

# Diabetes 2005

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## Macrovascular Risk and Type 2 Diabetes: Results of the PROactive Study

Important data on diabetes presented at the 41st Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2005**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2005** will be followed by a **Diabetes 2005** booklet (EASD and AHA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$25 processing fee to the Yale Office of Continuing Education, you will qualify for up to 5.5 Category 1 credits towards the Physician's Recognition Award of the American Medical Association to be issued by Yale University School of Medicine.

**Diabetes 2005** is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the important association between insulin resistance/metabolic syndrome and atherosclerosis in patients with Type 2 diabetes.
- Identify evolving and emerging management strategies for diabetes (e.g., combination antihyperglycemic therapy, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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### *The "Glucose-CVD Conundrum"*

Based primarily on the results of two large randomized, multicenter trials, it is widely recognized that tight glucose control in patients with diabetes reduces their microvascular disease risk. The Diabetes Control and Complications Trial (DCCT, *N Engl J Med* 1993) and the United Kingdom Prospective Diabetes Study (UKPDS, *Lancet* 1998) showed significant benefit on the progression of diabetic retinopathy and nephropathy in both Type 1 and Type 2 diabetes, respectively. The demonstration of benefit on macrovascular endpoints, however, has proven more elusive. In the DCCT, patients were generally young and the total cardiovascular disease (CVD) events relatively small. As a result, only a non-significant trend toward less macrovascular events was reported in the aggressively controlled patients. Recently, in the long-term observational study of former DCCT patients, known as EDIC (Epidemiology of Diabetes Interventions and Complications), a significant reduction in cardiovascular events was found in those DCCT subjects initially randomized to tight control. The EDIC results are quite impressive since, after the conclusion of the original study, the HbA1c concentrations became equivalent in both groups of patients. That is, those initially treated aggressively experienced an increase in their HbA1c, whereas the mean HbA1c in those initially randomized to conventional care actually improved.

In Type 2 diabetes, there is very little clinical trial evidence that glucose control matters as regards to cardiovascular complications. For example, in the UKPDS, a small and non-significant trend toward a modest decrease (-16%) in myocardial infarction (MI) in patients initially treated with sulfonylureas or insulin was observed. There was no effect whatsoever on stroke or all-cause mortality, as compared to diet therapy, despite the nearly 1% HbA1c difference between groups. A small subgroup of overweight patients treated with metformin monotherapy exhibited a significant

reduction in MI, and diabetes-related mortality as compared to diet therapy patients. However, when metformin was added in combination to patients failing sulfonylurea monotherapy, a puzzling increase in mortality was also noted. Thus, overall, the UKPDS results concerning macrovascular disease and antihyperglycemic therapy were disappointing and, to some degree, confusing.

Several explanations for this "glucose-CVD conundrum" have been proposed. First, it may simply reflect study methodology. Whereas microvascular risk is measured by relatively "soft" endpoints such as the progression of retinopathy by ophthalmoscopy or by the worsening of albuminuria, macrovascular risk is more rigidly defined by frank myocardial or cerebral infarction or actual patient demise. Another potential explanation would be that glucose may simply not be as important a factor for large vessel atherosclerosis as other frequently coexisting risk factors, such as obesity, hypertension, and dyslipidemia. However, epidemiological studies have clearly shown a very strong relationship between HbA1c and cardiovascular outcomes. Perhaps glucose levels need to be reduced much further than has been previously possible in these trials. Conceivably, the deleterious effects of glucose on the vasculature may exhibit a "threshold" effect. The counter argument here is that the epidemiological data instead suggest a *continuum* of risk, even down into the high-normal range of blood glucose. Moreover, reducing other CVD risk factors, such as blood pressure and LDL-cholesterol, has resulted in reduced event rates through a wide spectrum of abnormalities. Finally, the antihyperglycemic strategies generally employed by the older studies—i.e., increasing insulin supply vs. reducing insulin resistance—may have been suboptimal. Given the strong epidemiological association between insulin resistance/hyperinsulinemia and cardiovascular mortality, this possibility must be considered. Indeed, insulin-sensitizing medications appear to exert substantial benefit on a wide variety of CVD

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risk factors. Therefore, it is quite tenable that employing an antihyperglycemic approach that focuses on improving insulin sensitivity may lead to greater cardiovascular benefit.

