Cancer and Diabetes Medications: Is There a Link?

The association between diabetes and insulin is complex. Patients with diabetes are at increased risk for several malignancies, including cancers of the uterus, breast, pancreas, bladder, and colon. There are several biologically plausible mechanisms that link these conditions, including shared risk factors (e.g., obesity), hyperglycemia, the insulin/IGF-axis, and chronic inflammation. More recently, several anti-hyperglycemic medications have been linked to cancer risk as well. The growing use of pharmacoepidemiology plays a role in drug regulation policy, and it is critical for physicians to understand some nuances in interpreting these studies.

In September 2009, a collection of observational studies published in Diabetologia raised the concern that insulin glargine may contribute to the incidence of cancer in people with diabetes. One of these studies also indicated that metformin may be associated with a decrease in cancer rates. While these studies have been critiqued for the inherent weaknesses of retrospective analysis and mining large databases for findings, they did initiate a flurry of inquiry into the potential link between diabetes, its therapies, and cancer.

Over the last three years, investigators have examined large clinical databases, such as national healthcare registries, or existing data from prior clinical studies involving diabetes medications. This task is challenging because the clinical studies were not designed to examine cancer outcomes and have a relatively short duration of follow up. The healthcare registries contain information marred by the complexities of daily clinical care, in the absence of a controlled setting. However, the utility of observational studies is immediate hypothesis generation. Until more definitive studies such as randomized control trials (RCT) are complete, we are reliant on such data and meta-analyses to serve as an initial screen for associations between medical therapies and cancer outcomes.

In a Symposium entitled “The Pharmacoepidemiology of Diabetes—Defining Unexpected Risks and Benefits,” Samy Suissa, PhD an epidemiologist from McGill University, critiqued many of the recent studies. The majority of observational studies actually have significant methodological concerns. One problem is “immortal time bias” when, for instance, “ever users” of metformin are statistically ranked equal to long-term users of metformin. In this way, metformin is given an advantage in demonstrating a protective effect from cancer incidence. Since the outcome conclusions are dependent on the way data are analyzed, he asserts that “immortal time bias” likely accounts for much of the positive effect seen in the observational analyses involving metformin. When time-dependent bias is corrected for, metformin no longer demonstrates any protective effect.

In a related poster presentation, the Metformin Trials’ Collaboration (abstract 950-P) assessed 2,140 studies to identify 12 RCT’s of metformin versus active glucose-lowering therapy or placebo/usual care that contained data on cancer incidence. Each study was also required to have ≥500 patients and a follow-up period of at least one year. Nine RCT’s had relative risk (RR) data for a total of 407 cancers diagnosed during 50,055 person-years of follow-up. The summary RR for incident cancer in patients randomized to metformin versus any comparator was 1.07 (95% CI 0.86-1.32; I²=29%). There was no statistical difference (p=0.21) between RR’s in a subgroup analysis of metformin versus either placebo-controlled or active comparator trials. The investigators concluded that their data do not support the hypothesis that metformin lowers cancer risk.

With regard to insulin glargine, Dr. Suissa conducted a study of the United Kingdom General Practice Research Database (GPRD) involving 15,227 women over 40 years old with Type 2 diabetes on insulin therapy. 4,579 women received glargine, while 10,648 were on other insulins. 246 cancers of the breast were diagnosed during the 8 years of follow-up. The investigators differentiated between ever users versus prevalent users of glargine, and also adjusted for duration of insulin use and duration of diabetes. For breast cancer risk, he found that all users of glargine had a RR...
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of 1.0 (95% CI 0.7-1.4) versus other insulins, indicating no difference. However, in women using glargine for more than 5 years, the breast cancer RR was more concerning at 1.8 (95% CI 0.8-4.0), although still not statistically significant. In prevalent users of glargine for more than 5 years, the RR increased to 2.7 (95% 1.1-6.5), which was significant and sufficiently powerful to require further study.

