DIABETES CLOSE UP

Diabetes Close Up
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Do hospitals really care about diabetes care?

T h e S h o r t e r V e r s i o n

From the Editor: It has been such an incredibly interesting few weeks! So this issue's letter is about how much we love San Francisco. Now, you may think, there isn't that much about diabetes, in particular, that relates to San Francisco, is there? Well, maybe not per se. But just listen to what recent life has been like, going backwards!

- *Just last week, we had breakfast with the French-American Chamber of Commerce, who hosted a little roundtable, "Obesity-related diseases, a 21st century crisis." The room was packed with smart people asking excellent questions of a panel of stellar speakers including Mike Powell, Sofinnova Ventures Managing Director, Michael Hanley, PhD, Amylin's VP of Discovery Research, Dr. Mark McCamish, Pergelen's Chief Medical Officer, and Dr. Christian Vaisse of UCSF. Just what we learned about leptin alone was incredible. As it turned out, there was an excellent leptin twist, check this out – Dr. Vaisse did extensive leptin research as a post-doc at Rockefeller, Dr. McCamish studied leptin as part of his work at Amgen (pre-Pergelen), and Dr. Hanley will work with the compound even more closely moving forward as Amylin takes ownership from Amgen. It is the best when what is basically a community breakfast prompts dialogue like this.*
- *ADA Postgrad is always stellar, and we love that our fair city hosts it in even years. The quality of the talks was superb, as we continued to learn so much about the sea change in diabetes treatment. See inside for highlights and an in-depth discussion of Dr. Daniel Drucker's latest views on compounds just out and in development.*
- *We also love that San Francisco hosts so many other meetings – so many intriguing people come to visit! Thanks to biotech expert Michael King of Rodman & Renshaw equity research, who was in town for a cancer meeting, we had the chance to have dinner with Rockefeller basic science researcher Dr. Markus Stoffel. Fascinating. His perspective was so interesting because most of what we look at is in later stage development or on the market, whereas Dr. Stoffel is at the other end of the spectrum ~ we talked about everything from a shift in focus on the basic science side to fat metabolism (from purer focus on glucose in a vacuum) to what he really thinks about hot classes 11BHSD and PTP1B to biomarkers that could help accelerate clinical trials. See the December Cell Metabolism for an article by Dr. Stoffel – while one respected basic scientist recently told us he felt we were years away from a true, clinically useful biomarker, he conceded, science 'does move fast' looking skyward, as if to ask how it could possibly all be monitored – we feel the same way.*
- *Just as we always look so forward to JP Morgan's incredible investment conference to kick off each year (see DCU #55 for our in-depth notes on diabetes presenters), we can also always, knock on wood, count on San Francisco to host a number of other meetings – as long as doctors want to come here, we'll be in the learning zone. Think about the slew of 2006 meetings - the Critical Care meeting took place in January, ADA Postgrad in February, the Pediatric Annual Society happens in April, a new ADA Metabolic Syndrome meeting takes place in May, the Bariatric Surgery meeting is here in June – and that's only taking us through the first half!*
- *One of my favorite things about the Bay Area is that it's always been a fabulous place for perspective. If you need some in the next year, month, week, day, minute, micro-second just take a look at an essay we received last Monday by Andy Griffin, letting us know CSA (community supported agriculture) season is drawing near, right in time for St. Patrick's Day. In the meantime, take five minutes to drink in his essay. We urge you if you're in the area to indulge – not so much because they'll love it–they will–but because you will. http://www.ladybugletter.com/articles/lenabirthday.html*
- *Our title this month? Okay, it is slightly provocative – based on time we spent at the stirring AACE/ADA hospital meeting late last month. It's clear, given the evidence, that tight glycemic control in the hospital is a no-brainer. On that note, let's hope hospitals can aim to devote the necessary resources to achieve TGC; it's not easy, not even close, especially given sometimes perplexing editorials (see Feb 2 NEJM and page 23).*

-- by Kelly L. Close

In this issue:

Blogwatch – See below for blogs since our last monthly newsletter – you can see any update online at http://www.closeconcerns.com/ as well as subscribe to the blog feed.

- **March 8: Revised obesity projections darken picture of (near) future**
- **March 8: Dr. Irl Hirsch on the value of glucose monitoring**
- **March 1: NEJM piece addresses A1C reporting in NYC**
- **February 17: Strike one, strike two … Sanofi's rimonabant receives approv*able* letter for weight management and non-approvable for smoking cessation**
- **February 15: JAMA editorial on Sanofi's Acomplia – Damning with faint praise?**
- **February 13: Low-fat diet study creates media stir**
- **February 9: AMLN 4Q05 kicks!**
- **February 6: CC on WSJ on Amylin – overblown!**
- **February 5: On Nicholas D. Kristof on "Mike Huckabee Lost 110 Pounds. Ask Him How"**
- **January 31: Improving Inpatient Diabetes Care Consensus Conference – day two!**
- **January 31: Improving Inpatient Diabetes Care Consensus Conference – day one notes!**
- **January 29: Rodham & Renshaw and Close Concerns host Exubera call with Dr. Jay Skyler**
- **January 29: Novo Nordisk under investigation for insulin marketing**

T h e L o n g e r V e r s I o n

1. Conference Report: Hyperglycemia in the hospital? A look at the standard of care for diabetic inpatients

The American Association of Clinical Endocrinologists (AACE) and the ADA hosted a conference in Washington, DC January 30-31 entitled "Inpatient Diabetes and Glycemic Control: A Call to Action Conference." The two-day all-star program was inspiring *and* unsettling: while a number of talented researchers are leading the charge on inpatient glucose management, the need for further research is tremendous and the goals and questions daunting.

Significant progress appears to have been made (some would say from a low base) since the last AACE consensus meeting on the topic of inpatient glycemic control. At the December 2003 meeting (those that were there – all six dozen! – remember the blizzard outside and the excitement inside), most hospitals were only beginning to consider the issue, but this past January's conference began with an understanding of its relevance and focused more on implementation. The evidence for the need for better glycemic control was impressive, though it is not yet clear whether the consensus statement will mobilize the needed revolution in inpatient diabetes control – certainly, the 2003 statement detailing significant evidence hasn't yet.

The presentations, and our discussions with physicians, made clear that hospital attention to inpatient control is shockingly weak. It is only relatively recently that research has begun to highlight the importance of tight glycemic control (TGC) in the hospital – the first big paper emerging on this front was Dr. Greet Van den Berghe's *New England Journal of Medicine* paper in 2001; since then, we have seen considerable evidence underscoring the importance of glycemic control and have also learned a great deal about the barriers to improvement, which seem to be a fear of hypoglycemia, a labor shortage (particularly outside the ICU), and a lack of accountability for control of glycemia, broadly speaking. As most patients come into the hospital for reasons other than diabetes, HCP's attentions are focused elsewhere. Intensive insulin management is time-consuming, and in the face of a national nursing shortage and an already-heavy nursing workload, hospitals have been slow to address this problem.

In our fragmented system, it is challenging to prompt change. We would like to see TGC as a requirement for accreditation by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the organization that reviews hospitals to give them the required accreditation. JCAHO has recently developed a certification for "Advanced Disease Management," which includes TGC, but this certification is optional, and TGC is not currently required for accreditation. Though the consensus statement was thorough, spurring action in hospitals may require that TGC is mandatory for accreditation. While it is optional now, we expect that it will be required in the next five years, and in our view, the sooner, the better.

Some areas need more research (and there is demand for prospective, randomized controlled trials), but overall, TCG needs resources and implementation strategies. In particular, we believe continuous should play a special role and that it has enormous potential. The automation would alleviate labor issues, and alarms may assuage fears of hypoglycemia, which was identified as a reason nurses resist TGC. The availability of better tools for TGC in the hospital may also accelerate the addition of TGC as a requirement for accreditation, as some healthcare providers are hesitant because they believe adding TGC as a requirement right now will be unmanageable for staff or will result in many hypoglycemic incidents. The cost data coming out of the meeting—showing substantial savings due to shortened length of stay and reduced infection—would support a dramatic investment in intensive management. Notably, at the press conference, Dr. Rhoda Cobin of ACE stated that *"improved care for people with diabetes is an extremely critical issue,"* and Dr. Nathaniel Clark of the ADA emphasized that there is a large gap between *"what we know and what we do, what should happen and what does happen."* The written consensus statement from the conference is below; you can also find it online at:
http://www.diabetes.org/uedocuments/InpatientDMGlycemicControlPositionStmt02.01.06.pdf.
The position statement is divided into seven parts, according to the seven segments of the meeting, and it synthesizes the available data on each question.

Does improving glycemic control improve clinical outcomes for inpatients with hyperglycemia?

While the answer to this question is an obvious yes, data are strong in particular patient populations: in the surgical ICU, in myocardial infarction, in cardiac surgery, infection, and in critically ill patients. Data from ICU patients, both medical and surgical, indicate reduced mortality by 34%, sepsis by 46%, blood transfusion by 50%, as well as a

variety of other morbidities. Impressive data from Dr. James Krinsley have shown reduced length of ICU stay, and Dr. Anthony Furnary's data continued to show a significant reduction in mortality in cardiac surgery populations.

Is cost a barrier to improved inpatient care?

The data are fairly compelling, suggesting hospital costs can be cut by using diabetes care teams and intensive insulin therapy. Despite additional salary costs, expenses are still lowered with reductions in length of stay, opportunities for new DRGs, and fewer infections. **A more cost effective approach to glucose monitoring would generate additional savings, and evidence is building that will be convincing to hospital administrators.**

Data from Levetan and colleagues in 1995 calculated a 56% reduction in LOS per patient, for a cost reduction of $2,353 per patient. Dr. Van den Berghe has reported a 25% reduction in total hospitalization cost, and a focused look at catheter-related sepsis and length of stay by Dr. Christopher Newton in East Carolina showed a possible savings of $2.2 million per year for that hospital.

Has inpatient diabetes management become a quality and safety concern?

JCAHO has partnered with the ADA to develop the JCAHO-ADA Advanced Disease Management Certification, but this certification is optional, and inpatient management of hyperglycemia is not yet required for accreditation. While some physicians believe that adopting a requirement for intensive management too quickly would be unsafe for patients, others believe it is the only way to motivate hospitals on the issue. Despite the fact that most believe the evidence for TGC in the hospital is overwhelming, a recent survey by the Society of Critical Care Medicine showed that 28% of ICUs have initiated protocols for glycemic management and 17% plan to do so in the near future (yes, that math is right – 55% of ICUs don't have protocols or near-term plans).

What are the systematic barriers and challenges to improved hyperglycemia management?

The consensus statement identifies several barriers: nursing time, especially in the face of a national nursing shortage; skepticism about the importance of TGC; fear of hypoglycemia; lack of education about diabetes; lack of integrated information systems; lack of provider ownership of hyperglycemia (as most patients are admitted for reasons other than hyperglycemia and will have a variety of caregivers in the hospital).

What are effective strategies for achieving improved diabetes management in hospitalized patients?

Again, many of the presentations focused on the logistical aspects of diabetes management. While recent blood glucose management protocols are a huge step forward from the sliding scale, which was an ineffective reaction to hyperglycemia rather than proactive work toward euglycemia, it seems stable glucose control requires more attention than hospitals can provide. It is our hope that an inpatient continuous monitor could catalyze the already-rolling movement toward good care of diabetes patients in the hospital. In addition to the lives saved and complications avoided, Dr. Nathaniel Clark of the ADA noted that it is important to reinforce the message to patients that glucose control is important. If it is ignored in the hospital, much of the message in the outpatient setting is undermined.

Diagnosis and management of patients identified with hyperglycemia in the hospital

Our main takeaway from this point was that inpatient hyperglycemia represents an **untapped opportunity for identification of people with diabetes who may otherwise go undiagnosed for several years**. At present, patients who experience hyperglycemia in the hospital do not necessarily receive follow-up to ascertain whether it was transient stress-induced hyperglycemia, IGT, or diabetes.

What are the areas needing further research?

Though five separate categories for further research were noted, each with multiple questions, the main focus was on understanding the mechanism by which hyperglycemia develops and by which it causes harm, **as well as more practical questions of how to improve inpatient glycemic control**. The further questions also called for an analysis of what additional evidence and randomized controlled trials are needed, a point that was contentious: we agree with Dr. Anthony Furnary, who suggested that randomizing patients to conventional control (hyperglycemia) at this late stage in our knowledge would be unethical.

Highlights of the Meeting

Dr. Greet Van den Berghe unveiled new data:

- The legendary Dr. Van den Berghe spoke first, reviewing her data on intensive control in both surgical and medical ICUs. She emphasized that in her first study the difference in blood glucose levels between the intensive insulin therapy group and the non-intensive group was relatively small: the conventionally managed group had blood glucose levels around 150 mg/dL, not 300 mg/dL.
- New four-year follow-up data showed that the benefits of tight glucose control (TGC) were maintained long-term: even at four years, there was a lowering of mortality in the TGC group (p=0.006), demonstrating that TGC confers not just a short-term but also long(er)-term mortality benefit.
- While the 2001 study was in the surgical ICU, it was not initially clear that these results would apply to the medical ICU as well. The success of TGC in the surgical ICU was measured in prevented complications, such as blood stream infections, acute renal failure causing dialysis, etc. The population of a medical ICU is very different, often patients with HIV, cancer, or end-stage diseases.
- Dr. Van den Berghe's recent work included 767 patients who were in the medical ICU for at least three days. There was a higher mortality rate in the medical ICU than there was in the surgical ICU, and patients receiving intensive insulin therapy (IIT) had a lower mortality rate (43% compared versus 52%, p=0.009).
- One fascinating aspect of Dr. Van den Berghe's talk was her discussion of separating blood glucose and insulin as variables. She said that when she conducted her landmark 2001 trial, her hypothesis was that insulin deficiency might affect mortality, but what she found was that intensive insulin therapy benefited patients because of its impact on blood glucose levels.
- Data here were presented in the NEJM following the meeting; for a detailed summary of the 2006 study, see the literature review on page 23.

