Diabetes2017

From the 77th Annual Scientific Sessions of the American Diabetes Association ■ San Diego, CA

2014 2015 2016 **2017** 2018 2019 2020

Sponsored by **Yale School of Medicine**, Department of Internal Medicine, Section of Endocrinology

Volume **35** ■ June 10, 2017 ■ Issue **1**

Important data on diabetes presented at the 77th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2017**, a newsletter CME program that is being offered to you by Yale School of Medicine. After receiving the newsletters by e-mail, please go to www.cme.yale.edu and take the CME quiz. You will qualify for up to 5.0 *AMA PRA Category 1 Credits™* to be issued by Yale School of Medicine.

Diabetes 2017 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance, abnormal insulin secretion, and derangements in the incretin axis.
- Highlight new discoveries in the immunopathogenesis of Type 1 diabetes.
- Describe the evolving cellular mechanisms associated with the progression of diabetes and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the interrelationship between insulin resistance, hyperglycemia, inflammation, and atherosclerosis in patients with Type 2 diabetes.
- Underscore the importance of lifestyle change, exercise, and dietary interventions in the management of diabetes.
- Compare the mechanisms of actions of a growing array of oral and injectable pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper evidence-based role in the management of this disease.
- Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on healthcare systems.

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This CME program is supported in part through educational grants from Eli Lilly and Company and Merck & Co., Inc. It is understood that supporters will in no way control the content of this program.

A New Dawn for Glucose Lowering in Type 2 Diabetes: Impact of Recent CVOTs

In front of a packed audience on the first day of this year's Scientific Sessions, renowned researchers from around the world gathered to discuss an "Update on Cardiovascular Outcome Trials (CVOTs)." The landscape has certainly changed over just the past two years. Previously, there was significant concern that Type 2 diabetes therapies were not able to decrease cardiovascular (CV) events—the major morbidity and cause of mortality in this disease. From the UKPDS to ADVANCE to ACCORD and the VADT, no matter what strategy investigators tried, the effect of diabetes medications appeared to be minimal, with a small benefit on, perhaps, non-fatal myocardial infarction (MI) but with certainly no reduction in CV mortality. Then in 2015, with the EMPA-REG OUTCOME trial, there was new recognition that the *manner* in which glucose is lowered might be more important than the degree of glucose lowering. In that trial, the SGLT-2 inhibitor empagliflozin reduced CV mortality and heart failure hospitalization to a sizable degree. This was quickly followed by LEADER (liraglutide) and SUSTAIN-6 (semaglutide), both showing CV benefits from the GLP-1 receptor agonist (RA) class. So, we now have 3 drugs with strong evidence from clinical trials that refute the traditional notion that diabetes therapy is important solely for reducing microvascular complications but not macrovascular complications.

Professor Tina Vilsboll from the Steno Diabetes Clinic in Copenhagen, Denmark began the symposium by describing the results of SUSTAIN-6. This trial randomized 3297 Type 2 diabetes patients at high CV risk (mean age 64.6 years, weight 92.1 kg, diabetes duration 13.9 years, and HbA1c 8.7%) to semaglutide vs. placebo. Over 2 years, treatment with the weekly injectable GLP-1 RA resulted in a 26% reduction in major adverse CV events (MACE) (HR 0.74 [95% CI: 0.58-0.95; $p<0.001$ for non-inferiority and 0.02 for superiority). This composite was driven by a significant 39% reduction in non-fatal stroke and a non-significant 26% reduction in non-fatal MI. In contrast to liraglutide in LEADER, there was no effect on CV or all-cause mortality, however. A secondary outcome (as in LEADER), the progression of nephropathy was also benefited, with a 36% reduction, driven mainly by a reduction in macroalbuminuria. There was no change, however, in the doubling of serum creatinine or with the development of end-stage renal disease (ESRD). Semaglutide was also associated with larger reductions in HbA1c, body weight, and blood pressure vs. placebo.

