not severe.	Poor
13	Plosker GL, Foster RH.(2000) Eprosartan: a review of its use in the management of hypertension. *Drugs* 60(1), July, pp 177-201	Review N= > 100	the incidence of persistent dry cough was evaluated as the primary end-point, enalapril was several-fold more likely to induce this adverse event than eprosartan (the difference being statistically significant Eprosartan has a low potential for serious adverse events, and the drug has not been associated with clinically significant drug interactions. Unlike ACE inhibitors such as enalapril, eprosartan does not have a high propensity to cause persistent nonproductive cough.	Poor
14	Lasko BH, Laplante A, Hebert D, Bonnefis-Boyer S. (2001)	single-blind, single-arm, multicenter study	The overall incidence of adverse experiences per person-year, treatment related or otherwise, was 6.3 and 10.6 for the valsartan and placebo study periods respectively.	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	Canadian valsartan study in patients with mild-to-moderate hypertension. *Blood Press Monit* 6(2), Apr, pp :91-9	N=256 out-		
15	Botero R, Matiz H, Maria E, Orejarena H, Blanco M, Velez JR, Del Portillo H. (2000) Efficacy and safety of valsartan compared with enalapril at different altitudes. *Int J Cardiol*. 72(3), Feb 15, pp 247-54	Clinical Trial Multicenter Study Randomized Controlled Trial N= 142 adult Colombian outpatients receive either valsartan 80 mg once daily or enalapril 20 mg once daily for 8 weeks.	Adverse events irrespective of relationship to trial drug were reported by 12 patients (18.8%) on valsartan and by 15 (23.4%) patients on enalapril. Enalapril was associated with a significantly (P<0.05) higher rate of dry cough and more cases of headache than valsartan. CONCLUSIONS: Valsartan 80 mg once daily is as effective as enalapril 20 mg once daily in reducing blood pressure, with tolerability profile at least as good as enalapril's.	Poor
Agiotension Converting Enzyme Inhibitors (ACE Inhibitor)				
18	Lacouciere Y (2000) A multicenter, randomised, double-blind study of the antihypertensive eficacy and tolerability of irbesartan in patients aged > or = 65 years with mild to moderate hypertension *Clin Ther* 22 (10), Oct, pp 1213-24	Clinical Trial Multicenter Study, Randomised Control Trial N= - 70 -daily dose of irbesartan 150 mg - 71 enalapril 10 mg F/up- 8 weeks	No statistical difference discontinuations due to adverse events incidence of cough in enalapril was 15.5 %	Poor
19	Chiou KR, Chen CH, Ding PY, Chen YT, Huang JL, Chiang AH, Liu CP, Tseng CJ, Chao CT, Chang MS (2000)	Multicenter , double blind, randomise, parallel group study N= 116 patients	Headache, malaise and dizziness were the major adverse reaction observed drug related cough was significant higher (18%)	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	Randomised, double blind comparison of irbesartan and enalapril for treatment of mild to moderate hypertension *Chung Huah I Hsuah Tsa Chih*. 63 (5), May, pp :368-76	F/up: 8 weeks		
20	Malmqvist K, Kahan T, Dahl M. (2000) Angiotensin II type 1 (AT1) receptor blockade in hypertensive women: benefits of candesartan cilexetil versus enalapril or hydrochlorothiazide. *Am J Hypertens*. 13(5 Pt 1), May, pp 504-11	Clinical Trial Randomized Controlled Trial candesartan cilexetil, 8 to 16 mg (n = 140), enalapril, 10 to 20 mg (n = 146), or HCTZ, 12.5 to 25 mg (n = 143), for 12 weeks	Patients experienced less dry cough (P < 0.001) with candesartan cilexetil or HCTZ than with enalapril. No treatment differences were found in the incidence of dizziness and quality of life was well maintained in all groups. Compared with candesartan cilexetil and enalapril, HCTZ increased uric acid and decreased serum potassium (P < .001). Conclusion, candesartan cilexetil reduced blood pressure more effectively and was better tolerated than enalapril or HCTZ in women with mild to moderate hypertension.	Poor
21	Botero R, Matiz H, Maria E, Orejarena H, Blanco M, Velez JR, Del Portillo H. (2000) Efficacy and safety of valsartan compared with enalapril at different altitudes. *Int J Cardiol.* 72(3), Feb 15, pp 247-54	Clinical Trial Multicenter Study Randomized Controlled Trial N= 142 adult Colombian outpatients receive either valsartan 80 mg once daily or enalapril 20 mg once daily for 8 weeks.	Adverse events irrespective of relationship to trial drug were reported by 12 patients (18.8%) on valsartan and by 15 (23.4%) patients on enalapril. Enalapril was associated with a significantly (P<0.05) higher rate of dry cough and more cases of headache than valsartan. CONCLUSIONS: Valsartan 80 mg once daily is as effective as enalapril 20 mg once daily in reducing blood pressure, with tolerability profile at least as good as enalapril's.	Poor
22	Guitard C, Lohmann FW, Alfiero R, Ruina M, Alvisi V. (1997) Comparison of efficacy of spirapril	placebo-controlled, parallel-group study. N=251 patients	Both drugs were well tolerated, and there were very few adverse events or changes in hematological or biochemical parameters during the study. Conclusion, spirapril, 6 mg once daily, as the initial and maintenance dose, is at least as effective and well tolerated as enalapril individually titrated.	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	and enalapril in control of mild-to-moderate hypertension. *Cardiovasc Drugs Ther*. 11(3), Jul, pp 449-57			
23	Hazizi HM, Francillion A, Mottier D, Heintzmann F, Serrurier D (1998) Antihypertensive action and predictive factors of efficacy of benazepril in mild to moderate hypertension: clinical trial in general medical practice on 16,987 patients *Ann Cardiol Angeliol*, 47(1), Jan, pp :33-41	Ramdomised control trial N=16,987 patients	5% dropped out of the study 3% for adverse effect (AE) the most frequent AE were: cough 3.5%, headache 0.9 %, dizziness 0.8% asthenia 0.6% and nausea 0.5% ; 13 death due to cancer or stroke 6 raised serum creatinine level 3 cases of angio-odema 2 cases of hepatitis	Fair
24	Roca-Cusachs A, Oigman, W Lepe L; Cifkova R, Karpov Ya, Harron DW (1997) A randomized double blind comparison of the antihypertension efficacy and safety of once daily losartan compared to twice daily captopril in mild to moderate essential hypertension *Acta Cardiol.* 52(6), pp 495-506	Clinical Trial, Multicenter Study, Randomised Control Trial N= 192 – Losartan; 204-Captopril	The percentage of patients reporting a clinical adverse experience considered drug related by the investigator was 13% in the captopril group and 10 % in losartan group. The incidence of drug related cough was 2.6 % in the losartan group and 4.4 % in the captopril group. Conclusion The number pf patients with the side effect of cough was higher following captopril	Poor
25	Ol'binskaia LI, Sizova ZhM, Zheleznykh EA, Fitilev SB, Sergeeva TE, Pukhlianko ME, Potapova GN. (1999)		Tolerance of both drugs was good, serious side effects were absent. Discontinuation of the drugs was needed in 4% of patients, only. No negative action on bioelectric activity of the heart, clinical and biochemical blood indices were found. CONCLUSION: Sinopril and capoten demonstrate high antihypertensive activity	

