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SPECIAL EDITION

Utilizing Novel Therapies With a Basal Insulin Plus Oral Regimen Today and Beyond

CME-Certified Activity

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Jointly Sponsored by



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Utilizing Novel Therapies With a Basal Insulin Plus Oral Regimen Today and Beyond

CME-Certified Activity



Jointly Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ)—Center for Continuing and Outreach Education and *Medical Crossfire*/Liberty Communications Network.

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Educational Overview

The task of developing and maintaining a comprehensive insulin regimen for the patient with type 2 diabetes is wrought with challenges for both clinician and patient. Clinicians need to effectively position insulin therapy with their patients in order to overcome barriers, maximize compliance, and optimize treatment. In the setting of diabetes management and glucose control, clinicians require tools to close the gap between recommendations and results.

Along the continuum of care, how are glucose control and safety achieved with consideration of an individualized and physiologic approach? How does the practicing clinician proceed when faced with management challenges? From data to practice to optimal patient care, these issues elicit varying views, the expression and discussion of which are invaluable to the practicing clinician today and beyond.

Through debate and authoritative peer exchange, this *Medical Crossfire*[®] program, conducted in conjunction with the University of Medicine and Dentistry of New Jersey, will confront these and other issues related to optimizing glucose control in the patient with type 2 diabetes.

Target Audience

This educational activity is designed for endocrinologists, primary-care physicians, and other health care providers interested in or involved with the management of patients with type 2 diabetes.

Learning Objectives

- Review and discuss barriers to initiating insulin therapy faced by both clinicians and patients.
- Assess the process associated with identifying people with type 2 diabetes who are failing to achieve targeted levels of glucose control with oral agents.
- Discuss the initiation of a more physiologic approach to insulin treatment utilizing basal plus oral therapy to optimize glucose control and safety, and describe approaches to individualized treatment.
- Consider the components of a comprehensive insulin regimen that would address 24 hour glucose control.

Method of Instruction

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test consisting of a series of multiple-choice questions. The activity is complemented with references that contain the rationale for the correct answer to each question as well as a description identifying the section in the activity that contains the correct answer, allowing participants to review the material as needed, thus finalizing their educational participation.

Upon completing this activity as designed, participants will receive a letter of credit awarding AMA/PRA category 1 credit three to four weeks after receipt of the registration and evaluation materials. Estimated time to complete this activity as designed is one (1) hour.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of UMDNJ—Center for Continuing and Outreach Education and *Medical Crossfire*/Liberty Communications Network. UMDNJ—Center for Continuing and Outreach Education is accredited by the ACCME to provide continuing medical education for physicians.

UMDNJ—Center for Continuing and Outreach Education designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by Maya Raghuwanshi, MD; Sherry Gillis Funderburk, MD; Syed Naved Hasan, MD; and Kinshasa Morton, MD.

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Disclosure Declarations

In accordance with the disclosure policies of UMDNJ and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services, that relate to the content of their presentation/material, or the commercial contributors of this activity, that could be perceived as a real or apparent conflict of interest; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Faculty Disclosure Declarations

Dr. Davis has received grant/research support from Bayer, Eli Lilly and Co., and sanofi-aventis.

Dr. Edelman has received grant/research support from Amylin Pharmaceuticals, Eli Lilly and Co., Novo Nordisk, and Takeda Pharmaceuticals North America; and has been a consultant for and has served on the speakers' bureaus of Amylin Pharmaceuticals, Aventis Pharmaceuticals, Eli Lilly and Co., GlaxoSmithKline Pharmaceuticals, Novo Nordisk, and Takeda Pharmaceuticals North America.

Dr. Raskin has received grant/research support from, been a consultant for, and has served on the speakers' bureaus of Novo Nordisk Pharmaceuticals and sanofi-aventis.

Dr. Rosenstock has received grants for research from and/or has been a consultant for Amylin Pharmaceuticals, AstraZeneca Pharmaceuticals, Centocor, Bristol-Myers Squibb, Eli Lilly and Co., GlaxoSmithKline Pharmaceuticals, Johnson & Johnson, MannKind, Merck & Co., Novartis Pharmaceuticals Corp., Novo Nordisk Pharmaceuticals, Pfizer Labs, Sankyo Pharma, sanofi-aventis, and Takeda Pharmaceuticals North America.

Dr. Salgo has no financial arrangements or affiliations to disclose.

Dr. Raghuwanshi, Dr. Funderburk, Dr. Hasan, and Dr. Morton have no financial arrangements or affiliations to disclose.

Off-Label Usage Disclosure

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Utilizing Novel Therapies With a Basal Insulin Plus Oral Regimen Today and Beyond

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Although treatment standards and recommendations have been enacted by leading authorities such as the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE), diabetes care has remained suboptimal in many clinical settings, as only 37% of adults with diabetes achieve optimal hemoglobin A_{1c} levels. Misperceptions and resistance to early initiation of insulin therapy, failure to provide individualized treatment regimens and disease-related education, unfamiliarity with diabetes algorithms, and ill-equipped health-care facilities are just some of the challenges that must be overcome in order to more effectively manage this complex and chronic disease.^{1,2}

During this **Medical Crossfire**, a panel of national experts in diabetes, endocrinology, and metabolism discussed the myths associated with insulin use, the methodologies employed in identifying the need and staging of insulin regimens, and the barriers to individualizing treatment strategies for continuous glycemic control.

Overcoming Barriers Associated With Insulin Initialization

To begin this *Medical Crossfire* exchange, moderator Peter L. Salgo, MD elicited the panels' perspectives on barriers associated with the initiation of insulin therapy in patients with type 2 diabetes.

"The biggest barrier associated with insulin initiation is the clinician," replied Philip Raskin, MD. "Insulin resistance starts in the clinician's office," he explained, noting that both clinicians and patients alike avoid this treatment. "Clinicians do not push hard enough for insulin treatment earlier in the disease course." He reported that other noteworthy impediments to insulin therapy include patients' fear of needlesticks and myths surrounding insulin's effects on the body.