Professor Vilsboll next spent a good deal of time reviewing the retinopathy data from this trial. As an adverse event, and in spite of the renal benefit, retinal complications occurred in 3.0% of patients assigned to semaglutide and 1.8% of patients assigned to placebo (HR 1.76 [1.11-2.78]). In SUSTAIN-6, these by definition included vitreous hemorrhage, diabetes-related blindness, or the need for retinal photocoagulation or intravitreal injections—a total of 50 vs. 29 events, all independently adjudicated. Risk factors for these retinal events included longer diabetes duration, higher HbA1c at baseline, insulin therapy, and prior history of retinopathy. Given this surprise finding, which appeared to have no biological basis as regards to the class of drug, further inquiry into the reason(s) for this association were undertaken by the SUSTAIN-6 study group. It was determined that the patients at risk for retinopathy events tended to be those who experienced the most prominent reductions in HbA1c from the baseline value. This occurred more commonly in the semaglutide group because it is a highly efficacious GLP-1 RA, the mean end-of-treatment difference from placebo in HbA1c with the higher dose group being a full 1.0%. Our readers may recall that older trials using insulin appeared to suggest a

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A New Dawn...

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similar phenomenon—that rapid and significant glycemic reductions could predispose patients to worsening retinopathy.

Dr. Lawrence Leiter from the University of Toronto next addressed, "Rethinking CVOTs in Diabetes—What Should the Future Hold?" Dr. Leiter reviewed the history of diabetes randomized clinical trials (RCTs) over the past two decades, with a focus on those designed to assess CV outcomes. He concluded that the recent positive trials are noteworthy and apt to change practice. He looked forward to the results of CANVAS, the canagliflozin CVOT, and DEVOTE, the insulin degludec CVOT, both to be presented later this week. He then briefly described the ongoing trials in this space: DECLARE (dapagliflozin), VERTIS (ertugliflozin), CREDENCE (canagliflozin/renal), EXSCEL (exenatide QW), REWIND (dulaglutide), and HARMONY (albiglutide), remarking on how much more information we will have to make treatment decisions over the next 2-3 years. Dr. Leiter spent most of his remaining time describing the conclusions of an ADA-sponsored expert panel that is in the process of making recommendations about the direction for future CVOTs. The tentative proposals from this group are seen in Table 1.

Next was Professor Amanda Adler, consultant physician at Addenbrooke's Hospital in Cambridge, UK, former UKPDS epidemiologist, who has been involved in health policy for the National Health Service (NHS) in England for many years, specifically with her work in NICE (National Institute for Care Excellence). The title of her talk was "Translating CVOT Data into Clinical Practice—Cost Effectiveness of Newer Therapies." Dr. Adler proceeded to describe the complex analytics used by health systems to gauge cost-effectiveness of medications in general and diabetes therapies in particular. She emphasized that most health budgets are fixed and that new pharmaceutical entries into the market must be met with the cost-neutral disposal of less effective interventions. Unfortunately, these may at times cross therapeutic areas and even disease categories. Therefore, the actual value of new therapies to current clinical practice must unequivocally be demonstrated across a population. This must also include an assessment of the costs of side effects of any medications or procedures.

The final speaker of the symposium was Dr. Anne Peters of the USC Keck School of Medicine, her topic being "Translating CVOT Data into Clinical Practice—Should the Guidelines Change?" With the perspective of being a writing group member for the 2012 and 2015 *ADA-EASD Position Statements for the Management of Hyperglycemia in Type 2 Diabetes*, Dr. Peters underscored the importance of using the most up-to-date RCT data to adjust clinical guidelines as frequently as necessary. She herself proposed that the next iteration of the ADA-EASD guidelines must incorporate the new and emerging data from CVOTs. For example, she proposed a modified strategy for patients with Type 2 diabetes and established CVD, based on degree of renal impairment (Figure 1). Patients with reasonably intact renal function should be placed on empagliflozin (or other SGLT-2 inhibitor proven to reduce MACE), since these agents are not indicated in those with GFR <45 ml/min. In contrast, patients with substantially reduced renal function should be channeled towards a GLP-1 RA, such as liraglutide or other formulation shown to reduce MACE.

