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ROLE OF GLP-1 RECEPTOR AGONISTS IN THE TREATMENT CONTINUUM OF TYPE 2 DIABETES

In this Issue...

Most patients with type 2 diabetes mellitus (T2DM) currently receive metformin as their first line anti-diabetic drug, with a sulfonylurea agent often added when metformin alone becomes inadequate. Because 80% patients with T2DM are overweight or obese, GLP-1 agonists may be a better choice for the majority of patients after metformin failure—these agents have been shown to control diabetes over sustained periods of time, are consistently associated with weight loss, and have lower risk of hypoglycemia. Further, many studies have shown that GLP-1 agonists are as effective as basal insulin to maintain HbA1c levels, and in combination with basal insulin may be as effective as nutritional insulin to maintain glycemic control.

In this issue, we review the recent evidence describing how GLP-1 agonists may be appropriate at many different stages of T2DM.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe appropriate patients for GLP-1 agonist therapy.
- Explain how GLP-1 agonists can be used effectively in place of or along with basal insulin.
- Discuss how current data do not support concerns about the pancreatic safety of GLP-1 agonists.

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1.0 hour Physicians
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GUEST AUTHOR OF THE MONTH

Commentary:

Rajesh Garg, MD
Assistant Professor of Medicine
Harvard Medical School
Associate Physician, Division of Endocrinology, Diabetes and Hypertension
Brigham and Women's Hospital
Boston, Massachusetts

Guest Faculty Disclosure

Rajesh Garg, MD has indicated that he has received research funding from AstraZeneca.

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Rajesh Garg, MD has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

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COMMENTARY

The pathophysiology of type 2 diabetes mellitus (T2DM) involves insulin resistance, beta cell failure and incretin defect and is known to be a progressive disease caused by progressive beta cell failure.[1] While ideal therapy would stop beta cell failure or regenerate new beta cells, we currently do not have clinically proven effective therapies for this purpose. Therefore, in a particular patient, more and more drugs are often required over time to maintain glycemic control.

In previous years, algorithms had been developed to intensify drug treatment in a step-wise manner. However, over the last two to three years, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have

moved away from a standardized approach to drug treatment for T2DM. In the position statement, issued jointly by the ADA and EASD in 2012 and reviewed in this issue, a patient-centered approach was advocated. The current guidelines recommend that when selecting drug therapy, individual patient characteristics like age, body weight, comorbidities, and patient preferences should be taken into account.

Because most patients with T2DM are obese, weight loss is one of the goals when making a drug choice for treatment of T2DM. Weight loss helps control diabetes with fewer drugs and improves the cardiovascular metabolic profile. Common drugs used to treat T2DM, for example sulfonylureas and insulin, cause weight gain. Among the newer therapies, most agents are weight-neutral or cause only a small amount of weight loss. GLP-1 agonists are associated with the most weight reduction among antihyperglycemic agents currently available for T2DM. In a meta-analysis by Vilsbøll et al (reviewed in this issue), patients receiving GLP-1 agonists achieved a greater weight loss (about 3 kg) than those in the control groups. This meta-analysis provides evidence that treatment with GLP-1 agonists is consistently associated with weight loss. Therefore, GLP-1 agonists are an attractive choice for most of the obese T2DM patients. Moreover, these agents do not cause hypoglycemia, which may be an additional advantage in some patients with comorbidities.

In addition to their weight loss effect, some evidence suggests that GLP-1 agonists may have a more positive effect on beta cell function as compared to other drugs.[2] In a large, randomized, controlled trial reviewed in this issue, Gallwitz et al showed that exenatide was not only more effective in lowering HbA1c levels, but the effect was more sustained than with glimepiride. Although this study does not prove the beta cell protective effect of GLP-1 agonists, because early sulfonylurea failure is known from other studies,[3] it does suggest a role of for GLP-1 agonists early in the course of T2DM. Although sulfonylureas like glyburide, glipizide and glimepiride are still the most commonly used second-line drugs after metformin failure, the results of this study suggest that in patients inadequately controlled by metformin alone, using GLP-1 agonists as the second-line agents may be better than using a sulfonylurea drug. However, because they are injected, GLP-1 agonists may not be easily acceptable to patients, as many are unwilling to try injection therapy until they have run out of oral agent choices. Therefore, while there may be advantages to early initiation, GLP-1 agonists may be more appropriately recommended when insulin therapy is being considered.