Anthony Furnary stayed up all night to crunch complete 2005 data and wowed audience:

- Dr. Furnary wowed the crowd with his data from Portland, now totaling 5,619 patients. (www.portlandprotocol.com)
- He had four lessons from "trends in glycemic control":
    a. Insulin talks, glucose walks
    b. Hyperglycemia kills
    c. Insulin saves
    d. Time is on our side
- He made it clear that he thought glycemia was the villain, not diabetes.
- Although he is often criticized for not having powerful prospective, randomized controlled data, he reiterated that such a study wouldn't be ethical – very few patients have blood glucose over 150 mg/dL in his hospital now and since the patients have a much higher survival rate, he can't imagine putting some patients into a "control" group.
- His main metric is 3BG, which is average blood glucose for three days after surgery. 3BG is highly significant in altering mortality. 3BG for 2005 was a stunning 121 mg/dL. On average, it takes under three hours to get most (90%) patients under control. He said Portland hadn't had a 3BG >200 for the last three years. This is in contrast to the early days, when any pressure to move average 3BG lower was very controversial. 3BG is highly significant in altering mortality and Furnary urged that it be continued in all different databases. Over seven years, diabetic CABG morality is 0.9%, compared to national mortality STS database of 3.4% - thus, the data behind the infamous 'it's better to be diabetic in Portland' mantra.
- Furnary emphasized that duration of therapy is key – this is about getting the patient healthy long term, not just in the ICU. He was convincing in his belief that good glucose control is about the glucose levels, not about insulin levels – insulin is a mechanism to get there.

JCAHO Executive VP Charles Mowll presented on the Joint Commission's interest in diabetes:

- JCAHO has partnered with the ADA to develop the JCAHO-ADA Advanced Disease Management Certification, but this certification is optional, and inpatient management of hyperglycemia is not yet required for accreditation. While some physicians believe that adopting a requirement for intensive management too quickly would be unsafe for patients, others believe it is the only way to motivate hospitals on the issue. Despite the fact that most believe the evidence for TGC in the hospital is overwhelming a recent survey by the Society of Critical Care Medicine showed that only 28% of ICUs have initiated protocols for glycemic management and 17% plan to do so in the near future (yes, that math is right – 55% of ICUs don't have protocols or near-term plans).

- But good news! A steering committee made up of representatives from ADA, AACE, AADE, the American Association of Critical Care Nurses, the American Dietetic Association, Diabetes Care, and Education, the American Society of Health-System pharmacists, the Case Management Society of America and the Society of Hospital Medicine, have come together to with JCAHO to support and oversee the development, piloting, and implementation of core performance measures that could ultimately be required for JCAHO accreditation. We believe that work on core performance measures will complement the optional certification process until the necessary core performance measures for TGC can be added to the required accreditation process. A key function of the steering committee is to create awareness within the medical community and among industry partners regarding the need for improved management of diabetes and hyperglycemia in the hospital. We believe this initiative will help drive the JCAHO/ADA certification program, which offers tremendous opportunities for hospitals to being the quality improvement process. This, in turn, will help facilitate more efficient and "less painful" implementation of core performance measures once they become part of JCAHO accreditation.

A financial case for tight glycemic control in inpatients:

- The second session of the day featured three speakers addressing the question "Is cost a barrier to improved inpatient care?" Dr. Thomas Balcezak, a hospital administrator, spoke on "New clinical initiatives: the view from hospital administration," emphasizing that hospital administrators are concerned with the public's trust, public reporting, pay for performance, patient capacity, and financial solvency.
- Between 1996 and 2003, discharges of patients with diabetes were up 26%, compared with a 19% increase in discharges overall. In most inpatients with diabetes, the disease was a comorbidity, not the cause of hospitalization. While the length of stay (LOS) for the hospital overall had fallen by 2.5% to 6.55 days, a full day's difference remained between all patients and those with diabetes.
- In that time period, there had been a 30% decrease in overall mortality (2.79% to 2.22%), but an increase in mortality for patients with diabetes that translated to 40 excess deaths per year.
- The financial model: 6,314 admissions with diabetes mellitus annually, with 62% poorly controlled, yielded 3,915 eligible patients. If a team could see 30% of these patients, this would be 1,174 patients/year.
- He estimated the net savings to be $439,000 over three years, and the expense to be $225,750, for a diabetes team (not all members FTE).

Nursing issues as a barrier to improving inpatient diabetes care:

- Nurse and CDE Linda Haas (VA Puget Sound HCS, Seattle) began the second day with a presentation on this topic. In a survey of nurses, only 41% said that they believed they had access to adequate education on diabetes. While significant changes have occurred in diabetes care in the last five years, 28% of nurses reported no continuing education on diabetes in the past 2-15 years.
- A theme of the talk and of the day was the issue of timing: insulin is often given hours before food arrives, especially around shift changes, as tray delivery is unpredictable. Also complicating the picture, patients who are ambulatory eat food from vending machines or cafeterias, or visitors may bring food for patients.
- Nurses fear hypoglycemia: Haas said that it was *"common in an inpatient setting"* for nurses to skip basal and prandial insulin because of a two-digit BG reading—even a number like 80 or 90, well within the desired range. She suggested that ICU nurses are accustomed to elevated blood glucose levels and need to be reeducated about what is normal.
- CDE Geralyn Spollett of the Yale Diabetes Center emphasized the need to train a new generation of CDEs and better diabetes training for nurses in general. Spollett noted that while there are 20.8 million patients with diabetes, there were only 13,000 CDEs as of 2004.
- Spollett highlighted deficits in diabetes knowledge: a university-based hospital study found that on the Diabetes Basic Knowledge Test nurses scored a mean of 73%, a failing grade. Another study showed that the more staff nurses perceived they knew about diabetes, the less they actually knew.

Practical strategies and IV infusion protocols:

- The bulk of the sessions the second day were dedicated to question 5, "effective strategies for achieving improved diabetes management in hospitalized patients." Dr. Phil Goldberg of Yale discussed how his hospital had created its protocol. His presentation succeeded in making the problem of inpatient glucose management very apparent: his first case study was "a 61-year-old man with multiple myeloma, admitted with multilobar pneumonia. Required ventilator, broad-spectrum antibiotics, high-dose steroids, dopamine." His point was that, while all of the diabetes specialists in the room were thinking about diabetes, in the intensive care setting there are many competing priorities.
- Prior to 2001, Yale's top academic tertiary care center used sliding scale, and presentations of real charts and the "sawtooth" blood glucose levels were incredible.
- Dr. Goldberg emphasized that gradual implementation is important to avoid massive hypoglycemia, and for this reason he does not think JCAHO should mandate certain levels; he believes this would result in a dangerously rapid implementation of protocols at hospitals.
- He also spoke to the importance of educating nurses about what normal levels truly are. He related a story about asking the nurses to estimate their own BG and then using a glucose meter to take their actual measurements—most of the (non-diabetic) nurses estimated that they were 170 (the number they thought of as "normal") and were shocked to learn that they were at 72, a number they thought of as hypoglycemic.

—by Erin M. Kane and Kelly L. Close

2. **Sanofi-Aventis: Pre-FDA-decision public confidence persists**

The constant speculation about the fate of rimonabant, the obesity drug from Sanofi-Aventis, came to a screeching halt in mid-February with the announcement that it had received an approvable letter for weight loss and a non-approvable letter for smoking cessation. This revelation surprised some of the healthcare and investment communities, as the overwhelmingly confident statements made by Sanofi-Aventis had been presumed a clear sign that they would receive approval. Others who followed the data closely were less surprised by the decision than by the confidence, some would say arrogance, the company projected prior to the decision as well as during and followings its February 22 analyst meeting in Paris.

In fact, although Sanofi-Aventis's confidence was not based on communication from the FDA that they would receive approval, the company based not only public statements but also plans for dissemination of information and the launch on the solid expectation that they would receive approval before March 1. Sanofi refused to reveal its PDUFA date and the expected label, though it's now clear that they had applied for a weight loss indication as well as smoking cessation, and the company announced to analysts its expectation of a second quarter launch before hearing from the FDA.

Even more surprising to us is that the company's attitude has changed little since it released its terse press release announcing the setback Feb. 17. During its analyst meeting, Sanofi explicitly said that it anticipated launching rimonabant during the second half of 2006, and it reported that the FDA had not requested further weight management trials before approval of the drug. We can't imagine that public bravado is doing much to curry favor with the FDA. While the company's attitude may not have changed, it seems the trade name may. At the Feb. 22 analyst meeting, the word 'Acomplia' was nowhere to be found in the presentation – it doesn't, of course, take a detective to think that 'Acomplia' pretty distinctly implies 'accomplishment,' which may not be the first message one would want to send... while it used to be on the pipeline chart, the pipeline now just says rimonabant.

As a reminder, rimonabant received tremendous attention in the last year with results from three major Rimonabant In Obesity (RIO) trials being published in *The Lancet* (RIO-Europe, April 2005), *New England Journal of Medicine* (RIO-Lipids, November 2005), and the *JAMA* (RIO-North America, February 2006). At last year's ADA meeting, researchers reported the results of RIO-Diabetes, a yearlong multi-center trial comparing the effects of rimonabant on weight-loss and improvements in metabolic and cardiovascular variables for obese patients with diabetes. On February 1, 2006, researchers announced that a new phase 3 trial, STRADIVARIUS (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant-The Intravascular Ultrasound Study), will investigate whether rimonabant can slow the progression of atherosclerosis.

And while in the RIO trials, rimonabant has shown improvements in several parameters, including weight loss, waist circumference, HDL cholesterol, and incidence of metabolic syndrome, there are significant outstanding concerns

about psychiatric side effects. Despite the company's aggressive positive projections for the launch of rimonabant, we suspect its receipt of an approvable letter from the FDA was influenced largely by high rates of depression in the treatment group when compared with the placebo group.

In all three RIO trials, more patients taking rimonabant reported psychiatric disorders than patients taking placebo, which causes great concern. In RIO-Europe, there was a five-fold increase with the 20 mg/day dose: 1.5% of patients on 20 mg/day of rimonabant, 0.3% of patients receiving placebo, and 0.3% of patients receiving 5 mg of rimonabant reported psychiatric disorders. Three times as many patients on 20 mg of rimonabant (6.1%) reported having anxiety than patients on placebo (2.1%) in RIO-NA. In RIO-Lipids, the percentages of patients with psychiatric disorders recorded as a "serious adverse event" were comparable between patients taking rimonabant and patients taking placebo for a year (0.3% for all groups). However, more than twice as many patients on 20 mg of rimonabant reported anxiety than patients receiving placebo for a year (8.7% vs. 3.8%).

Along the same lines, more patients taking rimonabant dropped out of RIO trials for psychiatric reasons than patients taking placebo. Anxiety was a more common reason for discontinuation among patients taking rimonabant than among patients taking placebo. In RIO-Lipids, 1.7% of discontinuations in the 20 mg rimonabant group were due to anxiety, compared to 0.6% of discontinuations in the placebo group. These percentages were 1.0% for patients receiving 20 mg/day of rimonabant and 0.3% for patients receiving placebo in RIO-Europe and RIO-NA after one year. In addition, patients taking rimonabant cited depression as a motivation for discontinuation more often than those taking placebo. In RIO-Europe, the percentages of discontinuations due to depressed mood were 3.7% in the rimonabant 20 mg/day group, 2.3% in the rimonabant 5 mg/day group, and 3.0% for the placebo group. In RIO-Lipids, rimonabant was associated with nearly a five-fold increase in percentage of discontinuations due to depressed mood compared to placebo: 2.9% in the 20 mg/day group, 1.7% in the 5 mg/day group, and 0.6% in the placebo group. The percentages in RIO-NA were 2.2%, 2.1%, and 1.3%, respectively, after one year. Among patients in the same treatment group for both years in RIO-NA, the percentages of discontinuations due to depressed mood were comparable between patients receiving rimonabant and those receiving placebo, suggesting that the psychiatric effects of rimonabant occur early and are not different from placebo after two years of treatment.

Previous studies have found that diabetes doubles the risk of depression, and a study earlier this month in *Diabetes* (Musen et al.) indicated that diabetes is associated with structural changes in the brain such as abnormal gray matter densities. The exact nature of the association between obesity and depression is unclear, but the social consequences and stigma of obesity are profound. As such, it is especially worrisome to recommend without further study a drug that appears to produce or exacerbate depression in people who may already have an increased risk for the condition.

Of interest, the editorials accompanying RIO-NA, RIO-Lipids, and RIO-Europe have been mixed in tone. The *JAMA* editorial on RIO-NA points out the benefits of the study and what the researchers did well, and then highlights politely all of the issues with the statistical analysis, drop out rate and side effects. Simons-Morton et al. state frankly, "randomization no longer serves its purpose when investigators fail to analyze those who do not adhere." They are referring to the fact that the investigators in RIO-NA only measured one-year weight in 1,602 participants, out of a starting population of 3,045! Dr. Susan Yanovski, in her *NEJM* editorial accompanying RIO-Lipids, gives a mixed review as well. Dr. Yanovski recognizes that the development of drug therapies such as rimonabant is important because 5-10% weight loss among obese patients can significantly improve risk factors for obesity-related diseases and delay or prevent type 2 diabetes. Furthermore, if approved, rimonabant would offer an additional choice for patients and physicians in a field where choices and options are currently limited. At the same time, she points out the many limitations of RIO-Lipids—high drop-out rate, strict exclusion criteria, and only moderate weight loss—as well as expresses concern over the likelihood that obesity treatments such as rimonabant will be misused for cosmetic purposes by people of normal or near-normal weight. The commentary by Pagotto and Pasquali accompanying RIO-Europe in *Lancet*, however, was entirely positive. In response to the results of RIO-Europe, Pagotto and Pasquali report the trial was a "substantial advancement" and that rimonabant "could now be close to clinical practice"—and that was back in April 2005! While it is not surprising that there was much excitement after the first RIO trial results were published, the commentary did not even make mention of the trial's limitations or the side-effects of rimonabant.

We are glad to see that the FDA has been especially careful in its evaluation of rimonabant, as safety data for the drug has been hard to come by and often overlooked. Depression is not as visible a side effect as some, but it carries some obvious dangers (see footnote, JAMA, page 772, gunshot wound, under adverse events) meaningfully affects

quality of life and can be dangerous. Moreover, rimonabant would likely be taken by huge numbers of people for extended periods if approved. The possibility of such a sizable impact demands that we weigh the drug's benefits and risks very carefully. Sanofi has proclaimed that the FDA has not requested that any new weight management studies be done. Given their ongoing trial examining depression, we suspect the language around the FDA's lack of a need for "weight management studies" is deliberately specific.