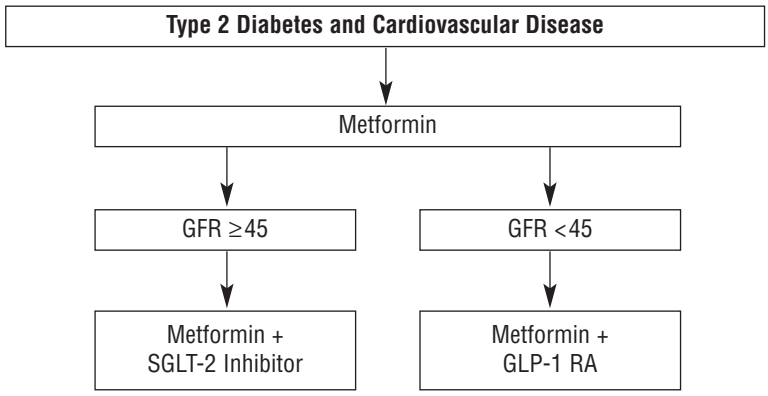
We think this approach makes sense—actually to develop two algorithms, one for patients with and one for those without CVD. In the latter, we might favor a DPP-4 inhibitor if there was no evidence of CVD and if the hyperglycemia is relatively mild, given this classes' relative paucity of side effects. Selected use of pioglitazone makes sense in the most insulin-resistant patient who has normal left ventricular function and no major risk factors for bone fracture. This drug might be particularly favored if the patient had suffered a stroke in the past, based on the IRIS data (Kernan *et al., NEJM* 2016) (see tomorrow's edition). We might also tend to favor an SGLT-2 inhibitor in the patient with prevalent heart failure. Sulfonylureas (see next article) could be used selectively in those with intact renal function, perhaps as third-line therapy in those patients not able to use other agents. They should be avoided in the elderly. If the HbA1c is very high, insulin therapy remains the most efficacious therapy so long as the dose is appropriately titrated. Of course, cost is a major issue with branded diabetes medications, and this important aspect of prescribing must be taken into account.

In all, the speakers and chair agreed that the symposium successfully highlighted emerging concepts in the management of patients with Type 2 diabetes—that is to utilize therapies proven to reduce CV events in those with pre-existing CVD.

Table1. Proposals for Future Clinical CV Trials In Diabetes

- Focus on lower risk/more diverse patient populations
- Use of active comparators instead of placebo
- Longer duration of follow-up than the traditional 2-4 years
- Modification of endpoints and analytical methods (heart failure, recurrent events)
- Standardization of all endpoint definitions,not just those pertaining to CV disease (CVD) (e.g. chronic kidney disease events)
- Inclusion of patient-reported outcomes and patient advisory groups
- Establishment of bio-repositories for clinical tissues or DNA samples
- Consideration of lower-cost alternatives to traditional RCTs ('real-world' observational studies, 'pragmatic' RCTs)

Figure 1. Proposed Strategy for Reducing Hyperglycemia in Patients with Both Type 2 Diabetes and CVD



STAY

Sulfonylureas: Stay or Go?

