

Diabetes2007

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Diabetes for the Cardiologist: Understanding the Epidemic



Important data on diabetes presented at the 2007 Scientific Sessions of the American Heart Association come to you in **Diabetes 2007**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals North America, Inc., Merck & Co., Inc., Novo Nordisk Inc., and Amylin Pharmaceuticals, Inc./Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2007** will be followed by a **Diabetes 2007** booklet (EASD and AHA 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 2007 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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In a symposium entitled, "Diabetes from Bench to Bedside: Understanding the Epidemic," speakers from around the US gathered to address a medical phenomenon of global impact—the growing obesity and diabetes rates throughout the world and their anticipated effect on the prevalence of cardiovascular diseases (CVD). Two speakers, Dr. Daniel Kelly from the University of Washington in St. Louis and Dr. Steven Marso from St Luke's Health System in Kansas City tackled the problem using the complementary approaches of basic and clinical science. Dr. Kelly described the epidemic of diabetes as a manifestation of a "fat overload" state, with several organs developing increased fat content after the body's usual storage depot, namely the adipocyte, is filled to capacity. When this occurs in skeletal muscle, insulin resistance and decreased glucose uptake is the primary manifestation. When involving the liver, steatohepatitis occurs. In the pancreatic islet, beta-cell dysfunction develops, resulting in hyperglycemia. And when such "lipotoxicity" affects the heart, a series of maladaptive molecular events are activated, resulting in a metabolic switch to increased fatty acid uptake and oxidation in preference to the more efficient glucose oxidation. These steps involve the up-regulation of fatty acid transporters and the nuclear transcription factor, PPAR- α , which drives the oxidative changes. There is indirect evidence that, over time, ventricular dysfunction may result. This might explain in part the increased rates of heart failure in the diabetic population.

In a series of elegant experiments in his laboratory, Dr. Kelly's group overexpressed PPAR- α in the hearts of transgenic mice, which were then placed on a high-fat diet. Not surprisingly, the murine cardiomyocyte increased its uptake and oxidation of fatty acids. Microscopically, these metabolic changes were accompanied by an increase in myocardial triglyceride content, and, over time, significant systolic and diastolic left ventricular impairment. Dr. Kelly related the changes in this transgenic model to that which

occurs in the lipotoxic human with obesity, insulin resistance, and diabetes.

In a follow-up series of experiments, when these mice were subsequently crossed with a separate strain engineered with a targeted defect in a cardiac fatty acid transporter, the metabolic, histological, and hemodynamic derangements were entirely prevented. In this model, despite increased expression of PPAR- α , uptake of fatty acid into cardiac cells was inhibited, not allowing for increased oxidation to occur. The mice were therefore rescued from the physiology of fat overload in the heart. In separate experiments, Dr. Kelly's group engineered mice to overexpress another nuclear receptor, PPAR- δ (often referred to as PPAR- β), again targeted to heart tissue. This model appeared to be protected against the cardiotoxicity from high-fat diet. Interestingly, this model also appeared to be partially resistant to ischemic injury during coronary artery occlusion experiments.

Dr. Kelly summarized his talk by describing the current increased obesity and diabetes rates as a "problem of bounty"—too many calories, and too much fat, with consequent activation of innate systems to handle the excess—systems that are quickly overwhelmed. His transgenic models might inform the development of effective pharmacological therapies for both diabetes and heart disease.

Dr. Marso next focused on the clinical aspects of the diabetic heart. He described the well-known fact that the person with diabetes is at increased risk for a variety of CVDs, including coronary artery disease (CAD), heart failure, and stroke. Moreover, when cardiovascular events occur, those with diabetes are at increased risk of adverse outcomes. The reasons for this phenomenon are multi-factorial, as outlined in Table 1. Importantly, it has been estimated that a child born in the US in the year 2000 has approximately a 1 in 3 chance of developing diabetes in his or her lifetime. With 19 million diabetics in this country already, and another 41 million with

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pre-diabetes (i.e., impaired glucose tolerance or impaired fasting glucose), the potential future cardiovascular impact is extremely concerning.

Data from the acute coronary syndrome (ACS) setting were next reviewed. When assessed using an oral glucose tolerance test, two out of three patients admitted with acute myocardial infarction (AMI) have either diabetes (previously recognized or newly diagnosed) or impaired glucose tolerance. In addition, hyperglycemia during AMI is an independent risk factor for both short-term and long-term mortality, as well as for the development of subsequent heart failure. Aggressive glycemic management during AMI has been associated with improved clinical outcomes, and several guidelines encourage intensive approaches including intravenous insulin.

Table 1. Diabetes + Acute Coronary Syndrome: Reasons for Worse Patient Outcomes

- The presence of more extensive CAD
- Increased reinfarction rates
- Impaired vascular collateralization
- Reduced post-PCI coronary flow rates
- Impaired ischemic preconditioning
- Underlying "diabetic cardiomyopathy"
- Frequently coexisting diastolic dysfunction
- Suboptimal use of evidence-based treatment strategies



Given the events over the past year concerning new safety concerns with thiazolidinedione (TZD) medications, specifically rosiglitazone, there is increasing interest in the cardiovascular impact of all anti-hyperglycemic therapies. Several presentations this week explored this issue with both established and emerging medications.

Patch *et al.* from the Mayo Clinic conducted a community-based epidemiological study to assess for potential adverse effects of sulfonylurea (SU) drugs on outcomes following AMI. This has been a contentious issue for decades, ever since the publication of the University Group Diabetes Project trial in the 1970s. This study, which has been roundly criticized, suggested an increased cardiovascular mortality with the older SU, tolbutamide, and led to a "black box" warning on all members of this class. Since then, the UK

Overall, however, the use of insulin, especially IV insulin, remains uncommon during most AMI hospitalizations in the US.

