

C L O S E R L O O K

Practical Ways to Achieve Targets in Diabetes Care

July 17-19; Keystone, Colorado – Full Commentary

We were extremely lucky to be able to attend this year's Keystone conference, held in Keystone, CO. There was some incredible coverage at the meeting that made us smarter about diabetes as related to current clinical practice. We really appreciated the patient and clinical-care centered focus of the conference. We especially appreciated the CGM patient panel led by Mary Voelmle (University of Colorado Denver, Aurora, CO), in which CGM users discussed their expectations for CGM, what they appreciated about the technology, and what they saw as its shortcomings. There is still incredible potential for innovation ahead, in our view. We were also very glad that physicians and educators were given the chance to engage in a Q&A session with Dr. Jay Skyler (University of Miami Miller School of Medicine, Miami, FL) at the meeting as we felt that the issues addressed (diet, obesity and cancer, nutritional supplements for diabetes) reflected much of the core of everyday clinical care concerns.

The faculty at this conference was remarkable: for example, we got to hear Dr. George Eisenbarth (University of Colorado Denver, Aurora, CO) speak again, following his incredible address at the ADA this year, where he gave the riveting Banting Lecture. There were so many important names, including Drs. Satish Garg, Jay Skyler, Ralph DeFronzo, Irl Hirsch, Rich Bergenstal, David Owens, and David Schade on a very intriguing panel addressing current controversies in diabetes and similarly important names talking about the futures of SMBG and CGM. Several experts rounded off the conference by putting the recent findings of several big studies—ACCORD, ADVANCE, 4T, APOLLO, ORIGIN, HEART2D, and several other big trials—in a patient, clinical care perspective. We thought the information delivered was stellar—much appreciation to Dr. Satish Garg for hosting such an unbelievably good meeting.

Highlights

- **Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL) presented several powerful theses on controversies in diabetes.** He drew six main conclusions in his presentation: 1) rosiglitazone does not cause heart disease, 2) tight glycemic control does not kill but unwarranted overaggressive treatment (i.e., not backing off treatment when patients are not responding could), 3) stricter FDA guidelines based on flawed studies could make it much harder for companies to put products to market, thus putting patients at a disadvantage, 4) glucose control in the hospital is still needed but hypoglycemia must be carefully monitored, 5) exenatide does not cause pancreatitis, and 6) insulin glargine does not cause cancer. He concluded by strongly advising the diabetes field against allowing medical journals to facilitate media coverage, thereby encouraging sensational reporting instead of careful analysis.
- **Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL), Irl Hirsch, MD (University of Washington, Seattle, WA), Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN), Ralph DeFronzo, MD (University of Texas Health Sciences Center, San Antonio, TX), David Owens, MD**

(Cardiff University, Penarth, UK), David Schade, MD (University of New Mexico, Albuquerque, NM), Satish Garg, MD (University of Colorado Denver, Aurora, CO) hosted a widely-awaited panel on current controversies in diabetes. Audience members questioned the panel on the implications of recent headlines. From our view, the most important information delivered was that insulin glargine (Sanofi's Lantus) cannot be definitively associated with cancer (this was in line with what we have reported of late; but all attendees have not necessarily been following all editorials and expert opinion closely so we felt this was critical). Yet, the panel noted that does not mean that insulin in general does not have oncogenic properties, and thus doctors should exercise judgment and take into account patients' medical histories when making decisions regarding insulin usage. A very poignant point was made that despite the controversies surrounding insulin analogs, therapies should be continued because diabetic patients are ultimately dying of heart disease and stroke—not of cancer. No consensus was reached on a timeline for insulin initiation, with several panel members advocating starting insulin therapy earlier to preserve beta cell function, while others held that there is no evidence insulin does this and we should thus focus on GLP-1s and TZDs. (We look very forward to seeing results from a trial being led by Dr. DeFronzo whereby newly initiated patients receive a combination therapy of metformin, a TZD, and Byetta.)

- **Steve Edelman, MD (University of California at San Diego, San Diego, CA) and Irl Hirsch, MD (University of Washington, Seattle, WA) discussed the merits of continuous glucose monitoring (CGM) at a DexCom sponsored corporate symposium.** Dr. Edelman noted that current glucose monitoring technology is still imperfect even when a patient follows all of the rules because it can only give a snapshot in time, not trends or long-term data. According to Dr. Edelman, those who are most likely to benefit from CGM would be those with severe hypoglycemia unawareness, those with elevated A1cs or wildly fluctuating glucose levels, and pregnant patients with diabetes. Ultimately, Dr. Edelman said CGM is most important for the patient—it can help the patient better understand their diabetes and thus deal better with everyday glucose variability.

Dr. Hirsch discussed the importance of CGM in the intensive care unit (ICU). He defined the concept of malglycemia, which encompasses hyperglycemia, hypoglycemia, and glucose variability—all predictors of poor outcome for ill patients. Malglycemia, he said, can only be avoided in the hospital with frequent checking of blood glucose; thus, euglycemia will only be achieved when CGM is integrated into the hospital setting.

- **Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN), emphasized that we must shift our thinking on self-monitoring of blood glucose (SMBG), putting emphasis on glucose management rather than just passive monitoring.** While some studies showed improvements in glucose control with SMBG (an A1c change of -0.42 over control in a meta-analysis of eight randomized controlled trials with 1,307 patients), other studies found no obvious effect of monitoring on A1c. Dr. Bergenstal attributed the difference between success and failure of SMBG in the studies to patients knowing how to respond to their readings. SMBG will be most beneficial if patients are educated about nutrition, exercise, and adjustments in therapy according to readings, are given feedback about their readings, and agree on glycemic goals, he said. We assume there may have been an effect of glycemic variability in these trials though we assume the impact would be unknown as CGM has only become accurate enough as of late to measure. We look forward to seeing CGM integrated in more trials to better understand how therapies affect control, variability, and “time in zone”.

- **David Schade, MD (University of New Mexico, Albuquerque, NM) touched upon some of the barriers to adoption of self-monitoring of blood glucose (SMBG) in type 2 diabetic populations not on insulin.** He noted that the high costs of testing supplies (about \$100 per month), which are often not reimbursed by insurance companies, are a major barrier to SMBG adoption. As we understand it, Medicare reimburses one strip per day for those on Medicare; those that want to test more must pay out of pocket. Dr. Schade said finger-stick testing can be inconvenient, painful, and can cause scarring, but there is little on the horizon, he said, that will give equally accurate readings. He said that compliance to SMBG in type 2 diabetic populations not on insulin is low and the discontinuation rate, even in clinical trials, is high. Given that studies have failed to show benefits of SMBG in type 2 diabetic patients not on insulin, Dr. Schade questioned whether resources would be better-spent putting patients on other regimens, such as once-weekly exenatide. Notably, he forecast that CGM will soon replace SMBG.
- **Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN), David Schade, MD (University of New Mexico, Albuquerque, NM), Irl Hirsch, MD (University of Washington, Seattle, WA), and David Owens, MD, (Cardiff University, Penarth, UK) held an impromptu panel discussion on the timeline for the phasing out of self-monitoring of blood glucose (SMBG) and the dominance of continuous glucose monitoring (CGM).** Dr. Hirsch noted that the accuracy of CGM needs to improve before it is completely adopted over SMBG, but that CGM will grow quickly in type 2 diabetic and pregnant populations. Several doctors commented that SMBG is inadequate in type 2 diabetic patients not on insulin because the snapshot it provides is not enough to help patients understand and monitor their diabetes, but the trends CGM provides are key. Dr. Owens held that because CGM gives so much more information, diabetes technology will go heavily in that direction.
- **Marian Rewers, MD, PhD (University of Colorado Denver, Aurora, CO) said that the incidence of coronary artery disease (CAD) is not improving in type 1 diabetic patients and that coronary artery calcification is a great test for determining the short risk prognosis of CV events.** CAD has become the leading cause of death among type 1 diabetic patients, surpassing nephropathy. The coronary artery calcification (CAC) test is a noninvasive test measuring the extent and progression of atherosclerosis. Dr. Rewers suggested that better control of A1c, blood pressure, cholesterol, and vitamin D can lower the risk of CAD but that additionally, all asymptomatic diabetic patients older than 30 should be screened for CAC. Those with scores over 400 should be further tested and those with perfusion defects or CAD symptoms should undergo proper treatment.
- **Aaron Kowalski, PhD (Juvenile Diabetes Research Foundation, New York, NY) outlined prospects for the development of an artificial pancreas, i.e., the “closed loop.”** He defined the goals of the JDRF-sponsored Artificial Pancreas Project as accelerating the availability of the artificial pancreas, ensuring wide availability and reimbursement of its components, and creation of a thriving, robust artificial pancreas market that gives diabetic patients many choices. Dr. Kowalski emphasized that the first-line goal of the project was to create a device that could prevent severe hypoglycemia by ceasing insulin delivery when patients are no longer responsive to “low” alarms. This is akin to the new Medtronic pump that has already been approved in the UK. The hypothetical pathway to an artificial pancreas will likely progress through 1) a pump that ceases delivery when glucose is very low, 2) a pump that ceases delivery when glucose is trending low, 3) a pump that minimizes both hypo and hyperglycemia, 4) an automated basal/hybrid closed loop, 5) a fully automated closed insulin loop, and finally 6) a fully automated multi-hormone (insulin and anti-insulin) closed loop. Dr. Kowalski said it was imperative that the industry now “takes the bull by the horns” to ensure eventual

commercialization of the artificial pancreas. We heartily agree. We had never quite heard a pathway as explicit as this; we found Dr. Kowalski's presentation very helpful and very inspiring. We thought the last step was particularly interesting and wonder whether he was referring to glucagon, pramlintide, etc.

