Glucose Control and Cardiovascular Complications: The VA Diabetes Trial

WILLIAM C. DUCKWORTH[1,2,3]
MADELINE MCCARREN[4]
CARLOS ABRAIRA[5,6]

The Veterans Affairs Cooperative Studies Program (VACSP) has just initiated a trial of the effect of intensive glucose control on cardiovascular complications in patients with type 2 diabetes. The name of the trial is "VACSP #465, Glycemic Control and Complications in Diabetes Mellitus type 2" (V.A. Diabetes Trial [VADT]). The trial is expected to generate discussion in the diabetes community because the central role of glucose control in preventing or delaying long-term complications is generally accepted.

The data on macrovascular disease are not yet conclusive. The VADT is directed at type 2 diabetic patients with established uncontrolled diabetes. This is the population most frequently encountered by the practicing physician.

Cardiovascular (CV) complications are the major causes of morbidity and mortality in patients with type 2 diabetes (1). Efforts to reduce glucose levels in these patients must be balanced between risks and benefits. Consideration of intensive therapy must include effects of glucose control on microvascular complications, macrovascular complications, complications of therapy, and socioeconomic issues, including patient quality of life, compliance with therapy, and distribution of available funds for care of patients with diabetes.

Microvascular disease

Both the Diabetes Control and Complications Trial (DCCT) (type 1 diabetes) and the UK Prospective Diabetes Study (UKPDS) (new-onset type 2 diabetes) showed a significant beneficial effect of glucose control on microvascular complications (2,3), as did the smaller Kumamoto study (4). Basic biochemical and animal studies provide a solid foundation for these findings, as do epidemiological studies. From a clinical standpoint, this issue is more complicated. Risk-to-benefit ratios must be considered. This has not been adequately addressed in older established patients with type 2 diabetes.

In the UKPDS the main effect of glucose control after 10.5 years was a 3/1,000 reduction in photocoagulation for retinal disease (from 1.1% in the standard arm to 0.8% in the intensive arm) (3). Glucose control did not have an effect on clinical end points, such as visual acuity or renal failure, or on cardiovascular events. Thus, in newly diagnosed patients, conventional control (standard glucose levels and visual and renal monitoring) resulted in clinical outcomes comparable with those achieved with more intensive glucose control.

For younger type 2 diabetic patients, intensive glucose control offers clear advantages for microvascular disease. One example is a 45-year-old newly diagnosed patient with no other significant disease. In this patient, projecting the estimates of the DCCT in type 1 diabetes, the estimated lifetime reduction in the risk for blindness by reducing the HbA_{1c} level from 9 to 7% is 2.6–0.3%, and the reduction for renal failure is 3.5–2.0%. In contrast, a 65-year-old patient with newly diagnosed diabetes has a relatively minor lifetime risk reduction of either blindness or renal failure if treated to an HbA_{1c} level of 7% from 9% (0.5–0.1% for blindness and 0.6–0.3% for renal failure). In either case, these reductions must be balanced against the risks and costs of intensive therapy (5).

On the other hand, achieving usual control levels (defined as an HbA_{1c} <9) has demonstrable positive effects with lesser risks. The development of complications is not a linear function of elevated glucose levels. Increases in HbA_{1c} level from 9 to 11% result in far greater increases in microvascular complications than increases from 7 to 9% (5). Clinicians know it is easier, less risky, and less costly to obtain levels in the 8.0–9% range than in the <7% range. Notably, there is yet no trial evidence in which mean HbA_{1c} levels in the intensive arm were <7%.

Results from new-onset patients cannot necessarily be extrapolated to older patients with established type 2 diabetes, in whom nondiabetic causes are the more frequent reason for loss of vision. Other approaches for managing microvascular complications could make tight glucose control a desirable but not essential component in the management of type 2 diabetes. Periodical eye examination and intervention may prevent 90% of diabetes-related vision loss (6). No glycemic control trial has yet demonstrated differences in visual acuity, but protection against visual deterioration was shown with modest blood pressure control goals (7).

From the [1]Endocrinology Section, Carl T. Hayden VA Medical Center, Phoenix; the [2]Molecular and Cellular Biology Program, Arizona State University, Tempe; the [3]Department of Medicine, University of Arizona, Tucson, Arizona; the [4]Cooperative Studies Program Coordinating Center, Department of Veterans Affairs, VA Hines Hospital, Hines, Illinois; the [5]Research Service and Endocrinology Section, Miami VA Medical Center; and the [6]Division of Endocrinology, University of Miami Medical School, Miami, Florida.