Dr. Marso then reviewed a series of clinical trials that have convincingly demonstrated that strategies to reduce cardiovascular risk in the setting of diabetes are highly effective, especially with regard to the management of dyslipidemia, hypertension, and anti-platelet therapy. The effects of anti-hyperglycemic therapy, in contrast, have been inconsistent, with some studies suggesting modest benefit (metformin in the UKPDS; insulin in DIGAMI; acarbose in STOP-NIDDM; pioglitazone in PROactive) and others (sulfonylureas and insulin in the UKPDS) showing no statistically significant impact. There is no data yet with some of the newer therapeutic approaches (i.e., GLP-1 mimetics [exenatide], DPP-4 inhibitors [sitagliptin]). Several ongoing or upcoming clinical trials were previewed, including ORIGIN, which will examine the cardiovascular impact of early diabetes therapy with basal insulin; ACE, to look at CVD endpoints with acarbose therapy; and INTENSIVE, which will explore the effect on infarct size, as assessed by PET scanning, of aggressive insulin infusion during AMI.

In his concluding remarks, Dr. Marso encouraged the audience to recognize the presence of diabetes more often, since approximately one-third of all diabetic patients still remain undiagnosed. Because of the high prevalence of diabetes and impaired glucose tolerance in patients admitted with ACS, the cardiologist may indeed be in a unique position to raise this possibility. If diabetes is present, treatment should be initiated.

Diabetes Drugs & the Heart

Prospective Diabetes Study (UKPDS) appeared to vindicate these agents, since their use therein was associated with a non-significant 14% relative reduction in the risk of MI. Retrospective surveys have subsequently been conflicting. Most recently, the A Diabetes Outcome Progression Trial (ADOPT) revealed the sulfonylureas to be as safe as metformin and arguably safer than rosiglitazone.

In the Mayo study, all AMIs that occurred in Olmsted County, Minnesota between 1979 and 2002 were confirmed based on evidence including symptoms, ECG findings, and biomarkers. Among 2,732 persons with AMI (mean age 70 ± 12 years, 44% men), 486 (18%) had diabetes and were treated with second generation SUs (24%), insulin (47%), or diet alone (22%). Not surprisingly, diabetic patients were more likely to be overweight and hyperlipidemic than non-diabetic patients. They also were more likely to have received reperfusion

Table 2. CVD Risk Reduction Strategies in Diabetes

<i>Glucose</i>	
■	HbA1c <7%
<i>Lipids</i>	
■	LDL-cholesterol <100 mg/dl (consider <70/mg/dl in those with overt CVD)
■	TGs <150 mg/dl
■	HDL >40 mg/dl (men); >50 mg/dl (women)
<i>Blood pressure</i>	
■	Systolic <130 mmHg
■	Diastolic <80 mmHg
<i>Anti-platelet therapy</i>	
■	Daily aspirin
<i>Lifestyle</i>	
■	Healthy diet
■	Weight reduction
■	Increased physical activity

If pre-diabetes is uncovered, lifestyle change should be encouraged. He also emphasized the need for evidence-based and aggressive CVD prevention strategies in all patients, especially in those who have already experienced a CVD event, a particularly high-risk cohort. These recommendations are summarized in Table 2. Finally, the scientific community and the pharmaceutical industry were challenged to design and carry out long-term efficacy and safety trials of all new anti-hyperglycemic drugs to ensure their proper use in the context of rational therapeutic regimens for our patients.



therapy during the hospitalization. Within one year from the MI, 518 patients had died. Diabetic patients taking SUs actually experienced better survival than patients without diabetes, while those diabetic patients on diet alone or insulin experienced worse survival (Figure 1). After adjustments for age, duration of diabetes, gender, and reperfusion status, an excess risk of death was detected among persons with insulin-treated diabetes, which was not found in those treated with SUs or diet. The investigators concluded that their data do not support any concern for adverse clinical impact of SU therapy in diabetic patients following AMI.

Diamond and Saul from Cedars-Sinai challenged the findings of Nissen and Wolski's widely publicized meta-analysis of rosiglitazone and cardiovascular outcomes (see *Diabetes 2007*, Volume 15, A "Sensitive" Topic!), which excluded

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four trials from the MI analysis and 19 trials from the cardiovascular mortality analysis because no events were observed. Diamond and Saul sought to determine if these exclusions biased the results, by comparing the index study to a Bayesian meta-analysis of the entire cohort of 42 trials. Instead of excluding studies without events, a statistical technique known as a continuity correction that adjusts for values of zero was employed with both fixed and random effects models. The results of this re-analysis are shown in Table 3. With odds ratios (OR) for MI now ranging from 1.43 to 1.22 and for cardiovascular death now from 1.64 to 1.13, it was clear that the corrected models substantially reduced the ORs while simultaneously reducing the confidence intervals (CIs). While the point estimates for each remained in excess of 1, none of the new p-values were significant at the $p < 0.05$ standard. The researchers felt that, given the fragility of the effect sizes and CIs, the charge that rosiglitazone increases the risk of cardiac adverse events is not supported by these revised analyses. The findings of Nissen and Wolski were likely the result, therefore, of excluding the trials without events from the original analysis. More data, preferably from randomized clinical trials (e.g., RECORD, BARI-2D), will be needed to better understand the role of rosiglitazone on cardiovascular risk.

Murakami and Japanese collaborators studied the long-term effects of TZD therapy on atherosclerosis in patients with diabetes already being treated with statins (abstract 2454). Thirty Type 2 diabetic patients with stable CAD were randomized to a TZD group where they received either troglitazone (400 mg/day; no longer available) or pioglitazone (30 mg/day), or to a group treated with non-TZD medications. Flow-mediated dilation (FMD) of brachial artery after five minutes of forearm occlusion, dilation of brachial artery after sublingual administration of nitroglycerin (NTG),

Table 3. Rosiglitazone and Cardiovascular Outcomes

Meta-Analysis	Myocardial Infarction		Cardiovascular Death	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Nissen and Wolski	1.43*	1.03-1.98	1.64	0.98-2.74
Fixed (uncorrected)	1.36	1.00-1.84	1.51	0.94-2.44
Random (uncorrected)	1.34	0.97-1.84	1.46	0.88-2.42
Fixed (corrected)	1.23	0.90-1.67	1.19	0.73-1.94
Random (corrected)	1.23	0.89-1.69	1.17	0.71-1.93
Bayesian (corrected)	1.22	0.91-1.65	1.13	0.75-1.71