—by Katelyn L. Gamson, Erin M. Kane, and Kelly L. Close

3. Leading diabetes researcher exudes confidence over exubera

Though he had spent almost 10 years researching inhaled insulin, Dr. Jay Skyler didn't appreciate its possible impact until last summer when he was interviewed by El Herald, the Spanish-language edition of the Miami Herald. When the front-page story on Exubera was published, his father-in-law called him from a Winn Dixie selling the Miami Herald and described the commotion that the product – still under FDA review – had created.

The furor continued over the next several days. "The impact that we had that week from telephone calls to inquire about it was something short of unbelievable," said Dr. Skyler, Professor of Medicine, Pediatrics & Psychology at the University of Miami. Though his research center is a leader in islet cell transplants and Dr. Skyler himself leads an NIH research group for diabetes prevention – areas that he says are "scientifically more intriguing" – those efforts do not elicit the kind of reaction that inhaled insulin does. "I think those of us who are healthcare-types, myself included to some extent, tend not to appreciate how much the public really wants this," he said in conference call sponsored by Mike King of Rodman and Renshaw, shortly after Pfizer's announcement.

Exubera, of course, received FDA approval last month, and while the product's manufacturers, Pfizer/Nektar, initially said it would not be available until June – coinciding with the ADA's annual meeting – we assume Exubera could well be launched sooner.

The other Great Unknown is price. Pfizer remains mum, but we suspect a pricing range between $4 and $6 a day – slightly higher than the $3-$4 we projected last month because upon doing some more work, we realize that the price ceiling on insulin has increased – patients taking Lantus are paying $90/vial and often need at least a couple of vials per month – when you add a rapid acting analog, the price comparison is quite high. Of course, for every patient on analogs, there are still an equal – more! – number of patients on the old, cheap insulins that can cost as low as $1/day – but the analogs are growing 50-plus percent or more, while the older insulins are growing very slowly, if at all. At least one investment firm is projecting about $4.40 a day, which – according to Dr. Skyler – would still be more than twice as much as taking the same amount of some insulins by injections. Nonetheless, if it is priced in the $4 range, that is the low end of expectations and we would perceive it as bad news for Lilly/Alkermes, Novo Nordisk, Mannkind, and Kos Pharmaceuticals. All of them are developing inhaled insulin, and while demand may indeed be significant, a $4 price point could squeeze profits.

Those considerations aside, Dr. Skyler is bullish on the product, and his views matter because he is one of America's most prominent diabetes researchers – his business card includes six lines of small type just defining his various jobs and titles. In 1996, Pfizer asked him to be an investigator on the Exubera Inhaled Insulin Program, and he chairs the company's global Exubera Advisory Committee. He also consults with most of the companies developing inhaled insulin.

While he spoke highly of competing products, he said that he doubted that any of them would get to market before 2009 or 2010. "Exubera has a path of being able to be the monopolistic [player] on the market for that period of time," he said. Dr. Skyler believes that relatively few patients currently taking injections will switch to inhaled insulin, as those individuals have grown accustomed to the needles. Exubera is not indicated for the type 1 population that would most welcome an alternative to shots – children. Regardless, it's safe to assume that inhaled insulin will not make huge inroads in the type 1 population because those patients would still need to take injections for their basal insulin; the inhaled variety is a short-acting pre-meal medication.

Of course, that still leaves a massive potential market – type 2 patients – and Dr. Skyler projects that inhaled insulin will be most popular among type 2s who are transitioning to medication or who have been on oral meds but have feared needles. "If this allows them to do that sooner than they otherwise would, I think that on a population basis

we're going to see a substantial improvement in the average blood sugar in the community at large, and that's going to be a real bonus for diabetes therapy in general and for reducing the burden of diabetes," he said.

But Dr. Skyler acknowledges that hurdles remain. For starters, the long-term effects on lung function are unknown. The label for Exubera recommends that lung function be tested at the beginning of treatment, as well as at six months, 12 months, and annually thereafter. Such tests are done with spirometers, but endocrinologists and primary care physicians don't usually do those tests in their offices. That means they'll have to either buy a spirometer (about $700) and train their staff on its proper use, or refer the test to a pulmonary lab, which will add a substantial cost. If the tests are done in-house, the process would need to be standardized – and the staff would need to be certified – to ensure accurate, reliable numbers.

"The question here is, without that kind of standardization and without that kind of certification, what kind of numbers are going to show up?" Dr. Skyler asked. "How are people going to interpret it? How are they going to implement it? Who's going to pay for it? Are the patients going to be willing to get it? It creates a burden that is unknown." For the $7 billion insulin market, another question is to what extent insurers will cover inhaled insulin. While Dr. Skyler did not express an opinion, we believe the coverage question is problematic. Insurers typically will not pay for a more expensive product or treatment that offers only an additional convenience – and inhaled insulin has not been demonstrated to improve glycemic control compared to injections. If anything, inhaled insulin has less precise dosing and may be a more difficult system for achieving tight control. While it may help those patients who fear needles, it is still largely a product of convenience – though from our perspective, the convenience provided is incredibly valuable if it lowers the average A1C, for example.

Perhaps a larger issue is to what extent health care providers will spend the time and energy to educate patients on inhaled insulin. In our view, these issues cut to the heart of why intensive therapy generally, and insulin specifically, is not more widely adopted. Insulin's proper use requires that doctors, nurses, or CDEs educate, train, and monitor patients – a time commitment, they say, that is difficult to make given current compensation levels. Providers say that they are not paid enough to provide even standard care, let alone exceptional care, for a complicated, time-consuming disease like diabetes. Why would inhaled insulin change that basic dynamic?

For his part, Dr. Skyler is more optimistic, saying that Pfizer's excellent sales and marketing staff will help with Exubera's acceptance. "They're really good about getting their products understood in the physician marketplace," he said. Further, he believes that what will ultimately drive inhaled insulin sales is not corporate advertising campaigns or physician support – but the patients themselves. "My view," he said, "is that docs like to do things that make their patients feel better and get better and happier, and they're going to respond because patients want this."

— by James S. Hirsch and Kelly L. Close

4. Conference Report: The ADA Postgraduate Sessions

Next up, we attended the 2006 ADA Postgraduate Sessions February 10-12 in San Francisco. There were nearly 700 attendees, as well as a range of exhibitors, including Abbott, Amylin, BD, Lilly, and TrialNet. Highlights are included below.

1. The Friday evening Novartis-sponsored symposium on "Improving Glycemic Control with Incretin-Based Therapy: Bridging Research and Clinical Perspectives" was very well attended and featured Drs. Lawrence Blonde (the Ochsner Clinic), Vivian Fonseca (Tulane University), and Julio Rosenstock (Dallas Diabetes and Endocrine Center). Most of the time was spent discussing GLP-1, though the DPP-4 inhibitors were discussed as well. A question arose in the Q&A about the pleiotropic effects of DPP-4 inhibitors, or the possibility that the inhibitors could affect other pathways, as DPP-4 is an enzyme that is present in multiple tissues and serves multiple purposes. The speakers were also asked about the utility of using DPP-4s in combination with GLP-1, and they noted that DPP-4 also degrades GIP, another gut hormone involved in metabolism, so there might be some added value in combining both. In the Q&A, the speakers discussed where they would use the drugs in the progression of type 2, saying that they thought sulfonylureas would be eliminated (it couldn't be fast enough, from our perspective) and that DPP-4 would be used earlier than insulin and exenatide because patients prefer oral drugs. (Inhaled insulin was not addressed.) Then, they said, insulin or GLP-1 would be used; while insulin causes weight gain and GLP-1 weight loss, we have a good deal of experience with insulin. Dr. Blonde added

that A1Cs will matter in the decision: a person with an A1C of 10 would require insulin to see an adequate drop. Dr. Rosenstock said that his favorite combination was a use (off-label) of exenatide and insulin, and that he thought there might be studies of this combination at the next ADA.

2. The lecture hall was absolutely packed for Dr. Dan Drucker's presentation on incretins — the moderator suggested that the people in the back might have to leave due to violation of the fire code! Dr. Drucker spoke on the incretin effect, reviewed the AMIGO studies, etc. We were especially intrigued by his comment on exenatide versus basal insulin, which was that exenatide is easy to use, whereas basal insulin leads to "more phone calls and self blood glucose monitoring and requirement for more dose adjustments." Dr. Drucker noted that the LAR results, which will be presented in more detail at ADA, showed a "striking" 2% reduction in A1C and a nine-pound weight loss in four months. He flashed a slide of the companies working on GLP-1. On the competitive landscape, he mentioned Novo Nordisk's liraglutide, citing its once-daily administration; this compound entered phase 3 testing earlier this month. Others on his list appear to be considerably further back, including Sanofi's AVE-0010 and ConjuChem's CJC-1131.
3. Dr. Drucker also noted that Novartis' vildagliptin and Merck's sitagliptin were DPP-4 inhibitors that have completed phase 3 testing. Of the DPP-4s, Dr. Drucker said that it was possible these would be available in 2007. He mentioned that they would be good to add to other medications, including metformin, sulfonylureas, glitazones, TZDs, and insulin, but that as a monotherapy, the head-to-head vildagliptin versus metformin trial had shown metformin to be superior. Dr. Drucker compared DPP-4s to GLP-1, stating that the most obvious difference was that one was injectable while the other was oral, but that other considerations included the nausea associated with exenatide and the greater antigenicity with injectable proteins. He said that no side effects have been detected with DPP-4 inhibitors thus far, though they may be detected later, and that DPP-4 inhibitors target a widely expressed enzyme and that it is still early in our understanding of what the pleiotropic effects of these agents might be. In terms of future considerations, Dr. Drucker said that he was very interested in looking at the efficacy of a second generation of these drugs that can be given less frequently, "once daily, or perhaps even once a week." He also noted that it will be important to follow whether there will be long-term durability of the effect on the beta cell.
4. Dr. Carl Grunfeld of UCSF spoke on "Atypical Diabetes," focusing on diabetes induced by anti-psychotic medications and anti-retroviral therapy for HIV/AIDS patients. Drug toxicity affects glycemia in these patients, but there are other glycemia-raising factors as well, including the stress of infection and the obesity that is common with schizophrenia. Though these might seem like small subpopulations, Dr. Grunfeld, who is based in San Francisco, said that about 25% of his patients are schizophrenic and another 30% have HIV/AIDS. Wow.
5. Dr. David Ludwig of Harvard addressed the topic of glycemic index and glycemic load. Short-term studies have shown that low glycemic index diets lead to increased satiety and reduced food intake when compared with high glycemic index diets. Glycemic load is a concept that incorporates both the glycemic index (how rapidly a particular carbohydrate is broken down into sugar) and the carbohydrate available in a serving a food, or essentially how dense a food might be. While carrots, for example, have a high GI, they have a low GL.
6. Dr. Vincent Poitout of the CRCHUM Hospital of Notre Dame detailed our current understanding of fat and "lipotoxicity," a term we love (albeit perversely). In recent years, scientists have discovered that adipose tissue, once thought to be inert, is actually metabolically active. As we know, visceral fat is especially dangerous because it interferes with key organ activity. The lipotoxicity hypothesis postulates that the accumulation of fat in non-adipose tissues induces insulin resistance and pancreatic beta-cell dysfunction. An excess of fat leads to fat in non-fat tissues, such as in the muscle where it causes insulin resistance, in the beta cell where it impairs insulin secretion, and in the liver, which becomes insensitive to the inhibiting effects of insulin on hepatic glucose production. In terms of treating lipotoxicity, Dr. Poitout discussed decreasing BMI, and he also identified the AMP kinase as a potential drug target. Upregulation of AMP kinase would decrease fatty acid esterification, increase fatty acid oxidation, and decrease ceramide synthesis. Exercise, leptin, adiponectin, TZDs, and metformin all upregulate AMP kinase.
7. Dr. Bill Polonsky's interactive session on "Implementing Behavioral Change in Diabetes" was packed and the audience was very engaged, especially so for late on a Saturday afternoon during the Chinese New Year parade. In a survey of 200 physicians, Dr. Polonsky found that the top reasons physicians believed their patients were not compliant was because they had poor self-discipline (53.2%), poor willpower (50.0%), were not scared enough (36.9%), or were not intelligent enough (16.3%). In reality, Dr. Polonsky said, the two main reasons patients are not compliant is because they believe it is not worthwhile or not achievable. Rates of depression are two to three times higher in people with diabetes. Dr. Polonsky discussed strategies for uncovering obstacles and helping patients to be motivated and encouraged.
8. Dr. Aaron Vinik's presentation on neuropathy was highly entertaining and very clinically oriented, focusing on

how patients would present with different forms of neuropathy. Our main take-away from this session was that incredible diversity exists in the types of neuropathy, and that neuropathy is not a single condition but rather a broad array of related conditions. Distal symmetric polyneuropathy is the most common and widely recognized form of diabetic neuropathy. Neuropathy can occur in either the large fibers or the small fibers and can affect motor neurons or sensory neurons. While certain types of neuropathy are reversible, sensory and autonomic neuropathies generally progress. Control of hyperglycemia is an important aspect of improving the condition. Clinical trials have shown that multiple metabolic abnormalities need to be addressed to improve neuropathy pharmacologically, and Dr. Vinik mentioned aldose reductase inhibitors, alpha-lipoic acid, gamma-linolenic acid, aminoguanidine, and human intravenous immunoglobulin as therapies that have been or are being investigated for treatment of neuropathy.