- **Richard Bergenstal, MD (International Diabetes Foundation, Minneapolis, MN), David Owens, MD (Cardiff University, Penarth, UK), and Jay Skyler (University of Miami Miller School of Medicine, Miami, FL) made clinical recommendations based on the findings of the ACCORD/ADVANCE, VADT, APOLLO, 4T, ORIGIN, and Heart T2D trials.**
- **Dr. Bergenstal reviewed the results of ACCORD** presented at this year's ADA, which suggested a higher risk of mortality associated with intensive glucose control. He noted that this increased risk was not necessarily due to hypoglycemia, and could be associated with "pushing too hard" on patients who were not responding to their therapy. Additionally, the risk of mortality was lower with lower A1cs. In light of these results, intensive glycemic control and a target A1c of <7% still make sense, but doctors must carefully monitor their patients' responsiveness to treatment.
- **Dr. Owens described the 4T's findings** that improvements in A1c were best with prandial and biphasic insulin therapy for patients with baseline A1cs >8.5%. Patients with A1cs <8.5% at baseline were equally likely to see A1c improvements with biphasic, prandial, or basal insulin. In general, adding insulin to oral therapies proved to have suboptimal responses in type 2 diabetic patients (A1c drop of 0.8% to 1.4%) and prandial and biphasic insulins were associated with more hypoglycemia and weight gain. Overall the results suggested that complex, multi-insulin regimes may be needed to achieve target glucose levels and years two and three of the 4T study will explore this (4T was first reported at EASD nearly two years ago; we had assumed the trial was finished by now). He also touched upon APOLLO's findings that insulin glargine and insulin lispro are essentially equivalent in their lowering of A1c and blood glucose, but that insulin glargine is associated with less hypoglycemia.
- **Dr. Skyler recapped ACCORD, ADVANCE and VADT's findings, including that lowering A1c below 7% reduces the risk of microvascular complications and CVD risk in diabetic patients, thus making an A1c target of 7% reasonable.** Along with discussing various suggestions regarding blood pressure, LDL cholesterol, and aspirin therapy, he made recommendations for a pathophysiologically based treatment algorithm focusing on lifestyle change, TZD, metformin, and exenatide (Amylin's Byetta) therapy (this combination was discussed in Dr. DeFronzo's Banting Lecture in 2008 at ADA) that would ideally bring A1cs below 6.0%. We thought it was notable to hear a clinician like Dr. Skyler talking again so openly about the virtues of A1cs under 6.0% for at least some patients; we haven't heard this since prior to when ACCORD was first released. We applaud this direction since from our view, patients are likely better off the closer they can get to normal blood glucose levels safely.
- **Peter Gottlieb, MD (University of Colorado Denver, Aurora, CO) emphasized that curing type 1 diabetes will mean successfully preventing loss of beta cell mass and outlined immunotherapeutic approaches to this goal.** After going through some of type 1 diabetes' basic immunology, he described several strategies currently aiming to preserve beta cells: therapies that block the activation of autoreactive T-cells, which ultimately kill beta cells, a pro-insulin DNA vaccine that would prevent autoimmunity, antigen-specific therapy that would block insulin being presented to T-cells, and anti-GAD, anti-thymocyte globulin, and anti-Interleukin-1 (a cytokine) therapies. He detailed many of the immunotherapy trials currently

underway and said that the best hope for remission or prevention will probably be an approach combining several immunotherapeutic options so that immunosuppression is lessened while positive effects are maximized. An important aspect of many of these therapies is that their greatest potency will be very early—either before disease onset or during honeymoon phases.

- **George Eisenbarth, MD, PhD, (University of Colorado Denver, Aurora, CO) discussed our genetic understanding of diabetes and how we can hopefully use this knowledge to cure and prevent the disease.** He began his lecture with some practical aspects of type 1 diabetes genetics, encouraging referrals to TrialNet for relatives of type 1 diabetic patients and suggesting several assays that could detect autoantibodies. He also recounted the immune basis of type 1 diabetes, explaining that certain HLA genes are highly associated with disease formation; as a reminder, HLA is the human molecule that allows for insulin recognition by autoreactive T-cells in diabetes. Because of type 1 diabetes' genetic basis, patients are very likely to develop autoimmunity if their parents are diabetic or they share high-risk genes with siblings. Through creation of animal models mimicking type 1 pathogenesis and trials such as the DAISY trial (which looks at the development of diabetes in genetically susceptible children), we will hopefully one day be able to predict and therefore treat or prevent type 1 diabetes, Dr. Eisenbarth said.
- **Boris Draznin, MD (University of Colorado School of Medicine, Denver, CO) gave hope for the prospects of islet transplants from pigs.** Because of the very limited supply of transplantable human islets and the extremely strong immunosuppressive regimes used for current transplantation protocols, another transplant method needs to be found, he said. His talk focused on the use of porcine islets, which can be isolated in large quantities and have the same physiological response to glucose as human islets. Some serious cons to use of porcine islets include the risk of animal virus transmission and strong immune rejection of the islets. Yet a solution may have been found in virus-free pig populations found on Auckland Island and in the encapsulation methods of a New Zealand company. The company has conducted trials with infusion of encapsulated porcine islets and had positive results in terms of A1c and mean glucose reduction. There are still many, many questions about this technology and Dr. Draznin noted that maybe patients will one day receive these islet infusions on a yearly basis for maximum efficacy. We aren't sure how broad the patient population would be. While we'd very much like to see this come to fruition, we feel the technology still has numerous challenges to overcome but are excited for future results.

David Harlan, MD (National Institutes of Health, Bethesda, MD) shared realistic, though not overly promising information about islet and pancreas transplantation. While there was lots of hope for the field following publication of the Edmonton protocol in 2000 (*New England Journal of Medicine*) and evidence that islet transplant reliably stores insulin independence (at least for the first year), this is no longer necessarily the case, Dr. Harlan said. It has been shown that the immunosuppressants given post-transplant significantly worsen renal function and that the risk of patient mortality never decreases post pancreas-alone transplantation. Thus, given the success of current insulin therapies and the low mortality rate associated with type 1 diabetes, any transplantation therapy will have to better patients' lives beyond what current methods can do. Other interesting facts from Dr. Harlan's lecture were that there is evidence that the native pancreas still secretes insulin many, many years after type 1 diagnosis, but that exogenous insulin therapy can actually suppress native insulin production, and that beta cells do not regenerate after age 30. We believe this information was gleaned, at least in part, from a failed NIH trial testing exenatide in type 1 patients. We wonder if there are plans to try exenatide in patients at risk of type 1 or who have it and are younger than 30.

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Detailed Discussion

Controversies in Diabetes Management and Insulin Initiation in Type 2 Diabetes

CONTROVERSIES IN DIABETES GUIDELINES—BEING HIT FROM ALL SIDES

Jay Skyler, MD, MACP (University of Miami Miller School of Medicine, Miami, FL)

Dr. Skyler rebuffed recent controversies in his talk, drawing six main conclusions: 1) rosiglitazone does not cause heart disease, 2) tight glycemic control does not kill but unwarranted overaggressive treatment (i.e. not backing off of treatment when patients are not responding) could, 3) stricter FDA guidelines based on flawed studies could make it much harder for companies to put products to market, thus putting patients at a disadvantage, 4) glucose control in the hospital is still needed but hypoglycemia must be carefully monitored, 5) exenatide does not cause pancreatitis, and 6) insulin glargine does not cause cancer. He concluded by strongly advising the diabetes field against allowing medical journals to facilitate media coverage, thereby encouraging sensational reporting over careful analysis.

- **Rosiglitazone does not cause heart disease.** Following the publication of Dr. Steve Nissen's (Cleveland Clinic) meta-analysis, which suggested that rosiglitazone was associated with myocardial infarction and death from cardiovascular disease (CVD), Avandia sales dropped by two-thirds and never recovered. Many patients who were on Avandia abandoned their treatment, never replacing it. The real data suggests rosiglitazone carries no risk of CVD, as supported by data from ACCORD, VADT, RECORD and BARI-2D. In VADT, which looked at the effect of rosiglitazone dosage on time until myocardial infarction or death, hazard ratios for patients on rosiglitazone were consistently less than one, even suggesting a beneficial effect of rosiglitazone treatment. RECORD suggested no impact of rosiglitazone on CV disease. BARI-2D said that insulin sensitizing therapy (rosiglitazone) did not increase risk of death, MI, or stroke over insulin providing therapy.
- **Tight glycemic control does not cause death, but pushing patients beyond their limits could.** Dr. Skyler said that initial analysis of ACCORD results suggested that there was a higher risk of death in the intensive control group, absolute differences in death percentages per group were small (0.011/year for control treatment vs. 0.014/year for the intensive group). He held he would not have stopped the study with that small of an absolute difference. Moreover, he felt that the approach taken in the study was too intense—changes in treatment were made if fasting glucose was >100 or the two-hour postprandial glucose was >160, even if a patient's A1c was below 6.0% (at target). So while the data clearly showed that risk of death increased with higher A1cs in the intensive control group, the disproportionate amount of deaths in the intensive group may have come from investigators "pushing too hard" when patients were not responding to treatment.
- **Dr. Skyler expressed his worry that stricter FDA guidelines, based on concerns from flawed studies, would make the approval process for new diabetes drugs much harder. This could ultimately disadvantage patients.** Following negative coverage regarding Avandia's linkage to an increase risk of cardiovascular events or cardiovascular-related death, the FDA instituted new, stricter guidelines in December of 2008. The guidelines required that any diabetes related drug not result in unacceptable CVD risk. If the upper bound of a hazard ratio 95% confidence interval is >1.8 for a drug, it must undergo a large safety study before approval. Between 1.3 and 1.8, the drug must undertake a postmarketing safety study, but if the hazard ratio is <1.3, a postmarketing study is not necessary. Dr. Skyler states that this is a huge extra burden for diabetes and that it is a pity that these guidelines were created based on flawed

studies. It has already caused suspension of alogliptin approval and will adversely affect patients in the long run, according to Dr. Skyler.

- **In hospital glucose control is still needed, but careful monitoring is necessary to avoid hypoglycemia.** Dr. Skyler felt that the increased risk of death and hypoglycemia in the intensive control group in NICE-SUGAR could have been attributed to a variety of confounding factors: frequency and accuracy of blood glucose measurements could have varied between centers, wide blood glucose variability could have occurred since CGM was not used in the study and blood glucose measurements were taken every 1-4 hours (explaining adverse results), the nutritional approach (enteral rather than parenteral) was different than in the Vandenberg study, or the blood glucose algorithm was different. Dr. Skyler did not think we should abandon tight glucose control in the hospital.
- **Exenatide does not cause pancreatitis.** Dr. Skyler attributes the scare over exenatide causing pancreatitis to a flawed MedWatch system where a disproportionate number of patients on exenatide were reported to have pancreatitis, thus skewing subsequent studies in that direction. Pancreatitis is three times more common in the diabetic population than in the general population and no studies were done with pancreatitis rates in metformin or sulfonylurea users. Thus the direct link cannot be solidly substantiated.
- **Insulin glargine does not cause cancer.** The question of whether insulin glargine causes cancer initiated from a German study whose results only show an increased risk of cancer with insulin glargine when adjusted for dosing (which according to Dr. Skyler, was done incorrectly). Without this adjustment, the German study actually showed a decreased risk of cancer with insulin glargine. The Scottish study did not show an increased risk of cancer in general with glargine, and the slightly higher risk of breast cancer (HR of 1.42, 95% CI 1.49, 1.27-1.6) could be attributed to the fact that there were only 6 breast cancer patients. The Swedish study showed even a decreased risk of cancer with either glargine monotherapy or glargine + another therapy. UK THIN showed that all insulins actually carry a risk for cancer. Dr. Skyler voiced concern that medications would be prematurely ceased and put patients at risk who were doing well on glargine treatment.
- **The diabetes field should be wary of sensationalist journalism, making sure accurate, balanced medical messaging is relayed.**

SHOULD WE FOCUS ON FASTING OR POST-PRANDIAL FIRST?

