CLINICAL DECISIONS
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Glycemic Management in a Patient with Type 2 Diabetes

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

Agnes is a 51-year-old widow with hypertension who received a diagnosis of type 2 diabetes a decade ago. She has been worried about her diabetes since then because she has not been able to gain complete control over it. Her glycated hemoglobin level was 7.0% for 1 year but gradually increased to 9.0%. For the past 2 years, she has been taking metformin. She is maintaining her weight at 165 pounds (75 kg), but she is not able to lose weight. Agnes goes to the gym and walks on a treadmill three times a week, but she jokes that the gym members who talk about a "runner's high" must be hallucinating. In short, she tells you that she has made as many lifestyle changes as she can.

Choose an option and comment on your choice at NEJM.org

Agnes's hypertension is well controlled with an angiotensin-converting–enzyme inhibitor; she also takes a statin. Her most recent laboratory tests showed a low-density lipoprotein cholesterol level of 85 mg per deciliter (2.2 mmol per liter) and a high-density lipoprotein cholesterol level of 62 mg per deciliter (1.6 mmol per liter). The glycated hemoglobin level was 8.0%. You advise her that she'll need an additional drug to reach the goal of 7.0%.

Agnes hates needles and won't use insulin. Her sister, who also has diabetes, was receiving glipizide but had episodes of hypoglycemia while taking that drug, including one episode that resulted in an auto accident. Agnes is also worried about weight gain associated with that drug. Her sister recently switched from glipizide to saxagliptin and reports to Agnes that she has had no further episodes of hypoglycemia. Agnes has also heard about a new class of diabetes drugs that works by eliminating excess glucose through the urine. She wants to know about the safety of the newer drugs and asks specifically about saxagliptin and the new class of drugs.

You explain to her that the drugs she is asking about are in different classes — dipeptidyl peptidase 4 (DPP-4) inhibitors ("gliptins") and sodium glucose cotransporter 2 (SGLT2) inhibitors ("gliflozins"). Both are considered to be effective; studies of the cardiovascular safety of the drugs are under way, and the results of two studies are reported in this issue of the *Journal*. However, these drug classes have distinct side-effect profiles and mechanisms of action, and careful deliberation is important before either one is prescribed.

Do you think a second drug should be added to the metformin Agnes is currently receiving? Are the recent studies that have been reported concerning the safety of gliptins reassuring to you? On the basis of your reading of published literature, other information sources, and your own clinical experience, choose between the two choices below.

1. Recommend adding a DPP-4 inhibitor to metformin therapy.
2. Recommend adding an SGLT2 inhibitor to metformin therapy.

To aid in your decision making, two experts in the field defend these approaches to treatment in the essays below. Given your knowledge of the patient's history and your assessment of the experts' opinions, which option would you choose? Make your choice and offer your comments at NEJM.org.

OPTION 1

Recommend Adding a DPP-4 Inhibitor to Metformin Therapy

Irl B. Hirsch, M.D.

In this era of personalized medicine, and as options for patients like Agnes increase, it is possible to provide this patient with a medication that will allow her to reach her glycemic target and will be in line with her preferences. A DPP-4 inhibitor is one acceptable option. Sitagliptin, which was introduced in the United States in 2006, was the first DPP-4 inhibitor. Since then, several others have been added. In preclinical studies and in actual experience after their launch, these agents have been shown to be both effective and safe, though there has been some recent controversy about a possible relationship with pancreatitis and pancreatic cancer.

DPP-4 inhibitors are oral agents that inhibit the degradation of glucagon-like peptide 1 (GLP-1) and cause modest elevations of circulating GLP-1 levels. They do not cause hypoglycemia unless they are used in combination with sulfonylureas or insulin, and they do not cause weight change. An initial meta-analysis suggests that these agents may have beneficial effects on cardiovascular outcomes,[1] although we await results from long-term cardiovascular outcome trials.

For Agnes, a DPP-4 inhibitor can be provided as a once-daily tablet, and her concerns about hypoglycemia (and weight gain) should be allayed. Although the simplicity of use of this agent is attractive, it must be noted that a DPP-4 inhibitor may not be adequately effective, depending on the glycemic target. For Agnes, the goal is to reduce the glycated hemoglobin level by at least 1 percentage point by adding the DPP-4 inhibitor to metformin, and adding a DPP-4 inhibitor after a patient has been receiving metformin for a period of time rarely results in that robust a response. One 52-week study showed that adding sitagliptin to metformin caused a reduction in the glycated hemoglobin level by 0.7 percentage points, with the greatest reduction at 24 to 30 weeks, and a subsequent gradual increase from 30 to 52 weeks raised concerns about durability.[2] It is possible that the baseline glycated hemoglobin level of 7.5% in that study would translate into a greater improvement in our patient, since larger absolute reductions are usually seen in patients who had higher baseline glycated hemoglobin levels. Nevertheless, after reviewing the drug class as a whole, we can reasonably conclude that these agents are more modest in their efficacy than are sulfonylureas or metformin.[3] Many questions related to the comparative efficacy and safety of DPP-4 inhibitors, sulfonylureas, GLP-1 receptor agonists, and insulin will be answered within the next few years.[4] Since the DPP-4 inhibitors are considerably more expensive than the older oral agents for type 2 diabetes, these comparative data will be welcomed.

