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# *Megatrials in Diabetes and Their Clinical Implications*

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In the last three decades lot of advances have taken place in the understanding of diabetes and its management. Studies have thrown light on the pathogenesis of both type 1 and type 2 diabetes leading to a more rationale approach to the management. Several newer molecules have been discovered which act at different sites modulating carbohydrate and lipid metabolism.

A new classification for diabetes based on the etiology and diagnostic criteria based on the risk of developing microvascular complications have been developed. This new classification and diagnostic criteria enunciated by the ADA and endorsed by the WHO expert committee provide us with a uniform standard for evaluation of the data of studies carried out throughout the world.

Several long term well planned trials have been conducted to evaluate several hitherto unanswered questions.

- i. The importance of tight metabolic control with intensive therapy in preventing the development and progression of complications of diabetes
- ii. The response and outcomes with different treatment modalities adopted for managing type 2 diabetes (Oral antidiabetic agents vs Insulin)

- iii. The evaluation of different molecules available for the treatment of type 2 diabetes on reduction of hyperglycemia and also benefits beyond glycemic control such as effects on beta cell mass and function

With the prevalence of diabetes rising all over the world it is assuming pandemic proportions, and this has evoked particular interest in studies on prevention of both type 1 and type 2 diabetes. Several studies have focused on screening of high risk subjects and identification of prediabetic states namely IGT and IFG in whom preventive strategies have been used.

In this presentation we will be discussing some of the landmark trials, their results and implications of these on the day to day management of diabetes.

While several animal and human studies gave some idea about the role of hyperglycemia in the development of vascular complication, it was not clear whether these complications could be prevented and what degree of control was necessary. It was also not clear whether there were differences in the outcome of treatment in terms of morbidity and mortality with different therapeutic modalities. Several trials have been carried out with an objective to clarify these issues.

A correlation between glycemic control and diabetic complications in patients with type

**Table 1 : UKPDS: Reduction in complications with intensive glycemic control (HbA1c 0.9% lower than conventional treatment)**


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12% for any diabetes related endpoint (p = 0.029)
25% for any microvascular endpoint (p = 0.0099)
16% for myocardial infarction (p = 0.052)
24% for cataract extraction (p = 0.046)
21% for retinopathy at 12 years (p = 0.015)
33% for albuminuria at 12 years (p = 0.00005)

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**Table 2 : UKPDS: Reduction in complications with Tight blood pressure control (144/82 vs 154/87 mmHg)**


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24% for any diabetes related end point (p = 0.046)
37% for any microvascular endpoint (p = 0.0092)
21% for myocardial infarction (p = 0.13)
44% for stroke (p = 0.013)
58% for heart failure (p = 0.0043)

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2 diabetes was first studied by the University Group Diabetes Program (UGDP)<sup>1</sup>. The UGDP followed 1000 patients with type 2 Diabetes, assigned to different therapies for about 5.5 years (range 3-8 years) and reported an increased risk of cardiovascular mortality in patients allocated to the sulfonylurea, tolbutamide, and phenformin and increased incidence of lactic acidosis with phenformin. The UGDP trial therefore threw up more controversies than giving any clarity on these issues<sup>1</sup>.

The DCCT (Diabetes Control & Complications Trial)<sup>2</sup> and Stockholm trials<sup>3</sup> were done in type 1 diabetic patients and demonstrated conclusively that tight control of blood glucose with intensive therapy leads to the reduction in the risk for development and progression of microvascular complications. The risk reduction for various outcomes ranged from 35-75%. Secondary analyses in these studies showed strong relationships between the risk of developing these complications and glycemic exposure over time. Moreover there was no discernible glucose threshold, i.e. there was a continuous reduction in complications as glycemic levels approached normal range. Macrovascular events e.g. combined cardiac, cerebrovascular and peripheral vascular