9. We attended a debate about use of insulin as initial therapy in type 2 diabetes between Dr. Mayer Davidson, of the Charles Drew University of Medicine and Science and the current editor of *Diabetes Care*, and Dr. Peter Butler of UCLA and the incoming editor of *Diabetes*. What struck us about the debate was that Dr. Davidson said that he still uses NPH, and that he believes "more than 90% of these patients can be successfully treated with sulfonylureas"—a drug that, in other settings, we have heard is about to be completely replaced by new therapies because of problems with hypoglycemia. On the other hand, Dr. Davidson spoke about his success with nurse-managed protocols, which was positive since we also heard that there are now 2,000 diabetologists for 20 million people with diabetes. Although Dr. Butler was representing the "pro" position, he began his presentation by saying that he was not really advocating beginning insulin early. Dr. Butler gave an overview of the reasons patients resist insulin (associations with death, feelings of guilt and failure, fear of pain, hypoglycemia, weight gain) and the reasons providers resist insulin (hassle, PCP fear of losing a patient to a specialist, hypoglycemia, idea that insulin is atherogenic). Both Drs. Davidson and Butler focused on lowering of glycemia and its importance. There will be another presentation on the early use of insulin at ADA in June.
10. Dr. Ronald Krauss of the Children's Hospital in Oakland spoke on atherogenic dyslipidemia. He discussed the pharmacologic options for lowering LDL, including statins, ezetimibe, and resin, as well as those for reducing TG and raising HDL, such as niacin and fibrates. He reviewed the major cardiovascular trials that have been done to date, most of which have focused on statin use. The VA-HIT trial focused on coronary artery disease for patients with a low HDL and found that gemfibrozil resulted in a 22% reduction in non-fatal MI, stroke, and CHD death. He reviewed the PROactive results (calling it a failed study because it did not reach its primary endpoint, although he said that "the primary endpoint was a screwy one") and the FIELD results. Of FIELD, which tested fenofibrate as in CVD prevention, he said that the statin trials came out during that time meant that many patients who were in FIELD then began statins, which may have confounded the results. There was a "barely perceptible" difference in HDL raising and the primary endpoint in CHD events was not met; however, if you adjust for statin use retroactively, the study has significant results, which is controversial.

— by Erin M. Kane and Kelly L. Close

5. More on Drucker: The incretin expert on world tour

We've seen a lot of the University of Toronto's Dr. Daniel Drucker lately—we squeezed into his crowded presentation on incretins at ADA Postgrad, co-hosted his recent call with Morgan Stanley with one of over 150 investors, and even got some time to catch up with him while he was in transit. And it's a good thing—as one of the world's leading expert on GLP-1, and DPP-4s, his comments are in high demand as interest in the incretin class intensifies. Below we include some of our key messages from Dr. Drucker – in the meantime, check out his website, www.glucagon.com. We will be watching for Dr. Drucker at AACE and ADA this year and before then, we look forward to watching him debate Dr. Michael Nauck on "DPP-4 lowers glycemia only by enhancing GLP-1 availability" in Amsterdam in late March at the First Annual Diabetes Forum (see our conference preview on page 28).

- At ADA Postgrad, Dr. Drucker explained the incretin effect: glucose that is administered via IV triggers less insulin than the same amount of glucose that is consumed orally. This is because gut hormones respond to the oral ingestion of food through a series of pathways. The two major hormones are GLP-1 and GIP. The amount of GLP-1 and GIP that is released is directly proportional to amount of food ingested. GLP-1 but not GIP stimulates insulin secretion in patients with type 2 diabetes. The actions of GIP are not preserved in type 2 patients, because they have a GIP-related defect.

- Other benefits include the induction of satiety and inhibition of food intake. There are clinical implications with respect to weight loss. The inhibition of gastric emptying can be a dose-limiting issue. Nausea and vomiting can be important dose-limiting side effects as well.
- GLP-1 affects IRS-2 phosphorylation as well as proliferation of beta cells and expansion of beta cell mass. IRS-2 activation is anti-apoptotic (animal data). In mice, there is less apoptosis (cell death) in islet beta cells in the presence of GLP-1. It is possible to produce the same types of experiments in human islets in the lab, but there are no long-term human RCTs. Studies are underway. Dr. Drucker emphasized that we should be a *"little cautious in our excitement about the pre-clinical data being extrapolated to long-term effects on human beta cells."*
- This question of whether beta cell mass expands looms large in honing projections about GLP-1-related agents, and Dr. Drucker described the state of our knowledge on this point: "*There are several dozen pre-clinical studies for GLP-1 receptor agonists, such as exenatide, but also with all the other agents, that demonstrate robust increases in beta cell proliferation, expansion of islet mass, inhibition of apoptosis, which is very exciting, particularly if you're a mouse or a rat with diabetes."* Dr. Drucker emphasized that that's all we know: that mice and rats with diabetes are especially lucky to have GLP-1-related agents because it actually reverses the disease process, but that we cannot extrapolate from this to humans, because while rodents provide useful models, they are very different from humans. We were curious about what kind of studies will need to be done to see whether humans with diabetes could do as well as mice and rats with diabetes, and Dr. Drucker addressed this as well: *"What would clinicians like to see? They know from natural history studies that after three years or so metformin-, or sulfonylurea-, or insulin-treated patients don't seem to hold their A1C down, and A1C often rises, and additional agents need to be added to the therapies. If we had active comparator studies, wherein we had patients on either metformin or sulfonylureas or TZDs and a DPP-4 inhibitor or exenatide, and over three or four years the patients' A1Cs stayed preferentially lower with a DPP-4 inhibitor or exenatide, relative to the natural increase in A1C after several years that we know happens with the other agents, then I think clinicians would begin to get a glimpse of particularly something different happening to the beta cell, and there would be more enthusiasm for using DPP-4 inhibitors and exenatide for that reason independent of the other mechanisms of action that we know currently exist."*
- GLP-1 appears to be cardioprotective, as it preserves cardiomyocytes. Major problems with morbidity and mortality in patients with diabetes arise as result of cardiovascular issues; hence, GLP-1 has a potential direct beneficial effect on the heart.
- GLP-1 infusion normalizes blood glucose, and its actions are glucose dependent. Insulin secretagogues, such as sulfonylureas and glitinides, work through the KATP channel. They result in an increased risk of hypoglycemia because their actions are not strictly glucose-dependent.
- Dr. Drucker said that GLP-1 can revitalize the beta cell and restores insulin sensitivity. Even 30 minutes of exenatide exposure robustly stimulates insulin secretion in human diabetic beta cells, so there is a high response, at least acutely. We don't have five-year data to see if these responses are maintained.
- In the six-week proof-of-concept study, there was a modest reduction in body weight – two pounds over six weeks – and a 1.3% reduction in A1C.
- Dr. Drucker noted that exendin-4 is a lizard GLP-1 receptor agonist, and he reviewed the pivotal AMIGO studies. Dr. Drucker said that that the most important mechanism of action is control of postprandial glucose. However, exenatide is not as effective at controlling overnight glucose, and it must be given twice daily, as it does not have pharmacokinetic profiles that allow it to work 24 hours a day. He added that some patients will not be able to tolerate the nausea.
- Injectable proteins cause antibody formation, and while 40-50% of patients were antibody positive at initiation, at 52 weeks approximately 35% of patients were antibody-positive. To date, no major adverse events have been associated with this, and antibodies did not predict the magnitude of an individual patient's A1C change.
- Mean A1C drop in AMIGO was 0.9-1.0% at 30 weeks. In the open label extension, the A1C remained stable. Weight loss continued with no plateau. After 30 weeks, patients on sulfonylureas lost two pounds, while those on metformin lost four pounds. Some patients don't lose any weight at all, and Dr. Drucker said that physicians can't promise that to patients. There are some patients who are "weight loss" responders and who do extremely well. There is a correlation between the magnitude of A1C reduction and the weight loss: a significant amount of weight loss leads to additional improvement in A1C.
- Dr. Drucker noted that the therapeutic challenge and complexity of choices is increasing: we now have insulin, inhaled insulin, and twice daily exenatide, and we do not have as many head-to-head studies as we would like. A study published in the *Annals of Internal Medicine* compared insulin glargine Lantus to twice daily exenatide. The reduction in A1C is nearly equivalent for those on insulin and those on exenatide, but there was a net

difference of weight of 4.1 kg over the 30-week study for those on Lantus. One criticism of the study is that the titration of insulin was not as enforced as it was in the treat-to-target study, but the A1C difference was not that far from treat-to-target study. Actually, we believe the study will result in more combination use of insulin and Byetta.

- Dr. Drucker reminded listeners that exenatide is easy to use, as it requires no dose adjustment, while basal insulin requires more time. He noted that the weight reductions for those who are nauseated versus those who are not is very similar – four pounds versus five pounds.
- Exenatide LAR is the same exenatide protein. The long-acting form is similar to other once-weekly LAR programs. The LAR study will be presented at ADA. Dr. Drucker called the results obtained in the high dose group "striking": a 2% reduction in A1C and a nine pound weight loss in four months. Dr. Drucker gave the caveat that these patients were likely very compliant, and he predicted a phase 3 study with 1,000 patients could probably garner 2/3 the effect, which would be good.
- In all venues, audience members have been curious about how exenatide will affect the treatment paradigm for type 2 patients. On this front, Dr. Drucker gave a description of how he approaches type 2 patients, with the caveat that every diabetes patient is unique, depending on whether they are more insulin resistant or have more beta cell failure, etc. "*I would probably start a patient on metformin. If they were failing metformin, I would probably add a TZD very early. If they were failing a TZD, I would probably go to exenatide, if I thought they were a good candidate. And failing all three of those agents, experimentally I would have to add insulin, either by modifying exenatide or withdrawing exenatide until we get more data. Some of my colleagues might well argue that sulfonylureas should be introduced earlier into that equation, and I would not argue with them, but I think many of us have concerns about sulfonylureas and hypoglycemia and weight gain and durability, but certainly they're widely used in many parts of the world and one could argue that I should have added sulfonylureas to the metformin TZD combination. That would be a sort of generalization, but one could have a dozen sequential combinations of therapy and still argue that it was good therapy.*"
- In discussing DPP-4 inhibitors, the other GLP-1 related compound nearing market availability, Dr. Drucker said that DPP-4 inhibitors inhibit the breakdown of GLP-1. DPP-4 has a dimeric structure and is present in two forms in the body. It is present on cell surface of many types of cells in the body, where it is also known as CD26. It also circulates as a soluble form. In knockout mice without DPP-4, the glucose excursion is lower. The enzyme is physiologically essential for control of blood glucose.
- Dr. Drucker said that the region where GLP-1 and GIP are secreted is important; these hormones have portal circulation, which then heads to the liver, passing neuronal circuits that engage the brain. The timing and route of where these hormones are delivered can play a critical role.
- Dr. Drucker reviewed Merck's sitagliptin (Januvia). It reduces meal-related glucose excursions in subjects with type 2, and the A1C reduction is directly proportional to the starting A1C. Vildagliptin (Galvus), formerly LAF237, has also completed the majority of phase 3 studies, and Dr. Drucker said that was possible these would be available in 2007. Levels of glucagon are potently suppressed with DPP-4 administration.
- The key question for exenatide and DPP-4's is the stability of the reduction of A1C. Dr. Drucker said that the one-year data on vildagliptin looks like the A1C drop is sustained.
- In a study comparing vildagliptin to metformin, there was significantly better lowering with metformin at one year. Dr. Drucker suggested that DPP-4 was a better add-on therapy and could potentially be added to metformin, sulfonylurea, glitazones, TZDs, insulin, or that it could be used as monotherapy.
- At both ADA Postgrad and in his call with Morgan Stanley, Dr. Drucker compared GLP-1 and DPP-4. GLP-1 receptor agonists, like exenatide, activate the GLP-1 receptor pharmacologically. On the other hand, DPP-4s allow the endogenous secretion of GLP-1 and GIP to remain in the body for longer. Dr. Drucker further explained some of the differences between the two approaches to the pathway: "*The way that DPP-4 inhibitors work, as we pointed out, is not through pharmacological activation of the GLP-1 receptor. The GLP-1 are not that elevated. So we don't get the nausea. We don't get the vomiting. We don't get the inhibition of gastric emptying. But conversely, we also, as a result, don't get the weight loss, the satiety effect, which are clearly desirable endpoints that one sees in many patients with Byetta.*" Another obvious difference is that exenatide is injectable while DPP-4 is oral. While DPP-4 is not associated with any side effects so far, we do not yet have a large body of experience with these compounds. Immunogenicity is a greater issue with injectable proteins, but DPP-4 inhibitors target a widely expressed enzyme, and it is still early in our understanding of what the unintended effects of these agents might be.
- Dr. Drucker said that he is very interested in looking at efficacy of second generation of these drugs that can be given less frequently, such as once a daily, or perhaps even once a week. In addition, it will be important to see whether there will be long-term durability on the beta cell.

- Dr. Drucker was asked to compare Januvia (sitagliptin) and Galvus (vildagliptin), the two DPP-4 inhibitors furthest along in development. With the caveat that there is no head-to-head data, he said that he believes "*they're both very potent DPP-4 inhibitors*" but that there is more publicly available phase 3 data on vildagliptin. Even with a head-to-head study, he does not believe that the difference between the two will be great enough to be distinguishable. *"We know from PK/PD type studies that vildagliptin seems to perhaps give a little bit less DPP-4 inhibition with a single dose at the end of the 24-hour period, but certainly produces very nice, potent suppression of DPP-4 activity over the daytime 12-hour period where potentiation of incretin action is most likely to be beneficial."* He added that while no distinction can be made between the two at present, *"if some drugs have to be given once a day versus twice a day, that may be an issue, if some drugs demonstrate differential adverse events profiles, that will be an issue, but we really can't make those comments yet, today, on publicly available data."*
- At ADA Postgrad, Dr. Drucker was asked about the possibility of thyroid cancer induced by Byetta. He said that there are concerns about the effect of exenatide on stimulation of proliferation and inhibition of apoptosis. In animal studies, rats treated with exenatide developed benign tumors of thyroid cells. Though these were preclinical studies, we need ongoing surveillance.

--by Erin M. Kane and Kelly L. Close

6. Patient blog yields fascinating Guardian RT insights

Medtronic Diabetes Care sales were on the weaker side last quarter, coming in below analyst estimates and at the lowest growth level since 2Q03. While Medtronic management discussed sales of pumps and disposables, little was said during the earnings report Feb. 21 about the Guardian RT. Information about the continuous monitor has been scarce. The 2005 trial data—with an impressive drop in both A1C and hypoglycemia—captured the interest of investors and healthcare providers alike. But since then, the Guardian RT release has come about in only seven cities, leaving patients searching for more information on the product.