Just last week, another headline made its way to this discussion. It was reported by Lewis and colleagues in Diabetes Care (2011; 34: 916-22) that the incidence of bladder cancer may be higher in users of pioglitazone for more than 2 years. The investigators employed a database from Kaiser Permanente. Overall, there appeared to be no significant relationship, with the hazard ratio (HR) for bladder cancer in pioglitazone users at 1.2 (95% CI 0.9-1.5). However, in those having had >24 months of therapy, there was an increased risk (1.4 [1.03-2.0]).

Similarly, a recent epidemiological study by France’s health insurance agency reported 2 weeks ago concerned 1.3 million patients taking antidiabetic medications between 2006 and 2009. Of these, 155,000 persons took pioglitazone. The study found an adjusted HR of 1.22 (95% CI 1.05-1.43) for bladder cancer among those on the TZD. This report actually led to a suspension of pioglitazone sales in France, and the Germans quickly followed suit. The issue is currently under review by the European Medicines Agency (EMA), which serves as a sort of FDA in the EU.

We would point out, however, that while further study is certainly needed, the ability for any drug to cause cancer within a time frame of 2 years would be unusual. Indeed, most true carcinogens exert their effects over a period of 15-20+ years. The drug that is known to be most carcinogenic in bladder, namely cyclophosphamide, has a latency period of at least 8 years. So, the findings of Lewis and the French group may reflect unmeasured confounders. For example, since diabetes itself is associated with bladder cancer, and since pioglitazone tends to be used later on in the disease course than other medications, the investigators could be uncovering a selection bias.

Pharmacoepidemiology has an important role in initiating investigation of links between diabetes, its therapies, and cancer. However, results from observational studies must be interpreted with caution due to the inherent weaknesses of the data sources and the potential biases of the methods used to analyze them. More research with higher levels of evidence remains to be done to dissect out the complexities of the relationship between diabetes and cancer.

Glucagon-like peptide-1 (GLP-1) is a neuroendocrine hormone produced by the gut which increases glucose-dependent insulin secretion, attenuates postprandial glucagon secretion, slows gastric emptying, and increases satiety. GLP-1 receptor agonists are now well entrenched in the Type 2 diabetes pharmacopeia, as are the dipeptidyl peptidase 4 (DPP-4) inhibitors, which restrain activity of the enzyme that rapidly metabolizes endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Dozens of abstracts and presentations in San Diego this week were devoted to these so-called incretin-based therapies.

Results of an open-label extension to the DURATION-3 trial were presented. Improved and sustained glycemic control and weight loss from baseline to 84 weeks, and reduced hypoglycemia risk were demonstrated with once-weekly exenatide, as compared to insulin glargine. The two strategies were added to oral anti-hyperglycemic agent(s) in Type 2 diabetes patients (abstract 277-OR). These results confirm and extend the published findings from the first 26 weeks of DURATION-3 (Diamant et al., Lancet 2010), which demonstrated greater HbA1c reductions with exenatide (n=228; -1.5%) than with glargine (n=220; -1.3%; treatment difference -0.16%, 95% CI -0.29 to -0.03). Mean (SE) change in body weight at week 26 compared with baseline was -2.6 kg (0.2) for exenatide-treated patients and +1.4 kg (0.2) for those using glargine (treatment difference -4.0 kg, 95% CI -4.6 to -3.5).

Of the 456 patients initially enrolled and randomized in DURATION-3, 388 (196 exenatide, 192 glargine) entered the extension study and 346 (173 in each group) completed 84 weeks. The mean (SE) daily insulin glargine dose was titrated from 31±1 units at 26 weeks to 35±2 units at 84 weeks. Glycemic control continued to be significantly better with exenatide, with a higher proportion of patients achieving an HbA1c target of ≤6.5% (Table 1). At endpoint, patients on exenatide lost weight, while those on glargine gained weight, as expected.