Louis Monnier, MD (Institut Universitaire de Recherche Clinique, Montpellier, France)

Both elevated hyperglycemia and glycemic variability have a role in oxidative stress, which increases the risk of diabetic complications. Chronic hyperglycemia is due to either basal or post-prandial hyperglycemia. The relative contribution of each depends on how well controlled a patient's A1c is. The three main insulin regimes are basal once daily, intermediary with biphasic twice daily, or prandial thrice daily. The 4-T study found that A1c improvements were better with prandial insulin, though APOLLO found that improvements were equal with basal or prandial. APOLLO found that glycemic variability was better treated with prandial insulin, though 4-T found no difference between the regimes. Both studies found that hypoglycemic episodes were more common with prandial insulin. Dr. Monnier concluded by saying that insulin therapy will work best if we understand that glycemic control is not deterministic, but rather stochastic. Diet and drugs do not affect metabolism in a straightforward fashion. It will take constant tuning to reach glycemic goals.

- **Both elevated hyperglycemia and glycemic variability have a role in oxidative stress, which increases the risk of diabetic complications. There are two fields of thought on how to control glucose.** Current insulin goals either focus on the glucose triad or the glucose tetrad. The glucose triad aims to achieve goals in A1c, fasting, and postprandial glucose. The glucose tetrad aims to achieve goals in all components of the glucose triad, but in glucose variability as well.
- **Chronic hyperglycemia is due to either basal or post-prandial hyperglycemia. The relative contribution of each depends on how well controlled a patient's A1c is.** Patients with lower A1cs, from below 6.5% to about 7.5%, have excess hyperglycemia after eating and thus require postprandial insulin (a short acting analog). Those patients with A1cs above 7.5% have high fasting glycemia and thus require basal insulin (a long acting analog). Patients with A1cs below 6.5% have normal nighttime glucoses but experience a spike post-breakfast (dawn phenomenon). Those patients with an A1c >7.5% have deteriorated glucose curves at all times during the day and thus have high glucose levels during the night.
- **The three main insulin regimes are basal once daily, intermediary with biphasic twice daily, or prandial thrice daily.** The 4-T study found that A1c improvements were better with prandial insulin, though APOLLO found that improvements were equal with basal or prandial. APOLLO found that glycemic variability was better treated with prandial insulin, though 4-T found no difference between the regimes. Both studies found that hypoglycemic episodes were more common with prandial insulin. Weight gain was positively correlated with increasing insulin dose and with decreasing A1c. Insulin efficiency increases with increasing insulin dose, but several studies have found that insulin efficiently decreases oxidative stress.
- **Dr. Monnier concluded by saying that insulin therapy will work best if we understand that glycemic control is not deterministic, but rather stochastic.** Diet and drugs do not affect metabolism in a straightforward fashion. Rather, they affect the factors controlling glycemia stochastically and it will take constant tuning to reach glycemic goals.

HOW EARLY SHOULD INSULIN BE INITIATED?

David Schade, MD (University of New Mexico, Albuquerque, NM)

The main cons cited of initiating insulin therapy are hypoglycemia, weight gain, and the fact that insulin is given through injections. Insulin does not necessarily save money in the long run. Most type 2 diabetic patients will eventually have to take insulin—it is simply a matter of time before insulin therapy is necessary. Hypoglycemia is an important concern—it is the most prevalent cause of falls in people age 65 and older. Moreover, insulin causes significant weight gain, decreases the basal metabolic rate and has limited storage—pills are much more stable. There may be a benefit in starting insulin earlier rather than later to maximally preserve beta cell function.

- **The main cons cited of initiating insulin therapy are hypoglycemia, weight gain, and the fact that insulin is given through injections.** Insulin does not necessarily save money in the long run. Analogs can be especially expensive (many patients are on NPH simply because it is half the price of glargine, regardless of its shortcomings). Hypoglycemia is an important concern—it is the most prevalent cause of falls in people age 65 and older. Moreover, insulin causes significant weight gain, decreases the basal metabolic rate and has limited storage—pills are much more stable.

- **Most type 2 diabetic patients will eventually have to take insulin—it is simply a matter of time before insulin therapy is necessary.** The medications that patients are currently taking reduce beta cell function. Data from Pima Indians shows that insulin decreases over time and several studies have shown that beta cell function decreases over time. Oral agents work best when patients have significant insulin secretion, so patients will likely eventually need insulin. Additionally, physicians should consider prescribing insulin to any patient whose A1c approaches 8% despite optimal oral therapy.
- **There may be a benefit in starting insulin earlier rather than later to maximally preserve beta cell function.**

Questions and Answers

Q: Do you measure islet auto-antibodies to pick out those who are type 1?

A: No, I don't because it costs \$100, and I personally haven't found it clinically useful because it's not a 100% test.

PANEL DISCUSSION ON RECENT CONTROVERSIES

Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL), Irl Hirsch, MD (University of Washington, Seattle, WA), Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN), Ralph DeFronzo, MD (University of Texas Health Sciences Center, San Antonio, Texas), David Owens, MD (Cardiff University, Penarth, UK), David Schade, MD (University of New Mexico, Albuquerque, NM), Satish Garg, MD (University of Colorado Denver, Aurora, CO)

Audience members questioned the panel on the implications of recent headlines. From our view, the most important information delivered was that insulin glargine (Sanofi's Lantus) cannot be definitively associated with cancer (this was in line with what we have reported of late; but all attendees have not necessarily been following all editorials and expert opinion closely so we felt this was critical). Yet, the panel noted that does not mean that insulin in general does not have oncogenic properties and thus doctors should exercise judgment and take into account patients' medical histories when making decisions regarding insulin usage. A point was made about which all seemed to feel very strongly - that despite the controversies surrounding insulin analogs, therapies should be continued because diabetic patients are ultimately dying of heart disease and stroke—not of cancer. No consensus was reached on a timeline for insulin initiation, with several panel members advocating starting insulin therapy earlier to preserve beta cell function, while others held that there is no evidence insulin does this and we should thus focus on GLP-1s and TZDs. (We look very forward to seeing results from a trial being led by Dr. DeFronzo whereby newly initiated patients receive a combination therapy of metformin, a TZD, and Byetta.)

Questions and Answers

Q: The results from a study preceding NICE-SUGAR brought to light that glycemic control could be useful in the ICU. Could what our discrepancies from NICE-SUGAR show is simply that such strict protocols are hard to implement in many centers?

Dr. Skyler: I believe that what NICE-SUGAR showed was that we need accurate CGM in the hospital.

Dr. DeFronzo: It also showed that maybe a fasting goal of 100 is too low. If you can maintain patient glucose in the 100-150 range, you are really in the best shape.

Consensus: The guidelines were made before NICE-SUGAR. When you work in a hospital with no algorithm and no real targets in place, there's a good chance that you can get glucose levels above 200.

While a target of 140-180 mg/dl is probably ideal, there were probably discrepancies among the centers just as there are in the general populations, leading to the results we see.

Q: How do we balance the need to publish our findings with trying to make sure the information we get across is not sensational?

A: The papers published did not adjust for naturally increased risk of breast and endometrial cancer associated with obesity. They should have. An editor's job is to make sure that people can voice their opinions. On the other hand, it is wrong to hype findings in one direction or another (either that something is dangerous or overly beneficial) without looking at the big picture and how this unfolds in the scientific literature.

This is even harder because almost every paper now has a press release and things are generally portrayed as more controversial.

Dr. Harlan: The ultimate problem is when people go to the press to sell their science. If it comes to the press and it's important, it shouldn't need a press release. It's tricky to put information out now because you're afraid the press will over-interpret things, misleading the general public.

Dr. Bergenstal: It would be great if in the future we could have databases to effectively control for all of these things. It would be a great opportunity if companies would put that together so that we could assess for example the relationships between one type of insulin and cancer.

Q: In the studies showing a possible link between insulin glargine and cancer, most people were high dose insulin users. Could this be indicative that hyperglycemia is associated with cancer rather than insulin glargine?

Dr. Draznin: Yes, in fact studies have shown that the worst combination is hyperglycemia in the presence of hyperinsulinemia.

Dr. DeFronzo: Individuals with insulin resistance syndrome have an increased risk of a variety of malignancies. That does not necessarily implicate insulin glargine in breast cancer. On the other hand, if I were a woman and I had breast cancer, I would probably not go on insulin glargine.

Q: If a woman had a history of bone sarcomas, would you then keep her on insulin?

Dr. DeFronzo: I have no answer to that question. The patient would have to make up her own mind. One thing to also keep in mind is that it's insulin, not glargine necessarily, that is responsible. A presentation by Dr. Jerry Reaven (Stanford University, Stanford, CA) showed that hyperinsulinemia could be supportive of proliferations and thus detrimental. A study from Yale showed that insulin was a factor in normal breast differentiation, and a study from the University of Miami showed that insulin could promote cancer *in vitro*. However these *in vitro* studies used nanomolar concentrations of insulin and in the body, insulin circulates in picomolar concentrations. In the long term, it's better then to ensure that patients don't end up on insulin.

A: We should remember that most pressing, diabetic patients are dying of atherosclerosis. The biggest concerns are still heart disease and stroke.

Q: It has been suggested that the earlier insulin is initiated, the lower the doses you will have to use and the better glycemic control you will obtain. In light of these findings, when is the proper time to initiate insulin?

A: In China, when patients are diagnosed with diabetes, they are put on in-hospital, intensive insulin therapy for two weeks. But many people are intimidated by insulin therapy, and the issues surrounding it are more complicated than just the cost of insulin itself.