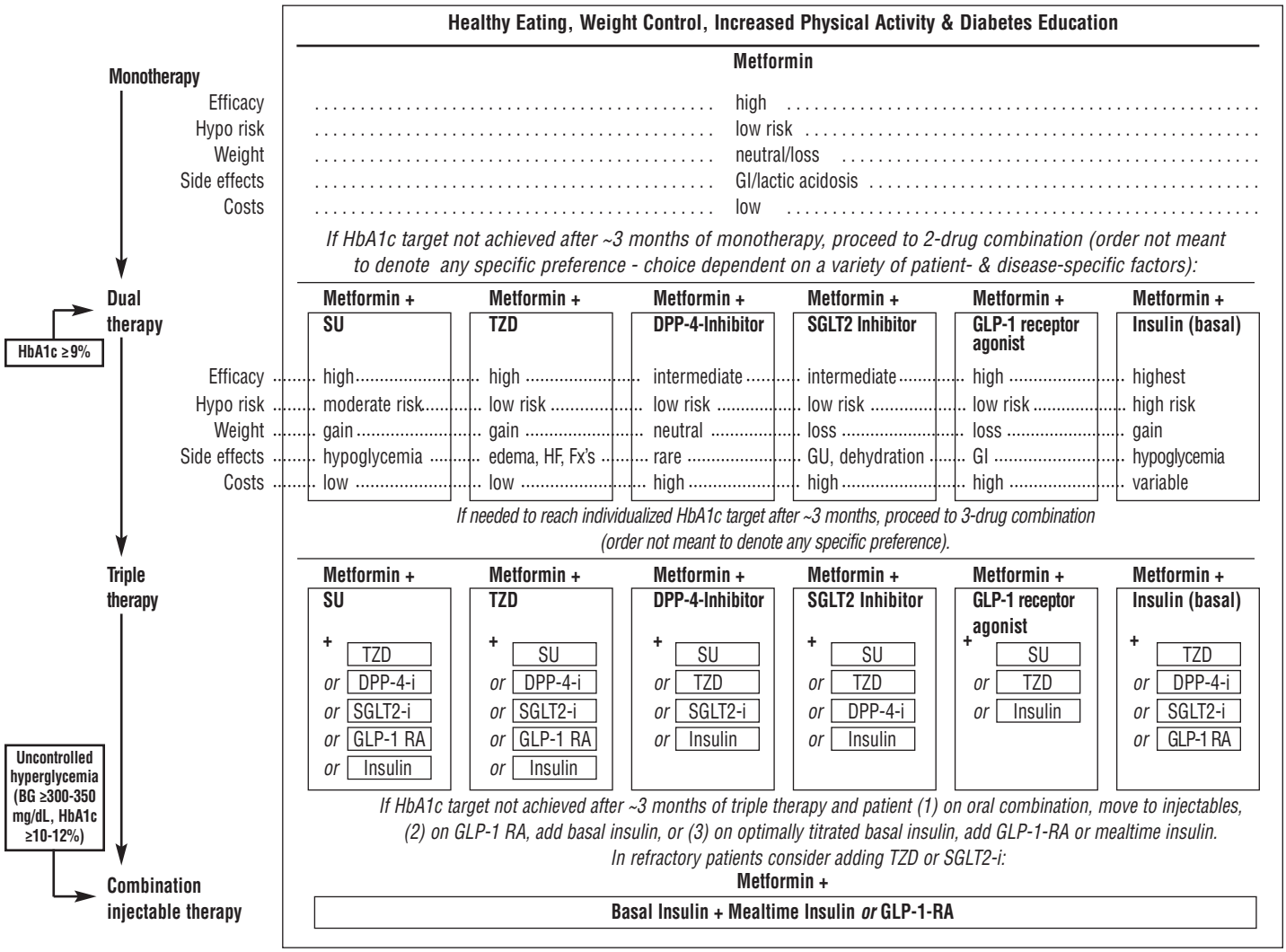
GO

A crowded lecture hall on the opening day of the ADA 2017 Scientific Sessions reflected the current interest among researchers and clinicians in an important topic discussed by Professor Kamlesh Khunti, University of Leicester, UK, "Sulfonylureas—Do They Have a Role in Contemporary Treatment of Type 2 Diabetes?"

Professor Khunti began his lecture by reminding attendees that sulfonylureas are frequently used in the treatment of patients with Type 2 diabetes because they remain effective in improving glycemic control. In a meta-analysis of 31 trials with a median duration of 16 weeks, sulfonylurea monotherapy lowered HbA1c by 1.5% more than placebo, by 1.6% more when added to oral diabetes treatment vs. other treatment, and by 0.5% when added to insulin (along with a lowered insulin dose) (Hirst *et al., Diabetologia* 2013;56:973-84). Sulfonylureas have also been shown to reduce microvascular complications in Type 2 diabetes (UKPDS 33; *Lancet* 1998;352: 837-53). Plus, they have the advantage of being relatively inexpensive. There are differences among the agents in risk of hypoglycemia, and specifically severe hypoglycemia, with advanced generations (e.g., gliclazide, glipizide, glimepiride) having the lowest risk.

Concerns regarding CV safety began early in the 1970s with results of the University Group Diabetes Program (UGDP), the first RCT that evaluated sulfonylureas for diabetes treatment (Meinert *et al. Diabetes* 1970; 19(Suppl):789-830). Meta-analyses of studies conducted since then evaluating the safety of sulfonylureas as a group (Gangji *et al., Diabetes Care* 2007;30:389-94; Monami *et al., Diabetes Obes Metab* 2013;15:938-53; Phung *et al., Diabet Med* 2013;30:1160-71) or in association with metformin (Rao *et al; Diabetes Care* 2008;31:1672-78) have reported contradictory results.

Figure 2. Antihyperglycemic Therapy in Type 2 Diabetes



Fx=fracture, HF=heart failure, i=inhibitor, RA=receptor agonist, SGLT=sodium-dependent glucose-linked transporter, SU=sulfonylurea, TZD=thiazolidinedione. *Diabetes Care* 2015;38:140-9; *Diabetologia* 2015;58:429-42.