* All odds ratios refer to risk of rosiglitazone-assigned patients vs. patients assigned to comparator.

both measures of endothelial function, and intima-media thickness (IMT) of the common carotid artery using high-resolution ultrasonography were each assessed serially over a period of greater than two years. Changes in FMD, NTG, and IMT were compared between the two groups. All the patients in the TZD group (n=15) manifested better glycemic control as compared to the non-TZD group. FMD (%) increased in the TZD group ($p < 0.01$) but remained unchanged in the non-TZD group ($p = 0.84$). NTG (%) remained unchanged in both groups. IMT (mm) decreased with TZDs ($p = 0.04$) but remained unchanged without ($p = 0.21$). There was no relationship between glucose reduction and these vascular effects. The investigators claimed that their results suggested long-term therapy with a TZD in diabetic patients receiving statins additionally improved endothelial function and reduced carotid atherosclerosis, independent of glycemic benefit. These results are provocative but need to be confirmed by more trials examining actual CVD endpoints instead of simply surrogate markers. We are actually surprised that any statistically significant changes could be demonstrated with such small patient numbers. On the other hand, the data are consistent with carotid IMT data seen in the CHICAGO trial (reported in this newsletter from last year's AHA meeting in Chicago).

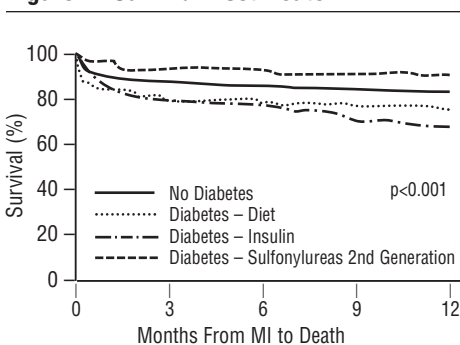
In the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) study, pioglitazone was compared to glimepiride in 462 patients with Type 2 diabetes, and carotid IMT (CIMT) was measured using ultrasonography. Despite equivalent glucose-lowering effect, pioglitazone-treated patients had reduced progression of CIMT as compared with those treated with the sulfonylurea. In fact, over the course of the 72-week trial, there was no appreciable change in CIMT with pioglitazone, whereas it increased with glimepiride (difference between groups, 0.0134 mm [$p = 0.02$]). Davidson and US colleagues sought to determine the baseline and on-treatment predictors of this benefit.

The researchers adjusted for a variety of individual predictors of change in CIMT, including baseline age, diabetes duration, weight, BMI, waist/hip ratio, metabolic syndrome components, smoking status, blood pressure, statin use, lipids, free-fatty acids, ApoB, ApoA1, HbA1c, fasting plasma glucose, insulin, pro-insulin, and hs-CRP. Inclusion of baseline values for cardiovascular risk parameters did not affect the significance of the pioglitazone effect on CIMT. At six months, treatment with pioglitazone significantly ($p < 0.01$) increased HDL (6.3 mg/dl) and decreased triglycerides (-22.6 mg/dl), HbA1c (-0.3%), fasting plasma glucose (-15 mg/dl), insulin (-48.3 pmol/l), pro-insulin (-23.3 pmol/l), and hs-CRP (-0.6 mg/l) relative to baseline. However, only the inclusion of changes in HDL and insulin levels in the model resulted in a loss of significance for the treatment effect on CIMT. Adjustment for the changes in HDL and insulin levels resulted in decreases of 30% and 20%, respectively, in the regression coefficient, rendering the treatment effect of pioglitazone on CIMT non-significant. The researchers concluded that, of all the clinical and biochemical parameters evaluated, only the changes in HDL and insulin levels with pioglitazone therapy explained a sizable component of the drug's treatment benefit on CIMT progression.

Morrow and American colleagues reported intriguing glycemic data from the MERLIN-TIMI 36 study, which assessed the cardiovascular efficacy and safety of the anti-anginal drug, ranolazine, in ACS patients (abstract 2453). This drug, at one time felt to be a fatty acid oxidation inhibitor, is now believed to exert its anti-ischemic effect through inhibition of late sodium currents in the contracting myocardium. As a consequence of this activity, calcium influx into cardiomyocytes is impeded, resulting in reduced diastolic tension. In earlier studies a modest benefit in glycemic parameters was also seen in diabetic patients treated with this drug.

In MERLIN, treatment-associated HbA1c (%) and the time to onset of worsening hyper-

Figure 1. Survival Post-Acute MI



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glycemia (>1% increase in HbA1c) were compared in patients with non-ST elevation ACS who were randomized to ranolazine vs. placebo and followed for one year. Among 4,306 patients with evaluable data, ranolazine significantly reduced HbA1c at four months compared with placebo (5.9 vs. 6.2%, Δ from baseline -0.30 vs. -0.04%, $p=0.001$). In diabetic patients on standard therapy (mean of ≥ 2 anti-hyperglycemic agents: 56% oral agents, 28% insulin), HbA1c declined from 7.5 to 6.8% (Δ from baseline -0.64%, $p<0.001$) (Figure 2). Also, worsening of hyperglycemia at one year was less likely to occur in diabetic patients treated with ranolazine (14.2% vs. 20.6%; HR 0.63, 95% CI 0.51-0.77, $p<0.001$). There was also some suggestion of diabetes prevention effects in those patients without diabetes at baseline; the incidence of new fasting glucose >110 mg/dl or HbA1c $\geq 6\%$ was 31.8% with ranolazine vs. 41.2% with placebo (HR 0.68, 95% CI 0.53-0.88; $p=0.003$). (We would point out that these cutpoints are not traditional ones employed in diabetes prevention trials.) Of note, the prevalence of hypoglycemia as reported by patients was similar between treatment groups (3% each). The mechanism of this effect is currently under investigation. If such efficacy is confirmed in a separate diabetes treatment trial, this drug, with demonstrated cardiovascular safety in a CAD population, may be an attractive option, particularly in light of recent concerns regarding currently available agents. A more sustained difference from placebo beyond eight months will be necessary, however.