While the jury is still out on how the market will respond, individual patients on the Guardian RT are spreading the word—anecdotally related in doctors' offices, and more publicly, on weblogs. This modern-day patient-to-patient communication has proved a fascinating source of new product information, as the users comment on the flaws and advantages of the RT. One Guardian RT-using blog writer in particular caught the attention of DCU—42-year-old type 1 William, whose blog can be seen online at http://lifeafterdx.blogspot.com/.

William, who runs a small business in New Mexico, flew to Austin to get the device, which he pays for himself. Before going on the Guardian RT,[1] he had an A1C of 6.2 and suffered from impaired hypoglycemic awareness. As expected, there is not yet reimbursement for the Guardian, and William is willing to pay out of pocket. The lengths to which patients like William go to obtain the Guardian—and we've heard of other families flying to Texas for the product—underscore the strong patient demand. William's blog also sheds a bit more light on questions of cost: in addition to the $40 three-day sensors, the transmitter is $400 and *must be replaced every year* as the batteries run out and cannot be replaced.

William justifies the increased cost with two huge advantages that come with the use of a continuous BG monitor. First, the predictive value of CGM is an enormous positive; the Guardian warns its user about falling BG long before levels actually qualify as hypoglycemic. Second, the Guardian dramatically improves access to data: "*Wearing a Guardian you have access to the entire continuum of your sugar readings. You can see the exact pattern of your sugars over a day, a week, a month. You can see exactly what that pizza did to you. With finger sticks you can only guess what your sugars are between checks*."

While William writes positively overall, he does run into some problems, including questions around accuracy. Perhaps most fascinating is the evolution of William's views on the accuracy of the Guardian. He describes several major episodes in which the reading on the Guardian is very different from the reading on his episodic monitor: more than 100 points difference in one case. He chronicles episodes in which the Guardian fails to tell him he is hyperglycemic (the Guardian reads 117, episodic monitor reads 243) and when he is hypoglycemic (Guardian reads 97, episodic monitor reads 66). Despite his initial frustration on this point, he describes a shift in the way he uses his Guardian that diminishes the importance of the point values. He writes at a later point that "*it doesn't matter if the*

[1] William refers to the Guardian RT as Guardian throughout his blog, which we do here as well.

BG is 145 or 135. What matters is which direction the numbers are flowing and how fast. The number by itself is meaningless and probably wrong anyway, whatever system is used to 'measure' it. The Guardian lets me see the motion of the BG. That is so amazing that I'm only beginning to truly understand the power and potential of this kind of info." William is a good example of how some patients look for accuracy early on with continuous monitors, but then relax their expectations once they become comfortable with a system, because seeing the direction of blood glucose is so valuable – even if the actual number on the Guardian is wrong.

William also struggles with damage to his skin from the strong adhesive used for the sensor. He writes that the tape is extremely abrasive: *"The transmitter-tape induced rash on my stomach has cleared up, but now the skin on my stomach is different colors. I have perfect light brown transmitter-shaped patches where the pigment of my skin seems to have changed color. There are several of them. I have no idea if it is permanent or not."* He has issues with infection at his sensor site and with a failed sensor that lasts for only 26 hours (and William thinks about the $40 that each three-day sensor is costing him). Upon removing the sensor, William discovers that the sensor has failed because it is covered in blood from an unlucky insertion.

Despite these problems, William praises the Guardian, listing many things he likes about it: its compact size, the ease of insertion, the relatively uncomplicated nature of the collected data, the snooze button on the alarm, and most importantly, what he considers a reliable security against hypoglycemia.

Having lived with a continuous monitor for three months, William says that he could never go back to living without one—we think many patients will feel the same, all label. In response to the question of whether he would recommend the Guardian to others, he writes, *"Yes. Absolutely. Double absolutely. Triple absolutely…I've had my ups and downs as you've all seen. But I think that the ups far, far, far outweigh the downs."* William is extremely positive on CGM and says that his health has improved and that his blood sugars have stabilized. Our overall take on William's blog is that while it is only the perspective of one person, it confirms our belief that among patients who fit William's description—type 1, intensively managed—CGM uptake will be strong.

We were intrigued by what some of William's responses to the Guardian might mean for the competitive landscape. As he becomes more familiar with the Guardian, he begins to rely less on the point readings and uses it more for a sense of direction and speed. He writes that, *"Now, I never look at a single reading. I check my NOW number and then quickly scroll back in time using the down arrow button. Five minutes per click. I usually glance at half an hour…I think about what I'm looking at. Direction? Is the BG going up or down? Or is it fairly stable? Speed? Speed I'm not always so good at, because that takes mental mathematics, which is my weak spot. That said I can get a rough idea of how fast things are moving."* It appears that patients will be looking for directional arrows and rate of change as key features in a continuous monitor, features we expect to see in later generations of Medtronic's Guardian and DexCom's STS.

In addition to those product features, we believe key differentiators will be the sensitivity and specificity of the hypo and hyper alarms, accuracy, and ease of use. With Abbott's Navigator and DexCom's STS still at the FDA, we expect the Guardian RT to gain some traction in the CGM market, and it's clear that demand is strong, though reimbursement remains elusive at this stage – we imagine payors will demand randomized controlled trial data (lots of patients over a long time period) to establish mainstream reimbursement. While Medtronic is not reporting on Guardian RT sales at present except anecdotally, we're staying tuned for news of an expansion of the release and a next generation product. We believe the ripple effect of CGM will be seen in the diabetes industry in a renewed focus on the importance of glycemic variability, an increase in pump sales, a concern about formerly silent post-prandial spikes, and a possible uptick in Symlin sales. We are truly on the verge of a new epoch in the management of type 1, and we are listening closely as pioneers like William report back from the front lines.

—by Erin M. Kane and Kelly L. Close

7. JDRF Launches Campaign for Artificial Pancreas

Continuous glucose sensing, perhaps the hottest area in diabetes technology research today, is getting a boost from the powerful Juvenile Diabetes Research Foundation (JDRF).

The JDRF has announced that it will spend up to $6.5 million for research on continuous sensors specifically and a "closed loop" system generally, which would tie sensors to insulin delivery in a partially or completely automated fashion. Such an "artificial pancreas," which would rely on computer algorithms to calculate insulin doses, has long been a goal of researchers. It has also been one of the JDRF's six "therapeutic goals." But recent advances in the continuous sensors, one of which is already available in select markets, persuaded the JDRF to launch its current initiative.

"We believe that continuous sensors can improve glucose control in virtually every person with diabetes," said Aaron Kowalski, JDRF's director of strategic research projects. The appeal is obvious: the sensors, inserted in the body, deliver real-time glucose data to a monitor, not only providing current readings but also trend lines so patients know if their blood sugars are rising or falling.

The artificial pancreas, if ever achieved, would have an even more profound impact by removing the potential for human error in administrating the correct dose of insulin. The importance of the JDRF's commitment cannot be overstated. The organization is a fundraising juggernaut – it's now in the midst of a $1 billion global fundraising campaign – and a lobbying heavyweight; its efforts, for example, helped pass California Proposition 71 for stem cell research, and its advocacy has significantly contributed to NIH funding for diabetes.

The speed with which the JDRF is moving on its Artificial Pancreas Project is impressive. Researchers are encouraged to check information out *now* since final applications are due April 15 and funding beginning as early as mid-June (even if it is beyond the deadline, we would urge strong applicants to check with the organization). Information about the applications for this initiative can be found on the homepage of its website (www.jdrf.org.) The organization wants to fund clinical trials that will demonstrate the effectiveness of continuous sensors in improving glycemic control. Such evidence could be used not only to facilitate regulatory approval but also to persuade insurers to cover the devices as a way to reduce costly complications. The JDRF also wants to fund researchers explicitly working on closing the loop. This could be, according to Dr. Kowalski, "a bridge to a biological cure" because maintaining normal blood glucose levels are central to such goals as beta cell regeneration or cellular transplants. On the path to the artificial pancreas, the primary other barriers are solid algorithms and a way for counterregulatory hormones to be part of the technology; we understand the JDRF looks to fund research on all these fronts.

The JDRF's renewed interest in continuous sensors arose last year when Jeffrey Brewer, one of its board members whose son has diabetes, attained a prescription to buy Medtronic's Guardian, the only sensor with FDA approval. Problem was, the sensor was unavailable. So the board asked the organization why that was the case and what could be done to make this technology more widely available. JDRF's work followed. The FDA is currently reviewing two other sensors in addition to having approved the Guardian RT last summer – Abbott's Navigator and Dexcom's STS, both of which have "fast track" status – and Kowalski said the JDRF hopes other companies join the fray as well. Said Brewer, "I am thrilled that the JDRF has moved so quickly on this important initiative. Continuous sensing holds tremendous power to improve patients' health in the short- and long-term and to raise patients' quality of life, and research on this front is absolutely critical to creation of the artificial pancreas. This is an inspired example of how the JDRF's support and advocacy can accelerate research, and I look forward to seeing the fruits of this important work."

Even if the continuous sensors are refined, reimbursement for the devices as well as for providers' time to help analyze data remains a problem. As things now stand, relatively few doctors and nurses have the time or expertise to assess the log records of individual glucose readings. The JDRF will be lobbying for reimbursement reform, urging public and private payors to increase compensation for providers – we believe that the successful creation of a thriving market hinges on reimbursement, and we are extremely hopeful about JDRF's efforts on this front.
Editor's note: JDRF is a client of Close Concerns.

—by James S. Hirsch and Kelly L. Close

8. DCU Company Watch

AMYLIN— Amylin files for expanded TZD indications ~ year-end results for pivotal year: Amylin announced March 1 it had filed for an expanded Byetta label that would expand the population of type 2 patients indicated for the drug. Expansion potential in the area of type 2 patients failing TZD therapy is significant today – about 1.5 million patients today, but if DREAM results, to be announced this fall, are positive – the expansion potential with TZDs is enormous. DREAM looks at progression to diabetes among those with impaired glucose tolerance – although a positive study would likely give a big boost to TZDs, weight gain is a major deterrent for a sizable percentage of patients. Cocktailing with Byetta might be a great answer. Too, we believe many patients on TZDs could be spurred to take Byetta as well once it is labeled, even if they aren't failing TZD therapy – again, the potential to stem the weight gain problem normally associated with TZD use could prove quite powerful to a high percentage of patients. Certain subgroups are likely to benefit substantially – say, for example, the top quartile of weight gainers on TZDs, probably most of whom could benefit from combination use of both TZDs and Byetta. TZDs, of course, offer help on the insulin resistance front, which Byetta doesn't do so much of (apart from the lower insulin resistance that is associated with weight loss) – we expect the combination, if approved, could become very popular and could ultimately become an important growth area if and when the official label comes through.

In other Amylin news, the company reported FY05 results on Feb. 9. There were many positives in our view, among them: no new safety issues for LAR or pramlintide (even at the high doses tested), great pramlintide data for obesity, obvious price implications at high doses (6x the current typical type 1 dose by our math, or potentially as much as $6,000/year to Amylin), outstanding retention rates for Byetta and Symlin, critical progress on label expansion for Byetta (TZDs), good LAR vibes in terms of filing requirements, positive movement on Symlin pen (a personal favorite), $250 mm Byetta run rate (and climbing), frequent scripts from Symlin docs, specialty sales force expansion, and Amgen leptin partnership (PYY-Leptin? Symlin-Leptin? Byetta-Leptin-PYY?). We are extremely curious to know about "other" compounds moving into clinic (besides obesity mentioned at JPM) and were surprised no one asked this though we know everyone is far more interested in the here and now. What was most positive to us was increased spending - more investment at this stage must mean, of course, that investment to date is w-o-r-k-i-n-g.

DEX COM – Still planning for a Q2 launch. Dex Com reported results February 28. The company is spending more than planned, but in order to hit it big, of course they have to invest properly. We would look for approval in the coming weeks – can you imagine the excitement in San Diego!? We think the chances of approval are 1.0, or as close as possible. How careful / restrictive the label is another question, but we believe on this submission, all the i's were dotted and t's were crossed. In contrast to larger-pharma brethren on the pharma front, Dex Com is careful on every reference to potential approval and commercial scale up ("yes, pending FDA approval." "yes, pending FDA approval" "If and when…"). On this quarter's call, we were impressed 1) to learn the company will have posters at both AACE and ADA (on the 7-day sensor); 2) that they are planning a 400-person, 20-center (to match the number of salespeople being hired?) "depending on timing of approval" trial and already have 130 patients recruited; 3) that they are very serious about a replacement claim (they've already done – in 2005! - a multi-center 35-person feasibility trial) and plan to file for the IDE to start the trial after they receive the STS decision; 4) that they are ready to submit the next-generation 7-day sensor upon receiving approval for the STS; and 5) that the pediatric indication is something that is clearly important to the company. What does remain surprising to us is that clear guidelines on what is needed to garner replacement approval remains so elusive.

ACADIA—Unfazed by rimonabant setback: Acadia, a biopharmaceutical company focused on treatment of central nervous system disorders, including Parkinson's and schizophrenia, has moved its cannabinoid CB1 receptor blocker program to preclinical status. Acadia's focus is on the central effects of the CB1 receptor, and the company's press release suggests that blocking the receptor—with its regulation of appetite and reward-related behaviors—may lead to "novel treatments for obesity, substance abuse, and disorders associated with cognitive deficits." Acadia announced on Feb. 22 that it is in "an advanced stage of lead optimization with orally available compounds that are potent and selective in blocking the CB1 receptor and well-tolerated at high doses."