The overall incidence of mild-moderate hypoglycemia (blood glucose [BG] ≤54 mg/dl) was 24% and 54% (p<0.001) for exenatide and glargine, respectively, within the subgroup taking metformin and sulfonylurea, and 8% vs. 32% (p<0.001), respectively within the subgroup taking only metformin. Exenatide patients reported significantly higher rates of GI side effects (diarrhea, nausea, vomiting) and injection site reactions.

Additional long-term data with once-weekly exenatide were revealed by Macconnell et al. from California, who presented results of an open-ended, open-label extension of the DURATION-1 trial (abstract 969-P). In the first 30 weeks of DURATION-1, once-weekly exenatide 2 mg elicited a greater glucose-lowering effect than did the twice daily formulation of exenatide (5 mcg BID) for the first 28 days then 10 mcg BID) (HbA1c change from baseline: -1.9% vs. -1.5%, respectively) in patients with Type 2 diabetes on various background therapies. Similar improvements in body weight, blood pressure, and fasting lipids were demonstrated with both forms of the drug (Drucker et al. Lancet 2008).

At the conclusion of the 30-week controlled period of the trial, all patients were continued or transferred to the once weekly formulation. Approximately two-thirds of patients completed 3 years of treatment (baseline HbA1c 8.2±1.0%, fasting plasma glucose [FGP] 167±44 mg/dl, weight 101±18 kg, therapy at screening: diet/exercise [15%], metformin [33%], metformin + sulfonylurea...
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Sustained improvements from baseline were observed in glycemia and body weight (Figure 1), accompanied by favorable changes in cardiovascular risk markers: systolic blood pressure (-2.1 mmHg [-4.5, 0.2]), LDL cholesterol (-7.0 mg/dl [-11.8, -2.1]), and triglycerides (-12% [-18, -6]). Nausea decreased over time (16% from week 30-156 vs. 27% during the initial controlled period).

Varanasi et al, from Buffalo, NY conducted a study of patients with well controlled Type 1 diabetes (mean HbA1c 6.5%) on continuous glucose monitoring (CGM) and intensive insulin therapy on CSII, with the aim of determining if the addition of liraglutide, another GLP-1 agonist, to insulin treatment would improve glycemic control (abstract 411-PP). The basis for their work is the known suppressive effect of GLP-1 on glucagon secretion. Glycemic control was optimized through careful regulation of patients’ carbohydrate intake and insulin regimens for at least 2 weeks, over which time no significant change in glycemic control or insulin dose was observed. Treatment with liraglutide was then initiated for either one week (n=14) or 24 weeks (n=14). Mean fasting glucose (130±10 to 110±8 mg/dl) and mean weekly glucose concentrations (138±20 to 115±12 mg/dl) decreased significantly, as did the basal (25±6 to 17±6 U/day) and bolus insulin doses (23±4 to 16±4 U/day) within 1 week. Oscillations in blood glucose concentrations were significantly reduced; the weekly coefficient of variation for glucose concentrations decreased from 39.6±10% to 22.6±7% (p<0.05). Patients who continued on liraglutide for 24 weeks maintained similar glycemic control mean (mean HbA1c increased from 6.5±0.5% to 6.1±0.4%, p<0.05) to those treated for 1 week, but had further reductions in insulin doses and significant weight loss (68.0±5 to 63.5±4 kg). The withdrawal of liraglutide resulted in rapid reversal of these effects and greater glycemic oscillations.

Figure 1. Once Weekly SC Exenatide Added to Oral Anti-hyperglycemic Agent(s) for 3 Years in Type 2 Diabetes Patients

Figure 2. Adjusted HbA1c Changes After 12 Weeks (Full Analysis Set*)

<table>
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<tr>
<th></th>
<th>All Patients</th>
<th>Patients with Baseline HbA1c ≥9.0%</th>
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<tr>
<td>Baseline HbA1c (%)</td>
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<td>Patients, n</td>
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<tr>
<td>Linagliptin 5 mg qd</td>
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<td>11</td>
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<tr>
<td>Placebo</td>
<td>62</td>
<td>13</td>
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<tr>
<td>Change from Baseline (%)</td>
<td>-0.8†</td>
<td>-1.5‡</td>
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<tr>
<td>Change from Baseline (mg/dl)</td>
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<td>Analysis of covariance (last observation carried forward), adjusted for continuous HbA1c, creatinine clearance, and background antidiabetic agents at baseline.</td>
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*Patients with at least one baseline and one on treatment HbA1c value.
†p=0.0071 vs. placebo; ‡p=0.0121 vs. placebo.