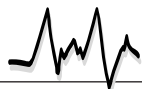
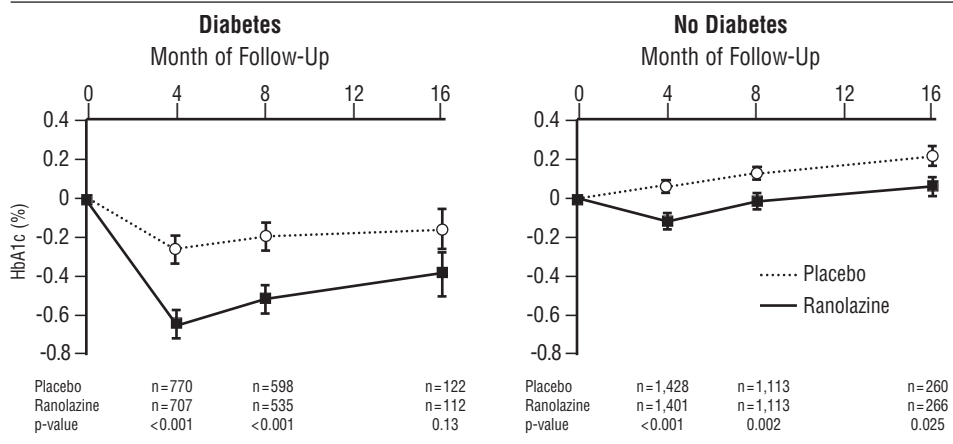
Kosiborod and US colleagues reported an interesting observation concerning the safety

of two insulin types (abstract 3737). It is widely recognized that insulin glargine causes modestly reduced hypoglycemia as compared with NPH in diabetic patients. It is not clear whether these changes might indicate any specific advantage from a cardiovascular standpoint. The investigators employed a national managed care administrative database, focusing on those patients with Type 2 diabetes who were on oral antihyperglycemic agents within six months prior to initiating either insulin glargine ($n=15,039$) or NPH ($n=5,666$) and who had at least 12 months of subsequent continuous plan enrollment between 2001-2005. The rates of subsequent MI events were then compared using a Cox proportional hazards model following initiation of glargine vs. NPH, after adjusting for baseline clinical characteristics, including demographics, concomitant medications, and baseline HbA1c.

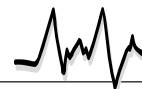
The mean age of the study population was 56 years, with approximately half being women.

The mean duration of follow up was two years. During the first year after the initiation of insulin, 8.7% patients on NPH vs. 7.5% on glargine had at least one claim for hypoglycemia (OR=1.17, 95% CI 1.05-1.31). In the unadjusted analysis, the prevalence of MI events was 4.4% with glargine vs. 7.7% with NPH ($p<0.0001$). After multivariable adjustment, the glargine group still had a lower risk of MI (HR=0.78, 95% CI 0.64-0.95), a difference that persisted even after taking into account the hypoglycemic episodes (HR=0.79, 95% CI 0.65-0.96). The investigators concluded that insulin glargine therapy is associated with reduced risk of MI as compared with NPH therapy, not accounted for by less hypoglycemia. The pathophysiological explanation for these findings was not offered. We find these results curious and wonder about baseline confounders, since the older NPH may be used by a different patient type than that prescribed glargine.

Figure 2. Change in HbA1c (%) with Ranolazine



Hyperglycemia During AMI: Identification and Implications



There continues to be interest in the cardiology community concerning the management of hyperglycemia during cardiac hospitalizations. Hyperglycemia is widely prevalent during admissions for AMI and appears to correlate almost linearly with mortality, more so, interestingly enough, in patients *without* a prior history of diabetes. Whether elevated blood glucose in these patients is a mediator or simply a marker of adverse outcomes is not completely clear. Randomized clinical trials using intensive insulin infusion therapy have had mixed results.

One question that appears to have been answered by Kosiborod and American collaborators

is whether the mean blood glucose during the entire hospitalization for AMI is a better predictor of outcomes than is admission blood glucose (abstract 3583). If not, that might suggest that hyperglycemia in this setting is nothing more than a surrogate for degree of illness (i.e., extent of infarction). This group evaluated 16,871 AMI patients (29% with diabetes) hospitalized in 40 hospitals from 01/00-12/05, using Cerner Corporation's Health Facts® database. Logistic regressions were performed using three metrics of blood glucose control: simple mean blood glucose; time-averaged glucose (similar to an "area under the curve" for glucose); and, the

hyperglycemia index (a time-average of only hyperglycemic values). Each was evaluated over three time "windows" (first 24 hours, first 48 hours, and the entire hospitalization). The metrics were then compared to the admission glucose for ability to predict mortality. Each of the average 'glucometrics' was found to be a better predictor of in-hospital mortality than admission glucose, and their discriminatory capacity improved as the window length increased. There was little difference amongst the metrics, allowing the researchers to conclude that mean hospitalization glucose appeared to be the most practical metric to use clinically to assess mortality risk.

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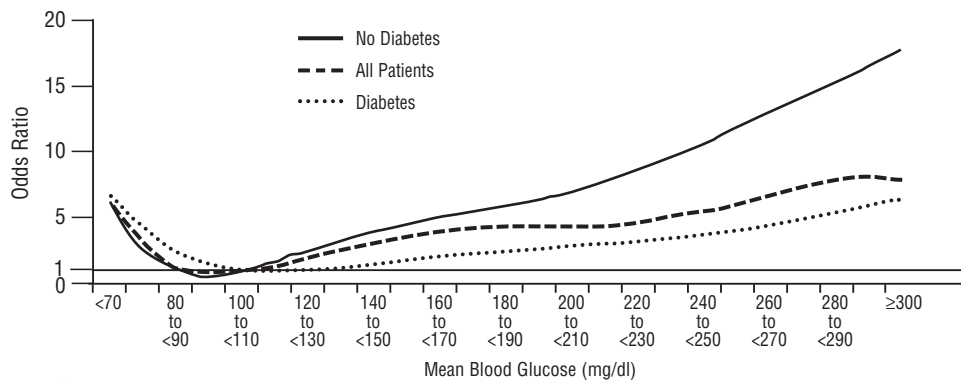
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This same group proceeded to further evaluate the nature of the relationship between average hospitalization blood glucose during AMI and inpatient mortality, adjusting for multiple demographic and clinical factors and repeating the analyses in diabetic and non-diabetic subgroups (abstract 3775). In contrast to previous findings, a true “J-shaped” relationship was observed (Figure 3). Mortality increased with mean glucose >120 mg/dl as well as mean glucose <80 mg/dl. As has been previously shown, the slope of the relationship was much steeper in those without a documented history of diabetes. The researchers concluded that average hospitalization blood glucose is a powerful predictor of short-term clinical outcomes during AMI and that both persistent hyper- and hypoglycemia are associated with worsened prognosis. Further investigation to determine the effects of insulin therapy in this cohort appears warranted.