A: I think the ideal solution would be to have better agents that would prevent insulin usage early. The exception would be to use insulin for two weeks to get rid of glucose toxicity and then use Ralph's triple therapy approach.

Dr. DeFronzo: I don't believe that there's a shred of evidence that insulin improves beta cell function. There is lots of evidence that GLP-1s and TZDs do. We should be starting those earlier, not insulin.

DexCom Corporate Symposium

Drs. Edelman and Hirsch discussed the merits of continuous glucose monitoring (CGM) at a DexCom sponsored corporate symposium.

Dr. Edelman noted that current glucose monitoring technology is still imperfect even when a patient follows all of the rules because it can only give a snapshot in time, not trends or long-term data.

According to Dr. Edelman, those who are most likely to benefit from continuous glucose monitoring would be those with frequent, severe, unawareness hypoglycemia, those with elevated A1cs or wildly fluctuating glucose levels, and pregnant patients with diabetes. Ultimately, Dr. Edelman said, CGM is most important for the patient—it can help the patient better understand their diabetes and thus deal better with everyday glucose variability.

Dr. Hirsch discussed the importance of CGM in the intensive care unit (ICU). He defined the concept of malglycemia, which encompasses hyperglycemia, hypoglycemia, and glucose variability—all predictors of poor outcome for ill patients. Malglycemia, he said, can only be avoided in the hospital with frequent checking of blood glucose and thus euglycemia will only be achieved when CGM is integrated into the hospital setting. Dr. Hirsch highlighted several technologies, including an intravenous blood glucose monitor being developed by DexCom and Edwards Life Sciences, that could be promising towards these goals.

PRACTICAL USE OF CONTINUOUS GLUCOSE MONITORING

Steve Edelman, MD (University of California at San Diego, San Diego, CA)

- **The development of continuous glucose monitoring is the greatest advance for type 1 diabetes since the discovery of insulin.**
- **Despite advances in meters, pumps, and designer insulins, glycemic control is not yet optimal.** The problem is that current meters give you readings for one point in time—even if patients are very proactive, they are lacking important information on where they're coming from. Patients are thus not meeting targets because home glucose monitoring only gives you snapshots, insulin treated patients experience wide glucose fluctuations, hypoglycemia is common and fears of hypoglycemia limit treatment intensification, and subcutaneous administration does not always give insulin levels that mimic physiologic levels well.
- **CGM will be most beneficial for people with frequent, severe, unaware hypoglycemia, those with widely fluctuating glucose levels, patients with elevated A1cs, and those patients who are pregnant or considering pregnancy.**
- **CGM has shown proven benefits.** It improves A1c and allows patients with A1cs <7% to have less hypoglycemia. CGM was shown to increase the time patients spent per day with a glucose of less than 70 and helps avoid patients stacking doses. It is also very helpful to patients delivering insulin via multiple daily injections or continuous subcutaneous insulin infusion.

- **Dr. Edelman emphasized that CGM was primarily for the patient, helping him deal with and respond to variability.**

MALGLYCEMIA: PRESENT AND FUTURE STATE OF GLUCOSE MANAGEMENT IN THE HOSPITAL

Irl Hirsch, MD (University of Washington, Seattle, WA)

- **Malglycemia is a predictor of poor outcomes. Malglycemia encompasses hyperglycemia, hypoglycemia, and glucose variability.** Van Den Berghe showed in a 2001 *New England of Journal Medicine* article that blood glucose control reduces the need for a number of hospital procedures including ICU mortality, sepsis, dialysis, and need for blood transfusion. Moreover, ICU mortality rises almost linearly as blood glucose increases. Tight glucose control often results in severe hypoglycemia, which Krinsley et al. showed in *Critical Care Medicine* to be an independent risk factor for mortality (risk ratio 2.28, 95% CI 1.41-3.70).
- **According to Dr. Hirsch, the severe hypoglycemia seen in NICE-SUGAR, which caused the authors to suggest not going for lower glucose targets with critically ill patients, could be attributed to a lack of good glucose monitoring. CGM could fix this.** “The devil was in the details” in NICE-SUGAR, Dr. Hirsch noted. In the study, the frequency of blood glucose measurements varied from hourly to every 2 to 4 hours. There were no strict guidelines for glucose testing frequency. Hypoglycemia occurred in many of the study’s patients, pushing the results to show that intensive control resulted in worse outcomes.
- **Thus, both hyperglycemia and hypoglycemia appear to be risk factors in the ICU, suggesting glycemic variability in general should be avoided. Moreover, optimal control is not being achieved with current technology.** Glycemic variability has been shown to be a predictor of death in surgical, medical, and pediatric intensive care units. Dr. Hirsch concluded that the sicker the patient, the more important reduction in glycemic variability is for survival—thus, we need CGM in the ICU.
- **When CGM is used in the ICU, it should have several important features.** These include automatic calibration, need for low volumes of blood samples, ability to measure venous or arterial blood glucose, accuracy and provision of continuous information and wireless connectivity with hospital information systems.
- **There are several promising CGM technologies being explored towards this end.** These include subcutaneous technologies, arterial blood glucose sensors, and sensors that use a microdialysis-catheter in the subcutaneous tissue. Dr. Hirsch mentioned that DexCom and Edwards Life Sciences are collaborating to produce an intravenous blood glucose sensor that would be placed inside a peripheral intravenous catheter—it would display real time data at the bedside, automatically calibrate and require little blood loss. The system is currently under investigational use.

Role of SMBG in Managing Diabetes

HISTORY OF SMBG

David Owens, MD (Centers for Disease Control and Prevention, Atlanta, GA)

Dr. David Owens gave a very interesting perspective on how far glucose testing has come in the last 50 years. He recalled how the first glucose test was a glucose oxidase test in which urine turned red if there

was glucose in it. This was low cost and painless, but did have limitations and was inaccurate. The first semi-quantitative estimations from a dry reagent strip came with Detrostix (Ames-Miles Lab).

Quantitative estimations arrived with the 1970 Ames Reflectance Meter (ARM), the 1972 Eyetone Meter, and the 1974 Reflomat Reflectance Meter. When blood glucose monitoring was first suggested by Priscilla White, a prominent physician and a founder of Joslin Diabetes Center, it was considered laughable. A key symposium in the 1980s consisting of Drs. Harry Keen, Jay Skyler, Peter Sonksen, Lois Jovanovic, and Robert Turner set self-monitoring of blood glucose on a positive path. The first generation meters had a narrow hematocrit range and could be easily swayed by user practices but were nevertheless groundbreaking.

Over the next 15 years, more and more improvements were made. Ferrocene based “mediated” sensors, electrochemical test strips, capillary methods for blood sampling, and ways to improve hematocrit ranges and error rates were developed. Now, SMBG requires low sample volumes, have low results times, better memories and weigh less.

Blood glucose meter improvement is an ongoing process. The hope is that next generation’s sensors are either noninvasive or intravenous.

SMBG FREQUENCY AND TITRATION GUIDELINES FOR INSULIN-TREATED SUBJECTS

Irl Hirsch, MD (University of Washington, Seattle, WA)

Dr. Hirsch emphasized that there is no hard data on what frequency of SMBG is ideal in insulin-requiring patients. While current ADA guidelines suggest that SMBG should be carried out thrice daily or more often for patients on pumps or on multiple daily injections, there are no hard rules. However, the data about relationships between SMBG frequency and A1c is not consistent. Some studies suggest that more frequent testing lowers A1c, but the relationship gets flatter with increased testing and a Scottish study found no relationship in type 2 patients (though the findings were positive for type 1 patients). Dr. Hirsch concluded that correct testing frequencies need to be individualized depending on personal characteristics and diabetes diagnosis. Testing frequency may decrease over time as CGM becomes more popular.

- **There is no hard data on what frequency of SMBG is ideal in insulin-requiring patients.** Current ADA guidelines suggest that SMBG be carried out three times a day or more for patients on multiple daily injections or insulin pump therapy. For patients using less frequent insulin or on other types of diabetes therapy, SMBG is suggested as a guide to successful therapy. But this is controversial and there are no hard rules.
- **Despite data showing that SMBG provided a strong stimulus for improved care in type 2 diabetes, the data about a relationship between SMBG frequency and A1c decreases is not consistent.** A study by Bode, et al. did find a negative relationship between frequency of testing and A1c, but the relationship gets flatter with significantly increased testing. In a large Northern California Kaiser Permanente observational trial, it was found that SMBG decreased A1c. Yet a Scottish observational study found that there was a correlation between increased testing and lower A1c in type 1 patients but no relationship in type 2 patients. These trials were all observational and thus conclusions cannot be drawn from their data.
- **Correct testing frequency needs to be individualized and may decrease over time as CGM becomes more popular.** For type 1 patients, frequency of testing should depend on use of CGM and hypoglycemia history. Type 2 patients should base their testing on the type of therapy they are on (basal-bolus, only basal) and their hypoglycemia profile.

ROLE OF SMBG IN NON-INSULIN TREATED SUBJECTS WITH TYPE 2 DIABETES

Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN)

Dr. Bergenstal emphasized that we must shift our thinking on self-monitoring of blood glucose (SMBG), putting emphasis on glucose management rather than just passive monitoring. While some studies showed improvements in glucose control with SMBG (an A1c change of -0.42% over control in a meta-analysis of eight randomized controlled trials with 1,307 patients), other studies found no obvious A1c effect of monitoring. Dr. Bergenstal attributed the difference between success and failure of SMBG in the studies to patients knowing how to respond to their readings. SMBG will be most beneficial if patients are educated about nutrition, exercise, and adjustments in therapy according to readings, are given feedback about their readings, and agree on glycemic goals, he said. We assume there may have been an effect of glycemic variability in these trials though we assume the impact would be unknown as CGM has only become accurate enough of late to measure. We look forward to seeing CGM integrated in more trials to better understand how therapies affect control and variability and “time in zone”.