Because of progressive beta cell failure, oral agents become ineffective over time, and most patients with T2DM eventually require injection therapy. The choice of drug at that point is a GLP-1 agonist or basal insulin. Numerous studies have compared GLP-1 agonists with basal insulin and found equal HbA1c reduction with both agents; however, GLP-1 agonists provide the additional advantages of weight loss and lower risk of hypoglycemia.[4] The 2014 clinical trial by Diamant et al, reviewed in this issue, investigated the durability of the effect of GLP-1 agonists versus basal insulin. In this trial, exenatide once weekly was compared with insulin glargine as the first injectable therapy for patients who were on maximum doses of metformin with or without a sulfonylurea drug. The study showed that exenatide was at least as effective as basal insulin, and the effect was sustained over three years. Thus, GLP-1 agonists could be a viable long-term, injectable treatment option in patients with T2DM who have not yet started taking insulin.

Another important milestone in the natural history of T2DM is the requirement for multiple insulin injections daily. When basal insulin alone becomes inadequate, the addition of nutritional insulin becomes necessary to control blood glucose levels. Many diabetes experts over the years have been using GLP-1 agonists along with basal insulin to delay starting nutritional insulin.[5] Use of nutritional insulin is not only unpleasant because of the need for multiple daily injections but is also associated with additional weight gain and a higher risk of hypoglycemia. In the clinical trial by Rosenstock et al, albiglutide once weekly was compared with three-times-daily insulin lispro as an add-on to once-daily insulin glargine. At week 26, the decrease in HbA1c was greater with albiglutide than with insulin lispro, showing that weekly albiglutide was at least as effective as nutritional insulin in improving glycemic control. Thus, GLP-1 agonists may offer a simpler therapeutic option than thrice-daily nutritional insulin when multiple daily insulin injections become necessary. In this context, a GLP-1 agonist may be added to a treatment regimen that already includes basal insulin, or basal insulin may be added to a regimen that already includes a GLP-1 agonist.

In spite of their distinct advantages described above, GLP-1 agonists have received adverse publicity in recent times because of concerns about an association between GLP-1 agonists and pancreatitis and pancreatic cancer. This concern was raised by basic research studies and supported by case reports and observational data.[6] In view of the anxiety among providers and patients, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) both conducted comprehensive evaluations of the safety of GLP-1 agonist agents. Both agencies looked extensively at the basic and clinical research data, and FDA conducted its own toxicology studies. They found no evidence of a causal relationship between incretin-based drugs and pancreatitis or pancreatic cancer. Though the FDA and the EMA have not reached a final conclusion and are continuing their surveillance, their extensive review provides reassurance about the safety of these drugs. The vigilance and strict scrutiny received by these drugs should provide confidence that any adverse effects, however minor, will be detected early and made public.

Overall, the evidence at the current time favors more frequent and early use of GLP-1 agonists, particularly in obese patients with T2DM.

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INDIVIDUALIZATION OF TREATMENT IN THE MANAGEMENT OF TYPE 2 DIABETES

Inzucchi SE, Bergenstal RM, Buse JB, et al; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012 Jun;35(6):1364-1379.

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This joint position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) is a consensus on the drug treatment of T2DM. It has now been incorporated into the ADA's clinical practice recommendations. Individualization of treatment is considered the key to success in the management of T2DM. Therefore, a patient-centered approach that takes in to account individual patient needs and preferences and involves the patient in the decision- making process is recommended.

Antihyperglycemic agents should ideally be directed at one or more of the pathophysiological defects in T2DM. Pathophysiology of T2DM involves insulin resistance, beta cell secretory defects, and abnormalities in the incretin system. However, the

contribution of individual defects in the pathogenesis of T2DM may vary among individuals. Therefore, the same treatment may not be appropriate for all.

The authors recommend healthy lifestyle as the foundation of treatment and metformin as the first line agent of treatment for T2DM. Because of the progressive nature of this disease, most patients with T2DM will require more and more medications over time and will eventually require insulin. However, about 80% of patients with T2DM are already overweight or obese, and many drugs used to treat T2DM cause weight gain. In obese T2DM patients, relatively small weight loss can remarkably improve glycemic control and cardiovascular risk factors. Therefore, a major consideration in the treatment of T2DM is preventing treatment-related weight gain and selecting therapies to help weight loss.

The authors acknowledge that among the available therapies, GLP-1 receptor agonists are associated with the most weight reduction, which in some patients may be substantial. Therefore, in obese T2DM patients, GLP-1 agonists may be preferred over the drugs that are weight neutral or associated with weight gain. However, because they are available only in injectable form, patients' preferences should be considered. Many patients may not be willing to accept injectable therapy until they have tried (and failed) all other oral agents. However, GLP-1 agonists should be considered after metformin failure in obese T2DM patients because these agents may be most appropriate for them. This may be especially true when insulin therapy is being considered that will necessitate injections anyway.