In contrast to these findings, Mellbin from Sweden reported that in the DIGAMI-2 study, any symptomatic or asymptomatic blood glucose event <54 mg/dl did *not* predict any adverse clinical outcomes over a median observation period of 2.1 years. The analysis included adjustments for age, sex, smoking, previous MI and heart failure, renal function, duration of diabetes, coronary interventions, and baseline blood glucose. This intensive insulin infusion study enrolled 1,253 diabetic patients with acute MI, 947 of whom were randomized to IV insulin for at least 24 hours. Of note, the DIGAMI-2 study was ultimately underpowered to test the hypothesis that intensive insulin therapy would improve post-MI cardiac outcomes. There were ultimately no outcome differences between the treatment groups.

In a related abstract, Elhendy *et al.* from the Netherlands measured glucose and HbA1c levels in 401 patients prior to major vascular surgery to assess the effects of both diabetes and hyperglycemia on post-surgical cardiac outcomes (abstract 3765). For purposes of this study, hyperglycemia was defined as a random glucose of 100-200 mg/dl. Diabetes was defined as the use of an anti-hyperglycemic drug or a random glucose of >200 mg/dl. Myocardial ischemia was assessed during and after surgery with a continuous 72-hour 12-lead ECG monitor and troponin T levels were also measured serially post-operatively. Cardiac events (Q-wave infarction or cardiac death) were recorded after 30 days and during a follow-up period that averaged 2.5 years. Myocardial ischemia by ECG, troponin T release, and 30-day and long-term adverse cardiac events occurred in 27%,

Figure 3. Association Between Mean Blood Glucose and In-Hospital Mortality After Multivariable Adjustment*



* Reference: Mean blood glucose 100 to 109 mg/dl.

22%, 6%, and 17% of patients, respectively. After multivariate analysis, patients with hyperglycemia and diabetes were at 2.2- and 2.6-fold increased risk, respectively, for myocardial ischemia, 3.8- and 3.9-fold for troponin T release, 4.3- and 4.8-fold for 30-day cardiac events, and 1.9- and 3.1-fold for long-term cardiac events (Table 4). Patients with HbA1c >7% (n=63, 16%) were at particularly increased risk (HR=2.8, 2.1, 5.3, and 5.6, respectively). The collaborators concluded that hyperglycemia and diabetes are important risk factors for cardiac ischemic events during and after vascular surgery. Whether aggressive glucose management in the pre-operative setting can mitigate this risk is not clear from these data, but logically proposed by the research group. At a minimum, based on this study, vigilance to detect post-operative cardiac complications appears warranted in hyperglycemic patients.

Finally, cardiologists from the Karolinska Institute in Sweden were amongst the first to detect a striking increased prevalence of glucose disorders in patients admitted with AMI. In their initial paper (Norhammar *et al.*, *Lancet* 2002), 20% of patients had known diabetes; of the 80% without a documented history of diabetes, an additional 25% had newly diagnosed diabetes by oral glucose tolerance testing (OGTT), 35% had impaired glucose tolerance, and only 40% were truly normal. Taken together these data indicate that two out of three patients admitted with AMI have some abnormality of glucose tolerance. In follow-up studies, these patients as a whole, and the newly diagnosed diabetics specifically, were found to be at increased risk of subsequent ischemic events. At this week's American Heart Association meeting, results from the prospective Euro Heart Survey were presented by Anselmino and European collaborators, who

Table 4. Effect of Glycemia on Post-Surgical Cardiac Outcomes

Characteristic	Myocardial Ischemia (n=108) OR (95% CI)	Troponin T Release (n=90) OR (95% CI)	30-Day Cardiac Events (n=23) OR (95% CI)	Cardiac Events During Follow-Up* (n=69) HR (95% CI)
Normal Glucose Levels (n=220)	1.0	1.0	1.0	1.0
Increased Glucose Levels (n=112)	2.2 (1.3-3.9)	3.8 (2.1-7.0)	4.3 (1.4-13.5)	1.9 (1.0-3.7)
Diabetes (n=69)	2.6 (1.4-4.9)	3.9 (2.0-7.7)	4.8 (1.4-16.6)	3.1 (1.5-6.4)
Absolute Glucose Levels, per mmol/l ↑	1.3 (1.1-1.4)	1.4 (1.2-1.5)	1.2 (1.0-1.3)	1.1 (1.0-1.2)
HbA1c >7% (n=63)	2.8 (1.3-6.0)	2.1 (1.1-6.5)	5.3 (1.7-16.6)	5.6 (2.1-14.6)
Absolute HbA1c Levels, per % ↑	1.5 (1.2-2.0)	1.3 (1.0-1.7)	1.5 (1.1-3.8)	1.4 (1.1-1.8)

*Average of 2.5 years.

