

Diabetes 2008

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Coming to an ACCORD...



Important data on diabetes presented at the 68th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2008**, a newsletter CME program that is being offered to you by Yale University School of Medicine. Fax or e-mail delivery to your office of **Diabetes 2008** will be followed by a **Diabetes 2008** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, 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 2008 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 third of this week's clinical trial tryptych is the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, presented on Tuesday morning, June 10th, to another capacity crowd at the Moscone Convention Center in San Francisco. Similar to ADVANCE (see Issue 2) and VADT (see Issue 4), this is a large, randomized, controlled trial designed to determine whether tight glycemic control improves cardiovascular disease (CVD) outcomes in patients with Type 2 Diabetes (T2DM). It received early press in February when the glycemic control portion of the study was halted due to excess total deaths in the intensively treated group. The presentations in this symposium focused in large part on interpreting this concerning finding.

Dr. David C. Goff from Wake Forest University, North Carolina, began the symposium by describing the study design and patient characteristics. ACCORD had 10,251 participants in the US and Canada, with a mean age of 62.2 years and baseline median HbA1c of 8.1%, randomized to either intensive (HbA1c target <6.0%) or standard therapy (target 7.0-7.9%). Other baseline characteristics included a 10 year median duration of patients with T2DM with approximately 1/3 having had a prior cardiovascular (CV) event. They were followed for a mean of 3.5 years, although due to different entry points, some were followed for as long as six years. The primary outcome was a composite of nonfatal myocardial infarction (MI), nonfatal stroke, or death from CV causes. The trial was designed with a double 2 x 2 factorial design in order to additionally evaluate the effect of intensively treated blood pressure and the addition of fenofibrate or placebo to statin therapy. These portions of the study remain ongoing. Secondary outcomes including microvascular disease complications, hypoglycemia, cognition, and quality of life are also to be presented at a later date.

Dr. Faramarz Ismail-Beigi from Case Western Reserve University in Cleveland discussed the glycemia management strategies used in ACCORD. Metformin was used most frequently in both groups (intensive, 94.7% vs. standard, 86.9%), followed by the secretagogues (either glimepiride or repaglinide, 86.6% vs. 73.8%). Insulin and rosiglitazone were used to a significantly greater

extent in the intensive arm (77.3% vs. 55.4% and 91% vs. 58%, respectively.) Other agents such as acarbose and exenatide were also available. The majority of patients in the intensive arm were on 3 to 5 oral medications as well as insulin, a regimen necessary to maintain glycemic targets. Within four months of randomization, intensively treated patients experienced a large fall in their HbA1c, from 8.1% to 6.7% (in contrast to a much slower rate of fall in the ADVANCE intensive arm). Stable median HbA1c levels of 6.4% and 7.5% were reached by the respective groups by two years and remained stable throughout the trial. The greater use of insulin and a thiazolidinedione (TZD) in the intensive group likely explains greater weight gain in the group (3.5 kg vs. 0.4 kg at three years) and greater incidence of weight gain >10 kg (27.8% vs. 14.1%). Patients in the intensive arm also experienced hypoglycemia three times more frequently than those undergoing standard care. The majority of the hypoglycemic episodes occurred in the first two years after randomization, although the intensively treated group still had more hypoglycemia even after three years.

Dr. Hertzell Gerstein from McMaster University in Hamilton, Canada, presented ACCORD's main results (Figure 1). The composite primary CVD endpoint did not show statistical difference between the groups, occurring in 352 people in the intensive arm versus 371 people in the standard arm (HR 0.90 [95% CI: 0.78, 1.04]; p=0.16). Although the intensive arm did have a lower rate of nonfatal MI than with standard care (3.6% vs. 4.6%; HR 0.76 [0.62, 0.92]; p=0.004), it also had a higher rate of death from CV causes (2.6% vs. 1.8%; HR 1.35 [1.04, 1.76]; p=0.02). Although this latter result was unexpected, the greater surprise was the significant increase in all-cause mortality in the intensive therapy group (5.0% vs. 4.0%; HR 1.22 [1.01, 1.46]; p=0.04).