Address correspondence and reprint requests to William C. Duckworth, Endocrinology (CS/111E), VA Medical Center, 650 E. Indian School Rd., Phoenix, AZ 85012. E-mail: duckworth.william@med.va.gov.

Received for publication 5 October 2000 and accepted in revised form 26 January 2001.

W.C.D. has received honoraria and research support from Novartis, Aventis, Eli Lilly, Roche Diagnostic, Novo Nordisk, SmithKline Beecham, Kos, and Bristol Meyers Squibb. C.A. has received honoraria and grant/research support from SmithKline Beecham, Aventis, Kos, Roche, Novo Nordisk, and Bristol Meyers Squibb.

Abbreviations: CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; PVD, peripheral vascular disease; UGDP, University Group Diabetes Program; UKPDS, UK Prospective Diabetes Study; VACSP, Veterans Affairs Cooperative Studies Program; VADT, VA Diabetes Trial; VACSDM, Veterans Affairs Cooperative Study on Glycemic Control and Complications in NIDDM.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Macrovascular disease

All of these issues pale with consideration of CV complications. Over two-thirds of all morbidity, mortality, and health care costs in patients with type 2 diabetes are caused by CV disease. In type 2 diabetes, the macrovascular mortality is 40 to 70-fold higher than that of microvascular disease (8). We have no intervention trial data showing improvement in CV outcomes with glucose control. Epidemiological studies have shown mixed results, with some showing a positive correlation between marginally increased glucose levels and cardiovascular complications, and others showing no correlation (rev. in 9–11); the issue is thus unresolved.

Clinical trials

Clinical relevance of glucose control relies on prospective trials. For CV disease, these are few. The University Group Diabetes Program (UGDP) was the first major prospective trial to examine the effect of glucose control on CV events. The subsequent focus on the adverse effects of oral agents has limited consideration of the finding that glucose lowering with insulin did not reduce CV events (12).

In the UKPDS there was no effect of better glucose control by sulfonylureas or insulin on total CV events in new-onset patients. Subset analyses showed a nonsignificant trend ($P = 0.052$) to reduction in nonfatal myocardial infarction (MI), but other results were heavily dependent on treatment method and patient characteristics. For example, newly diagnosed obese patients treated with metformin had a reduction in MI ($P < 0.01$), but sulfonylurea failures treated with added metformin had an increase in MI ($P = 0.039$) (13). The modest glycemic separation, the progressive deterioration, the relatively modest doses of insulin used, and the complexity of the UKPDS protocol limit interpretation of the data on macrovascular disease.

A more recent trial in insulin-dependent type 2 diabetes, the Veterans Affairs Cooperative Study on Glycemic Control and Complications in NIDDM (VACSDM), found a strong tendency toward worsening of CV outcomes in patients with intensive control (14). This was a feasibility study used to develop the current VA diabetes trial on glucose control and cardiovascular complications in type 2 diabetes. In the VACSDM no clinically significant adverse effects on microvascular complications were seen with patients under continued conventional treatment. This study had an excellent separation (2%) in A_{1c} levels between the study groups and was directed at the same population as the current trial, i.e., in established patients with poor glucose control. This study raises the possibility that intensive glucose control could have adverse CV effects.

The Kumamoto study did not show significant effects on CV events (4). The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study showed significant reduction in recurrent MI in diabetic patients treated with intravenous insulin after an acute episode (15). Because a similar protocol results in similar reductions in nondiabetic patients (16), glucose control does not appear to be the explanation for the beneficial effect. Other possibilities include direct insulin effects on fatty acid metabolism or myocardial protein degradation.

Adverse effects of intensive treatment

Adverse effects can be divided into general and treatment-specific effects. General effects include cost, patient inconvenience, and medical resource use (related but not identical to cost). Specific effects include hypoglycemia (and related consequences), weight gain, early worsening of angiopathy (2), the putative risk of hyperinsulinemia (17,18), drug side effects, unknown drug interactions, and reduced responses to hypoglycemia.

A 10-fold increase in mild to moderate hypoglycemic episodes occurs in almost all trials involving intensive glucose control. Cognitive dysfunction can result from repetitive hypoglycemia; this has been commonly reported in type 1 diabetes studies, and almost all studies in type 2 diabetes have shown similar results (19,20). Recurrent hypoglycemia can also result in noncognitive psychological abnormalities (21).