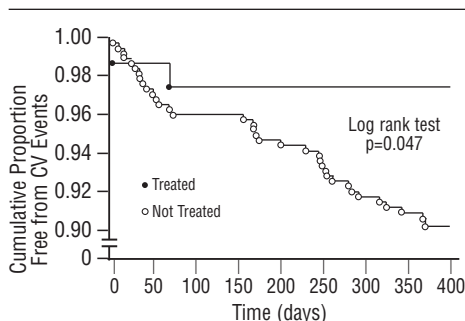
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included the Karolinska investigators (abstract 3736). 3,940 patients with CAD were enrolled at 110 centers in 25 countries; 1425 (36%) had known diabetes and 452 had newly diagnosed diabetes after undergoing an OGTT. Of these, 77 (17%) were started on pharmacological antihyperglycemic therapy (insulin 5%, oral agents 94%, both 1%) while 375 (83%) were not prescribed any glucose-lowering drug. Baseline characteristics did not differ in patients receiving or not receiving pharmacological therapy. Notably, none of the treated patients died during follow-up, as compared to 25 of those who remained untreated ($p=0.002$). Kaplan-Meier curves for CV event-free survival are shown in Figure 4. Adjusting for age, sex, previous cardiovascular disease, and use of evidence-based medications in a Cox proportional hazard regression model, patients receiving anti-hyperglycemic therapy had a lower risk for cardiovascular events during follow-up (HR 0.22, 95% CI 0.05-0.97; $p=0.041$) compared to those who remained untreated. These data, while of an observational nature, underscore the importance of identifying

Figure 4. CV Event-Free Survival in Patients Treated (or Not) With Glucose-Lowering Agents



Patients at Risk				
Treated	77	75	75	75
Not treated	375	360	354	342

and treating patients with new diabetes at the time of their acute cardiovascular event.

In a related presentation from these same investigators, outcomes in 437 patients enrolled in Euro Heart who had a prior history of diabetes were revealed, based on the anti-hyperglycemic strategy employed (abstract 3735). 139 (32%) were prescribed insulin and 197 (45%) were

given oral agents. (101 [23%] were treated with both or had missing data.) Except for a higher proportion of smokers in the oral agent group and higher percutaneous coronary intervention (PCI) rates in insulin-treated patients (43 vs. 28%, $p=0.004$), the treatment groups did not otherwise differ significantly. Specifically, there were no differences in the use of other medications, left ventricular ejection fraction, or fasting plasma glucose. After multivariable adjustments, the hazard ratios for death (HR 3.53, 95%CI 1.57-7.94; $p=0.002$) and cardiovascular events (HR 1.46, 95%CI 0.86-2.46; $p=0.15$) were higher in patients on insulin than in those on oral agents. The investigators proposed that insulin may not be the best therapy in this setting if other modalities are still available. However, this conclusion is not justified given the non-randomized nature of this study. More likely, certain unadjusted confounders, such as duration of diabetes and/or other diabetic comorbidities may have been responsible for the observed outcomes differences.

We look forward to ongoing studies in this important area from both the cardiology and diabetology communities.



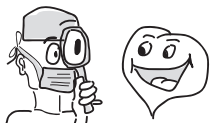
The Failing Diabetic Heart



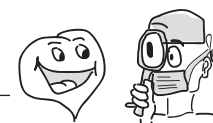
Heart failure and diabetes are frequently encountered in the same patient and their prognosis is generally poor. McKelvie and international investigators examined clinical outcomes in heart failure patients and preserved ejection fraction ($\geq 45\%$) with (27% of the population) and without diabetes (abstract 3640). The primary endpoint was time to all-cause mortality or CVD hospitalization (MI, stroke, worsening heart failure, atrial or ventricular arrhythmia, or unstable angina). A secondary endpoint included heart failure mortality and hospitalization. Among patients with diabetes, 17% and 11% had primary and heart failure events, respectively, during a one-year follow-up period. For patients without diabetes, the corresponding figures were 11% and 6%, respectively. In a multivariate analysis (which included symptoms, signs, clinical history, biochemical, and hematological findings), diabetes was a significant predictor of primary events (HR 1.48, 95% CI 1.22-1.79) and heart failure events (HR 1.67, 95% CI 1.32-2.12). These data indicate that diabetic heart failure patients with preserved ejection fraction still have significantly worse outcomes than those without diabetes and this increased risk is independent of other factors associated with a worse prognosis.

In a related presentation, Corvera-Tindel of Los Angeles described a study designed to quantify the impact of diabetes on heart rate recovery after peak exercise in heart failure patients (abstract 1816). The study population of 74 patients (mean age 62.7 ± 10.7 years; ejection fraction $27 \pm 9\%$; 59 [80%] NYHA Class II, 15 [20%] NYHA Class III-IV) was divided into four groups based on the presence or absence of diabetes and depression. Heart failure patients with diabetes demonstrated lowered reactivation of vagal tone, as measured by heart rate recovery—heart rate one minute after maximal exercise (bicycle ergometry)—than did those without diabetes ($p=0.007$, two-way ANOVA analysis controlling for age, beta-blocker use, and smoking history). There were demonstrable effects for diabetes ($F=4.53$, $p=0.03$), but not for depression, and no interactive effects of diabetes and depression on heart rate recovery. This finding suggests that the diminished vagal tone of heart failure may be exacerbated in patients with diabetes and may be accompanied by exaggerated sympathetic activation. Heart failure patients with diabetes may require extra treatment to restore autonomic balance.

Drs. Scarabelli from Michigan conducted a retrospective review of 336 patients with implantable cardioverter defibrillators (ICDs) to determine the impact of diabetes ($n=141$) on mortality (abstract 1534). Mean age was 66.8 ± 9.6 years in the overall population, with no significant difference in baseline characteristics between the diabetes and no diabetes groups, with the exceptions of beta-blocker use (84% vs. 93%, $p=0.02$, respectively), serum creatinine, and estimated glomerular filtration rate (56 ± 23 vs. 64 ± 20 ml/min/1.73m², $p=0.0005$). Although the incidence of ventricular tachycardia was not significantly different between the two groups, mortality was higher in the diabetes group (27.7% vs. 11.3% in non-diabetes group, $p=0.0002$) over a 2.5-year period. Based on multivariate logistic regression analysis, diabetes was an independent predictor of mortality (OR 2.38, 95% CI 1.30-4.36, $p=0.005$). Given that these devices are typically inserted in patients with significant left ventricular systolic dysfunction, these data likely reflect the already recognized poorer outcomes in heart failure patients with coexisting diabetes—an under-appreciated and growing clinical problem.