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Sulfonylureas: Stay or Go?

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This is likely due to inclusion of observational studies, inclusion of first-generation sulfonylureas, and lack of consideration for type 2 error. Observational studies are limited by selection and attrition bias, and one can infer only association, not causation, from the results.

A recently published meta-analysis including only RCTs of second-and third-generation agents showed that sulfonylureas are actually not associated with increased risk of all-cause mortality, CV mortality, MI, or stroke (Rados *et al., PLoS Med.* 2016; 13(4):e1001992).

Khunti then discussed practical considerations for treating Type 2 diabetes patients. Worldwide, approximately 415 million persons are affected, 80% in low- or middle-income countries. The financial burden of diabetes treatment is substantial, collectively including agents needed to reduce glucose, as well as treat common comorbidities. In this regard, the relatively low cost of sulfonylureas distinguish them from other second-line antihyperglycemic choices after metformin, as recommended by the ADA (Figure 2) and IDF.

He cited a recently published study in which the use of glucose-lowering drugs was reported to have changed dramatically over a recent 8-year period (2006-2013) among Type 2 diabetes patients in the US, notably with sulfonylureas decreasing (38.8 to 30.8% of patients). Yet overall glycemic control did not improve and the overall rate of severe hypoglycemia remained largely unchanged (Lipska *et al., Diabetes Care* 2017;40:468-75).

Among the summary messages, the speaker suggested the use of the lowest dose of sulfonylurea to achieve target HbA1c and minimize hypoglycemia, use of early combination therapy, and the avoidance of tight control in the elderly. He noted than the risk and benefits of sulfonylureas have been established over more than six decades of experience. Risk of hypoglycemia is substantially reduced with second- and third-generation agents. And, RCTs show benefit on microvascular endpoints. Taken together, the speaker considers sulfonylureas, when selected and dosed appropriately, to be an affordable choice with favorable efficacy and safety profile for treatment of patients with Type 2 diabetes.

We might add that the CAROLINA study is likely to inform this discussion. This is an ongoing RCT directly comparing CV events in patients with Type 2 diabetes randomized to the DPP-4 inhibitor linagliptin or the sulfonylurea glimepiride. Since it is now clear that DPP-4 inhibitors are neutral for CV events, if the number of events with linagliptin vs. glimepiride in CAROLINA are similar, this will imply that sulfonylureas have similarly neutral CV effects. These data will not be available, however, for another 2 to 3 years.

The Sky-Rocketing Costs of Insulins

In a thought-provoking symposium chaired by Irl Hirsch, MD, Seattle, WA, the rising cost of insulins was discussed from several perspectives. Kasia Lipska, MD, New Haven, CT led the discussion providing an introduction and historical background. She shared a patient case that is representative of many patients seen by practitioners today. An elderly man presenting with an HbA1c of 16%, primarily due to the fact he can no longer afford what has now become almost an $800 out-of-pocket expense for his monthly insulin. Dr. Lipska stated that the rise in retail costs for commonly used insulins has been dramatic. In the time period of 2004-2017, the out-of-pocket costs for 10 mL vials of lispro, aspart and glargine have increased from $59 to $320, from $68 to $324, and from $58 to $280, respectively. She proceeded to provide the history of insulin discovery at the University of Toronto in 1921, revealing the irony that the first insulin patent was sold by its discoverers, Frederick Banting, Charles Best, and James Collip, in 1923 for $1 each with the goal of making it available to all patients in need!

Despite the lifesaving advance, shortcomings of 1920s insulin, specifically short duration of action and impurities leading to immunologic reactions, led to subsequent improvements and evolution of insulin products. Duration of action was improved with the addition of protamine and zinc in the 1940's and 1950's and recombinant DNA technology allowed for the introduction of human insulin in the 1980s, ultimately replacing animal products. With each improvement, patents extended well into the 21st century. This enabled, as Dr. Lipska described, "The Paradox of Incremental Innovation." Patent protections limited generic ("biosimilar") competition and subsequently contributed to the rising costs. Three insulin manufacturers dominate. Novo Nordisk, Eli Lilly, and Sanofi control 52%, 23% and 17% of the global market, respectively.