Dr. Robert Byington from Wake Forest addressed the higher incidence of both hypoglycemia and death in the intensive arm. The ACCORD trial cannot determine whether these are related or independent findings. However, by sub-grouping participants based on severe hypoglycemia, it became clear that mortality was indeed higher among those who had experienced a severe hypoglycemia episode,

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regardless of which treatment they received.

Dr. Michael Miller, also of Wake Forest University, discussed the concern that the means of lowering glucose may have contributed to mortality differences. The study was actually not designed to examine the effect of the individual medications on final CVD outcomes. However, mortality hazard ratios were calculated for each anti-hyperglycemic agent. Three medications had a hazard ratio that did not cross unity, indicating a significant difference in risk between those receiving vs. not receiving the medication. Rosiglitazone was *not* one of these agents, and appeared, at least by this statistical analysis, not to be contributing to any excess mortality. Rapid-acting bolus insulin and pre-mixed insulins were associated with a higher risk of death, whereas, exenatide was associated with a reduced risk of death. Rapid insulin and exenatide were used more frequently in the intensive arm, but pre-mixed insulin was used more often in the standard

arm. The data was unable to identify a single agent or combination that accounted for the imbalance in mortality between the two treatment arms. Even when all-cause mortality data was adjusted for baseline participant characteristics and type of medications used, there was still a 19% greater risk of death in the intensive arm (HR 1.19 [0.95, 1.49]).

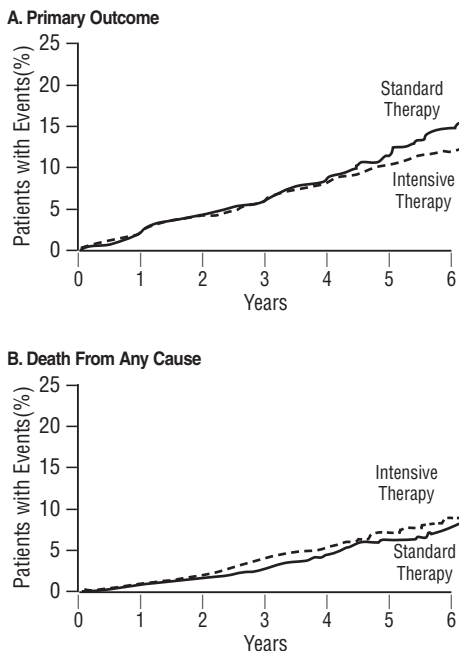
In her summary of the study findings, Dr. Denise Simons-Morton from the National Heart, Lung and Blood Institute (NHLBI), Bethesda, MD, noted the primary differences between the intensive and standard arms. The intensive arm had a lower HbA1c, greater use of multiple medications (62% of the intensive arm were on 3-5 oral hypoglycemic agents plus insulin vs. 18% in the standard arm), and more adverse consequences of treatment (hypoglycemia, weight gain). ACCORD appeared to identify a previously unrecognized harm from a strategy of intensive glucose lowering in high risk individuals with T2DM. The 20% greater mortality risk in the intensive arm was consistent across sub-group analyses. However in a strategy trial like ACCORD, potential causes are difficult if not impossible to distinguish. Also, any effect of intensive glucose control on microvascular disease in this T2DM population remains to be analyzed.