The VADT

The VADT has been developed to address the effect of intensive glucose therapy on CV complications in type 2 diabetes. The VADT will include 1,700 men and women in 20 VAMCs randomized to either intensive (HbA_{1c} goal <6%) or conventional (HbA_{1c} goal of 8–9%) therapy. The expected mean HbA_{1c} levels are 6.5% for intensive and 8.5% for conventional therapy, an adequate separation for meaningful results.

The VADT will be limited to type 2 patients inadequately controlled on standard therapy. Inclusion criteria require C-peptide levels consistent with endogenous insulin secretion and HbA_{1c} levels >7.5%, despite maximal doses of one or more oral agents and/or insulin therapy. Thus, the trial will be directed at type 2 diabetes that is difficult to control, focusing on the patients of most concern to care providers.

Exclusions are limited to factors that may impede adherence or study results. Patients with renal insufficiency, severe congestive heart failure, or recent history of CV event, (<6 months previously) will be excluded. Substance abuse and unreliability will also be criteria for exclusion.

The primary end points of the trial are the following clinical CV events: acute MI, death from CV disease, stroke, congestive heart failure, amputation from peripheral vascular disease (PVD), surgical intervention for coronary or PVD, and critical limb ischemia. Secondary end points include angina, claudication, retinopathy, nephropathy, neuropathy, quality of life, cognitive function, and cost-effectiveness.

Factors other than glucose levels will be treated identically in both groups. All patients will be managed according to standards of care established by the American Diabetes Association and the VA. Education on diet, exercise, and smoking cessation will be given. Lipid and blood pressure levels will be treated to the goals established by these groups. Monitoring and care of the eyes and kidney and other complications will also be performed according to the standards of care.

The glycemic treatment approach common to both arms in the VA study is combination therapy because all patients have inadequate control on monotherapy. The algorithm is initial therapy with metformin (obese) or glimiperide (lean), followed by rosiglitazone, followed by insulin. Conventional therapy will adhere to the same algorithm, but maximal doses will be restricted in the initial steps.

Although ultimate doses of pharmacological agents will be different in the two groups, the goal is to have equal distribution of therapeutic classes of agents (e.g., insulin secretagogues, insulin sensitizers, and exogenous insulin). This study will not try to address possible differences among the various agents, but rather at-

tempt to follow what has become the usual approach to therapy (i.e., combination therapy). This is the rationale behind the choice to limit initial doses of agents in the standard group in order to accelerate combination therapy using multiple drugs. This approach may well be standard usual therapy in the future, given the success of the metformin glyburide combination and other formulations in development. In particular, the protocol was designed to insure that the use of exogenous insulin would be similar in the two groups. Obviously, separation of HbA_{1c} levels requires differences in therapy. We chose to make these differences due to dose of agent rather than type of treatment.

Safety issues

Data from the feasibility trial (14) suggest that significant deterioration of microvascular complications is unlikely in the standard group. In fact, the expected improvement in lipid and blood pressure control due to the close monitoring and follow-up should provide microvascular benefits to the standard group over usual care in these patients. All patients will be monitored closely for development or progression of retinopathy, nephropathy, and other complications, with interventions as appropriate.

Glucose control in the standard group will not be worsened by inclusion in this trial. Patients already under excellent control (HbA_{1c} <7.5%) or on a less-than-maximal dose of an oral agent and/or on insulin will be excluded. The expected HbA_{1c} in the standard group is 8.5%. The average HbA_{1c} in the patients thus far randomized is 9.0%. Therefore, glucose control in the trial will be better than current care.

Finally, an independent Data and Safety Monitoring Board will follow progress and results closely to ensure that patient safety is not compromised.

CONCLUSION — This trial has been in development since 1988, when the planning for the feasibility trial began. Despite the success of the feasibility study, financial limitations have delayed initiation of the full trial until now (22). This is the most costly trial ever performed by the VA and is only possible through extramural VA research support, including support from VA clinical services, the American Diabetes Association, and various pharmaceutical companies, including SmithKline Beecham, Novo Nordisk, Aventis, Roche, and Kos. This broad-based support reflects the importance of this trial. Its results are expected to provide firm information on the relative effect of glycemic control on the prevention of CV morbidity and mortality of established type 2 diabetes in older patients. The importance of glycemic control would not be a question if there were no potential adverse effects of intensive control. Even the minor benefits in retinopathy or nephropathy seen with lowering HbA_{1c} levels from 9 to 7% would be justified if this could be achieved without potential harm. Unfortunately, intensive therapy has a downside; it increases hypoglycemia, which has physical, mental, social, and economic impacts. Intensive therapy also increases health care costs, drug side effects, patient and physician efforts, complexity of therapy (potentially leading to reduced compliance and quality of life), and possibly acceleration of established complications. Given limited resources (financial, health care provider, and patient capability), should we put our efforts into glucose control in older established patients or into other areas, e.g., blood pressure control, lipid therapy, support systems, etc.? The VADT is designed to address these issues. It is not designed to compare bad control (HbA_{1c} levels >10) with intensive therapy (HbA_{1c} levels <6) or very good control (HbA_{1c} <7.5) with intensive therapy. It will compare good control (HbA_{1c} <9) with excellent control (HbA_{1c} <6.9%).