Other issues unique to the US also play a role. For example, with respect to insulin glargine (Lantus®), the European Medicines Agency (EMA) considers its direct competitor, Abasaglar®, a biosimilar. Whereas in the US, the FDA approved the like-kind product Basaglar® as a "follow-on" product through the 505(b)(2) pathway, which allows for 5 years of market exclusivity. Despite creating competition for the brand Lantus®, data demonstrate that cost does not significantly decrease with the first generic/biosimilar competitor. Rather it takes several (up to 8 or 9 generics) to truly see a meaningful improvement in cost.

The final component is the medication supply chain that begins with the pharmaceutical manufacturer selling product to wholesalers, then the variety of "middle men" such as pharmacy benefits managers (PBMs) that impact cost of medications dispensed by pharmacies to patients. PBMs are third-party administrators of prescription drug programs for both commercial and governmental health plans. (e.g., Medicare Part D). They significantly impact formulary status, contracts with pharmaceutical companies, and receipt of rebates that are not required by law to be shared with consumers or payers. Dr. Lipska closed with the recognition that insulins, despite being safer and more convenient for patients since their discovery in the 1920s, have become extremely expensive and generally "out of reach" for a significant portion of the patient population with diabetes.

Alan Carter, Pharm.D., Kansas City, MO, followed with the presentation "Understanding the Players in the Rising Costs of Insulin." He detailed multiple steps in the production and distribution of insulin, beginning with suppliers of raw materials to the pharmaceutical manufacturers, wholesalers, pharmacies, to the prescribers and, finally, patients with diabetes. He emphasized the complexity of manufacturing insulins given their heterogeneity due to post-translocational modifications. Minor changes in the production process can lead to major changes in the final product. Dr. Carter reported considerable variability in quality standards between the various manufacturers. Insulin quality control after FDA approval is based

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The Sky-Rocketing Costs of Insulins

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on the "honor system" with internal quality monitoring and periodic FDA inspection. He shared concerns that the primary mode of quality monitoring is via post-marketing surveillance documenting adverse drug events.

From Dr. Carter's perspective, the biggest area of concern relative to cost relates to regulatory and legislative issues. The biosimilar processes within the US are state-regulated—meaning there are potentially 50 states with differing substitution guidelines. Also, although the Affordable Care Act and Medicare Part D enhance patient access to care and medications, the US government is not permitted to negotiate drug prices on behalf of Medicare. Alternatively, PBMs establish formularies for various health care plans. Details of price negotiation, rebates, and net prices are considered proprietary and not publicly shared; specific details are between the PBM and manufacturer. Overall, Dr. Carter expressed his concern that both quality and cost are "hiding behind the curtain", which hinders the availability of affordable insulins for glycemic control.

The third presenter, David Robbins, MD, Kansas City, KS, challenged the audience with several controversial queries related to accepted standards of care in his presentation, "Clinical Decision-Making in a Cost-Containment Era." He began with a common agreement that the goals of diabetes care include optimal glycemic control, quality of life, freedom from complications, longevity, convenience, and affordability. However, how one might achieve these goals must be examined. He stated that data to guide using older medications are limited and distorted by market forces. Practitioners are human and subject to these forces and innate motivations that are not necessarily based on fact. For example, do we really know that use of urine glucose testing is inferior to the more costly self-monitored blood glucose in Type 2 diabetes? Similarly, what are the data that might justify use of a low cost alternative such as NPH insulin versus glargine? For example, in a recent Cochrane meta-analysis, the use of branded basal insulins was deemed to have only modest benefits compared with NPH in Type 1 diabetes, primarily decreased nocturnal hypoglycemia.

Another provocative question dealt with the role of bariatric surgery. Should we be introducing this option much sooner? Based on one analysis (*J Med Econ* 2010;13:339-360), the return on investment is approximately 2 years. Dr. Robbins asked if this might be another option for patients to avoid the expense associated with diabetes medications over a lifetime.

Another concern is that new drug studies are often designed to favor branded medications. In one analysis, published studies were 4 times more likely to favor the newer medication instead of the older comparator. A variety of conflicts of interest also prevail. When physicians are queried regarding potential bias, 80% deny any. However, when asked if their colleagues may be biased in favor of a given drug, 80% report this to be true.

He challenged health care providers to be tough, but fair critics and to demand better guidelines with evidence comparing newer versus older therapies. Patients should also be well-informed consumers and should question payer decisions, if necessary. He even challenged the ADA to recognize its potential financial conflicts when publishing national consensus guidelines. The government/FDA should have a much higher bar than the traditional placebo-controlled trials for new drug approvals to better protect and guide the consumer. Lastly, he remarked that the pharmaceutical industry should demonstrate cost effectiveness data, stop blocking the ability of Medicare to employ competitive bidding for drug prices, and support profit margins that are reasonable.

