Important data on diabetes presented at the 60th Annual Scientific Sessions of the American College of Cardiology come to you in Diabetes 2011, 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 2011 will be followed by a Diabetes 2011 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 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

Diabetes 2011 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Describe the mechanisms of ß-cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapies.
- Understand the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of action of diabetes therapies, their risks, benefits, and proper roles in disease management.
- Identify evolving and emerging therapeutic strategies in diabetes care.
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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Cardiovascular disease (CVD) is the number one cause of morbidity and mortality in diabetes mellitus. Therefore, development of effective strategies to reduce its risk among patients with diabetes is of critical importance. At the American College of Cardiology (ACC) meeting in New Orleans this week, Dr. Donna Polk from Hartford discussed the important link between diabetes and CVD. She opened her talk with a series of map graphics showing how the obesity epidemic in the US has been paralleled by a rapid increase in the prevalence of diabetes, estimated to affect 8.2% of the population in 2008. The common risk factor for both diabetes and CVD is, of course, abdominal obesity.

Diabetes has long been recognized to be a coronary artery disease (CAD) equivalent (although this has recently been disputed—see below). In an often-quoted, older study by Haffner et al. (NEJM 1998), the 7-year incidence of fatal and non-fatal myocardial infarction (MI) was similar among patients without diabetes but with prior MI (18.8%) and those with diabetes and no prior MI (20.2%). Not unexpectedly, the incidence of subsequent MI was highest in those with a history of both prior MI and diabetes (45.0%)—a group at extremely high risk for subsequent CVD events. Even though the relationship between diabetes and CVD is strong and well-recognized, individuals with diabetes are less likely to report concern about their risk for cardiovascular complications than for microvascular complications, such as limb amputations or blindness, which tend to occur comparatively much less frequently. In fact, over half of patients with diabetes do not realize that their disease is a risk factor for CAD.

There is a continuum of risk for cardiovascular events in patients with disorders of glucose metabolism. Insulin resistance, which is followed by impaired glucose tolerance, appears long before overt hyperglycemia supervenes. Coronary heart disease, CVD, and all-cause mortalities increase across the spectrum of patients, progressing from those with normal glucose metabolism, to those with metabolic syndrome, individuals with overt diabetes, patients with prior CVD, and, finally, those with both co-existing CVD and diabetes.

How do we prevent diabetes and avoid its complications? Dr. Polk reviewed the data from the Diabetes Prevention Program study in which patients with impaired glucose tolerance, and therefore at high risk for diabetes, were randomized to placebo, metformin therapy, or intensive lifestyle intervention (NEJM 2002). The trial demonstrated a 31% decrease in diabetes incidence with metformin and a 58% decrease with lifestyle intervention (which included 150 minutes/week of exercise and 7% body weight reduction), compared to the control group. This landmark trial showed that it is clearly possible to prevent diabetes in high-risk individuals. One can make extrapolations regarding downstream CVD risk, but the study was not designed to assess these—larger and longer-term trials would be needed to answer this important question.

Once diabetes ensues, the focus is on reduction of risk for subsequent complications. What is the impact of glycemic control on these outcomes? In epidemiological studies, there is a strong association between glucose measures (fasting plasma glucose, post-prandial glucose, HbA1c) with subsequent mortality and coronary heart disease risk. Data from the UKPDS trial (Lancet 1998) showed that intensive glucose lowering (HbA1c 7% vs. 7.9%) reduced microvascular events by 33% (p<0.01), MI by 16% (p=0.052), and any diabetes complications by 12% (p=0.03). Data from the small UKPDS subgroup of obese patients treated with metformin showed a significant decrease in MI and coronary death. Long-term follow-up from the UKPDS study showed a 15% reduction in MI (now with a p-value of 0.001), suggesting that the benefits of intensive glucose lowering may not be apparent for many years.

More recent trials (ACCORD, ADVANCE, VADT), however, demonstrate that aggressive glucose lowering with HbA1c targets below 7%

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are not associated with macrovascular benefits. Recent guidelines from the ACC/ADA/AHA 2009 still suggest a target HbA1c <7% in most uncomplicated patients and in those with macrovascular disease, and state that lower goals may be appropriate to reduce microvascular disease risk. However, the focus has shifted to individual goal setting, with less stringent targets in those with multiple comorbidities and advanced diabetes.

Although Haffner’s study showed that diabetes (at least in the 1990s) was a CAD equivalent, this assertion has been recently questioned by several studies. With comprehensive management of diabetes in clinical trials, cardiovascular event rates have been surprisingly low—have we improved the risk profile of these patients to the extent that this older assertion no longer applies? Saei and colleagues from Liechtenstein hypothesized that diabetes may simply be a marker for subclinical coronary lesions (abstract 1006-362). They prospectively followed 750 patients who presented for evaluation of stable coronary disease (baseline age 63 years, male 68%, BMI 27.2 kg/m², Type 2 diabetes 22%, HbA1c 5.8% in those without and 7.5% in those with diabetes). All patients underwent coronary angiography and 61% were found to have significant (≥50%) stenoses. As in prior studies, the presence of any coronary lesion and significant stenoses, as well as the extent of coronary disease, were increased in patients with diabetes. Over 8 years of follow-up, 257 vascular events occurred, defined as cardiovascular mortality, MI, stroke, coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI), and non-cardiac revascularization. The incidence of vascular events was higher in patients with diabetes (p < 0.001) and in those with significant coronary artery stenoses at baseline. Patients were then stratified into four groups based upon diabetes status and the presence of significant coronary lesions at baseline. The investigators found that the incidence of vascular events was similar in patients who had neither diabetes nor CAD at baseline and those who had diabetes but no CAD (Figure 1). In contrast, patients with coronary artery lesions but no diabetes and those with both diabetes and CAD had a significantly higher incidence of vascular events. The investigators stated that it is the baseline CAD status that determines cardiovascular risk in patients with Type 2 diabetes. Therefore, they concluded that diabetes per se can no longer be considered a coronary artery equivalent.

