Clinical Implications of the DREAM Study

In response to an article (1) published in 2003 demonstrating that both diet and exercise as well as pioglitazone reduced insulin resistance in upper-body obese, sedentary, nondiabetic individuals, I wrote an editorial (2) discussing whether the treatment of insulin resistance independent of any effect on glycemia could be beneficial for reducing the risk of cardiovascular disease (CVD). At that time, evidence for a beneficial effect rested on surrogate end points and intermediate outcomes of CVD. The final sentence in the editorial was, "If the ongoing clinical trials demonstrate a reduction in hard clinical events, difficult decisions will need to be made." Although thiazolidinediones (TZDs) continued to lower many of the surrogate risk factors associated with and early manifestations of CVD (e.g., endothelial dysfunction, intima media thickness of carotid arteries) in subsequent studies, the effect on preventing hard clinical outcomes in the first clinical trial reported was less robust than many had anticipated (3). Now the Diabetes Reduction Assessment with Rampipril and Rosiglitazone Medication (DREAM) study (4) has been published, raising the question of treating nondiabetic individuals with a TZD, to reduce the risk of developing type 2 diabetes rather than CVD.

The DREAM study (4) randomized over 5,000 individuals with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) to receive either 8 mg rosiglitazone or placebo over a median of 3 years. There was an ~60% less chance of those receiving the TZD to develop diabetes compared with those receiving the placebo. For every 1,000 subjects with IFG and/or IGT given rosiglitazone, 144 would be prevented from developing diabetes. There would be, however, four to five excess cases (i.e., over what would have occurred if a TZD had not been given) of heart failure. In addition to the small increase in heart failure, the cost of the TZD (approximately $2,000 per year) must also be factored in when deciding how to incorporate these findings into clinical practice. Thus, for an outlay of $2 million per year or $6 million for 3 years, 144 individuals will avoid diabetes over that period and 856 will ostensibly not have benefited. The latter may not entirely be true because the resultant decrease in insulin resistance may be beneficial by helping to preserve β-cell function (5).

If one were to use a TZD to delay or prevent the development of type 2 diabetes, it would be most efficient to target a population that is at highest risk. Individuals with IGT are certainly at increased risk. In subjects in the control groups of the Finnish Diabetes Prevention Study (6), the Diabetes Prevention Program (7), the STOP-NIDDM trial (8), and the DREAM study (4), 14–26% developed diabetes after 2 years, 21–37% after 3 years, and 23–46% after 4 years. It should be noted that most of the subjects in the Finnish study (6) had first-degree relatives with type 2 diabetes and that the inclusion criteria in the Diabetes Prevention Program (7) and the STOP-NIDDM (8) studies required fasting plasma glucose (FPG) concentrations ≥95 or ≥100 mg/dl, respectively, thus increasing the risk beyond simply IGT alone.

Be that as it may, diagnosing IGT for the purpose of identifying individuals who may benefit from a TZD is problematic. The oral glucose tolerance test (OGTT) is inconvenient and not ordered by many physicians to diagnose diabetes in those felt to be at risk (9). Moreover, nearly 50% of individuals with IGT on an OGTT will have normal glucose tolerance if the OGTT is repeated within 2–6 weeks (10–12). Thus, almost half of these individuals who would seem eligible to receive a TZD might not be at that high of a risk for developing diabetes. This comes from the San Antonio Heart Study, in which the sensitivity of simply using the IGT alone to predict incident diabetes was only 51% with a false-positive rate of 10% (13).

Might measuring an FPG concentration be helpful? Although certainly more convenient than an OGTT, FPG concentrations also suffer from some imprecision. Using the 1997 American Diabetes Association criterion of 110–125 mg/dl to diagnose IFG, one-third of individuals were normal on repeat testing (14). Furthermore, other risk factors greatly influence the risk of an elevated FPG concentration (13). For instance, Table 1 shows the progressive increase in the risk of developing type 2 diabetes from obesity, a positive family history, a low HDL cholesterol, and hypertension. Therefore, other clinical factors must be taken into account in deciding whether an FPG concentration places the individual in a high enough risk category to warrant a TZD.