"Patients have many misconceptions associated with insulin therapy and diabetes, and this translates to psychological barriers to treatment," reported Steven V. Edelman, MD. Often, insulin therapy instills patients' fear

that "their diabetes is getting worse," he rationalized. Dr. Edelman shared his own method of motivating patients to begin insulin therapy: "I always reassure the patient that if the insulin injections are too painful, if the blood sugars do not decrease, and if they do not feel better, we will stop the therapy." Patients are often shocked by this recommendation, noted Dr. Edelman, adding that, "I have never had a patient return and ask to stop their insulin regimen."

Defining Dr. Edelman's treatment approach as "patient contracting," Dr. Raskin acknowledged that it is an acceptable and effective means of negotiating and reinforcing treatment among patients, and he has achieved similar successful results.

Focusing on specific barriers, Dr. Salgo asked, "What are the physiologic barriers associated with insulin therapy?"

"There are not many physiologic barriers associated with insulin therapy," Dr. Edelman disclosed. Although severe arthritis or ampu-

tation of the upper extremities presents insulin administration challenges, he believes that the primary treatment obstacles are psychological.

In certain scenarios, a non-physiologic approach can be a barrier to insulin treatment, noted Julio Rosenstock, MD. “We are attempting to deliver insulin in a way that is different than nature intended. We have always looked at insulin as a treatment; we need to look at it as a replacement. When patients realize early on that they are receiving something that their body lacks naturally, they understand the need for therapy much better, and become more receptive to insulin,” he counseled. Educating patients about insulin is critical in order for them to understand their therapies.

Rationalizing Weight Gain

“How prevalent is patient fear of weight gain associated with insulin, and is it warranted?” inquired Dr. Salgo.

Weight gain with insulin treatment “is a real occurrence,” and a prevailing patient concern, verified Dr. Rosenstock. However, “weight gain must be put into context, as patients perceive relatively small increments in weight, 1 kg to 3 kg, as a significant increase, but in reality the weight gain is relatively mild or modest and depends on patients adherence to their nutritional plan” he noted. Most studies have shown that a 1% improvement in hemoglobin A1C, for the most part, results in a 2 kg weight gain. Presumably, earlier treatment may reduce the likelihood of weight gain associated with insulin treatment, noted Dr. Rosenstock. “If insulin is initialized early when the patient still has mild hyperglycemia and lower insulin doses are used, then presumably weight gain is not going to be a major issue,” he suggested. Dr. Rosenstock added that weight gain can also be managed through medical nutrition therapy (MNT).

Dr. Raskin clarified that, “change in weight is directly proportional to improve-

ment in A1C, unless there is extreme nutritional or exercise intervention.” Weight change with insulin treatment is a complex issue, and “glycosuria is only part of the equation.” In general, weight gain in the presence of diabetes improvements is not correlated with increased food intake. “Patients actually eat less,” he pointed out. Weight gain and necessary daily insulin dose were found to be greater for patients with type 2 diabetes receiving biphasic insulin aspart compared with patients receiving once-daily insulin glargine in a study by Raskin and colleagues.³

Reiterating the importance of patient education, Dr. Edelman suggested that clinicians “inform patients that weight gain is expected with insulin initialization to avoid any surprises.” Moreover, he stressed that patients should monitor their diet and exercise during this critical time.

Elucidating Hypoglycemia and Insulin Therapy

Seeking the panels’ perspective, Dr. Salgo asked, “How real is the fear of hypoglycemia on the part of clinicians and patients?”

“Hypoglycemia is a complication of diabetes, and it is a real fear among both healthcare providers and patients,” declared Stephen N. Davis, MD. Coupled with the fact that there is a 90% risk of hypoglycemia associated with insulin administration, the occurrence of hypoglycemia “can be life-altering.” Dr. Davis cautioned that, “it only takes one severe episode of hypoglycemia for patients to refrain from insulin,” despite the proven benefits.⁴

Dr. Raskin agreed that hypoglycemia is a major concern in individuals with type 1 diabetes. “In those with type 2 diabetes,” he contended, “it is relatively uncommon. Patients may experience some shaking before mealtime.” However, in his view, “this is not an impediment to treatment,” he explained.

Hypoglycemia is contingent on how it is defined, but fear of hypoglycemia is real and

cannot be easily quantified, responded Dr. Rosenstock. “Most people in the United States, based on the National Health and Nutrition Examination Survey (NHANES), have chronic hyperglycemia,” he pointed out. As targets in treatment algorithms are lowered, “we will be seeing a higher prevalence in hypoglycemia,” he speculated. He remarked that clinicians know very little about the negative impact of hypoglycemia in type 2 diabetes and countered that, “I do not think it is just a little shakiness. The adrenergic surge and catecholamines in the middle of the night cannot be good for a patient with coronary artery disease.”

Dr. Rosenstock, in further assessing the risk of hypoglycemia, agreed with hypoglycemia experts like Cryer and colleagues; “Hypoglycemia is the major barrier with available therapies, and it hinders clinicians from getting patients to goal, if it wasn’t for hypoglycemia, we could potentially normalize glycemia in all of our patients” he declared.^{5,6}

Cryer and colleagues reported that iatrogenic hypoglycemia, which causes morbidity and mortality in patients with diabetes, is often the result of the interplay of absolute or relative insulin excess and compromised glucose counterregulation in type 1 and advanced type 2 diabetes.^{5,6}

“Hypoglycemia may prevent clinicians from getting their patients to 5.6%, however, it does not prevent them from aiming for 7.0% or 6.5%,” declared Dr. Raskin. Achieving good glycemic control, he counseled, “is not a result of only the clinician and the treatment agent. It is the patient who controls the outcome.” Intensive diabetes treatment, in Dr. Raskin’s opinion, “has very little to do with insulin, and requires continuous patient commitment and management, which can be very challenging.”

Myths and Misconceptions of Insulin Therapy

Shifting the dialogue to explore patients’ beliefs, and how they may influence treatment

approaches, Dr. Salgo inquired, “Are there myths and misconceptions associated with insulin therapy that should be addressed?”

Affirming that misconceptions “cause the delay in starting insulin,” Dr. Edelman pointed out that, “By the time patients begin insulin therapy, they have significant complications. Unfortunately, patients often equate their complications with insulin initialization.”

