

# Effects of Glycemic Control on Diabetes Complications and on the Prevention of Diabetes

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Randomized controlled clinical trials (RCTs), completed during the past several years or currently underway, are defining the scientific basis of contemporary diabetes care. RCTs have clearly and unambiguously demonstrated the benefits of meticulous glycemic control, aggressive blood pressure control, control of lipid abnormalities, laser photocoagulation, and aspirin therapy. Contemporary diabetes care practices have a strong evidence base.

This article reviews those RCTs that have addressed glycemic control. These include studies in established diabetes, which are designed to measure the effects of glycemic control on chronic complications, and studies in pre-diabetes, which are designed to prevent progression to diabetes. The outcome of completed studies is summarized, as is the design of ongoing studies.

## GLYCEMIC CONTROL

### Evidence of Effects on Complications

Several RCTs have demonstrated the effects of improved glycemic control on microvascular and neurological complications of diabetes. These include two studies in patients with type 1 diabetes—the Diabetes Control and Complications Trial (DCCT)<sup>1</sup> and the smaller Stockholm Diabetes Intervention Study (SDIS)<sup>2</sup>—and two studies in patients with type 2 diabetes—the U.K. Prospective Diabetes Study (UKPDS)<sup>3,4</sup> and the smaller Kumamoto Study.<sup>5</sup> Before the completion of these studies, a number of older, smaller RCTs were also included in a meta-analysis (that did include SDIS), which also suggested a significant relationship between

glycemia and complications.<sup>6</sup> Here, details of the DCCT and UKPDS are provided.

**DCCT.** The DCCT included 1,441 subjects with type 1 diabetes. Of these, 726 were in the primary prevention cohort and had a duration of diabetes < 5 years, no retinopathy, and normal albumin excretion at baseline. The remaining 715 were in the secondary intervention cohort and had a duration of diabetes < 15 years, mild to moderate background retinopathy, and either normal albumin excretion or microalbuminuria at baseline.<sup>1</sup>

Subjects were randomly assigned either to intensive therapy or conventional therapy. Intensive therapy consisted of insulin administered either by continu-

ous subcutaneous insulin infusion with an external insulin pump or multiple daily insulin injections (three or more injections per day). Insulin therapy was guided by self-monitoring of blood glucose (SMBG) three to four times daily, with additional specified samples, including a weekly overnight sample. It also included meticulous attention to diet and monthly visits to the treating clinic. Conventional therapy consisted of no more than two daily insulin injections; urine glucose monitoring or SMBG no more than twice daily; periodic diet review; and clinic visits every 2–3 months.

The intensive group achieved a median hemoglobin A<sub>1c</sub> (A1C) of 7.2% versus an A1C of 9.1% in the conventional group ( $P < 0.001$ ). Mean blood glucose was 155 mg/dl (8.6 mmol/l) in the intensive group and 230 mg/dl (12.8 mmol/l) in the conventional group. Mean follow-up was 6.5 years (4–9 years), for 9,300 patient-years of observation.

Risk reductions for microvascular and neurological end points in the DCCT were dramatic: > 70% for clinically important sustained retinopathy, 56% for laser photocoagulation, 60% for sustained microalbuminuria, 54% for clinical grade nephropathy, and 64% for confirmed clinical neuropathy. Macrovascular end points demonstrated trends in risk reduction—42% risk reduction for all macrovascular events combined ( $P = 0.082$ ) and 78% risk reduction for cardiac events ( $P = 0.065$ ).

After the close of the DCCT, subjects in the conventional therapy group were offered intensive therapy and instructed in its use. Patients received subsequent care from their own physi-

## IN BRIEF

Randomized, controlled clinical trials (RCTs), completed during the past several years or currently underway, are defining the scientific basis of contemporary diabetes care. In terms of glycemic control, landmark RCTs have demonstrated that meticulous glycemic control reduces risk of microvascular and neurological complications of diabetes. Studies in pre-diabetes have shown that early intervention slows progression to diabetes. Ongoing studies are examining the effects of glycemic interventions on macrovascular complications of diabetes, the impact of early treatment on the course of diabetes, and whether there are differences depending on the nature of the intervention used.

cians, and most were enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC) long-term observational study.<sup>7,8</sup> EDIC compared the long-term effects of the intensive or conventional therapy provided during the DCCT on the development of retinal and renal complications of diabetes.

Although the difference in median A1C results between the groups narrowed and merged during follow-up, during the next 8 years the impact of previous intensive therapy was sustained, with dramatically less progression of both retinopathy and nephropathy.

