Introduction
Hypertension is a worldwide epidemic, one billion hypertensive in the world and three million die annually as a direct result of hypertension. Hypertension is recognized worldwide as a major CV risk factor. JNC-VII Guidelines, 2003 for management of hypertension recommended, thiazide diuretics are the preferred initial therapy for hypertension. Indapamide is an antihypertensive diuretic related to the thiazides. Indapamide SR is very well tolerated with unimpaired metabolic profiles, innovative SR formulation and optimal efficacy-acceptability ratio. It is a new reference antihypertensive diuretic with complete 24-hours blood pressure controlling effect. It regresses LVH, reduces microalbuminuria in type-2 diabetic hypertensives. Indapamide can be used in all hypertensives patients. It is the drug of choice for elderly hypertensive.

Key Words
Indapamide SR, Diuretics, Antihypertensive.

Hypertension
Hypertension is recognized worldwide as a major CV risk factor. Cardiovascular diseases accounts for 30% of the world's deaths. Lowering of blood pressure causes average percent reduction of stroke incidence by 35-40%, myocardial infarction by 20-25% and heart failure by 50%.

Target blood pressure in patient with hypertension without diabetes mellitus or renal failure is <140/90 mm of Hg. Goal pressure in patient with hypertension with diabetes mellitus or renal failure or coronary artery disease is <130/80 mm of Hg. In patient with isolated systolic hypertension blood pressure goal is <140 mm of Hg. Hypertensive patients are at risk of cerebrovascular disease, coronary heart diseases, heart failure, renal insufficiency, peripheral vascular diseases and premature death.

So goal of prevention and management of hypertension are to reduce morbidity and mortality, maintain systolic blood pressure below 140 mmHg and diastolic blood pressure below 90 mmHg, control other modifiable risk factors, prevent stroke, preserve renal function and prevent or slow heart failure progression.

Sometimes hypertensive patient cannot reach to goal BP in spite of adequate drug therapy (at least 3 drugs in optimum dosages) is the condition of refractory hypertension. Causes of refractory hypertension are unsuspected secondary cause, poor adherence to therapeutic plan, continued intake of drugs that raise blood pressure (e.g., NSAIDs), failure to modify lifestyle including weight gain, heavy alcohol intake and volume overload due to inadequate diuretic therapy, progressive renal failure, high sodium intake. Some condition requires immediate blood pressure reduction like hypertensive encephalopathy, acute LVF, acute aortic dissection, post CABG, eclampsia. If patient had hypertensive intracerebral bleeding, acute subarachnoid haemorrhage, unstable angina or acute MI require immediate BP reduction only when it is excessively high.

JNC-VII Guidelines, 2003 for management of hypertension recommends aggressive treatment, simplified classification system also recommends thiazide diuretics are the preferred initial therapy for hypertension.

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For persons over age 50, SBP is more important than DBP as a CVD risk factor. Starting at 115/75 mmHg, CVD risk doubles with each increment of 20/10 mmHg throughout the BP range1.

Persons who are normotensive at age 55 have a 90% lifetime risk for developing HTN. Those with SBP 120-139 mmHg or DBP 80-89 mmHg should be considered prehypertensive who require health-promoting lifestyle modifications to prevent CVD. Thiazide-type diuretics should be initial drug therapy for most, either alone or combined with other drug classes. Certain high-risk conditions are compelling indications for other drug classes. Most patients will require two or more antihypertensive drugs to achieve goal BP. If BP is >20/10 mmHg above goal, initiate therapy with two agents, one usually should be a thiazide-type diuretic1.

The prevalence of isolated systolic hypertension is near 10% and increases with age2. Furthermore, most elderly hypertensive patients have primarily systolic hypertension with only minor elevations of diastolic blood pressure. Reports from the Framingham Study have emphasized that systolic hypertension is a greater risk for causing cardiovascular events than diastolic hypertension3, and the combination of high systolic and low diastolic pressure (widened pulse pressure) is a major predictor of cardiovascular disease. The widened pulse pressure reflects atherosclerotic thickening of the major capacitance vessels. In the Framingham Study for individuals aged 55 to 65 years the lifetime probability of developing hypertension is nearly 90%-4. In a meta-analysis of treatment of isolated systolic hypertension in the elderly, Staessen et al5 reported that active treatment of hypertension reduced cardiovascular mortality by 18%, all cardiovascular complications by 26%, stroke by 30% and all coronary events by 23%. Absolute benefit was greater in men than women. Despite the enormous evidence indicating the benefits of treatment, only a small percentage of patients are adequately controlled. Hypertension is poorly controlled, with less than 25% controlled in developed countries and less than 10% in developing countries1. The reasons are multiple: lack of knowledge by health professionals of the importance of treating systolic hypertension, drug side effects and medication expense, to mention a few.