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	Antihypertensive efficacy, tolerance and safety of lisinopril (sinopril) and captopril (capoten) in patients with mild and moderate arterial hypertension] *Ter Arkh.* 71(11), pp 61-4			
26	Kukushkin SK, Lebedev AV, Manoshkina EM, Shamarin VM. (1998) Ramipril effects on 24 hour profile of blood pressure in patients with mild and moderate hypertension] *Ter Arkh*. 0(9), pp69-71	21 single dose 2.5-10 mg/day. Captopril controls received 100 mg twice a day.	Side effects of long-term application of ramipril occurred 2 times less frequently than in application of captopril.	Poor
27	Van der Does R, Euler R (2001) A randomized, double-blind, parallel-group study to compare the anti-hypertensive effects of imidapril and nifedipine in the treatment of mild-to-moderate essential hypertension. *J Int Med Res* 29(3), May-Jun, pp :154-62.	Clinical Trial Multicenter Study Randomized Controlled Trial N= 320 patients- imidapril (n = 157) or nifedipine SR (n = 163).	Fewer patients in the imidapril-treated group than the nifedipine group withdrew due to adverse events that occurred on treatment with study medication (3.2% versus 16.0%) or experienced adverse events (40.1% versus 49.7%). In addition, fewer adverse events were causally related to imidapril (24.2%) compared with nifedipine SR (41.7%).	Poor
28	Dews I, VandenBurg M. (2001) A 24-week dose-titration study of the angiotensin-converting enzyme inhibitor imidapril in the treatment of mild-to-moderate essential		At least one adverse event was reported by 46% of patients in the imidapril group and 53% of patients in the hydrochlorothiazide group.	