Pressing further to explore other areas of misconception regarding insulin treatment, Dr. Salgo mentioned the notion that insulin leads to cardiovascular problems as well as endothelial dysfunction. In attempting to either substantiate or dispel these ideas, Dr. Salgo asked whether these are justified concerns.

Insulin resistance is a topic of current debate, advised Dr. Rosenstock. “Primary-care physicians’ confusion comes when they associate insulin therapy with insulin resistance and hyperinsulinemia, but do not always recognize that insulin resistance refers to elevated endogenous insulin which is like the peak of the iceberg of the metabolic syndrome,” he lamented. Dr. Rosenstock confirmed that intensive insulin treatment by reducing glucotoxicity with insulin administration “actually improves insulin resistance.”

Nonglycemic benefits of insulin use include inhibiting production of triglyceride-rich particles and platelet aggregation and increasing vasodilation. In individuals with normal insulin sensitivity, these actions are anti-atherogenic. In individuals who are insulin resistant, insulin’s normal anti-atherogenic actions are defective resulting in hypertriglyceridemia, increased platelet aggregation, and endothelial dysfunction. Patients with type 2 diabetes receiving insulin therapy may experience improvements in insulin sensitivity, lipid profile, and endothelial function leading to improved cardiovascular health.^{7,8}

Dr. Davis underscored recent findings from the Diabetes Control and Complications Trial (DCCT). In this study, after 12 years of good glycemic control with intensive

insulin, “there was a 50% reduction in cardiovascular events and stroke,” he reported.^{9,10}

“Does the average clinician have sufficient time with patients to dispel insulin-related myths and misconceptions?” asked Dr. Salgo.

“Time is a major barrier, especially for the primary-care physician,” declared Dr. Davis. “Initializing insulin therapy takes time and clinicians have to work through the feedback algorithms.” He acknowledged that administering intensive insulin therapy and achieving good glycemic control in a single office visit “is very difficult.”

“It is our fault for making insulin strategies so complicated,” declared Dr. Rosenstock. He blamed the complex, intensive treatment regimens used to educate clinicians, lamenting that they “are too overwhelming for the physician and more so for the patients. They are not the best or the simplest, nor can they be translated into clinical practice.” Offering his own technique to overcome patient fear, Dr. Rosenstock recommended that at the first visit with a patient with type 2 diabetes, insulin should be mentioned as part of the treatment options that eventually will be used. Furthermore, at the time that self-blood glucose monitoring is instructed, a shot of saline with a fine insulin syringe needle should be administered to dispel fears with future insulin therapy. “We need more insulin regimens that are simple and non-threatening for clinicians and patients. Complexity has been the barrier and not necessarily the needle itself,” he suggested.

Intrigued by the panel’s assertion of misconceptions and how greatly they impact treatment options, Dr. Salgo asked, “How should clinicians move past these barriers and get patients on the right regimen?”

Dr. Edelman identified multidisciplinary diabetes centers and diabetes educators as a solution for helping inform patients about their disease and treatments. Through the multidisciplinary team approach, “we could truly work to overcome these barriers,” he offered.

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—Dr. Rosenstock

Stratifying Treatment Approaches in Type 2 Diabetes

Regarding treatment approaches, Dr. Salgo asked if clinicians generally wait too long before initializing insulin.

“This implicates clinicians as the main problem,” objected Dr. Edelman. “The barriers are three-fold involving the clinician, the patient, and the healthcare system.” Dr. Edelman identified several challenges, including clinicians who are ill-equipped to initialize insulin in their practice setting, patient resistance to proposed regimens, and a lack of support for adequate follow-up from healthcare systems. In a study conducted by the Oregon Kaiser Permanente healthcare system, “it took clinicians as long as 20 months to add a second oral agent once the A1C was >8.0%,” he reported.¹¹ He proposed “addressing all aspects of the diabetes community, including patients, because they are instrumental in attaining treatment goals.”

“The problem that was demonstrated in the Kaiser Permanente study can be defined as treatment inertia. Treatment actions should be driven by the glycemic targets and this is not happening,” countered Dr. Rosenstock. He explained that if patients cannot reach their glucose targets, then the treatment needs to be advanced and other agents need to be added. For example, “The issue of monotherapy is basically a historical issue, and patients should probably commence with combination therapy or rapidly add a second agent with complementary action, once the agent initiated first is well-tolerated. If the A1C has not reached <7.0%, then the clinician should proceed to the next step,” advised Dr. Rosenstock. He believes that, “there has to be effort from both sides—the physician willing to act and the patient pressing for action—when they are not achieving their glucose targets.”

According to Dr. Raskin, “In diabetes, we treat failure. We do not alter treatment until we fail.”

Identifying Glycemic Targets

Seeking consensus, Dr. Salgo inquired, “What is the target that the diabetologist should be aiming for?”

“The A1C target should be the same as individuals without diabetes, if the target can be achieved safely,” declared Dr. Raskin. Advocating a “lower is better” philosophy, he cited the DCCT’s results that after 6.5 years with an A1C at about 7.1, that patient “will do well for a very long time in terms of microvascular disease.” Based on his participation in the DCCT, Dr. Raskin stated that, “the goal was to achieve A1C <6.5%, because that is what it is for individuals without diabetes. However, we could only achieve, on average, 7.1%.” In the DCCT, intensive treatment was defined as retaining A1C levels as close as possible to the normal value defined as <6.0%. As explained by Dr. Raskin, 6.5 years after the DCCT’s inception A1C levels averaged 7.0% in the intensively-treated group and 9.0% in the conventionally-treated group. Although the A1C values of study participants have leveled off during the EDIC follow-up study to approximately 8.0% in both treatment groups, the benefits of previous improved glycemic control persist.^{9,10}

Additionally, the AACE recommends an A1C treatment target of 6.5% as goal. Commenting further on the role of target levels in diabetes treatment, Dr. Edelman declared that, “We should all be aiming for A1C levels in the nondiabetic range as long as we do it safely.”

“What are some practical suggestions for optimizing the clinician approach to the diabetes treatment algorithm?” wondered Dr. Salgo.