The closing speaker of the symposium, Robert Ratner, MD, Washington, DC, former Chief Science Officer of the ADA, addressed "What's the Solution to High Insulin Prices?" He began by sharing recent actions by the ADA working toward making insulin more affordable including: (1) symposia at the last three Scientific Sessions dedicated to addressing high insulin costs; (2) position statement in October 2015 proposing transparency in pricing; promoting across the board Tier 1 pricing for off-patent medications; supporting price negotiation by Medicare; and value-based reimbursement; (3) a March 2016 publication in *Diabetes Forecast*, "The Insulin Boom. Why the Cost of this Lifesaving Drug is Reaching New Heights"; and, (4) The Board of Directors approval of a public petition to reduce insulin costs calling for congressional hearings which has already acquired 250,000+ signatures.

Dr. Ratner next identified three categories of solutions to the insulin cost problem.

(1) *Free Market Competition*, which should include biosimilar production, potential return to direct-to-consumer sales of insulin (human insulins do not require a prescription, where analogs do), and legal challenges to the contractual arrangements.
(2) *Regulatory Controls*, including simplification of the biosimilar pathway, potential importation of insulin, and anti-trust action from the Federal Trade Commission.
(3) *Legislative Controls*, such as Medicare negotiation on drug pricing and price controls.

He ultimately closed his presentation with a simple answer to the question: What is the solution to high insulin costs? Someone has to make less money!

Glucose Monitoring: How, Which, and In Whom?

Glucose self-monitoring is an essential part of management to provide real time feedback to patients and trend spotting for providers. However, using this data effectively toward HbA1c improvements can be challenging. Owens from Wales, UK presented a meticulously designed RCT of glucose self-monitoring in non-insulin-treated Type 2 diabetes with poor control (mean HbA1c 8.6%) (abstract 61-OR). The study compared a proactive, structured monitoring program with standard monitoring in 447 patients over 12 months, within both primary care and referral centers in the UK. Group 1 received standard of care self-monitoring, while traditional fingerstick glucose data were downloaded and analyzed every 3 months for Group 2, with additional monthly teleconferences in Group 3. Nurses were trained to provide patient education, interpret glucose patterns, and manage glycemic treatment using algorithms (Parsons *et al., BMC Endocrine Disorders* 2017; 17:4). The primary endpoint of HbA1c at 12 months for the 323 participants who completed the study was 8.3±1.3% (Group 1,

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Glucose Monitoring...

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p<0.01), 7.4±1.2% (Group 2, p<0.001), and 7.3±0.9% (Group 3, p<0.001). The percent of participants reaching target HbA1c of <7.0% was 17%, 47%, and 44% for Groups 1, 2, and 3, respectively (p<0.0001). This study demonstrated that a structured self-monitoring of blood glucose delivered by trained nurses to willing, informed patients results in early and successful glycemic control.

An opposing argument was posed by Young *et al.* in this week's *JAMA Internal Medicine* (published online: June 10, 2017. doi:10.1001/jamainternmed.2017.1233) who found no benefit of glucose self-monitoring on glycemic control or health-related quality of life in an open-label, randomized trial of patients with Type 2 non-insulin-treated diabetes. However, they did not employ the same support system implemented by Owens. Clearly, self-monitoring of blood glucose is most helpful when the data and their trends are regularly assessed and interpreted with patient feedback.

Innovations in technology are pushing the boundaries well beyond fingersticks, however, toward continuous glucose monitoring (CGM), providing data more automatically. Price of Dexcom presented data from the DiaMonD study examining the effect of CGM on glycemic control in adults with both Type 1 and Type 2 diabetes, using multiple daily insulin injections (abstract 65-OR). Participants with a mean HbA1c of 8.6% were randomized to either CGM (n=184, 52±14 years old) obtaining glucose determinations every 5 minutes from subcutaneous interstitial fluid or traditional finger stick blood glucose (n=132, 57±11years old), and provided with an insulin self-titration schedule as per their physician. After 24 weeks, mean change in HbA1c from baseline was modestly better at -0.9±0.7% in CGM users versus -0.5±0.8% in participants using finger-stick monitoring (p<0.001).

