Important data on diabetes presented at the 70th Annual Scientific Sessions of the American Diabetes Association come to you in Diabetes 2010, 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 2010 will be followed by a Diabetes 2010 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 2010 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Describe the mechanisms of β-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.

Yale University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education activity for a maximum of 11 AMA PRA Category 1 Credits™ (5.5 credit hours per test). Physicians should only claim credit commensurate with the extent of their participation in the activity.

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### Hospital Glucose Management

The inpatient management of hyperglycemia continues to draw intense interest at the American Diabetes Association (ADA) Scientific Sessions, and this year was no exception. A well-attended symposium on Sunday brought together experts from around the country to discuss the implications of both hyper- and hypoglycemia in the hospital setting, review current guidelines, and discuss implementation strategies.

**Table 1. AACE-ADA Consensus Guidelines for Inpatient Hyperglycemia**

<table>
<thead>
<tr>
<th>ICU Patient</th>
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<tbody>
<tr>
<td>Use IV insulin by validated protocol</td>
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<tr>
<td>Need frequent BG monitoring</td>
</tr>
<tr>
<td>Begin IV insulin at BG no higher than 180 mg/dl</td>
</tr>
<tr>
<td>BG target: 140-180 mg/dl</td>
</tr>
<tr>
<td>Lower target (110-140 mg/dl) acceptable</td>
</tr>
<tr>
<td>Targets &lt;110 mg/dl no longer considered safe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-ICU Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain BG &lt;140 mg/dl pre-meal</td>
</tr>
<tr>
<td>Maintain all post-meal BG &lt;180 mg/dl</td>
</tr>
<tr>
<td>More stringent targets in selected, stable patients with prior tight control</td>
</tr>
<tr>
<td>Less stringent targets in patients with severe comorbidities</td>
</tr>
<tr>
<td>Consider adjusting regimen once BG &lt;100 mg/dl</td>
</tr>
<tr>
<td>Basal-bolus insulin therapy preferred approach</td>
</tr>
<tr>
<td>Avoid prolonged use of RISS</td>
</tr>
<tr>
<td>Oral agents usually not appropriate.</td>
</tr>
<tr>
<td>Use clinical judgment to optimize control and avoid hypoglycemia</td>
</tr>
</tbody>
</table>

**BG = blood glucose, RISS = regular insulin sliding scale.**

Dr. Mikhail Kosiborod next discussed the important issue of hypoglycemia. Like hyperglycemia, hypoglycemia is also associated with increased mortality. In elegant retrospective studies, Dr. Kosiborod’s group has found evidence that insulin-induced hypoglycemia (i.e., iatrogenic) is not associated with adverse outcomes, whereas spontaneous hypoglycemia is. This suggests that underlying patient comorbidities, such as sepsis, liver and renal disease, and malnutrition may actually be driving the increased mortality. Nonetheless, hypoglycemia in the hospital setting, especially when severe, should be avoided for obvious reasons.

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after the patient has stabilized.

The sessions’ final speaker, Dr. Steve Clement from Georgetown University took a case-based approach and highlighted the complexity of managing glycemia outside of the ICU, where frequent interruptions, dietary indiscretions, and changes in the patient’s condition can greatly impact control. He endorsed basal-bolus therapy in most patients requiring insulin in this setting, but emphasized the need to individualize approaches in all patients.