Patients with Type 2 diabetes may have atypical symptoms of CAD or may present with no symptoms at all. Similarly, women are known to present with acute MI more frequently having atypical symptoms. Yet, the presentation of patients with Type 2 diabetes and stable coronary disease has not been systematically studied. Using the large BARI-2D study, Krishnaswami and colleagues from San Jose and Pittsburgh analyzed symptoms in a large population of patients with diabetes (abstract 1074-361). BARI 2D randomized patients with Type 2 diabetes and stable CAD (defined as either a ≥50 percent stenosis of a major epicardial coronary artery associated with a positive stress test, or ≥70 percent stenosis and classic angina) in a factorial design to prompt revascularization vs. medical therapy, as well as to insulin sensitizing agents (metformin, rosiglitazone) vs. an insulin providing strategy (sulfonylureas, insulin). The trials’ overall findings showed no differences in outcomes between the groups. Among the 2319 patients evaluated in BARI 2D, 19% had typical angina, 21% had atypical symptoms, 42% had both typical and atypical symptoms, and 18% had no angina symptoms at all. In multivariable analyses, prior PCI and beta-blocker use were both associated with typical angina symptoms whereas age >60 years, male gender, regular exercise, and thiazolidinedione (TZD) use were associated with atypical symptoms or lack of symptoms. Regardless of revascularization status, men presented without symptoms more often than women. Overall, an overwhelming majority (82%) of patients with Type 2 diabetes undergoing angiography for stable CAD presented with symptoms. More than 60% of these patients with diabetes had typical angina, either with or without other atypical symptoms. Certainly, this study was limited by the original inclusion criteria for the BARI 2D trial (one of which involved having angina!) and further investigations into the association of symptoms with eventual patient outcomes will be needed.

The association between elevated HbA1c levels and the presence of CAD in patients with diabetes has been previously reported. However, there are no data on the association between HbA1c levels and angiographic severity of CAD in non-diabetic patients. Bourji and collaborators from New York studied 100 patients undergoing elective angiography with no prior history of CAD or diabetes and HbA1c <6.5% (abstract 1006-361). Twenty-five patients had CAD on coronary angiography: 12 had single vessel and 13 multi-vessel disease. Interestingly, HbA1c level did not correlate with the presence of CAD (HbA1c 5.9% vs. 5.8% in those with and without CAD, p = 0.11). Among the patients with CAD on angiography, HbA1c levels were slightly higher in those with multi-vessel disease (HbA1c 6.0%) vs. in those with single-vessel disease (HbA1c 5.8%, p = 0.005). There was no correlation between HbA1c and whether or not patients underwent revascularization. In this study, there was no significant association between HbA1c levels in patients without diabetes and the presence of CAD on coronary angiography, but the study was limited by its small size. Of note, several epidemiological studies (Norfolk Study, Ann Intern Med 2004; Atherosclerosis Risk in Communities Study, NEJM 2010) have shown that the risks for CVD events and/or mortality do not reach a nadir until the HbA1c is well within the normal range (<5%).

The role of aggressive HbA1c-lowering to improve long-term outcomes of patients with diabetes has been controversial. As mentioned above, recent trials showed no benefit of intensive glucose lowering on macrovascular events. To establish the value of pre-procedural HbA1c levels for cardiovascular complications, Goo et al. from South Korea followed a large population of patients with diabetes undergoing PCI with stent placement (abstract 2515-562). Patients from a registry of the Korean Working Group on Myocardial Infarction (n = 952) underwent PCI in 2008-2009 and were stratified according to pre-procedural HbA1c: <7% (n = 429) and >7% (n = 523). The primary outcome was major cardiovascular events at one year defined as cardiac and non-cardiac mortality, MI, and target vessel revascularization. At baseline, patients in the higher HbA1c (>7%) group were more likely to have Type 1 diabetes (45.5% vs. 26.3%, p < 0.001), larger BMI, and higher baseline blood glucose levels (201 vs. 138 mg/dl, p < 0.001). There were no differences with respect to NSTEMI vs. STEMI status, treatment at discharge with anti-platelet agents, beta-blockers, angiotensin converting enzyme (ACE)-inhibitors, or statins, and no angiographic or procedural differences between the two groups. At 1-year, HbA1c was not

Figure 1. 8-Year Vascular Event Rate by CAD and Diabetic Status

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an independent predictor of major cardiovascular events (HR 0.85, 95% CI 0.54-1.28, p=0.35) in multivariable analysis. In contrast, age, STEMI, cardiogenic shock, history of heart failure, and chronic kidney disease were all predictors in these analyses. When death, MI, and target vessel revascularization were analyzed separately, there was still no association between pre-procedural HbA1c and these outcomes. The investigators concluded that HbA1c does not predict cardiovascular morbidity in patients with diabetes and CAD undergoing PCI. We would point out that these were observational data and it is possible that post-procedural medical therapy may have impacted these associations. However, they provide further evidence that HbA1c levels in very advanced CAD may not have the same prognostic value as they do in those with less established disease.