- **Most studies show that SMBG improves glycemic control, though not significantly, in non-insulin treated diabetic patients.** A meta-analysis of 8 randomized control trials with 1307 patients showed an A1c decrease of 0.42 over control in SMBG patients. A study by Farmer et al. also only showed a 0.42 improvement. A large cohort study (n=24,312) by Northern California Kaiser Permanente showed that type 2 insulin therapy patients who tested at or above the defined frequency had a 0.6 A1c improvement and type 2 insulin naïve patients had a 0.4 improvement. Such progress could possibly be made with oral therapy alone.
- **A study by Dr. Rena Wing showing that SMBG did not improve dietary compliance for obese patients with type 2 diabetes helped highlight the fact that SMBG can only be useful when patients know what to do with their readings.** Dr. Wing’s commentary on the study noted that previous studies had only shown improvements because doctors had told patients what to do with the data. That was just the point, Dr. Bergenstal suggested—patients should not only be taught the methodology of SMBG but given advice on exercise, nutrition, and how therapy adjustments should be made.
- **For SMBG to work, patients must have clear goals. As a field, diabetes should also change its outlook from self monitoring of blood glucose to self management of blood glucose.** Goals should not only look at A1c, but at the triple goals of A1c<7, no hypoglycemia with insulin use, and weight loss. Professionals advising about SMBG should give consistent readings and feedback that helps patients respond to readings.

Questions and Answers

Q: How often should pre-diabetic patients be testing?

A: There haven’t been enough studies on this and nothing definitive showing a benefit. It would help patients be more motivated, perhaps preventing them from progressing to the diabetes stage. But I’m not sure if it would be cost-effective for five or 10 years.

BARRIERS & CHALLENGES IN SMBG ADOPTION

David Schade, MD (University of New Mexico, Albuquerque, NM)

Dr. Schade touched upon some of the barriers to adoption of self-monitoring of blood glucose (SMBG) in type 2 diabetic populations not on insulin. He noted that the high costs of testing supplies (he cited about \$100 per month – obviously this can range widely depending on meter used, testing frequency, etc.), which are often not reimbursed by insurance companies, are a major barrier to SMBG adoption. As we understand it, Medicare reimburses one strip per day for those on Medicare on oral drugs and three strips per day for those on insulin; those that want to test more must pay out of pocket. Dr. Schade said finger-stick testing can be inconvenient, painful, and can cause scarring, but there is little on the horizon, he said, that will give equally accurate readings. He said that compliance to SMBG in type 2 diabetic populations not on insulin is low and the discontinuation rate, even in clinical trials, is high. Given that studies have failed to show benefits of SMBG in type 2 diabetic patients not on insulin, Dr. Schade questioned whether resources would not be better-spent putting patients on other regimens, such as once-weekly exenatide. Notably, he forecast that CGM will soon replace SMBG.

- **SMBG is expensive.** The cost of SMBG is about \$100 per month (Ed. note – this varies depending on testing frequency, brand used, etc.), and more expensive for patients without insurance. Even for those with good coverage, co-pays can pile up as testing strip co-pays are added to those for anti-hypertensives, anti-lipid medication, etc. Dr. Schade made the point that caregivers often don't appreciate how big the SMBG market is. Current SMBG sales are \$4 billion, excluding the non-home market, he said – globally, we point out the market is \$8 billion.
- **SMBG is viewed as painful and inconvenient.** Constant testing can cause finger scarring and reduce finger sensitivity. Finger testing ends up giving the most accurate readings and is thus propagated. Other technologies in development are unlikely to be used for diabetes.
- **Many patients stop CGM—even those in controlled clinical trials.** In a study of glucose testing in type 2 diabetes patients, it was found that half of patients on more intensive monitoring (testing more than 2x a week) quit. Even patients in controlled clinical trials, who were monitored and reimbursed, often stopped monitoring. (Studies about SMBG are controversial at best in our view.)
- **A cost-benefit analysis could show that there could be more fruitful treatment options for type 1 diabetics and thus SMBG could decline as CGM grows.** If, as an estimate, testing only lowered A1c by 0.3% per year, a cost of \$100 per month could be more efficiently used on medication. Dr. Schade suggested that physicians should perhaps put these resources into once weekly Byetta or another more convenient, more efficacious treatment.

IMPROMPTU PANEL ON SMBG ADOPTION

Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN), David Schade, MD (University of New Mexico, Albuquerque, NM), Irl Hirsch, MD (University of Washington, Seattle, WA), and David Owens, MD, (Cardiff University, Penarth, UK)

Dr. Hirsch noted that the accuracy of CGM needs to improve before it is completely adopted over SMBG, but that CGM will grow quickly in type 2 diabetic and pregnant populations. Several doctors commented that SMBG is inadequate in type 2 diabetic patients not on insulin because the snapshot it provides is not enough to help patients understand and monitor their diabetes, but the trends CGM provides are key. Dr. Owens held that because CGM gives so much more information, diabetes technology will go heavily in that direction.

Q: What do other speakers think about the death of SMBG?

Dr. Hirsch: I think there needs to be better CGM accuracy before SMBG can be totally replaced. We will definitely see a rising use of CGM in type 2 patients, particularly pregnant type 2 patients and those with severe hypoglycemia. I think CGM will grow, but maybe not as fast as Dr. Bergenstal suggests. I don't think SMBG will ever go away, but we won't be as dependent on it.

Dr. Owens: The first thing people who now use CGM realize is how little information they had previously. CGM is really the only way to go in the future. There are still lots of questions though about cost and accuracy, but the information from CGM (especially trends) is invaluable.

Dr. Harlan: I think this is pretty provocative and think a timeline of two years for the death of SMBG is a little too fast.

Q: What would it take to get CGM approved for extra indications?

Dr. Bergenstal: The mistake is that the FDA is not a scientific organization. The FDA is much more worried about conflicts of interest than about getting scientific information. So it would take a lot to get extra indications approved.

Prevention of Diabetes and Early Detection of CAD

GLP-1 ANALOGS AND DPP-4 INHIBITORS

Ralph DeFronzo, MD (University of Texas Health Sciences Center, Austin, TX)

Current drugs are not preserving beta cell function and could actually be furthering atherosclerosis. The ideal treatment for type 2 diabetes will require multiple drugs in tandem. Incretins are desirable as a first-line therapy. A short while after ingestion of a meal, both GLP-1 and GIP-1 are released, stimulating insulin release and gastric emptying. GLP-1 also inhibits gluconeogenesis (important because many type 2 diabetics have increased sensitivity to hepatic glucose production). Incretins will not cause hyperglycemia and thus can be titrated up very far, depending on a patient's' needs. Newly diagnosed patients can achieve an A1c of 6.0% with GLP-1 therapy. Additionally, some data shows that incretins could stimulate beta cell proliferation and neogenesis. Exenatide is currently the most studied and effective incretin. While liraglutide could cause a slightly larger decline in A1c, it does not decrease glucose variability as effectively as exenatide. DPP-4 inhibitors are not as desirable as a first-line therapy, but data suggests that TZDs help preserve beta cell function. This regimen could prevent newly diagnosed patients from ending up on insulin.

- **Current drugs are not preserving beta cell function and could actually be furthering atherosclerosis. The ideal treatment for type 2 diabetes will require multiple drugs in tandem.** People in the upper tertile of insulin glucose tolerance, who are maximally insulin resistant, have already lost 75-80% of their beta cell function.
- **Incretins are desirable as a first-line therapy.** Glucagon-like-peptide-1 (GLP-1) is responsible for 90% of the incretin effect. A short while after ingestion of a meal, both GLP-1 and GIP-1 are released, stimulating insulin release and gastric emptying. GLP-1 also inhibits gluconeogenesis (important because many type 2 diabetics have increased sensitivity to hepatic glucose production). Incretins will not cause hyperglycemia and thus can be titrated up very far, depending on a patient's' needs. Newly diagnosed patients can achieve an A1c of 6.0% with GLP-1

therapy. Additionally, some data shows that incretins could stimulate beta cell proliferation and neogenesis.

- **Exenatide is currently the most studied and effective incretin. While liraglutide could cause a slightly larger decline in A1c, it does not reduce glucose variability as effectively as exenatide.** Exenatide reduces A1c, preserves beta cell function, promotes weight loss, corrects known pathophysiologic defects, does not cause hypoglycemia, and has an excellent safety profile. A 30-week placebo controlled trial showed that exenatide obliterated post-prandial rises in glucose and did not cause the 2 kg weight increase usually seen with any 1% A1c decrease achieved with insulin therapy. In fact, mean weight loss with exenatide is 4-5 kg. Exenatide also increases HDL, lowers blood pressure, and may reduce risk of cardiovascular disease (CVD). Liraglutide effectively lowers A1c, and fasting and postprandial glucose levels, but does not eliminate glucose variability as effectively as exenatide.
- **DPP-4 inhibitors are not as desirable as a first-line therapy, but data suggests that TZDs help preserve beta cell function.** Sitagliptin given once a day improves both fasting and postprandial glucose levels. In a head to-head study of sitagliptin versus exenatide, however, exenatide inhibits the post-meal glucagon response much better than sitagliptin. DPP-4s also do not promote weight loss, while GLP-1 agonists do. TZDs are very good insulin sensitizers and like metformin, they act at the level of the liver.
- **This regimen could prevent newly diagnosed patients from ending up on insulin.** Dr. DeFronzo said he had been using this regimen for five years and 95% of his patients on this therapy did not end up on insulin. He feels that this regimen will effectively address the “ominous octet” (decreased insulin secretion, increased glucagon secretion, increased lipolysis, decreased incretin effect, increased glucose reabsorption, increases hepatic glucose production, and kills islet beta cells) that causes diabetes.

SIX-YEAR FOLLOW-UP OF CACTI STUDY

Marian Rewers, MD, PhD (University of Colorado Denver, Aurora, CO)

Dr. Rewers said that the incidence of coronary artery disease (CAD) is not improving in type 1 diabetic patients and that coronary artery calcification (CAC) is a great test for determining the short risk prognosis of CV events. Coronary artery disease has become the leading cause of death among type 1 diabetic patients, surpassing nephropathy. The CAC test is a noninvasive test measuring the extent and progression of atherosclerosis. Dr. Rewers suggested that better control of A1c, blood pressure, cholesterol, and vitamin D can lower the risk of CAD, but that additionally, all asymptomatic diabetic patients older than 30 should be screened for CAC. Those with scores over 400 should be further tested and those with perfusion defects or CAD symptoms should undergo proper treatment.

- **Little progress has been made in preventing coronary artery disease (CAD) in diabetic patients.** Survival is improving among type 1 diabetic patients—those diagnosed with diabetes recently are much less likely to die than those diagnosed in the 1960s. However, the incidence of CAD is not improving—patients with diabetes for 20 years don’t have a better outcome if they were diagnosed in the 1970s as opposed to the 1960s. Moreover, CAD is becoming the leading cause of death for type 1 diabetic patients—surpassing diabetic nephropathy. Men with type 1 diabetes progress fastest to CAD, followed by women with type 1 diabetes (who have a greater risk than non-diabetic men).