**UKPDS.** This study included 5,102 subjects with newly diagnosed type 2 diabetes. Subjects were 25–63 years of age (median 53 years) at entry.<sup>3,4</sup> Subjects were randomly assigned either to intensive treatment policy or conventional treatment policy. Intensive policy aimed at achieving fasting plasma glucose of 108 mg/dl (6.0 mmol/l) using various pharmacological agents. Conventional policy attempted control with diet alone, adding pharmacological therapy when symptoms developed or fasting plasma glucose exceeded 270 mg/dl (15 mmol/l).

The intensive policy group achieved a median A1C of 7.0% versus an A1C of 7.9% in the conventional policy group ( $P < 0.001$ ). Mean follow-up was 11 years (6–20 years). Although there was a progressive deterioration in glycemia over time, glycemic separation was maintained.

The primary outcome measures in the UKPDS were three aggregate end points: “any diabetes-related end point,” “diabetes-related death,” and “all-cause mortality.” Of these, only “any diabetes-related end point” was significantly affected, with a 12% risk reduction. In addition, risk reductions were seen for other end points, including 25% risk reduction in microvascular end points (most because of a 29% risk reduction for retinal photocoagulation), 24% risk reduction for cataract extraction, 21% risk reduction for deterioration in retinopathy, and 33% risk reduction for

microalbuminuria. Reduction in microvascular complications was seen regardless of primary treatment modality for intensive therapy—insulin, sulfonylureas, or metformin. The only macrovascular end point that demonstrated a trend in risk reduction in the main analysis was myocardial infarction (MI) (16% risk reduction), which did not quite reach statistical significance ( $P = 0.052$ ).

In the metformin subgroup analysis within the UKPDS, however, there were significant reductions in diabetes-related deaths (42% risk reduction), any diabetes-related end point (32% risk reduction), and MI (39% risk reduction).<sup>4</sup>

### Ongoing Studies

Ongoing studies are addressing several issues concerning glycemic control. These include the impact of more intensive glycemic control, the impact of earlier intervention, and the potential added benefit of specific classes of glycemia drugs in reducing cardiovascular complications or sustaining pancreatic  $\beta$ -cell function.

#### *More stringent glycemic control.*

The Veterans Affairs Diabetes Trial (VADT) is addressing the question of whether intensive glycemic control will improve cardiovascular morbidity and mortality in older men with type 2 diabetes.<sup>9</sup> In VADT, 1,792 subjects are being followed for 5–7 years, with a goal A1C in the intensive group of 6%. The study, slated to conclude in 2008, includes aggressive control of lipids and blood pressure in both groups.

Also addressing the impact of more stringent glycemic control on cardiovascular end points is the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.<sup>10</sup> This 5-year trial involving > 10,000 subjects is aiming for an A1C of < 6% in the intensive glycemia group and 7.0–7.9% in the control glycemia group. ACCORD is also assessing the impact of stringent blood pressure control and that of meticulous control of lipids. It is targeted for completion in 2010.

**Earlier glycemic intervention.** An important question concerning control of glycemia is whether intervention is worthwhile to control glycemia commencing at glucose levels currently considered to be “pre-diabetes,” i.e., either impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).<sup>11</sup> Indeed, this might be considered intervention that prevents or slows development of diabetes, as defined by current glycemic criteria.

A number of studies using a variety of interventions have demonstrated that levels of glycemia that are diagnostic of diabetes can be postponed. This can be accomplished with lifestyle interventions, as was shown in the Chinese Da Qing Study,<sup>12</sup> the Finnish Diabetes Prevention Study (FDPS),<sup>13</sup> and the U.S. Diabetes Prevention Program (DPP).<sup>14</sup> It can also be accomplished with medications. These have included metformin in the DPP,<sup>14</sup> acarbose in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM),<sup>15</sup> troglitazone in the Troglitazone in the Prevention of Diabetes Mellitus (TRIPOD) study,<sup>16</sup> and xenical in the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study.<sup>17</sup> The DPP also began with a troglitazone arm, but this was aborted because of side effects, although a treatment effect was still seen.<sup>18</sup> The results of these studies are summarized in Table 1.