Once CAD is present in patients with diabetes, management is aimed at secondary prevention. Subgroup analyses from prior trials suggest that patients with diabetes and multi-vessel disease have a better event-free survival after CAGB compared to PCI. The original BARI trial randomized 1,829 patients with two- or three-vessel disease to CAGB or PCI. Among a subgroup of patients with diabetes, CAGB was associated with significantly lower mortality compared to PCI at 5.4 years (19 vs. 34%) and this benefit was seen at 7 and 10 years of follow-up. Patients with diabetes requiring insulin therapy appeared more likely to benefit from CAGB. The aforementioned BARI 2D trial randomized 2,368 patients with Type 2 diabetes and stable CAD to either revascularization (CAGB or PCI, based upon cardiologist’s recommendations) and intensive medical therapy or to intensive medical therapy alone. After 5 years, mortality and major cardiovascular events did not differ between the two groups. However, in a subgroup analysis, patients in the CAGB stratum had a lower rate of major cardiovascular events in the revascularization group (22.4%) than in the medical-therapy group (30.5%).

Therefore, our evidence base is currently confined to sub-group analyses of several randomized controlled trials that overall suggest that patients with diabetes and multi-vessel CAD have better outcomes with CAGB than with PCI. Stub and Australian investigators (abstract 2512-535) compared long-term mortality using the National Death Index data in an observational study of 3,455 patients with diabetes who underwent PCI (n=1,112) or CAGB (n=2,343) between 2004-2008. Both PCI and CAGB groups had similar age, ejection fraction, and BMI. Patients undergoing CAGB were more likely to be male, dyslipidemic, hypertensive, have cerebrovascular and peripheral arterial disease, prior MI, heart failure, greater need for an intra-aortic balloon pump (IABP), and multi-vessel CAD (all p<0.0001). Over 2.2 years of follow-up, mortality was similar between the CAGB and PCI cohorts (6.0% vs. 5.4%, p=0.47). Significant predictors of mortality in multivariable analysis included age (HR 1.05 per year; 95% CI 1.03-1.06, p<0.0001), creatinine (HR 4.3 per each unit increase in creatinine; 95% CI 2.9-6.4, p<0.0001), IABP use (HR 3.0; 95% CI 1.7-5.3, p<0.0001), and prior MI (HR 1.5; 95% CI 1.1-2.1, p=0.01), but not the mode of revascularization (HR 0.99; 95% CI 0.7-1.5, p=0.94). Based upon this registry data, it appears that physicians in Australia are selecting patients for PCI and CAGB with resulting similar mortality outcomes. However, given non-randomized design, this data cannot be used as evidence for equivalent benefits of CAGB and PCI in patients with diabetes.

Patients with diabetes are clearly at high risk for CVD. Effective risk reduction depends upon comprehensive management of all of the risk factors associated with diabetes, including co-existing corona ry disease, dyslipidemia, and elevated blood pressure. Although HbA1c is associated with increased risk for CVD, the simple adage of “lower is better” is now in question. It is apparent that how glucose is lowered may matter and that overly aggressive attempts may be harmful rather than beneficial. It is also becoming clear that the effect of glucose lowering on outcomes may significantly vary in different populations (with duration of diabetes, age, comorbidities such as advanced heart failure, and established diabetic complications). More data are needed to guide us to effectively lower the risk of CVD in our patients with diabetes.

At an opening-day session on hypertension management, Drs. Stanley Franklin, University of California Irvine and William Cushman, University of Tennessee College of Medicine and VA Medical Center, Memphis, discussed whether the target blood pressure in diabetes patients should be below 130/80 mmHg, or not. This is the current blood pressure goal for diabetes patients set by both the American Diabetes Association (ADA) and Joint National Committee (JNC)-7 on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Franklin began his presentation by reminding us that cardiovascular event rates and mortality are strongly and directly related to blood pressure, regardless of age, down to at least 115/80 mmHg, below which there is little evidence of additional advantage.

The results of several hypertension studies of diabetes patients were discussed. While the benefit of blood pressure reduction to <140/80 mmHg has been shown in hypertensive patients with Type 2 diabetes (Table 1), there is no conclusive evidence, based on CVD risk reduction, for lowering of systolic blood pressure to <130 mmHg. The most recently conducted studies are summarized below.

**ADVANCE**

In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, 11,140 patients with Type 2 diabetes (mean age 66±6 years, diabetes duration 8±6 years, 32% prior history of vascular disease, BMI 28±5 kg/m²) were randomized to one of two anti-hyperglycemic treatment arms and one of two blood pressure treatment arms in a 2x2 factorial design (25% received more intensive blood pressure lowering only, 25% more intensive blood glucose lowering only, 25% both strategies, and 25% neither). Patients were followed for 5 years. The primary endpoint was a composite of major cardiovascular events (death from a cardiovascular cause, non fatal MI, nonfatal stroke) and major microvascular events (new or worsening retinopathy or nephropathy); these endpoints were assessed both jointly and individually.