MEDTRONIC—Slow growth pinned on disposables: Medtronic Diabetes Care reported 3Q results on Feb. 21. Medtronic reached revenue of $182 million for the quarter, up just 6% (9% excluding the impact of foreign exchange), below analyst estimates. As always, from a bigger base, it is harder to keep up growth rates, and the company is now annualizing at $728 million a year for pumps, which is very impressive, given that Animas probably sold about $65 million for the year and was the #2 company in the US - because the J&J acquisition closed

recently, we will not get year-end numbers for Animas. It was noted that Medtronic profitability had risen, despite weak sales. Although we know the sensor-augmented pump has had a limited launch in some international markets, nothing was said about plans for this product. When asked about the Guardian RT, management basically said it had only launched in seven cities, adding that they are experiencing some supply constraints on the product. We were very curious to learn more about clinical trials for continuous monitoring as we think data stemming from such trials – at least, the big, randomized, controlled trials – will be what makes or breaks reimbursement. Yes, there has been a steadily increased demand for more and more level 1 evidence – nowhere will that demand likely be more present than with continuous monitoring, we think. Management said the Star 1 trial (150 patients, 30% pediatrics) was fully enrolled and that the Star 2 (smaller, observation/training trial) would be enrolled by the end of April and that results would start to be available in calendar year 2007. The big trial, Star 3, the one that would be a 350-person randomized controlled trial (RCT) will be the exciting one to watch - that is supposed to compare sensor augmented pumps versus MDI (insulin analogs) and should garner terrific data toward reimbursement that should help the entire industry. Endpoints are A1C reductions, improvements in quality of life and reduction in overall costs of managing diabetes.

We definitely don't think the pump market is slowing, despite the higher base – and to boot, we think there are three specific drivers that will aid 2006 sales: 1) approval of more continuous glucose monitors that highlight poor management and propel patients toward better management; 2) approval of the sensor augmented pump – current patients will be able to upgrade relatively inexpensively; and 3) broader introduction of Insulet's new pump, which we believe would be attractive to anyone who has considered and rejected pump therapy. On guidance, management expressed that diabetes would return to mid to high teens revenue growth in future quarters – we assume that new products will be of big help as will reimbursement.

INSULET – Success, again, on the fundraising front: Disposable pump manufacturer Insulet is generating substantial interest, as reflected by its success in its latest round of financing of a $50 million. The investor group, led by OrbiMed Advisors, included The Federated Kaufman Fund, Pequot Ventures, Prism Venture Partners, Schroeder Ventures Life Sciences, and Versant Ventures. Nice one! Insulet President and CEO Duane DeSisto relayed that this funding will be used for an expansion of production capacity. We wrote about the Omnipod in last month's newsletter, when we discussed the company's first investor presentation at the JP Morgan conference – this market is absolutely capable of big expansion if executed right, in our view – we view the new disposable pump as a very novel device capable of prompting serious market expansion.

DIOBEX—Speeding into phase 2: Diobex announced Feb. 22 that its novel cortisol synthesis inhibitor has moved into phase 2 clinical trials. In the next trials, patients with type 2 will be treated with the cortisol synthesis inhibitor, DIO-902. Glucocorticoids have received increasing attention for their role in obesity, insulin resistance, and metabolic syndrome, and we are interested in following DIO-902 as a potential first in a new class of drugs designed to limit cortisol. The company press release notes that DIO-902 is one of two enantiomers present in the drug ketoconazole, which has been demonstrated to control glucose levels and lower blood pressure and cholesterol in patients with type 2 patients with diabetes. The drug ketoconazole is a mixture containing two enantiomers, or substances whose molecular structures are mirror images of one another. A mixture of equal quantities of two enantiomers (which have the same molecular formula, despite an opposite spatial configuration) is known as a racemate. DIO-902 is believed to be the key enantiomer in the racemate mixture and as such the isolated enantiomer may be more potent and may be safer than the ketoconazole racemate.

SANOFI, Round 2—Emphasizing blockbuster Lantus growth: Sanofi reported 4Q earnings Jan. 30. While the buzz has focused on its rimonabant debacle (see related story on page 7), Sanofi has provided updates on its insulins recently as well. It emphasized its long-acting insulin glargine, Lantus, which was not surprising, given the impressive Lantus results: nearly $1.5 billion in global sales, up ~50% - a great result for Lantus, which continues its very strong successes that have fed off one of the most successful diabetes strategies of all time – just keep it *simple*. Historically, Sanofi has marketed Lantus on "one shot a day, one pill a day..." but then Amaryl went generic – as did the message. For new insulin prescriptions, Lantus has as 32% share versus premix at 27%, mealtime insulin at 26%, and NPH at 14%.

MERCK—Januvia leapfrogs over Galvus in DPP-4 game: The FDA accepted the Januvia (sitagliptin) filing Feb. 15. Assuming Novartis only recently filed Galvus (formerly vildagliptin, LAF 237), Januvia is the first DPP-4 to file. DPP-4s are the new class of drugs for type 2 patients that will follow GLP-1, and many companies have

extremely active programs in development. Merck will present phase 3 data at ADA; we assume it filed for monotherapy and combination therapy, but indication has not been discussed. Januvia advantages, as compared with Byetta, would be a once-daily oral and relatively good tolerability; the main disadvantages would be relatively low potency, and high cost. The safety profile is unclear but appears to be prompting less concern from thought leaders than a couple of years back. While the best time to use Januvia for type 2s would likely be early in disease therapy in combination with other drugs, reimbursement will likely be an uphill battle since the first line of therapy of choice seems still to be metformin, which is cheap, safe, and weight neutral. Merck will probably try to position this as a new alternative that patients need given poor glucose results, and as an important add-on. It will be interesting to see how durability looks (in terms of A1C and weight neutrality) for this class. We do think if Merck is successful with reimbursement, doctors might look at this as another dart to throw: "well, let's just see what happens if we add this to your therapy ..." We believe overall success for the class will hinge on add-on success, reimbursement, and durability. We'd love to see quartile data for monotherapy to see if there is some sub-group that benefits particularly.

OSI Pharmaceuticals—Initiating phase 1 study for GKA: OSI Pharmaceuticals announced on Feb. 15 that its Glucokinase Activator (GKA) had advanced to phase 1, with a single-center study of 80 non-diabetic volunteers. Pre-clinical studies suggested that GKA lowers blood glucose by increasing glucose uptake in the liver and insulin secretion from the pancreas. The GKA compound was developed by OSI's Prosidion subsidiary, which also has a DPP-4 inhibitor, PSN9301, in phase 2 trials.

METABASIS – Another entry into phase 1: Metabasis has initiated a phase 1 trial of MB07803, its second drug for type 2 diabetes. Both compounds are new in a class that inhibits glucose production by the liver through inhibition of an enzyme known as fructose 1,5 biphosphatase (FBPase). The other FBPase, CS-917, is currently in a phase 2b clinical trial, in partnership with Sankyo Co., Ltd. Elsewhere in Metabasis' pipeline, the company is looking for clinical compounds that will target the AMP kinase. Dr. Vincent Poitout at ADA Postgrad Feb. 10 noted that the AMP kinase (AMPK) would be an excellent drug target for the treatment of lipotoxicity—his term for an overabundance of fat that impairs the functions of non-fat tissues, such as the liver, beta cells, and skeletal muscle.

TOLERRX—Type 1 drug deemed 'orphan' by FDA: TolerRx, a company focused on therapies for immuno-mediated diseases, including type 1 diabetes, psoriasis, and lupus, announced on Feb. 14 that it had received orphan drug designation from the FDA for its therapy for new-onset type 1, TRX4. TRX4 is a humanized anti-CD3 antibody that is being developed in collaboration with Genentech, and the FDA designation guarantees exclusive US marketing rights for seven years as well as access to research funding, tax credits, and other financial benefits. TRX4 is a compound designed "to block the function of autoreactive T-effector cells that attack the body's tissues and cause autoimmune disease." A study published in NEJM in June 2005 showed that TRX4 was successful in preserving the function of beta cells for at least 18 months after one six-day course of the medication – 18 months is a minimum bar to hit and we'll be very interested to see longer-term data.

PFIZER—Basking in Exubera approval glow: Pfizer held its analyst day on Feb. 10. Although new news on Exubera was scarce, the company did say it is actively pursuing a second-generation device but said that it is too early to discuss. In response to a question about what else they are doing in diabetes, management said diabetes was a major focus but that it's too early to talk about and that there are two compounds in the clinic right now. One sounds like it could be a CTEP inhibitor in the works but information remains scarce. On PFT testing, management downplayed the hassle "patients just need to blow in a white tube, all physician offices should have one…" Interesting. We see a lot of potential liability issues here. Amazingly, management actually stated that the requirements were "pretty far down" on the label …!

NEKTAR—Required pulmonary testing framed as minor: In a Feb. 8 presentation at Merrill Lynch, Nektar management didn't share much new information on inhaled – one had the idea that Pfizer was really limiting what it could say. There were several interesting questions, however. First, Nektar's management team was asked if they would compete against Byetta; they said it was a new product with attractive features like weight loss and lower A1C "but it is injectable ... and a lot of those patients will go on to use insulin eventually." In general, the tone on Byetta was very respectful. Smart! Second, on where the low-hanging fruit is in terms of patient targets, they said poorly controlled patients with A1Cs over 9, particularly those who had resisted insulin, although they implied many of those on insulin would want to go on Exubera. Third, on the label, they said they are excited and it is as "broad as could be." Given that it was possible type 1s would be left out, which would've created more of a psychological barrier (for type 2s and docs), we saw this as reasonable: it was basically expected that many groups (smokers,

COPD, etc.) would be left out. Fourth, regarding pulmonary testing, they implied this would not be a big deal; we are not so sure about this. They said a desktop machine is ~$2000 and there are a handheld models (who knew!) for ~$100. Fifth, they were asked about how many patients were on insulin - they said 4.5 million and -- similar to everyone else in industry -- they couldn't seem to say what percentage took long acting only versus long acting and mealtime. They said a lot of patients still took the "old regimen" of mixes and NPH etc and that a big opportunity for Exubera was to convert patients to mealtime insulin – this of course is the same group that Lilly, Novo, and Sanofi is trying, successfully, to attract to rapid acting analogs.

ALKERMES—Balancing AIR and LAR: Alkermes reported 3QFY06 earnings Feb. 7. CEO Richard Pops gave an overview of in-line products and the pipeline. "We continue to make great progress in our AIR insulin and exenatide LAR programs." Alkermes is "focused on advancing product candidates that could transform the diabetes treatment landscape by providing these simpler dosing regimens, thereby potentially increasing adherence and leading to better health outcomes for the patient over time." Pops highlighted the two long-term safety and efficacy studies underway for AIR Insulin in partnership with Lilly – a 24-month study in 400 type 1 patients that started in July 2005 and a 12-month study in 600 type 1 and type 2 patients with lung impairment (mild-to-moderate asthma or COPD). Additional phase 3 studies are planned for 2006. Alkermes said it will continue to give updates on their progress over the course of the year. As for the recent approval of Exubera in the U.S. and Europe, Alkermes views this as "a testament to the interest in and need for inhaled insulin." More importantly, "there's now a clear, proven regulatory pathway to approval in both the U.S. and in Europe for inhaled insulin."

Management said that exenatide LAR "holds ... promise of providing patients with new treatment options to give them better opportunities to control their BG levels over time." In January 2006, Alkermes, Lilly, and Amylin announced the successful completion of a phase 2 multi-dose study of LAR. Plans are now underway to initiate a long-term study of LAR during the first half of calendar 2006. These studies will evaluate the safety and efficacy of LAR and will include a Byetta arm for reference. As for manufacturing, management noted that Amylin has assumed responsibility for funding a manufacturing facility and for manufacturing the commercial product, with Alkermes overseeing the construction and transferring certain required technology to Amylin.

Discussions with the FDA regarding LAR's clinical program and path of registration are ongoing. Alkermes will leave disclosure regarding next steps in the clinical program "as usual" to partners Amylin and Eli Lilly. In discussing its goals for 2006, management specifically mentioned that it anticipates "continued progress in [its] diabetes pipeline including the initiation of a long term study of exenatide LAR in the first half of 2006 and the presentation of new clinical data."

ORSENSE—Success in fundraising: OrSense, another interesting company pursuing tight glycemic control in the hospital, announced Feb. 6 the addition of Mr. Carlo Salvi to its Board of Directors. In the same press release, the company announced that it had achieved an additional $6 million in financing. The investment was led by Israel Healthcare Ventures (IHCV) and included STAR Ventures and Lewis Trust Group (LTG).

ROCHE—Innovating in diagnostics, still waiting for FDA on pumps: Roche reported 4Q05 earnings Feb. 1. Roche Diabetes Care posted 2,886 million CHF ($2.25 billion) in sales in 2005, a 3% increase from last year. US business continues to be very competitive from what we understand – basically a pretty tough year all around. Diabetes now represents 35% of Roche Diagnostic's sales. In the second half of 2005, Roche also launched its next generation of Accu-Chek diabetes management products worldwide to replace older flagship offerings in its diabetes portfolio. These included Accu-Chek Compact Plus, a glucose monitoring system with a built-in test strip drum and lancing device, and Accu-Check Aviva, a successor to the Accu-Check Advantage monitor. In addition, Roche launched Accu-Chek Spirit, a menu-driven insulin pump, and Accu-Chek Pocket Compass 3.0, its latest software for mobile diabetes self-management. The FDA has completed its inspection of the Roche Diagnostics facility in Burgdorf (Switzerland), though the final decision on whether to lift the US import alert on pumps made at the facility is still pending.

In 2006, Roche plans to globally launch Accu-Chek Go S, a successor meter for Accu-Chek Go that offers improved features and design. In response to a question about R483, Roche's insulin sensitizer that many are following, William Burns (CEO Division Roche Pharma) said that "this class of drugs had to have long term carcinogenicity studies shared with the FDA before going into clinical phase 3 studies longer than six months. Roche has got that data and is waiting on the FDA meeting." After Roche has its meeting with the FDA, it will share the results and any

impact the results may or may not have on the phase 3 program. As for the Aviva launch, Roche feels that the launch is "fully on-track" and was one of the fastest ramp-ups in the history of diagnostics. Roche was "surprised" by the speed of erosion in Accu-Chek Advanced since it was "faster than expected." However, Roche believes that Accu-Chek Aviva is "an extremely competitive product," so it will "overcome the washout effect" of Accu-Chek Advanced by the middle of this year. Finally, as for why Roche terminated its development of Xenical in Japan, Burns said it was "due to competing priorities."

