“The person with diabetes who knows the most lives the longest” – Elliot P. Joslin

Introduction
How true and incredibly contemporary are these words spoken almost seven decades ago and they befit a hypertensive diabetic to the finest tune. Diabetes and hypertension are the two faces of the same coin and they co-exist to the tune of 20 – 60% depending upon obesity, ethnicity and age of the person.\textsuperscript{1} We continue to grapple with this apparently insurmountable barrier even to this day. Hypertension is twice as prevalent in a diabetic as compared to a non-diabetic. In type 2 diabetes, hypertension may be present at the time of diagnosis or even before the development of hyperglycaemia. While, in type 1 diabetes, hypertension develops after several years of the disease and usually re ects the development of diabetic nephropathy and ultimately affects ~30% of individuals with type 1 diabetes\textsuperscript{2,3}. Hypertension in diabetic patients is associated with accelerated progression of both micro vascular (retinopathy and nephropathy)\textsuperscript{4} and macro vascular (atherosclerotic) complications.\textsuperscript{5}

Definition of Hypertension in Diabetic Population
Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in May 2003 in it’s VIIth report (JNC VII 2003) has recommend a target blood pressure of <130/80 mmHg in hypertensive patients with diabetes, as compared with <140/90 in patients without diabetes\textsuperscript{6}. It has further concluded that the risk of Cardio-vascular Disease (CVD) beginning at 115/75 mm Hg doubles with each increment of 20/10 mm Hg. The Hypertension Optimal Treatment (HOT) study and the U.K. Prospective Diabetes Studies (UKPDS) have shown the benefits of achieving tighter blood pressure control.\textsuperscript{7,8} For example, in HOT, patients with diabetes randomized to a target diastolic blood pressure of 80 mmHg or less had a 50% reduction in major cardiovascular events compared with those with a target diastolic blood pressure of 90 or less. Moreover, the benefits of tight blood pressure control in patients with diabetes exceed the benefits of tight glycaemia control and extend not only to the prevention of macro vascular disease, but also to the prevention of micro vascular complications. The American Diabetes Association has long advocated that “hypertension should be treated aggressively to achieve and maintain blood pressure in the normal range.”\textsuperscript{9}
Pathophysiology
Various theories have been proposed but in diabetics with hypertension, hyperinsulinemia secondary to insulin resistance and decreased insulin clearance has been observed. Insulin resistance is also associated with a decreased vasodilator response to insulin in skeletal muscle and an increased vasoconstrictor response to various vasopressors. Hyperinsulinemia may possibly be associated with increased renal sodium resorption and sympathetic nervous system overactivity, leading to hypertension in obese individuals and other insulin-resistant states. In the presence of nephropathy, extra cellular fluid volume and total body sodium levels are increased. The activity of the renin-angiotensin-aldosterone system (RAAS) is reduced in these patients, and the hypertension is volume-dependent, similar to other nephropathies.

Hypertension and Diabetic Renal Disease
Hypertension is closely linked to nephropathy and anti-hypertensive treatment has been shown to retard its progression. Approximately 20–30% of patients with type 1 diabetes and 10–20% with type 2 diabetes will develop end-stage renal disease (ESRD). Diabetes now accounts for ~50% of all new patients with ESRD and is the most common cause of this condition in adults. Familial and genetic factors play an important role in the development of this complication. Longitudinal studies have shown that blood pressure is already rising in patients with TYPE 1 DM before the development of overt proteinuria, in the phase known as microalbuminuria and the presence of this predicts cardiovascular disease. The increase in cardiovascular disease is about threefold in microalbuminuric patients with TYPE 1 DM when compared with age- and duration- matched normoalbuminuric patients with diabetes. In TYPE 2 DM, hypertension is not closely linked to renal disease and often occurs before the diagnosis of diabetes.