## TZDs and CVD Risk

Since their release in 1997, there has been speculation that the thiazolidinediones (TZDs) might decrease CVD risk. In short-term studies, these drugs reduce hyperinsulinemia, blood pressure, microalbuminuria, inflammatory markers, and hypertriglyceridemia, while increasing HDL-cholesterol as well as endothelium-dependent vasodilatation. Their mechanism of action, which involves activation of the nuclear receptor peroxisome proliferator-activated receptor (PPAR)- $\gamma$ , is associated with improvement in several fundamental vascular biological processes that control atherogenesis, including smooth muscle cell proliferation and the elaboration of local pro-atherogenic cytokines, metalloproteinases, and adhesion molecules. This class of drug, which has become increasingly popular in the management of hyperglycemia in Type 2 diabetes patients, is therefore, uniquely positioned to clinically test the insulin resistance-CVD connection.

## The PROactive Study Design

The first study to address this important question is the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive). The long-anticipated results of this first TZD outcomes trial were presented today in Athens, Greece at the 41st Annual Meeting of the European Association for the Study of Diabetes (EASD) to a standing-room only crowd in the Hippocrates Amphitheatre of the Olympic Peace and Friendship Stadium. The two-hour session was chaired by Dr. Ferrannini of Italy. The study results were serially presented by the principal investigators, Drs. Massi-Benedetti of Italy, Carbonnel of France, Dormandy of the UK, and Erdmann of Germany. Dr. Lefebvre of Belgium, chair of the study's Data Safety Monitoring Board, presented the safety data. Finally, independent critical analysis was provided by Dr. Yki-Jarvinen of Finland.

This randomized, double-blind outcome study, conducted at 321 centers in 19 European countries involved 5,238 patients with Type 2 diabetes, aged 35-75 years, who were being managed with either diet or oral agents (with or without insulin). PROactive patients were considered to be at high cardiovascular risk, since each had established macrovascular disease prior to study

enrollment. Evidence for this included a history of MI, stroke, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) at least six months prior to enrollment; or documentation of acute coronary syndrome at least three months prior to enrollment. Other allowable objective evidence of macrovascular disease included known coronary artery disease (CAD) as defined by at least one coronary stenosis of  $\geq 50\%$  of luminal diameter by coronary angiography or a positive myocardial perfusion scan, and peripheral arterial disease (history of claudication confirmed with an abnormal ankle: brachial pressure index or a history of amputation). An additional inclusion criterion was a baseline HbA1c above 6.5%. Exclusion criteria were a prior history of TZD use; Type 1 diabetes; insulin as the sole form of antihyperglycemic therapy within one year of diagnosis; symptomatic heart failure of New York Heart Association Class II or higher; leg ulceration, gangrene, or pain at rest; ongoing hemodialysis; and severely impaired hepatic function.

Patients were randomized to receive either pioglitazone or placebo, added to their baseline antihyperglycemic therapy. During the first two months of study enrollment, pioglitazone (or placebo) was force-titrated from 15 mg QD to 45 mg QD. The objective was to maintain patients on the maximal tolerated dose. (As a result of this strategy, 93% of patients were maintained on 45 mg QD.) Investigators were encouraged to maintain blood glucose levels below the International Diabetes Federation (IDF) HbA1c target of 6.5%. Any other non-TZD antihyperglycemic therapy could be initiated and dose titrated during the study, including insulin, to achieve this. In addition, investigators were encouraged to maintain lipid and blood pressure control, also based on IDF guidelines.