Continuous glucose monitoring (CGM) technology continues to improve and now plays an important role in the management of diabetic patients on intensive insulin regimens, particularly those using insulin pumps. CGM measures interstitial fluid glucose through a subcutaneously inserted sensor that reads glucose every 5 minutes or less. Results are reported to a pocket-sized display device or may instead be directly communicated to a pump—the latter has opened the door to a fully-automated ‘artificial pancreas’ glucose control system.

Dr. Roman Hovorka, Cambridge, UK led a session entitled When Will We Close the Loop? A Progress Update. He began by describing the

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artificial pancreas as one that includes: (1) a glucose sensor; (2) a control algorithm; and (3) an insulin pump. A fully ‘closed loop’ system is one where the glucose concentration triggers insulin release and no additional insulin is administered by the patient. A ‘semi-closed loop’ system allows for the patient to administer a standard bolus which is shared with the control algorithm. Semi-closed systems often provide better postprandial glucose control. Dr. Hovorka shared that overall, these systems decrease glucose variability, increase time in target range (70-145 mg/dl), decrease risk of hypoglycemia, and generally have similar insulin requirements as continuous subcutaneous insulin infusions (CSI).

Zisser, et al. (California) presented an initial evaluation of a fully automated artificial pancreas (or closed loop system) (abstract 152-OR). The investigators developed the Artificial Pancreas System (APS)® using it to evaluate a control strategy to manage glucose, including unannounced meals. APS® uses multi-parametric model predictive control (mpMPC) and an “insulin-on-board” (IOB) safety constraint. The initial step is to use 3 days of ambulatory data from CGM, CSII, and meal information to develop a personalized model and control algorithm. This is followed by an APS® evaluation during a clinical day that includes an unannounced meal. Five such sessions have been completed to date. Post-meal challenge, all subjects returned to euglycemic range with the average time spent there being 77%. There was one episode of mild hypoglycemia that was traced to an elevated sensor signal due to sensor drift. All results were in the favorable A+B zones of the Clarke Error Grid, which quantifies the accuracy of values obtained via CGM versus blood (refer to Issue No. 3 for description of Clarke Error Grid).

Also presenting at the symposium was Edward Damiano, PhD, from Boston University, who shared experience from 1-day and 2-day inpatient feasibility studies using a ‘bi-hormonal’ closed loop artificial pancreas. This system delivers insulin and glucagon to more finely regulate glycemia. A laptop computer served as the controller algorithm. The mean blood glucose after 51 hours in test subjects (n=6) who each returned and repeated two experiments was 141 mg/dl. The controller algorithm appears to respond well to events that cause a precipitous fall in blood glucose (i.e., exercise) with appropriate doses of glucagon. This study also permits head-to-head comparison of the various glucose sensors. Damiano’s group is now preparing for a 5-day inpatient feasibility study that will run a portable mobile device (i.e., IPOD Touch). This study is anticipated to begin in late 2011/early 2012.

The final presentation was delivered by Boris Kovatchev, PhD who shared that several new glucose sensors are in development, utilizing varying technologies to improve overall accuracy and as well as the ability to detect hypoglycemia. Additionally, controller algorithms are getting “smarter.” The immediate future is likely to include dual sensors to be used for real-time detection of glucose levels should one sensor fail. Also, the portability controller algorithms will be drastically improved (i.e., portability, size).