- **Coronary artery calcification (CAC) is a noninvasive measure of the extent and progression of atherosclerosis. It is a great test for the short-term risk of CV effects.** The procedure can give significant information about how people are progressing in terms of atherosclerotic burden. It uses much less radiation and is much less invasive than other tests. CAC is tightly correlated with all CVD risk. In short term follow up studies, CAC was successfully able to predict myocardial infarctions. The procedure can also uncover premature CAD that would not otherwise be uncovered.
- **If patients have high CAC scores, they should be screened for myocardial perfusion and other CV complications and be followed up with.** A study of 4,252 patients from the University of California at Los Angeles showed a dramatic relationship between CAC progression and total mortality. The risk factors for CAD are known—they include hyperglycemia (an A1c above 6.5%), race, gender, age, vitamin D deficiency, and the relationship between obesity and insulin dose. The practical implications of this, Dr. Rewers said, are that we should be taking care of the ABCD factors—A1c, blood pressure, cholesterol, and vitamin D. Even asymptomatic patients should be screened: all those with a CAC score of > 400 should be tested for myocardial perfusion and followed up with.

NEW BIOCHEMICAL MARKERS

Paresh Dandona, FRCP, MD, PhD (State University of New York at Buffalo, Buffalo, NY)

Dr. Dandona highlighted for us some of the main markers that can be implicated in diabetes. He began by discussing the C-reactive protein (CRP), which has been shown to be able to predict morbidity and mortality. Patients with a 3-fold enhanced CRP have a high risk of morbidity and mortality, those with a 2-fold increase an enhanced risk, and those under 1, a normal risk. Type 2 diabetics are normally in the insulin group. Statins have been shown to reduce CRP levels and while the relationship between CRP and LDL cholesterol is not understood, the safest profile is one with LDL <70 and CRP <1. Yet it is not completely understood how CRP relates to CVD risk.

Other markers have to do with inflammatory and nitric oxide mediated damage very prevalent in diabetes. There are marked increases in iNOS, nitrotyrosine, toll-like receptors and reactive oxygen species in hyperglycemic or obese patients.

Interestingly, several studies have shown that insulin may be anti-inflammatory. Recent data suggests that insulin can reduce heart damage and many of the steps in important stress-related inflammatory processes. Experiments using either insulin or dextrose infusions have shown that relative levels of inflammatory markers p47^{phox}, NF-κβ, soluble ICAM-1, MCP-1, MMP-2 and MMP-9, and CRP are reduced upon insulin infusion. In a study by Grover et al., insulin was able to reverse the vein constriction induced by norepinephrine. Expression of toll-like suppressors was also shown to be uniformly decreased two and four hours after insulin infusion. Insulin was unable, however, to inhibit platelet aggregation in diabetics.

This is very exciting data looking at a different side of insulin's effects. We would love to see more about this so that the pros and cons of insulin usage can be weighed to decide optimal diabetes treatment and insulin's role in it.

Continuous Glucose Monitoring/Continuous Home Monitoring

REAL LIFE ISSUES WITH ACCEPTING CHM

Mary Voelmle, FMP (University of Colorado Denver, Aurora, CO)

This was an extremely interesting panel featuring three patients who used continuous glucose monitors (CGM). Mary Voelmle began by noting that only 70% of patients who start on CGM continue with the regimen. (Ed. note – we believe this varies widely depending on patients and education and resources.) Patients often have expectations not fulfilled by the devices, are frustrated by lag times in readings, and are surprised when they find themselves using self-monitoring of blood glucose (SMBG) even more frequently after CGM use. From our view, hearing patients discuss it, it seemed a classic discussion about a therapy early on in its innovation cycle; there are many cycles of innovations to come in our view.

Question: What were your expectations when you initiated CGM use? What have you found most frustrating about it?

Patient #1: I started glucose monitoring to raise my consciousness. I had an expectation that it would be accurate. But it's not always so and I find my dosing becomes somewhat of a game to me—I stack my insulin doses but it doesn't always match exactly what the monitor is saying or where I should be.

Patient #2: I initiated the monitor so my wife wouldn't have to worry about my lows during the night. It's taken care of that—now an alarm goes off and I can eat something if my blood sugar is low during the night. The sensor is the most frustrating part about it though.

Patient #3: The most frustrating thing about the sensor is the alarm—it's very hard when the alarms are so far off from where your glucose actually is.

Patient #4: It's often hard to wear it every day—it's pretty unsexy to wear and I don't have my purse with me at all times so I try to take breaks from it every once in a while.

Question: What have you changed most about your diabetes with CGM use?

Patient #1: I've stopped checking my blood glucose as often because of the arrows. A year ago when I was on SMBG, I would check my glucose all the time because I had to know where I was. I think my consciousness has gone down somewhat and I'm stacking insulin more.

Patient #2: The biggest change has been my awareness of what certain foods do to my blood glucose. For example, pizza raises your glucose very high but causes you to crash afterwards. CGM has changed my eating habits and made me become a healthier eater.

Patient #3: CGM has made me check my blood sugar much more often. Before I would check two to four times a day. Now, I check up to 15 times a day and notice very carefully which foods do what to my blood glucose.

Question: What would you like to see in the future in a CGM?

Patient #1: I would want to see it work with an iPhone. I would also want to see it have a bolus calculator so that you would make no mistakes in dosing.

Patient #2: I would want to see the infusion site and sensor all in one so the system didn't have two separate pieces. A new type of adhesive would be great as well because the current ones are tough on the body.

Patient #3: It would be good if the sensor's accuracy could improve so that I could rely more on the meter.

HEALTH OUTCOMES AND PATIENT AND PROVIDER EXPECTATIONS FROM CGM

Irl Hirsch, MD (University of Washington, Seattle, WA)

Dr. Hirsch gave the audience some practical tips about initiating patients on CGM. He suggested that patients attend a pre-sensor class before starting on the device that would discuss realistic expectations for use. He then gave several tips for approval letter-writing to insurance companies. Patients should then undergo CGM training. Most patients will require several months of CGM use before they learn how to best use the device. Some things that could make clinic visits and CGM use fruitful and efficient would be having many office personnel trained in CGM downloading and patients reading their meters often to enhance management.

- **Before patients are initiated on a CGM, they should attend a pre-sensor class.** At Dr. Hirsch's clinic, the classes are currently held monthly by an RN and an RD. At these classes, CGM devices and their respective pros and cons are reviewed. Realistic expectations regarding CGM are emphasized and basic CGM skills—including trending, downloading, and the need to continue SMBG.
- **Doctors may find several tips helpful when writing to insurance companies for approval:** letters should be individualized and if possible, the topics of hypoglycemia and pregnancy should be mentioned as reasons for initiating CGM. Data from randomized clinical trials (not anecdotal evidence) should be discussed as insurance companies will not take into account information from uncontrolled trials.
- **Patients should then undergo CGM training. Most patients will require several months of CGM use before they learn how to get the best use out of the device.** Patients should either be initiated with industry or clinic training. The patient should then return to the clinic for monitoring two weeks after treatment initiation. While some patients figure CGM out quickly and some never figure it out, most actually adjust over time.
- **Dr. Hirsch gave suggestions for making clinic visits and CGM use fruitful and efficient.** Doctors should ask patients to download their CGM readings or have them downloaded at the clinic. Medical Assistants, ARNPs, RNs, RDs, PharmDs, and even receptionists should all be trained how to download CGM information. Patients should be encouraged to read their meters often and to download their CGM data between visits to enhance management. Doctors should take as much time as possible to make sure patients understand their management – non-physician providers can also help with this.

CAN WE REALLY CLOSE THE LOOP?

Aaron Kowalski, PhD (Juvenile Diabetes Research Foundation, New York, NY)

Dr. Aaron Kowalski outlined prospects for the development of an artificial pancreas, i.e., the “closed loop.” He defined the goals of the JDRF-sponsored Artificial Pancreas Project as accelerating the availability of the artificial pancreas, ensuring wide availability and reimbursement of its components, and creation of a thriving, robust artificial pancreas market that gives diabetic patients many choices. Dr. Kowalski emphasized that the first-line goal of the project was to create a device that could prevent severe hypoglycemia by ceasing insulin delivery when patients are no longer responsive to “low” alarms. This is akin to the new Medtronic pump that has already been approved in the UK. The hypothetical pathway to an artificial pancreas will likely progress through 1) a pump that ceases

delivery when glucose is very low, 2) a pump that ceases delivery when glucose is trending low, 3) a pump that minimizes both hypo and hyperglycemia, 4) an automated basal/hybrid closed loop, 5) a fully automated closed insulin loop, and finally 6) a fully automated multi-hormone (insulin and anti-insulin) closed loop. Dr. Kowalski said it was imperative that industry now “take the bull by the horns” to ensure eventual commercialization of the artificial pancreas. We heartily agree. We had never quite heard a pathway as explicit as this; we found Dr. Kowalski’s presentation very helpful and very inspiring. We thought the last step was particularly interesting and wonder whether he was referring to glucagon, pramlintide, etc.

- **Dr. Kowalski defined the goals of the Juvenile Diabetes Research Foundation’s (JDRF’s) Artificial Pancreas Project:** to accelerate the availability of the artificial pancreas, to ensure the pancreas and its components are widely available, to ensure that devices from multiple companies are reimbursed and approved, to stimulate a robust market that gives people with diabetes many choices and spurs investment in the artificial pancreas, and to have the product judged by patients as bettering their lifestyle.
- **The main goal of this new artificial pancreas would be to prevent continuing insulin disbursement during severe hypoglycemia.** While many people envision an artificial pancreas quickly restoring euglycemia in diabetic patients to a state similar to patients without diabetes, this is unlikely to be the case.
- **The presentation detailed six progressions of an artificial pancreas:** 1) A low glucose insulin pump that turns all systems off when people are not responsive to hypoglycemic alarms, 2) A hypoglycemia minimizer that warns of impending (trending towards) hypoglycemia and turns off insulin delivery if there is no response to alarms, 3) A system that recognizes trends towards both hypo and hyperglycemia. If alarms are not noted, insulin will either be halted (trending low) or disbursed (trending high). Such a system could have the added benefit of preventing children missing boluses, but also carries the risk of false CGM readings perturbing treatment. 4) A basal-insulin hybrid system, 5) a fully closed-loop insulin system, and a 6) closed loop multi-hormone system.
- **Dr. Kowalski very inspiringly said that it is time for “industry to take the bull by the horns” and make the artificial pancreas a commercial reality.** We thought the last step was particularly interesting and wonder whether he was referring to glucagon, pramlintide, etc.