In a following expert panel discussion moderated by Dr. Harold Lebovitz, Drs. Robert Rizza of the Mayo Clinic, Robert Sherwin of Yale, Sue Kirkman of the American Diabetes Association, Eberhard Standl of the Munich Diabetes Research Institute, and Rury Holman of Oxford discussed the clinical implications of the week's landmark presentations. Dr. Standl provided evidence that, based on the natural history of CVD, the current trials were too short, requiring at least 10 years of treatment and follow up to see significant differences in CV outcomes. Professor Holman re-emphasized that these trials were, essentially, secondary prevention trials, and it may be too difficult to intervene this late in the disease process and expect differences in treatment outcomes within a short period of time. Dr. Kirkman commented that the increased mortality in the intensive treatment group was likely due to a complex interplay between the duration of diabetes, type of medications used, and multiple other risk factors. She noted that people with a shorter duration of diabetes did better with intensive therapy in all

three trials. Dr. Sherwin made the observation that it is very uncommon in clinical practice to have patients on 3 to 5 oral agents in addition to insulin. Also, hypoglycemia is very concerning as a side effect because diabetic patients develop hypoglycemia unawareness, and hypoglycemia can contribute to sudden death. He emphasized that earlier detection and treatment of diabetes is the best means of reducing atherosclerotic risk. The panel agreed that current ADA and European guidelines for glycemic control should remain at current levels given overall benefits. Dr. Sherwin stated that all of the trials reported this week demonstrated a significant reduction in event rates relative to older studies. This provides indirect indication that current guidelines for glycemic, blood pressure, and lipid therapy are working to improve the health of those with T2DM.

In the box, we have summarized some of the key points that have emerged from this week's landmark presentations—they may be useful to our readers in the care of their patients with diabetes.

Figure 1. Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause.



T2DM & CVD Risk Reduction: "Take-Home" Messages from the Editors

- First and foremost, focus on blood pressure, lipids, anti-platelet therapy, and smoking cessation.
- For glucose control, an *individualized* approach is required, particularly for those patients with advanced disease.
- Lowering glucose is important, but primarily to prevent microvascular complications (renal, retinal).
- If glucose control reduces CVD risk, it does so modestly and primarily in those with early diabetes without advanced macrovascular disease. In these individuals, reduce the HbA1c to <7%. Further reductions may have long-term benefits, but the magnitude is unclear.
- Be cautious in your glucose lowering strategies in older, high-risk patients with longstanding diabetes. Maintaining HbA1c close to 7% (but not necessarily <7%) may be the optimal target for these individuals.
- Avoid hypoglycemia.



TZDs: Yes or No?



The recent controversy surrounding the potential for the thiazolidinedione (TZD) rosiglitazone to increase the risk of myocardial ischemic events ensured that a symposium entitled "PPARs—Yes or No?" was presented before a packed audience

at the ADA, on Sunday, June 8th. Around 65% of patients with Type 2 diabetes ultimately die from CVD; therefore the effects of oral anti-hyperglycemic therapy on CVD risk is a very important issue in diabetes care. The meta-analysis published

last year in the *New England Journal of Medicine* by Nissen and Wolski indicated that rosiglitazone was associated with an increased risk of MI and a strong trend toward increased risk of CV death. The paper was understandably read with great

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TZDs: Yes or No?

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concern by both patients and physicians providing their care. Subsequent commentaries questioned the methodology used in the meta-analysis, in light of a strong basic science suggestion that activation of the nuclear transcription factor, peroxisome proliferator-activated receptor (PPAR)- γ , as with TZD therapy, should decrease atherosclerosis.

To address some of these questions, Dr. Mahoney, a Senior Clinical Reviewer in the Endocrine and Metabolism section of the Food and Drug Administration (FDA), and her colleagues performed a meta-analysis of all currently available data at the FDA on the effect of TZDs on cardiac end-points. The FDA meta-analysis included 42 double-blind trials with over 14,000 patients. Most trials were of short duration (<6 to 12 months) and most did not include cardiac end-points as adjudicated outcomes; therefore the analysis is based on individual adverse events reported from these trials. The FDA found an overall risk of myocardial ischemia events of 2.0% with rosiglitazone and 1.5% with all comparators (odds ratio [OR] 1.4 [1.1, 1.8]), a risk difference of ~1 event per 100 patient-years. However, when the risk associated with rosiglitazone was compared with other active therapies (*ie*, where the subject was taking an alternate agent and not placebo), this difference did not prove statistically significant. Furthermore, in an analysis of high-risk patients, two interesting findings were made. Firstly, removing the small group of high-risk patients from the analysis abolished any difference between rosiglitazone- and placebo-treated patients. Secondly, within the high-risk group, it was the use of nitrate therapy that appeared to confer the increased risk of myocardial ischemic events.