Intriguingly, several studies of non-glycemic interventions have observed a potential effect of lessening the risk of development of diabetes in nondiabetic subjects enrolled to evaluate other outcomes. These include the angiotensin-converting enzyme (ACE) inhibitor ramipril in the Heart Outcomes Prevention Evaluation (HOPE) trial;<sup>19</sup> the angiotensin receptor blocker (ARB) losartan in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study<sup>20</sup> (although in comparison to atenolol rather than placebo); pravastatin in the West of Scotland Coronary Prevention Study (WOSCOPS),<sup>21</sup> and hormone replacement therapy in post-

**Table 1. Interventions During Type 2 Pre-Diabetes**

<b>COMPLETED STUDIES</b>			
<b>Study</b>	<b>Intervention</b>	<b>Sample Size</b>	<b>Risk Reduction for Diabetes</b>
<i>Lifestyle</i>			
Da Qing <sup>12</sup>	Diet and/or exercise	577	32–39%
FPDS <sup>13</sup>	Diet and exercise	522	58%
DPP <sup>14</sup>	Diet and exercise	3,234	58%
<i>Medication</i>			
DPP <sup>14</sup>	Metformin	3,234	31%
STOP-NIDDM <sup>15</sup>	Acarbose	1,429	32%
TRIPOD <sup>16</sup>	Troglitazone	236	56%
XENDOS <sup>17</sup>	Xenical	3,305	45%
DPP <sup>18</sup>	Troglitazone	585	23%
<i>Unexpected nonglycemic prevention findings</i>			
HOPE <sup>19</sup>	Ramipril	5,270	34%
LIFE <sup>20</sup>	Losartan	7,998	25%
WOSCOPS <sup>21</sup>	Pravastatin	5,974	30%
HERS <sup>22</sup>	Estrogen/progesterone	2,029	35%
<b>ONGOING STUDIES</b>			
<b>Study</b>	<b>Intervention</b>	<b>Sample Size</b>	<b>Expected Date of Completion</b>
<i>Glycemic interventions for prevention</i>			
DREAM <sup>24</sup>	Rosiglitazone	5,269	2005
NAVIGATOR <sup>25</sup>	Nateglinide	9,518	2007
ACT-NOW <sup>26</sup>	Pioglitazone	600	2007
ORIGIN <sup>27</sup>	Insulin glargine	10,000	2008
<i>Nonglycemic prevention studies</i>			
DREAM <sup>24</sup>	Ramipril	5,269	2005
NAVIGATOR <sup>25</sup>	Valsartan	9,518	2007
ORIGIN <sup>27</sup>	Omega-3-fatty acids	10,000	2008

menopausal women in the Heart and Estrogen/Progestin Replacement Study (HERS).<sup>22</sup>

None of these studies, which are also included in Table 1, were designed to assess development of diabetes. But they have served as the basis for a number of ongoing studies that are further evaluating these possible effects. The flip side of this was seen in the STOP-NIDDM study, in which acarbose was shown to reduce the incidence of hypertension by 27%.<sup>23</sup>

A number of RCTs are currently being conducted in subjects with pre-diabetes. These are designed to assess the benefits of the interventions being tested both on progression to diabetes and on cardiovascular outcomes.

One such study is the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study.<sup>24</sup> This 3- to 5-year study, expected to be completed in 2005, is assessing the impact of the ACE inhibitor ramipril and/or the thiazolidinedione rosiglitazone in 5,269 subjects with either IGT or IFG who are therefore at high risk of developing diabetes.

Another is the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial.<sup>25</sup> This 3- to 6-year study, expected to be completed in 2007, is assessing the impact of the ARB valsartan and/or the short-acting insulin secretagogue nateglinide in 9,518 subjects with pre-diabetes (fasting plasma glucose of

95–125 mg/dl and 2-hour plasma glucose of 140–199 mg/dl).

Actos Now For Prevention of Diabetes (ACT-NOW)<sup>26</sup> is a 2- to 3.5-year study, expected to be completed in 2007, of the effects of pioglitazone in 600 subjects with IGT and one or more components of the metabolic syndrome. In addition to assessing progression to diabetes, the study is a mechanistic study evaluating insulin sensitivity,  $\beta$ -cell function, body composition, and cardiovascular risk factors.

A fourth is the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study.<sup>27</sup> This 3- to 5-year study, expected to be completed in 2008, is assessing 10,000 subjects at least 50 years of age with at least one cardiovascular risk factor and either pre-diabetes (IFG, IGT) or early type 2 diabetes. The question being posed is whether insulin replacement therapy targeting fasting normoglycemia (< 95 mg/dl) with insulin glargine reduces the risk of cardiovascular events more than standard approaches to glycemic control and, in a factorial design, the impact of omega-3 fatty acids.