events were reduced by 54%.<sup>2</sup>

The United Kingdom Prospective Diabetes Study (UKPDS)<sup>4</sup> recruited 5102 patients with newly diagnosed type 2 Diabetes, aged between 25-65 years, in 23 centers with in the UK between 1977 and 1991. Those with fasting plasma glucose greater than 110 mg/dl on two mornings 1-3 weeks apart were included in the study. The study extended over 20 years to accumulate sufficient events. The patients were stratified by their body weight. Non-obese patients were assigned to intensive treatment with insulin (30%) or sulfonylurea (40% of patients), chlorpropamide, glipizide, or glibenclamide or conventional treatment policy with diet (30% of patients). The obese patients were similarly assigned to intensive treatment with insulin (24%), or sulfonylurea - chlorpropamide or glibenclamide (32%), metformin (20%) or conventional treatment with diet (24%). The conventional treatment policy aimed at maintaining the fasting plasma glucose below 270 mg/dl without symptoms.

The mean HbA1c achieved in the intensively treated group was 7.0% as compared to 7.9% in the conventionally treated group and this reduction in HbA1c brought about a remarkable decline in the development and progression of microvascular complications of diabetes (Table 1) The results of UKPDS have also brought into focus many more issues relating to the management of type 2 diabetes which are important and have far reaching consequences.

- i. Almost 50% of patients with type 2 diabetes at presentation have pre-existing diabetes related tissue damage, despite this, improved blood glucose and blood pressure control reduces the risk of diabetic complications that cause both morbidity and premature mortality.
- ii. Type 2 diabetes is associated with progressive hyperglycemia and decreasing  $\beta$  cell function irrespective of the therapy used.
- iii. Tight blood glucose control is clearly the key and all means of achieving it have the same effect. The use of insulin per se confers neither

additional advantages or disadvantages, while the use of sulfonylureas does not lead to additional risks. (chlorpropamide did perform worse as its use was associated with a rise in blood pressure over the years).

- iv. Metformin is a better choice as initial therapy in obese type 2 diabetic patients.
- v. Non-response to sulfonylureas after a certain duration of diabetes is because of progressive  $\beta$  cell failure.
- vi. Intensive insulin therapy does not produce any adverse effects on macrovascular disease.
- vii. Tight blood pressure control overall has larger benefits which manifest sooner than those after blood glucose control. ACE inhibitors or  $\beta$  blockers are equally effective in achieving the benefits of lowering blood pressure.<sup>5</sup>
- viii. There is no overall deterioration in the quality of life as a result of intensified treatment.

All physicians treating diabetes should therefore be aware of the importance of good control and should ensure to pass on this information in a positive way to their patients. Most patients will respond to oral drugs initially- the choice of an appropriate agent is important in achieving good control. UKPDS has shown that the effectiveness of these oral agents will gradually diminish and addition of insulin to the above agents or substitution of therapy with insulin will eventually be required.

## Steno 2 Study

The Steno-2 Study<sup>6</sup> was designed in 1990, when there was no evidence base for the treatment of type 2 diabetes, and studies such as the UKPDS were ongoing. Steno-2 was an attempt to validate the efficacy of daily clinical practice, i.e., the multifactorial treatment of type 2 diabetes, in high-risk type 2 diabetes patients.<sup>6</sup> The aim of the study was to investigate the impact on microvascular and cardiovascular disorders, of a target driven behavior modification and polypharmacy as

compared to a conventional multifactorial treatment of high-risk type 2 diabetic patients with the metabolic syndrome including microalbuminuria. One hundred and sixty patients with type 2 diabetes and the metabolic syndrome including microalbuminuria were assigned to conventional therapy with their GP, or to intensive care at Steno Diabetes Center. After 4 years a 50% reduction in microvascular endpoints – nephropathy, retinopathy and neuropathy was reported. The intensive group was treated differently by means of individualized risk assessment, ambitious goal setting, focused behavior modification, more drugs and higher doses prescribed, and continued patient education and motivation. After 7.8 years duration the study showed an absolute risk reduction of 20% for CVD, and the relative risk reductions for microvascular events were as follows: nephropathy 61%, retinopathy 58% and autonomic neuropathy 63%.<sup>6</sup>