Although much of this symposium might appear futuristic, several abstracts evaluated the here and now. Bergenstal and North American co-investigators presented data from the 6-month continuation phase of the STAR-3 Study (abstract 407-P). The initial trial randomized patients with Type 1 diabetes to receive insulin via a sensor-augmented pump (SAP) or by multiple daily injection (MDI) therapy for 12 months. The continuation phase crossed over the MDI group to SAP. The original SAP group demonstrated a sustained HbA1c response and the crossover patients demonstrated a relatively rapid and safe (hypoglycemia, 2.0 events per 100 patient-years) transition, achieving a significant decrease in HbA1c (Figure 2).

At this year’s meeting, we heard major progress in the development of functional closed-loop systems by several other groups, including Youssef from Oregon (abstract 149-OR), Danne from Germany (abstract 150-OR), Elleri from the UK (abstract 153-OR), Sherr from Connecticut (abstract 154-OR), and Renard and collaborators from France, Italy and the US (abstracts 151-OR & 155-OR). Each of these groups reported impressive improvements in maintaining targeted glucose control with sensor-augmented insulin pumps, as compared to traditional ‘open-loop’ systems. Most of the studies reported were in the controlled environment of clinical research centers, however. We look forward to ongoing improvements and the creation of a fully functional and reliable artificial pancreas for our patients with Type 1 diabetes.

Novel Therapies

There are over 100 new targets or mechanisms of action for potential drugs to manage diabetes and seemingly a nearly equal number of pharmaceutical companies in pursuit of exploring such compounds. A symposium, “Novel Therapies for Type 2 Diabetes—Today and Tomorrow,” explored agents that are in clinical trials and/or are considered to be the most promising for future clinical investigation.

Ernest Wright, PhD, UCLA began with a discussion of inhibitors of sodium glucose co-transporters 1 (SGLT1) and 2 (SGLT2). SGLT1 is expressed predominantly in the intestine and inhibits glucose transport in the gut. SGLT2, expressed in the kidney, is responsible for glucose reabsorption in the proximal tubule. Compounds that inhibit SGLT2 promote urinary glucose excretion, ultimately lowering plasma glucose. Although there is a SGLT1 inhibitor in Phase 1 trials (DSP-32325), the majority of drug investigation has focused on selective SGLT2 inhibition. There are currently 3 agents in Phase 3 clinical trials: canagliflozin, dapagliflozin, and BI-10773. To date, these products appear to produce favorable effects on glycemic control, as assessed by HbA1c. Also, due to their mechanism of action, which involves daily excretion of approximately 50-70 g of glucose (and therefore some 200-280 kcal), they lead to modest weight loss.

Dapagliflozin was compared to metformin (titrated to 2000 mg), each as monotherapy and in combination, in 2 randomized controlled trials in treatment-naïve patients with Type 2 diabetes.

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Henry and international colleagues studied 5 mg dapagliflozin in one study and 10 mg doses in the second (abstract 307-OR). Change in HbA1c from baseline to 24 weeks was the primary endpoint for the combined analysis and secondary measures included FPG and body weight. The combination of the two modalities was more effective than monotherapy with either agent with respect to HbA1c and FPG (Table 2). However, the higher dose (10 mg) of dapagliflozin produced a significant decrease in weight when compared to metformin. Patients in the dapagliflozin arms had a higher numerical incidence of events suggestive of genital and urinary tract infections. However, statistical significance was not reported.

One concern with these products is the long-term effects of blocking this naturally occurring cotransporter in humans. That is, is a normally functioning SGLT2 needed for health? Dr. Wright opined that this fear has been tempered based on the experiences from a rare autosomal recessive disorder, Familial Renal Glucosuria. Patients with this disorder have a mutation in SGLT2, rendering it dysfunctional. Other than glucosuria, this patient population has no evidence of other renal function abnormalities and the condition is considered benign. Indeed, affected patients appear to be resistant to developing diabetes. Accordingly, other than the issue of urinary and genital infections directly related to glucosuria, this class of drugs is not expected to have additional side effects. Of course, long-term trials will be needed to confirm this.