The study's primary composite endpoint was time from randomization to occurrence of any of the following events: all-cause mortality, non-fatal MI, acute coronary syndrome, CABG, PCI, stroke, major leg amputation (above the ankle), or leg revascularization. Secondary endpoints included the composite of all-cause mortality, non-fatal MI, and stroke (the *principal* secondary endpoint); cardiovascular mortality; and each of the individual events comprising the primary endpoint. PROactive was an event-driven study, with plans to stop the study after 760 events were reached and each enrolled patient had been followed for at least 30 months. PROactive was supposed to extend into 2006, but was stopped early because the predefined termination criteria were achieved more than one year ahead of schedule.

**Table 1. Baseline Characteristics of PROactive Patients**

<i>Demographics</i>	
Age (years)	61.8 $\pm$ 7.7
Diabetes duration (years)	9.5 $\pm$ 7.0
% Female	33.9%
% Caucasian	98.5%
Body mass index (kg/m <sup>2</sup> )	30.9 $\pm$ 4.8
Current / past smoking	13.8% / 45.0%
<i>Laboratory Data (Means)</i>	
HbA1c (%)	8.1
LDL-cholesterol (mg/dl)	114
HDL-cholesterol (mg/dl)	45
Triglycerides (mg/dl)	198
<i>Microvascular Complications</i>	
Retinopathy	23.2%
Nephropathy	14.2%
Neuropathy	25.6%
<i>Macrovascular History</i>	
MI	46.7%
Acute coronary syndrome	13.7%
PCI/CABG	30.8%
Other evidence of CAD	48.1%
Stroke	18.8%
Peripheral arterial disease	19.9%
1 of the above entry criteria	51.5%
2 of the above entry criteria	23.4%
3+ of the above entry criteria	25.1%
<i>Baseline Antihyperglycemic Therapy</i>	
Sulfonylurea	19.1%
Metformin	9.9%
Sulfonylurea + metformin	24.7%
Insulin (with oral agents)	33.6%
Other	11.7%
None	4.1%
<i>Lipid Lowering Therapy</i>	
Statins alone	40.8%
Fibrates alone	8.6%
Statins + fibrates	2.1%
<i>Anti-hypertensive Therapy</i>	
ACE inhibitors	62.7%
ARBs	6.8%
Beta-blockers	54.6%
Calcium channel blockers	35.4%
<i>Antiplatelet Agents</i>	
Aspirin	73.1%

## Baseline Description of Patients

Baseline characteristics of the entire study cohort are seen in Table 1 (as previously reported in *Diabetes Care* 27:1647, 2004). This was a typical high-risk European Type 2 diabetes population, generally obese with diabetes duration of nearly 10 years. (We would note the paucity of

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study subjects from ethnic minorities, a point that needs to be considered when the PROactive results are extrapolated to the US diabetic population.) Approximately one-half had two or more macrovascular inclusion criteria at baseline. The vast majority of patients were managed with oral agents, with about one-third additionally treated with insulin. In general, at baseline, the use of statins was lower than might be expected at about 40%, but about 70% were taking either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), and nearly 75% were using prophylactic aspirin. Use of these drugs during the course of the study increased but not markedly so. There were no significant differences between the two treatment groups at baseline.

## Study Results

The mean follow-up in PROactive was 2.8 years. Approximately 16% of patients in each arm stopped study drug prematurely, mainly because of adverse events; only two patients were lost to follow-up during the study. Compliance was high at 95%.

Metabolic outcomes are seen in Table 2. HbA1c was, on average -0.5% lower in the pioglitazone patients than in controls, despite the study goal to equal glucose control between the two groups. At the final study visit, the average HbA1c was 6.9% in the pioglitazone group and 7.5% in the placebo group. There were small differences in blood pressure and major differences in lipid levels, with an overall 5.3% lower LDL-cholesterol, an 8.9% higher HDL-cholesterol, and 13.2% lower triglycerides in the active therapy group.