**ADOPT**<sup>7</sup> was the first large, multicenter, randomized, double-blind, controlled clinical trial designed to compare the durability of glycemic control of the TZD rosiglitazone with that of metformin or the sulfonylurea glyburide as monotherapy, based on factors related to disease progression in patients with newly diagnosed (< 3 years) type 2 diabetes. ADOPT assessed the time interval of loss of glycemic control once a participant reached the maximum effective dose of each therapy and allowed investigation of the effects of beta-cell function and insulin resistance on disease progression and long-term glycemic control, among other outcomes. This international study included 4360 patients who were followed for 4 to 6 years.

The primary outcome measure was the time to monotherapy failure, defined as hyperglycemia confirmed by fasting plasma glucose (FPG) level greater than 180 mg/dL for subjects at the maximum-dictated or maximum-tolerated dose after at least 6 weeks of therapy. As patients reached the defined action point level of confirmed FPG of 140 mg/dL, they were further uptitrated to the next

highest dose level based on the respective study arm. Secondary measures included the effects of monotherapy in delaying the progressive loss of glycemic control based on cumulative incidence of FPG greater than 140 mg/dL and the percentage of patients remaining on monotherapy (HbA1C < 7%).

Results from ADOPT demonstrated that initial treatment with rosiglitazone significantly reduced the risk of monotherapy failure by 32% compared with metformin ( $P < .001$ ), and by 63% compared with glyburide ( $P < .001$ ) at 5 years. Similarly, rosiglitazone was significantly more effective in delaying the progressive loss of glycemic control as measured by FPG and HbA1C levels. Risk reduction of decreasing glycemic control was 34% compared with metformin ( $P = .002$ ) and 62% compared with glyburide ( $P < .001$ ). Additionally, mean HbA1C levels of less than 7% were maintained at 60 months with rosiglitazone compared with only 45 months for metformin and 33 months for glyburide.<sup>7</sup>

This study also demonstrated that rosiglitazone significantly improved insulin sensitivity vs metformin or glyburide ( $P < .001$  at 4 years) and reduced the loss of beta-cell function vs metformin ( $P = .02$ ) and glyburide ( $P < .001$ ). Safety assessments were followed for 6 years in ADOPT, with no unanticipated results. Commonly reported adverse events across the treatment groups for rosiglitazone, metformin, and glyburide, respectively, were edema (14.1%, 7.2%, 8.5%); weight gain (6.9%, 1.2%, 3.3%); gastrointestinal events (23%, 38.3%, 21.9%); and hypoglycemia (9.8%, 11.6%, 38.7%). Similar rates of discontinuation were reported in the rosiglitazone and metformin groups (37% and 38%, respectively) and were highest in the glyburide group (44%) due to an increase in hypoglycemia. Similarly, low rates of congestive heart failure (CHF) serious adverse events were reported with rosiglitazone (0.8%) and metformin (0.8%), while fewer such events were reported with glyburide (0.2%). Of these serious events, an independent cardiology review found 21 of 51 to be true CHF, involving 9 patients with no deaths in the rosiglitazone group, 8 patients with 1

death in the metformin group, and 4 patients with 1 death in the glyburide group. For all investigator-reported CHF events, there was a slight difference observed with rosiglitazone compared with metformin (1.5% vs 1.3%, respectively), with fewer events reported for glyburide (0.6%;  $P = .05$ )<sup>7</sup>.

ADOPT is the first long-term study to demonstrate that progressive loss of glycemic control can be delayed and that durable control of targeted glycemic levels can be maintained for a longer duration with rosiglitazone than with metformin or glyburide. Therefore, these results provide evidence that suggest earlier treatment with a TZD in the management of type 2 diabetes may be warranted. In addition, this study provides the rationale that when combination therapy is required to maintain glycemic control, a TZD should be considered for use with other agents. These results, along with the potential risks and benefits, adverse events profile, and costs, must be considered by healthcare providers in choosing optimal management strategies for patients with type 2 diabetes.