Syndrome –X
The “quintet” of central obesity, hypertension, dyslipidemia (high triglyceride and low HDL), and glucose intolerance characterizing the metabolic syndrome plays a pivotal role in HT with DM. Obesity may affect BP via leptin, which increases sympathetic activity and may mediate increases in catecholamines, or via activation of the renin-angiotensin system (RAAS). Angiotensin II levels are high in obesity and the presence of increased glomerular pressures suggests activation of RAAS. The underlying association between hypertension and diabetes in this syndrome remains unknown, but it is possible that endothelial dysfunction as a result of both hypertension and diabetes could be an important factor in the high incidence of vascular disease in individuals with both conditions.

Treatment
The importance of aggressive treatment of hypertension in the setting of diabetes cannot be over emphasized. Hypertensive patients with diabetes are at considerably greater risk for cardiovascular events. Consequently, lowering of blood pressure will prevent more cardiovascular events than similar reductions in nondiabetic patients. However, undertreatment of chronic medical conditions such as hypertension and diabetes appears to be common, even when clinicians agree with guideline recommendations. Recently, Phillips et al. proposed the term “clinical inertia” to describe this phenomenon. They ascribed it to clinician overestimation of the intensity of care they provided, the absence of organizational supports necessary to treat to “target” and the use of “soft” reasons to justify not intensifying therapy.

Goals of Therapy
Strive for a blood pressure of less than 125/75 mm Hg if individual with diabetes also has proteinuria of over 1 gram/day or any type of renal insufficiency. In rest of the diabetics try to maintain blood pressure below 130/80 mm Hg. This more aggressive goal for persons with diabetes has been established...
because control of hypertension in persons with diabetes has been demonstrated to reduce the rate of progression of diabetic nephropathy and reduce the complications of hypertensive nephropathy, cerebrovascular disease, and cardiovascular disease (ADA, 2003). In the HOT Study, people with diabetes who kept their diastolic blood pressure at 80 mm Hg (versus 90 mm Hg) had a 51% lower risk of experiencing a cardiovascular event. Controlling systolic blood pressure dropped cardiovascular events by 62-70% in the Systolic Hypertension in Europe Trial (Syst – Eur). The UKPDS suggested that aggressive treatment of even mildly elevated blood pressure is beneficial. It showed that lowering blood pressure to a mean level of 144/82 mm Hg significantly reduced vision loss, diabetes-related deaths, strokes, heart failure, and various micro vascular complications.

Treatment through Lifestyle Modification
There is no second thought that healthy eating and lifestyle modifications act as double edged sword for controlling this duo of DM & HT. Weight reduction can reduce blood pressure independent of sodium intake and can also improve blood glucose and lipid levels. The loss of one kilogram in body weight has resulted in decreases in mean arterial blood pressure of ~1 mmHg. A dose response effect has been observed with sodium restriction and results from controlled trials in essential hypertension have shown a reduction in systolic blood pressure of ~5 mmHg and diastolic blood pressure of 2–3 mmHg with moderate sodium restriction (from a daily intake of 200 mmol [4,600 mg] to 100 mmol [2,300 mg] of sodium per day). The Dietary Approaches to Stop Hypertension (DASH) study, which dealt with people who had slightly elevated blood pressure levels, found that a meal plan high in fruits, vegetables and low fat dairy products lowered blood pressure as effectively as drug therapy. The meal plan had more potassium, calcium, magnesium, fibre, protein, and carotenoids than the control diet as well as less fat, saturated fat, and cholesterol.

Regular aerobic physical activity plays a role in preventing cardiovascular disease, can improve glycaemia control and may help with blood pressure control. A pre-activity examination is also recommended to look for previously undiagnosed neuropathy, retinopathy, nephropathy and, particularly, ischemic heart disease, all of which could be aggravated by some forms of activity (ADA, 2003). If there are no contraindications, 30 minutes of moderate intensity physical activity, such as walking or riding a stationary cycle, on most days is recommended. Older, inactive people may need to begin with 5 to 10 minutes of activity each day and progress to 20 to 30 minutes of activity over 5 to 10 weeks.

