

## EDITORIAL

# Long-Term Beneficial Effects of Good Glycemic Control on Macrovascular Disease: Results from UKPDS 10 – Year Post Trial Monitoring

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**ABBREVIATIONS**

ACCORD = Action to Control Cardiovascular Risk in Diabetes  
ADVANCE = Action in Diabetes Vascular Disease-Preterax and Diamicon Modified Release Controlled Evaluation  
CVD = cardiovascular disease  
DCCT/EDIC = Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications  
HbA1c = glycated hemoglobin A1c  
T1DM = type 1 diabetes mellitus  
T2DM = type 2 diabetes mellitus  
UKPDS = United Kingdom Prospective Diabetes Study  
UKPDS – PTM = United Kingdom Prospective Diabetes Study 10 year post trial monitoring  
VADT = Veterans Affairs Diabetes Trial

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**ABSTRACT**

Cardiovascular disease is a significant cause of morbidity and mortality in patients with diabetes mellitus. The impact of tight glycemic control in the mortality has been investigated in large randomized clinical trials. The data are controversial, as some trials (ACCORD, ADVANCE and VADT) have found that intensive glycemic control either has no impact on cardiovascular outcomes or even worsens them. On the other hand, results of the 10-year follow-up of the UKPDS study suggest that tight glycemic control of younger, newly diagnosed patients with type 2 diabetes may have long-term beneficial cardiovascular effects. All these data have led to the adoption of clinical guidelines suggesting a different strategy according to the patient's age and duration of diabetes.

**INTRODUCTION**

It is well known that patients with diabetes have more than a two – fold increase of death rate from cardiovascular disease (CVD) compared to those without diabetes.<sup>1</sup> Adequate glycemic control is considered the cornerstone of the therapeutic strategy and the main target of treatment with antidiabetic drugs is to achieve a low value of glycated hemoglobin (HbA1c). Several studies and meta – analyses have clearly demonstrated that the lowest risk of CVD was seen in patients with HbA1c <5% while the greatest risk was associated with HbA1c >7%.<sup>2,3</sup> However, current knowledge suggests that hyperglycemia in type 2 diabetes mellitus (T2DM) causes more often microvascular complications, such as nephropathy and retinopathy, than macrovascular adverse effects.<sup>4</sup> Moreover, the effect of tight glycemic control is less clear on macrovascular disease compared to microvascular complications.<sup>3,5</sup> New data have been added recently about the impact of tight glycemic control in reducing the burden of macrovascular complications, especially from the results of the United Kingdom Prospective Diabetes Study 10-year post trial monitoring (UKPDS – PTM), which enrolled patients with T2DM from the UKPDS cohort.<sup>6-8</sup>

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### UKPDS DESIGN AND PATIENTS CHARACTERISTICS

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The original UKPDS trial was designed to evaluate the effect of tight glycemic control on the complications of T2DM in newly diagnosed patients.<sup>4,6,7</sup> About 5102 patients were recruited from a total population of 7616 referred patients from 1977 to 1991 with fasting plasma glucose more than 108 mg/dl. Among them, 2514 were excluded since they met various exclusion criteria such as ketonuria, chronic renal failure (creatinine >2.0 mg/dl), myocardial infarction in the previous year, severe illness limiting life expectancy and disinclination to accept the rules of the protocol. After a 3-month dietary run-in period only patients with a fasting plasma glucose level of more than 108 mg/dl but less than 270 mg/dl were finally eligible to participate in the trial. Thus, 3867 patients were randomized to receive either conventional glucose control (dietary advices from a dietician) or intensive glucose control therapy (sulfonylurea or insulin). It must be noted that the patients who were overweight (>120% ideal body weight) were assigned to receive metformin.<sup>6</sup> All these patients were followed up in the UKPDS morning clinics every 3 months and after 1990 every 4 months. The median follow-up period for the sulfonylurea – insulin and metformin groups was 10 and 10.7 years respectively.<sup>6,7</sup> At the end of the study there was a borderline non significant reduction ( $p=0.052$ ) of 16% in the relative risk of myocardial infarction in the intensive glucose therapy sulfonylurea – insulin group compared to conventional therapy. On the other hand, treatment of the overweight patients with metformin resulted in a significant reduction of the risk for myocardial infarction (39%,  $p=0.001$ ) and death from any cause (36%,  $p=0.001$ ).<sup>6</sup> Regarding the microvascular endpoints, a significant risk reduction of about 25% ( $p=0.0099$ ) was noted in the intensively treated group.<sup>6</sup>