Lifestyle modification, such as weight reduction, low sodium diet, reduced alcohol intake, cessation of smoking and increased physical activity should be an adjunct to all drug therapy. The blood pressure level, cardiovascular risk factors, and target-organ damage should be evaluated in planning antihypertensive treatment1,6,7.

**Thiazide diuretics in hypertension**
Thiazide-type diuretics are useful in slowing demineralization in osteoporosis. Thiazide-type diuretics have been the basis of antihypertensive therapy in most outcome trials. Diuretics enhance the anti-hypertensive efficacy of multidrug regimens, can be useful in achieving BP control and are more affordable than other antihypertensive agents. Thiazide and Thiazide-type diuretics in recent guidelines, JNC-VII; 2003 recommended “Thiazide-type diuretics should be used as initial therapy in most patients with hypertension, either alone or in combination with one of the other classes (ACEIs, ARBs-blockers, CCBs)”1.

Several reports have recommended low-dose diuretics as an effective, relatively cheap medication with few side effects. The recent JNC-VII guidelines in hypertension recommend diuretics as first-step therapy for most hypertensive patients, including those at-risk such as elderly hypertensives, hypertensives with recurrent stroke, high coronary disease risk, heart failure or type 2 diabetes4. Diuretics are also recommended as the second-choice drug when other first
choice drugs fail to control the hypertension. For example, in the Life Trial Study, a diuretic was added as a second line therapy in all patients who did not attain target blood pressure with primary drug, losartan or atenolol. At the 12-month visit over 60% of patients were on a diuretic. Also, in the AASK Study, a diuretic was the second-choice drug.

These recommendations were based upon a number of long-term clinical trials that demonstrated the beneficial effects of diuretics in preventing cardiovascular complications in hypertension patients, especially in preventing strokes and heart failure.

In the SHEP Study (Systolic Hypertension in the Elderly Study) reported in 1991, there was a 33% decrease in stroke and 55% decrease in heart failure over 5 years. The main drug used was a thiazide diuretic. In several trials using diuretics, all cardiovascular disease was reduced by 32% SHEP, 40% STOP 1, 17% MRC and 31% in the Syst-Eur Study using CCB. When compared with other drugs in a given trial, diuretics were never found to be inferior in preventing CV events.

In 1998, Moser pointed out the steady decline in the use of diuretics in the USA despite the clinical evidence supporting their use. The reasons include concern over metabolic effects, such as increased cholesterol and blood glucose and hypokalemia and heavy promotion of newer drugs. The data, however, indicated that with low doses the metabolic effects are minor and do not lessen the beneficial effects of diuretics. Recently, the role of diuretics in treating hypertension received a major boost with the publication of the ALLHAT Trial (The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial). The ALLHAT is one of the most important antihypertensive trials. ALLHAT compared three different classes of medications: lisinopril (representing ACE inhibitors), amlodipine (representing dihydro-pyridine calcium channel blockers: DHP-CCB) and doxazosin (representing α-blockers) with Chlorthalidone (representing standard thiazide treatment). The planned follow-up was long (4 to 8 years).

The rest of the study ended in 2002. Each drug reduced blood pressure substantially, but the blood pressure decrease and drug tolerance with the thiazide diuretic was better than with the ACE inhibitor.

The major finding of ALLHAT was that all three medications were equally effective in preventing the primary outcome event, namely coronary heart disease, death and non-fatal myocardial infarction. However, for some secondary outcomes there were differences. The thiazide diuretic was better than the calcium channel blocker in preventing heart failure. Surprisingly, the thiazide diuretic was superior to the ACE inhibitor in preventing stroke, especially in black patients and in combined cardiovascular disease and possibly heart failure.

Despite the mild adverse metabolic effects in some patients, such as hypokalemia, hypercholesterolemia and increase in blood glucose, there were no excess cardiovascular events in the whole study population or in the subgroup of diabetic patients. The ALLHAT report recommended that diuretics should be preferred for first choice antihypertensive therapy, especially in those patients with high risk cardiovascular disease.