In the blood pressure arm of the trial, patients were randomized to the combination of the ACE inhibitor, perindopril, plus the thiazide diuretic, indapamide (Patel et al., Lancet 2007; 370:829-40). The more aggressive program resulted in statistically significant relative benefits for the majority of the primary and secondary endpoints assessed: 9% less combined major cardiovascular and microvascular events, 14% less mortality, 18% less cardiovascular death, 21% less total renal...

**Targeting Blood Pressure**

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events, and 14% less total coronary events. Irrespective of baseline blood pressure, all patient groups experienced benefit, even those with systolic blood pressure below 130 mmHg.

ACCORD
In the blood pressure arm of ACCORD (Action to Control Cardiovascular Risk in Diabetes), 4,733 Type 2 diabetes patients at high risk for CVD (baseline mean age 62 years, blood pressure 139/76 mmHg, Cr 0.9 mg/dl, HbA1c 8.3%, BMI 32 kg/m², 34% with prior CVD, diabetes duration 10 years) were randomized to receive intensive blood pressure control or standard management (Cushman et al., NEJM 2010;362:1575-85). Intensive blood pressure control targeted a systolic blood pressure (SBP) <120 mmHg and achieved a mean level of 119.3 mmHg at one year. In the standard therapy group, the target SBP was <140 mmHg and the mean level was 133.5 mmHg at one year.

Over a ~5 follow-up period, there was a small absolute difference between groups for stroke, a pre-specified secondary outcome, which occurred at an annual rate of 0.32% in the intensive arm versus 0.53% with standard therapy (HR 0.59; 95% CI 0.39-0.89; p=0.010). Otherwise, there appeared to be no benefit from more intensive blood pressure control based on the primary outcome (i.e., nonfatal MI, nonfatal stroke, or death from cardiovascular causes) or the other secondary outcomes. Adverse events (such as hypotension) were more frequent in the intensive blood pressure group. The findings in the ACCORD trial, therefore, do not support blood pressure lowering to a target of 120/80 mmHg in patients with diabetes. Prior studies of blood pressure control in diabetic patients showed reduction in cardiovascular events with tight control, but the intensively-treated patients in these trials had much higher mean SBPs (144 mmHg) than those in ACCORD (subgroup analysis of Hypertension Optimal Treatment [HOT] trial and UKPDS). Whether or not additional lowering of blood pressure from 140/90 to the current target of 130/80 mmHg is warranted is currently not entirely clear.

It was noted that the ACCORD study was limited by possible ‘type 2’ error for cardiac events, which occurred at a lower rate than was anticipated (and upon which the study sample size and power were based). White-coat hypertension may have contributed to a healthy-cohort effect (low risk based on home measurement of blood pressure), further enhanced by high use of statins and aspirin. As a consequence, a longer evaluation period may have been required to show benefit.

INVEST
In a post-hoc analysis of INVEST (International VErapamil SR—Trandolapril Study), a large trial of hypertensive patients with CAD, outcomes in the diabetic cohort (n=6,400) were segmented by the degree of SBP control: tight (<130 mmHg), usual (131-139 mmHg), and uncontrolled (≥140 mmHg) (Cooper-DeHoff et al., JAMA 2010; 304:61-8). During 16,893 patient-years of follow-up, there was no difference between the tight and usual blood pressure control groups based on the primary endpoint (first occurrence of all-cause death, nonfatal MI, or nonfatal stroke), which occurred in 12.7% of patients in the tight-control group and 12.6% of patients in the usual-control group (adjusted HR, 1.11; 95% CI, 0.93-1.32; p=0.24). Of note, risk of all-cause mortality was actually increased among the patients with the lowest SBP values in the tight-control group (HR=2.18, p=0.02 for SBP <110 mmHg; HR=1.63, p=0.06 for SBP 110-115 mmHg), although there was no increased risk if the SBP was maintained at 115 mmHg or above.

Treatment Guidance
Lifestyle modification is the first step for blood-pressure reduction (Table 2) for diabetes patients with a blood pressure of 130-139/80-89 mmHg. For patients who do not achieve target blood pressure after 3 months of lifestyle modification and for those with more severe hypertension (≥140/≥90 mmHg), the ADA recommends pharmacotherapy with an ACE-inhibitor or an angiotensin receptor blocker (ARB), with the addition of a diuretic if needed (Figure 2). Of note, inhibitors of the renin-angiotensin system [RAS] have collateral favorably effects on the progression of diabetic nephropathy and albuminuria.) As many diabetes patients with hypertension require 3 drugs to achieve a target blood pressure of

<table>
<thead>
<tr>
<th>Study</th>
<th>Achieved Mean Blood Pressure</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS 36</td>
<td>154/87</td>
<td>144/82</td>
</tr>
<tr>
<td>ABCD</td>
<td>138/86</td>
<td>132/78</td>
</tr>
<tr>
<td>HOT</td>
<td>144/85</td>
<td>140/81</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>140/73*</td>
<td>136/73*</td>
</tr>
<tr>
<td>ACCORD</td>
<td>134/71</td>
<td>119/64</td>
</tr>
<tr>
<td>INVEST†</td>
<td>149/85</td>
<td>144/85</td>
</tr>
</tbody>
</table>

* at 60 months. † subgroup analysis.

Table 1. Impact of Systolic Blood Pressure Reduction on CVD Risk in Patients With Type 2 Diabetes

<table>
<thead>
<tr>
<th>Modification</th>
<th>SBP Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction among individuals who are overweight or obese (target BMI of &lt;18.5 to 24.9 kg/m²)</td>
<td>5-20 mmHg/10 kg weight loss</td>
</tr>
<tr>
<td>Adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan, which targets diet rich in vegetables, fruit, and low-fat dairy products</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Reduce sodium intake (&lt;1500 mg per day)</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity (30 minutes aerobic exercise most days of the week)</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderate alcohol consumption (1 drink/day for women and 2 drinks/day for men)</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

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Patients with diabetes are at higher risk for developing heart failure than those without diabetes. This relationship with heart failure is only partly explained by the co-occurrence of other risk factors, such as CAD and hypertension. There appears to be something else about diabetes per se that raises the risk for heart failure, and better glucose control seems to attenuate this risk. However, once heart failure develops in a diabetic patient, there is no evidence that tight glucose control will change the course of heart failure. Additionally, there are important therapeutic considerations in heart failure patients with respect to the use of glucose-lowering agents. For example, metformin has been previously contraindicated in heart failure due to the possible risk for lactic acidosis. This contraindication was lifted several years ago, but caution is obviously still required, and metformin should not be used in those with severe and progressive ventilricular dysfunction or acute decompensations, which can be associated with hypoxemia, hypoperfusion, and lactic acidosis.

On the other hand, thiazolidinedione use has been associated with increased fluid retention and increased risk for heart failure. These agents should therefore be avoided in patients with symptomatic heart failure and physicians should consider this risk when starting a diabetic patient on these agents. Given these concerns, it is critically important to know what benefits may be expected from glucose lowering in these patients—however, these data are presently lacking.

The prognosis of heart failure in patients with co-existing diabetes appears to be worse than among patients without diabetes. However, the exact relationship between diabetes, CAD, left ventricular ejection fraction (LVEF), and outcomes is uncertain. Saely et al. from Liechtenstein examined 629 patients with invasive ventriculography to determine their LVEF (age 63 years, male 68%, Type 2 diabetes 22%), and all patients underwent coronary angiography (abstract 1006-358).

Although baseline CAD on angiography was more frequent in patients with diabetes, there was no difference in LVEF between patients with and without diabetes (65% vs. 67%, p=0.25). Patients were followed prospectively for 8 years for vascular outcomes (vascular mortality, cardiac mortality, non-fatal MI and stroke, CABG, PCI and non-cardiac revascularizations). The incidence of vascular events was, not surprisingly, higher in the diabetic group (43.8% vs. 30.1%, p=0.003) and in those with baseline CAD by angiography (p<0.001). Likewise, LVEF was significantly predictive of vascular events in multivariable models in the entire cohort (HR 0.79, 95% CI 0.71-0.88).

However, the relationship between LVEF and vascular outcomes was significantly different based upon diabetes status (interaction p-value = 0.047). Among patients with diabetes, LVEF was not associated with vascular events (HR 1.00, p=0.71) whereas among those without diabetes, LVEF was associated with this outcome (HR 0.72, p<0.001). In summary, both angiographically determined baseline CAD and low baseline LVEF significantly predicted vascular events in patients with diabetes.
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without diabetes. In diabetic patients, baseline CAD, but not a low LVEF, predicted vascular events. Therefore, it appears that diabetes has a significant impact on the cardiovascular risk conferred by low systolic function. The reasons for this are not immediately clear, but it is possible that diastolic dysfunction may play a larger role in patients with diabetes—and this effect cannot be captured with a single standard measure of LVEF.

Tomova and colleagues from California set out to evaluate the relationship between HbA1c levels and subsequent outcomes in patients with advanced heart failure (abstract 1054-8). They followed 846 patients from the UCLA Cardiomyopathy Center between 1999-2010 for a primary endpoint of death or urgent heart transplantation after 2 years of follow-up. Patients were stratified by diabetes status and then individually grouped according to quartiles of baseline HbA1c levels: <6.4% (n=90), 6.5-7.2% (n=94), 7.3-8.5% (n=86), and >8.6% (n=88) in those with overt diabetes; and <5.6% (n=130), 5.7-6% (n=120), 6.1-6.5% (n=143), and >6.6% (n=94) in those without known diabetes. Among the entire cohort and in the diabetic patients, the incidence of the primary endpoint was lower in those in the higher quartiles of baseline HbA1c (Figure 3). In fact, diabetic patients in the two lower HbA1c quartiles (<7.3%) had significantly higher rates of death and transplantation. In a multivariable model adjusted for age, gender, BMI, and LVEF, each 1% increase in baseline HbA1c among patients with diabetes was associated with lower incidence of the primary endpoint: HR 0.86 (95% CI 0.76-0.96); in contrast, in patients without diabetes, the relationship was not significant (HR 1.07, 95% CI 0.85-1.39). This observational study suggests that in patients with advanced heart failure and diabetes, higher HbA1c levels may actually be associated with improved outcomes. The limitations of this study are its observational nature, with no data on either follow-up HbA1c values or subsequent changes in therapy. In addition, advanced heart failure may be associated with cachexia, renal failure, and other comorbidities that could result in both lower HbA1c levels and higher risk for death. Nevertheless, this provocative finding merits further investigation; new data are needed on how to best manage glucose in diabetic patients with advanced heart failure.