The Treat-to-Target study provided the proof of concept that changed the current treatment paradigm; “it demonstrated that it is feasible to achieve glycemic targets with basal insulin supplementation to oral agents using simple but structured insulin titration regimens in the office setting,” according to Dr. Rosenstock. He explained that previously,

clinicians relied solely on the delta change or decreases in A1C, and “now we are focused on getting the patient to target A1C below 7.0.” Although diabetologists have been successful in getting type 1 diabetes to be “in charge” with frequent insulin adjustments according to self-blood glucose monitoring, Dr. Rosenstock admitted, “we have failed in empowering patients with type 2 diabetes to do any insulin adjustments to attain and maintain an A1C of $\leq 7.0\%$.” Clinicians must educate patients on target levels, “and provide tactics that allow the patient to make informed decisions, because the patient is the key player,”¹² he concluded.

Results from the Treat-to-Target Trial support the feasibility of an A1C target of $< 7.0\%$ in type 2 diabetes. In this randomized, open-label, parallel 24-week multicenter trial, 756 overweight adults with type 2 diabetes (A1C $> 7.5\%$) inadequately controlled with oral therapies received bedtime glargine or NPH once daily, and titrated to achieve a fasting plasma glucose of < 100 mg/dL. Approximately 60% of patients achieved A1C $< 7.0\%$ with each insulin type.¹²

“A simplified patient-centered approach is the means to achieving target glucose levels,” advised Dr. Edelman. Intensive insulin treatment, in his opinion, “is not administering 10 injections and testing blood glucose 10 times daily; it is achieving an A1C below 7.0% without wide fluctuations.”

Patient education with regard to achieving glycemic targets is the key, confirmed Dr. Davis, as they “have to understand why it is important and how to achieve this goal.”

In a position statement issued by the ADA, reducing A1C was associated with a reduction in microvascular and neuropathic complications of diabetes, as well as a decreased risk of myocardial infarction and cardiovascular death. The recommended A1C for adults with diabetes is $< 7.0\%$, however in individual patients or during pregnancy, more stringent goals may be indicated (e.g., A1C $< 6.0\%$). Less aggressive A1C targets may

be required in pediatric and elderly patients, those with a history of severe hypoglycemia, in the presence of certain comorbidities, and in those with a limited life expectancy.¹

Oral Therapies Versus Insulin

Presenting a hypothetical scenario in which a patient is unsuccessful with two oral therapies, Dr. Salgo questioned, “How should clinicians decide if a third oral therapy is needed, or if the insulin regimen should be simplified?”

In such a patient, “insulin is nature’s answer and the solution to hyperglycemia,” purported Dr. Davis. Along with high blood glucose, there is insulin deficiency and insulin resistance, and he recommended replacing the insulin. “We also know that the higher the A1C, the greater the impact of contribution of fasting glucose. Therefore, the simple tactic is normalizing the fasting glucose and administering basal insulin while continuing the oral agents,” he recommended. “This method, will achieve very good results in a majority of patients.”

Adding a third oral agent in this case is a decision based on the individual patient, according to Dr. Edelman. “If the patient’s A1C was 6.8% and is now 7.2%, and if their A1C is not increasing further, they may be a candidate for a third oral agent,” he offered. As a general rule, if the patient is $> 1\%$ from goal, “I would rather start basal insulin to decrease the fasting blood sugar. Benefits may be achieved from adding the third oral therapy later on,” he disclosed.

“A simplified patient-centered approach is the means to achieving target glucose levels.”

—Dr. Edelman

“Overall, allowing patients to voice their treatment desires and goals will promote patient commitment to therapy.”
—Dr. Rosenstock

Discussing therapeutic options with a patient “is a mutual contract and an ongoing negotiation process,” remarked Dr. Rosenstock. He elaborated that, “it is not up to us to decide between three pills or two pills and insulin. Patients will tend to go for a third pill but we need to inform patients that if their A1C is >9.0%, adding another pill is unlikely to get them to target and most of them will go for adding a basal insulin.”

Pharmacoeconomics and adverse events also figure prominently in the treatment decision process, he noted. In weighing the pros and cons of a third pill, Dr. Rosenstock contended that some patients will opt for insulin when presented with the cost, the potential for weight gain, and the fluid retention associated with some oral therapies. “Overall, allowing patients to voice their treatment desires and goals will promote patient commitment to therapy,” he maintained.

Correcting fasting glucose may not achieve desired A1C values, noted Dr. Edelman. He explained that he prefers adding nighttime insulin, insulin glargine, or NPH to daytime oral therapies when therapy needs to be escalated. “This allows me to prepare for the next treatment step if needed.” Complex regimens initiated too aggressively in some patients may not be appropriate.”¹³

Evaluating Basal Insulin Therapy

“What is the role of insulin in achieving target ranges in patients who do not respond to oral therapies?” asked Dr. Salgo.

Basal insulin involves two components, explained Dr. Davis. First, basal insulin restrains glucose production by the liver to stop the breakdown of fat and protein. Second, a normal pancreas will secrete insulin in a bolus fashion to coat for preprandial glucose. Clinicians, he advised, “should always be thinking about the basal bolus approach. Overnight, basal insulin can facilitate hepatic glucose production and a patient will awaken with a normal fasting glucose.” He noted that the bolus component is available in pills or other agents.

“The role of basal insulin is contingent on how early insulin was instituted, as well as the staging of the beta cell reserve or how advanced the type 2 diabetes is. The earlier the better, to take advantage of the endogenous insulin secretion,” Dr. Rosenstock pointed out. Agreeing with Dr. Edelman, he commences basal insulin if a patient is unsuccessful with pill formulations. Early intervention, according to Dr. Rosenstock, “corrects or reduces hepatic glucose production overnight, and the patient starts the day with a normal blood sugar.” Then the insulin secretagogue and insulin sensitizer play a major role to potentiate and enhance the prandial insulin response, “the patient has enhanced endogenous insulin secretion that will take care of the postprandial blood glucose,” he maintained.^{13,14}

Because basal insulin does not have a pronounced peak, Dr. Davis argued that, “an intermediate-acting insulin does not last 24 hours and will cause hypoglycemia in the middle of the night or day.”