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GLP-1 AGONIST USE IS ASSOCIATED WITH WEIGHT LOSS

Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2012 Jan 10;344:d7771.

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This report is a meta-analysis of 25 randomized controlled trials that enrolled adults with a body mass index of 25 or higher, with or without type 2 diabetes mellitus, who received exenatide twice daily, exenatide once weekly, or liraglutide once daily at clinically relevant doses for at least 20 weeks. The analysis was conducted to determine whether treatment with GLP-1 agonists results in weight loss in overweight or obese patients with or without T2DM. Control interventions included placebo, oral antidiabetic drugs, or insulin.

The results show that GLP-1 agonists achieved a greater weight loss (about 3 kg) than control groups. Weight loss was observed in the GLP-1 agonist groups for patients without diabetes as well as patients with diabetes. In addition, GLP-1 agonists had beneficial effects on systolic and diastolic blood pressure, plasma cholesterol, and better glycemic control in patients with diabetes. However, GLP-1 agonists were associated with nausea, diarrhea, and vomiting but did not cause hypoglycemia.

This meta-analysis provides evidence that treatment with GLP-1 agonists consistently leads to weight loss in overweight or obese patients with T2DM. Weight loss is one of the major goals of treatment in obese patients. Most other drugs approved for T2DM are associated with weight gain or are weight-neutral or cause relatively smaller weight loss. Therefore, GLP-1 agonist may be most appropriate in these patients.

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GLP-1 AGONISTS HAVE A MORE DURABLE EFFECT THAN SULFONYLUREAS AFTER METFORMIN FAILURE

Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. *Lancet*. 2012 Jun 16;379(9833):2270-2278.

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Glycemic control deteriorates progressively over time in patients with type 2 diabetes. In the "A Diabetes Outcome Progression Trial" (ADOPT) trial that compared glyburide, rosiglitazone and metformin as first-line therapies, glyburide failed to maintain glycemic control earlier than the other drugs.[1] Similar observations have been made in other studies showing that effects of sulfonylurea are of short duration. Therefore, the best options for treatment escalation after failure of first-line treatment with metformin remain controversial.

In this 2012 large, multicenter, randomized, controlled trial, exenatide was compared with glimepiride for glycemic control in patients with T2DM inadequately controlled by metformin alone. Exenatide twice daily or glimepiride once daily was added to metformin. The primary outcome was time to inadequate glycemic control and need for alternative treatment, defined as an HbA1c concentration of more than 9% after the first three months of treatment, or more than 7% at two consecutive visits after the first six months. The study included 515 patients in the exenatide group and 514 in the glimepiride group, of whom 490 versus 487 were included in the intention-to-treat population. The patients were followed for an average of two years. Two hundred eighteen (44%) of 490 patients in the exenatide group and 150 (31%) of 487 in the glimepiride group achieved an HbA1c concentration of less than 7% ($P < 0.0001$), and 140 (29%) vs 87 (18%) achieved concentrations of 6·5% and less ($P = 0.0001$). Two hundred three (41%) patients had treatment failure in the exenatide group, compared with 262 (54%) in the glimepiride group (risk difference 12·4, hazard ratio 0·748; $P = 0.002$). Median time to inadequate HbA1c control was 180 weeks with exenatide versus 142.1 weeks with glimepiride ($P = 0.032$). In addition, there was a significantly greater decrease in body weight in patients given exenatide than in those given glimepiride ($P < 0.0001$). Significantly fewer patients in the exenatide group than in the glimepiride group reported documented symptomatic ($P < 0.0001$), nocturnal ($P = 0.007$), and nonnocturnal ($P < 0.0001$) hypoglycemia. Discontinuation because of adverse events (mainly gastrointestinal) was significantly higher ($P = 0.0005$) in the exenatide group than in the glimepiride group in the first six months of treatment, but not thereafter.

These findings provide evidence for the benefits of exenatide versus glimepiride for control of glycemic deterioration in patients with T2DM inadequately controlled by metformin alone. These findings suggest that exenatide can achieve the HbA1c goal in more patients and it remains effective for a longer duration than the glimepiride. This effect of exenatide may be related to the beta cell protective effect of GLP-1 agonists, or it may due to the well-known early failure of sulfonylurea drugs.