Predicting Events Non-Invasively



Diabetes is considered as a CAD risk equivalent and affected patients are at high risk for future cardiovascular events. The predictive role of non-invasive screening tests in this high-risk group was the subject of several presentations made at the AHA Scientific Sessions this week. Two are highlighted below.

Malik *et al.* from the US conducted a longitudinal study of 6,814 persons (29% met criteria for metabolic syndrome; 15% for diabetes) without CVD at enrollment in the Multiethnic Study of Atherosclerosis (MESA) to determine the value of coronary artery calcium (CAC) and carotid intimal medial thickness (CIMT) in predicting coronary heart disease (CHD) (abstract 3780). In patients with diabetes and individuals with metabolic syndrome, the cumulative probability of CHD events (i.e., MI and CHD death) occurring over a mean (\pm SD) follow-up interval of 2.8 ± 0.9 years was analyzed by CAC score group (0, 1-99, 100-399, and ≥ 400) and by common CIMT quartiles. Increasing CAC scores consistently predicted CHD events in persons with and without metabolic syndrome or diabetes, independently of the Framingham risk score (Table 5). Neither common nor internal CIMT quartiles independently predicted CHD events (results not shown). To improve CHD risk prediction, these data suggest a role for CAC, but not CIMT, in screening persons with metabolic syndrome or diabetes for subclinical atherosclerosis.

Bangalore *et al.* from New York city assessed

Table 5. Risk of Coronary Heart Disease Events* by CAC Score Group

	No MS/No Diabetes (n=3,800)	MS/No Diabetes (n=1,996)	Diabetes (n=1,018)
CHD Events	49	40	37
Adjusted HR† (95% CI)			
CAC 1-99	2.4 (0.6-9.2)	2.3 (0.4-14.1)	4.4 (0.9-21.5)
CAC 100-399	9.7 (2.9-31.7)	11.2 (2.4-53.2)	5.2 (1.0-27.8)
CAC 400+	13.6 (3.9-47.0)	8.2 (1.5-44.1)	6.8 (1.3-34.8)

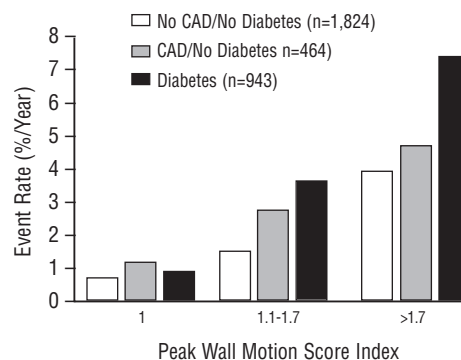
* MI and CHD death.

† Multivariable Cox regression hazard ratios for CHD events according to CAC category, adjusted for Framingham risk score and ethnicity, with CAC=0 as the reference group.

CHD=coronary heart disease, HR=hazard ratio, MS=metabolic syndrome.

the value of stress echocardiography (59% using dobutamine) in predicting CHD (endpoints of non-fatal MI and cardiac death) (abstract 3761). In 3,258 consecutive patients with/without diabetes and CHD undergoing stress echo, the cumulative probability of CHD events occurring over a mean (\pm SD) follow-up interval of 2.7 ± 1.1 years was analyzed. The validated "stress wall motion score index" (WMSI) was employed with 1=normal, 1.1-1.7=mildly to moderately abnormal, and >1.7 =markedly abnormal. Normal results of stress echocardiography predicted a benign prognosis in all patients, regardless of the presence or absence of diabetes and CAD. In those with an abnormal stress echo, diabetics had the worst prognosis, interestingly even more so than patients with known CAD (Figure 5).

Figure 5. CHD Events Based on Stress Echo Results



So Many Posters, So Little Time...



Urinary albumin excretion is one of the strongest predictors of both adverse renal and cardiovascular outcomes in patients with Type 2 diabetes. Estacio *et al.* from Colorado reported on the results of a 10-year longitudinal analysis of the prospective, randomized Appropriate Blood Pressure Control in Diabetes (ABCD) trial, including 393 Type 2 diabetic patients with hypertension (abstract 3781). In a multivariable model that adjusted for multiple cardiovascular risk factors, reduction in log urinary albumin excretion at one-year was one of the strongest predictors of reduced cardiovascular mortality (HR 1.42, 95% CI 1.06-1.92). This association was at all levels of urinary albumin excretion—normal, microalbuminuria, and macroalbuminuria. Thus, an early reduction in urinary albumin excretion rates, even

within the normal range, is associated with improvements in long-term cardiovascular mortality. These data support aggressive screening for urinary albumin excretion in all Type 2 diabetes patients and suggest that serial urinary albumin excretion measurements after initiation of therapy may have some clinical value. These data are too preliminary, however, to support treating nonhypertensive, normoalbuminuric patients with ACE inhibitors or ARBs.

The impact of low-dose aspirin (100 mg on alternate days) on the development of diabetes was assessed by Pradhan and associates from Brigham & Women Hospital, Boston (abstract 3503). The study population included 38,716 women, aged ≥ 45 years and free of diabetes and cardiovascular disease, who were enrolled in the Women's Health Study. The rationale for this

investigation is the well-documented link between inflammation, insulin resistance and beta-cell dysfunction in patients with Type 2 diabetes. Over the median follow-up period of 10 years, 1,696 cases of confirmed Type 2 diabetes accrued—849 cases in the aspirin group vs. 847 in the placebo group (HR 1.01; CI 1.00 to 1.02), indicating that chronic low-dose aspirin does not prevent the development of Type 2 diabetes in apparently healthy middle-aged and older American women. Of note, smaller studies suggesting a benefit of aspirin therapy on glucose metabolism used much higher doses, which are not safe for long-term use.

Raya *et al.*, from Washington DC assessed the impact of contrast administered during PCI on renal function in 570 consecutive diabetic patients with normal pre-procedure serum creatinine (abstract

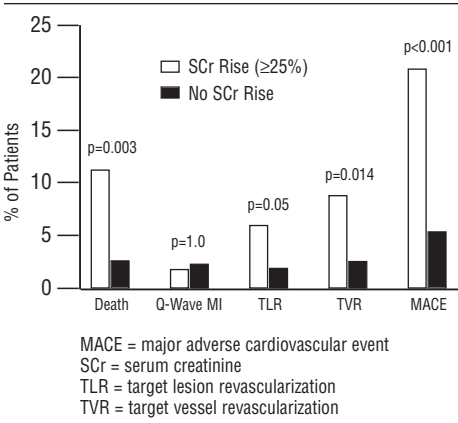
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So Many Posters...