Bile acid sequestrants (BAS) were the subject of the next presentation delivered by David Mangelsdorf, PhD, University of Texas Southwestern Medical Center, Dallas. These agents (e.g., cholestyramine and colesuvelam) are well known for their impact on cholesterol synthesis. A serendipitous finding over a decade ago was that in addition to lowering cholesterol, patients with Type 2 diabetes receiving these agents had improved glucose homeostasis (Garg A, et al. Ann Int Med. 1994). Subsequent studies confirmed this unexpected finding. Dr. Mangelsdorf proceeded to describe the multiple animal studies that ensued to identify the specific mechanism of action responsible for glycemic control with BAS. The likely mechanism is one that is independent of lipid-lowering effects. BAS activate a protein receptor, TGR5, in the colon. This activation signals the release of intestinal glucagon-like peptide 1 (GLP-1). Elucidation of this pathway has opened the door for even further research relative to molecules that impact TGR5.

Jorge Plutzy, MD, from Harvard, was the next presenter who discussed selective peroxisome proliferator-activated receptor (PPAR) agonists. The current PPAR-γ agonists, the TZDs, have an adverse event profile that is less than desirable (e.g., cardiovascular risk with rosiglitazone; increase in body weight, fluid retention, and bone fractures with rosiglitazone and pioglitazone). Plutzy introduced the concept of PPAR “modulation” versus absolute agonist activity. Modulators have partial or selective agonist activity at various PPAR receptors (alpha, delta, and gamma) and are not linked to a specific dose-response. The goal is to develop the ideal balance of selective or partial activity at various receptors to retain the desirable effects on glycemic control, but eliminate toxicities. This class of PPARs is termed SPPARMs for “Selective PPAR Modulators.” SPPARMs would each have a distinctive transcriptional response, different clinical effects, and unique side effect profiles. Even the well known PPAR agonists, pioglitazone, rosiglitazone, and troglitazone, have transcriptional profiles that are not identical (but do overlap)—which would explain their distinct effects.

Finally, Dr. Charles Burant, University of Michigan provided an overview of what he described as next-generation compounds. One group is the fatty acid elongases. These are enzymes present in liver microsomes that carry out progressive elongation of saturated and monounsaturated fatty acids. Elongase-6 inhibitors alter fatty acid composition, resulting in an increase in insulin sensitivity. Data are limited to animal models at this point, but have been promising. The second target is the enzyme 11 beta hydroxysteroid dehydrogenase (HSD)-1. This is an NADPH-dependent enzyme highly expressed in liver, fat, and the central nervous system. It is responsible for the conversion of inactive cortisol to active cortisol in adipocytes and liver, producing metabolic changes consistent with metabolic syndrome. Inhibition of this enzyme has been demonstrated to improve insulin sensitivity and is particularly efficacious in patients with increased BMI and visceral fat. Potential side effects include increased ACTH secretion with downstream hyperandrogenism.

Another new drug class is the G-protein coupled receptors (GPRs). There are approximately 850 such proteins with a wide variety of ligands and diverse effects. GPR40 is highly expressed in 8 cells and enteroendocrine cells and mediates free fatty acid-induced insulin secretion. TAK-875 is a GPR40 agonist evaluated in a Phase 1, double-blind, placebo-controlled trial by Leifke et al. of the US (abstract 414-P). In this dose-ranging study, 59 patients with Type 2 diabetes received TAK-875 or placebo for 2 weeks while pharmacokinetic and pharmacodynamic responses were tracked. TAK-875 resulted in reduced FPG and postprandial glucose versus baseline following an OGTT. There was no change in fasting insulin or C-peptide levels. It was well tolerated, with no dose-related adverse effects, including symptomatic hypoglycemia. From this preliminary investigation, the researchers suggest that TAK-875 acts as a glucose-dependent insulinotropic agent.