Questions and Answers

Q: With a closed-loop system, will patients still have to take boluses?

A: Yes. The system will first work to prevent very highs and very lows. In the meantime, patients will have to take boluses.

Outcomes of Large Clinical Trials in Diabetes

ACCORD/ADVANCE

Richard Bergenstal, MD (International Diabetes Foundation, Minneapolis, MN)

Dr. Bergenstal reviewed the results of ACCORD presented at this year’s ADA, which suggested a higher risk of mortality associated with intensive glucose control. He noted that this increased risk was not necessarily due to hypoglycemia and could be associated with “pushing too hard” on patients who were not responding to their therapy. Additionally, the risk of mortality was lower with lower A1cs. In light

of these results, intensive glycemic control and a target A1c of <7% still make sense, but doctors must carefully monitor their patients' responsiveness to treatment.

- **ACCORD's main goal was to assess the effect of intensive glucose therapy on diabetes given compelling evidence that tight control reduces microvascular disease.** The open-label trial enrolling 10,251 patients used a double 2x2 factorial design studied treatment for glycemia, blood pressure, and lipids across 77 sites in the US and Canada. The key question for the glycemia study was whether targeting an A1c <6% (the intensive arm actually achieved 6.4%) would improve cardiovascular outcomes compared to a treatment strategy that achieved an A1c of 7-7.9%.
- **Post-ADA 2008, many were saying that tight glucose control is not important. 1 year later, a more detailed secondary analysis of ACCORD and VADT suggested we can stick with our <7% A1c goal and that the risks are not so high.**
- **In terms of baseline characteristics, only A1c, taking aspirin, and a history of neuropathy were associated with an increased risk of death.** BMI and use of anti-depressants had only a marginal effect on mortality risks.
- **Analysis showed that those with the lowest A1c in the intensive group had the lowest mortality, showing that intensive control itself was not responsible for excess mortality in that group.** In ACCORD, an intensive glycemic treatment strategy was associated with a higher risk of death over 3.4 years of follow-up. However, in the whole ACCORD population, a 20-22% greater risk of death was associated with each 1% higher average A1c, confirming results from other trials like UKPDS and HOPE. Analysis showed that rapid reduction of glucose values or lower A1c values, independent of other factors, did not lead to the excess risk of death in the intensive strategy in ACCORD. In fact, those in the intensive control group who achieved the lowest A1c had the lowest mortality.
- **Severe hypoglycemia was the severe rate limiting event in the study. Hypoglycemia risks were higher if initial attempts to drop A1c were unsuccessful—this might be the key to effective intensive control.** Hypoglycemia was more common in the intensive arm of ACCORD (2-3.5% vs. 1% incidence). In the standard group, there was a 5% increase in mortality for those with one hypoglycemic event while there was only a 2.8% increase in mortality in the intensive group. There was a higher risk of mortality in the intensive group as compared to the standard group in patients with no severe hypoglycemia. However, these analyses do suggest that some persons with type 2 diabetes can safely achieve A1c levels below 7% using an intensive strategy, whereas other persons who do not readily achieve these lower A1c levels may be at risk if they persist in this strategy.
- **Thus, the key may be not pushing patients past their limits and reassessing treatment options if patients are not originally responsive to treatment.**

APOLLO/4T TRIALS

David Owens, MD (Cardiff University, Penarth, United Kingdom)

Dr. Owens described the 4T's findings that improvements in A1c were best with prandial and biphasic insulin therapy for patients with baseline A1cs >8.5%. Patients with A1cs <8.5% at baseline were equally likely to see A1c improvements with biphasic, prandial, or basal insulin. In general, adding insulin to oral therapies proved to have suboptimal responses in type 2 diabetic patients (A1c drop of 0.8% to 1.4%) and prandial and biphasic insulins were associated with more hypoglycemia and weight gain.

Overall the results suggested that complex, multi-insulin regimes may be needed to achieve target glucose levels and years two and three of the 4T study will explore this (4T was first reported at EASD nearly two years ago; we had assumed the trial was finished by now). He also touched upon APOLLO's findings that insulin glargine and insulin lispro are essentially equivalent in their lowering of A1c and blood glucose, but that insulin glargine is associated with less hypoglycemia.

- **The goal of the 4T study was to evaluate effectiveness of insulin initiation with three regimens: twice a day biphasic insulin (NovoMix30), thrice daily prandial insulin (NovoRapid), or once-daily basal insulin (detemir) before bed.** Insulin was initiated in 708 patients from 58 study centers in the UK and Ireland whose diabetes was inadequately controlled on oral agents. Patients were randomized to one of three study groups. The study's primary outcome was A1c levels achieved by each of the regimens. Secondary outcomes were the proportion of patients with A1c < 6.5%, proportion of patients with unacceptable hyperglycemia after 24 weeks of treatment, hypoglycemia rates, weight gain, quality of life, capillary glucose profiles, and the proportion requiring a morning basal injection. Starting doses were calculated with a gender-specific formula incorporating fasting plasma glucose, weight, and height.
- **A1c reductions were greatest with biphasic and prandial regimens. Patients with a baseline A1c > 8.5% were unlikely to reach an A1c < 6.5% with basal insulin. For patients with a baseline A1c < 8.5%, there was no difference between prandial, basal, and biphasic regimens in achieving an A1c < 6.5%.** Though biphasic and prandial regimens had the greatest A1c reductions, they were also associated with greater risks of hypoglycemia and more weight gain.
- **Overall, adding a single analog to metformin and sulfonylureas lowered A1c between 0.8 and 1.4% - this response was somewhat suboptimal however. Overall, the study suggested that patients with an A1c of around 8.5% will need more than one type of insulin to achieve target levels.** Oral agents could possibly achieve the same targets, with less inconvenience and cost. The final two of three years of the trial will examine the use of complex insulin regimens (two or more insulins) in patients.
- **The goal of the APOLLO study was to compare glycemic improvement in patients poorly controlled on oral agents in once daily glargine therapy vs. thrice daily lispro.** The open-labeled randomized control trial in 69 European and Australian centers enrolled 415 patients for 44 weeks. Patients received either oral antidiabetic agents (OAD)+ glargine once daily or OAD + lispro thrice daily. The primary endpoint was achievement of a 0.4% A1c difference between glargine and lispro treatment. Secondary endpoints were the proportion of patients achieving an A1c < 6.5% or 7.0%, a fasting plasma glucose < 5.5 mmol/l, SMBG profiles, hypoglycemia prevalence, and adverse events.
- **Both treatment regimens effectively reached A1c goals for patients with a baseline A1c of > 7%, but less effectively for those with a baseline < 6.5%.** SMBG profiles were shifted downwards for both groups between baseline and endpoint, but postprandial glucose excursions remained. Benefits of insulin glargine are its simplicity of administration, and thus its patient friendliness.
- **There were many more hypoglycemic events in the lispro group. There was an increase in treatment satisfaction in both groups over treatment with OADs.** There was no difference in safety analysis between the two groups.

ORIGIN, HEART 2D, AND OTHER ONGOING DIABETES CLINICAL TRIALS.

Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL)

Dr. Skyler recapped ACCORD, ADVANCE and VADT's findings, including that lowering A1c below 7% reduces the risk of microvascular complications and CVD risk in diabetic patients, thus making an A1c target of 7% reasonable. Along with discussing various suggestions regarding blood pressure, LDL cholesterol, and aspirin therapy, he made recommendations for a pathophysiologically based treatment algorithm focusing on lifestyle change, TZD, metformin, and exenatide (Amylin's Byetta) therapy (this combination was discussed in Dr. DeFronzo's Banting Lecture in 2008 at ADA) that would ideally bring A1cs below 6.0%. We thought it was notable to hear a clinician like Dr. Skyler talking again so openly about the virtues of A1cs under 6.0% for at least some patients; we haven't heard this since prior to when ACCORD was first released. We applaud this direction since from our view, patients are likely better off the closer they can get to normal blood glucose levels safely.

- **Recent studies have created questions about basic guidelines regarding aspirin/anti-platelet therapy, blood pressure control, cholesterol control and statin therapies, diet, exercise, glucose control, and weight reduction.**
- **Current guidelines suggest a blood pressure of <130/80 mmHg, but there are suggestions that treatment targets should be 110/70 mmHg.** Studies have shown that regardless of baseline, there was a significant reduction in risk of stroke with a diastolic blood pressure <70. The question then arises: should all people be treated with anti-hypertensive agents regardless of current blood pressure?
- **Current lipids goals are <70 mg/dl or <100 mg/dl. If patients cannot reach goals on maximally tolerated statin therapy, a 30-40% reduction from baseline will suffice. Moreover, statins should be added to lifestyle therapy for diabetic patients with overt CVD or without CVD who have CVD risk factors.**
- **Current aspirin guidelines suggest aspirin as a primary prevention strategy in those with diabetes at increased CVD risk or those over 40 with additional risk factors.** Aspirin has been shown to reduce serious vascular events from 0.57% to 0.51% per year but increased the risk of serious bleeds from 0.07% to 0.10%. Additionally, combination therapy with aspirin or clopidogrel is reasonable for 1 year after an acute coronary episode.
- **In terms of glycemic control, the ADA A1c target is <7% and ideally as close to 6% as possible without significant hypoglycemia.** The realistic target, however, is the lowest A1c level possible without unacceptable adverse effects. In general, an A1c <7 % has been shown to lower the risk of microvascular complications in both type 1 and type 2 diabetes and is associated with lower CVD risk. Moreover, glycemic control seems to provide a CVD benefit if it is initiated early in the disease course.
- **Thus, glycemic goals should remain unchanged with a 7% A1c goal.** Higher A1c targets are acceptable for people with hypoglycemia unawareness and established CVD.
- **A1c does not necessarily tell the whole story. Both A1c and estimated average glucose (EAG) give only an average and do not show variability.** High postprandial glucose and glucose variability correlate with poor outcomes. Yet there is no proof that treating specifically to reduce postprandial glucose or variability definitively improves outcomes.
- **Dr. Skyler suggested a new algorithm—the Skyler algorithm—that would differ from the current ADA and EASD treatment algorithms. The algorithm suggests lifestyle changes, then metformin + DPP4 treatment, exenatide, and lastly basal insulin.** The

algorithm would suggest DPP4s instead of SFUs as second line treatment after lifestyle changes and metformin because DPP4s moderate glucagon secretion and do not cause hypoglycemia or weight gain. Other treatment components, such as cholesterol and blood pressure control, should be kept in place.