Continued from page 7

1693). An increase in serum creatinine (defined as $\geq 25\%$ change from baseline) was observed in 12.3% of the study cohort, from which patients presenting with AMI, shock, and age >75 years were excluded. According to multivariate analysis, independent predictors of serum creatinine increase were female gender (HR 0.5, $p=0.02$), lower BMI (HR=0.9, $p=0.03$), and blood transfusion (HR=17.0, $p<0.001$). The researchers also noted that post-PCI rise in serum creatinine in diabetics with normal baseline renal function is a marker of late major adverse cardiac events (MACE) (Figure 6). These data suggest greater emphasis on monitoring for and preventing renal dysfunction in diabetic patients undergoing PCI.

Figure 6. Major Adverse Cardiac Events at Six Months Based on Serum Creatinine Following PCI



In a cross-sectional study of 16,333 adults (mean age: 59 ± 14 years; 61% women) conducted by Martins and Portuguese investigators, the

overall prevalence of metabolic syndrome (defined by NCEP-ATP III criteria) was 29% (abstract 3554). The risk was higher in women and increased with age. Hypertension and central obesity were the most common of the metabolic syndrome associated components. While the prevalence of metabolic syndrome was high in obese and overweight patients, even those in the upper range of normal weight had a higher prevalence of metabolic syndrome, as well as hypertension and fasting hyperglycemia (>110 mg/dl) than was expected (Table 6). Thus, screening in individuals with normal weight for metabolic syndrome components, especially hyperglycemia, should still be considered.

Tamis-Holland and co-investigators examined the relationship between presenting symptoms and extent of CAD in a high-risk population with Type 2 diabetes and known CAD who were enrolled in the BARI 2D trial (abstract 2868). BARI-2D is examining the comparative effects on cardiovascular outcomes of two glucose-control strategies in patients with Type 2 diabetes and stable CAD: insulin provision (sulfonylurea, insulin) vs. insulin sensitization (metformin, rosiglitazone). Of the 2,321 patients enrolled, 686 (30%) are female and 1,635 (70%) are male. There were significant differences in clinical presentation and coronary anatomy by gender. Women were more symptomatic than men, yet they had less extensive and significant CAD—despite a longer duration of diabetes (12.2 ± 9.6 vs. 9.7 ± 8.1 years, respectively; $p<0.0001$). In the six weeks prior to enrollment, 68.5% of women and 60.8% men had ischemic type chest pain ($p=0.0005$). Coronary angiography highlighted discrepancies: Women had a lower average number of significant lesions ($\geq 50\%$ stenosis) (2.3 vs. 2.8, $p<0.0001$), had a lower prevalence of multivessel

disease ($p<0.0001$), and were less likely to have significant ($\geq 50\%$) proximal LAD involvement (11.4% vs. 15.7%, $p=0.007$) or chronic total occlusion (30.8% vs. 45.2%, $p<0.0001$). These data suggest that factors other than epicardial CAD severity influence symptom presentation in women with diabetes. The impact of these findings on outcomes in BARI-2D is unknown. We look forward to the results from this landmark clinical trial in 2009.

Danchin and French coworkers assessed mortality rate following AMI over a 10-year period to determine if innovations in management have translated into improvements in outcomes (abstract 2391). The study population included 7,504 consecutive patients who presented less than 48 hours after symptom onset and were admitted to a CCU. The investigators found that the mortality in both diabetic and non-diabetic patients has decreased considerably from 1995 to 2005, but that there was a persistent gap between the groups. Kaplan-Meier survival at six months in diabetes patients increased from 76% (1995) to 79% (2000) to 84% (2005) ($p<0.001$) and in non-diabetes patients, from 85% to 89% to 91%, respectively ($p<0.001$). The relative risk reduction in mortality from 1995 to 2005 in diabetic and non-diabetic patients was 37% and 46% for STEMI and 34% and 25% for NSTEMI, respectively. These data provide encouragement but more work needs to be done to lower mortality further in the AMI population, especially those with diabetes.

In a randomized, double-blind, placebo-controlled study, simvastatin reduced both insulin sensitivity (measured using the QUICKI equation) and adiponectin levels (a cytokine that is associated with insulin sensitivity) in hypercholesterolemic patients at all doses studied (10 to 80 mg for two months) (abstract 3516). Simvastatin 10, 20, 40, and 80 mg decreased plasma adiponectin levels by 4%, 12%, 5%, and 10%, respectively, and insulin sensitivity by 5%, 8%, 6%, and 6%, respectively, relative to baseline (all $p<0.05$). The treatment effect was significant as compared with placebo ($p=0.011$ for adiponectin and $p=0.034$ for insulin sensitivity by ANOVA); a dose response for these indices was not observed despite such differences in LDL-cholesterol reduction. The importance of these modest changes is unclear, particularly since simvastatin is amongst the most widely studied HMG Co-A reductase inhibitor drugs, with demonstrated major benefits on cardiovascular risk.

Table 6. Prevalence of Metabolic Syndrome and Individual Components by BMI (kg/m²)

	Normal Weight			Overweight	Obese
	18.5-20.9	21.0-22.9	23.0-24.9	25.0-29.9	≥ 30.0
Metabolic syndrome	3.6%	10.8%	18.3%	37.1%	60.0%
Metabolic syndrome components					
Waist circumference	6.1%	12.5%	23.3%	53.3%	90.6%
Hypertriglyceridemia	10.4%	17.6%	24.4%	33.4%	41.4%
Low HDL-cholesterol	14.4%	19.7%	19.9%	25.4%	33.6%
High blood pressure	40.4%	45.8%	59.5%	70.5%	78.9%
Fasting hyperglycemia	7.0%	11.2%	16.9%	25.1%	35.1%

Each $p<0.001$.

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