**Cardiovascular outcomes in type 2 diabetes.** Cardiovascular outcomes are included in virtually all of the diabetes prevention studies noted above. In addition, several RCTs are studying the effects of individual agents on cardiovascular and other outcomes (Table 2). ORIGIN includes subjects with early type 2 diabetes and thus falls into this category, as well.

One study specifically addressing this is A Diabetes Outcome Progression Trial (ADOPT).<sup>28</sup> This 4- to 6-year study, planned to be completed in 2006, involves 4,356 drug-naïve subjects with recently diagnosed (within 3 years) diabetes. It seeks to assess whether monotherapy with rosiglitazone, metformin, or glyburide affects disease progression,  $\beta$ -cell function, or risk markers for macrovascular complications in early type 2 diabetes.

Similarly, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation

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**Table 2. Glycemic Interventions Assessing Cardiovascular Disease in Diabetes**

ONGOING STUDIES			
Study	Intervention	Sample Size	Expected Date of Completion
<i>Glycemic interventions for cardiovascular disease</i>			
ORIGIN <sup>27</sup>	Insulin glargine	10,000	2008
ADOPT <sup>28</sup>	Rosiglitazone	4,356	2006
RECORD <sup>29</sup>	Rosiglitazone	3,966	2009
PROactive <sup>30</sup>	Pioglitazone	5,000	2005
Look AHEAD <sup>31</sup>	Weight loss	5,000	2012
BARI-2D <sup>32</sup>	Insulin sensitizing versus insulin augmenting	2,300	2008

of Glycemia in Diabetes (RECORD) study<sup>29</sup> is assessing whether the combination of rosiglitazone plus either metformin or sulfonylurea may be superior to the combination of metformin plus sulfonylurea for cardiovascular outcomes in people with type 2 diabetes. This 6-year study, planned to be completed in 2009, involves 3,966 subjects with diabetes inadequately controlled on metformin or sulfonylurea.

Another glitazone study is Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive),<sup>30</sup> a 4-year events-driven study, planned to be completed in 2005 or whenever 760 cardiovascular events are encountered. This study involves ~ 5,000 subjects with diabetes and high cardiovascular risk. PROactive is assessing whether therapy with pioglitazone can reduce total mortality and macrovascular morbidity.

The Look AHEAD (Action for Health in Diabetes) study<sup>31</sup> is an 11-year trial involving 5,000 subjects and expected to be completed in 2012. Look AHEAD is investigating the effectiveness of an intensive lifestyle intervention, which is designed to achieve and maintain weight loss through caloric restriction and increased physical activity, on cardiovascular outcomes in subjects with type 2 diabetes.

Finally, the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI-2D) study<sup>32</sup> is a 3- to 6-year study, expected to be completed in 2008, comparing an insulin-sensitizing treatment strategy (metformin and/or

rosiglitazone) with an insulin-augmenting strategy (sulfonylurea and/or insulin). It includes 2,300 subjects with type 2 diabetes who are at least 25 years of age and have coronary artery disease documented by coronary arteriography showing one or more vessels with at least 50% stenosis. In addition to this glycemic comparison, in a factorial design BARI-2D is assessing whether a treatment strategy of immediate revascularization (angioplasty or coronary artery bypass grafting) combined with aggressive medical therapy results in decreased 5-year mortality rates compared with aggressive medical therapy alone.

**CONCLUSIONS**

RCTs have demonstrated the importance of glycemic control. Ongoing trials are designed to assess whether even more stringent glycemic control is possible and beneficial. Another issue being addressed is how early intervention should be initiated, and particularly whether it is beneficial during the phase of pre-diabetes. An important issue for which data are still lacking is to what extent addressing glycemic control will influence the macrovascular cardiovascular end points. Ongoing trials are also addressing this question. Finally, some trials are addressing whether the way glycemic control is achieved influences outcome.

Patients with diabetes have long suffered from the devastating complications that threaten their lives. The challenge for all health providers caring for diabet-

ic patients is to recognize that there is a growing body of evidence, based on controlled clinical trials, that demonstrates that the impact of this dread disease can be dramatically lessened. To benefit from recent advances, patients with diabetes must understand the treatment goals and strive to attain not only excellent glycemic control, but also aggressive control of blood pressure and normalization of lipids. They also should avoid cigarette smoking, use prophylactic aspirin therapy, take excellent care of their feet, have regular medical examinations, and avail themselves of appropriate interventions as needed.

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