The FDA next looked at rosiglitazone trials of longer duration, and compared the risk of major adverse cardiovascular events (MACE) and total mortality between the TZD and placebo. In this analysis the overall OR was <1, indicating no increased risk with rosiglitazone. Finally, the FDA also analyzed the observational data they have on file, which is a database of >1 million patients taking rosiglitazone, and, once again, no increased CV risk was observed.

Dr. Mahoney then briefly reviewed the data for pioglitazone. While less data are currently available, and some study reports have not yet been submitted to the FDA, their analysis also revealed no increased risk of myocardial ischemic events with pioglitazone. PROactive (Prospective pioglitazone Clinical Trials in MacroVascular Events) was a double-blind, placebo-controlled study in patients with Type 2 diabetes and macrovascular disease randomized to pioglitazone

or placebo, in addition to existing glucose-lowering medications. In PROactive, pioglitazone therapy was associated with a decreased incidence of MI, stroke, and mortality in these high-risk patients.

In the FDA analysis, both TZDs were, however, associated with an ~two-fold increased risk of heart failure, which has been reported before. This risk appears to relate not to any deleterious effect on ventricular function, but, instead, increased extracellular fluid due to these drugs' recognized effects on renal sodium handling.

In subsequent presentations, Dr. Zachary Bloomgarden from Mt. Sinai School of Medicine and Dr. Philip Raskin from the University of Texas at Dallas, both reviewed the literature on CV risk associated with TZD therapy and pointed out the weaknesses and strengths of many of these analyses. In agreement with the FDA, they also concluded that this literature does not support the findings of Nissen and Wolski, a report that they both criticized. They concluded that TZD therapy should not be stopped in individuals with Type 2 diabetes because of concerns about potential CV events, although it may be appropriate not to use this class of compounds in high-risk patients, and especially those on nitrate therapy, until a clearer understanding of the effect of TZDs in this population is achieved. Also, they should be avoided in the setting of preexisting heart failure.

Just prior to these talks Dr. Bart Staels of Lille University in France, reviewed potential future developments in the PPAR field. He reminded the audience that, while statins have a clear role to play in the treatment of dyslipidemia in diabetes, reducing overall CV risk by ~30-40%, there remains a significant risk of CV events despite optimal lipid-lowering therapy. In particular, in diabetes there is the added risk associated with low HDL-cholesterol and high triglycerides that is not fully addressed by statins. PPAR- α agonists (*eg*, fibrate drugs) may have a particular role to play in treating this lipid abnormality. Evidence from sub-group analyses of major studies, such as the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, indicate significant benefit of PPAR- α activation in those individuals with a low HDL-cholesterol and a triglyceride >200 mg/dl. Dr. Staels commented on the PPAR- δ agonists, which appear to have an anti-inflammatory effect and may also help reduce CV risk. He elegantly reviewed the molecular pathways activated by PPARs, noting the importance of their co-activators and co-repressors that further influence gene transcription.

Dormandy and European colleagues performed a sub-analysis of the larger PROactive study to compare CVD outcome rates according to the presence of peripheral arterial disease

(PAD) at baseline (abstract 302-OR). From the total population of 5,238 patients, 1,274 had PAD (n=619 on pioglitazone and n=655 on placebo). When compared to those with no PAD at baseline, patients with PAD showed significantly higher rates of the primary endpoint (disease- and procedural-specific events), main secondary endpoint (disease-specific events), all-cause mortality (all $p < 0.0001$), and stroke ($p = 0.0175$). In patients with no PAD at baseline, the event rates of the primary endpoint ($p = 0.0160$), main secondary endpoint ($p = 0.0453$), and acute coronary syndrome ($p = 0.0287$) were significantly lower with pioglitazone vs. placebo. Interestingly, this beneficial effect of pioglitazone was not seen in patients with baseline PAD.