Questions and Answers

Q: I am more confused than ever about blood pressure goals. Should the ideal then be 140/90?

A: I think a reasonable goal is 130/80. The big question that arises from these studies is should we initiate everybody on an ACE or an ARM? I say we should because it reduces diabetic retinopathy risk.

Q: Is type 1 diabetes significantly different enough from type 2 diabetes to warrant a different set of guidelines? Is there enough info for type 1 diabetes guidelines?

A: The main focus in type 1 diabetes should be prevention of renal disease and we should be using ACE and ARM inhibitors towards that end.

Novo Nordisk Corporate Symposium

Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL)

In an excellent symposium, Dr. Jay Skyler took questions from the audience. We were thrilled with the tone of the symposium and some of the questions asked. We thought it was so important that doctors, CDEs, nurses, and researchers got to discuss the issues important to them and felt that some very real, clinically relevant information came out of the symposium.

Questions and Answers

Q: I am a CDE from a rural program where the doctors that refer patients to me are satisfied with A1cs of 8 or 9%, which I know are not optimal. It's hard for me to advocate for my patients to get under 7% and many of my patients are not on insulin when they should be. What are my options?

A: This is a very difficult problem. Usually, the argument between the AADE and the ADA is whether A1cs should be 6 or 7%. Nobody believes A1cs should be at 8 or 9%. The best route would be to try to convince the doctors that between 6 and 7% are the current standards. But I understand it's a hard situation because if you frustrate the doctors, you run the risk of them not sending you patients anymore.

Q: When will the ADA start saying that low-carb diets are beneficial for lowering blood sugar?

A: The ADA will not say anything until they have definitive data for one type of diet versus another. The Duke RICE study for obesity used a 95% carb diet where people ingested 400-800 calories per day. It had a tremendous benefit in terms of metabolic improvement.

In the end, I think it doesn't matter what type of diet it is as long as it's below the calorie threshold. The benefits of a low-carb diet are that it prevents glucose excursions so maybe patients don't have to take insulin with meals. The principle is really that during active weight loss, a low-calorie diet is needed, and later, patients should eat whatever keeps them happy and healthy as long as it can sustain the weight loss and we know how to deal with it.

Q: I have understood that the ADA's position is that there is no science behind supplement use. Could you talk about this?

A: I received an email from a fellow doctor with a patient's question regarding a supplement that consisted of a variety of compounds. The patient wanted to know if it was beneficial for his diabetes. I wrote back to my colleague that "there is nothing wrong with this although the benefits may be overhyped."

Q: Do you think obesity is a major risk factor for cancer? Should we make people forcefully lose weight?

A: It's always a good thing to get patients to lose weight. The biggest health problem on a worldwide basis is obesity. We need to figure out that challenge as a society with all the important stakeholders—Coca Cola, McDonalds, etc. Obesity and insulin resistance are interesting things. We now have to figure out how to solve those challenges, have to figure out why people eat past the point where they're satiated.

Q: What is the difference between each of the analogs ability to bind to various receptors (especially the IGF-1 receptor)?

A: The problem is that experiments have not been done in *in vitro* systems with insulin at levels and conformations that normally circulate in the body. For example, when insulin glargine enters the subcutaneous space, it loses two arginines. So which form of insulin should we be looking at in *in vitro* systems, the shortened one, or the analog that's introduced? Also, in the body insulins circulate in the body at picomolar concentrations but are introduced in nanomolar concentrations. So which do we test? Answers will have to come from epidemiological studies and human trials to answer questions about insulins being associated with cancers. At the end of the day though, there's not that much difference between the analog insulins.

Q: What do you recommend for initial glucose lowering?

A: To get rid of glucose toxicity, I would start patients on a 0.2 units/kg of basal insulin and lifestyle changes, then assess if that's gotten rid of the "toxic stuff." After that, it's up to you and the patient whether to stay on insulin or start on another kind of therapy.

Q: A lot of patients are on regular insulin because they can't afford the insulin analogs. Can we make this work?

A: Yes you can. These insulins are a little more sluggish in coming on, and they have a tail after a meal. So the question ends up being how early before a meal should you take it. They also cause more hypoglycemia. You can make it work, but it's not ideal. Yet the price differential between NPH and the analogs is very big, and I think that if we could convince HMOs that the price differential for analogs was worthwhile, we would see a lot less hypoglycemia.

Q: Do you know of any more rapid-acting insulins in the pipeline?

A: The closest to market rapid acting insulin is MannKind's Afresa, the inhaled insulin. However, I'm rather underwhelmed with Afresa. Halozyme's recombinant human PH2O (rHuPH2O) hyaluronidase enzyme is 20 minutes faster, which isn't that significant, and does not compare to Afresa. I don't know about anything else—the three major insulin manufacturers won't answer questions about this.

Immune Modulation & Cure of Type 1 Diabetes

IMMUNOTHERAPY TRIALS IN TYPE 1 DIABETES

Peter Gottlieb, MD (University of Colorado Denver, Aurora, CO)

Dr. Peter Gottlieb emphasized that curing type 1 diabetes will mean successfully preventing loss of beta cell mass and outlined immunotherapeutic approaches to this goal. After going through some of type 1 diabetes' basic immunology, he described several strategies currently aiming to preserve beta cells: therapies that block the activation of autoreactive T-cells, which ultimately kill beta cells, a pro-insulin DNA vaccine that would prevent autoimmunity, antigen-specific therapy that would block insulin being presented to T-cells, and anti-GAD, anti-thymocyte globulin, and anti-Interleukin-1 (a cytokine) therapies. He detailed many of the immunotherapy trials currently underway and said that the best hope for remission or prevention will probably be an approach combining several immunotherapeutic options so that immunosuppression is lessened while positive effects are maximized. An important aspect of many of these therapies is that their greatest potency will be very early—either before disease onset or during honeymoon phases. We will review in our full company report the various companies associated with these efforts.

GENETICS OF TYPE 1 DIABETES

George Eisenbarth, MD, PhD (University of Colorado , Aurora, CO)

Dr. George Eisenbarth discussed our genetic understanding of diabetes and how we can hopefully use this knowledge to cure and prevent the disease. He began his lecture with some practical aspects of type 1 diabetes genetics, encouraging referrals to TrialNet for relatives of type 1 diabetic patients and suggesting several assays that could detect autoantibodies. He also recounted the immune basis of type 1 diabetes, explaining that certain HLA genes are highly associated with disease formation; as a reminder, HLA is the human molecule that allows for insulin recognition by autoreactive T-cells in diabetes. Because of type 1 diabetes' genetic basis, patients are very likely to develop autoimmunity if their parents are diabetic or they share high-risk genes with siblings. Through creation of animal models mimicking type 1 pathogenesis and trials such as the DAISY trial (which looks at the development of diabetes in genetically susceptible children), we will hopefully one day be able to predict and therefore treat or prevent type 1 diabetes, Dr. Eisenbarth said.

PIG ISLETS AS A SOURCE OF ISLET TRANSPLANTATION

Boris Draznin, MD, PhD (University of Colorado Denver School of Medicine, Aurora, CO)

Dr. Boris Draznin gave hope for the prospects of islet transplants from pigs. Because of the very limited supply of transplantable human islets and the extremely strong immunosuppressive regimes used for current transplantation protocols, another transplant method needs to be found, he said. His talk focused on the use of porcine islets, which can be isolated in large quantities and have the same physiological response to glucose as human islets. Some serious cons to use of porcine islets include the risk of animal virus transmission and strong immune rejection of the islets. Yet a solution may have been found in virus-free pig populations found on Auckland Island and in the encapsulation methods of a New Zealand company. The company has conducted trials with infusion of encapsulated porcine islets and had positive results in terms of A1c and mean glucose reduction. There are still many, many questions about this technology and Dr. Draznin noted that maybe patients will one day receive these islet infusions on a yearly basis for maximum efficacy. We aren't sure how broad the patient population would be. While we'd very much like to see this come to fruition, we feel the technology still has numerous challenges to overcome but are excited for future results.

BETA CELL REPLACEMENT/REGENERATION

David Harlan, MD (National Institutes of Health, Bethesda, MD)

Dr. David Harlan shared realistic, though not overly promising information about islet and pancreas transplantation. While there was lots of hope for the field following publication of the Edmonton protocol in 2000 (New England Journal of Medicine) and evidence that islet transplant reliably stores insulin independence (at least for the first year), this is no longer necessarily the case, Dr. Harlan said. It has been shown that the immunosuppressants given post-transplant significantly worsen renal function and that the risk of patient mortality never decreases post pancreas-alone transplantation. Thus, given the success of current insulin therapies and the low mortality rate associated with type 1 diabetes, any transplantation therapy will have to better patients' lives beyond what current methods can do, Dr. Harlan said. Other interesting facts from Dr. Harlan's lecture were that there is evidence that the native pancreas still secretes insulin many, many years after type 1 diagnosis, but that exogenous insulin therapy can actually suppress native insulin production, and that beta cells do not regenerate after age 30. We wonder what plans are to try exenatide in patients at risk of type 1 or who have it and are younger than 30.

PANEL ON IMMUNE MODULATION AND CURE OF TYPE 1 DIABETES

Peter Gottlieb, MD (University of Colorado at Denver, Denver, CO), George Eisenbarth, MD, PhD (University of Colorado at Denver, Denver, CO), Boris Draznin, MD, PhD (University of Colorado at Denver, Denver, CO), and David Harlan, MD (National Institutes of Health, Bethesda, MD).

Questions and Answers

Q: Do you automatically check children of parents with type 1 diabetes for autoantibodies or do you wait until symptoms appear?

A: We would suggest checking before symptoms. In Colorado, one child dies at onset of disease every two years. TrialNet will check for autoantibodies for free for children deemed genetically at risk.

Q: Could you talk about the differentiation between type 1 and type 2? Are they different diseases or just different spectrums of disease?

Dr. Eisenbarth: Type 1 is not one disease—it is an autoimmune disease that involves many factors. Type 1 and 2 are very distinct genetically and etiologically.

Dr. Draznin: In type 2, beta cells are not completely gone, they are just not functioning well. Whether this has to do with an inflammatory process, we're not sure.

Dr. Harlan: We know for sure that having type 1 diabetes does not prevent you from developing type 2 diabetes.

--by Lisa Rotenstein and Kelly Close