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### UKPDS POST TRIAL 10-YEAR MONITORING

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After the completion of the trial on September 30<sup>th</sup> 1997, the investigators decided to continue the follow up of these patients for 10 more years in order to gather some additional data about the long term effects of intensive glycemic control on macrovascular events. A total of 3277 patients (2118 from the sulfonylurea – insulin group, 880 from the conventional therapy group and 279 from the metformin group) attended the UKPDS clinics for the first 5 years. During this period, no attempt was made to maintain them in their previous therapy arm. Measurements of blood pressure, fasting plasma glucose, HbA1c, plasma creatinine and the ratio of albumin to creatinine were included in the follow-up. From years 6 to 10, all patients were assessed only through questionnaires

every 3 years and this post trial monitoring was successfully accomplished on September 30<sup>th</sup>, 2007. The median follow-up periods in the sulfonylurea – insulin and metformin groups were 16.8 and 17.7 years respectively.<sup>8</sup>

The surprising result from this post trial monitoring was the significant reductions in myocardial infarction rates and in all-cause mortality in both sulfonylurea – insulin (15%,  $p=0.01$  and 13%,  $p=0.007$  respectively) and metformin groups (33%,  $p=0.005$  and 27%,  $p=0.002$ ). The authors suggested that the benefit of tight glycemic control in patients with T2DM extends beyond a definite period of intensive management and called this phenomenon a “legacy effect” (or “metabolic memory”). Moreover, in the sulfonylurea – insulin group, relative reductions in risk persisted at 10 years for any diabetes-related endpoint (9%,  $p=0.04$ ), and microvascular disease (24%,  $p=0.001$ ) and risk reductions emerged over time for diabetes-related deaths (17%,  $p=0.01$ ). In the metformin group, significant reduction persisted for any diabetes-related endpoint (21%,  $p=0.01$ ) but not for microvascular disease (8%,  $p=0.31$ ) (Table 1). Additionally, no significant reductions were observed for stroke and peripheral vascular disease. It must be noted that baseline differences in mean HbA1c levels were lost within one year of stopping the randomly assigned therapy and there were not any significant differences between groups in the mean body weight.<sup>8</sup>

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### DOES TIGHT GLYCEMIC CONTROL PREVENT MACROVASCULAR DISEASE?

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Data from UKPDS – PTM showed that in patients with T2DM, the intensive antidiabetic therapy reduced almost 15% the risk of myocardial infarction ( $p=0.01$ ) 10 years after the end of the trial. This was observed even though there was no difference in HbA1c among the groups one year after the end of the study. Similar results emerged from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), which studied patients with type 1 diabetes (T1DM). In these patients intensive glucose plasma lowering was associated with significant long term beneficial cardiovascular effects and the similarity with UKPDS – PTM was the long lasting follow up (about 9 years) in comparison to other clinical trials.<sup>9</sup> Many possible explanations have been proposed to interpret these results. A plausible explanation is that the long-term intensive therapy reduces both hyperglycemia and formation of advanced end glycation products.<sup>10</sup> However, a recent study clearly showed that the contribution of hyperglycemia to cardiovascular risk is much greater in T1DM than in T2DM.<sup>11</sup> In this trial, a 1% increase in HbA1c was associated with more than 50% increase in cardiovascular risk in patients with T1DM compared to those with T2DM. Moreover, during UKPDS – PTM a reduction in the progression of renal disease was observed