Dr. Raskin employs a different approach consisting of “two injections of a mixture of intermediate and short-acting insulin.” If a patient is not doing well with two pills, he supports insulin administration, “but not a single bedtime injection.” Moreover, Dr. Raskin would discontinue the secretagogue because “there are no data that it is synergistic with the insulin. Synergy exists between insulin and metformin or thiazolidinedione.”¹⁵ In this patient, “I would continue the sensitizers and add two small injections of 70/30; one before breakfast and one before supper,” he outlined. “Patients need insulin, and they need it early,” he concluded.

Dr. Rosenstock agreed that, “there is no question that insulin is the most potent agent but it is limited by hypoglycemia, especially with unpredictable premixed preparations.”

Further exploring the utility of basal insulin, Dr. Salgo surveyed the panelists’ thoughts on the advantages and disadvantages associated with this treatment.

Reviewing the function of insulin, Dr. Edelman stated that, “all patients require basal insulin, diabetic or not. Dr. Edelman offered that low dose NPH should ideally be administered four times daily, or every six hours, because of its pharmacokinetic profile.”¹⁴

“What does the evidence suggest regarding the effects of these different insulins on the incidence of hypoglycemia?” asked Dr. Salgo.

“Numerous studies address hypoglycemia with insulin,” including those conducted by Yki-Järvinen, Riddle, Janka, Rosenstock, and Raskin, cited Dr. Davis. Based on previous research, “if a clinician uses a true basal insulin head-to-head versus a peaking intermediate-acting insulin, the patient will experience a 20% to 30% reduction in hypoglycemia with the analog,” he explained. Likewise, Dr. Davis cited a study conducted by Dr. Raskin demonstrating that, “if a 70/30 analog twice daily is paired with a sensitizer, we can achieve a slightly greater reduction in A1C. However, a five-fold increase in the incidence of hypoglycemia was seen with this method.”^{3,12,16,17,18}

Clarifying the prevalence of hypoglycemia in his study, Dr. Raskin explained that, “our study was not stopped and we achieved the glycemic targets, despite report of hypoglycemic symptoms. Hypoglycemia is not good; however, it is not always a negative occurrence in type 2 diabetes as it is in type 1 diabetes.”

Dr. Davis challenged his colleague’s view. “I do not believe there is any patient that I have come in contact with who felt well with a blood glucose of <56 mg/dL.”

“I am not suggesting that they felt well. I am simply pointing out that this is not an impediment to achieving targets, or that it may not be as serious a concern as it is in type 1 diabetes,” Dr. Raskin noted.

The responsibility of conveying the right message to patients rests with clinicians, educators, and diabetologists, Dr. Rosenstock interjected. “Our charge is to translate clinical research to the general community.” For

example, “all insulins do work; we have learned to use and titrate insulin much better, and if hypothetically, we were to bring back the old bovine insulins, we would potentially get better results but presumably will have more unpredictable hypoglycemia,” he analogized.

In agreement, Dr. Raskin stressed that results from research, “do not reflect the real world.”

Shifting to treatment techniques, Dr. Salgo inquired, “Is there a better way to reduce hemoglobin A1C? Are there data that support a different method?”

Clinicians are still learning how to strategically reduce A1C levels, and the treatment techniques have not been fully mastered. Dr. Rosenstock cited that, “most of the studies conducted involve patients who have lived with diabetes for eight to ten years.” If patients with diabetes for only two to three years were to be studied, he speculated that because of their potentially better beta cell function, “we would likely be able to get their A1C in the 6.5% range with basal insulin only.” He promoted a simplified approach of “fixing the fasting first with one shot daily of basal insulin. If that is ineffective, then add on the prandial insulin with the main meal to ameliorate postprandial hyperglycemia.”

Dr. Rosenstock reported that, “the LANMET study demonstrated that a combination of glargine plus metformin resulted in an A1C decrease from 9.5% to 7.1% ($P < 0.001$) versus NHP plus metformin.” Since A1C reductions $< 7\%$ were not achieved in this study, he suggested that, “something else is needed, perhaps more basal insulin, or adding a sulfonylurea or supplementing basal with prandial insulin.”¹⁸

“We should redefine what we mean by basal insulin,” interjected Dr. Davis. “Basal insulin is insulin that is going to last 24 hours without peak action at any time,” he described.

In terms of reducing A1C levels, Dr. Edelman uses a simplified approach of

glargine or NPH at bedtime. Depending on the patient, “If the A1C level is not at goal, I then advance to a preprandial analog insulin or a premix,” he offered.

An elevated A1C is correlated with a dysfunction in endogenous insulin secretion, Dr. Raskin noted. Therefore, “if a patient can produce insulin, they are not going to have a hemoglobin A1C of 9.0% or 10.0%,” he reasoned. Based on his recent study comparing BIAsp 70/30 with glargine and metformin alone or with other oral agents, Dr. Raskin reported that, “if the hemoglobin A1C is $> 8.5\%$, there is less endogenous insulin secretion and prandial coverage is required.” Although glargine insulin is effective, “it is flat and unyielding with food intake.” Therefore, in his study, “the two injections of the analog mix were more effective because there was prandial breakfast and prandial supper coverage,” he claimed.³

“What are the characteristics of the different types of basal insulin, and do they affect treatment selection?” queried Dr. Salgo.

In his practice, Dr. Rosenstock stated that although he offers patients treatment options, “therapy must be driven by targets.” When employing oral therapies, he maximizes the combination oral treatment depending on tolerability and side effects. If this approach is insufficient to reach an A1C $< 7\%$ then basal insulin supplementation is needed. In selecting basal insulin, Dr. Rosenstock looks for “24-hour coverage without peaking. Glargine is an alternative.”

He continued, prandial insulin is employed when needed, “to take care of the postprandial effect if the A1C remains above 7% despite having corrected the fasting glucose to < 100 mg/dL.” Additionally, timing of insulin initiation may reduce treatment complexity. “If clinicians initialize insulin within five years of diagnosis, those patients will likely need just basal insulin without any, or at the most one, additional prandial insulin at the main meal,” he suggested. Dr. Rosenstock’s position is that he does not

see the need for complex regimens of basal/bolus in patients with type 2 diabetes, and stressed that, “type 2 diabetes is not type 1 diabetes.”