Devries *et al.* of the Netherlands presented data from two efficacy and safety trials of a new implantable glucose sensor (abstract 67-OR). The Eversense® CGM System (Senseonics Inc., MD) is an implantable long-term (90 day) fluorescence-based sensor. It has a removable transmitter that wirelessly communicates with a smartphone-based medical app to display glucose results, provide alerts, and trend data. The implantable sensor, the size of a US 5¢ coin, is inserted into the upper arm using a trocar in the office, and the transmitter is worn using adhesive directly over the sensor site. The trials enrolled 161 adults, predominantly with Type 1 diabetes, who wore the sensor for 90 days. During in-center visits of 8 to 24 hours, venous reference glucose measurements were taken to compare with CGM data. Both trials demonstrated sustained accuracy throughout the trial period. With changes to the glucose calculation algorithm, the accuracy measure of mean absolute relative difference (MARD) improved from 11.6% in the first trial to 8.8% in the second trial. Adverse events included 3 people with skin reactions, including 2 infections requiring antibiotics.

The available options for daily glucose monitoring are increasing, and we look forward to new developments in this field to enhance the capability of our patients to track their glycemic trends with more meaningful information and less effort than is now required. Due to a significantly higher cost in using this newer technology, there needs to be continuous assessments of efficacy (and safety), particularly in the population with Type 2 diabetes.

So Many Posters, So Little Time....

Mitochondrial Effects of Exercise

Mitochondrial fragmentation, resulting in a loss of membrane potential, has been implicated in a number of metabolic diseases, including Type 2 diabetes and obesity. Axelrod and associates from Cleveland conducted a study of 12 sedentary, older (65.8±4.6 years) obese (34.3±2.4 kg/m^2) adults who underwent 12 weeks of supervised aerobic exercise training (achieving 85% of maximal heart rate for 1 hour daily, 5 times per week) to determine the effect of chronic exercise training on muscle mitochondrial dynamics (abstract 59-OR). After the 12-week intervention, insulin sensitivity (assessed by hyperinsulinemic-euglycemic clamp) improved, as did aerobic capacity and fat oxidation (all p<0.01) and body weight, BMI, fat mass, and fasting plasma glucose decreased (all p<0.001). Exercise training also increased skeletal muscle MFN2, OPA1, and OMA1 (p<0.05), while decreasing FIS1 and Parkin (p<0.05) protein expression, assessed via Western blot. These changes reflect a beneficial remodeling of mitochondrial architecture towards a more fused, tubular network. These changes may contribute to the increase in insulin sensitivity and improvement in substrate utilization following exercise training.

Case Report of Omental Scaffold Islet Transplantation

While, to date, the liver is the preferred site for clinical islet transplantation, several factors limit successful engraftment. Baidal *et al.* from Miami reported safety and efficacy of islet transplantation in the omentum within a resorbable biologic scaffold in a 43 year-old woman with 25-year history of Type 1 diabetes complicated by severe hypoglycemia/hypoglycemia unawareness. Pre-transplant insulin requirements were 31 units/day, HbA1c 6.8%, and BMI 21.5 kg/m^2 (abstract 86-OR)

In brief, 602,395 islet equivalents from a single donor were combined with autologous plasma and layered laparoscopically on the omentum. Recombinant thrombin was added followed by an additional autologous plasma layer to generate a 'scaffold' of sorts, adherent to the omental surface. The omentum was folded over the scaffold and additional thrombin used to seal the edges. Induction immunosuppression consisted of anti-thymocyte globulin and etanercept; tacrolimus and mycophenolate sodium were used for maintenance. There were no surgical complications.

Insulin independence was attained on post-transplant day 17. Fasting C-peptide and glucose were, respectively, 0.80 ng/mL and 107 mg/dL at day 75 and 0.43 ng/mL and 120 mg/dL at 1 year (with HbA1c 6.0%). At 15 months, insulin degludec (4 units daily) was introduced, resulting in stabilization of glucose control. The patient maintained excellent glycemic control at 16 months with 7-day mean capillary blood glucose of 100±14 mg/dL (n=28) on 4 units of basal insulin and without hypoglycemia.

Long-term follow-up and additional patients will obviously be required to determine the effectiveness and the sustainability of graft function with this novel strategy and implantation site.

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