GPR119 is also highly expressed in the pancreatic β cells and enteroendocrine cells. Preliminary studies have suggested an effect on both insulin as well as GLP-1 secretion. The GPR119 agonist, PSN821, was evaluated in Type 2 diabetes patients by Goodman and colleagues from the UK and the Netherlands (abstract 306-OR). Varying doses were administered, either as monotherapy or added to metformin and compared to placebo for 14 days. FPG was decreased in all treatment groups. There was also a reduction in glucose exposure following meal challenge. Active treatment groups experienced weight loss. PSN821 was well tolerated with no discontinuations.
to proliferate. The question at this point might be, “Do we have enough already?” This was the topic of a debate on the penultimate day of the Scientific Sessions, with Dr. David Nathan from Harvard and Dr. Richard Bergenstal from the International Diabetes Center in Minnesota tackling this important question. Only 15 years ago, the diabetes armamentarium included solely sulfonylureas and insulin. Now, physicians and patients have access to 11 different classes of agents with varied mechanisms of action. Do we really need any more?

Dr. Nathan began by addressing this question in the context of diabetes prevention. He reviewed data from the Diabetes Prevention Program and its Outcomes Study and argued that we have both an effective lifestyle intervention strategy and a safe medication (metformin) for diabetes prevention. Implementation of these effective measures could substantially reduce the incidence of diabetes, particularly if applied to those individuals at highest risk. Yet, funding for implementation and delivery of these programs has been modest, while new classes of drugs flood the market.

In terms of management of patients who do go on to develop diabetes, Dr. Nathan reviewed data from the classic trials that show reduction in microvascular complications with control of glycaemia and argued that a goal of HbA1c <7% is justifiable for most individuals in order to reduce these microvascular events. How do we achieve this goal? The ADA/EASD antihyperglycemic therapy consensus document was next reviewed, which provides recommendations with respect to choice of therapy. For most patients, the recommended backbone of diabetes therapy is metformin. Addition of a second agent is primarily guided by considerations of safety, tolerability, side effect profile, effectiveness on glucose lowering, and cost. Recommended “first tier” therapies include sulfonylureas and insulin, while less evidence-based regimes (“second tier”) include addition of pioglitazone or a GLP-1 agonist. In terms of the newer agents on the market, Dr. Nathan argued that they are not as potent in achieving HbA1c reduction and considerably more expensive. We might add that long-term safety data, which is not available for newer agents, is also an important issue to consider.

The ADA/EASD consensus algorithm has never been directly tested, and Dr. Nathan argued for more comparative effectiveness research on glucose-lowering agents that are already available. Such research will eventually provide guidance to physicians and patients in making decisions about how best to individualize therapy.

Dr. Bergenstal took the opposite view on the issue of new drug development in diabetes. He argued that novel drugs can help fill the quality gap, i.e. improve glycemic control in the ~50% of patients in the US who are currently not meeting the established goal of HbA1c <7%. He provocatively asked, “Where is the patient in these diabetes performance measures?” He argued that diabetic patients care about the effectiveness of therapy but are also concerned about tolerability, hypoglycemia risk, and quality of life. And in this respect, he argued, we need more drugs—those that are well-tolerated and to which patients are most apt to adhere.

Bergenstal argued that there has been substantial progress in drug development for diabetes, with agents that reduce HbA1c (albeit modestly), do not cause hypoglycemia or weight gain, and have minimal side effects (such as DPP-4 inhibitors). There are also other agents (such as GLP-1 receptor agonists) that result in HbA1c lowering and substantial and sustainable weight loss. Most of all, he supported an individualized approach to diabetes therapy—choosing from all the available therapeutic options—to improve glycemic control and, at the same time, address specific concerns of individual patients.

The two speakers agreed on the need to individualize therapy. But questions from the audience arose on how this individualization should be achieved. Moreover, current performance measures in diabetes care are based upon strict glycemic, blood pressure, and lipid targets. Individualization of therapy will require a decisive shift in how diabetes care is delivered and, in turn, evaluated.