Cardiovascular outcomes are shown in Table 3. The primary endpoint of any macrovascular event or death was reduced by 10%, from 23.5% in the placebo group to 21.0% in the active therapy group, a difference that did not reach statistical significance. The prespecified *principal* secondary endpoint of all-cause mortality, non-fatal MI, or stroke was reduced by 16%, from 14.4% with placebo to 12.3% with pioglitazone. The difference between the two composites was mainly explained by an increased number of peripheral vascular procedures performed in the pioglitazone group. Most of the other individual components of the primary endpoint were consistently less frequent in pioglitazone patients (Table 4), but the study was not powered to show significance in these.

**Table 2. Metabolic Changes During Study**

	Pioglitazone	Placebo	p-value
HbA1c	-0.8%	-0.3%	<0.001
Systolic blood pressure	-3 mmHg	0 mmHg	0.033
Diastolic blood pressure	-2 mmHg	-1 mmHg	0.133
LDL-cholesterol	-7.2 mg/dl	-4.9 mg/dl	<0.003
HDL-cholesterol	+19 mg/dl	+10.1 mg/dl	<0.001
Triglycerides	-11.4 mg/dl	+1.8 mg/dl	<0.001

**Table 3. Composite Cardiovascular Outcomes**

	Pioglitazone	Placebo	Relative Risk	95% CI	p-value
Primary Composite Endpoint (All-Cause Mortality, Non-Fatal MI, Acute Coronary Syndrome, Major Amputation, Coronary or Leg Revascularization)	21.0%	23.5%	0.904	0.802-1.018	0.0951
Principal Secondary Composite Endpoint (All-Cause Mortality, Non-Fatal MI, Stroke)	12.3%	14.4%	0.841	0.722-0.981	0.0273

**Table 4. Individual Cardiovascular Endpoints**

	Pioglitazone n=2,605	Placebo n=2,633
Death	110	122
Non-fatal MI	85	95
Silent MI	20	23
Stroke	76	96
Leg amputation	9	15
Acute coronary syndrome	42	63
Coronary revascularization	101	101
Leg revascularization	71	57
Any endpoint	514	570

A large number (n=53) of prespecified subgroup analyses (including age, BMI, blood pressure, lipids, baseline antihyperglycemic drug status, and the extent of macrovascular disease) were also conducted. No significant heterogeneity was demonstrated.

Although not a prespecified outcome, the presenters observed that the need for the subsequent addition of insulin was reduced by 53% in the pioglitazone treated group (11% instead of 22%; p<0.0001). This should not be surprising, since pioglitazone has obvious antihyperglycemic effects, and since the control group could not be started on a TZD during the study.

## Safety Issues

Table 5 shows the incidence of heart failure and other adverse events between the groups. The investigator-determined diagnosis of and hospitalization for heart failure were both increased in the pioglitazone group compared to placebo. The actual excess incidence of hospitalization for heart failure was small (1.6% absolute increase) and there was no increase in heart failure mortality. Since true heart failure in diabetes would be expected to have a significant negative effect on mortality, it is quite tenable that the increase in "heart failure" diagnoses was the result of fluid retention and peripheral edema, well known side effects of TZDs.

## Study Limitations

Several important limitations of PROactive must be considered. As previously mentioned, the study population was nearly devoid of members of ethnic minorities, particularly those of African and Hispanic extraction, who comprise substantial percentages of the American Type 2 diabetic population. Also, cardiovascular risk factor reduction remained suboptimal in a significant minority of patients even by study end, particularly concerning the use of statins. One wonders what the results may have looked like if nearly 100% of patients were on a full complement of cardiovascular drugs. The study's design does not allow any conclusions concerning the potential benefit of