Dr. Raskin offered details of a study with an entry criteria of A1C of >7.0% that he is currently conducting in patients with newly-diagnosed type 2 diabetes. Patients in this study are initialized on two injections of analog 70/30 insulin and metformin. Alluding to preliminary study results, he revealed that, “the starting hemoglobin A1C in this group of patients was 10.4%, and at the end of three months it was 5.9%.”¹⁹

Dr. Rosenstock stated that these findings are not unexpected, given that these patients were newly-diagnosed and still likely had good beta cell reserve. He questioned whether the insulin was stopped after a time in the study Dr. Raskin described. While Dr. Raskin maintained that the insulin was not stopped, Dr. Davis interjected, “We cannot trivialize targets based on the latest scientific developments.” He elaborated that, “The latest science is showing us that individuals with an A1C <5.5% have complications of diabetes and macrovascular and microvascular disease. A1C values below 7.0% or 6.5% may be too high.”

Deciphering the Next Treatment Steps

Moving forward, Dr. Salgo asked the panel, “Where do we go from here? What’s the next step for the patient who still fails to achieve goal despite combination therapy as we’ve been discussing it?”

“I start with the agents that I think will be best for the patient. If that is ineffective, I move to more injections and terminate premixed insulin,” responded Dr. Raskin. Before each meal, he instructs patients to measure blood sugar and take a dose of insulin, similar to what a patient with type 1 diabetes requires. “Aggressive therapy, particularly with sensitizers, can achieve positive results,” he emphasized.

“We cannot trivialize targets based on the latest scientific developments.

The latest science is showing us that individuals with an A1C <5.5% have complications of diabetes and macrovascular and microvascular disease.

A1C values below 7.0% or 6.5% may be too high.”

—Dr. Davis

When combination therapies fail, “we need to control fasting glucose and postprandial glucose,” explained Dr. Davis. Newer treatment options include pramlintide and exenatide, “to smooth out postprandial levels,” and other agents such as basal insulin to control fasting glucose, he indicated.

Once the basal dose has been adjusted, “we must use fast-acting analogs to control postprandial glucose levels. We now have extra tools in our armamentarium to do this,” offered Dr. Edelman. Commenting on his experience with pramlintide, a beta cell hormone that is released along with insulin from the beta cells with meals, he claimed that, “it could help to improve postprandial glycemic control. If pramlintide is used properly, and basal insulin is appropriately adjusted, I believe patients will experience less ups and downs, including less hypoglycemia, and no weight gain,” he predicted.^{20,21}

Dr. Rosenstock cited disagreement with Dr. Edelman’s comments regarding pramlintide, and clarified, “Pramlintide is a postprandial hormone for patients who are already on insulin and taking prandial insulin three times daily.” He explained that, “these patients are well into insulin treatment.” He shifted the discussion back to the proposed treatment paradigm including oral agents and the initiation of insulin. In patients taking oral agents who are close but not yet at target, Dr. Rosenstock reinforced his “fix fasting first,” treatment regimen. Fixing the fasting glucose “is getting the fasting glucose below 100 mg/dL, and this is where the patient needs to continue pushing the dose of basal insulin as long as there are no symptoms or evidence of hypoglycemia,” he directed.

“Once the fasting glucose is decreased, wait a few weeks before judging what is happening during the rest of day,” Dr. Edelman instructed, as this is a common error on the part of clinicians and patients.

Dr. Salgo probed, “Are oral therapies discontinued before moving to the next treatment?”

“I withdraw secretagogues and alpha-glucosidase inhibitors,” said Dr. Raskin. “However, I do not discontinue metformin or thiazolidinediones because a patient is on four injections of insulin unless there is a specific contraindication or problem.”

If a basal insulin is used at night, Dr. Edelman remarked that he continues sulfonylurea, especially if the patient’s A1C is high. Even though the patient is failing sulfonylurea, “we know quite clearly that patients get worse if it is discontinued,” he advised. “If the fasting blood sugar is reduced and the patient develops hypoglycemia during the day, then I discontinue or reduce sulfonylurea.”

He added that if the regimen is changed to insulin twice daily, “there is no question—I will stop the sulfonylurea.”

Returning to the issue of staging, Dr. Rosenstock maintained that patients taking basal insulin require, “in addition to an insulin sensitizer, an insulin enhancer, such as a secretagogue to enhance endogenous insulin secretion.” He added that, “If I need to move on to the next therapeutic step, adding a prandial fast-acting insulin analogue, then I will stop the sulfonylurea.”

“What is the role of fast-acting insulin in this setting?” wondered Dr. Salgo.

The need for fast-acting insulin is contingent on home glucose monitoring results, Dr. Edelman explained. For example, “if the patient is started on a simple regimen such as basal insulin at night plus oral agents, their fasting glucose will decrease.” With this regimen, “the fastings are under excellent control, but the A1C may not be at goal yet. Therefore, the patient is possibly becoming hyperglycemic after meals. Fast-acting analogs are effective after meals, and their administration depends on home glucose monitoring results throughout the patient’s daily schedule,” he concluded.¹³

“If, in controlling diabetes, the goal is to mimic normal insulin secretion, are all patients with diabetes in need of basal bolus?” Dr. Salgo asked.

“Absolutely, as that is the normal physiology,” said Dr. Davis. “Patients with type 1 and type 2 diabetes require basal bolus insulin.”

Dr. Rosenstock is a firm believer that the basal/bolus strategy in type 2 diabetes is different than in type 1 diabetes and may only be needed when advancing to the next treatment step in patients with long-standing diabetes (i.e., 10 to 15 years) who cannot control their diabetes with one to two injections of insulin. “It is all about changing the current treatment paradigm. Research is suggesting that if you initiate within the first five years, patients are going to have enough endogenous insulin secretion to complement the basal insulin replacement.” Administering insulin “is a concept of replacing and supplementing, which does not necessarily mean increasing to four injections daily.”