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	hypertension in the elderly. *J Int Med Res* 29(2), Mar- Apr, pp100-7			
29	Shal'nova SA, Martsevich SIu, Deev AD, Kutishenko NP, Kukushkin SK, Manoshkina EM, Alimova EV, Semenova IuE, Lebedev AV, Koniakhina IP, Zagrebel'nyi AV.(2000) Comparative study of spirapril (quadropril) and amlodipine efficacy. Results of randomized trial in patients with mild to moderate arterial hypertension] *Ter Arkh.* 72(10), pp 86-9	non-blind randomised parallel study N=80 patients -40 patients each. Patients of group 1 received monotherapy with quadropril, while those of group 2 were treated with amlodipine.	Side effects were observed significantly more often in the amlodipine group, then in the quadropril group. The main quadropril side effect was cough. Side effects observed in the amlodipine group were edemas, tachycardia, weakness. CONCLUSION: tolerability of quadropril was better.	Poor
30	Kohlmann Junior O, Jardim PC, Oigman W. (1999) Brazilian multicenter study on efficacy and tolerability of trandolapril in mild-to-moderate essential arterial hypertension. EMBATHE substudy with ambulatory blood pressure monitoring.] *Arq Bras Cardiol.* 72(5), May, pp 547-57	double-blind, placebo-controlled multicenter study Multicenter Study N=262 patients enrolled in this study, 127 were treated with trandolapril 2 mg/day for 8 consecutive weeks, and the remaining 135 patients received placebo for the same period of time.	The adverse event profile was similar in both trandolapril and placebo groups. CONCLUSION: Our results demonstrate, for the first time in a large group of hypertensive patients from different regions in Brazil, good efficacy and tolerability of trando-lapril during treatment of mild-to-moderate essential systemic hypertension.	Poor
31	Neutel JM, Frishman WH, Oparil S, Papademitriou V, Guthrie G. (1999) Comparison of telmisartan with lisinopril in patients with	Randomized, multicenter, double-blind, double-dummy, parallel-group, dose-titration study N=578 patients	Treatment-related side effects occurred in fewer telmisartan-treated patients (28%) than in lisinopril-treated patients (40%; P =.001). Significantly fewer patients (P =.018) receiving telmisartan experienced treatment-related cough (3% v 7%), and cough led to discontinuation significantly less often (P =.007) with telmisartan treatment than with lisinopril treatment (0.3% v 3.1%). In addition, two cases of angioedema were observed, both in the lisinopril group. The selective AT (1) receptor antagonist, telmisartan, is	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	mild-to-moderate hypertension. *Am J Ther* 6(3), pp 161-6	52-week	extremely effective in the treatment of mild-to-moderate hypertension both as monotherapy and in combination with HCTZ and is at least comparable in efficacy to lisinopril, with a tolerability profile that may offer advantages in terms of a reduced incidence of adverse events.	
32	Spinar J, Vitovec J (1998) Ramipril in the treatment of moderate to moderately severe hypertension. A multicenter open study] *Vnitr Lek*. 44(6), Jun, pp 332-5	N=685 patients F/up: twelve-week open trial	The preparation was well tolerated, the total number of undesirable effects was 11% (three patients discontinued because of a cough). The effectiveness was evaluated by the attending physician as very good in 88%, the tolerance in 97%.	Poor
33	Ruddy TD, Fodor JG (1997) Nisoldipine CC and lisinopril alone or in combination for treatement of mild to moderate ysytemic hypertension. Canadian Nisoldipine CC Hypertension Trial *Cardiovasc Drug Ther,* 11 (4), Sep, pp 581-90	Randomised Controlled Trial N= 278 patients F/up:8 weeks	Combination of nisoldipine dan lisinopril was effective and well tolerated with blood pressure not controlled by monotherapy alone	Good
Calcium Channel Blockers				
34	Sanz Guajardo D; Espejo martines J (1997) Randomised, Comparative study to evaluate efficacy and safety of	Clinical Trial, randomized Control Trial N= 61 patients : 31 patient received 1-16 mg of doxazosin	Global assessment of adverse events was similar for both treatment (46.7% for doxazosin and 44.8% for nitrendipine) Nitrendipine treated patients presented facial rush (20%) Withdrawal due to adverse effect were high 20.7%	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	doxazosin verses nitrendipine in the treatment of mild to moderate hypertension *An Med Internal* .14(1), Jan, pp 15-9	and 30 patients assigned to 10-20 mg of nitrendipine F/up 14 weeks		
35	Van der Does R, Euler R (2001) A randomized, double-blind, parallel-group study to compare the anti-hypertensive effects of imidapril and nifedipine in the treatment of mild-to-moderate essential hypertension. *J Int Med Res.* 29(3), may -Jun , pp 154-62.	Clinical Trial Multicenter Study Randomized Controlled Trial N= 320 patients- imidapril (n = 157) or nifedipine SR (n = 163).	Fewer patients in the imidapril-treated group than the nifedipine group withdrew due to adverse events that occurred on treatment with study medication (3.2% versus 16.0%) or experienced adverse events (40.1% versus 49.7%). In addition, fewer adverse events were causally related to imidapril (24.2%) compared with nifedipine SR (41.7%).	Poor
36	Kloner RA, Weinberger M, Pool JL, Chrysant SG, Prasad R, Harris SM, Zyczynski TM, Leidy NK, Michelson EL; (2001) Comparative effects of candesartan cilexetil and amlodipine in patients with mild systemic hypertension. Comparison of Candesartan and Amlodipine for Safety, Tolerability and Efficacy (CASTLE) Study Investigators. *Am J Cardiol* 87(6), mar,15, pp 727-31	Clinical Trial Multicenter Study Randomized Controlled Trial N=251 adult patients (received candesartan cilexetil 16 mg (n = 123) or amlodipine 5 mg (n = 128) once daily.)	A total of 3.3% of patients on candesartan cilexetil discontinued treatment, compared with 9.4% of patients on amlodipine, including 2.4% versus 4.7% for adverse events and 0% versus 1.6% for peripheral edema, respectively. Peripheral edema, the prespecified primary tolerability end point, occurred with significantly greater frequency in patients on amlodipine (22.1%; mild 8.7%, moderate 11.8%, severe 1.6%) versus patients on candesartan cilexetil (8.9%; mild 8.1%, moderate 0.8%) (p = 0.005). Candesartan cilexetil offers a significant tolerability advantage with respect to less risk of developing peripheral edema.	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
37	Whitcomb C, Enzmann G, Pershadsingh HA, Johnson R, Ciuryla V, Reisin E. (2000) A comparison of nisoldipine ER and amlodipine for the treatment of mild to moderate hypertension. *Int J Clin Pract* 54(8), Oct, pp :509-13	Multicentre, double-blind, double-dummy, randomised trial N=161 patients.	Tolerability profiles were similar between treatments.	Poor
38	Yosefy C, Viskoper JR, Leshem Y, Rav-Hon Y, Rosenberg GI, Yaskil E. (1999) Multicenter community-based trial of amlodipine in hypertension in Israel *Harefuah* 137(3-4), Aug, pp 89-93, 176	open non-comparative trial N=266 patients	The most common AML-related AE requiring cessation of the drug was pedal edema in 2.6% of the 266 patients; in 3.7% it persisted during therapy. Other AE occurring in > 1% were dizziness in 1.8%, headache 1.5%, flushing 1.1% and fatigue 1.1%. conclude that AML is an effective and well-tolerated antihypertensive suitable for most hypertensive patients.	Poor
39	Sowunmi A, Walker O, Salako LA. (1996) Amlodipine as monotherapy in hypertensive Africans: clinical efficacy and safety studies. *Afr J Med Med Sci* . 25(3), Sep, pp 213-6	Controlled Clinical Trial N=20 patients over a 10 week period	Dizziness and weakness occurred in one patient, otherwise, the drug was well tolerated. Laboratory tests, including plasma lipids done at the start and end of the trial, remained unchanged.	Fair
40	Cheung BM, Lau CP, Wu BZ. (1998) Amlodipine, felodipine, and isradipine in the treatment of Chinese patients with mild-to-moderate hypertension. *Clin Ther* 20(6), Nov,-Dec, pp	amlodipine (n = 41), felodipine (n = 38), or isradipine (n = 39) for 8 weeks,	No serious adverse events occurred, but mild adverse effects, including headaches, flushing, tachycardia, dizziness, and edema, were reported; 1 (2%), 6 (16%), and 5 (13%) patients receiving amlodipine, felodipine, and isradipine, respectively, withdrew from the study ($P < 0.05$). The results of this study indicate that all three drugs are highly effective in lowering blood pressure and are well tolerated in Chinese patients with mild-to-moderate hypertension.	Poor