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pioglitazone in patients with Type 2 diabetes who have no overt macrovascular disease. Moreover, the vast majority of patients in PROactive had pioglitazone added to their established glucose-lowering therapy, and therefore the study's results cannot be assumed to apply to the use of pioglitazone as monotherapy to reduce CVD events in high-risk patients. We would also point out that there was a small but significant HbA1c difference between the treatment groups during the study. It is therefore difficult to know whether pioglitazone's apparent benefits were due to the drug's direct effect on the vasculature or mediated through this glycemic improvement. In fact, the cardiovascular benefit of pioglitazone may just as easily be ascribed to a number of other metabolic benefits from the drug (e.g., insulin sensitivity, triglycerides, HDL-cholesterol). In the end, the precise mechanism or mechanisms here may be unimportant—they are likely multifactorial, since PPAR- $\gamma$  agonists have pervasive benefits on vascular biology and a wide variety of CVD risk factors. PROactive is not able to address the potential benefit or harm from other PPAR agonists in this setting. Several studies are underway, including the National Institutes of Health (NIH)-sponsored BARI-2D trial, which will assess the effect of the other available TZD, rosiglitazone, on cardiovascular events.

## Critique & Audience Participation

In an invited, independent critique of the PROactive study results, Dr. Yki-Jarvinen from Helsinki raised several provocative concerns. First, she noted that the inclusion of *procedural*

Table 5. Safety of Study Drugs

	Pioglitazone n=2,605	Placebo n=2,633
Heart failure diagnosis	10.8%	7.5%
Heart failure admission	5.7%	4.1%
Heart failure deaths	0.96%	0.84%
Edema	21.6%	13.0%
Malignancy	3.7%	3.8%
Serious adverse events	46.2%	48.4%
Non-serious adverse events	59.0%	59.5%

outcomes in the primary composite may have led to the non-significant effect on the primary outcome. A differential application of these procedures (i.e., coronary or peripheral vascular revascularizations) between patient groups due to physician- or hospital-associated factors (as opposed to disease-associated factors) would tend to bias the study toward the null—obscuring the differences in outcomes between groups. She also discussed the implications of the heart failure outcomes extensively, and wondered whether the overall benefit on mortality, MI, and stroke is worth the associated risk. As several members of the audience pointed out, however, the actual diagnosis of heart failure was not adjudicated and TZD-associated edema may have been misinterpreted by some as an indication of cardiac decompensation.

Other audience members remarked that, while relatively small compared to most major cardiovascular trials, the 16% relative risk reduction in the principal secondary endpoint should be viewed as impressive, since it was superimposed upon other standard CVD risk reduction therapies, including aspirin, ACE inhibitors or ARBs, and lipid lowering drugs.

## Where Do We Go From Here?

In summary, compared to placebo, the addition of pioglitazone to ongoing antihyperglycemic therapy in high-risk Type 2 diabetic patients with established macrovascular disease had no significant effect on the primary composite endpoint of all CVD events and mortality. However, pioglitazone did reduce the secondary endpoint of the composite incidence of death, non-fatal MI, and stroke by 16%. The absolute risk reduction is 2.1%, translating to a number-needed-to-treat of 48 patients over three years to prevent one such "event." Importantly, for the first time, an oral agent for Type 2 diabetes has been shown to reduce macrovascular endpoints in high-risk patients. As with any study, however, perhaps more questions have been raised than answered. We look forward to a more careful read of the PROactive study results when they appear in next week's *Lancet*. Undoubtedly, multiple secondary papers will be forthcoming. We would be particularly interested in a stratified analysis based on insulin therapy and one based on a pre-existing diagnosis of heart failure. We would also be interested in further statistical analysis of the patients' need for the addition of insulin therapy—especially as to whether the difference between groups actually widened as the study progressed, suggesting a possible beneficial effect on  $\beta$ -cell function. Lastly, we anxiously await cardiovascular studies currently underway with rosiglitazone in high-risk diabetic patients, and with both TZDs in lower risk diabetic patients, as well as future studies that will test the hypothesis that improving insulin resistance in non-diabetic patients reduces their cardiovascular risk.