**TABLE 1.** Endpoint differences between UKPDS and UKPDS – PTM

	UKPDS <sup>6</sup> (randomized trial)	UKPDS – PTM <sup>8</sup>
<b>Sulfonylurea – Insulin group</b>	<b>n=2729</b>	<b>n=2118</b>
Any diabetes related end point	12%, p=0.029	9%, p=0.04
Diabetes related death	10%, p=0.34	17%, p=0.01
Death from any cause	5.5%, p=0.44	13%, p=0.007
Myocardial infarction	18%, p=0.052	15%, p=0.01
<b>Metformin group</b>	<b>n=342</b>	<b>n=279</b>
Any diabetes related end point	32%, p=0.02	21%, p=0.01
Diabetes related death	42%, p=0.017	33%, p=0.01
Death from any cause	36%, p=0.001	27%, p=0.002
Myocardial infarction	39%, p=0.001	33%, p=0.005

UKPDS: United Kingdom Prospective Diabetes Study; UKPDS–PTM: United Kingdom Prospective Diabetes Study 10-year post trial monitoring

which had a direct protective effect in the development of cardiovascular complications. Supportive to this explanation are the recently published data from Steno – 2 study, which enrolled patients with T2DM and microalbuminuria and showed a significant reduction in cardiovascular risk (p=0.008), after a long term follow up of 13 years, in patients who were treated with drug combinations for hypertension, dyslipidemia and microalbuminuria.<sup>12</sup>

On the other hand, three large clinical trials with opposite results from those of the UKPDS – PTM follow up study regarding the impact of intensive glucose therapy on cardiovascular mortality were recently published. Although ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation)<sup>13</sup> and VADT (Veterans Affairs Diabetes Trial)<sup>14</sup> found no effect of intensive glucose control on major cardiovascular events, ACCORD (Action to Control Cardiovascular Disease in Diabetes) showed an increased risk for cardiovascular death and total mortality associated with intensive glucose control.<sup>15</sup> The main features and the hazard ratios of these trials additionally to those of UKPDS – PTM are summarized in Table 2. All the above three trials similarly concluded that good glycemic control did not reduce the major cardiovascular event rate in short term follow up. Specifically, the ACCORD trial was halted in 2008 due to the higher number of total and cardiovascular deaths (257 vs. 203, p=0.04) in the group randomized to intensive glucose therapy. The authors' opinion was that possible explanations for this unexpected result were the rapid reduction in glycosylated hemoglobin levels

in both study groups (1.4% in the intensive therapy group and 0.6% in the standard-therapy group) within the first 4 months after randomization, the usage of multiple drugs to achieve glucose control, the positive history of cardiovascular disease in the majority of participants and the higher rate of hypoglycemia in the intensive treatment group. More episodes of serious hypoglycaemia (blood glucose <50 mg/dL) requiring medical assistance were found among patients receiving the intensive therapy (10%) than among those following the standard treatment (3.5%).<sup>15</sup> However, among these patients, the risk of death was lower in the intensive group compared to the standard group.<sup>16</sup>

One of the basic differences between ADVANCE, ACCORD and VADT trials with UKPDS – PTM was that the last one had a longer follow up period and the enrolled patients in the original UKPDS study were newly diagnosed without severe macrovascular disease history. It is possible that a longer follow up period in the ACCORD and ADVANCE trials could have led to an improved outcome in the intensive treatment group compared to conventional therapy one. Actually, the two curves representing macrovascular complications and death seem to deviate after about 3 years with a non significant decrease in the rate of primary outcome emerging in intensive treatment group. This suggests a trend for a possible positive result if the trial had longer follow up period.<sup>15,17</sup>