Further questioning the current treatment paradigm, Dr. Rosenstock postulated, “If we are going to get 10 to 12 million people with type 2 diabetes to achieve an A1C goal as low as <6.0%, assuming that the results in the future of the ACCORD study (Action to Control Cardiovascular Risk in Diabetes) turn out to be positive, the full basal bolus strategy may prove to be too complex, and we may not have the resources to do it.”²²

Dr. Raskin remarked that more complicated regimens are needed in long-standing diabetes. In presenting basal bolus insulin as a treatment option to patients whose A1C levels are not at goal, he offered that, “up front, I ask patients if they feel that they can handle this tough regimen.” He then designates treatment based on their response.

Dr. Salgo continued, “Are such treatment regimens practical in weighing patient compliance? Does this work in the real world?”

“I think it does,” declared Dr. Rosenstock. “Although the snapshot we have of the real world derived from clinical studies is difficult

to translate, these treatment regimens do work,” he contended. Referring to the decrease of A1C to 7.1% with glargine and metformin in the LANMET study, he stressed that, “this was very close to target.” If investigators in this study had continued with a sulfonylurea or an additional prandial insulin injection to control postprandial glucose levels, he speculated, “that may have yielded an A1C of 6.9% and potentially 6.7%,” respectively.¹⁸

Dr. Salgo proposed a final question to conclude the panel’s discussion. “Is simpler indeed better when it comes to therapeutic regimen?” he asked.

“Simpler is better if it gets patients to target. However, if the target is not reached a clinician needs to move into more complex regimens,” advised Dr. Raskin.

Individualized treatment is the preferred method, Dr. Edelman contended. “The bottom line is, there are many ways a clinician can approach a patient, and there are many different types of tools. Clinicians must look at each patient individually and attempt to select a therapy that works best for that person.”

Final Thoughts

In his concluding message from this *Medical Crossfire* exchange, Dr. Rosenstock stressed that insulin is an essential component in the clinician’s armamentarium, “and should be instituted much earlier than it currently is. Insulin therapy should be considered when the A1C is above 7.0% and dietary and oral therapy have been maximized,” he advised. Dr. Rosenstock advocated basal insulin, “because the doses can be slowly pushed with continued low-dose insulin titrations, as long as there is no evidence of hypoglycemia, until the clinician fixes the fasting glucose below 100 mg/dL.” If the A1C remains >7.0%, “then tackle the postprandial levels,” he concluded.

Two basic treatment approaches Dr. Raskin encourages clinicians to adopt are

“insulin earlier than later, and simpler rather than complicated.” Giving a simple analogy for the rationale behind insulin treatment, he offered, “if your patient is willing to drive the car, you have to ensure that there is fuel in the tank.”

“We have to empower our patients so they truly understand where their glucose target should be,” proclaimed Dr. Davis. “Overall, the goal of blood glucose should be as low as possible without hypoglycemia, as this is a major barrier to achieving good glycemic control in patients.”

Providing education on the management and treatment options for type 2 diabetes is fundamental for both clinicians and patients, summarized Dr. Edelman. In his final words from this *Medical Crossfire*, he emphasized that, “a community diabetes educator can enhance the clinician’s ability to overcome difficult issues in diabetes management and treatment challenges. Armed with this knowledge, clinicians can instruct and motivate patients with individualized regimens. This process is extremely important in promoting treatment compliance.” ■

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Utilizing Novel Therapies With a Basal Insulin Plus Oral Regimen Today and Beyond

CME Test

- Weight gain with insulin treatment is a patient concern. Regarding a change in weight, the impact upon A1C levels indicates that**
 - weight gain in the presence of diabetes improvements is correlated with increased food intake.
 - weight gain is not related to diabetes improvements.
 - earlier insulin treatment may increase the likelihood of caloric weight gain associated with insulin treatment.
 - weight gain in this context is not related to nutritional intervention.
- Beyond controlling blood glucose, intensive insulin administration provides**
 - up to a 20% reduction in cardiovascular events and stroke.
 - up to a 30% reduction in cardiovascular events and stroke.
 - up to a 40% reduction in cardiovascular events and stroke.
 - up to a 50% reduction in cardiovascular events and stroke.
- An appropriate blood glucose target for a pregnant woman with type 2 diabetes is an A1C of**
 - 7.0%.
 - 6.5%.
 - 6.1%.
 - <6.0%.
- In a patient who has an A1C of 8.0% and fails to respond to two oral therapies, the panel recommended that a treatment strategy would be to**
 - initialize insulin therapy and continue oral therapies such as secretagogues and alpha-glucosidase inhibitors, and sulfonylurea at this stage.
 - initialize insulin therapy and discontinue all oral therapies.
 - add a third oral therapy.
 - design a rigorous and complex treatment regimen consisting of multiple approaches to get the patient to goal, irrespective of cost and compliance.
- Clinicians can foster patient commitment to insulin therapy early on by**
 - drafting a written contract to ensure treatment adherence.
 - prescribing an intensive and complex treatment regimen.
 - allowing the patient to communicate their concerns and treatment goals.
 - prescribing a regimen to accelerate achievement of target glucose levels.
- According to the panel, fear of hypoglycemia results in**
 - a barrier to early insulin initiation and an impediment to reaching targets in type 2 diabetes.
 - patients with type 2 diabetes being placed at even greater risk due to this condition being heavily associated with severe hypoglycemia.
 - a rise in treatment targets to avoid the risk of hypoglycemia.
 - a minimal impact on treatment choices.
- Insulin therapy begun earlier in the course of type 2 diabetes**
 - may simplify future treatment regimens.
 - does not have an impact upon the patient's ability to attain A1C target ranges.
 - may yield an A1C that falls within ADA, AACE or ACCORD target ranges and/or possibly result in an achievement of 6.5%.
 - both a and c
- If combination oral agents and basal insulin therapies do not achieve A1C target,**
 - all oral therapies should be discontinued.
 - sulfonylurea should be discontinued immediately.
 - pramlintide should be avoided.
 - sulfonylurea should be discontinued in the presence of daytime hypoglycemia.
- According to the panel, basal insulin**
 - can facilitate hepatic glucose production and a patient will awaken with a normal fasting glucose.
 - influences hepatic glucose production overnight and results in unbalanced blood sugar in the morning.
 - results in erratic glucose levels overnight.
 - is equally effective independent of whether it is instated early or very late in the course of the disease.
- Based on the _____, a target A1C of <6.0% may reduce the risk of cardiovascular (CVD) disease in patients type 2 diabetes.**
 - DIGAMI study
 - Treat-To-Target study
 - Action to Control Cardiovascular Risk in Diabetes (ACCORD) study
 - LAMNET study