In a late-breaking presentation on Monday, June 9th, Dr. Ralph DeFronzo presented the findings of the Actos Now for the Prevention of Diabetes (ACT NOW) study. This study tested the hypothesis that pioglitazone would reduce progression to Type 2 diabetes in patients with impaired glucose tolerance (IGT). This was a prospective, randomized, placebo-controlled trial. Patient entry criteria included the presence of IGT with fasting plasma glucose 95-125 mg/dl, and at least one additional risk factor (metabolic syndrome feature, family history of diabetes, history of gestational diabetes or polycystic ovary disease, or a member of a high-risk ethnic group). The primary outcome measure was time to conversion to Type 2 diabetes. 602 patients were randomized into pioglitazone 45 mg (n=303) or placebo (n=299), with a mean follow-up duration of 2.6 years. At baseline the two groups were almost identical for all physical, metabolic, and CV parameters.

The rate of conversion from IGT to Type 2 diabetes in placebo-treated patients was 6.8% per year, as compared to 1.5% per year in the pioglitazone treated group. This represented a marked relative risk reduction of 81% (HR 0.19; [0.09, 0.39]; $p < 0.00001$). Clinicians would need to treat between three to four IGT patients for one year to prevent one case of diabetes. Adverse events reported were few other than edema, which occurred in 15% of placebo and 22% of pioglitazone patients. CV events, heart failure, death, and fractures rates were all uncommon and did not differ significantly between groups, although this study was of relatively short duration.

The ACT-NOW data, in combination with data from the DREAM trial using rosiglitazone, now provide confirmation that TZDs prevent diabetes. The more difficult challenge is whether and how these drugs should be used in high-risk individuals. There remain significant safety and cost concerns that must be considered.



The Heart of the Matter



The importance of CVD in patients with diabetes is obvious, and is reflected in the large numbers of symposia and abstract presentations at recent international diabetes meetings. There was particular emphasis on cardiac complications of diabetes at this week's meeting, with the findings from three large, randomized clinical trials being reported—ADVANCE (See page 1, Issue 2), VADT (see page 1, Issue 4), and ACCORD (see page 1).

Enumerable studies have now confirmed that blood glucose levels during acute CV events predict subsequent adverse outcomes. Most data come from studies in patients with acute coronary syndromes (ACS). There is comparatively less data in those with stroke. Golas and US colleagues reported on outcomes in 1,286 stroke patients admitted to two hospitals between 2003-07 (abstract 897-P). They restricted their analysis to patients who had at least one blood glucose (BG) determination. The patients were divided into two groups, those with first BG <130 mg/dl and those with first BG ≥130. Within these two groups, patients were further distinguished into those with and without a prior history of diabetes, based on discharge diagnoses. Admission hyperglycemia was present in 42% of patients, with an average reading of 203 ± 80 mg/dl. Two-thirds of these individuals had diabetes documented, but one-third did not. Those with hyperglycemia but no diabetes experienced an eight-fold (20% vs. 2.5%) increase in in-hospital mortality and a 40% increase in the cost of care, mainly driven by a greater than one day length of stay increase compared to normoglycemic patients (with and without diabetes) (Table 1). In contrast, hyperglycemic patients with recognized diabetes experienced a mortality increase only approximately two-fold higher (6.6%) than normoglycemic patients. It remains unclear from these data whether hyperglycemia may simply be serving as a marker of more severe strokes, and it is certainly unknown if treating hyperglycemia in stroke patients will reduce mortality. Moreover, it is not clear if the 'non-diabetic' hyperglycemic patients actually had diabetes, which had to that point eluded diagnosis—a phenomenon which may itself render these individuals at higher risk.