Pharmacological Treatment
There are excellent clinical trial data proving that lowering BP with several classes of drugs, including Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin Receptor Blockers (ARBs), Beta-blockers (BBs), Calcium Channel Blockers (CCBs) and Thiazide Type Diuretics will all reduce the complications in Diabetic Hypertensives.

ACE inhibitors
These drugs are useful in the management of hypertension in diabetic patients with or without diabetic nephropathy. The UKPDS-HDS showed beneficial effects of the ACE inhibitor captopril on diabetes-related mortality and micro vascular and cardiovascular complications in patients with type 2 diabetes. They are also effective in decreasing cardiovascular mortality and morbidity in patients with congestive heart failure and post-myocardial infarction. ACE inhibitors have been extensively studied in the treatment of diabetic nephropathy and are effective in preventing progression of retinopathy. HOPE trial documented decreased cardiovascular end points despite quite minor changes in blood pressure raises the possibility that ACE inhibitors have benefits for diabetic patients that are independent of their antihypertensive effect.
ARBs
Angiotensin II receptor blockers have been shown to decrease proteinuria and retard the development and progression of nephropathy. Losartan, irbesartan, telmesartan, candesartan, eprosartan, and valsartan are effective antihypertensive agents.\textsuperscript{10}

Calcium channel blockers
The dihydropyridine group (DCCBs) are effective antihypertensive agents. The benefit of DCCBs in decreasing cardiovascular events in hypertensive diabetic patients has been shown in the Syst-Eur and HOT trials.\textsuperscript{18,7} However, in both trials most patients were also receiving a \( \beta \)-blocker or an ACE inhibitor in order to achieve the goals of therapy. A recent meta-analysis suggests that calcium channel blockers may be equivalent in protecting against stroke but less effective in reducing myocardial infarction and combined major coronary events than ACE inhibitors, \( \beta \)-blockers, or diuretics. All-cause mortality was found to be equivalent among all classes of drugs given equivalent control of blood pressure. These findings did not seem to be affected by the presence of diabetes\textsuperscript{10}. Small studies of short duration using diltiazem and verapamil have been associated with decreased proteinuria in patients with overt diabetic nephropathy.

\( \beta \)-Blockers
The \( \beta \)-blocker atenolol and the ACE inhibitor captopril were equally effective in decreasing the risk of diabetes-related end points and micro vascular events in subjects with type 2 DM and HT.\textsuperscript{8} \( \beta \)-Blockers have demonstrated efficacy in patients with myocardial infarction with relative reductions in mortality of \( \sim 25\% \). Various interventional studies using beta-blockers and diuretics have demonstrated reductions in the rate of deterioration of GFR in type 1 diabetic patients with nephropathy. In a long-term study, atenolol and lisinopril produced similar reductions in the decline of GFR in patients with type 2 diabetes and nephropathy. Beta – blockers may be substituted for calcium channel blockers if angina, heart failure or arrhythmia is present.

Diuretics
Thiazide-type diuretics have been the basis of anti-Hypertensive therapy in most outcome trials.\textsuperscript{24} In these trials, including the recently published Anti-Hypertensive and Lipid Lowering Treatment to prevent heart attack trial (ALLHAT)\textsuperscript{25}, Diuretics have been virtually unsurpassed in preventing the cardiovascular complications of HT. The SHEP study also showed that low-dose thiazide treatment of systolic hypertension in older diabetic subjects was associated with a significant reduction in cardiovascular events. Thiazides may not be effective in subjects who have significantly decreased renal function (i.e., GFR <60 ml \( \cdot \) min\(^{-1} \) \( \cdot \) 1.73 m\(^2\)). Loop diuretics are recommended for patients with decreased renal function (GFR <60 ml \( \cdot \) min\(^{-1} \) \( \cdot \) 1.73 m\(^2\))\textsuperscript{10}, usually in combination with other agents. Diuretics enhance the Anti-Hypertensive efficacy of multi drug regimens, can be useful in achieving BP control, and are more affordable than other anti-hypertensive agents. Despite these findings, diuretics remain underutilized.