TAKEDA— Actos continues blockbuster status … and unveils some portfolio …Takeda reported earnings Jan. 30 for its fiscal 3Q. Takeda sold 177 billion JPY ($1.5 billion) in Actos, year to date, up 22%, so it is on track for $2 billion for the year. It appears that TZDs will be the losers of inhaled strength, assuming inhaled gains reimbursement, which remains speculative. The pipeline isn't too stirring. They discussed AD 4833, which is the Actos/metformin combo; they have filed (or plan to soon) for the reduction of risk of macrovascular events in patients with type 2 and pre-existing macrovascular disease. Also in the pipeline is SYR 322, a DPP-4 that recently moved into phase 3 ahead of schedule. There is also ATL-962, the me-too lipase inhibitor in phase 2.

NOVO NORDISK— Marketing practices further examined: A lengthy *New York Times* story on Jan. 28 disclosed that prosecutors are investigating possible criminal violations by Novo Nordisk. In January, Novo said it had received a subpoena from US attorney for the Eastern District of New York for documents related to its marketing of its insulin products. According to the *Times*, Novo has tried to boost insulin sales by paying at least one Rite Aid pharmacist to switch patients from Lilly's Humalog to its fast-acting analog, Novolog. The story also alleged that Novo paid doctors' assistants when prescriptions were switched. The *Time*s cited company documents and quotes former sales reps and company officials. Novo said it "believes the (prosecutors') investigation is limited to its insulin products." It denied any wrongdoing in its dealings with Rite Aid, saying the program was designed to educate patients or improve care. As the *Times* points out, from December 2001 through November 2005, Novo's insulin sales rose 364 percent to $963 million while Lilly's insulin sales rose only 13 percent to $1.43 billion (albeit, from a much larger base). For more details, see our Jan. 28 blog online.

MANNKIND—Positive phase 2b data unveiled: MannKind announced Jan. 17 that its 227-patient phase 2b trial of Technosphere Insulin showed that patients on Technosphere Insulin experienced a drop in A1C 0.79% greater than was observed in the placebo group over the eight weeks of the study. Baseline A1C values were not given. The 0.79% reduction in A1C was in the group of patients receiving 56 units (n=45), and that group also saw a 63% reduction in maximal postprandial glucose excursion when compared to the placebo group. The study also confirmed that pulmonary function did not decline over the period of the study. Perhaps most interestingly, the therapy was weight neutral, a factor that might give Technosphere an edge should it come to market.

— by Rachael Hartman, James S. Hirsch, Erin M. Kane, Win Rosbach, and Kelly L. Close

9. Van den Berghe, et al. "Intensive Insulin Therapy in the Medical ICU." NEJM. 2 February 2006. Malhotra, A. "Intensive Insulin in Intensive Care." NEJM. 2 February 2006. 354(5): 516-518.

In 2001, Van den Berghe et al. published the results of their randomized, controlled study of intensive insulin therapy among patients in a surgical intensive care unit (ICU). The study demonstrated that intensive insulin therapy reduced morbidity and mortality in these patients, with the greatest benefit occurring in the subgroup of patients who stayed in the ICU for at least three days. Five years later, Van den Berghe and her colleagues published a similar prospective, randomized, controlled study, this time conducted in a medical ICU. The original article was published in the February 2 issue of the *New England Journal of Medicine* this year. Patients in medical ICUs tend to be more severely ill and have a higher risk of death than patients in surgical ICUs, and as such, it was unclear whether intensive insulin therapy would also improve the prognosis of patients in medical ICU patients. Since the study in a surgical ICU showed the most pronounced benefit on mortality and morbidity after three days of intensive insulin therapy, Van den Berghe et al. targeted patients who were expected to require a stay of at least three days in the medical intensive care unit. Thus, surgical ICU patients and patients able to receive oral nutrition were excluded, because such patients usually need less than three days of intensive care. Patients with do-not-resuscitate orders on admission were also excluded.

Subjects were randomly assigned to one of two treatment groups upon admission to the medical ICU: intensive insulin treatment or conventional insulin treatment. Conventional treatment consisted of continuous insulin infusion

with a target blood glucose level of 180-200 mg/dL. Insulin infusion was started only when the blood glucose level exceeded 215 mg/dL and was tapered and eventually stopped with the blood glucose level fell below 180 mg/dL. In the intensive insulin treatment group, the target blood glucose range was 80 to 110 mg/dL (normoglycemia), and insulin infusion was started when the blood glucose level exceeded 110 mg/dL. The maximal continuous insulin infusion was set at 50 insulin units per hour. After discharge from the ICU, a conventional approach to glycemic control was used, with a target blood glucose of 200 mg/dL or less. Nurses in the ICU made the adjustments to insulin dosage, on the basis of whole-blood glucose levels measured at one-to-four hour intervals.

To minimize bias, patients were considered ready for discharge as soon as they no longer needed vital-organ support and were receiving at least two-thirds of their caloric intake by the enteral route or when they were sent to a ward. Physicians on the general wards did not have access to the results of blood glucose testing and were not aware of the study treatment assignment.

Of the 1,200 patients enrolled in the study, 767 stayed in the ICU for at least three days. There was a higher occurrence of hypoglycemia in the intensive-treatment group than in the conventional-treatment group, with the severity of hypoglycemic episodes being similar between the two groups. Most patients who had hypoglycemia only had one episode, and there were no hypoglycemic episodes that caused hemodynamic deterioration or convulsions. After data analysis, the authors found that hypoglycemia was an independent risk factor for death. Among patients in the ICU who had hypoglycemia, mortality was 66.7% in the conventional-treatment group and 46.4% in the intensive-treatment group ($p=0.1$); the in-hospital mortality was 73.3% in the conventional-treatment group and 61.9% in the intensive-treatment group ($p=0.4$). Independent risk factors for hypoglycemia were intensive insulin therapy ($p<0.001$), stay in the ICU for at least three days ($p<0.001$), renal failure requiring dialysis ($p=0.006$), and liver failure ($p=0.04$).

The effect of intensive insulin therapy on morbidity and mortality varied between the intention-to-treat population (n=1,200) and the population of patients who stayed for more than three days in the ICU (n=767). In both populations, there was no significant difference between the two treatment groups in the use of medications other than insulin. Morbidity in the intention-to-treat population was reduced by intensive insulin therapy, as indicated by a reduction in newly acquired kidney injury (8.9 to 5.9%, $p=0.04$), accelerated weaning from mechanical ventilation ($p=0.03$), accelerated discharge from the ICU ($p=0.04$), and accelerated discharge from the hospital ($p=0.05$).

Intensive therapy also reduced morbidity in the population of patients who stayed in the medical ICU for more than three days. In such patients, intensive therapy accelerated weaning from mechanical ventilation ($p<0.001$), discharge from the ICU ($p=0.002$), and discharge from the hospital ($p<0.001$), compared to conventional treatment. Intensive treatment also reduced newly acquired kidney injury (12.6% in the conventional-treatment group and 8.3% in the intensive-treatment group, $p=0.05$), the fraction of patients reaching a peak serum creatinine level above 2.5 mg/dL (39.4 and 32.5%, respectively; $p=0.04$), and the incidence of hyperinflammation (74% in the conventional-treatment group and 67% in the intensive treatment group; $p=0.03$). More patients in the conventional-treatment group than in the intensive-treatment group had hyperbilirubinemia (55.2% and 47.3%, respectively; $p=0.04$). Intensive insulin therapy also reduced the cumulative Therapeutic Intervention Scoring System 28 (TISS-28) scores by 20%, indicating a reduction in ICU costs.

A reduction in mortality with intensive insulin therapy only occurred among patients who stayed in the ICU for more than three days (in-hospital mortality in the intensive-treatment group was 43.0%, compared to 52.5% in the conventional-treatment group; $p=0.009$). Among the intent-to-treat population of 1,200 patients, in-hospital mortality was not significantly reduced by intensive insulin therapy (37.3 vs. 40.0%, $p=0.33$). Among the 433 patients who stayed in the medical ICU for less than three days, mortality was actually greater among those receiving intensive insulin treatment than among those receiving conventional insulin treatment (56 vs. 42 patients). Whether intensive insulin treatment actually increased the risk of mortality among patients who stayed in the ICU less than three days is questionable, as the statistical significance of the increased mortality varies according to method of data analysis: $p=0.05$ with the chi-square test; hazard ratio, 1.09; 95% CI, 0.90 to 1.32; $p=0.35$ using uncorrected proportional-hazards analysis; hazard ratio 1.09; 95% CI, 0.89 to 1.32; $p=0.41$ after correcting for baseline risk factors.

Van den Berghe et al. propose possible explanations for the difference in mortality between patients staying less than three days in the ICU and patients staying longer. One potential cause is the higher number of patients in the

intensive-treatment group for whom intensive care was limited or withdrawn for reasons of futility within 72 hours after admission to the ICU. A more likely explanation is that intensive insulin therapy requires a certain amount of time (apparently about three days) to exert its benefit. Linked to this explanation is the fact that intensive insulin therapy during intensive care is not aimed at curing diabetes but rather at preventing complications that occur during intensive care. Supporting this hypothesis is the finding from this study that among patients staying at least three days in the medical ICU, the reduction in in-hospital mortality associated with intensive insulin therapy was greater than the reduction in ICU mortality in such patients. This indicates that intensive insulin therapy during intensive care has a carryover effect, benefiting patients even after they are discharged from the ICU.

In Malhotra's editorial, he outlines possible reasons for the difference in mortality between patients staying in the ICU less than three days and those staying longer. One explanation relates to hypoglycemia and the failure of the secretion of counterregulatory hormones that could prevent hypoglycemia, such as epinephrine, glucagon, cortisol, and growth hormone. He writes, "the effect of intensive insulin therapy may have been to unmask patients in whom counterregulatory hormones such as catecholamines could not be released… rather than demonstrating a harmful effect of intensive insulin therapy or hypoglycemia itself." Alternatively, hypoglycemia itself, resulting from intensive insulin therapy being poorly matched well to parental nutrition, may have a negative effect on long-term neurocognitive functioning.

One limitation of the study by Van den Berghe et al. is that it was not possible to achieve strict blinding, since insulin titration must be accompanied by monitoring of blood glucose levels. Malhotra goes as far as to say that the study was "essentially unblinded." Another limitation is that this was a single-center study.

Based on the results of their study, Van den Berghe et al. concluded that intensive insulin therapy (targeting blood glucose levels to below 110 mg/dL) during intensive care reduced morbidity but not mortality among all patients in the medical ICU. Among patients who stayed in the ICU for at least three days, however, intensive insulin therapy reduced both morbidity and mortality. The results of this study leave us with a bit of a conundrum. Intensive insulin therapy did not benefit survival benefit in the intention-to-treat group, while such therapy improved mortality and morbidity in patients staying in the ICU for at least three days. Since it is not possible to know for certain upon admission, which patients will stay in the ICU at least three days, the question remains of whether to use intensive insulin therapy in any patients upon admission to a medical ICU. Malhotra argues that patients should receive exogenous insulin therapy adjusted to target glucose values less than 150 mg/dL during the first three days in the ICU, and intensive insulin therapy (target blood glucose 80-110 mg/dL) thereafter. Van den Berghe et al. report that large-scale trials in the medical ICU, involving at least 5,000 patients, are needed to determine whether intensive insulin therapy should be used in patients in medical ICUs. Fortunately, the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE – SUGAR) study, with an expected enrollment of 5,000 patients, is underway and is expected to conclude in February 2007.

Our Commentary

The release of Dr. Van den Berghe's data met with mixed response. Dr. Malhotra's response cast a negative light on the study, but many clinicians have disagreed with his criticisms, and Dr. Van den Berghe herself has gone on record stating that she disagrees with the editorialist. We expect to see responses to both the article by Van den Berghe and colleagues and to the editorial in a coming issue of the *New England Journal* but in the meantime, we provide here our take on the key points of controversy.

First, Dr. Malhotra suggests that intensive insulin therapy may harm patients. He notes that in the subgroup analysis, while those patients staying in the ICU more than three days saw a *decrease* in mortality with intensive insulin therapy (from 52.5% to 43.0%, p=0.009), those staying less than three days saw *an apparent increase* in mortality with intensive therapy (56 patients, or 24.5% in the intensive-treatment group, versus 42 patients, or 18.8%, in the conventional-treatment group). We note that the statistical significance of this trend is far from clear. When analyzed with a chi-square test, p=0.05, but when baseline risk factors are corrected for, p=0.41 by proportional hazards analysis. As correcting for baseline risk factors seems appropriate, we believe this statistical association does not look to be meaningful.

Of course, Dr. Malhotra makes the important point that hypoglycemia is dangerous, particularly in a fragile population such as that of the ICU. We agree, but we are not persuaded that intensive insulin therapy does more

harm than good. We do believe that safety should be emphasized, and as such we look forward to the introduction of alarmed, continuous glucose sensors to the inpatient setting, at which time hypoglycemia will be all but eliminated. Dr. Malhotra suggests that "insulin has pluripotent effects and may induce deleterious consequences not just from hypoglycemia but also through other biologic actions." Dr. Malhotra does not elaborate on what effects he would give as examples of this, and such a claim, which appears a remnant of the 1950s and goes against current medical thought, surely requires more substantiation than the two questionable footnotes he gives—one a citation from 1986.

In the overall analysis of the 1,200 patients, the reduction in mortality in the intensive therapy group is not found to be significant. Dr. Van den Berghe and her colleagues discuss this in the paper, stating that the study was underpowered to detect a small difference (among the 1200 patients, mortality rates were 37.3% in the intensive therapy group and 40.0% in the conventional therapy group). Dr. Van den Berghe's study was powered to find a 7% difference in this size population; to detect a less than 3% difference would require a sample of 5,000, according to author commentary. The subgroup analysis, however, suggests that in those patients who receive IIT for longer than three days, there is a significant benefit. More research is needed on this point, but certainly to call this study negative would be misleading.

Dr. Malhotra suggests that the best way to practice evidence-based medicine in light of this publication is to target blood glucose values of 150 mg/dL until the third day of ICU care, after which time physicians should target blood glucose values to be between 80 and 110 mg/dL. He recommends this because he believes that the data support the importance of tight glycemic control after the third day, but not before. While we hope hospital ICUs will conduct practice in the way they believe will most benefit patients, we find Dr. Malhotra's suggestion to be misguided. The data may suggest that IIT is most beneficial when continued for three days or longer—in which case beginning on the third day would mean patients would only benefit if they remained until day six. IIT requires time to work and help the patient; there is nothing else magic about the third day. In addition, the target of 150 mg/dL for the first three days appears to be plucked from the air and based on absolutely zero evidence.