Reference

1. Kahn SE et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006 Dec 7;355(23):2427-2343.

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GLP-1 AGONISTS ARE AS EFFECTIVE AS BASAL INSULIN

Diamant M, Van Gaal L, Guerci B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. *Lancet Diabetes Endocrinol*. 2014 Jun;2(6):464-73.

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Because of progressive beta cell failure, most patients with T2DM require more and more antidiabetic agents over time. When patients with T2DM require their first injectable therapy, clinicians can choose between GLP-1 agonists or basal insulin.

In this 2014 trial, exenatide once weekly was compared with insulin glargine as the first injectable therapy in an open-label randomized trial. Patients were eligible when they had suboptimal glycemic control (HbA1c 7.1-11.0%) despite maximum tolerated doses of metformin alone or with a sulfonylurea for at least three months, a stable body weight for at least three months, and a BMI of 25-45 kg/m2. Patients were randomly assigned to once-weekly exenatide (2 mg subcutaneous injection) or once-daily glargine (titrated to target) to be given in addition to their existing oral glucose-lowering regimens. The primary efficacy measure was change in HbA1c from baseline at three years. Patients given at least one dose of the assigned drug were included in analyses (modified intention-to-treat analysis).

Four hundred fifty-six patients underwent randomization and received at least one dose of the assigned drug (233 given exenatide, 223 glargine). At three years, least-squares mean HbA1c change was -1.01% (SE 0.07) in the exenatide group versus -0.81% (0.07) in the glargine group (least-squares mean difference -0.20%; P = 0.03). Transient gastrointestinal adverse events characteristic of GLP-1 agonists were more frequent with exenatide than with insulin glargine, although the frequency of these events decreased after 26 weeks in the exenatide group. The proportion of patients who reported serious adverse events in the exenatide group (36 patients [15%]) was the same as that in the glargine group (33 [15%]). The exposure-adjusted rate of overall hypoglycemia was three times higher in patients given glargine (0.9 events per patient per year) than in those given exenatide (0.3 events per patient per year).

This study shows that exenatide was at least as effective as basal insulin and that the effect was sustained for three years. Other studies have also demonstrated the efficacy of GLP-1 agonists similar to basal insulin when oral agents alone are insufficient to control diabetes. Thus GLP-1 agonists could be a viable long-term injectable treatment option in patients with T2DM who have not yet started taking insulin.

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GLP1 AGONISTS WITH BASAL INSULIN TO AVOID NUTRITIONAL INSULIN

Rosenstock J, Fonseca VA, Gross JL, et al; for the Harmony-6 Study Group. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care*. 2014 Jun 4.

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For a large number of patients with T2DM, nutritional insulin becomes essential at some stage of their diabetes because basal insulin alone is no longer adequate to control their blood glucose levels. Many diabetes experts over the years have advocated using GLP-1 agonists along with basal insulin when nutritional insulin is necessary. This 2014 randomized, open-label, clinical trial compared GLP-1 agonists with prandial insulin for advancing insulin therapy in patients with T2DM.

This trial tested albiglutide once-weekly versus thrice-daily prandial insulin lispro as an add-on to titrated once-daily insulin glargine. Patients taking basal insulin (with or without oral agents) with HbA1c 7–10.5% entered a glargine standardization period, followed by randomization to albiglutide, 30 mg weekly (n = 282), subsequently up-titrated to 50 mg, if necessary, or thrice-daily prandial lispro (n = 281) while continuing metformin and/or pioglitazone. Glargine was titrated to fasting plasma glucose of < 100 mg/dl. Insulin lispro was titrated to achieve a preprandial glucose level of 80–130 and peak (1-2 h) postprandial glucose of < 180 mg/dl based on average of the two previous days' home glucose monitoring results. The primary end point was the difference in the HbA1c change from baseline at week 26.

At week 26, HbA1c decreased from baseline by - 0.82 ± 0.06% with albiglutide and -0.66 ± 0.06% with lispro [treatment difference, -0.16% (P < 0.0001)], meeting the noninferiority end point (margin, 0.4%). Weight decreased with albiglutide but increased with lispro (-0.73 ± 0.19 kg vs. + 0.81 ± 0.19 kg). There was no significant difference in glargine dose. Adverse events for albiglutide vs lispro included:

	ALBIGLUTIDE	LISPRO
Severe Hypoglycemia	0	2
Documented Symptomatic Hypoglycemia	15.8%	29.9%
Nausea	11.2%	1.4%
Vomiting	6.7%	1.4%
Injection Site Reactions	9.5%	5.3%

The overall findings show that weekly albiglutide was as effective as nutritional insulin in improving glycemic control. The authors conclude that GLP-1 agonists may offer a simpler therapeutic option than thrice-daily nutritional insulin when multiple daily insulin injections are required. Moreover, GLP-1 agonists result in weight loss and carry a lower risk of hypoglycemia.