No	*Author, title, Journal*	*Study design, Sample size, Follow up*	*Outcomes & Characteristic*	*Grade & Comment*
	1159-69			
41	Kalke S, Shah BV, Nair KG, Gala D, Sood OP, Bagati A. (1999) Clinical trial of benidipine in mild to moderate hypertension. *J Assoc Physicians India.* 47(2), Feb, pp 195-7	N=34 patients	Most of the patients tolerated the drug well. Three patients had mild side effects like headache and heaviness in the head. One of them also had puffiness of face and body (on benidipine 8 mg/day) and was withdrawn from the study. One patient had mild constipation. conclude that benidipine is well tolerated in the dose of 4-8 mg/day and is an effective antihypertensive agent for treatment of patients with mild to moderate hypertension.	Poor
42	Sanz Guajardo D; Espejo martines J (1997) Randomised, Comparative study to evaluate efficacy and safety of doxazosin verss nitrendipine in the treatment of mild to moderate hypertension *An Med Internal.* 14(1), Jan, pp 15-9	Clinical Trial, randomized Control Trial N= 61 patients : 31 patient received 1-16 mg of doxazosin and 30 patients assigned to 10-20 mg of nitrendipine F/up 14 weeks	Global assessment of adverse events was similar for both treatment (46.7% for doxazosin and 44.8% for nitrendipine) Withdrawal due to adverse effect were high 6.7%	Fair