## **Trials of Lipid Lowering and Atherosclerosis in Diabetes**

The Multiple Risk Factor Intervention Trial (MRFIT) demonstrated that increases in total cholesterol levels are associated with an increase in the incidence of coronary artery disease in diabetes. The most common lipoprotein abnormalities in diabetes are an increase in the levels of the triglyceride-rich lipoproteins, decrease in HDL and increase in small dense LDL, without a significant rise in LDL levels.

### **Statin trials**

The Scandinavian Simvastatin Survival Study (4S)<sup>8</sup> was a secondary prevention study that included 201 patients with type 2 diabetes. The diabetics in the active treatment group had a 55% decrease in future coronary events ( $P = 0.002$ ). The Cholesterol and Recurrent Events (CARE) trial included 603 diabetic subjects<sup>9</sup>. Coronary event reduction in

the diabetics on pravastatin was 25% ( $P = 0.05$ ). In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study,<sup>10</sup> another secondary prevention trial, there were 782 type 2 diabetics. In this study, active treatment with pravastatin reduced coronary events in the diabetics by 19% (not significant).

The Collaborative Atorvastatin Diabetes Study (CARDS) was a multicenter, randomized, placebo-controlled, 4-year, double-blind trial of atorvastatin 10 mg/day that was the first to evaluate statin therapy prospectively and specifically in patients with type 2 diabetes.<sup>11</sup> Study participants were patients aged 40–75 years with type 2 diabetes, low-density lipoprotein cholesterol (LDL-C) concentration 160 mg/dL or less, fasting triglycerides 600 mg/dL or less, and at least one additional risk factor (hypertension, retinopathy, microalbuminuria or macroalbuminuria, or current smoking) but no history of CHD, cerebrovascular accident, or severe peripheral vascular disease.

Of 4053 subjects screened, 3249 (80%) entered baseline assessment, and 2838 (70%) were randomized; 1410 subjects were allocated placebo (1398 [99.1%] of whom completed follow-up) and 1428 to atorvastatin 10 mg/day (1421 [99.5%] of whom completed follow-up). The median time of follow-up was 3.9 years. The group treated with atorvastatin 10 mg/day had an average 26% (54 mg/dL) reduction in total cholesterol and 40% (46 mg/dL) reduction in LDL-C. The average reduction in triglyceride levels was 19%, with a 1% increase in HDL-C levels compared with placebo.

The relative risk reduction in the primary endpoint of first acute CHD event (MI including silent infarction, unstable angina, acute CHD death, resuscitated cardiac arrest), coronary revascularization procedures, or stroke (fatal or nonfatal) was significantly reduced by 37% with atorvastatin 10 mg/day compared with placebo ( $P = 0.001$ ). Stroke was significantly reduced by 48% ( $P = 0.016$ ) and all-cause mortality was reduced by 27% ( $P = 0.059$ ). The reduction in CHD, stroke,

and mortality endpoints with atorvastatin may have been understated because (1) some of the placebo group received nonstudy statin treatment and (2) the trial was stopped 2 years early for ethical reasons. Had the trial been allowed to continue, the differences in CHD and stroke outcomes between treatment groups may have been greater.

**Implications and Clinical Relevance:** CARDS showed that in patients with type 2 diabetes mellitus with lower LDL-C levels, atorvastatin 10 mg daily was safe, well tolerated, and significantly efficacious in reducing the risk of first CHD events. CARDS supports recommendations such as that made by the American Diabetes Association that patients with type 2 diabetes mellitus should be considered as candidates for statin treatment—even at lower LDL-C levels. Subgroup analysis revealed that irrespective of whether the baseline LDL-C was at or above, or below the median of 120 mg/dL, atorvastatin patients in both subgroups had similar relative risk reductions of 37–38% for the primary endpoint.