## Update on Post-Prandial Glucose



In recent years evidence has emerged that implicates post-prandial hyperglycemia as an independent risk factor for macrovascular disease. This has highlighted the limitations of relying solely on HbA1c as the standard for assessing overall glycemic control in our diabetic patients. Since it represents average glucose levels over a two to three month period of time, an individual's HbA1c provides little information on variability in glucose control (a factor that may also be important in determining risk of severe hypoglycemia). A series of presentations at the EASD dealt with recent advances in this area.

### Screening Techniques

Kato *et al.* from Tokyo, Japan, looked at the potential use of post-prandial urinary glucose as a screening test for post-prandial hyperglycemia (abstract 718). They compared results from an oral glucose tolerance test with fasting blood glucose and two-hour urinary glucose in 160 patients with Type 2 diabetes (mean age  $54 \pm 1$  years for men,  $60 \pm 1$  years for women, and BMI  $25 \pm 0.3$  kg/m<sup>2</sup>). Had the investigators used fasting blood glucose for diagnosis, 67% of the diabetic patients would have been diagnosed, whereas 98% (156/160) of the diabetic patients had a urinary

glucose  $>100$  mg/dl. The presenters concluded that a one-hour urinary post-prandial glucose may offer a simple option for screening for diabetes in the future.

Dungan and colleagues (abstract 719) reported on the use of 1,5-anhydroglucitol (1,5-AG), a serum marker that drops as serum glucose exceeds its renal threshold,  $\sim 180$  mg/dl. They studied well controlled (HbA1c 6.5% - 8%) patients with either Type 1 or 2 diabetes, who used the Continuous Glucose Monitoring System (CGMS) for two consecutive 72-hour periods and looked at area under the curve (AUC) for glucose  $>180$  mg/dl (AUC-180), comparing it to 1,5-AG, fructosamine,

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and HbA1c measured at baseline and at days 4 and 7. Both mean ( $r = -0.45$ ,  $p = 0.006$ ) and study-end 1,5-AG ( $r = -0.46$ ,  $p = 0.008$ ) correlated with AUC-180 more than did mean HbA1c ( $r = 0.33$ ,  $p = 0.057$ ), or mean fructosamine ( $r = 0.38$ ,  $p = 0.088$ ). On the other hand, HbA1c was found to correlate better with mean overall glucose as well as with pre-prandial glucose readings. The authors concluded that 1,5-AG may offer a complementary marker that, in addition to HbA1c, will provide more information about an individual's overall glucose control.

## Treatment Implications

The concerns over post-prandial hyperglycemia have also led to the development of

therapies designed to reduce post-prandial glucose excursions, such as the alpha-glucosidase inhibitors and the short-acting non-sulfonylurea secretagogues, repaglinide and netaglinide. Lu *et al.* from China, compared repaglinide with glibenclamide, using CGMS, in 20 patients with newly-diagnosed Type 2 diabetes (abstract 783). Perhaps not surprisingly, repaglinide had a greater effect on mean post-prandial blood glucose, but less of an effect on 3 AM blood glucose than did glibenclamide (an overseas version of glyburide). One wonders whether combination therapy, including both a long-acting and a short-acting insulin secretagogue, may have some role in the therapy of patients with Type 2 diabetes.

Finally, in a study that will appeal to some of our patients, Fatema and colleagues from Sydney, Australia, looked at the impact of a pre-dinner alcoholic beverage on glucose excursions after a

meal (abstract 737). Subjects were given water, beer, wine, gin, or water on separate occasions prior to a standard meal and then glucose and insulin responses were measured over the next two hours. The authors reported that, in comparison to pre-meal water, the ingestion of beer, wine, and gin all reduced post-prandial hyperglycemia (25%, 23%, and 19% reductions in AUC, respectively), possibly related to ethanol's recognized effect on lowering hepatic glucose production.

Together, these presentations highlight the potential importance of addressing post-prandial glucose in clinical practice, and being aware of the limitations of HbA1c measurements when reviewing an individual's overall glycemic control. We would caution, however, that prospective data do not yet prove that targeting post-prandial glucose definitively affects patient outcomes.