1. c. Yki-Järvinen and colleagues realized in a controlled, randomized, multicenter, open-label, parallel group trial of 110 patients with type 2 diabetes (A1C >8.0%) that weight increases were greater at nine months in patients treated with NPH versus insulin glargine (3.5 + 0.7 kg versus 2.6 + 0.5 kg, respectively). With insulin therapy, “Change in weight is directly proportional to improvement in A1C unless there is extreme nutritional or exercise intervention,” Dr. Raskin explained.

Locator: Overcoming Barriers Associated With Insulin Initialization/Rationalizing Weight Gain and Insulin Therapy

2. d. Recent findings from the Diabetes Control and Complications Trial prove that with good, long-term (12 years) glycemic control, patients can reduce their risk of cardiovascular events and stroke up to 50%. Good intensive glycemic control in this study entailed patients keeping blood glucose as close to normal with at least three insulin injections daily or with an insulin pump in addition to frequent self-monitoring of blood glucose.

Locator: Overcoming Barriers Associated With Insulin Initialization /Refuting Myths and Misconceptions of Insulin Therapy

3. d. In individualized patients or during pregnancy, the American Diabetes Association indicates that more stringent blood glucose targets may be necessary, such as an A1C <6.0%. For adults with diabetes, the recommended A1C is <7.0%, however, less stringent goals may be indicated in certain populations or circumstances such as in elderly or pediatric patients, in those with a history of severe hypoglycemia, in the presence of specific comorbidities, and those with a limited life expectancy.

Locator: Stratifying Treatment Approaches in Type 2 Diabetes/Identifying Glycemic Targets

4. a. In this patient scenario, Dr. Davis offered that the “simple tactic is normalizing the fasting glucose and administering basal insulin while continuing the oral agents.” If the patient is >1% from A1C goal, Dr. Edelman disclosed that, “I would rather start insulin to decrease the fasting blood sugar.” He added that, “I am a proponent of adding nighttime insulin, insulin glargine, or NPH to daytime oral therapies as this allows me to prepare for the next treatment step.”

Locator: Stratifying Treatment Approaches in Type 2 Diabetes /Oral Therapies Versus Insulin

5. c. According to Dr. Edelman, “Complex regimens and rushing to achieve target early on is likely to turn the patient off” to insulin therapy. Allowing patients to voice their treatment desires and goals will promote their commitment to insulin therapy. Dr. Rosenstock noted that for the clinician, discussing therapeutic options with a patient is a “negotiation process.”

Locator: Stratifying Treatment Approaches in Type 2 Diabetes/Oral Therapies Versus Insulin

6. a. “Hypoglycemia is a complication of diabetes, and it is a real fear among both healthcare providers and patients,” declared Dr. Davis. Coupled with the fact that there is a 90% risk of hypoglycemia associated with insulin administration, the occurrence of hypoglycemia “can be life-altering.” Dr. Davis cautioned that, “it only takes one severe episode of hypoglycemia for patients to refrain from insulin,” despite the proven benefits. Dr. Raskin agreed that hypoglycemia is a major concern in individuals with type 1 diabetes. “In those with type 2 diabetes,” he contended, “it is relatively uncommon. This is not an impediment to treatment.”

Locator: Overcoming Barriers Associated With Insulin Initialization/Elucidating Hypoglycemia and Insulin Therapy

7. d. Timing of insulin initiation may reduce treatment complexity, according to Dr. Raskin. “If clinicians initialize insulin before five years, those patients will need just basal and one additional prandial insulin,” he claimed. As most of the clinical trials evaluating insulin involve patients with diabetes for eight to ten years, Dr. Rosenstock speculated that if patients with diabetes for two to three years were examined, “we would probably be able to get their A1C in the 6.5% range with basal insulin.”

Locator: Stratifying Treatment Approaches in Type 2 Diabetes /Positioning Basal Insulin Therapy

8. d. Offering his treatment recommendation, Dr. Edelman admitted that if nighttime insulin glargine or NPH is used, he continues sulfonylurea even if it not helping the patient. “We all know quite clearly that patients get worse if it is discontinued,” he counseled. If the patient’s fasting blood glucose is reduced, and “the patient develops hypoglycemia during the day, then I discontinue sulfonylurea,” he maintained. Additionally, if the treatment regimen is changed to twice-daily insulin, “there is no question that I stop it,” Dr. Edelman concluded.

Locator: Deciphering the Next Treatment Steps

9. a. Basal insulin involves two components, explained Dr. Davis. First, basal insulin restrains glucose production by the liver to stop the breakdown of fat and protein. Second, a normal pancreas will secrete insulin in a bolus fashion to coat for preprandial glucose. Clinicians, he advised, “should always be thinking about the basal bolus approach. Overnight, basal insulin can facilitate hepatic glucose production and a patient will awake with a normal fasting glucose.” He noted that the bolus component is available in pills or other agents. Agreeing with Dr. Edelman, Dr. Rosenstock noted that he commences basal insulin if a patient is unsuccessful with pill formulations. Early intervention, according to Dr. Rosenstock, “corrects or reduces hepatic glucose production overnight, and the patient starts the day with a normal blood sugar.”

Locator: Stratifying Treatment Approaches in Type 2 Diabetes/Positioning Basal Insulin Therapy

10. c. Currently, the National Heart, Lung, and Blood Institute is conducting the ACCORD study to evaluate the risk and benefits of three medical strategies to reduce CVD in 10,000 patients with diabetes mellitus. The ACCORD study recommends a target A1C of <6/0%.

Locator: Deciphering the Next Treatment Steps