### **Fibrate trials**

The Helsinki Heart Study<sup>12</sup> was a primary prevention trial using gemfibrozil as the active agent. There were 135 subjects with type 2 diabetes in whom active treatment reduced adverse coronary events by 68%, although because of the small sample size, this result was not statistically significant. The Veterans Administration High Density Lipoprotein Intervention Trial (VA-HIT)<sup>13</sup> also used gemfibrozil as the active agent in subjects with existing CHD. In this study there were 627 type 2 diabetics in whom gemfibrozil reduced future coronary events by 24% ( $P = 0.05$ ).

**Diabetes Atherosclerosis Intervention Study:** DAIS included 418 men and women with type 2 diabetes who were randomised to receive micronised fenofibrate (200 mg/day), or placebo, and followed for 3 years.<sup>14</sup> Half of the participants had previous clinical coronary heart disease but all had at least one lesion visible on coronary angiography. In this angiographic study, the primary endpoints were

changes in minimum lumen diameter, mean segment diameter, and mean percentage stenosis.<sup>15</sup>

Fenofibrate had predictable effects on the plasma lipids, with moderate but significant decreases in total and low-density lipoprotein (LDL) cholesterol, a more substantial and significant decrease in plasma triacylglycerol, and a significant increase in high-density lipoprotein (HDL) cholesterol. In terms of the primary endpoints, the fenofibrate group had a 40% reduction in progression of angiographic changes as judged by minimum lumen diameter ( $P = 0.029$ ), 42% less progression as judged by changes in percentage diameter stenosis ( $P = 0.02$ ), and 25% less progression in mean segment diameter ( $P = 0.171$ , not significant).

Because of the relatively small numbers of participants in a trial lasting 3 years, clinical events were not primary endpoints. It was therefore predictable that differences in clinical endpoints between the fenofibrate and placebo groups were not statistically significant. However, it was encouraging to note that when considering a composite clinical endpoint (death, myocardial infarction, coronary angioplasty, coronary bypass surgery, and hospitalisation for angina) there were 38 events in the fenofibrate group compared with 50 in the placebo group. Although not statistically significant, the magnitude of the decrease in clinical events was similar to that observed in the diabetics in other trials.<sup>14,15</sup>

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial<sup>16</sup>: In this trial 9795 type 2 diabetics were randomized to receive either Fenofibrate (200 mg/day) or placebo for 5 years. After a mean follow-up of five years, fenofibrate was associated with a non-significant 11% relative reduction in the primary outcome of coronary events, comprising coronary heart disease (CHD) death and non-fatal myocardial infarction (MI). There were significant reductions in non-fatal MI (24%), total cardiovascular disease events (11%), coronary revascularisation (21%) and all revascularisation (20%), with a non-significant

reduction in total stroke. In contrast, there were non-significant increases in CHD mortality (19%), total mortality (11%), and cardiovascular disease mortality (11%). Treatment effects appeared after approximately two years, with five-year event rates for total cardiovascular disease of 12.5% and 13.9% for the fenofibrate and placebo groups, respectively. For the primary outcome, benefit was significantly larger for patients with no previous cardiovascular disease (19% reduction,  $p = 0.004$ ), and in younger (< 65 years) rather than older patients (20% reduction,  $p = 0.003$ ).

Fenofibrate reduced progression of albuminuria and significantly lowered the rate of laser treatment for retinopathy. These results are likely to be important among patients without previous CVD and where the prevention of both non-fatal macrovascular events and microvascular complications are important. Fenofibrate was well tolerated when used alone or in combination.