Finally, there has been concern recently about a possible association of DPP-4 inhibitors with pancreatitis, pancreatic cancer, and pancreatic neuroendocrine tumors. However, the Committee for Medicinal Products for Human Use of the European Medicines Agency and later the U.S. Food and Drug Administration found no justification for this new concern, although acute pancreatitis has been noted in postmarketing reports. Furthermore, a recent analysis of autopsy results suggested that the concern about pancreatic cancer is "overstated and a misrepresentation of the information available."[5]

In conclusion, a DPP-4 inhibitor is a reasonable choice for Agnes at this time. It will be important to follow her closely to ensure that she has adequate short-term and long-term benefits from its use.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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OPTION 2

Recommend Adding an SGLT2 Inhibitor to Metformin Therapy

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Type 2 diabetes progresses owing to the loss of insulin secretory capacity. Patients often require additional medications to control their diabetes.[6] Agnes has been taking metformin as her initial pharmacologic treatment in addition to lifestyle modification — currently an almost universally recommended approach.[6,7] Now, a second medication would be in order. Given her age and the duration of the diabetes, a glycated hemoglobin goal of less than 7.0% is both realistic and recommended in an effort to avoid long-term complications.

Eleven unique classes of medications are approved in the United States for the treatment of diabetes.[7] Factors to consider when choosing a second drug include efficacy, safety, cost, and the presence of potential confounding factors, such as decreased glomerular filtration rate (GFR). Agnes has had difficulty losing weight, and because of her sister's experience, she is also frightened of hypoglycemia; therefore, sulfonylureas are not appropriate for her. Because she "hates needles," insulin and GLP-1 receptor agonists are also removed from consideration. Thiazolidinediones are generally falling out of favor because they have been associated with weight gain, an increased risk of fracture in women, possible cardiovascular safety issues (with rosiglitazone), and a possible increase in bladder cancer (with pioglitazone).

The DPP-4 inhibitors and the new class of SGLT2 inhibitors are both reasonable choices for this patient. In normal persons, virtually all glucose filtered by the kidney is reabsorbed; about 90% is reabsorbed early in the proximal tubule by SGLT2, and the remaining 10% further down in the proximal tubule by SGLT1, which is also active in the intestine.[8] The reabsorptive capacity of the kidney becomes overwhelmed when plasma glucose levels reach about 180 mg per deciliter (10.0 mmol per liter) in normal persons and at somewhat higher levels in persons with diabetes. When SGLT2 is partially blocked by these inhibitors, glucose spills into the urine when the plasma glucose is in the range of only 70 to 90 mg per deciliter (3.9 to 5.0 mmol per liter). This spilling of 60 to 80 g per day of glucose into the urine results in a lowering of fasting and postprandial glucose levels, with a reduction in glycated hemoglobin levels of about 0.7 to 0.9%.[8-10] Self-monitoring of glucose levels once a day is generally sufficient with a regimen that consists of only oral agents. Since 60 to 80 g of glucose corresponds to 240 to 320 kcal lost through the urine, most patients lose 3 to 4 kg over the course of 1 year, and systolic blood pressure drops about 3 to 4 mm Hg.[9,10] However, a downside of increased glycosuria is an increased risk of genital candidiasis (in about 10 to 11% of women receiving SGLT2 inhibitors, as compared with 3% receiving placebo).[9,10] Candidiasis is usually easily treated, but about 10% of patients with candidiasis have repeated infections. Urinary bacterial infections are only minimally increased, and hypoglycemia is not increased.[9,10]

Given Agnes's desire to lose weight, lower her blood pressure, and reach a glycated hemoglobin level near 7.0%, I would favor treating her with an SGLT2 inhibitor. However, I would not prescribe that class of drug if she reports a history of repeated candida infections. I would also calculate her estimated GFR (eGFR), since the SGLT2 inhibitors are not very effective when the eGFR is less than 45 ml per minute per 1.73 m^2 of body-surface area. If the initial eGFR is more than 80 ml per minute per 1.73 m^2, yearly monitoring is sufficient, but as the level approaches 60 ml per minute per 1.73 m^2, monitoring every 3 to 6 months is indicated.

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1. Patil HR, Al Badarin FJ, Al Shami HA, et al. Meta-analysis of effect of dipeptidyl peptidase-4 inhibitors on cardiovascular risk in type 2 diabetes mellitus. Am J Cardiol 2012;110:826-33.
2. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2007;9:194-205.
3. Stein SA, Lamos EM, Davis SN. A review of the efficacy and safety of oral antidiabetic drugs. Expert Opin Drug Saf 2013;12:153-75.
4. Nathan DM, Buse JB, Kahn SE, et al. Rationale and design of Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care 2013;36:2254-61.
5. Harja E, Lord J, Skyler JS. An analysis of characteristics of subjects examined for incretin effects on pancreatic pathology. Diabetes Technol Ther 2013;15:609-18.
6. Inzucchi SE, Bergenstal RM, Buse JB, et al. 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;35:1364-79. [Erratum, Diabetes Care 2013;36:490.]
7. Qaseem A, Humphrey LL, Sweet DE, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2012;156:218-31.
8. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr Rev 2011;32:515-31.
9. Rosenstock J, Aggarwal N, Polidori D, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012;35:1232-8.
10. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes. A systematic review and meta-analysis. Ann Intern Med 2013;159:262-74.

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