In a related session earlier in the week, Dr. Guillermo Umpierrez from Emory reported on his RABBIT 2-Surgery study in which basal-bolus therapy with glargine and glulisine was compared to traditional regular insulin sliding scale (RISS). 211 patients with a blood glucose between 140-400 mg/dl and a history of Type 2 diabetes for more than 3 months who were undergoing general surgery were randomized to one of the two treatment arms (33-OR). Mean age was 58±11 years, admission glucose 190±92 mg/dl, and HbA1c 7.7±2.2%. According to the study protocol, the total daily dose of the basal-bolus regimen was started at 0.5 U/kg, given half as glargine once daily and half as glulisine before meals. RISS was given 4 times per day for glucose >140 mg/dl. The mean daily glucose levels after the first day were 145±32 mg/dl and 172±47 mg/dl, respectively (p<0.01), and the percentages of glucose readings <140 mg/dl were higher with basal-bolus (53±30% vs. 31±28%, p<0.001). There was no difference in mortality (1% each). There were numerical reductions with basal-bolus in wound infection (2.9% vs. 10.3%, p=0.05), pneumonia (0% vs. 2.8%; p=0.24), and acute renal failure (3.8% vs. 10.3%; p=0.10), which at most trended toward significance. However, the prespecified primary endpoint, a composite of these adverse outcomes was significantly and dramatically reduced with the more aggressive regimen (8.6% vs. 24.3%; p=0.003). In those requiring critical care transfer, ICU length of stay was also reduced (1.2±0.6 vs. 3.2±2 days, p=0.003). Hypoglycemia was more common with glargine-glulisine: <70 mg/dl in 23.1% of patients (1.9% of blood glucose readings) vs. 4.7% of RISS patients (0.3% of blood glucose readings), p<0.001. Readings <40 mg/dl occurred in 3.8% and 0%, respectively.

The investigators concluded that a basal/bolus insulin regimen is preferable to RISS in the hospital management of general surgery patients with Type 2 diabetes. These data have been long awaited. Those of us who manage hospitalized patients can now say that more aggressive control of post-operative glucose will result in better clinical outcomes, but at the expense of some hypoglycemia. These data should be replicated in a larger, multicenter trial.

The Cholesterol Chronicles

In a session entitled, Key Issues in the Management of Dyslipidemia, the optimal LDL-cholesterol (C) goal for diabetes patients and the current roles, if any, for fibrates and niacin were discussed. The morning began with a debate between Dr. Sergio Fazio from Tennessee, who defended an LDL-C target of <70 mg/dl, and Dr. Lawrence Leiter from Toronto who took the opposing view.

Dr. Fazio began by noting that up to 80% all diabetes mortality is related to atherosclerosis (75% of this from coronary and 25% from cerebral and peripheral) and 75% of hospitalizations for diabetes are related to cardiovascular disease (CVD). He next reviewed multiple randomized controlled clinical trials providing evidence that lowering LDL-C using HMG-CoA reductase inhibitors (statins) significantly reduces the risk of events. He reminded the audience that no other drugs for dyslipidemia, other than statins, have been validated with such robust outcomes data.

Dr. Fazio recognized that the goal LDL-C in each of the trials was not specifically <70 mg/dl, however, it is clear that “lower is better.” While the specific number, 70, was never the target, several studies brought their mean LDL-C close to this, conferring a significant benefit vs. standard therapy/placebo arms, which maintained LDL-C in the low 100’s mg/dl. For example, in the treatment arm of the Collaborative Atorvastatin Diabetes Study (CARDS, Lancet 2004; 364:685-96), the mean LDL-C was 82 mg/dl vs. 121 mg/dl in the placebo group. Similarly, in the Treat to New Targets (TNT) trial (Diabetes Care 2006; 29:1220-26), the high-dose atorvastatin group (80 mg) achieved a mean LDL-C of 77 mg/dl versus the low-dose group (10 mg), which resulted in a mean LDL-C of 99 mg/dl. In each of these investigations, active therapy patients experienced major reductions in their cardiovascular events.

Dr. Fazio therefore was in full accord with the present lipid guidelines as recommended by the ADA (Table 2). He also noted that for individuals without overt CVD the suggested target is LDL-C <100 mg/dl, but that he suggested lowering it with statins by 30 to 40%, regardless of the baseline value.

Table 2. ADA 2010 Lipid Guidelines

<table>
<thead>
<tr>
<th>Parameter and Patient Characteristics</th>
<th>Target</th>
</tr>
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<tbody>
<tr>
<td>LDL cholesterol in patients with CVD</td>
<td>&lt;70 mg/dl</td>
</tr>
<tr>
<td>LDL cholesterol in patient without CVD</td>
<td>&lt;100 mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol in men</td>
<td>&gt;40 mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol in women</td>
<td>&gt;50 mg/dl</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;150 mg/dl</td>
</tr>
</tbody>
</table>

CVD=cardiovascular disease.

Dr. Leiter assumed the opposing view and began with two brief cases. The first patient was a 22 year-old female, diabetes duration of 1 year, with an active, healthy lifestyle and laboratory values (e.g., HbA1c, blood pressure, etc.) well within desired ranges. The second individual was a 54 year-old male smoker with hypertension, sedentary lifestyle, diabetes duration of 15 years, and an HbA1c of 9.4%. He pointed out that these two individuals do not have similar risks despite lack of overt CVD. He then reviewed several studies (e.g., OASIS, HOPE, MR FIT) that have demonstrated that diabetes confers a lower risk of CV events in those without prior cardiovascular history than in those with overt CVD but without diabetes. Alexander et al. (Diabetes 2003; 52:1210-14) used the NHANES III database to identify age-adjusted prevalence of CVD in patients over 50 years categorized by diabetes and metabolic syndrome. Those with highest risk had both diabetes and metabolic syndrome (19.2%), and those with the lowest risk had diabetes, but not metabolic syndrome (7.5%). The other two categories, no diabetes/no metabolic syndrome and no diabetes/metabolic syndrome had risks of 8.7% and 13.9%, respectively. Therefore, at least in this cohort, diabetes did not confer additional risk unless other metabolic risk factors were also present.

He then questioned the target of <70 mg/dl, restating that most of the study results identified by Dr. Fazio had not actually achieved

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that specific goal. Leiter also shared the Canadian, Joint European, and Joint British Societies guidelines, which target LDL-C values of <80 mg/dl, <100 mg/dl, and <70 mg/dl, respectively. In his closing remarks, Leiter concluded that although the data are mixed, diabetes is not a coronary risk equivalent, as is often stated. There is significant heterogeneity in risk among patients and, thus, LDL-C target should not be simplified for all. In addition, the current LDL-C targets are not as evidence based as many believe.

**Beyond Statins**

Henry Ginsberg, MD from Columbia in New York addressed the issue of identifying patients in whom fibrates may be beneficial. Reviewing their pharmacology and clinical trial data, fibrates generally decrease triglycerides by 25% to 40%, increase HDL-C by 5% to 20%, with a variable impact on LDL-C. Other than the Helsinki Heart Study from the 1980’s, which demonstrated a 34% reduction in event rates in the gemfibrozil 600 mg twice daily arm, fibrates have failed to achieve statistically significant reduction in CV events for patients with diabetes in recent clinical trials, such as FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD (Action to Control Cardiovascular Risk in Diabetes). However, in a subgroup analysis of FIELD (Diabetes Care 2009; 32:4938), the relative reduction in CVD was 27% (95% CI, 9.4-42%, p=0.005) for patients with elevated triglycerides (≥200 mg/dl) and low HDL-C (<40 mg/dl). Similarly, in a pre-specified subgroup analysis of ACCORD (NEJM 2010; 362:1563-74), patients with the combination of high triglycerides (>204 mg/dl) and low HDL-C (<34 mg/dl) treated with fenofibrate experienced a primary outcome rate of 12.4% versus 17.3% in the placebo group, approaching statistical significance (p=0.057). For all other patients, outcome rates were 10.1%. Despite these generally disappointing trial results, he suggested that fibrates may still be worth adding to the often complex medication regimens in patients with diabetes, in particular, those with high triglycerides (>200 mg/dl) and low HDL-C values (<35-40 mg/dl).

John Guyton, MD, from the University of North Carolina closed the symposium with the presentation, The Case for Add-On Niacin Therapy in Diabetes. He described HDL-C as critically important in the removal of cholesterol from atherosclerotic plaque. In epidemiologic studies, HDL-C is typically far superior to LDL-C with respect to predictive value for atherosclerosis. Although there are some non-pharmacologic means of increasing HDL-C (e.g., weight loss, exercise, smoking cessation, ethanol ingestion), drug therapy may be more efficient. In terms of increasing HDL-C, niacin has the greatest impact, with an average increase of 25%. Pioglitazone, fenofibrates, and statins increase it by approximately 15%, 3-15%, and 2-14%, respectively. Guyton recognized that primary prevention data supporting the use of niacin are lacking. However, there are secondary prevention and anatomic endpoint studies that support its use. For example, Lee et al. conducted an MRI study in patients with CVD (n=71, 68% diabetes) and determined that extended-release niacin 2000 mg/day significantly decreased carotid atherosclerosis (p=0.003) and increased HDL-C by 23% after 12 months of treatment (JACC 2009; 54:1787-94).

Insulin: New and Improved?

The emerging global diabetes pandemic, associated with rising prevalences of obesity and metabolic syndrome, has created the need for better insulins, especially so in developing countries where there are unique challenges relating to storage and use. To this point was a symposium at the ADA Scientific Sessions entitled, “Never Insulins—As They Approach Availability What Should We Know?”

**Warp-Speed Insulins**

The first speaker, Michael Weiss, MD, PhD, from Case Western Reserve University, Cleveland Ohio reviewed the status of “warp-speed insulins” in development. With the objective of mimicking meal-time insulin secretion of a healthy pancreas, Weiss mentioned that new ultra-fast insulins must improve upon currently available rapid insulin analogues, by reducing early postprandial hyperglycemia and late-phase postprandial hypoglycemia. He reviewed in detail various development paths being taken. The first was co-injection of rapid-acting insulin with hyaluronidase, which depolymerizes the subcutaneous site and enhances insulin absorption. Results of several studies presented in posters this week showed that hyaluronidase co-injection accelerates the pharmacokinetics and glucodynamics of rapid insulin analogs.

Aspirin is commonly used in the US to reduce flushing, as this continues to be a significant side effect associated with niacin. For best results, Guyton specifically recommends a 325 mg dose, administered 30 minutes prior to niacin. An agent currently available only in Europe, laropiprant, inhibits prostaglandin release and has been used in combination with niacin to reduce flushing.

He advised that niacin ‘extended-release’ is the preferred product and should be taken twice daily in the middle of the breakfast and dinner meals. The extended release formulation is associated with the most extensive outcomes data and appears to be better tolerated than ordinary formulations. In contrast, so-called, ‘slow-release’ niacin should be avoided due to an increased potential for hepatic toxicity.

Reports of niacin-induced hyperglycemia have recently been corroborated (Am J Card 2010; 105:487-94). Guyton explained that the majority of data suggest that elevated blood glucose is a short-term phenomenon (within first 12 to 24 weeks of therapy), generally returning to baseline over the course of a year. While each presenter made valid points, we remain skeptical concerning additional lipid-lowering therapy beyond the aggressive use of statins in our patients with diabetes, unless the triglyceride or HDL-C levels are markedly abnormal, in which case adjuvant therapy may be considered. (Extremely high triglycerides [>500-1000 mg/dl] are associated with pancreatitis.) Certainly, the evidence base for the use of fibrates or niacin remains unconvincing. We also continue to be concerned about the potential diabetogenic effects of niacin, as well as potential drug interactions with statins, although admittedly this appears to be mainly an issue with the older fibrate, gemfibrozil.

In a 6-way crossover euglycemic clamp study, Morrow et al. from California studied the pharmacokinetic and pharmacodynamic responses of 3 rapid-acting insulin analogs (glulisine, lispro and aspart), each administered SC with and without co-injected recombinant human hyaluronidase (HruPH20), in 14 healthy volunteers (353-OR). Hyluronidase accelerated the absorption of all 3 rapid-acting analogs, resulting in more physiologic profiles. Insulin exposure in the first hour increased to 191%, 229%, and 246% of control and, after 2 hours, decreased by 43%, 54%, and 57% for the respective insulin analogs. In a related double-blind crossover study, Hompesch et al. from...
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California found that co-injection of rhuPH2O with lispro significantly reduced postprandial hyperglycemia following a liquid meal (mean 2-hour level from 159 to 138 mg/dl; p=0.019) and reduced hypoglycemia (66% reduction in area under 70 mg/dl; p=0.03) in patients with Type 2 diabetes (abstract 387-PP).

Another platform mentioned by Weiss for improving the kinetics of rapid insulin is the combination of recombinant human insulin with an EDTA-containing diluent, which removes zinc (thereby destabilizing insulin’s zinc-mediated hexamer assembly). This results in a rapidly absorbed monomeric insulin. One such formulation in development is VIAject® Rodbard et al. from the US and Germany conducted a 6-month, open-label, multicenter study in which they treated 471 patients with Type 2 diabetes with either VIAject® or regular human insulin (RHI) in combination with previously prescribed insulin glargine, metformin, and/or thiazolidinedione (abstract 36-OR). HbA1c was 8.2% at baseline and decreased by -0.6% in the VIAject group and -0.7% in the RHI group (95% CI -0.05, 0.32) at study endpoint. In addition to comparable glycemia control, study patients receiving VIAject achieved a 2-fold reduction in rate of non-severe hypoglycemia (0.33 vs. 0.66 events/month with RHI, p<0.02) and significantly less weight gain (0.46 vs. 1.35 kg, p<0.05), as compared to patients in the RHI group. There has been little data, however, comparing this new insulin with currently available rapid analogues.

Weiss also described very early protein engineering projects, for instance halogenic substitution at phenyalanine B24 and efforts to create absorbed monomeric insulin. One such formulation of RHI with a spray propellant for oral administration has undergone studies for decades. Oral-lyn™ RapidMist®, a liquid formulation of RHI with a spray propellant for oral administration, results in a more rapid increase in insulin action compared to SC regular insulin administered at mealtime (Heinemann L. J Diabetes Sci Technol 2009; 3:568-84).

In insulin in pill form would be ideal, however, enzymatic degradation in the GI tract, binding by the mucosal barrier, and first-pass hepatic clearance have converged to thwart all attempts to date at developing a clinically viable p.o. formulation. Several lines of investigation suggest that tenacity may pay off, however. An oral insulin candidate, IN-105 (Biocon), is a human insulin molecule conjugated on position B29 with polyethylene glycol via an acyl chain to reduce degradation. In phase 1 studies, a “second-generation” tablet is absorbed rapidly and has shown dose-dependent glucose lowering, with maximum effect when taken ~20 minutes before a meal. In a recently published proof-of-concept study, Kapitza et al. demonstrated that absorption of oral insulin (combined with a delivery agent) under fasting conditions was feasible, leading to greater maximum insulin concentration and faster onset compared to RHI. However, between-subject variability in absorption was high (Diabetes Care 2010; 33:1288-90).

Inhaled insulin leverages the large (size of tennis court) surface area of the alveolar tree for absorption. As noted, one such product passed

Table 3. Alternative Delivery of Insulin

<table>
<thead>
<tr>
<th>Alternative Delivery</th>
<th>Insulin</th>
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<tbody>
<tr>
<td>Nasal</td>
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<tr>
<td>Sublingual</td>
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<tr>
<td>Buccal</td>
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<tr>
<td>Oral</td>
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<td>Inhaled</td>
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<tr>
<td>Transdermal</td>
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<tr>
<td>Intraperitoneal</td>
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least squares mean T_{max} (time to maximum), based on estimated exogenous insulin, was significantly shorter with Nasulin™ (mean±SD, 18.7±2.73 minutes) than for lispro 10 IU (43.1±3.46 minutes) or lispro 20 IU (41.4±3.5 minutes) (both, p<0.001), with a smaller counterregulatory glucagon response afterwards. Symptomatic hypoglycemia occurred less frequently in the Nasulin™ group.

As for sublingual administration of insulin, Cefalu briefly mentioned Viatab technology. Data from pre-clinical laboratory models have demonstrated rapid onset of insulin effects, improved shelf-life of the insulin, and pharmacodynamic activity. The thin, highly permeable mucosa of the sublingual area lends itself to drug absorption. Buccal delivery of insulin has undergone study for decades. Oral-lyn™ RapidMist®, a liquid formulation of RHI with a spray propellant for oral administration, results in a more rapid increase in insulin action compared to SC regular insulin administered at mealtime (Heinemann L. J Diabetes Sci Technol 2009; 3:568-84).

In insulin in pill form would be ideal, however, enzymatic degradation in the GI tract, binding by the mucosal barrier, and first-pass hepatic clearance have converged to thwart all attempts to date at developing a clinically viable p.o. formulation. Several lines of investigation suggest that tenacity may pay off, however. An oral insulin candidate, IN-105 (Biocon), is a human insulin molecule conjugated on position B29 with polyethylene glycol via an acyl chain to reduce degradation. In phase 1 studies, a “second-generation” tablet is absorbed rapidly and has shown dose-dependent glucose lowering, with maximum effect when taken ~20 minutes before a meal. In a recently published proof-of-concept study, Kapitza et al. demonstrated that absorption of oral insulin (combined with a delivery agent) under fasting conditions was feasible, leading to greater maximum insulin concentration and faster onset compared to RHI. However, between-subject variability in absorption was high (Diabetes Care 2010; 33:1288-90).

Inhaled insulin leverages the large (size of tennis court) surface area of the alveolar tree for absorption. As noted, one such product passed
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all efficacy and safety approval hurdles of the FDA, but was subsequently removed from the US market by its developer. Another currently under review by the FDA is Technosphere®, an ultra rapid-acting inhaled insulin with a pharmacokinetic profile that suggests earlier control of post-prandial plasma glucose may be possible. Rosenstock et al. recently showed that prandial Technosphere® insulin plus bedtime insulin glargine led to comparable reduction in HbA1c compared to premixed bipart insulin 70/30 (-0.68% vs. -0.76%, respectively), and attenuated weight gain after 1 year of treatment of Type 2 diabetes patients (Lancet 2010; 375:2244-53). Consistent with the Exubera experience, Cefalu mentioned that FEV1 decreases slightly with this inhaled formulation, although not progressive, with apparent remission with long-term administration.

In a symposium devoted to renal disease in diabetes, Dr. Mark Molitch of Northwestern University addressed “Controlling Glycemia in CKD—What Are the Targets and How to Achieve Them?” Dr. Molitch began the session by reminding the audience that diabetes continues to be the leading cause of renal failure in the US. In addition, once dialysis is initiated, overall and specifically cardiovascular mortality is much worse in diabetic patients vs. their non-diabetic peers. He summarized the main goals of diabetes care as they relate to the kidneys to be:
1.) Reduce the total number of patients with diabetes;
2.) Reduce the number of patients with diabetes who develop nephropathy; and
3.) Slow the rates of progression once nephropathy is present.

Focusing on the second and third goals, a multifaceted approach to care is important. This involves, in addition to diabetic management, meticulous blood pressure control, judicious use of drugs that block the renin-angiotensin axis, and the avoidance of acute renal injury (Table 4). Next, Dr. Molitch reviewed what is known about glucose control and the development and progression of kidney disease. From the DCCT to the Kumamoto study to the UKPDS, it is quite clear that tight glycemic control prevents renal microvascular complications. The relationship between HbA1c and albuminuria is curvilinear, with much of the incorporated into the usual antihyperglycemic regimen (n = 656; mean ± SD dose =141.7 ± 62.9 U) or continued on their baseline program (i.e., insulin, oral hypoglycemics, and/or diet and exercise; n = 678) (abstract 359-OR). At 2 years, there was comparable reduction from baseline in HbA1c between the 2 groups (Figure 1, p = 0.30) and less hypoglycemia among patients who received inhaled insulin (0.15 vs. 0.24 events per patient-month for usual-care patients treated with insulin injections (p = 0.03 overall). Weight gain was observed in both groups (+1.56 kg vs. +1.75 kg, respectively; p = 0.67).