## Management of Hypertension in Diabetes

The primary goal of antihypertensive treatment is to prevent clinical complications and not simply to lower elevated blood pressure. Evidence from the Systolic Hypertension in the Elderly Program and the Systolic Hypertension in Europe Trial showed that, compared with placebo, treatment of hypertension in patients with type 2 diabetes prevents major clinical complications. Data from the Hypertension Optimal Treatment trial and the U.K. Prospective Diabetes Study (UKPDS) suggest that, in patients with diabetes, greater blood pressure reduction results in greater clinical benefits.<sup>5</sup> Although these studies document that treatment of high blood pressure is beneficial in hypertensive patients with type 2 diabetes, none of these trials provides information on the relative therapeutic benefit of individual antihypertensive agents.

Recent comparative trials and observational studies in diabetes have suggested that, for the prevention of cardiovascular events, ACE inhibitors

may be superior to alternative antihypertensive agents. That the greater benefit of ACE inhibitors was not explained by better blood pressure control indicates that other mechanisms linked to ACE inhibition may have played an additional role in the prevention of major clinical events.

There are 4 major trials (UKPDS, ABCD, CAPPP, FACET)<sup>5, 17-19</sup> in which patients with type 2 diabetes and hypertension were randomized to either an ACE inhibitor or to an alternative antihypertensive treatment and were followed for  $\geq 2$  years. The cumulative results of 3 trials (the ABCD trial, the CAPPP, and the FACET) showed a significant benefit of ACE inhibitors compared with alternative treatments on the outcome of acute myocardial infarction (63% reduction,  $P < 0.001$ ), cardiovascular events (51% reduction,  $P < 0.001$ ), and all-cause mortality (62% reduction,  $P = 0.010$ ). On the other hand in the UKPDS no difference was noted with either Captopril compared to Atenolol. The ACE inhibitors did not appear to be superior to other agents for the outcome of stroke in any of the trials.

ACE inhibitors may reduce cardiovascular risk by improving endothelial dysfunction, by reducing inflammation, and by promoting fibrinolysis through inhibition of plasminogen activator inhibitor 1. The Heart Outcome Prevention Evaluation (HOPE)<sup>20</sup> trial showed that the reduction in cardiovascular events with an ACE inhibitor was much greater than that expected from blood pressure reduction alone compared with placebo, which supports the view that additional mechanisms contribute to the prevention of cardiovascular events with ACE inhibition. In summary, blood pressure reduction per se is necessary to prevent clinical complications in hypertensive patients, but additional clinical benefits can be achieved by non-blood pressure mechanisms.

**Benefit of Angiotensin Receptor Blockers in Diabetes:** Three major clinical trials – the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)

study,<sup>21</sup> the Irbesartan Microalbuminuria Type 2 Diabetes in Hypertensive Patients (IRMA II)<sup>22</sup> study, and the Irbesartan in Diabetic Nephropathy Trial (IDNT)<sup>23</sup> have studied the role of selective AT-1 angiotensin receptor blockade (ARB) in reducing the progression of renal disease in patients with type 2 diabetes and high blood pressure (BP). In these trials, while standard care for diabetes was maintained, hypertension was managed with conventional therapy with diuretics, beta-blockers, and calcium channel blockers (but no ACE inhibitors or other ARBs), and placebo versus losartan (RENAAL) or irbesartan (IRMA II & IDNT). BP control was similar in the placebo and ARB-treated groups. In the RENAAL study, losartan compared to placebo reduced the risk of diabetic nephropathy progressing to renal failure. A similar effect was demonstrated with irbesartan in the IRMA II and IDNT trials. Thus, the concept has emerged from these 3 trials that ARBs protect the kidney independent of BP reduction.

The JNC 7<sup>24</sup> has defined the targets for blood pressure control as 130/80 mmHg or lower in patients with diabetes and lower than 125/75 mmHg in those diabetics with nephropathy. With regard to the selection of antihypertensive agent in a diabetic, the important role of ACEI and ARB has been recognized and diabetes has been identified as a compelling indication for the use of these agents in preference to the other class of drugs.<sup>24</sup>

## **Trials on Primary Prevention of Diabetes**

Several trials have focussed on interventions in individuals with prediabetes – IGT and IFG with the objective of preventing their progression to diabetes. All of these studies have brought out the important role of life style measures in achieving this. Addition of drugs such as metformin, alphasglucosidase inhibitors and glitazones has also been studied.