The distribution of glucose concentrations in most populations is unimodal, which makes the choice of what cut points to use to designate various abnormalities of carbohydrate metabolism somewhat arbitrary (15). The National Diabetes Data Group (NDDG) (16) in 1979 decided that the level to diagnose diabetes should predict the development of its specific complication, i.e., retinopathy. They chose a 2-h value on the OGTT of ≥200 mg/dl based on the results of three studies (17) in which 1,213 subjects were followed for 3–8 years during which period 77 of them developed retinopathy. There was no reason given for defining IGT as 2-h glucose values on the OGTT of 140–199 mg/dl. (One suspects that it was because clinical observations suggested that normal individuals would have glucose concentrations <140 mg/dl 2 h after eating.)

Since A1C data, reflecting 3–4 months of glycemia, were not available at that time, the NDDG's decision was based on one glycemic point in time. Subsequent studies following over 2,000 diabetic patients for 6–9 years have evaluated the association between A1C levels and the development or progression of diabetic retinopathy (18,19) and nephropathy (20–22). All five studies showed that if the average A1C level was <7%, there was virtually no development or progression of these microvascular complications.

Although A1C assays differ somewhat, it is generally accepted that the normal range for a Diabetes Control and Complications Trial (DCCT) standardized assay is 4–6%. Therefore, following the reasoning of the NDDG of diagnosing diabetes at a glycemic level that is associated with its microvascular complications and utilizing A1C levels, values between 6 and 7% would reflect pre-diabetes. This contention is supported by two studies that have evaluated A1C levels and incident diabetes. One (23) utilized an assay with a normal range of 4.0–6.0%, and followed 1,253 veterans between the ages of 45–64 years for 3 years. The diagnosis of diabetes was made by an FPG ≥126 mg/dl, an A1C level >7.0%, or by self-report. The annual incidence of diabetes for patients with baseline A1C levels

Table 1—*Influence of other clinical risk factors on the effect of an increased FPG concentration on incident diabetes*

FPG (mg/dl)	BMI (kg/m^2)	Family history	HDL cholesterol	Blood pressure	10-year incidence rate of diabetes (%)*
115	22	Negative	Normal	Normal	42
115	30	Negative	Normal	Normal	57
115	30	Positive	Normal	Normal	69
115	30	Positive	Low	Normal	81
115	30	Positive	Low	High	95

*Calculated from the Cardiometabolic Risk Calculator provided by Michael Stern, MD, based on the data in reference 13.

<5.5, 5.6–6.0% , and 6.1–6.9% was 0.8, 2.5, and 7.8%, respectively. After adjusting for baseline A1C levels, only baseline BMI, but not age, race, family history, or hypertension, was associated with an increased risk of developing diabetes. In a French study (24), incident diabetes over 6 years was evaluated after measuring a baseline A1C level in a DCCT standardized assay in 2,820 subjects, aged 30–65 years. Diabetes was defined as an FPG concentration ≥126 mg/dl or treatment with an oral antihyperglycemia drug or insulin. Baseline A1C levels were divided into deciles. The A1C levels in the last three deciles were 5.7, 5.8, and 5.8–7.1%, respectively. The proportion of individuals who developed diabetes in these deciles was 3, 5, and 12%, respectively. After adjustment for age, A1C levels predicted diabetes at 6 years independent of sex, blood pressure, smoking, and physical inactivity. Unlike the prediction of diabetes by FPG concentrations, which is influenced by other risk factors (Table 1), prediction by A1C levels is largely independent of these other risk factors. Thus, society would get a big "bang for the buck" if individuals with A1C levels between 6 and 7% were to receive a TZD.