EVIDENCE TABLE: COST

No	Author, Title, Journal	Study design, sample size,	Outcomes & characteristic	Grade & comment

		follow up		
43	Whitecomb C; Enmann G, Pershadsingh HA, Johnson R, Ciuryla V, Reisin E (2000) A comparison of nisoldipine ER and amlodipine for the treatment of mild to moderate hypertension *Int J Clin Pract.* 54(8), Oct, pp 509-13	Multicenter Study, double blind, double dummy Randomised controlled Trial 161 patients F/up: 8 Weeks	The drug acquisition cost per mm Hg DBP reduction was 40 % lower with nisoldipine, an acquisition cost analysis revealed that amlodipine was 80 % more expensive than nisoldipine for treating hypertension	Poor
44	Pearce KA, Furberg CD, Psaty BM, Kirk J (1998) Cost-minimization and the number needed to treat in uncomplicaticated hypertension *AM J Hypertension*, 11(5), May, pp 618-19	Meta Analysis	the estimate wholesale drug acquisition cost to prevent major event (MI or stroke or death) ranged from $ 4730 to $346,236 among middle aged patients. A,d from $ 1595 to $116,754 in the elderly, generic diuretic or beta blocker therapy was more economical than treatment with ACEI, alpha blocker or CCB . diuretic therapy remained more cost effective even-thought newer drugs is 50% more effective in preventing major events. Treatment cost to prevent major hypertension complications using diuretic and beta-blocker are much lower than ACEI. CCB or alpha blocker especially in middle aged patients	Good

APPENDIX 1

LEVEL OF EVIDENCE SCALE

Level	Strength of evidence	Study design
1	Good	Meta-analysis of RCT, Systematic Review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Fair	Case control studies
8	Poor	Non-controlled clinical series, descriptive studies, multi-center
9	Poor	Expert committees, consensus, case reports, anecdotes

(Adapted from Catalonian Agency of Health Technology Assessment & Research)