Sourij *et al.* from Austria and Lichtenstein assessed the prevalence of IGT in patients undergoing coronary angiography (abstract 629-P). The investigators enrolled 1,040 patients (mean age 63.7 ± 10.2 years) who underwent catheterization for evaluation of established or suspected CAD. In those without known diabetes, an oral glucose tolerance test (OGTT) was performed.

Vascular events were then tracked over a period of three years. 394 patients had normal glucose tolerance (NGT), 190 had IGT, and 456 had Type 2 diabetes (244 previously known, 212 newly diagnosed). The incidence of vascular events in NGT patients was 8.9%. In contrast, the incidence was significantly higher in those with IGT (14.9%, $p = 0.029$) and diabetes (13.4%, $p = 0.004$). In fact, vascular risk was not statistically different between the IGT and diabetes groups. Multivariate Cox regression analysis demonstrated an HR of 1.89 (95% CI 1.11, 3.24) for vascular events in patients with IGT and 1.73 (1.10, 2.74) for those with diabetes. The investigators recommended OGTT for IGT patients undergoing cardiac catheterization for purposes of CV risk stratification.

Fatty liver disease is widely prevalent in the Type 2 diabetic population. Recent data suggests that the presence of increased liver fat may increase the risk of CVD, independent of other CVD risk factors. Saluja & Saluja of India (abstract 657-P) studied 1,079 patients with Type 2 diabetes, performing liver sonography to assess the degree of steatosis. The prevalence of non-alcoholic fatty liver disease (NAFLD) was extremely high at 75%, and increased with age (67% in those <50 years and nearly 80% in those >60 years). Severity of NAFLD varied with glycemic control, with mean HbA1c of 7.3 ± 0.3%, 8.2 ± 0.6% and 9.3 ± 0.7% in those with mild, moderate, or severe disease. The prevalence of CAD was also significantly higher in those with NAFLD (34% vs. 19% in those without, $p < 0.01$) as was cerebrovascular disease (16% vs. 7%, $p < 0.01$). The group concluded that NAFLD is widely prevalent in Indian Type 2 diabetic patients, its severity linked in part to glycemic status. It also appears

to be an important CVD risk factor. A multivariate analysis, incorporating BMI, lipid levels, and glucose control was not conducted and this would have demonstrated whether liver fat may be playing an independent role. If such a role is confirmed, a new avenue to CVD prevention may be revealed.

Postprandial glucose is more tightly associated with CVD than is fasting glucose. Whether control of meal-time glucose excursions may translate into improved CV outcomes is not known. Nishimura *et al.* from Japan addressed this problem with a randomized trial of the rapid-acting analogue, aspart vs. regular insulin delivered before meals in 274 patients with Type 2 diabetes (abstract 163-P). The primary endpoint was a CV composite of MI, angina, revascularization, and transient ischemic attack (TIA)/stroke. Intermediate- or long-acting insulin was used as necessary in both groups to achieve glycemic control, and aspirin, angiotensin-renin system blockers (ACEIs, ARBs), and statins were administered according to current guidelines. Baseline characteristics were similar between groups. After a median of 4.5 years, HRs were calculated, and adjusted for age, BMI, gender, blood pressure, LDL-cholesterol, and smoking status. Post-prandial glycemia was significantly improved in the analogue group, as manifested by a 90-minute mean post-prandial glucose of 142 ± 58 mg/dl vs. 226 ± 48 mg/dl, $p < 0.05$. There was no difference, however, in fasting glucose (128 ± 42 mg/dl vs. 133 ± 54 mg/dl) or in HbA1c (7.5% in both groups). The cumulative event rate was dramatically reduced from 11.1% to 6.4% in those receiving rapid analogue therapy (HR=0.57, [0.34-0.95]). There was no difference, however, in CV or all-cause mortality.