#### CURRENT EVIDENCE-BASED RECOMMENDATIONS IN CLINICAL PRACTICE

On the basis of these large randomized clinical trials, the American Diabetes Association (ADA), the American Heart Association (AHA) and the American College of Cardiology (ACC) jointly published a statement about the intensive glycemic control and the prevention of macrovascular and cardiovascular disease one year ago.<sup>17</sup> The overall impression from DCCT and UKPDS – PTM was that intensive glycemic control had beneficial cardiovascular effects in T1DM and T2DM only after the standard randomization period during an extended follow up. Thus, the therapeutic target of HbA1c below or around 7% appears to be reasonable in the early diagnosed diabetes and it has been associated with long term risk reduction of macrovascular disease (ADA, B level recommendation, ACC/AHA, class IIb recommendation, level of evidence-LOE: A).<sup>17</sup> Lowering HbA1c ≤7% has been shown to reduce microvascular complications in both T1DM and T2DM (ADA, A level recommendation, ACC/AHA, Class I recommendation, LOE: A).<sup>17</sup> In patients with short duration of diabetes, long life expectancy, no hypoglycemic episodes and a negative history of significant cardiovascular disease, it might be reasonable to achieve HbA1c values closer to normal (ADA, B level recommendation, ACC/AHA, class IIa recommendation, LOE: C). However, in patients with a history of long standing diabetes, advanced macrovascular and microvascular complications, severe hypoglycemia episodes

**TABLE 2.** Comparison of Patients' Characteristics and Clinical Endpoints in Four Clinical Trials, ACCORD, ADVANCE, VADT, UKPDS – PTM<sup>8,13-15</sup>

	ACCORD	ADVANCE	VADT	UKPDS – PTM
<b>Characteristics</b>				
number of patients	10251	11140	1791	3277
mean age (years)	62	66	60	63
BMI (kg/m <sup>2</sup> )	32	28	31	SI:29, M:32
diabetes duration (years)	10	8	11.5	>20 (original UKPDS)
follow up duration (years)	3.4	5	6	17
history of CVD (%)	35	32	40	-
mean HbA1c(%)	8.1	7.5	9.4	SI:7.9, M:8.4
mean BP (mm Hg)	136/75	145/80	132/76	137/78
antidiabetic drugs	≥2 antidiabetic drugs in both groups	multiple drugs plus/without gliclazide	glimepiride or metformin, plus rosiglitazone, or insulin	Intensive therapy (SI or in overweight pts M) vs. conventional therapy (dietary measures)
<b>Endpoints</b>				
definition of primary endpoint	CVD death, nonfatal stroke & MI	nonfatal stroke, CVD death, microvascular & macrovascular complications	nonfatal MI & stroke, hospitalization for HF, CVD death, revascularization, amputation for ischemia	death from any cause, any diabetes related endpoint, MI, peripheral vascular disease, microvascular disease
HR for primary endpoint (95% CI)	0.90 (0.78 – 1.04), <i>p</i> =0.16	0.9 (0.82 – 0.98), <i>p</i> =0.01	0.88 (0.74 – 1.05), <i>p</i> =0.14	SI: 0.91 (0.83 – 0.99), <i>p</i> =0.04 M: 0.79 (0.66 – 0.95), <i>p</i> =0.01
HR for mortality (95% CI)	1.22 (1.01 – 1.46), <i>p</i> =0.04	0.93 (0.83 – 1.06), <i>p</i> =0.28	1.07 (0.81 – 1.42), <i>p</i> =0.62	SI: 0.87 (0.79 – 0.96), <i>p</i> =0.007 M: 0.73 (0.59 – 0.89), <i>p</i> =0.002

BMI = body mass index; BP = blood pressure; CI = confidence intervals; CVD = cardiovascular disease; HF = heart failure; HR = hazard ratio; M = metformin; MI = myocardial infarction; pts = patients; SI = sulfonylurea-insulin

or limited life expectancy, a less tight glyceemic control seems to be desirable with concomitant use of multiple antidiabetic drugs plus insulin.<sup>18</sup>

## CONCLUSION

The main finding of the long-term follow up in UKPDS – PTM trial is that tight glyceemic control seems to be beneficial if it is achieved in the early stages of T2DM. On the other hand, the serious adverse events, such as the hypoglycemias, of those treatment strategies would be possible harmful in some patients. We need more data from new studies in order to enroll all these treatment approaches in our daily clinical practice. Until then, all the clinicians have to perform an individualized multifactorial intervention in each T2DM patient, including treatment with antidiabetic regimens, statins, renin – angiotensin blockers and aspirin, since it has been shown

to reduce the total risk of death and cardiovascular events in patients.

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