## Diabetes in Pregnancy: Diagnosis & Prognosis



Gestational diabetes mellitus (GDM) is defined as diabetes that first becomes manifest during pregnancy. In the vast majority, the pathogenesis is similar to that which occurs in Type 2 diabetes, albeit compressed over a period of nine months. That is, patients who develop GDM are insulin resistant at baseline and their insulin sensitivity declines further during gestation, predominately due to placental factors.  $\beta$ -cell compensation does not occur in these individuals and hyperglycemia ensues. GDM typically resolves post-partum, although affected women remain at high risk for the future development of permanent Type 2 diabetes. In a minority of patients, Type 1 diabetes may be first diagnosed during pregnancy.

The finding of two or more abnormal glucose values during a three-hour 100 gram oral glucose tolerance test (OGTT) is considered diagnostic of GDM in the US (Table 6) and significantly increases the risk for preterm delivery and the need for cesarean section (Dalfrà *et al.*, Italy, abstract 862). The meaning of a single abnormal value on an OGTT has been controversial, however. According to a retrospective analysis of 4,137 women with a positive glucose challenge test by Cuccuru and Italian colleagues, the metabolic parameters (e.g., triglyceride values and HOMA-IR values [a calculated marker of insulin resistance]) and the degree of impairment of insulin secretion observed in 747 women with one abnormal value were indistinguishable from those of 722 women with two or more abnormal values (abstract 867). There are few data, however, on long-term pregnancy outcomes in these patients.

**Table 6. Diagnostic Criteria for Gestational Diabetes**

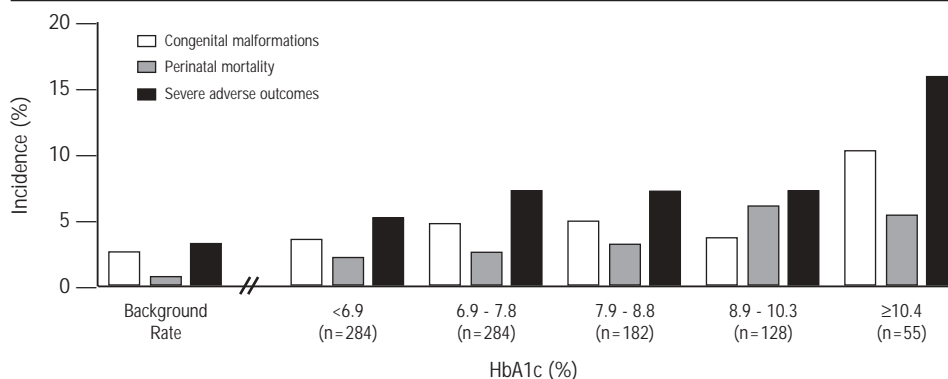
$\geq 2$  abnormal values (venous plasma) on 3-hour OGTT with 100-gram glucose load:

	mg/dl	mmol/l
Fasting	95	5.3
1-hour	180	10.0
2-hour	155	8.6
3-hour	140	7.8

By O'Sullivan and Mahan, as modified by Carpenter and Coustan.

Normalization of blood glucose minimizes the risks for maternal and fetal complications in those with GDM as well as in those with preexisting Type 1 diabetes. Jensen and Danish colleagues (abstract 53) found that preconception HbA1c was predictive of the risk for severe congenital malformations, perinatal mortality, and severe adverse outcomes in a population-based nationwide study of 966 women with Type 1 diabetes. These increased risks occurred at even slightly increased levels of HbA1c. Marked increases in risk for congenital malformation and severe adverse outcome were found at HbA1c  $\geq 10.4\%$  and for perinatal mortality at HbA1c  $\geq 8.9\%$  (Figure 1).

**Figure 1. Incidences of Congenital Malformations, Perinatal Mortality, and Severe Adverse Outcomes by Preconception HbA1c**



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