In a related trial with opposite findings, Dr. Itmar Raz from Israel presented preliminary data

Table 1. In-Hospital Outcomes in Stroke Patients by Admission Blood Glucose

	Normoglycemic Group (Admission Blood Glucose < 130 mg/dl)		Hyperglycemic Group (Admission Blood Glucose ≥ 130 mg/dl)	
	No Diabetes (n=568)	Diabetes (n=170)	No Diabetes (n=180)	Diabetes (n=364)
Mean admission (first) BG (mg/dl)	103 ± 14	100 ± 124	165 ± 47	221 ± 86
Mean in-hospital BG (mg/dl)	107 ± 17	134 ± 29	139 ± 27	177 ± 43
Actual mortality (%)	2.5	2.5	20.0	6.6
Risk-adjusted expected mortality (%)	7.8	7.7	14.0	11.3
LOS (d)	7.0	7.0	8.3	8.4
Risk-adjusted expected LOS	7.2	7.1	9.0	8.8
Cost of care (\$)	23,817	21,799	30,942	28,957

BG=blood glucose, LOS=length of stay.

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The Heart of the Matter

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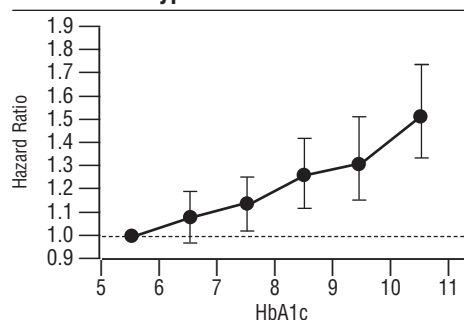
from the multinational HEART2D study in a "Late Breaker" abstract session on Monday, June 9th. This trial was designed to assess the CV impact of two treatment strategies for blood glucose control in Type 2 diabetic patients with recent acute MI. The hypothesis was, as in the Nishimura presentation, that a strategy directed at controlling post-prandial glucose would reduce recurrent CV events to a greater extent than one targeted at fasting glucose. In all, 1,116 patients were enrolled and randomized to one of two treatments. In one arm, post-prandial glucose was addressed with another rapid-acting insulin analogue, lispro, dosed pre-meal and titrated to minimize glucose excursions; in the other, basal insulin alone (NPH BID or glargine QD) was used, titrated to fasting and pre-meal glucose levels. Both insulins were adjusted per algorithm. The mean age was 61 years and the baseline HbA1c was 8.3-8.4%. In both groups, a near identical HbA1c was achieved (7.7-7.8%), but, as expected, fasting glucose was more stringently controlled with the basal insulin regimen, whereas post-prandial glucose was reduced to a greater extent with the rapid analogue. Notably, however, the predicted wide separation between the groups for post-prandial glucose was not achieved. Ultimately, there was no effect (HR 0.98 [0.80, 1.21]) from the prandial regimen on the primary endpoint, a CV composite involving CV mortality, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for ACS. We note that the main difference between the Japanese study and HEART-2D was that, in the former, both groups received some basal insulin, with the primary difference between groups being the type (and rapidity of action) of the mealtime insulin. In HEART-2D, the insulin regimens were, essentially, 'either-or.' One might speculate about whether better outcomes could have been achieved had basal insulin been used in addition to the lispro. Nonetheless, the negative outcome of HEART-2D gives no support to the long-held theory that post-prandial hyper-

glycemia is more detrimental to the vasculature than fasting hyperglycemia.