So Many Posters, So Little Time....

BNP Levels Affect Risk of Diabetes
BNP-type natriuretic peptide (BNP) is released primarily from the cardiac ventricles in response to myocyte stress. It is synthesized as an inactive prohormone, which is split into the active hormone BNP and an inactive N-terminal fragment (NT-proBNP). Binding of BNP to its receptors (natriuretic receptor A [NPR-A]) on the surface of target cells leads to the intracellular generation of cyclic guanosine monophosphate (cGMP), which mediates most of the peptide hormone’s biological effects. BNP is metabolized by natriuretic receptor C (NPR-C) and degraded by plasma endopeptidase. NT-proBNP is cleared mainly by renal excretion.

At a physiological level, natriuretic peptide hormones, such as BNP, have many effects, including natriuresis/diuresis, peripheral vasodilation, and inhibition of both the sympathetic nervous system and the renin-angiotensin-aldosterone axis (Table 3). Their measurement is useful in the diagnosis and prognosis assessment of various cardiometabolic disorders, particularly heart failure. And, the drug nesiritide, a recombinant form of human BNP, is now available as a therapeutic modality for compensated heart failure.

Table 3. Effects of Natriuretic Peptides

<table>
<thead>
<tr>
<th>Renal</th>
<th>Vascular</th>
<th>Cardiac</th>
<th>SNS/RAAS</th>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ GFR</td>
<td>↓ arterial tone</td>
<td>↑ myocardial relaxation</td>
<td>↑ vagal tone</td>
<td>↑ lipolysis</td>
</tr>
<tr>
<td>↓ sodium resorption</td>
<td>↓ venous tone</td>
<td>antifibrotic</td>
<td>↓ SNS activity</td>
<td>↑ insulin sensitivity (?)</td>
</tr>
<tr>
<td>antiproliferative</td>
<td>antiproliferative</td>
<td>renin release</td>
<td>aldosterone release</td>
<td></td>
</tr>
</tbody>
</table>

GFR=glomerular filtration rate, SNS=sympathetic nervous system, RAAS=renin-angiotensin-aldosterone system.

BNP (and atrial natriuretic peptide, ANP) has been shown to stimulate lipolysis via a cGMP-dependent pathway that does not involve phosphodiesterase-3B inhibition or CAMP production. In humans, a functional polymorphism in the BNP gene is associated with increased glucose levels and Type 2 diabetes risk. Wang and Framingham co-investigators have shown that prevalence of diabetes is associated with low
BNP levels after adjustments for age, BMI, hypertension, smoking status, serum creatinine, and other possible confounding factors (adjusted OR = 1.51 for men and 1.95 for women) (Circulation 2004). Framingham data have also demonstrated that low BNP levels are associated with insulin resistance.

Dr. Everett and Women’s Health Study co-investigators evaluated the impact of NT-proBNP levels on the risk of incident Type 2 diabetes using a case-cohort approach (n=491 cases, n=561 in the reference subcohort) (abstract 1149-298). Women with incident Type 2 diabetes were younger (median age 53.3 vs. 56.9 years, p<0.001) and had higher median BMI (29.4 vs. 25.0 kg/m², p<0.001) and HbA1c (5.3 vs. 5.0%, p<0.001) than controls. Median (IQR) baseline NT-proBNP levels among women with incident Type 2 diabetes (46.8 pg/mL [26.1, 83.2]) were significantly lower than among women in the reference group (66.7 pg/mL [39.3, 124.7]); p<0.001. High levels of NT-proBNP were associated with reduced risk of incident diabetes: in proportional hazards models adjusting for age, race, BMI, and renal function, women in the highest quartile of NT-proBNP had a 45% reduced risk of incident Type 2 diabetes (Model 3, Table 4). Further adjustments for family history of diabetes, menopausal status, physical activity, and alcohol use did not affect the association (Model 4). These prospective and highly preliminary data suggest a role for BNP in the development of Type 2 diabetes.

**Screening for CAD**

Tandon and the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Study co-investigators conducted a post-hoc analysis to determine the influence of gender on silent myocardial ischemia (SMI) and cardiac event rate in patients with diabetes and assess whether screening affects clinical outcomes (abstract 1063-228). In the DIAD study conducted a study to determine the prognostic value of diabetes and hyperglycemia for inpatient and long-term mortality following acute MI (abstract 1073-368). A total of 1,429 acute MI patients (mean age 64.5±0.34 years, 73% men, and 30% with a history of diabetes) who were treated at a single tertiary-care institution were followed for up to 11.7 years after discharge (abstract 1073-368). Inpatient mortality rates for diabetics and non-diabetics were 12.7% and 9.6%, respectively (p=0.08). In a multivariable model which accounted for history of diabetes, admission blood glucose level, and 13 other baseline variables, glucose (OR=1.01 per each 1 mg/dL increase, p<0.001), age (OR=1.07 per each 1 year increase, p<0.001), ST-elevation acute MI (OR=1.54, p<0.001), and the presence of diabetes were significantly associated with inpatient mortality.