### Indapamide, thiazide-type diuretics

Indapamide is indoline derivatives of chlorosulphonamide. It differs chemically from thiazides and contains only one sulphonamide group and no thiazide ring.

**Mode of action**

Indapamide is an anti-hypertensive diuretic related to the thiazides. The anti-hypertensive effect is associated with an improvement in arterial compliance and a reduction in total and arteriolar peripheral resistance. The mechanism of vascular action of Indapamide...
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appears to involve: stimulation of renal synthesis of prostaglandin PGE$_2$, with its vasodilator hypotensive actions and increase in synthesis of prostacyclin PGI$_2$ with its vasodilator and anti-platelet actions in the endothelium.

Indapamide as a first step antihypertensive, has two properties beyond diuresis. First, there is added vasodilation$^{15}$. A second unusual property is a high concentration class I and III antiarrhythmic effect$^{16}$. If this were also clinically relevant, it could protect from ventricular arrhythmias, while also carrying a theoretical risk of torsades de pointes in the presence of hypokalemia or cotherapy with certain other antiarrhythmics. Indapamide has a terminal half-life of 14 to 16 hours and effectively lowers the blood pressure over 24 hours. The initial dose is 1.25 mg once daily for 4 weeks, then if needed 2.5 mg daily. Indapamide appears to be more lipid neutral than other thiazides$^{17}$ but seems equally likely to cause other metabolic problems such as hypokalemia, hyperglycemia or hyperuricemia. With a reduced but still antihypertensive dose of only 0.625 to 1.25 mg combined with the ACE inhibitor perindopril 2-4 mg, the serum potassium fell by only 0.11 mmol/L over 1 year, while the blood glucose was unchanged from placebo$^{18}$. Regarding regression of LV hypertrophy, indapamide was better than enalapril in the LIVE study (LVH with Indapamide Versus Enalapril) $^{19}$. Indapamide SR is very well tolerated with unimpaired metabolic profiles, innovative SR formulation, optimal efficacy-acceptability ratio, new reference antihypertensive diuretic, complete 24-hours blood pressure control, metabolic neutrality, reduction of microalbuminuria in type 2 diabetic hypertensives, used in all hypertensive patients.

A smooth pharmacokinetic profile of Indapamide SR 1.5 mg than Indapamide IR 2.5 mg, elimination of unnecessary peaks of plasma concentration. Also full antihypertensive efficacy found at lower dose of Indapamide SR 1.5 mg.

Systolic blood pressure increases risk of MI, HF and stroke than diastolic blood pressure. Indapamide SR is the best choice for superior and sustained reduction of systolic blood pressure comparable to amlodipine and ARB.

The LIVE study$^{21}$, European multicenter prospective, double-blind, randomized clinical trial indapamide SR versus enalapril 20 mg/day for 12-month duration, in 577 hypertensives with echo-proven LVH, shows significant reduction of LVH with indapamide SR.

NESTOR study$^{22}$ Natrilix SR vs Enalapril Study in Type 2 diabetic hypertensives with microalbuminuria, international multicenter study, randomized, double-blind, controlled study, Indapamide SR versus enalapril 10 mg/day, 1-year duration, 570 type 2 diabetic hypertensives with microalbuminuria. Indapamide SR significantly reduces microalbuminuria in type 2 diabetic hypertensives. Indapamide SR is as effective as enalapril in reducing microalbuminuria with equivalent MBP control.

Indapamide SR is very well tolerated with unimpaired metabolic profiles, innovative SR formulation, optimal efficacy-acceptability ratio, new reference antihypertensive diuretic, complete 24-hours blood pressure control, metabolic neutrality, regression of LVH$^{23}$, reduction of microalbuminuria in type 2 diabetic hypertensives, used in all hypertensive patients.

Conclusion

JNC-VII guidelines in hypertension, strongly recommend diuretics as first-step therapy for most hypertensive patients. Diuretics have been virtually unsurpassed in preventing the cardiovascular complications of hypertension.
If not chosen first-line, diuretics as ideal second-step antihypertensive therapy.

In conclusion indapamide has powerful antihypertensive efficacy, protecting from Cardiovascular events, well tolerated and drug of choice for elderly hypertensive used in all hypertensive patients.

Reference
20. Ambrosioni E, et al. Low-dose antihypertensive therapy with 1.5 mg