References

1. Geiss S, Herman WH, Smith PJ: Mortality in non-insulin-dependent diabetes. In *Diabetes in America/National Diabetes Data Group*. 2nd Ed. Harris M., Ed. Bethesda, Maryland, National Institutes of Health, 1995, p. 133–155 (NIH publ no. 95-1468)
2. The Diabetes Control and Complication 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* 329: 977–986, 1993
3. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risks of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
4. Shichiri M, Ohkubo Y, Kishikawa H, Wake N: Long-term results of the Kumamoto study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 23 (Suppl. 2):B21–B29, 2000
5. Vijan S, Hofer T, Hayward R: Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. *Ann Intern Med* 127:788–795, 1997
6. Ferris FL: How effective are treatments for diabetic retinopathy?. *JAMA* 269:1290–1291, 1993
7. UK Prospective Diabetes Study (UKPDS) Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 317:703–713, 1998
8. Turner R, Cull C, Holman R: United Kingdom Prospective Diabetes Study 17: the effect of improved metabolic control on complications of NIDDM. *Ann Int Med* 124:136–145, 1996
9. Barrett-Connor E: Does hyperglycemia really cause coronary heart disease? *Diabetes Care* 20:1620–1623, 1997
10. Laakso M: Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes* 48:937–942, 1999
11. Meigs J, Singer D, Sullivan L, Dukes K, D'Agostino R, Nathan D, Wagner E, Kaplan S, Greenfield S: Metabolic control and prevalent cardiovascular disease in non-insulin-dependent diabetes mellitus (NIDDM): the NIDDM Patient Outcomes Research Team. *Am J Med* 102:38–47, 1997
12. University Group Diabetes Program II: Mortality results. *Diabetes* 19 (Suppl. 2): 789–830, 1970
13. UK Prospective Diabetes Study (UKPDS) group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–864, 1998
14. Abraira C, Colwell J, Nuttall F, Sawin C, Henderson W, Comstock J, Emanuele N, Levin S, Pacold I, Lee HS, the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes (VACSDM) Group: Cardiovascular events and correlates in the VA Feasibility Trial (VACSDM). *Arch Intern Med* 157: 181–188, 1997
15. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L, on behalf of the DIGAMI Study Group: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI) study: effects on mortality at 1 year. *JACC* 26:57–65, 1995
16. Apstein CS: Glucose-insulin-potassium for acute myocardial infarction: remarkable results from a new prospective randomized trial. *Circulation* 98:2223–2226, 1998

17. Duckworth W, Saudek C, Giobbie-Hurder A, Henderson WG, Henry RR, Kelley DE, Edelman SV, Zieve FJ, Adler RA, Anderson RJ, Hamilton BP, Donner TW, Kirkamn S, Morgan NA: the Veterans Affairs Implantable Insulin Group study: effect on cardiovascular risk factors. *Diabetes Care* 21:1596–1602, 1998
18. Abraira C, Maki KC: Does insulin treatment increase cardiovascular risk in NIDDM? *Clin Diabetes* 13:29–31, 1995
19. Davis EA, Jones TW: Hypoglycemia in children with diabetes: incidence, counterregulation and cognitive dysfunction. *J Pediatr Endocrinol Metab* 11:177–182, 1998
20. Gold A, MacLeod K, Deary I, Frier B: Hypoglycemia-induced cognitive dysfunction in diabetes mellitus: effect of hypoglycemia unawareness. *Physiol Behavior* 58: 501–511, 1995
21. Gold AE, Deary IJ, Frier BM: Hypoglycaemia and non-cognitive aspects of psychological function in insulin-dependent (type 1) diabetes mellitus (IDDM). *Diabetic Medicine* 14:111–118, 1997
22. Abraira C, Colwell JA, Nuttall F, Emanuele N, Comstock J, Levin S, Sawin C, Silbert C: A critical issue: intensive insulin treatment and macrovascular disease. *Diabetes Care* 21:669–671, 1998