In the DREAM study, rosiglitazone increased the likelihood of regression to normoglycemia by ~70–80% suggesting that the drug was treating dysglycemia as well as decreasing the frequency of developing diabetes (4). Therefore, if the TZD were given to individuals with A1C levels between 6 and 7%, many of these values would no doubt return to within the normal range. Regardless of whether one believes that some of these individuals, if given an OGTT, might already have diabetes by the rather arbitrary, but apparently sacrosanct, criterion of a 2-h value of ≥200 mg/dl rather than by a glycemic level associated with the microvascular complications, restoring euglycemia can only be beneficial. Of 819 people diagnosed with diabetes by an OGTT, 42% had a normal A1C level and another 26% had a value which corresponded to one between 6 and 7% in a DCCT standardized assay (15).

Based on the positive results of the DREAM study, the time for decisions concerning under what circumstances TZDs should be used in people without documented diabetes is now upon us. They won't be easy decisions.

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References

1. Shadid S, Jenson MD: Effects of pioglitazone versus diet and exercise on metabolic health and fat distribution in upper body obesity. *Diabetes Care* 26:3148–3152, 2003
2. Davidson MB: Is treatment of insulin resistance beneficial independent of glycemia? *Diabetes Care* 26:3184–3186, 2003
3. Dormandy JA, Charbonnel B, Eckland DJA, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J, on behalf of the PROactive investigators: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 366:1279–1289, 2005
4. 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. *Lancet* 368:1096–1105, 2006
5. Xiang AH, Wang C, Peters RK, Trigo E, Kjos SL, Buchanon TA: Coordinate changes in plasma glucose and pancreatic β-cell function in Latino women at high risk for type 2 diabetes. *Diabetes* 55:1074–1079, 2006
6. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, for the Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
7. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
8. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, for the STOP-NIDDM Trial Research Group: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. *Lancet* 359:2072–2077, 2002
9. Orchard TJ: From diagnosis and classification to complications and therapy. *Diabetes Care* 17:326–338, 1994
10. Mooy JM, Grootenhuis PA, de Vries H, Kostene PJ, Popp-Snijders C, Bouter LM, Heine RJ: Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. *Diabetologia* 39:298–305, 1996
11. Ko GTC, Chan JCN, Woo J, Lau E, Yeung VTF, Chow CC, Cockram CS: The repro-

ducibility and usefulness of the oral glucose tolerance test in screening for diabetes and other cardiovascular risk factors. *Ann Clin Biochem* 35:62–67, 1998
12. Brohall G, Behre CJ, Hulthe J, Wikstrand J, Fagerberg B: Prevalence of diabetes and impaired glucose tolerance in 64-year-old Swedish women. *Diabetes Care* 29:363–367, 2006
13. Stern MO, Williams K, Haffner SM: Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? *Ann Intern Med* 136: 575–581, 2002
14. Ko GTC, Chan JCN, Woo J, Cockram CS: Use of the 1997 American Diabetes Association diagnostic criteria for diabetes in a Hong Kong Chinese population. *Diabetes Care* 21:2094–2097, 1998
15. Davidson MB: Clinical irrelevance of the current diagnostic criteria for abnormal carbohydrate metabolism in asymptomatic individuals. *Curr Opin Endocrinol Diabetes* 12:437–443, 2005
16. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
17. Davidson MB, Peters AL, Schriger DL: An alternative approach to the diagnosis of diabetes with a review of the literature. *Diabetes Care* 18:1065–1071, 1996
18. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995
19. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furnyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
20. Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 332:1251–1255, 1995
21. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R: Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care* 21:116–120, 1998
22. Warram JH, Scott LJ, Hanna LS, Wantman M, Cohen SE, Laffel LM, Ryan L, Krolewski AS: Progression of microalbuminuria to proteinuria in type 1 diabetes: nonlinear relationship with hyperglycemia. *Diabetes* 49:94–100, 2000
23. Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ: Utility of hemoglobin A1c in predicting diabetes risk. *J Gen Intern Med* 19:1175–1180, 2004
24. Droumaguet CD, Balkau B, Simon D, Caces E, Tichet J, Charles MA, the DESIR Study Group: Use of HbA1c in predicting progression to diabetes in French men and women: Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR). *Diabetes Care* 29:1619–1625, 2006