**Acute Hyperglycemia in Acute MI**

Nicolau and coworkers from Brazil conducted a study to determine the prognostic value of diabetes and hyperglycemia for inpatient and long-term mortality following acute MI (abstract 1073-368). A total of 1,429 acute MI patients (mean age 64.5±0.34 years, 73% men, and 30% with a history of diabetes) who were treated at a single tertiary-care institution were followed for up to 11.7 years after discharge (abstract 1073-368). Inpatient mortality rates for diabetics and non-diabetics were 12.7% and 9.6%, respectively (p=0.08). In a multivariable model which accounted for history of diabetes, admission blood glucose level, and 13 other baseline variables, glucose (OR=1.01 per each 1 mg/dL increase, p<0.001), age (OR=1.07 per each 1 year increase, p<0.001), ST-elevation acute MI (OR=1.54, p<0.001), and the presence of diabetes were significantly associated with inpatient mortality.

**Table 4. Risk of Incident Diabetes Among Apparently Healthy Women by Level of NT-proBNP**

<table>
<thead>
<tr>
<th>Quartile of NT-proBNP</th>
<th>Quartile 1 (&lt;37.8 pg/mL)</th>
<th>Quartile 2 (37.8 to &lt;64.3 pg/mL)</th>
<th>Quartile 3 (64.3 to &lt;117.4 pg/mL)</th>
<th>Quartile 4 (≥117.4 pg/mL)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=195</td>
<td>1.0</td>
<td>0.56 (0.40-0.78)</td>
<td>0.61 (0.43-0.86)</td>
<td>0.40 (0.27-0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N=117</td>
<td>1.0</td>
<td>0.84 (0.64-1.25)</td>
<td>0.94 (0.62-1.43)</td>
<td>0.55 (0.34-0.89)</td>
<td>0.05</td>
</tr>
<tr>
<td>N=116</td>
<td>1.0</td>
<td>0.84 (0.57-1.26)</td>
<td>0.95 (0.63-1.45)</td>
<td>0.55 (0.34-0.91)</td>
<td>0.058</td>
</tr>
<tr>
<td>N=63</td>
<td>1.0</td>
<td>0.87 (0.58-1.33)</td>
<td>0.97 (0.63-1.52)</td>
<td>0.51 (0.31-0.85)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

NT-proBNP=N-terminal fragment, B-type natriuretic peptide.

Model 1: adjusted for age and race.
Model 2: adjusted for age, race, BMI.
Model 3: adjusted for age, race, BMI, and estimated GFR.
Model 4: adjusted for age, race, BMI, estimated GFR, hormone use, exercise, alcohol, and family history of diabetes.

1,123 asymptomatic patients with Type 2 diabetes (522 women, 601 men) were randomized to screening with a nuclear pharmacological stress test (adenosine myocardial perfusion imaging [MPI]) versus no screening (Young et al., JAMA 2009;301:1547-55). In the published findings of the core study, prevalence of SMI was lower than anticipated (22%) and the 4.8-year cardiac event rate (cardiac death and nonfatal MI) was low (2.9%) and essentially unaffected by screening. According to the post-hoc analyses, the overall prevalence of abnormal MPI findings was similar between genders (19% and 24% of female and male patients, respectively; p=0.20); there was a trend for women having less moderate/large perfusion abnormalities than men (p=0.07). The cardiac event rate over a 5-year follow-up period was significantly lower among the women than among men (1.7% vs. 3.8%, p=0.05), and, within each gender sub-group, was similar between patients randomized to screening vs. no screening. When patients were stratified by their baseline risk using the UKPDS risk engine, the 5-year cardiac event rate was higher for men compared to women at high risk, but similar between genders among those at intermediate or low risk (Table 5). Taken together, these results from DIAD suggest that routine screening of asymptomatic female diabetic patients cannot be justified even in those seemingly at the highest risk. In men in the highest risk category, event rates were substantial. Although screening might be considered in this group, DIAD was not powered to evaluate the utility of screening these individuals.

**Table 5. 5-Year Coronary Event Rate by Baseline Risk (UKPDS)**

<table>
<thead>
<tr>
<th>Baseline Risk (UKPDS)</th>
<th>Female Patients (n=522)</th>
<th>Male Patients (n=601)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence of Risk</td>
<td>Cardiac Events Over 5 Years n (%)</td>
</tr>
<tr>
<td>Low</td>
<td>73%</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Medium</td>
<td>24%</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>High</td>
<td>3%</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Comparing cardiac event rate between female and male patients.
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p=0.03), history of heart failure (OR=2.82, p<0.001), and hypertension (OR=0.58, p=0.005) were significantly associated with in-patient mortality. The mean survival time was 7.9 years and 9.0 years for patients with and without a history of diabetes before acute MI, respectively (p<0.001). In a multivariable model (all 15 variables), history of diabetes (OR=1.31, p=0.02), age (OR=1.05 per each 1 year, p<0.001), history of previous acute MI (OR=1.67, p<0.001), heart failure (OR=1.61, p=0.010), and previous stroke (OR=1.73, p=0.013) were significant risk factors for long-term mortality. Analyses excluding inpatient deaths did not alter the findings. Thus, admission blood glucose appears to be a better predictor of inpatient mortality following acute MI than is history of diabetes, whereas the opposite appears to be true for mortality after hospitalization.