Dr. Malhotra also implies that the study design of both this publication and the 2001 Van den Berghe paper is flawed in both trials were "essentially unblinded." Van den Berghe et al. describe the precautions they take to avoid bias in the study at length, and Dr. Malhotra does not suggest how these procedures could be improved or modified. In fact, as a study of this topic can not be wholly blinded, we do not see a way that the blinding procedures could have been any more rigorous.

In sum, while dialogue about the evidence coming from the study is clearly important and helpful, particularly with results as complex as those presented in the Van den Berghe paper, Dr. Malhotra's critiques of the study appear inflated and misleading. His suggestion that "the theory of short-term, adaptive elevations in blood sugar levels, as described historically may actually have some merit" borders on irresponsible in the face of evidence from Dr. Furnary, Dr. Van den Berghe's study in the surgical ICU, Dr. Krinsley's data, and the work of many other thought leaders. Like Dr. Malhotra, we anticipate the results from the large-scale, multicenter, randomized trials exploring glycemic control in the ICU—the Glucontrol study and the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study—and hope that they will further illuminate what is a complex but critical issue emerging in inpatient care.

—by Katelyn L. Gamson, Erin M. Kane, and Kelly L. Close

Review of RIO-North America:

Pi-Sunyer FX, et al. "Effect of Rimonabant, a Cannabinoid-1 Receptor Blocker, on Weight and Cardiometabolic Risk Factors in Overweight or Obese Patients. RIO-North America: A Randomized Controlled Trial." JAMA. 15 Feb 2006.

RIO-North America was an investigation of the efficacy and safety of rimonabant in conjunction with a hypocaloric diet in promoting weight loss and improvement of cardiometabolic risk factors to counter obesity. Inclusion criteria included age over 18 years and BMI >27 with treated or untreated hypertension or dyslipidemia or BMI ≥30. Exclusion criteria included weight change of >5 kg in the 3 months prior to the beginning of the study; clinically significant cardiac, renal, hepatic, GI tract, neuropsychiatric, or endocrine disorders; pharmacologically treated type 1 or type 2 diabetes; use of medications that alter body weight or appetite; a history or current substance abuse; or

changes in smoking habits within the past 6 months. Patients were 85% white and~80% women and were an average of 45 years old and 231 lbs with a BMI of 38.

Patients were instructed to follow a hypocaloric diet (600 kcal/day deficit) and increase their level of physical activity. They were randomized to one of three double-blind treatment groups for one year: placebo, 5 mg/day of rimonabant, or 20 mg/day of rimonabant. For the second year, rimonabant-treated patients were re-randomized to receive placebo or the same rimonabant dose, while the placebo group continued to receive placebo.

Of 4604 patients screened, 3045 patients completed the initial four-week, placebo run-in and were randomized to one of the three treatment groups: placebo (n=607), 5 mg rimonabant (n=1216), and 20 mg rimonabant (n=1222). The trial was severely undermined by high drop-out rates: 51% of placebo group patients completed year one, compared to 51 % of patients on 5 mg/day rimonabant and 55% on 20 mg/day rimonabant. Completion rates for year 2 were higher, at 77% for patients who received 20 mg rimonabant both years and 70-72% for patients who received placebo both years, for those who received 5 mg rimonabant both years, and for those who received rimonabant the first year and placebo in the second year. These higher year 2 completion rates aren't that surprising given the high first-year drop-out rates.

At year one, weight from baseline was significantly lower in patients taking 20 mg or 5 mg rimonabant than in patients taking placebo: mean weight reduction of -6.3 kg (13.9 lbs) in the 20 mg rimonabant group, compared to -1.6 kg (3.5 lbs) in the placebo group ($p<0.001$). 26.1% of patients on 5 mg rimonabant, 48.6% of patients on 20 mg rimonabant, and 20% of patients on placebo achieved at least 5% weight loss. The percentage of patients achieving at least 10% weight loss was 25.2% for 20 mg rimonabant, 10.6% for 5 mg rimonabant, and 8.5% for placebo. Waist circumference also decreased more in patients receiving 20 mg rimonabant (-6.1 cm vs. -2.5 cm in placebo; $p<0.001$).

Mean weight loss from baseline among participants who receiving 20 mg rimonabant both years was 7.4 kg (16.3 lbs). Patients who were re-randomized from rimonabant to placebo regained most of the weight loss and reduction in waist circumference they had experienced during the first year, although their mean body weight was still slightly lower than the mean body weight among patients who received placebo for both years. While patients treated with 20 mg rimonabant both years lost significantly more weight than patients receiving placebo both years, this trend did not hold true for those receiving 5 mg rimonabant both years. More patients receiving 20 mg rimonabant both years lost at least 5% of baseline weight than patients receiving placebo both years (40% vs. 19%; $p<0.001$), and more patients on 20 mg rimonabant both years lost at least 10% of baseline weight (17% vs. 8%; $p<0.001$). On average, a 5% loss is just ~11-12 lbs and a 10% loss would be 23 lbs. It would be very interesting to see the weight loss quartiles, as the standard deviation for starting weight was fairly high. The two-year mean change from baseline in waist circumference was -5.0 cm for 20 mg rimonabant both years, compared with -2.2 cm for placebo ($p<0.001$).

The authors also highlight that rimonabant promoted beneficial changes in cardiometabolic risk factors. The levels of fasting insulin and HDL cholesterol increased during year one in patients receiving rimonabant (% change in HDL cholesterol, +12.6 for 20 mg rimonabant vs. +5.4 for placebo; $p<0.001$). In year one, triglyceride levels decreased meaningfully in patients on the 20 mg/day rimonabant but not among patients on 5 mg/day. According to the ATP III criteria, the prevalence of the metabolic syndrome declined more among patients receiving 20 mg rimonabant (from 35% at baseline to 21% at year one) than among patients on placebo (from 32% to 29%; $p<0.001$) – while this was not an insignificant change, it was not as positive as we would have expected for this motivated population. Total cholesterol and LDL cholesterol levels did not differ significantly among any of the treatment groups. Insulin resistance increased among patients receiving placebo but did not change among patients receiving 20 mg rimonabant. Blood pressure also did not change significantly in any group, though it did decrease slightly in patients receiving rimonabant.

The effects on HDL cholesterol, triglycerides, fasting insulin, and insulin resistance in patients receiving 20 mg/day rimonabant were about twice that attributable to weight loss alone, and HDL cholesterol levels increased continuously throughout the two years of the study in patients receiving 20 mg rimonabant, even while body weight stabilized. These findings suggest that rimonabant has a *direct* pharmacological effect on glucose and lipid metabolism, which the authors speculate may be mediated by adiponectin and reduction of abdominal obesity.

Patients who were re-randomized from rimonabant to placebo at the end of year one had higher triglyceride levels and lower HDL cholesterol levels at year two than patients who continued to receive rimonabant therapy. HDL cholesterol levels continued to increase from baseline during year two in patients who completed the study and who were receiving either placebo or 20 mg rimonabant group for two years, although the increase was significant only in patients receiving 20 mg rimonabant ($P < 0.001$).

The authors report that rimonabant was "generally well tolerated." The percentage of patients reporting at least one adverse event was similar across treatment groups (~82-85%), although the incidence of adverse events leading to study withdrawal in year one was higher among patients receiving 5 mg rimonabant (9.4%) or 20 mg rimonabant (12.8%) than among patients receiving placebo (7.2%). According to the authors, this was "mainly due to psychiatric, nervous system, and gastrointestinal tract adverse events" – they don't elaborate on this. There were no differences among the treatment groups in changes over time in the anxiety or depression subscales, but we would have liked to have seen "average" scores throughout the year rather than just the reported "last value in year 1." Notably, 6.2% of patients on 20 mg rimonabant reported a psychiatric disorder during year one, compared to 3.6% among patients receiving 5 mg and 2.3% of patients receiving placebo. Among these, 2.2 % of 20 mg rimonabant patients reported depressed mood, compared to 2.1% receiving 5 mg rimonabant and 1.3% receiving placebo. In year two, rates of adverse events and study withdrawals were lower and there were no differences in overall rates among the treatment groups, suggesting that the adverse effects of rimonabant occur early and that 5 mg and 20 mg doses of rimonabant have a comparable safety and tolerability profile with placebo. Upper respiratory tract infection, nasopharyngitis, and influenza occurred more frequently in rimonabant-treated patients for both years.

The primary limitation of this study is the low retention rate of about 50% in all treatment groups. Patients who benefited less and dropped out more frequently may affect the results of the study, and data from patients who did complete the study may not be representative of the overall study population. Another limitation is the lack of racial diversity and the high proportion of white women in the study.

The authors conclude that 20 mg/day of rimonabant reduces body weight and waist circumference and promotes improvements in several cardiometabolic risk factors. The finding that patients who were switched from rimonabant to placebo during year two regained most of their weight while those who remained on rimonabant both years maintained their weight loss supports the theory that sustained weight loss and associated benefits in cardiometabolic risk factors require continuous long-term treatment. The authors compare the need for continuous long-term weight loss treatment to the need for continuous treatment for other chronic conditions, such as diabetes and hypertension. Importantly, studies with larger patient populations and longer durations are still needed to assess the adverse effects and the long-term safety of rimonabant.

—by Katelyn L. Gamson

10. Conference Preview – What a Spring!

- **Advanced Glycation End Products and Diabetic Complications, March 17-19, Cambridge, MA:** The ADA is hosting a research symposium in Cambridge on advanced glycation end products (AGE). The first session on the chemistry and biological products of AGE includes a presentation by Dr. Michael Brownlee of the Albert Einstein College of Medicine titled "Methylglyoxal: A Novel Regulator of Gene Expression by Hyperglycemia." Session two, effects of internal/external advanced glycation endproducts, includes a presentation by Dr. Scott Grundy of the University of Texas Southwestern Medical Center on "Diabetic Dyslipidemia and Lipid Oxidation" and Dr. Timothy Lyons on "Glycation and Vascular Endothelium." A presentation by Dr. Paul Beisswenger of Dartmouth will focus on the postprandial state and AGE—"Postprandial Elevation of Serum Dicarbonyls and AGEs Results from Postprandial Hyperglycemia." The final session will explore new therapies, with Dr. Peter Libby of Harvard delivering the plenary address on "Inflammation and Diabetic Vascular Disease." Dr. Jorge Plutzky of Harvard will discuss "Anti-inflammatory Effects of PPARs." The research symposium will be rich in detail, and we will be there to monitor what is happening on the basic research front in complications and AGE. http://www.diabetes.org/for-health-professionals-and-scientists/age.jsp
- **Diabetes UK, March 29-31, Birmingham, England:** It seems that no matter which country we're in, there are some superstar physicians and researchers who are presenting at all of the top conferences. We look forward to seeing Dr. James Shapiro and Dr. Stephanie Amiel in the session on islets and transplantation. Like other large conferences, Diabetes UK spans the range from basic science to clinical practice to public health, and we look

forward to getting an update on diabetes practice Europe more broadly. We're also interested in the opportunity for some informal polling to gauge response to and interest in the Exubera approval, prospects for rimonabant, and how views on insulin are evolving in the midst of an influx of new products. http://www.diabetes.org.uk/apc/index.html

- **Clinical Diabetes Technology Meeting, April 21-23, Boston, MA:** We attended the sister meeting to the Clinical Diabetes Technology Meeting—the Diabetes Technology and Therapeutics Meeting—in San Francisco in the fall, and we will be traveling to the opposite coast for this meeting in late April. With one day devoted to continuous glucose monitoring and the other to insulin delivery, this meeting is unique in its exclusive focus on technology and its high degree of relevance to type 1 diabetes, though glucose monitoring and insulin delivery of course apply to both type 1 and type 2. Hot topics to be addressed include decreasing glycemic variability, how to interpret data from CGM, and pramlintide, exenatide, and inhaled insulin. Dr. Barry Ginsberg of B-D will speak to CGM, and Dr. Lawrence Blonde of the Oschner Clinic will discuss A1C, glycemic variability, and other outcome markers. We also look forward to Dr. Howard Wolpert of the Joslin Diabetes Center and his discussion of using CGM in diagnosing and managing hypoglycemia unawareness and industry representatives Dr. Jay Dunigan of Abbott and Dr. Claudia Graham of Medtronic on "What Will It Take to Get CGM Reimbursed." http://www.clinicaldiabetestechnology.org/
- **AACE, April 26-30, Chicago, IL**
  If not for a compelling line up, we might think twice about leaving temperate San Francisco for the Windy City of Chicago, but we couldn't pass up the opportunity to hear everyone from Dr. Bob Henry to Newt Gingrich—the keynote speaker on Thursday. Dr. Lois Jovanovic will speak on diabetes and pregnancy, while Dr. John Service is scheduled to present on hypoglycemia. AACE offers a wide range of topics from all of endocrinology, and we'll be keeping you posted as this meeting nears. http://www.aace.com/
- **Pediatric Academic Societies, April 29-May 2, San Francisco, CA**
  At the Moscone Center in San Francisco the last weekend of April, the Pediatric Academic Societies meeting comprises many, many different tracks of almost every topic within pediatrics one could imagine. On the diabetes front, we'll be interested in the presentation by Dr. Mark Sperling of the Children's Hospital of Pittsburgh on neonatal diabetes, updates on Trial Net and STOPPT2D, the cleverly titled "Obesity Symposium—the BIG Picture," and a session on the treatment of metabolic syndrome in children. http://www.pas-meeting.org/
- **Second Metabolic Diseases World Summit, May 18-21, Long Beach, CA**
  This metabolic disease summit will have some world-class speakers, many from industry (J&J, Abbott, Amgen, Wyeth, Hoffmann-La Roche, Merck, Sanofi, Pfizer, DiObex, GSK, Lilly, Regeneron, Takeda) as well as some academic luminaries. In particular, we're very excited to hear Dr. Dan Einhorn of Scripps talk about "The Clinician and Metabolic Syndrome," since the area has been so controversial. (*"It doesn't exist." "Yes it does!" "No it doesn't!" "Well, it isn't clinically useful…." "What about…?"*) http://www.gtcbio.com/hotal.asp?cid=17

—by Erin M. Kane