Antihypertensive Drugs - Side Effects
\( \beta \)-Blockers and thiazide diuretics may influence glycaemic control in a deleterious manner.\textsuperscript{-}These agents can also have unfavourable effects on lipids by increasing triglycerides and decreasing HDL cholesterol levels. \( \beta \)-Blockers may exacerbate symptoms of peripheral vascular disease, a condition which is more common in diabetic patients. In patients with IDDM who are at a high risk of hypoglycaemia, \( \beta \)-blockers may reduce the symptomatic manifestations of hypoglycaemia and inhibit the metabolic counter-regulatory response. Recently, it has been shown that the deleterious effects of thiazide diuretics on lipid and glucose metabolism are dose related and do not generally occur if low doses are used.

The \( \alpha \)-blockers, such as prazosin, and the calcium- channel blockers do not have adverse effects on
glucose or lipid levels. ACE inhibitors have been shown to enhance insulin sensitivity. However, these modest effects on insulin resistance do not appear to be associated with a dramatic improvement in glycaemia control in diabetic patients. Nevertheless, ACE inhibitors, α-blockers and calcium-channel blockers, do not adversely affect lipid or glucose levels. ACE inhibitors are commonly used in diabetic patients with nephropathy. However, these agents may uncommonly be associated with life-threatening hyperkalaemia, particularly when hyporeninaemic hypoaldosteronism is present - a condition often associated with renal impairment and autonomic neuropathy in diabetes. Renal artery stenosis should always be considered in the presence of recent-onset hypertension in a diabetic patient. Bilateral renal artery stenosis is often associated with rapid deterioration of renal function if ACE inhibitors are given.

Combination Therapy
In general, combination therapy may help to improve compliance, as one drug may antagonize the adverse effects of another. Diuretic agents in combination with adrenergic blockers have been used in several nephropathy studies and in the UKPDS-HDS and SHEP study. ACE inhibitors have been used in combination with diuretics and calcium channel blockers and are found to be very effective.

Summary
The aim of blood pressure reduction includes retardation of the progression and prevention of diabetic complications. Since many studies demonstrate the benefits of ACE inhibitors on multiple adverse outcomes in Type 1 and 2 diabetics with either mild or severe hypertension, the established practice of choosing an ACE inhibitor as the first-line agent is reasonable. In patients with microalbuminemia or clinical nephropathy, both ACE inhibitors (type 1 and 2 patients) and ARBs (type 2 patients) are considered first-line therapy for the prevention and progression of nephropathy. The beneficial effects of ACE inhibitors are seen even in the absence of systemic HT in type 1 diabetics and delay the development of overt proteinuria.

However, other strategies including diuretic and β-blocker–based therapy are also supported by evidence. Because of lingering concerns about the lower effectiveness of DCCBs (compared with ACE inhibitors, ARBs, β-blockers, or diuretics) in decreasing coronary events and heart failure and in reducing progression of renal disease in diabetes, these agents should be used as second-line drugs for patients who cannot tolerate the other preferred classes or who require additional agents to achieve the target blood pressure. Other classes, including β-blockers, may be used under specific indications (such as symptoms of BPH for β-blockers) or other agents have failed to control the blood pressure or have unacceptable side effects. Blood pressure, orthostatic changes, renal function, and serum potassium should be monitored at appropriate intervals. The importance of aggressive treatment of hypertension in the setting of diabetes cannot be over emphasized. Achievement of the target blood pressure goal ≤ 130/80 with a regimen that does not produce burdensome side effects and is at reasonable cost to the patient is probably more important than the specific drug strategy. Winds of change are sweeping over the whole world and the world of DM and HT care is no exception.

References
1. American Diabetes Association : Treatment of HT in Adults with DM. Diabetes Care 2003; 26:s80-s82.