The specific link between acute hyperglycemia and adverse outcomes continues to perplex investigators. Some feel it is merely a marker for the sickest patients (either from a hemodynamic or a metabolic standpoint [or both]), whereas others are convinced that elevated blood glucose may set up a pro-coagulant and pro-inflammatory milieu that is deleterious for the patient suffering an acute myocardial ischemic event. There is evidence to support each of these views. Unfortunately, randomized clinical trials have not been able to provide a consistent answer to this question.

Prognostic Value of CAC

Rana and associates from California used computed tomography to measure coronary artery calcium (CAC) scores in 36,138 asymptomatic individuals (men ≥40 yrs, women ≥50; n=2,067 with diabetes) who were referred for assessment of possible sub-clinical atherosclerosis (abstract 1170-198). Cox proportional hazards models were used to estimate 5-year risk for all-cause mortality. One model included traditional risk factors (age, sex, tobacco use, history of hypertension, high cholesterol) and a second model added CAC score to these factors.

During a median 5-year follow-up period, estimated mortality rate was significantly higher for patients with than without diabetes (6.7 % vs. 2.2%; p<0.001). Among patients with a CAC score of 0, the event rate was low, irrespective of diabetic status (Figure 4). There was no difference in event rates between the non-diabetic and diabetic cohorts when categorized into risk groups based on traditional risk factors. Addition of CAC score to the prediction model significantly improved the estimation of mortality risk, regardless of diabetic status.

HDL and CVD Risk

High-density lipoprotein cholesterol (HDL-C) is considered critically important in the removal of cholesterol from atherosclerotic plaque for transport back to the liver (reverse cholesterol transport). It also has potent anti-oxidant effects. Clinical and epidemiologic studies have consistently shown that low levels of HDL-C are strongly associated with increased risk of CAD. Moreover, mice with genetic defects in HDL-C metabolism are markedly atherosclerotic, providing evidence for HDL as a key modulator of CVD in animal models. These observations, combined with the residual risk of statin-treated patients with coronary disease, have prompted investigations of interventions to raise HDL-C levels. These studies are of particular interest to those of us managing patients with diabetes, since the classical diabetic dyslipidemia is marked by low HDL-C concentrations.

Interested in the association between changes in HDL-C and CVD risk, Nichols and associates from Georgia and Oregon conducted an observational cohort study of 30,067 members of Kaiser Permanente (mean age 60.9±12.6 years, 51% male, mean diabetes duration 5.4±4.3 years) who had Type 2 diabetes and 2 HDL-cholesterol (HDL-C) measurements 6-24 months apart in 2001 to 2006 (abstract 920-7). After calculating change in HDL-C, they used the date of the second measurement as the index date and followed patients through 2009. Over a mean follow-up of 4.7 years, 3,717 (12.4%) patients had a CVD-related hospitalization. After multivariable adjustment (baseline HDL-C, demographic and clinical risk factors, comorbidities, and use of pharmacologic agents), higher baseline HDL-C was significantly associated with lower CVD risk (HR 0.93 per 5 mg/dL, 95% CI 0.92-0.95) and each 5 mg/dL increase in HDL-C was associated with a 5% reduction in CVD risk (HR 0.95, 95% CI 0.93-0.97). In categorical, adjusted analyses (relative to individuals with stable HDL-C), a 6.5 mg/dL decrease in HDL-C was associated with a 15% increase in CVD risk (HR 1.15, 95% CI 1.05-1.27), whereas a 6.5 mg/dL increase was associated with a 10% reduction in risk (HR 0.90, 95% CI 0.83-0.98). These results are consistent with the findings from multiple other clinical and epidemiologic studies in which low levels of HDL-C have been shown to be strongly associated with increased risk of CAD.

These results are limited by the observational nature of the study, but they are consistent with atheroprotective properties of HDL seen in cell culture and animal models. Benefit in primary or secondary prevention studies of HDL-C raising will be needed before pharmacotherapy targeting HDL is added to treatment guidelines for Type 2 diabetes patients.

Although there are non-pharmacologic means of increasing HDL-C (eg, weight loss, exercise, smoking cessation, modest ethanol ingestion), drug therapy may ultimately prove to be more efficient. In this regard, of currently available agents, niacin likely has the greatest impact, with an average increase in HDL-C of 20-25%. Pioglitazone, fenofibrates, and statins increase it by approximately 12-15%, 3-15%, and 2-14%, respectively. Despite these findings, primary prevention data supporting the use of HDL-C raising therapy are lacking. For example, in FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD, fenofibrate had no overall effect on the composite primary cardiovascular outcomes. Moreover, initial studies using drugs known as cholesterol ester transfer protein (CETP)-inhibitors, which markedly raise HDL-C concentrations (>50%), were disappointing. The effect on cardiovascular outcomes of pioglitazone remains controversial and that drug activates many more pathways with possible antiatherogenic properties than solely HDL. Finally, statins likely exert their beneficial cardiovascular effects through LDL-lowering and anti-inflammatory properties. In summary, the role of HDL-C as a therapeutic target remains uncertain.

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