**Malmo Feasibility Study :** 217 middle aged men with IGT, divided into two groups - 161 treated with diet & exercise, 56 in reference group. Dietary

advise and exercise training was imparted to those in the intervention group, in the initial 6-12 months. At the end of 5 years, 11% of the intervention group & 21% of the reference group developed diabetes. Therefore a 50% reduction in incidence of diabetes was brought about by lifestyle intervention.<sup>25</sup>

**Finnish Diabetes Prevention Study:** 522 middle aged overweight subjects (172 men & 350 women) with a mean age of 55 years and mean BMI of 31 kg/m<sup>2</sup> with impaired glucose tolerance (IGT) were randomly assigned to receive either brief diet and exercise counseling (control group n = 257) or intensive individualized instructions on weight reduction, food intake and guidance on increasing physical activity (intervention group n = 265). The goals set for the intervention group were i) reduction in weight by 5% or more; ii) reduction in fat intake to less than 30% total energy intake; iii) reduction in saturated fat intake to < 10% of total energy intake; iv) increase in fiber intake to at least > 15 gm/day/1000 Kcal diet and v) increase in exercise to at least 30 min/day (> 150 min/week).<sup>26</sup>

After an average follow up of 3.2 years, 11% in the intervention group compare to 23% in the control group developed diabetes. There was a 58% reduction in the incidence of diabetes in the intervention group compared with the control group.<sup>26</sup>

Ranking of the subjects in both groups on the basis of success of achieving the goals showed a strong inverse correlation between the success score and the incidence of diabetes. None of the subjects who achieved four of the five goals (49 subjects in the intervention group and 15 in the control group) developed diabetes.

**Diabetes Prevention Program**<sup>27</sup>: 3234 non-diabetic persons with elevated fasting (95-125 mg/dl) and post-load glucose (140-199 mg/dl) to either intensive lifestyle modification program (1079) with an objective to achieve 7% weight loss and 150 min of physical activity per week; or to placebo (1082) or metformin 850 mg twice daily (1073). The latter two interventions were combined with standard diet and exercise

recommendations. The mean age of the subjects was 51 years and mean BMI was 34.0 kg/m<sup>2</sup>

After an average follow up of 2.8 years (range 1.8 - 4.6 years), a 58% relative reduction in the progression to diabetes was observed in the lifestyle group, a 31% relative risk reduction in the progression to diabetes in the metformin group (absolute incidence 4.8% in intensive lifestyle group, 7.8% in metformin group compared with 11% in control subjects). On an average 50% of the lifestyle group achieved the goal of  $\geq 7\%$  weight reduction and 74% maintained at least 150 min/week of modestly intense activity. No serious side effects were noted in any of the groups.

The Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) study<sup>28,29</sup> was a large-scale, international, multi-center, randomised, double-blind, controlled, 2 x 2 factorial design trial which aimed to determine if treatment with an ACE inhibitor (ramipril) and/or a thiazolidinedione (rosiglitazone) can delay or prevent the development of type 2 diabetes (T2DM) in people with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). A total of 5269 patients (4531 IGT and 738 IFG) were randomized to either rosiglitazone, ramipril or placebo and followed for a minimum of three years with regular assessment to ascertain the occurrence of the primary outcome (new onset T2DM or all cause mortality) as well as predefined secondary outcomes.

Among study participants taking rosiglitazone, only 12 per cent developed diabetes, compared to 26 per cent who were taking the placebo. Rosiglitazone also normalized glucose levels in 51 per cent of participants versus 30 per cent of those taking a placebo. Rosiglitazone therefore reduced the chance of getting type 2 diabetes by 60 per cent among those at high risk. It benefited all participants, and particularly those who weighed the most. Ramipril, the other drug studied, did not reduce the risk of diabetes, which affected 18 per cent of participants on that drug and 20 per cent on placebo. However, significantly more people taking ramipril (43 per cent) than the placebo (38 per cent) had normal glucose levels by the end of the study.