Dozens of studies have demonstrated a linear relationship between glucose levels and CV event rates. Drury and collaborators from New Zealand have now presented perhaps the largest work of this kind (abstract 164-OR). Their prospective study was conducted between 2000-05 and explored the relationship between HbA1c and CVD among 48,444 Type 2 diabetic patients in New Zealand without known CVD at baseline. The primary outcome was time to first recorded fatal or non-fatal CVD event (coronary heart disease, stroke, TIA, or peripheral vascular disease), as assessed by medical records. Cox proportional hazard models incorporated age at diagnosis, duration of diabetes, gender, ethnicity, socioeconomic status, smoking, systolic blood pressure, total cholesterol:HDL-cholesterol ratio, BMI, and urine albumin:creatinine ratio. The median age was 60 years, duration of diabetes three years, median BMI 31 kg/m², HbA1c 7.1%, and BP 138/81 mmHg. Fifteen percent were current smokers. Overall, 11.7% of patients suffered a primary event. For every 1% increase in HbA1c, there was a concomitant 8% increase in the risk of a CVD event ($p < 0.001$) (Figure 2). Importantly, there appeared to be no threshold for risk, down to an HbA1c of 5.5%. These data conclusively reveal a linear relationship between CVD events and HbA1c. Why it's been so difficult to demonstrate that glucose reduction mitigates this risk is not clear.

Wackers *et al.* from US & Canada reported the final outcome results from the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study (abstract 169-OR). In DIAD, 1,123 patients with Type 2 diabetes but no history or symptoms of CAD were randomly assigned to undergo screening pharmacological (adenosine) stress testing with nuclear myocardial perfusion imaging (MPI) with sestamibi vs. no screening. This group had previously reported a 22% rate of silent myocardial ischemia in the screened cohort. Mean age was 61 ± 7 years, diabetes duration 8 ± 7 years, 54% were male, and 22%

Figure 2. Risk of First CVD Event by HbA1c in Type 2 Diabetes Patients



from ethnic minorities; mean HbA1c was 7.1 ± 1.5%. Subsequent medical care was left to the discretion of the primary care provider. Over an average follow-up of 4.8 years, CVD event rates (non-fatal MI or CV death) were extremely low: 15/558 (2.0%) vs. 16/551 (2.1%) in the screened and unscreened groups, respectively (~5% per year). In patients who underwent screening, those with moderate to large MPI defects and those with non-perfusion abnormalities (ischemic ECG changes during adenosine infusion) had higher event rates than those with a negative MPI (13.2% and 6.7%, respectively; $p = 0.01$). Predictors of cardiac events included: male gender (HR 3.1, $p = 0.02$), peripheral vascular disease (HR 3.3, $p = 0.007$), LDL-cholesterol (HR 1.18 per 10 mg/dl increase, $p = 0.003$), serum creatinine (HR 1.17 per 0.1 mg/dl increase, $p < 0.0001$), heart rate response to standing (a measure of cardiac autonomic dysfunction) (HR 3.3, $p = 0.002$), moderate/large MPI defect (HR 6.6, $p = 0.001$), and nonperfusion abnormality (HR 5.2, $p = 0.03$). However, there were no outcome differences between the screened and unscreened groups. The investigators concluded that the Type 2 diabetic cohort in DIAD had an unexpectedly favorable five-year prognosis on contemporary therapies and that, overall, routine screening for CAD appeared to be an ineffective strategy once subsequent cardiac events were assessed.



So Many Posters, So Little Time....



There are ongoing research efforts to develop less invasive glucose monitoring methods. Mueller *et al.* (US & Germany) evaluated the utility of a subconjunctival glucose sensor in a five diabetic patients (abstract 41-OR). The implants contain fluorophore molecules that are displaced in the presence of rising glucose concentrations, causing an increase in fluorescence, measured by a hand-held fluorophotometer. There was excellent correlation

($r = 0.96$) between subconjunctival interstitial fluid glucose and blood glucose. The sensors were well tolerated over the five-month study. A novel glucose "breath test" was the subject of presentations made by Lee *et al.* from California (abstract 412-P) and Walton *et al.* from the UK (abstract 44-OR). Each actually measures exhaled volatile organic compounds

that increase in concert with plasma glucose concentrations. The investigators also reported excellent correlations (eg, $r = 0.97$ in Lee's study) albeit also in small samples under tightly controlled conditions. It is too early to know whether these investigational non-invasive glucose monitors will ever be shown to be accurate and reliable enough for clinical use.

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