We remain wary about these insulins on several fronts. First is cost—these products are bound to be appreciably more expensive than current insulins. Second, potential safety issues for inhaled products will need to be resolved. Finally, the bioavailability of some agents may be unreliable, especially the oral products.

Renal Reports

Table 4. Preventing/Delaying Renal Disease in Diabetes

- Glycemic control
- Blood pressure reduction
- Renin-angiotensin-aldosterone axis inhibition
- Avoid acute kidney injury
  - Avoid/minimize use of NSAIDs
  - Avoid/minimize use of radiocontrast dyes
  - Prevent or treat promptly any urinary tract infections

benefit occurring when HbA1c is dropped from the 11-12% range down to 9%, less so—but still demonstrable—when reduced further to 7%, and negligible additional improvement as 6% is approached. In the follow up to the DCCT, past more intensive glucose control continued to benefit renal outcomes, even after 20 years. For example, by the end of the follow-up period, the development of serum creatinine (SCr) levels >2 mg/dl was reduced by more than 60% and the need for dialysis or transplantation by more than 70%. Based on these data, the widely accepted HbA1c target of <7% appears to be a reasonable goal in most patients.

Dr. Molitch next turned to the metabolic changes in diabetic patients with decreasing glomerular filtration rate (GFR). There are notable changes in the renal contribution to gluconeogenesis

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Insulin Therapy in Extreme Insulin Resistance

The obesity epidemic is shaping the landscape of Type 2 diabetes both in its prevalence as well as its therapeutic challenges. Obesity often confers severe insulin resistance, with resulting endogenous hyperinsulinemia. As the beta cell fails and Type 2 diabetes becomes apparent, obese patients tend to require larger amounts of insulin to maintain glycemic control. It is no longer uncommon in clinical practice to have patients with severe resistance, defined as the requirement of more than 200 units of insulin per day. A vicious cycle of weight gain and up-titration of insulin dosing is not only frustrating, but also may be counter-productive to promoting health. Hyperinsulinemia is implicated in cardiovascular disease and cancer (see “Diabetes and Cancer: Making the Link,” page 1). Therapeutic means of reducing the total daily insulin dose needed to achieve glycemic control may be beneficial. A symposium on Monday addressed managing insulin therapy in the obese, extremely insulin-resistant patient.

Wendy Lane, MD an Endocrinologist from Asheville, North Carolina spoke about the use of U-500 in this population. U-500 is a regular human insulin formulation that is five times more concentrated than regular insulin, and has a pharmacodynamic profile between that of regular insulin and NPH. It is administered by injection two to three times daily, and may be infused from an insulin pump, although this is still off-label. U-500 is generally initiated in order to decrease the volume and frequency of injections as well as to improve insulin absorption. Another important advantage is significant cost savings as compared with U-100 insulins, and especially vs. newer insulin analogues. Despite the growing need for concentrated insulin, there are fewer than 10 published studies on the use of U-500 in practice, and half of them are uncontrolled, retrospective reports. However, their take-home messages are progressive dose reductions when SCr levels rise, but only stopping the drug if the estimated GFR falls below 30 ml/minute. Clearly, more evidence-based guidelines would be helpful.

Dr. Molitch concluded his presentation by reminding the audience that the leading cause of death in patients with diabetes and CKD is cardiovascular disease, a much more frequent occurrence than the need for dialysis. As a result, stringent control of other cardiovascular risk factors, especially lipids and blood pressure, are of utmost importance. There is early evidence of potential benefits on the cardiovascular system from treatment of secondary hyperparathyroidism with vitamin D analogues as well as addressing anemia with erythropoietin analogues.