The clear messages that have emerged from these trials are that tight metabolic control is important in preserving the health of a diabetic patient. Therefore an aggressive approach to achieve tight metabolic control should be our target. Attention to the comorbid conditions with the appropriate drugs forms an important component of the management strategy to avoid microvascular and macrovascular complications. Primary prevention of diabetes should also be aimed at with the use of life style alterations and therapeutic agents when indicated.

## References

- University Group Diabetes Program: A study of the effects of hypoglycaemic agents on vascular complications in patients with adult onset diabetes. *Diabetes* 1978;1: 252-61.
- Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977-86.
- Reichard P, Nisson BY, Rosenquist V. The effect of long term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1970; 229: 304-309.
- UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J*. 1998;317:703-713
- UK Prospective Diabetes Study Group: Efficacy of atenolol and captopril in reducing the risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998; 317:713-720.
- Gæde P, Vedel P, Parving H-H, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes and microalbuminuria: the Steno type 2 randomised study. *Lancet* 1999;353:617-22.
- Kahn S, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355:2427-2443.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9
- Sacks FM, Pfeffer MA, Moye LA et al. for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9
- The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57
- Colhoun HM, Betteridge DJ, Durrington PN et al. on behalf of the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo- controlled trial. *Lancet* 2004; 364: 685-96.
- Frick MH, Elo O, Haapa K et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidaemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237-45
- Robins SJ, Collins D, Wittes JT et al. for the VA-HIT Study Group. Veterans Affairs High-density Lipoprotein Intervention Trial. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomised controlled trial. *JAMA* 2001;285:1585-91
- Diabetes Atherosclerosis Intervention Study Investigators Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomized study *Lancet* 2001;357:905-910.
- Vakkilainen J, Steiner G, Ansquer J-C, et al. Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease The Diabetes Atherosclerosis Intervention Study (DAIS). *Circulation* 2003;107:1733-1737.
- Keech A, Simes RJ, Barter P, et al. FIELD Study Investigators Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes (the FIELD study): randomized placebo-controlled trial *Lancet* 2003;361:2005-2016.
- Schrier RW, Estacio RO, Mehler PS, Hiatt WR. Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. *Nat Clin Pract Nephrol*. 2007; 8: 428-38.
- Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A; CAPPP Study Group. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the Captopril Prevention Project. *Diabetes Care*. 2001;24:2091-6.
- Pahor M, Tatti P. The Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) and combination therapies. *Am J Cardiol*. 1999; 83:819-20.
- The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. *N Engl J Med*. 2000; 342:145-153.
- Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861-869.
- Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the

- development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345(12):870-878.
23. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):851-860.
  24. Aram V, Chobanian; George L. Bakris; Henry R. Black; William C. Cushman; Lee A. Green; Joseph L. Izzo Jr; Daniel W. Jones; Barry J. Materson; Suzanne Oparil; Jackson T. Wright Jr; Edward J. Roccella. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report *JAMA*, 2003; 289: 2560 - 2571.
  25. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr. Physical activity and reduced occurrence of non-insulin dependant diabetes mellitus. *N Engl J Med* 1991; 325: 147-152.
  26. Tuomilehto J, Lindstrom J, Eriksson J, Valle T, Haanpää M, Ilanne-Parikka P et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344: 1343-1350.
  27. Diabetes Prevention Program Research Group: Reduction in the Incidence of Type 2 diabetes with Lifestyle Intervention or Metformin. *N Engl J Med* 2002; 346: 393-403.
  28. The DREAM Trial Investigators. Effect of Ramipril on the Incidence of Diabetes *N Engl J Med* 2006; 355:1551-1562.
  29. The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial *The Lancet* 2006; 368: 1096-1105.