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REPORTS ON THE PANCREATIC SAFETY OF GLP-1 AGONISTS

Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. *N Engl J Med*. 2014 Feb 27;370(9):794-797.

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In view of concerns about pancreatitis and pancreatic cancer in relation to incretinomimetic drugs, U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) independently conducted a comprehensive evaluation of the safety of these drugs and reported their findings in this article.

The FDA evaluated more than 250 toxicology studies conducted in nearly 18,000 healthy animals (15,480 rodents and 2475 nonrodents) submitted with marketing applications. Microscopic examinations from these toxicology studies, as submitted, had found no evidence of overt pancreatic toxicity or pancreatitis. The EMA conducted a similar review of the studies for drugs currently authorized for use in the European Union and found no evidence of pancreatic toxicity. Drug-induced pancreatic tumors were also absent in healthy rats and mice that had been treated for up to 2 years (their life span) at doses that greatly exceeded the level of human clinical exposure. Further, the FDA asked the manufacturers of incretin-based drugs to conduct 3-month pancreatic toxicity studies in rodent models of diabetes, including extensive histopathological evaluation of the endocrine and exocrine pancreas. No treatment-related adverse effects on the pancreas were reported in these studies. In addition, three FDA pathologists independently and blindly examined approximately 120 pancreatic histopathology slides and their findings concurred with drug companies' findings. The FDA also performed its own pancreatic toxicology studies with exenatide. Data from the studies of the pancreatitis mouse and diabetic rat models did not identify exenatide-related pancreatic injury.

Clinical safety databases from over 200 clinical trials were also reviewed by the FDA. These data included nearly 41,000 study participants, of whom more than 28,000 had been treated with an active drug; 15,000 for 24 weeks or more, and 8500 for 52 weeks or more. A similar review was conducted by the EMA, including all studies performed with the

incretin-based drugs authorized in the European Union. Small imbalances in the incidence of pancreatitis were found in these trials. However, the overall number of events was small, and no definitive conclusion could be derived.

The FDA and the EMA have also independently reviewed a number of observational studies that have explored a possible link between incretin-based drugs and acute pancreatitis. These studies are based on insurance claims data or other large databases. The FDA and EMA found that these observational studies were mostly flawed and yielded inconsistent results. The methodological problems in these studies include limited power, inadequate outcome validation, incomplete covariate ascertainment, and inadequate confounding control.

Thus, the FDA and the EMA, after exploring multiple streams of data pertaining to pancreatic safety of incretin-based drugs, found that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. Though the FDA and the EMA have not yet reached a final conclusion about such a causal relationship, in their view, the totality of the data provides reassurance about these drugs. The agencies have decided to continue surveillance to look for any further safety signal.

Such vigilance will warn the patients and providers about any small signals about the harms of these drugs, although any major risk is unlikely.

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STATEMENT OF NEED

- Clinicians do not appropriately intensify therapy as necessary to maintain glycemic control.
- Conflicting data about the safety of incretin agents may unduly deprive patients of treatment benefits.
- Clinicians are not aware of and/or are not implementing strategies to maximize the value of SMBG readings to improve patient outcomes.
- Clinicians do not adequately understand or treat to control CVD risk factors in their patients with T2D.
- Clinicians do not have a sufficiently current knowledge base to effectively consult patients about potential T2D therapeutic advances.
- Clinicians do not adequately counsel and treat their overweight/obese patients with T2D.

INTENDED AUDIENCE

The target audience for this initiative includes: endocrinologists, primary care clinicians, nurse practitioners, physician assistants, Certified Diabetes Educators, and other health care practitioners whose work/practice includes treating patients with T2D.

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Johns Hopkins University School of Medicine
Office of Continuing Medical Education
Turner 20/720 Rutland Avenue
Baltimore, Maryland 21205-2195

Reviewed and Approved by
General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

HARDWARE & SOFTWARE REQUIREMENTS
Pentium 800 processor or greater, Windows 98/NT/2000/XP/7 or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K or better modem, Windows Media Player 9.0 or later, 128 MB of RAM, sound card and speakers, Adobe Acrobat Reader, storage, Internet connectivity, and minimum connection speed. Monitor settings: High color at 800 x 600 pixels.

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This activity was developed in collaboration with DKBmed.

COMPLETE THE POST-TEST

Step 1.
Click on link to download instructions for the post-test and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST